2020-2134, 2020-2136, 2020-2137

United States Court of Appeals for the Federal Circuit

CEPHALON, INC., EAGLE PHARMACEUTICALS, INC., TEVA PHARMACEUTICALS INTERNATIONAL GMBH,

Plaintiffs-Appellees,

– v. –

SLAYBACK PHARMA LIMITED LIABILITY COMPANY,

Defendant,

APOTEX INC., APOTEX CORP., FRESENIUS KABI USA, LLC, MYLAN LABORATORIES LIMITED,

Defendants-Appellants.

On Appeals from the United States District Court for the District of Delaware in Nos. 1:17-cv-01154-CFC, 1:17-cv-01164-CFC, 1:17-cv-01201-CFC and 1:17-cv-01790-CFC, Honorable Colm F. Connolly, Judge

BRIEF OF DEFENDANTS-APPELLANTS APOTEX INC. AND APOTEX CORP.

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ORIGINALLY FILED: NOVEMBER 4, 2020
CORRECTED: APRIL 27, 2021

U.S. Pat. No. 9,597,399 **(asserted claims: 13, 15)**
1. A method of treating cancer or malignant disease in a subject, comprising parenterally administering a volume of about 100 ml or less of a liquid composition comprising: a) from about 0.05 to about 12.5 mg/ml of bendamustine or a pharmaceutically acceptable salt thereof; b) a solubilizer comprising propylene glycol in an amount of from about 4.5 mg/ml to about 51 mg/ml and polyethylene glycol; c) a parenterally acceptable diluent; and optionally d) an antioxidant; over a period of less than or equal to about 15 minutes to a subject in need thereof.
3. The method of claim 1, wherein the volume administered is from about 50 ml to about 65 ml.
9. The method of claim 1 wherein the concentration of bendamustine or pharmaceutically acceptable salt thereof is about 5.6 mg/ml.
12. The method of claim 9, wherein the composition is administered intravenously.
13. The method of claim 12, wherein the composition is administered intravenously over a time period of about 10 minutes or less.
14. The method of claim 3, wherein the composition is administered intravenously.
15. The method of claim 14, wherein the composition is administered intravenously over a time period of about 10 minutes or less.

U.S. Pat. No. 9,144,568 **(asserted claims: 11, 18, 22)**
1. A method of treating chronic lymphocytic leukemia or indolent B cell non-Hodgkin's lymphoma comprising parenterally administering to a subject a volume of about 100 ml or less of a liquid composition comprising: a) from about 0.5 to about 5.6 mg/ml of bendamustine or a pharmaceutically acceptable salt thereof; b) a solubilizer comprising polyethylene glycol and propylene glycol, wherein the amount of solubilizer is from about 0.5 to about 26.5% vol; c) a parenterally acceptable diluent; and optionally d) an antioxidant; over a period of less than or equal to about 15 minutes to the subject.
9. The method of claim 1, wherein the bendamustine is administered to treat chronic lymphocytic leukemia.
10. The method of claim 9, wherein the composition is administered intravenously in a volume of about 50 ml in 10 minutes or less on days 1 and 2 of a 28 day cycle.
11. The method of claim 10, wherein the composition is administered in about 10 minutes.
16. The method of claim 1, wherein the bendamustine is administered to treat indolent B cell non-Hodgkin's lymphoma.
17. The method of claim 16, wherein the composition is administered intravenously in a volume of about 50 ml in about 10 minutes or less on days 1 and 2 of as 21 day cycle.
18. The method of claim 17, wherein the composition is administered in about 10 minutes.
22. The method of claim 16, wherein the liquid composition comprises from about 2.19 mg/ml to about 5.59 mg/ml of bendamustine or a pharmaceutically acceptable salt thereof.

U.S. Pat. No. 9,572,797 **(asserted claims: 9, 11)**
1. A method of treating leukemia, Hodgkin's disease, or multiple myeloma in a mammal, comprising administering to the mammal, a liquid bendamustine-containing composition comprising: a) bendamustine or a pharmaceutically acceptable salt thereof; and b) a non-aqueous pharmaceutically acceptable fluid comprising about 5% to about 10%, based on the volume of the pharmaceutically acceptable fluid, of propylene glycol, polyethylene glycol, and a stabilizing amount of an antioxidant selected from the group consisting of thioglycerol, monothioglycerol, lipoic acid, propyl gallate, methionine, cysteine, metabisulfites, sodium formaldehyde sulfoxylate, phenol-containing aromatic and aliphatic compounds and dihydrolipoic acid; the bendamustine-containing composition having less than or equal to 0.11% total PG esters at about 1 month of storage at a temperature of about 5° C.; wherein the ratio of polyethylene glycol to propylene glycol is selected from the group consisting of: about 95:5, about 90:10, about 85:15, about 80:20, and about 75:25.
9. The method of claim 1, wherein said bendamustine-containing composition has less than or equal to 0.43% total PG esters at about 3 months of storage at a temperature of about 25° C.
11. The method of claim 1, wherein the antioxidant is thioglycerol or monothioglycerol.

U.S. Pat. No. 9,265,831 **(asserted claims: 2, 3, 5)**
1. A non-aqueous liquid bendamustine-containing composition, comprising: a) bendamustine or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable fluid comprising; i) about 5% to about 10% by volume propylene glycol, ii) polyethylene glycol, and iii) a stabilizing amount of an antioxidant selected from the group consisting of thioglycerol, monothioglycerol, lipoic acid, propyl gallate, methionine, cysteine, metabisulfites, sodium formaldehyde sulfoxylate, phenol-containing aromatic and aliphatic compounds and dihydrolipoic acid; the bendamustine-containing composition having less than or equal to 0.11% total PG esters at about 1 month of storage at a temperature of about 5° C.; wherein the ratio of polyethylene glycol to propylene glycol is selected from the group consisting of: about 95:5, about 90:10, about 85:15, about 80:20 and about 75:25.
2. The liquid bendamustine-containing composition of claim 1, wherein said bendamustine-containing composition has less than or equal to 0.18% total PG esters at about 12 months of storage at a temperature of about 5° C.
3. The liquid bendamustine-containing composition of claim 1, wherein the amount of propylene glycol in the pharmaceutically acceptable fluid is about 10%.
4. The liquid bendamustine-containing composition of claim 1, wherein the bendamustine concentration is from about 20 mg/mL to about 60 mg/mL.
5. The liquid bendamustine-containing composition of claim 4, wherein the bendamustine concentration is from about 25 mg/mL to about 50 mg/mL.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number	2020-2134; -2136, -2137
Short Case Caption	Cephalon, Inc. V. Slayback Pharma Limited
Filing Party/Entity	Apotex Inc., Apotex Corp. Defendants-Appellants

Instructions: Complete each section of the form. In answering items 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance. **Please enter only one item per box; attach additional pages as needed and check the relevant box**. Counsel must immediately file an amended Certificate of Interest if information changes. Fed. Cir. R. 47.4(b).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 04/27/2021 Signature: /s/ Sherry L. Rollo

Name: Sherry L. Rollo

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☐ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☐ None/Not Applicable
Apotex Inc.	None	Apotex Pharmaceutical Holings, Inc.
Apotex Corp.	None	Apotex Holdings Inc.

☐ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☐ Additional pages attached

Jeffrey A. Cohen of Flaster Greenberg, PC	Damien Tancredi of Flaster Greenberg, PC	Jeremy S. Cole formerly of of Flaster Greenberg, PC
John C. Phillips of McLaughlin & Hall PA	Megan C. Haney of McLaughlin & Hall PA	David A. Bilson of McLaughlin & Hall PA

5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

☐ None/Not Applicable ☐ Additional pages attached

Cephalon, Inc. v. Slayback Pharma Limited, Appeal No. 20-2136 (Fed. Cir.) (Fresenius Kabi USA, LLC)	Cephalon, Inc. v. Slayback Pharma Limited, Appeal No. 20-2137 (Fed. Cir.) (Mylan Laboratories Limited)	Eagle Pharmaceuticals, Inc. v. Hospira, Inc., No. 1:18-cv-1074-CFC (D. Del)
Eagle Pharmaceuticals, Inc. v. Slayback Pharma LLC, No. 1:18-cv-1459-CFC (D. Del)	Cephalon, Inc. v. Aurobindo Pharma, Ltd., No. 1:20-cv-632-CFC (D. Del)	

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☒ None/Not Applicable ☐ Additional pages attached

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STATEMENT OF RELATED CASES

No appeal in or from this same civil action in the lower court was previously before this or any other Court of Appeals.

In addition to the consolidated cases that led to this appeal, there are two patent infringement cases pending in the District of Delaware involving patents at issue here: (1) *Teva Pharmaceuticals International GmbH et al v. Aurobindo Pharma, Ltd. et al.*, 1:20-cv-00632-CFC; (2) *Eagle Pharmaceuticals, Inc. et al v. Hospira, Inc.*, 1:18-cv-01074-CFC-CJB; which are ongoing; and (3) *Eagle Pharmaceuticals, Inc. v. Slayback Pharma LLC,* 1:18-cv-01459-CFC, which has been stayed by stipulation.

JURISDICTIONAL STATEMENT

The District Court had subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338 (a) for Plaintiff's suit under 35 U.S.C. § 271 (e)(2)(A). Appx207-268. After a bench trial on the issues of validity and infringement, the District Court entered a final judgment and a permanent injunction. Appx25-30. Apotex timely appealed on August 4, 2020. Appx21600-21601. This Court has appellate jurisdiction under 28 U.S.C. § 1295.

STATEMENT OF THE ISSUES

1. Whether the district court legally erred in failing to conclude that the asserted claims to a concentrated, polyol-based, liquid bendamustine formulation with a "stabilizing amount" of an antioxidant would have been obvious based on a flawed teaching away analysis, where the prior art already taught the benefits of formulating bendamustine this way rather than as a lyophilized powder using polyols, and suggested the use of antioxidants and other routine stabilization methods with such formulations, and by failing to find whether the stability of such an obvious formulation was inherent where Plaintiffs' expert admitted that stability was an inherent property of a formulation.

2. Whether the district court legally erred in failing to conclude that the asserted claims to administering the liquid bendamustine formulations of the (now prior art) formulation patents over a period of 10-15 minutes or less in a volume of 50-100 ml, or less, using a known bendamustine dosing schedule would have been obvious in view of the prior art as a whole, by applying an overly stringent motivation test that disregarded express teachings and suggestions to do what was claimed, and by again misapplying teaching away.

3. If not obvious, whether the district court legally erred by failing to find the claims of the formulation patents with stability limitations were invalid for lack of enablement.

STATEMENT OF THE CASE

Teva, Cephalon, and Eagle sued Apotex alleging infringement of the following U.S. Patents under 35 U.S.C. § 271 based on Apotex's filing of Abbreviated New Drug Application ("ANDA") No. 210601 with the U.S. Food and Drug Administration ("FDA") seeking approval for commercial manufacture, use, and/or sale of a generic liquid bendamustine hydrochloride injection products for use in the treatment of chronic lymphocytic leukemia and indolent B-cell non-Hodgkin lymphoma (Appx207-268):

Teva's Patent

8,791,270 (the "'270 patent") (Appx21817-21845)

Eagle's Formulation Patents

8,609,707 (the "'707 patent")(Appx26103-26111), 9,265,831 (the "'831 patent")(Appx26112-26120), 9,572,796 (the "'796 patent")(Appx26121-26130), 9,572,797 (the "'797 patent")(Appx26131-26140)

Eagle's Administration Patents

9,034,908 (the "'908 patent")(Appx26078-26090), 9,144,568 (the "'568 patent")(Appx26152-26163), 9,572,887 (the "'887 patent")(Appx21877-21894), 9,597,397 (the "'397 patent")(Appx26164-26176), 9,597,398 (the "'398 patent")(Appx26177-26189), 9,597,399 (the "'399 patent") (Appx21895-21907),

9,000,021 (the "'021 patent")(Appx26202-26208), and 9,579,384 (the "'384 patent")(Appx26209-26216).

Apotex challenged each of the patents as invalid and/or not infringed. Appx14949. Prior to trial Plaintiffs and Apotex stipulated to the dismissal of all the '270 patent claims and counterclaims. Appx18637-18638.

At trial, Appellees asserted claims 2, 3, 5 of the '831 patent; claims 9, 11 of the '797 patent; claims 11, 18, 22 of the '568 patent and claims 13 and 15 of the '399 patent against Apotex. Appx26. After a bench trial, the district court held those patent claims infringed and not invalid, and entered a final judgment and a permanent injunction. Appx25-30.

Based on the court's interpretation of the Parties' Stipulation, (Appx18517-18521) and the record at trial with respect to the claims in the preceding paragraph, the court found that Apotex's ANDA also infringes claims 7, 12, 14, 18, 20 of the '707 patent; claims 5, 7, 18, 20, 24 of the '796 patent; claims 2, 3, 5, 7, 8, 10, 20, 21 of the '797 patent; claims 1, 5, 8-10, 14, 19, 22, 23 of the '908 patent; claims 6, 8, 15, 21 of the '568 patent; claims 3, 12, 13, 18, 21, 22, 25, 29 of the '887 patent; claims 3-7 of the '397 patent; claims 2, 3 of the '398 patent; claims 2, 4, 17 of the '399 patent; claims 3-5, 9, 11, 14, 15, 17, 19, 21, 24, 26, 28, 29 of the '021 patent; and claims 7, 12, 13, 18, 19, 23 of the '384 patent, even though these patents were not tried. Appx26, Appx21588-21593.

This appeal followed.

STATEMENT OF THE FACTS

This case is about a regulatory and marketing strategy, not scientific innovation, and certainly not an innovation worthy of the 13 patents and over 250 claims (with more applications pending) that Eagle obtained and Teva licensed to jointly try to create a patent thicket to prevent generic competition for years to come.

The at-issue patents fall into two families. The formulation patents are directed to non-aqueous, ready-to-dilute, liquid bendamustine concentrates (25mg/ml-50mg/ml) that utilize a polyol-based solvent system (PEG(95%-75%):PG(5%-25%) and a "stabilizing amount" of an antioxidant, including monothioglycerol, and certain resulting impurity levels. Appx49.

The administration patents are directed to diluting and infusing the concentrates of the formulation patents (which were prior art to the administration patents) in convenient 50-100ml bags over 10-15 minutes to treat two types of cancer, chronic lymphocytic leukemia (CLL) and non-Hodgkin's lymphoma (NHL), utilizing standard dosing schedules, and certain resulting diluted concentrations. Appx71-72.

The court found no unexpected results, no teaching away, no longfelt need, no failure of others and no commercial success that bear on the obviousness of what is claimed for either set of patents. Appx68-69, Appx88-92.

A. BENDAMUSTINE WAS OLD.

Bendamustine hydrochloride is the active ingredient in Eagle's liquid bendamustine product, marketed under the tradename Bendeka®. Appx40. Bendamustine is a nitrogen mustard chemotherapy drug developed in East Germany in the 1960s that was used to treat cancer, including CLL and NHL. Appx40. Bendamustine was marketed from 1971-1992 in Germany as Cytostasan® and subsequently as Ribomustin®. Appx22191-22202 at Appx22197 (1:40-45).

In the U.S., Salmedix began developing a bendamustine product in the early 2000s and, in 2003, obtained an exclusive license from Fujisawa, who manufactured Ribomustin®. Appx69, Appx25379-25406 at Appx25379-25380, Appx25397, Appx19053 (1233:18-1234:25), Appx19060-19061 (1263:21-25; 1266:9-1267:8).

In 2005, Cephalon acquired Salmedix, which included the information licensed from Fujisawa in 2003. Appx69, Appx19051 (1226:24-1227:1). Cephalon (which later became part of Teva) launched a lyophilized bendamustine product, Treanda®, in 2008. Appx40-42.

B. POLYOL BASED LIQUID BENDAMUSTINE FORMULATIONS WITH BENDAMUSTINE CONCENTRATIONS OF 25MG/ML-100MG/ML WERE KNOWN.

Bendamustine was known to hydrolyze in water, and for that reason it was originally formulated and marketed as a lyophilized (freeze-dried) powder. Appx50-51. However, a powder must be reconstituted before being administered, which is inconvenient and also exposes medical personnel to some risk because the drug is cytotoxic. Appx50-51.

There's good reason that, when first approached about developing a liquid bendamustine formulation, inventor Palepu looked at bendamustine's structure and said it would be a "slam dunk". Appx18064 (310:23-312:2). As the court found, "[t]o avoid lyophilization while still avoiding the use of water, a POSITA would have been motivated to create a non-aqueous liquid bendamustine product," and "other inventors sought to create non-aqueous liquid bendamustine formulations before the priority date." Appx56.

One known, non-aqueous liquid bendamustine formulation was disclosed in the "Olthoff" patent. Appx22208-22223. The court found that Olthoff taught a stable, non-aqueous injectable liquid concentrate of 25-100mg/mL bendamustine dissolved in polyols rather than water. Appx51. Olthoff's objective was to "produce a stable and ready-to-use injection solution out of N[itrogen]-mustard compounds, avoiding the technical solution of a dry ampoule [*i.e.*,

lyophilization]." Appx51. "Olthoff disclosed that bendamustine has 'a[n] extraordinarily high chemical stability for the production of injection solutions in' monovalent alcohols, glycols and polyols." Appx51. "Olthoff specifically proposed dissolving bendamustine in 'polyols, particularly 1,2-propylene glycol [*i.e.*, PG].'" Appx51-52. Polyols are another name for non-aqueous solvents that have multiple -OH groups. Appx52. Both PEG and PG are polyols. Appx52.

Olthoff explained that although polyols contain -OH groups, its polyol-based bendamustine solutions unexpectedly did not undergo a break-down reaction called alcoholysis. Appx22219. Olthoff further taught to prepare and store its liquid bendamustine formulations in an inert gas, such as argon or nitrogen, rather than oxygen, which a POSITA would interpret as susceptibility to oxidation. Appx22221, Appx18393 (413:14-19), Appx18446 (623:8-624:1). Olthoff taught the solubility of bendamustine in PG was 125mg/ml. Appx66, Appx22221.

PEG and PG were "well-described and commonly used" solvents in liquid injectable formulations. Appx36879-36892 at Appx36885, Appx19191 (1576:7-25). Not surprisingly, after Dr. Palepu saw Olthoff, which already taught to use polyols as solvents for concentrated bendamustine formulations (commenting "eureka!" as soon as he saw it), it only took a couple of months to arrive at the

claimed formulations.[1] Appx18065 (314:22-315:14), Appx25036-25047. Dr. Palepu wrote: "Gentlemen, here is the German patent! It is in German. Whatever little I gathered from this patent is that they use propylene glycol, 25-100 mg/mL to make a solution of bendamustine." Appx25036, Appx18065 (315:15- 316:6). Dr. Palepu requested that Olthoff be translated (Appx18065 (316:3-6)) and sent co-inventor Dr. Buxton another email referring to Olthoff, stating: "Gentlemen: Bendamustine has shown excellent solubility in PG (125 mg/ml), ethanol (50 mg/ml) and glycerin (50 mg/ml). I want you to reexamine the solubility in PEG 400 [sic] and DHLA-PEG [polyethylene glycol]." Appx25034-25035, Appx18065-18066 (317:8-319:20). Dr. Palepu testified that this email meant "they should reexamine the numbers [of Olthoff] and also do it with PEG 400." Appx18066 (318:15-319:14). Approximately three months after receiving Olthoff, Dr. Palepu and SciDose had the basic non-aqueous, liquid bendamustine formulation containing 50 mg bendamustine, 90:10 PEG:PG, and an antioxidant (alpha lipoic acid) claimed in the formulation patents. Appx18375 (338:7-341:16), Appx23478-23502 at Appx23501, Appx25018-25019. The ratio was just a matter of routine optimization, as exemplified by Alam, which

[1] Unlike Archimedes who shouted "eureka" upon discovering something new, here, the inventors exclaimed "eureka" upon finding something old, namely, the Olthoff prior art reference.

similarly taught to vary the ratios of PG(10%-90%) and PEG(90%-10%) in another nitrogen mustard formulation. Appx53, Appx18396 (424:2-25:5), Appx18397 (428:6-12), Appx19100 (1421:18-24), Appx22091.

Eagle later switched the antioxidant to monothioglycerol in the commercial Bendeka® formulation because monothioglycerol was an FDA approved ingredient and lipoic acid was not. Appx18375 (340:6-23), Appx22339-22356 atAppx22344, Appx24235-24435 at Appx24334-24339. It already was known in the art to use an antioxidant to stabilize a formulation that was susceptible to oxidation (Boylan), including in formulations that contained PEG (Rowe), and those that contained bendamustine (Drager). Appx55, Appx18375 (340:6-23), Appx22092-22136 at Appx22111, Appx22344, Appx22349, Appx22200; Appx24332-24336. Tait also used monothioglycerol in injectable formulations for an anticancer drug "related to the nitrogen mustards." Appx36342-36356 at Appx36343, Appx36351, Appx36355-36356.

C. DRAGER CORROBORATED MUCH OF OLTHOFF.

Drager was Teva's patent on its liquid bendamustine formulations. Appx22191-22202. Drager did not publish until after Eagle filed its earliest provisional application (January 28, 2010), but is prior art under 35 U.S.C. § 102(e). Appx52.

The court found that Drager taught liquid bendamustine formulations using aprotic (non-OH containing solvent) combined with protic (OH-containing non-aqueous solvents) like the polyols disclosed in Olthoff. Appx52-53. The court explained: "The reason for that degradation, according to Drager, was that (1) PG causes bendamustine to degrade at the nitrogen mustard group, and [] (2) PG's-OH groups cause bendamustine to degrade at the carboxylic acid group through esterification [citations omitted]." Appx52-53. So Drager reduced the number of -OH groups that were causing the problem by including a solvent like dimethylacetamide (DMA), which did not contain any OH groups. Appx18398-18399 (431:7-13; 434:22-437:21). Drager exemplified a stable formulation of 66%DMA and 34%PG. Appx58-59. This reduced the number of OH groups available to cause esterification, as compared to a PG-only formulation. Appx18399 (436:20-437:15).

While Drager's inventors were aware of Olthoff and tried to distinguish it in their patent, Drager's data corroborates much of Olthoff. Appx25323-25328 at Appx25325, Appx18589-18590 (936:3-937:5).

Drager teaches using mixtures of PG and PEG as solvents for bendamustine. Appx22198 (3:36-48). Teva admitted through a continuation application that Drager taught the core components of the asserted claims. Appx25440-25476 at Appx25474-25475. The continuation claimed "about 5

mg/mL to about 200 mg/mL" bendamustine with "up to about 90% of a mixture of polyethylene glycol and propylene glycol" (claim 1); an antioxidant (claim 2); low levels of PG esters ("1.5% or less") (claim 3); and treating cancers including CLL and NHL by diluting the formulation and administering it (claims 4-6). Appx25474-25475, Appx19190-19191 (1571:17-1573:13). These claims do not recite an aprotic solvent and do not require DMA. Appx19191 (1573:2-4). The specification for this application is the same as for Drager. Appx25440-25475; Appx22191-22202.

Consistent with Olthoff, Drager found that a 99% PG-only formulation did not induce alcoholysis. Appx18673 (1082:2-1084:20), Appx18676-18677 (1095:11-1098:10). Drager also found that the 99% PG-only formulation was stable for six months under refrigeration, which Drager described as commercial storage conditions. Appx22198 (3:25-35), Appx18676-18677 (1095:11-1098:10). Drager did not include any adverse stability data or other test data for PEG-PG combinations that ultimately got claimed in the formulation patents. Appx18414 (496:14-16).

Drager's solution of mixing PG with an aprotic solvent to reduce the number of -OH groups available for reaction, is similar to what happens when PG is mixed with PEG because PEG has significantly less OH groups per unit volume than does PG. Appx18399-18341 (437:8-443:12). Appellees' chemistry

expert Dr. Anslyn testified that the proportion of -OH groups in a 90:10 PEG:PG mixture is about the same as the number of -OH groups in Drager's preferred 66%DMA/34%PG solvent mixture. Appx18668 (1065:1-10).

Drager's use of aprotic solvents such as DMA was far from a perfect solution. For example, DMA was known to dissolve plastic used in some injection devices. Appx18398-18399 (433:11-433:16; 436:10-436:15). Ultimately this caused Teva to have to provide a warning on its commercial bendamustine liquid formulation. Appx19202(1619:8-1619:16). While the court suggested that other aprotic solvents like NMP and DMSO could have been used instead, those solvents were not FDA approved for use in injectables. Appx18440 (601:4-10); Appx18056 (281:18-282:2). Accordingly, the POSITA would try to avoid DMA if it could. Appx19190 (1570:25-1571:3). Mixing PG with PEG instead of DMA would have accomplished an equivalent reduction in OH-burden and taken advantage of Drager's teaching to reduce overall number of -OH groups to help stabilize the formulation. Appx18668 (1065:1-10), Appx18399 (437:8-15).

D. ADMINISTERING HIGH DOSES OF BENDAMUSTINE IN A SHORT AMOUNT OF TIME WAS NOTHING NEW.

The administration patents are about taking advantage of the properties of the highly concentrated 25-50mg/ml liquid bendamustine formulations of the formulation patents (which are prior art to these patents ("Palepu 2011")), by

administering them in a short (10-15 minutes), low volume infusion to treat CLL and NHL using the standard Treanda® dosing schedule (100 or 120mg/m^2 on days 1, 2 of a 21 or 28 day cycle). Appx71-73.

The court found Palepu 2011 "established a motivation to use its formulations" because it touted the advantages of its concentrated formulations stating "that they have substantially improved long term stability when compared to currently available formulations," and "are advantageously ready to use or ready for further dilution" and thus "[r]econstitution of lyophilized powder is not required." Appx72, Appx77.

The court found "a POSITA also would have been motivated to combine Palepu 2011 with the Treanda® Label to come up with the claimed doses and dosing schedule." Appx77.

The Treanda® Label required administration of Treanda® in a volume of 500 ml. But administering this large amount of fluid to patients was being questioned. Appx75. The court found (Appx75) that Barth suggested administering bendamustine in a smaller volume of 100-250 ml, instead of 500 ml) for a 30-minute infusion:

> The 30-minute short infusion that is practiced in Germany can be readily achieved with infusion volumes of 100 to 250 ml 0.9% NaCI.

> It is unclear why the American prescribing information specifies 500 ml 0.9% NaCI or a final concentration of 0.2-0.6 mg/ml is unclear. A short infusion with such a volume is difficult to implement.

Appx24089-24094 at Appx24093, Appx75, Appx18455 (658:12-20), Appx18526 (681:21-683:8).

Witnesses for both sides testified there were known advantages to administering bendamustine quicker and in less volume, including "convenience" (Appx18526 (683:9-15), Appx18529 (696:20-25)), "advantages for patients" (Appx19059 (1257:19-25)), and "productivity and workflow" benefits (Appx19071 (1306:3-22)).

It already was known that bendamustine could be administered in lower volumes and shorter infusion times than those specified in the Treanda® label. For example, Preiss 1985 discloses administering bendamustine (280-375 mg) as a 3-minute IV drip to cancer patients. Appx73-74. Preiss 1998, which was both a pharmacokinetic study and a safety study, disclosed administering bendamustine in 3-10 minute bolus injections to more than 50 tumor patients. Appx73-74. Preiss 1998 disclosed a single-day maximum tolerated dose of 215mg/m^2 (which was far in excess of Treanda®'s 100-120 mg/m^2) and multi-day (85mg/m^2 per day) maximum tolerated dose of 340mg/m^2. Appx24037-24040 at Appx24040, Appx18524 (675:12-76:1), Appx18567-18568 (847:25-852:12). The Preiss study concluded only mild toxicities occurred despite the high dosages and regardless

of whether it was given in one day or repeatedly over four days. Appx73-74. It did not report any localized toxicity reactions such as thrombophlebitis. Appx24037-24040, Appx18568 (852:6-12). Preiss 1998 also reported that bendamustine had "linear dose-independent kinetics," which means there's direct proportionality between the dose and the exposure to the drug. Appx24039, Appx18567 (846:4-847:24). So, for a given dose, a patient gets the same amount of drug regardless of whether it is administered in 10 minutes or 30 minutes. Appx18525 (677:24-680:19), Appx18567 (846:25-847:7).

Subsequent studies by Schoffski found the side effects observed in Preiss's 3-10 minute infusions were comparable to those seen in 30-minute infusions, and does not identify any local toxicity concerns for either administration. Appx75, Appx18525-18526 (677:24-681:13), Appx24023-24029 at Appx24023, Appx24031-24036 at Appx24031, Appx18531 (704:8-25), Appx18568 (852:6-12). Schoffski confirms that the total dose rather than the administration time (30mins vs. 10mins) is determinative of side effects. Appx18525-18526 (680:20-681:13), Appx18533 (712:6-21). Dr. Sundaram, inventor on the administration patents, observed that the Preiss side-effects mentioned in Schoffski were "related to dose and not necessarily the infusion duration because [Schoffski] goes on to say that the 30 min infusion (at lower doses) also result[s] in similar effects."

Appx25581-25596 at Appx25581, Appx18031 (178:9-181:24), Appx24027-24028.

Experts from both sides agreed administration time, volume, and concentration are all interdependent for a given dose, and therefore once one is determined the other elements follow. Appx19065-19066 (1283:24-84:9), Appx18455 (660:14-24); Appx18566-18567 (844:10-45:10). Because Preiss administered bendamustine in 3-10 minutes a POSITA would have known that the volume must be small. Appx18455 (660:14-24). Additionally, although Preiss does not explicitly disclose the volume used in its 3-10 minute infusions, (Appx84), Preiss 1998 did disclose bendamustine was administered intravenously as bolus injection. Appx24038. A bolus cannot be a large volume of liquid. Appx18528 (690:10-14), Appx18548 (770:13-771:17). The patents-at-issue define a bolus as 50 mL or less. Appx21849 (4:31-34), Appx21850 (5:58-60). Olthoff similarly disclosed using small volumes to administer concentrated liquid bendamustine formulations, including 25-100mg/ml bendamustine concentrate and dilution ratios of 1:5-1:20. Appx22223, Appx18565 (837:15-39:8). Olthoff exemplified preparing a ready to inject solution of bendamustine by placing 1mL of a 25mg/ml bendamustine concentrate in a 10mL ampoule, and adding 9ml of diluent. Appx18565 (837:5-39:8), Appx22222-22223. Glimelius, disclosed

infusions of cancer drugs using standard 50-100mL minibags typically would take only 10-20 minutes. Appx76, Appx18566 (841:6-42:11).

SUMMARY OF THE ARGUMENT

The district court legally erred in failing to hold the at-issue patents invalid for obviousness by applying a flawed teaching away analysis and an overly rigid motivation standard. As discussed in Sections I and II of the argument below, there was nothing new about a polyol-based liquid bendamustine concentrate. Nor was there anything new about administering bendamustine in a fast, low volume infusion. This had all been done before. Some of the claims include stability limitations, but those do not save the claims because stability is an inherent property of an obvious formulation, or those claims are not enabled. Sometimes facially obvious claims are saved by objective indicia of nonobviousness. But here the court did not find any unexpected results or other objective indicia either. Appx68, Appx88. Yet, according to the court the POSITA could not even get started with either the claimed formulation or the methods of administration.

How, then, did the district court fail to invalidate the asserted claims for obviousness? Fundamental to the district court's flawed obviousness analysis was its basic misunderstanding of when a reference does, and does not, "teach away" from the claimed invention. Appx57-61, Appx64, Appx82-83.

The district court evidently thought that stating a preference for A over B is a "teaching away" from B. Appx64 (finding other methods were preferred over

using an antioxidant). In patent law, however, "the teaching away inquiry does not focus on whether a person of ordinary skill in the art would have merely *favored* one disclosed option over another disclosed option." *Bayer Pharma AG v. Watson Labs., Inc.,* 874 F.3d 1316, 1328 (Fed. Cir. 2017)(court's italics). The focus of the teaching away inquiry is on whether the prior art as a whole teaches that the claimed approach would not work for its intended purpose. *Id*. ("unlikely to be productive of the result sought"); *Par Pharma., Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014)(same); *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) ("unlikely to work").

The district court also erred by classifying as teach-aways references that did not even address the claimed approach and by failing to take into account of all the relevant prior art as whole not just for what it expressly stated but for what it fairly taught the POSITA. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017-1018 (Fed. Cir. 2017) ("Bressler does not even mention sinewave commutation."); *Par*, 773 F.3d at 1199 ("Graham never mentioned nanoparticle technology.")

The administration patents claim a known bendamustine formulation used to treat known diseases in a dosing schedule that was known to be efficacious for those diseases in a time, volume, and concentration that was not only suggested or taught in prior art, but was studied and reported in the prior art as safe. To find

these patents nonobvious, the court did not perform the full obviousness analysis of determining the differences between the prior art and claimed subject matter and assessing whether those differences would have been obvious to a POSITA. 35 U.S.C. § 103; *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 405 (2007). Instead, the court applied an overly rigid analysis that set the motivation bar beyond the level of reasonable expectation of success, requiring near certainty of success before a POSITA could even get started in applying a reference. In so doing, the court rejected explicit teachings or suggestions in the prior art to do what was claimed.

The district court's judgment upholding the obviousness of the asserted claims should therefore be reversed. The district court's judgment of lack of enablement for formulation claims also should be reversed if those claims are not otherwise held obvious.

ARGUMENT

Section 103 of the Patent Act "forbids issuance of a patent when 'the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art.'" *KSR*, 550 U.S. at 405 (quoting 35 U.S.C. § 103)).

Standard of Review

"The ultimate conclusion of whether a claimed invention would have been obvious is a question of law reviewed *de novo*." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007). That question is based on "underlying findings of fact," which are "reviewed for clear error." *Id.* The factual determinations underlying the legal conclusion of obviousness include: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) evidence of secondary factors, known as objective indicia of non-obviousness. *Id.* at 1360.

"[I]f the trial court bases its findings upon a mistaken impression of applicable legal principles, the reviewing court is not bound by the clearly erroneous standard." *Inwood Labs., Inc. v. Ives Labs.*, Inc., 456 U.S. 844, 855 n.15 (1982). Thus, this Court has the "power to correct … a finding of fact that is predicated on a misunderstanding of the governing rule of law." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 975 (Fed. Cir. 1995). Where a "district court … base[s] its conclusion of nonobviousness" on an incorrect legal standard, it "err[s] as a matter of law." *See, e.g., Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1364 (Fed. Cir. 2001).

I. THE DISTRICT COURT LEGALLY ERRED IN FAILING TO HOLD THE FORMULATION PATENTS INVALID FOR OBVIOUSNESS.

The court legally erred in failing to conclude that the asserted formulation claims to a concentrated, polyol-based, liquid bendamustine formulation with a "stabilizing amount" of an antioxidant would have been obvious. The court employed a flawed teaching away analysis, discounting express teachings in the prior art regarding the benefits of formulating bendamustine as a nonaqueous liquid rather than a lyophilized powder using polyols, and suggested the use of antioxidants and other routine stabilization methods with such formulations. The court also failed to find whether the stability of such an obvious formulation was inherent where Appellees' expert admitted that stability was an inherent property of a formulation.

The obviousness of the formulation claims can be summed up with two common sense principles, neither of which are inventive; both of which would have been done by any formulator and were expressly taught by the prior art.

- If your drug is unstable in water, don't use water in your liquid formulation, use polyols.
- If your formulation degrades in oxygen, use an antioxidant.

The claims recite bendamustine dissolved in about 5%-25% of the solvent propylene glycol (PG) mixed with the 75%-95% of the solvent polyethylene

glycol (PEG). Appx40, Appx49. Various ratios of PEG to PG are claimed, including 90:10 PEG:PG. Appx49. Besides these solvents, the claimed formulation includes a stabilizing amount of antioxidant, with one claim specifying monothioglycerol. *Id*. One claim also recites the bendamustine concentration is 25-50mg/ml. *Id*. A formulation containing 25-50mg/ml of bendamustine, 90:10 PEG:PG, and monothioglycerol is representative of what is claimed. Appx49.

Each choice of an ingredient would have been an obvious, suitable choice from which the prior art did not teach away, *Bayer,* 874 F.3d at 1328; *Par*, 773 F.3d at 17-98, and the remaining claim limitations are inherent consequences of those choices, *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329-1330 (Fed. Cir. 2020). PG and PEG were known bendamustine solvents from Olthoff and Drager, Appx22198 (3:40-46), and were FDA approved for use in injectables. Appx22339-22356 at Appx22350, Appx22353. Monothioglycerol was a known antioxidant, FDA approved for injectables (Boylan, Tait), and Drager taught that an antioxidant could be included a liquid bendamustine formulation. Appx55, Appx22092-22136 at Appx22111, Appx36342-36356 at Appx36343, Appx36351, Appx36355-36356. Other references (*e.g.*, Rowe) taught that it was common to include an antioxidant with a PEG-containing formulation). Appx18375 (340:6-23), Appx22344, Appx22349. These

ingredients would have been suitable options from which the prior art does not teach away. *Bayer*, 874 F.3d at 1328; *Par,* 773 F.3d at 1197-98. The relative percentages would have been readily determined by routine optimization, and doing this sort of optimization was expressly taught by Alam, which combined various percentages of PEG(10%-90%) and PG(90%-10%) in another nitrogen mustard formulation. *Merck Sharp & Dohme Corp. v. Hospira, Inc*., 874 F.3d 724, 730 (Fed. Cir. 2017); *Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1349 n.2 (Fed. Cir. 2009). The claimed formulation produces no unexpected results or other objective indicia of nonobviousness. Appx68. It is at most an unpatentable "ordinary innovation." *KSR,* 550 U.S. at 427.

Some claims further recite maximum amounts of impurities permitted under specified conditions. Appx49, Appx67. These stability limitations were inherent properties of an obvious formulation, but the district court made no findings regarding the inherency of these stability limitations in that formulation despite Appellees' expert's admission that stability is an intrinsic property. Appx68, Appx18675 (1091:11-1092:7). As explained below, the asserted claims should be held invalid because test results show that these are inherent properties of that obvious formulation. Alternatively, this case should be remanded with instructions to make findings concerning inherency.

A. THE DISTRICT COURT LEGALLY ERRED BY CONVERTING DRAGER'S DISTINGUISHING OF OLTHOFF INTO A TEACH-AWAY WITHOUT ADDRESSING THE FULL SCOPE OF EACH REFERENCE.

The court found that "viewed in isolation" Olthoff would have led a POSITA to use PEG and PG in a liquid bendamustine formulation stating "Olthoff provided a short, finite list of solvent options that included PEG and PG. Specifically, Olthoff reported that bendamustine is stable in monovalent alcohols and polyols, [citations omitted]; and the disclosure of 'polyols' would have given a POSITA just three polyol options: PEG, PG, and glycerol [citations omitted]." Appx57.

While Appellees tried to dispute that Olthoff's disclosure of polyols would teach both PG and PEG, their expert Dr. Siepmann ultimately conceded that this was true when confronted with his own patent, which showed just three common pharmaceutical polyols: PG, PEG and glycol. Appx23589-23680 at Appx23599. When confronted with that disclosure, he admitted: "Yes, but I didn't -- at that time I didn't know that I would be sitting here today." Appx57, Appx19191 (1575:2-76:1).

Yet, instead of finding the claims obvious, the court used a flawed teaching away analysis to convert Drager's alternative bendamustine liquid formulation, its failure to reproduce Olthoff's results and its professed theory about how its formulation worked into a complete refutation of Olthoff and the claimed

formulations. Appx57-61. As a result, the claimed, facially obvious, polyol formulations (that ended up working just as Olthoff said they would) were held non-obvious. Appx.57-58 ("Drager, however, teaches away from Olthoff's teaching of using polyols such as PEG and PG alone with bendamustine.").

This finding is all the more remarkable given that the claimed formulations exhibit no unexpected results and Drager was 102(e) art that had not published at the time the inventors were spurred to their formulation just a few months after their "eureka!" moment upon seeing Olthoff. Drager, which discloses using up to 90% of protic solvents such as PEG and PG either alone or in combination, and an antioxidant in a liquid bendamustine formulation, should have been compelling evidence of obviousness. Instead, the inventors, who followed Olthoff's teachings while remaining blissfully ignorant of Drager, had their patent upheld.

"[A] reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant," but an "obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Teaching away arguments require consideration of the prior art as a whole, not isolated disclosures. *Merck & Cie v. Gnosis Bioresearch S.A.*, 808 F.3d 829,834-

836 (Fed. Cir. 2015); *South Alabama Medical Science Foundation v. Gnosis S.P.A.*, 808 F.3d 823, 826 (Fed. Cir. 2015); *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1166 (Fed. Cir. 2006) ("Where the prior art contains 'apparently conflicting' teachings (*i.e.*, where some references teach the combination and others teach away from it) each reference must be considered 'for its power to suggest solutions to an artisan of ordinary skill ... consider[ing] the degree to which one reference might accurately discredit another.'" (quoting *In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991))).

The court notes that Drager professed it was unable to replicate findings of long-term stability for Olthoff's PG-only formulation. Appx58. However, Drager's data showed that such a 99% PG-only formulation had good stability – about 6-months at refrigerated temperatures – that Drager described as "commercial" level stability. Appx22198 (3:25-35 (table 3)), Appx18676-18677 (1095:11-1098:10).

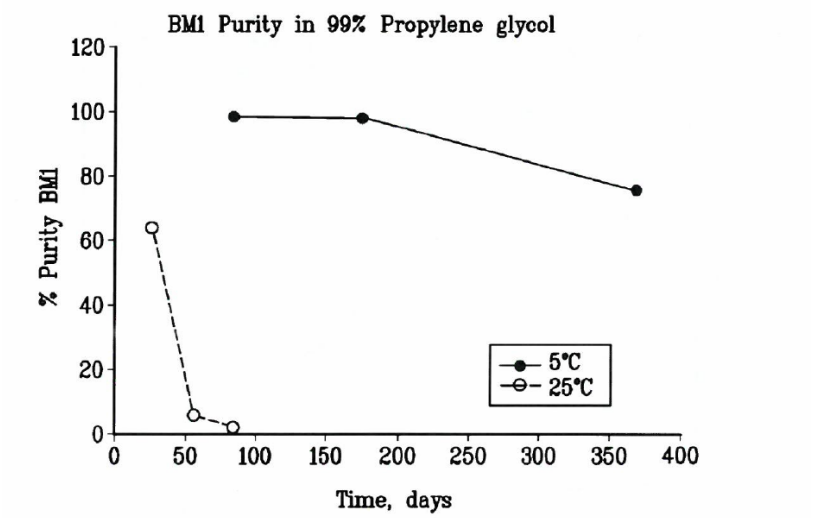

FIG. 3

Drager explains: "Typical commercial storage conditions include time periods of, for example, about 30 days, about 90, about 180 days" under "refrigerated temperatures below ambient room temperature, for example, about 5°C." Appx22198 (3:25-33). Appellants' expert Dr. Siepmann agreed that the POSITA would have expected the product to be refrigerated. Appx19107(1449:22-25), Appx19130(1542:12-16). Despite Drager's statements about commercial storage conditions, the court disregarded Drager's favorable data at 175 days of refrigeration and, instead, credited Dr. Siepmann's testimony that the stability after a year of refrigeration was "not good." Appx52, Appx58. But by Drager's own terms six months of stability is not bad, and even the presence of some negative data at longer storage does not establish a teach-away. *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009). If anything, this data would

have motivated a POSITA to give attention to how that might be extended. Appx18446 (623:8-624:11).

The court's teach-away analysis is further undercut because Drager did not appear to have fully replicated Olthoff. Olthoff requires mixing the formulation in an inert gas atmosphere and Drager is silent on whether this was followed. Appx22221. This could have significantly affected the stability observed. Appx18393 (413:14-413:19). *In re Young*, 927 F.2d at 591 (affirming Board rejection of a teach-away reference "did not test [invalidating reference] according to its teachings").

Additionally, Drager disclosed using only 99% pure PG, with no disclosure of what constituted the other 1%. As Dr. Anslyn testified, PG is "not typically entirely anhydrous," and that 1% could have been water, which also could have affected stability. Appx18673(1084:21-1085:17), Appx18393 (413:14-19), Appx18446 (623:8-624:1).

The context of Drager trying to get a patent over Olthoff, with a very similar formulation, also should be kept in mind. The inventors of Drager knew that it would be difficult to get a patent on formulations that were too similar to Olthoff. Appx25323-25328 at Appx25325, Appx18590 (940:11-24).

Even taking Drager at face value, the court's teach-away analysis still is legally erroneous because Drager only reports stability data for PG, not PEG, and

has no adverse stability data for a combined PG + PEG system, which the court found would otherwise have been obvious to try from Olthoff. Appx18414 (496:14-16). A reference cannot be said to teach away from a formulation that it did not test. *Galderma Labs v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013).

A fair reading of Drager demonstrates that it actually reinforced Olthoff's findings and also would have motivated a POSITA towards the PEG:PG combination that was claimed. Appx18446-Appx18447 (624:2-626:17). One of the issues that Drager reports for PG is that it has a tendency to form esters over time because of the concentration of -OH groups. *Id.* Drager's solution to this problem was to add an aprotic solvent, such as DMA, which contain no OH groups. *Id.* But PEG, which is a much bigger molecule than PG, has a significantly lower concentration of -OH groups. *Id.* As Dr. Anslyn explained, a 90:10 PEG:PG formulation had about the same number of -OH groups as Drager's preferred 66%DMA/34%PG formulation. Appx18668 (1065:1-10).

Olthoff "surprisingly" found that a polyol solvent system did not cause alcoholysis. Appx22219-22220. Drager actually corroborates this finding with data that shows no greater alcoholysis impurities forming when comparing a DMA/PG formulation with a DMA-only formulation. Appx22200(8:50-66 (Table II)), Appx18676 (1095:11-1096:14), (1096:17-1097:1).

Further belying the court's conclusion that Drager would de-motivate a POSITA to use PEG:PG is Drager's claiming in a later continuation application based on this same specification of "about 5 mg/mL to about 200 mg/mL" bendamustine with "up to about 90% of a mixture of polyethylene glycol and propylene glycol" (claim 1); an antioxidant (claim 2); low levels of PG esters ("1.5% or less") (claim 3); and treating cancers including CLL and NHL by diluting the formulation and administering it (claims 4-6). Appx25474-25475, Appx19190-19191 (1571:17-1573:13). These claims do not recite an aprotic solvent and do not require DMA. Appx19191 (1573:2-4). The court's analysis also fails to account for drawbacks of Drager's approach of using aprotic solvents. Even DMA, the one aprotic solvent improved for injections was found to dissolve plastic and ultimately this caused Teva to have to provide a warning on its commercial bendamustine liquid formulation. Appx19202(1619:8-16), Appx18398 (433:11-16), Appx18399 (436:10-15), (Appx18440 (600:4-600:8), Appx19190 (1570:17-1571:3), Appx19202 (1619:8-1620:25).

The court said that, as alternatives to DMA, Drager disclosed the aprotic solvents NMP and DMSO that had been "commercially" used, without considering what these "commercial" uses had been. Appx59. But these aprotic solvents had not been approved as injectables. Appx18440 (601:4-10); Appx18056 (281:18-282:2). On cross-examination Appellants' formulation

expert Dr. Siepmann conceded that Mottu (2000) listed PG and PEG as "well-described and commonly used for intravascular applications," but listed DMSO and NMP as "not yet established." Appx19191 (1576:2-19), Appx36885. The evidence cited by the district court is not to the contrary. For example, Strickley's discussion of NMP and DMSO is for uses other than IV injections. Appx36923 (subcutaneously, subgingivally, intravesically (but "not for intravenous")).

Drager refutes the court's teach-away conclusions.

B. THE DISTRICT COURT LEGALLY ERRED BY FAILING TO CONSIDER THE TEACHINGS OF DRAGER AND OLTHOFF AS A WHOLE.

As explained above, Drager did observe an esterification issue, which it attributed to an over-abundance of -OH groups in a PG-only formulation. Knowing that Olthoff already had patented a polyol-only formulation, Drager went a slightly different direction, by combining an aprotic solvent with a protic solvent to reduce the number of -OH groups. As explained in Drager, as little as 10% of an aprotic solvent could be used together with the protic solvents such as PEG and PG. Drager's own words refute the court's teach-away conclusions. Appx22198 (3:49-4:32).

The court concluded, "Drager also taught that protic solvents – *i.e.*, solvents, including PEG and PG, that have -OH groups – are acceptable to use with bendamustine but ***only*** when combined with aprotic solvents." Appx53

(emphasis added). However, none of the three cited paragraphs from Drager support this conclusion. *Galderma*, 737 F.3d at 739 ("teaching that a composition may be optimal or standard does not criticize, discredit, or otherwise discourage investigation into other compositions" and does not "teach away from the claimed invention"). The court erroneously converted Drager's teaching of one solution to limiting ester formation into the only solution. The first cited paragraph states that formulations "can" be prepared by combining bendamustine with aprotic solvents. Appx22198 (3:3-3:10). There is no statement that this is the "only" way.

The second cited paragraph states that formulations "can" be prepared by combining bendamustine with mixtures of aprotic and protic solvents. Appx22198 (3:36-3:48). Again, there is no statement that this is the "only" way. Indeed, the next paragraph states that formulations using a mixture of aprotic and protic solvents will "typically" have 90% or less of the protic solvent. Appx22198 (3:49-4:7), Appx22200 (7:5-10). "Typically" does not mean the "only" way. Rather, it states what is frequent, but allows for the existence of some others.

The third cited paragraph merely states a "theory" where it is "believed" that "if the concentration of the polar protic solvent is kept within the scope of the present invention," then unwanted impurities do not form. Appx22198 (4:18-24).

Later paragraphs identify these impurities as esters. Appx22198 (4:33-5:43). This "theory" may serve to explain why the mixture of an aprotic with the protic may work to reduce impurities, but does not claim this is the "only" way to use protic solvents with bendamustine. Other ways are not discussed, much less excluded. At most Drager's "theory" explains one way of doing things, but does not demonstrate that it is the "only" way.

The court also cited Dr. Pinal's testimony at Appx18440 (601:11-17) where he simply agreed that "Drager lists various protic solvents in column 3." That says nothing about adding an aprotic solvent being the "only" way to use a protic solvent.

Importantly Drager never reports *any* adverse data for the combination of PEG and PG that the district court found was suggested and motivated by Olthoff, and never concluded anything about the stability of such a compound. It was legal error for the district court to find a teaching away based on Drager without considering what the court found to be the full breadth of Olthoff's disclosure. *Allergan Inc. v. Apotex Inc.*, 754 F.3d 952, 965-66 (Fed. Cir. 2014); Alza *Corp. v. Mylan Labs.*, 464 F.3d 1286, 1290-91, 1294 (Fed. Cir. 2006).

Moreover, there is no teaching away just because a prior art reference suggests that the claimed approach would present a problem if that suggested problem is one that the POSITA would know how to fix. *Bayer*, 874 F.3d at 1328

n.6; *Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1381-82 (Fed. Cir. 2015); *In Re Icon Health and Fitness, Inc.*, 496 F.3d 1374, 1382 (Fed. Cir. 2007). Here, the potential esterification issue with a PG formulation was readily addressed with FDA approved ingredients and routine precautions. That was a less daunting challenge than the unfixable problem of DMA's dissolving plastic used in some injection devices. Appx18398 (433:11-16), Appx18399 (436:10-15), Appx19190 (1570:17-1571:3), Appx19202 (1619:8-1620:25). The use of PG was not "so flawed that that there was no reason to upgrade it." *KSR*, 550 U.S. at 425-426; *accord*, *Bayer*, 874 F.3d at 1328.

The only conclusion consonant with applying prevailing case law to all the relevant facts is that Drager did not teach that the claimed invention would not work for its intended purpose, and so it cannot be a teaching away reference.

C. THE DISTRICT COURT APPLIED AN ERRONEOUS LEGAL STANDARD IN DETERMINING THAT THE PRIOR ART TAUGHT AWAY FROM USING AN ANTIOXIDANT.

The court found patentable significance in the addition of an ***any*** stabilizing amount of an antioxidant (even a tiny amount) to the polyol formulation that Olthoff already taught was susceptible to oxidation. Appx65, Appx95. The court again violated the principle that a prior art teaching of alternative solutions does not establish a teaching away sufficient to avoid

obviousness. *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012); *Galderma*, 737 F.3d at 739.

According to the court, an antioxidant would not have been obvious based on a general (not specific to bendamustine) 2003 draft European Medicines Agency guidance that an antioxidant should be used in a formulation only if needed. Appx64, Appx37030-37039 at Appx37032. The EMA draft regulatory guidance demonstrates that scientifically a POSITA would know to use an antioxidant to stabilize a formulation susceptible to oxidation. Afterall, it's called an "antioxidant," and as the draft guidance explains, "Antioxidants are used to reduce the oxidation of active substances and excipients in the finished product." Appx37038. The U.S. FDA has no such guidance. Appx19130-19131 (1543:16-1544:9).

The court also cited a book chapter on parenteral formulations that explained that antioxidants were among the excipients that "may be useful in preventing chemical and physical instability." Appx36368-36392 at Appx36379. This reference states (just before the part quoted by the court): "Antioxidants are included in parenteral formulations, although their use is now in decline [citing to EU guidelines and referring to a section about the Regulatory Environment] . . ." The court cited a second portion of this reference that "A preferred method of preventing oxidation is simply to exclude oxygen . . ." Appx64. The court

inserted the words "[over antioxidants]" into this passage. *Id.* At most, these references show that other ways of controlling oxidation are generally preferred, but that is not enough to constitute a teaching away. *Bayer*, 874 F.3d at 1327-28, 1329; *Mouttet*, 686 F.3d at 1334.

Prior art such as Boylan and Rowe taught that antioxidants were commonly used in formulations, particularly formulations that included PEG, as well as those that contained bendamustine. Appx55; Appx22092-22136 at Appx22111, Appx22339-22356 at Appx22349. While the court (Appx64) notes four commercial PEG-containing formulations that it asserts did not include antioxidants, all this shows is that those formulations did not need an antioxidant, not that an antioxidant should not or could not be used with bendamustine. Drager itself confirms that its bendamustine formulations may include antioxidants. Appx22200 (7:1-18), Appx18418-18419 (513:20-514:14). Far from describing an antioxidant as exotic or requiring caution, Drager describes antioxidants as "pharmaceutically acceptable excipients," which "are known in the art." Appx18418-18419 (513:20-514:14). Because Drager is specific to bendamustine, it trumps the non-bendamustine prior art cited by the district court. In addition, Tait taught the use of monothioglycerol in injectable formulations for an anticancer drug "related to the nitrogen mustards." Appx36342-36356 at Appx36343, Appx36351, Appx36355-36356. Monothioglycerol is an FDA-

approved antioxidant commonly used in injectables. Appx55, Appx64, Appx22111, Appx22344, Appx18412 (487:12-488:24), Appx19132 (1548:22-1549:14). These references, which are more pertinent than the ones cited by the district court, demonstrate that the prior art as a whole does not teach away from using an antioxidant. *Gnosis,* 808 F.3d at 834; *Medichem*, 437 F.3d at 1166; *Para-Ordnance Mfr., Inc. v. SGS Importers Intern., Inc.*, 73 F.3d 1085, 1090 (Fed. Cir. 1995).

As to the amount of monothioglycerol, the district court found that the claim term "stabilizing amount of antioxidant" meant "any amount that decreases the amount of bendamustine degradation after any time period and at any temperature." Appx97. Boylan discloses typical monothioglycerol concentrations of 1 to 10 mg/ml, Appx22111, Appx18413 (492:9-493:3), and selecting a suitable amount would have been a matter of routine experimentation. Appx18413 (492:9-493:16); *Hospira*, 874 F.3d at 730; *Ecolab*, 569 F.3d at 1349 n.2. In short, there was no scientific advance in including an antioxidant, including monothioglycerol, to help stabilize a liquid bendamustine formulation.

D. THE PEG:PG RATIO WOULD HAVE BEEN DETERMINED BY ROUTINE EXPERIMENTATION.

The court did not make a finding that the claimed ratio of PEG(75%-95%) or PG(5%-25%) in the formulations was itself inventive, just that a POSITA after Drager would not have been motivated to use PEG and PG, and therefore never

would have arrived at those ratios. *E.g.*, Appx62-63. However, the prior art expressly taught the routine experimentation needed to arrive at these ratios based on the amount of bendamustine that needed to be dissolved. Appx18401 (442:25-443:5); Appx18409 (475:8-24); Appx18409 (477:20-479:7); *see also* Appx19188 (1562:10-17) (Dr. Siepmann conceding that stability and solubility testing are routine); Appx22088-22091 at Appx22091 (Alam prior art reference exemplifying preparing and testing a series of PEG:PG ratios). In finding these ratios unobvious, the district court legally erred by failing to address the issue of routine experimentation. Appx62-63.

For example, Alam tested cyclophosphamide's stability in mixtures of three polyols-PG, PEG and glycerol-and found that the formulation containing PEG and PG had "less degradation than the others." Appx53, Appx18396 (424:2-25:5), Appx18397 (428:6-12), Appx19100 (1421:18-24), Appx22091. Alam evaluated PG ratios from about 10% to about 90% and PEG ratios from about 90% to about 10%, to determine optimal ranges for a given amount of cyclophosphamide to be dissolved. Appx54, Appx22090 (4:6-12); Appx18396 (425:6-14).

The court found that Alam was not analogous art because it utilized a different nitrogen mustard (cyclophosphamide) than bendamustine. Appx53, Appx63. But that misses the point. Alam taught to vary the PEG:PG ratio to

ensure that the nitrogen mustard was optimally dissolved. Appx53-54, Appx18397 (426:1-11). That is what a POSITA would have done here and arrived at the claimed ranges. Appx18397 (426:1-11). No one disputed that the highly skilled POSITA team was capable of doing the routine experimentation needed to arrive at the optimal ranges.

Further, as explained above, the POSITA would have been interested in 90:10 PEG:PG because it would have the same number of -OH-groups as Drager's preferred formulation, and so that ratio would have been one of those tested. Appx18399 (437:8-15), Appx18400 (438:13-441:13), Appx18668-18669 (1065:1-1067:17).

It has long been the law that the recitation of a parameter that would have been determined by routine experimentation does not rescue a formulation from obviousness. *Hospira,* 874 F.3d at 730; *Ecolab*, 569 F.3d at 1349 n.2; *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996); *Merck & Co., Inc. v. Biocraft*, 874 F.2d 804, 809 (Fed. Cir. 1989); *In re Aller*, 220 F.2d 454, 459 (CCPA 1955); *In Re Swain*, 156 F.2d 239, 243 (CCPA 1946) (*Swain I*); *In re Swain*, 156 F.2d 246, 248 (CCPA 1946) (*Swain II*).

For example, in *Swain I* applicant's claim recited a weight ratio of cellulose acetate to melamine resin of about 9:1. *Id*. at 240. The applicant argued that this ratio was of patentable significance because it stated their upper limit of

compatibility. *Id*. at 242. The Patent Office conceded that this upper limit could not be predicted. *Id*. at 243. But it could be determined by "routine experimentation." *Id*. The CCPA affirmed the rejection. *Id*. ("[I]t is precisely because those skilled in the art cannot predict with certainty that they ever make experiments or tests. It does not follow that the results of such experiments amount to invention. . . . [I]t is old in the art to establish such limits by experimentation.") (quoting the Solicitor's brief with approval).

The district court does not discuss the law regarding routine experimentation, and ignores without comment how routine it would have been to test for suitable PEG:PG ratios. Appx42-48, Appx62-63. That is reversible error.

No unexpected results or other secondary considerations support the nonobviousness of any of the claimed ratios. Appx68-69; *Huang*, 100 F.3d at 139; *Aller*, 220 F.2d at 456-59; *Swain II*, 156 F.2d at 248. Accordingly, the only permissible conclusion is that the recited PEG:PG ratios are of no patentable significance.

E. THE RECITATION OF A 25 TO 50 MG/ML BENDAMUSTINE CONCENTRATION DOES NOT IMPART PATENTABILITY.

The recitation in Claim 5 of the '831 patent of a bendamustine concentration of about 25 to about 50 mg/ml adds nothing not already in the prior art.

Olthoff claimed 25-100mg/ml, and exemplified 25mg/ml. Appx22222 (Example 1), Appx22223 (Claim 1), Appx18402 (448:20-25), Appx18565 (837:9-20), Appx18565 (840:8-9). Drager specified similar concentrations, specifically calling out 30, 40, and 50mg/ml. Appx22199 (6:58). There is no evidence of unexpected results or other secondary considerations that might otherwise indicate nonobviousness. Appx68.

As the district court explained, "the bendamustine concentration [must] remain below the formulation's bendamustine solubility limit so that the bendamustine would completely dissolve and dangerous precipitation would not occur." Appx67, Appx18438-18439 (593:23-594:4). But, as Dr. Anslyn explained, solubility "is an inherent property of the system." Appx18675 (1090:11-1091:10), Appx18409 (475:8-24), Appx18410 (478:15-479:7), Appx18410 (481:13-18), Appx18439 (595:18-22), Appx18411 (484:5-11). The POSITA would have simply done routine testing to find out which ratios had adequate bendamustine solubility.

Olthoff reported the solubility of bendamustine in PG was 125mg/ml. Appx66, Appx22221, Appx18402 (449:13-17). While bendamustine's solubility in PEG was not reported in the prior art, Drager teaches using PEG as a bendamustine solvent, so it must have some solubility. Appx66, Appx18402 (449:18-20), Appx22198 (3:46). Another Teva bendamustine patent, Brittain,

similarly disclosed no issues with dissolving a 15 mg/mL bendamustine concentration in water, and taught increasing bendamustine stability with increasing alcohol concentrations, including both PG and PEG as viable bendamustine solvents. Appx22160 (¶0150) (selecting 15mg/mL), Table 3 (reporting stability in water alone); Table 4 (reporting increased stability with increased alcohol content "regardless of the alcohol"), Appx19189 (1565:12-1566:11).

PG's 125 mg/ml bendamustine solubility is more than sufficient to support bendamustine concentrations in the 25-50 mg/ml range if PG alone were used as the solvent (Appx18402 (448:20-25), Appx18410 (479:14-23)), but if PEG's number were different and very low, some mixtures with a high PEG:PG ratio might not support bendamustine concentrations in the 25-50 mg/ml range, and of course then those ratios would not have been utilized in the patents. Again, there are no unexpected results. The district court did not find that routine testing would have failed to show that a 90:10 PEG:PG formulation would permit a bendamustine concentration of 25-50 mg/ml. Appx66-67. Instead, it erroneously found that "a POSITA would not have been motivated to conduct such testing" on a PEG + PG formulation in general or on a 90:10 PEG:PG formulation in particular. *Id*. This cannot be squared with the court's earlier finding that Olthoff taught the use of PEG + PG. As explained above, Drager did not teach away

from that and in fact also taught that PG and PEG could be combined in its own formulations. As explained above, the POSITA would have been particularly drawn to 90:10 PEG:PG because it would have about the same number of OH groups as Drager's 66% DMA/34% PG. Appx18668 (1065:1-10). Thus, the POSITA would have been motivated to test a series of PEG + PG formulations, including 90:10 PEG:PG.

Perhaps the district court was concerned that the POSITA would not know ahead of time whether the 90:10 PEG:PG formulation would have adequate solubility. But that is the very reason why formulators do testing. *Swain I*, 156 F.2d at 243 ("[I]t is precisely because those skilled in the art cannot predict with certainty that they ever make experiments or tests."). The POSITA would have known that at least some PEG:PG ratios would have the desired bendamustine solubility, and so would have tested to find ratios above any lower limit of solubility. *Swain I*, 156 F.2d at 243 (not obvious to do routine testing to find the ratio representing the limit of compatibility).

F. SOME OF THE CLAIMS HAVE STABILITY LIMITATIONS, BUT THEY ARE INHERENT PROPERTIES OF OBVIOUS FORMULATIONS.

The stability limitations of the asserted claims are inherent properties of obvious formulations. Appx18413-18414 (493:17-494:5), Appx18415 (499:24-500:8), Appx18419-18420 (516:23-520:1), Appx18423 (530:13-531:12), Appx18426 (544:9-545:13). Because they are inherent properties of at least one

obvious embodiment of the asserted claims, they cannot serve to avoid obviousness. *Hospira,* 946 F.3d at 1329-1330; *Par,* 773 F.3d at 1194-96, *on remand*, 120 F.Supp.3d 468, 473-75 (D. Md. 2015) (inherency found; claims invalid), *aff'd*, 624 Fed.Appx. 756 (Fed. Cir. 2015). "If a property of a composition is in fact inherent, there is no question of a reasonable expectation of success in achieving it." *Hospira*, 946 F.3d at 1332.

Appellees' expert, Dr. Anslyn admitted on cross that stability is "an intrinsic property of the system." Appx18675 (1091:13-1092:7).

The district court did not find that these were not inherent properties. Instead, the court disposed of this issue by stating "[b]ecause I find that the combination of elements that Defendants allege inherently result in the stability limitations is not obvious, such limitations are not obvious through inherency." Appx68.

At trial the parties' experts agreed that a POSITA would also have added sodium hydroxide (NaOH) to ensure stability of the formulation by neutralizing acid that would catalyze the esterification reaction, and that doing so resulted in the claimed stabilities. Appx18412-18413 (489:17-491:10), Appx18418 (512:5-9), Appx18413-18414 (493:17-494:5), Appx18415 (499:24-500:8), Appx18419-18420 (516:23-520:1), Appx18423 (530:13-531:12), Appx18426 (544:9-545:13); Appx22356, Appx36343 line 8, Appx36348 line 19, Appx36350 line 6; *Hospira*,

946 F.3d at 1329-30 (Testing of nonprior samples may be used to prove inherency.); *Par*, 120 F.Supp. 3d at 474 (same).

In discussing obviousness, the district court never addressed the use of NaOH. In its discussion of the § 112 defenses, the district court was of the view that using NaOH to stabilize the formulation was within the level of ordinary skill. Appx99-100. Accordingly, as inherent properties of an obvious embodiment, the claimed stabilities do not impart patentability and the asserted claims should be held invalid.

G. ALTERNATIVELY IF THE STABILITY LIMITATIONS ARE NOT INHERENT IN THE CLAIMED FORMULATIONS, THEN THE CLAIMS HAVING THEM SHOULD HAVE BEEN HELD INVALID FOR LACK OF ENABLEMENT.

If the stability limitations are not inherent properties of these claimed formulations, then the claims should have been held invalid for lack of enablement. Enablement is a question of law based on underlying facts. *See, e.g.*, *Wyeth and Cordis Corp. v. Abbott Laboratories*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). Appellants demonstrated at trial that NaOH may be needed to reliably obtain claimed levels of impurities. Appx18423 (530:13-532:14); Appx18425-18426 (541:11-45), Appx22016-22077 at BDM-172-173, Appx18375-18376 (341:17-344:10), Appx18379 (355:2-18), Appx25421. The need to use NaOH is demonstrated by Eagle's later-filed '879 application (abandoned), which explains "the control samples, which did not include NaOH did not provide long term

storage stability," and "exhibited more than 28% total esters compared to initial after six months of storage at 25º C." Appx25437 (¶0135) (citing Figs. 4A and 4B), Appx18379-18380 (357:15-358:10). Nothing in the patents-in-suit mentions the use of NaOH, and so its use could only be provided by the POSITA's own skill. Therefore, if not obvious, then the stability limitations are not enabled because the patent specification fails to disclose how to arrive at those limitations beyond using the claimed formulation elements of PEG + PG + an antioxidant. *Enzo Life Sciences, Inc. v. Roche Molecular Systems, Inc.,* 928 F.3d 1340; 1348 (Fed. Cir. 2019) ("Although 'a specification need not disclose what is well known in the art,' that rule is "not a substitute for a basic enabling disclosure." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997)"); *Alza Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010) (a patentee "cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification.").

Alternatively, this case should be remanded for further findings concerning obviousness with respect to the inherency of the stability limitations and lack of enablement.

H. THE DISTRICT COURT FOUND THAT NO OBJECTIVE INDICIA POINTED AWAY FROM THE OBVIOUSNESS OF THE FORMULATION CLAIMS.

Plaintiffs made no assertion of unexpected results at trial. Appx68. Given the court's finding that Drager taught away from Olthoff's polyol-only formulations, one might have thought that there would be something unexpectedly superior about the claimed formulations. There was not. They performed exactly as a POSITA would have expected. The district court further found that Plaintiffs' assertions of commercial success did not support a conclusion of nonobviousness. Appx68-69. No other objective indicia of nonobviousness were asserted by Plaintiffs. Appx68.

When correct law is applied to all the relevant facts adduced at trial, the only correct conclusion is that the formulation claims are invalid for obviousness.

II. THE DISTRICT COURT LEGALLY ERRED IN FAILING TO FIND THE ADMINISTRATION CLAIMS INVALID FOR OBVIOUSNESS.

The court legally erred in not finding the administration patents obvious by failing to assess the differences between claimed subject matter in view of the prior art as a whole, ignoring express teachings and suggestions in the art to administer bendamustine in the way that Eagle ended up claiming in favor of an overly rigid motivation test and legally flawed teaching away analysis.

Obviousness requires a determination of whether "the differences between the subject matter sought to be patented and the prior art are such that the subject

matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art…" 35 U.S.C. § 103; *KSR*, 550 U.S. at 405.

There are scant differences between what is claimed and what already was taught in the prior art about how to use and administer a concentrated bendamustine formulation. The court found a POSITA would have been motivated to use the concentrated liquid bendamustine formulations from the prior art Palepu 2011 to treat CLL and NHL with the dosing schedule from the Treanda® label because Palepu 2011 instructed administering the formulations in accordance with the Treanda® dosing schedule. Appx77.

The other claim elements-- administration time (10 minutes or less), volume (50-100mL), and the resulting concentration (0.05-12.5mg/ml)--were not new either. Preiss 1985 and 1998 already taught that bendamustine could be safely administered in 3-10 minute bolus to treat cancer patients, and experts for both sides agreed that for a given dosage, administration time, volume and concentration are interdependent. Appx19065-19066 (1283:24-1284:9), Appx18455 (660:14-24), Appx18566-18567 (844:10-845:10). Appellees' expert Dr. Leoni explained in response to questioning from the court: "There was a correlation between volume and concentration and time, of course, ..." Appx19065 (1280:1-1284:9). So a short infusion time would suggest a lower

infusion volume and higher concentration. Appx19065-19066 (1283:24-1284:9), Appx18455 (660:14-24), Appx18566-18567 (844:10-45:10). As Glimelius explained, infusions of 10-20 minutes are typically given in 50ml or 100ml minibags. Appx22203-22207. The art also suggested infusion volumes lower than Treanda®'s 500ml, with the Barth reference questioning why so much fluid was being infused in the U.S., and suggesting that the volume be reduced. Appx85, Appx24089-24094 at 24093.

Dr. Leoni explained that all other things being equal, lower infusion volume "hypothetically would have been an advantage." Appx19059 (1258:7-11), Appx21898 (1:61-66) ("Furthermore, the Background of the Invention portion of the patents-in-suit state that "[h]igher infusion volumes may be associated with higher likelihood of weight gain and edema. Shorter infusion times and smaller infusion volumes result in a better quality of life for the patient . . . [and] reduce the potential extravasation." Appx21848, Appx21898 (1:61-66). Such admissions in the specification are binding on the patentee for purposes of determining obviousness. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007) ("Admissions in the specification regarding the prior art are binding on the patentee for purposes of a later inquiry into obviousness.").

The court also found that there were no unexpected results or any other secondary indicia of nonobviousness to save the claims. Appx88-92.

A. THE DISTRICT COURT LEGALLY ERRED BY USING AN OVERLY STRINGENT MOTIVATION TEST, WHICH CAUSED IT TO DISCOUNT TEACHINGS AND SUGGESTIONS IN THE ART TO DO WHAT WAS CLAIMED.

Had the court conducted the proper obviousness analysis, it would have found nothing nonobvious because there is no patentable innovation in using a known formulation administered for a known purpose, pursuant to a known dosing schedule, with a protocol taught and suggested by the prior art to obtain an expected benefit. Instead, the court discounted these express teachings to do what was claimed, because, according to the court, a POSITA would not have been sufficiently motivated to use them "to determine the safety of a short infusion time, lower infusion volume, or higher infusion concentration." Appx80. This sets the motivation bar too high. Obviousness is not defeated by the need to do additional testing to determine whether the claimed invention would work. *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014).

Even the expectation of success portion of the obviousness analysis requires only a reasonable expectation of success not absolute certainty. *Id.* at 1331 ("Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success."); *PharmaStem,*491 F.3d at 1363-64 ("Scientific confirmation of what was already believed to be true may be

a valuable contribution, but it does not give rise to a patentable invention."); *Medichem*, 437 F.3d at 1165 (reasonable expectation of success does not require certainty of success); *Accorda Therapeutics, Inc. v. Roxane Laboratories, Inc.*, 903 F.3d 1310, 1334 (Fed. Cir. 2018) ("[A] perfectly designed clinical trial" is not required for a reasonable expectation of success.).

For motivation, Appellants need only identify a "reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 550 U.S. at 418; *see also Bayer*, 874 F3d at 1328. Thus, "[a] claim can be obvious even where all of the claimed features are not found in a specific prior art references, where 'there is a showing of a suggestion or motivation to modify the teachings of [the prior art] to the claimed invention.'" *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299, 1307 (Fed. Cir. 2006) (quoting *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1356 (Fed. Cir. 2000)). Appellants also did not have to prove that a particular combination was "the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention." *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004).

1. The district court's rigid motivation standard erroneously rejected Preiss' teaching administering bendamustine in 3-10 minutes in a bolus injection or infusion.

The prior art gave good reason to administer bendamustine in a short, low-volume infusion. Preiss already had done it, and it worked. The court rejected Preiss 1985, which taught administering high doses(280-375mg) of bendamustine to 7 cancer patients as "3-minute infusion," reported "only rather mild side effects," and showed efficacy by decreasing leukocyte count in 40% of the cases because according to the court it "did not provide enough data points or information to allow a POSITA to rely on them for safety information." Appx73-74, Appx24016, Appx18455 (660:11-13), Appx18456 (664:13-20), Appx18527 (686:6-22).

Over ten years later, Preiss 1998 again administered 3-10 minute bolus injections of high dose (215 mg/m^2) bendamustine, well in excess of doses used for Treanda® or Bendeka®, this time to 50 cancer patients and still reported only mild side effects. Appx24037-24040, Appx18524-18525 (674:16-677:18). The court discounted Preiss 1998 because "it did not disclose when the side effects it reported were monitored or how many times side effect information was collected from patients." Appx81. However, Preiss 1998 did disclose the toxicities were reported using World Health Organization (WHO) grading system, provided data

on the toxicity profile of the bendamustine administration, and found only mild toxicities. Appx24038-24040.

The court did not articulate how much additional information would have been required to convince a POSITA to rely on Preiss 1985, but it is worth noting that Eagle itself told FDA that Preiss 1985 taught the safety of a short, high dose infusion. Appx24512-24559 at Appx24525 ("The clinically tolerated dose of BDM HCl, when administered as a 3 minute bolus, has been reported to be 215 mg/m^2 [citing Preiss 1985]; well above the 120 mg/m^2 maximum proposed for the Eagle product.") Additionally, Appellees' expert, Dr. Leoni, admitted on questioning from the court, that Preiss 1998 included "a safety portion." Appx19065 (1280:1-1283:18).

An express teaching that bendamustine already had been safely administered this way to treat cancer patients should have been sufficient even under this Court's old TSM test to establish motivation. *Persion Pharmaceuticals LLC v. Alvogen Malta Operations LTD.*, 945 F.3d 1184, 1192 (Fed. Cir. 2019), ("However, as the district court explained "'[t]he standard to find motivation to combine is far below what is sufficient to prove safety and efficacy to the FDA,' . . ." (citation omitted)).

This degree of scrutiny of Preiss' express conclusions and data goes far beyond anything that this Court has required in assessing motivation. In *KSR*, the

Supreme Court found the TSM test to be too rigid, and rejected it in favor of a more flexible approach. Yet here, the district court rejected express teachings as not sufficiently motivating.

2. The court's overly rigid motivation test failed to appreciate the correlation between short infusion time and low volume from Preiss and Glimelius.

The court also discounted the Preiss articles as motivating references because they did not explicitly disclose volume. For obviousness the prior art does not need to explicitly recite each claim element. *Biocraft,* 874 F.2d at 807 ("[T]he mere absence from the prior art of a teaching or limitation recited in the patent at issue is insufficient for a conclusion of nonobviousness."). Common sense is also part of the obviousness calculus. *KSR*, 550 U.S. at 421 ("Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it."). Preiss' 3-10 minute bolus injection has to be a small volume because only so much volume can be given in 3-10 minutes. Additionally, a bolus cannot be a large volume of liquid because only so much liquid can be given in a bolus and certainly nowhere near the 500ml that the court found was the standard administration for Treanda® at the time. Appx18528 (690:10-14). The patents-at-issue themselves define a bolus as 50 mL or less. Appx21849 (4:31-34; 5:58-60). Because Preiss also was

giving high doses (over twice the 100mg/m^2 dose suggested in the Treanda® label for CLL), these short infusions had to be highly concentrated.

Glimelius taught that 10-20 minute infusions typically correspond to 50-100ml of fluid, which is given in readily available 50 or 100ml minibags. Appx76, Appx22203-22204. But the court rejected Glimelius because it involved a different cancer drug (5-Fluorouracil) than bendamustine. Appx76, Appx85-86. That misses the point. Glimelius demonstrates that a POSITA would have reason to use a 50ml minibag for a 10-minute infusion.

3. The district court's overly rigid motivation test caused it to reject the express suggestion from Barth to lower infusion volumes from the 500 ml that was typically being used with Treanda®.

The court's overly stringent motivation test also caused it to discount Barth as a further motivating reason for a POSITA to give a lower-volume bendamustine infusion. While the court found that Barth "suggested" lowering infusion volumes down from 500ml, it concluded that it would not motivate a POSITA to use a lower-volume because according to the court Barth only gave "hypothetical" volumes not supported by data. Appx85. But Barth was describing the actual practice of using lower 100-250ml infusion volumes in Europe and the rest of the world, and questioning why the U.S. still was using 500ml. Appx75, Appx24093, Appx18526 (682:9-83:2). Thus, Barth gives a

POSITA another reason to lower infusion volumes. Appx18455 (658:12-20), Appx18566 (842:25-844:9).

With the admitted correlation between dosing time and volume, a POSITA could just as easily have started with Barth and its desire for a low volume infusion, and then looked to Preiss and Glimelius to know that high doses of bendamustine given in 3-10 minute bolus infusions were safe. Appx18526 (681:25-683:2), Appx18566 (841:3-844:9), Appx18570 (858:6-859:1).

In *Merck & Co. v. Teva Pharms.*, 395 F.3d 1364, 1373-75 (Fed. Cir. 2005), this Court found that a mere suggestion in an industry publication (*Lunar News*) to administer the drug alendronate in a once-weekly dosing regimen was sufficient to motivate a POSITA to administer the drug that way, even though the reference contained no data, suggested a different dose than what was claimed, and there were concerns about gastrointestinal side effects. *Id.* at 1368. The obviousness record here is even stronger than *Merck* because Barth discloses actual clinical practice of lowering administration volumes, and there already was human data from Preiss about giving bendamustine in 3-10 minutes at even higher doses than those claimed.

4. The court's overly stringent motivation test prevented the court from letting a POSITA take full advantage of the Palepu 2011 concentrated liquid bendamustine formulation that the court found a POSITA would have been motivated to use.

Despite the court's finding that Palepu 2011 "established a motivation to use its formulations," the court's overly stringent motivation test prohibited the POSITA from using the Palepu 2011 formulations in a way that capitalized on the advantages and teachings the court found Palepu 2011 had. Appx77.

The court noted that Palepu 2011, which disclosed concentrations ranging from 10-100mg/ml, including the claimed 25-50mg/ml, touted its formulations as "'advantageously ready to use or ready for further dilution'. . ." Appx72, Appx77, Appx24007-24008. Thus, Palepu 2011 taught an advantage of its formulations was being able to use them with or without dilution. The POSITA would have appreciated that Palepu 2011's formulations permit low-volume, fast-infusions because it discloses a predilution bendamustine concentration of 50mg/ml that is ten times higher than the 5mg/ml in the prior art Treanda® label. Appx24008, Appx24010, Appx24013, Appx25285, Appx18428 (550:25-551:5). This ten times greater concentration means that one can administer the drug in a ten times smaller volume. Appx18428 (550:25-551:15; 553:15-20), Appx18563 (831:13-22). So, instead of the 500ml dilution bag used with the prior art Treanda® product, one can use a standard 50ml "minibag" of diluent, which is

advantageous for those patients requiring low volumes. Appx18428-18429 (550:25-551:15; 553:15-20; 554:2-9), Appx18526 (683:9-15). Formulations in a 50ml bag can be administered in about 10 minutes, much faster than the 30 and 60 minutes for the prior art Treanda® product. Appx76, Appx22203, Appx25284.

Olthoff taught how concentrated (25mg/ml-100mg/ml) liquid bendamustine formulations can be "diluted before medical application in a ratio of 1:5 to 1:20." Appx22223 (claim 1), Appx18565 (837:15-839:8). In example 1, Olthoff teaches to dilute 1mL of a 25mg/ml bendamustine concentrate in a 10mL ampoule, with 9ml of diluent immediately before injection. Appx18565 (837:5-839:8), Appx22222-22223. No one disputed that Olthoff said this, but the court nevertheless rejected Olthoff because it found the sponsoring witness "not credible".[2] But Olthoff says what it says, is analogous prior art and was admitted

[2] The court explained in footnote 7 that it rejected Olthoff because it was discussed by Dr. Yates, an expert that the court described as a "professional witness" who was "rejected" by "all Defendants but Apotex." In fact, Dr. Yates also testified on behalf of defendant Slayback. Appx18558 (810:16-24). The court found that Dr. Yates "is a professional witness with limited relevant experience who has testified repeatedly for Apotex," but Dr. Yates, has degrees in both pharmacology and medicine, worked for a number of pharmaceutical companies including Merck and Takeda, where he was the President of Research & Development, and had actually developed cancer drugs, designed clinical trials and given infusions to patients. Appx18558-18559 (812:4-817:2). This Court relied on his testimony in *Roche,* 748 F.3d at 1334. The district court also

as evidence. Appx22223, Appx19194 (1588:1-10). The court erred in rejecting Olthoff as a teaching of how to prepare low volume, concentrated bendamustine for injection.

From Preiss, the POSITA would have expected these faster, lower-volume infusions to work just fine. Appx18453 (652:19-20) ("Administrative volume usually does not have any impact on safety or efficacy."), Appx18525 (677:14-18) ("safe and feasible"), Appx73-74.

The district court found that the POSITA team would not have relied on Preiss to "determine" a safe administration. Appx80-82, Appx92-93. But this finding is contradicted by Preiss' inclusion of safety data and identification of a maximum tolerated dose, and by Appellee's expert's testimony that Preiss 1998 included a safety portion:

> So Preiss was there and it represented safety information. If you note the 1985 Preiss publication, it's not in that data, but Preiss 1998, because it does contain the second portion of the trial, the study, was actually a safety portion.

Appx19065 (1282:9-13).

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described him as "an admitted non-formulator," but his discussion of Olthoff was with respect to the administration claims, not the formulation claims.

Because the only actual data for such fast infusions reported no serious side effects, the POSITA team would have expected subsequent testing to confirm that fast infusions are sufficiently safe. There were no unexpected results. Appx88.

B. THE SUBSEQUENT PRIOR ART DID NOT TEACH AWAY FROM PREISS.

As with the formulation patents, the court applied the wrong legal standard when it found that subsequent prior art references taught away from the Preiss studies. Appx83. The court states that a POSITA would have "considered later prior art references that used 30 to 60 minute infusions and a 500 mL volume." Appx83. As explained above, mere preference for something else does not constitute a teaching away from the claimed invention. *Bayer*, 874 F.3d at 1327-28, 1329; *Mouttet*, 686 F.3d at 1334. Moreover, these references do not criticize 3-10 minute infusions of bendamustine, as would be required if they truly were teach-aways. *Id*.

The court cites two Schoffski papers to support teaching away but, as the court found, Schoffski "compared its results to the three-to-ten-minute infusions disclosed in Preiss 1998" and reported Schoffski's 30 minute infusions have similar side effects to Preiss' 3-10 minute, 215 mg/m^2 bolus infusions. Appx75, Appx83, Appx24023-24028, Appx24031-24036 Appx18525 (677:14-680:13). That is a teaching of similarity, not a teaching away. Schoffski's comparison to Preiss's safety data also undermines the court's conclusion that a POSITA would

not rely on Preiss in determining a safe administration method because Schoffski demonstrates the total dose, not the administration time, is responsible for the side effects. (Appx18525-18526 (680:20-681:13), Appx18533 (712:6-712:21). Thus, a POSITA would expect a 10-minute infusion to be comparably safe to a 30 minute infusion. Appx25581-25596 at Appx25581, Appx18031 (178:9-81:24), Appx24027-24028. This is corroborated by inventor Dr. Sundaram's internal correspondence stating that the Preiss side-effects mentioned in Schoffski were "related to dose and not necessarily the infusion duration because [Schoffski] goes on to say that the 30 min infusion (at lower doses) also result in similar effects." Appx25581, Appx18031 (178:9-181:24), Appx24027-24028.

The court treats Preiss 2003's use of a 30 minute infusion as a disavowal of his earlier 3-10 minute studies, but in 2003, Preiss was studying the renal effects of an existing treatment protocol, not an evaluating alternative ones. Appx26073-26076 at Appx26073. It says nothing one way or the other about 3-10 minute infusions. *Id*. "[S]ilence does not imply teaching away." *Allergan*, 754 F.3d at 964. A reference that does not discuss the claimed approach cannot be said to teach away from it. *Nidec,* 868 F.3d at 1017-1018.

The court additionally cites the Ribomustin Monograph as a reference that specifies 30-60 minutes in 500mL of bendamustine because of local toxicity concerns focusing on a single statement that "[l]ocal irritations and

thrombophlebitis occur occasionally, especially after intravenous bolus injections. These side effects can be reduced by administering bendamustine over 30 to 60 minutes." Appx83, Appx23942, Appx23995. However, this erroneous reading is a consequence of taking a single paragraph divorced from the remaining monograph that provides context. As explained by Appellees' expert, Dr. Derendorf, reading the Ribomustin Monograph as a whole shows that the Ribomustin Monograph's statement is based on a Ruffert study, also described in the Monograph in Section 6.1.1. Appx23953-23954, Appx18689 (1146:8-1147:6). The Monograph explains that Ruffert was not a bendamustine monotherapy, but rather administered bendamustine together with vincristine and prednisolone, in a therapy designated "CyVP." Appx23953, Appx26063, Appx19076 (1324:18-1326:8, Appx18527-18528 (686:13-691:22). Vincristine was a known vesicant and exhibits common complications such as the local toxicities mentioned in the monograph. Appx18527-18528 (688:13-14; 689:4-9; 691:21-22) ("A vesicant is chemotherapy drug that damages veins and the subcutaneous tissue if it's infiltrated."). The monograph also shows that the bendamustine in this study was given over one-hour. (Appx23953). The Ruffert publication shows that the bendamustine was administered in 500ml over one-hour. Appx26061-26065 at Appx26063(Table2). Plaintiffs' expert Dr.

Derendorf agreed that in Ruffert the vincristine was administered by bolus and the bendamustine by one-hour infusion. Appx18689 (1148:11-1149:5).

The prior art cited by the court makes no comment on what Preiss 1998 did, namely, administer bendamustine (alone, without a known vesicant) in 3-10 minutes. Appx24038. There is no teaching away when the alleged teaching reference does not address the claimed approach. *Nidec*, 868 F.3d at 1017-1018; *Par*, 773 F.3d at 1199; *Para-Ordnance*, 73 F.3d at 1090. Thus, nothing in the prior art refutes Preiss 1998's finding that such administration produces "only mild toxicity even at high doses" – doses that greatly exceed those in the Treanda® label and the asserted claims. Appx24040, Appx18524 (675:16-676:1).

That the commercial versions of bendamustine at the time had been administered as 30-60 minute infusions also does not demonstrate that 3-10 minute infusions had been rejected as not scientifically feasible. *Roche*, 748 F.3d at 1332 (FDA approval of 2.5mg dose did not teach away from 5mg dose "because [FDA] was never asked to approve that dose."). For obviousness, the court was required to evaluate the differences between what was claimed and the prior art as a whole, not just the commercial embodiment. *Galderma ,* 737 F.3d at 737 ("Nothing in the statute or our case law requires [defendant] to prove obviousness by starting with a prior art commercial embodiment and then

providing motivation to alter that commercial embodiment."); *Biocraft,* 874 F.2d at 808 ("the proper focus of an obviousness inquiry is on whether 'the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art…'").

The evidence at trial showed that a primary reason that bendamustine was commercialized as a 30-60 minute product was because of regulatory hurdles and economics. Prior to being acquired by Cephalon and then Teva, Salmedix began developing bendamustine in the U.S. with the assistance of an exclusive license agreement from Fujisawa, manufacturer of Ribomustin. Salmedix received a "very significant competitive advantage due to [its] relationship with Fujisawa and that it would be difficult for another group to register the drug in the U.S. before Salmedix because of the transfer of information concerning pharmacology, toxicology, clinical trial databases, etc. from our partner." Appx25297-25320 at Appx25298, Appx19061 (1267:16-1269:18). The data obtained from Fujisawa permitted Salmedix to use pre-existing data for the Ribomustin 30-60 minute administration in 500mL to expedite the regulatory process. Appx19062-19063 (1271:13-1273:4), Appx25321-25322 at Appx25322 ("[b]y acquiring products with prior human clinical experience, Salmedix seeks to improve the probability

of success, reduce the costs of drug development, and shorten the time to commercialize products.").

Teva made similar use of the information as explained by former Teva employee turned Eagle consultant, Dr. Grebow, confirmed:

> The 30min time was driven by "that's how they did the clinical studies" and we did not touch it.
>
> That was why we did not screw around with the infusion time as we developed the product (actually my decision as I am starting to recall the issues).

(Appx23877-23882 at Appx23877-23879, Appx18029-18030 (172:17-175:11).

C. THE CONCENTRATION NUMBERS ADD NOTHING PATENTABLE.

The asserted administration claims variously include a bendamustine concentration after dilution of from 0.05 mg/mL to 12.5 mg/mL, including about 5.6 mg/ml, with "about" defined as plus/minus 15% for volumes and concentrations. Appx21849 (3:43-46), Appx21857, Appx21881 (3:53-56), Appx21893-21894, Appx21899 (3:53-56), Appx21907.

The recitation of these diluted bendamustine concentrations including "about 5.6 mg/ml" adds nothing patentable. This parameter follows from the high predilution bendamustine concentrations in Palepu 2011. No additional choice is required. The rest is dictated by the medical parameters of the prior art Treanda® dosing schedule that is incorporated by reference in Palepu 2011.

Appx24009, Appx25285. The claimed post-dilution bendamustine concentration is just an inherent consequence of this obvious combination.

The parties themselves recognized this inherency in a pretrial stipulation: "The parties stipulate that, after dilution as recited in the asserted claims of the '568 and '399 patents, one or more formulations disclosed in the '831 and '797 patents, and U.S. Patent Publication No. 2011/0184036 ('Palepu 2011') would fall within both the concentration of bendamustine and volume percentage and concentration of polyethylene glycol and propylene glycol recited in the asserted claims of the '568 and '399 patents." Appx.17981-17985 at Appx.17983-17984. Interpretation of this stipulation is a legal question reviewed de novo. *Kearns v. Chrysler Corp.*, 32 F.3d 1541, 1545 (Fed. Cir. 1994).

Per that stipulation, what remained disputed was whether the POSITA would have used Palepu 2011's formulations and diluted them in reduced volumes: "Plaintiffs dispute that the POSA would have had a motivation or reason to use [1] one or more of the formulations set forth above or [2] the dilution volumes or [3] bendamustine concentrations claimed in the '568 or '399 patents or had a reasonable expectation of success in making and using the claimed inventions." Appx18517-18521 at 18520 (bracketed material added). None of these three issues preclude finding the claimed post-dilution bendamustine concentration unpatentable. First, the district court found that

Palepu 2011 itself provided adequate reasons to use its formulations. Appx76-77. Second, as explained above, the POSITA team would have taken advantage of Palepu 2011's high pre-dilution bendamustine concentrations to use standard 50 ml mini-bags of diluent. Appx18428-18429 (550:25-551:15; 553:15-20; 554:2-9). Third, as the first quoted sentence stipulates, the claimed post-dilution bendamustine concentrations follow from preparing to treat patients by diluting Palepu 2011's formulations in the claimed 50 ml of diluent. Appx18519-18520 ("The parties stipulate that, after dilution as recited in the asserted claims . . . formulations disclosed in . . . U.S. Patent Publication No. 2011/0184036 ('Palepu 2011') would fall within . . . the concentration of bendamustine . . . recited in the asserted claims".). In other words, the "about 5.6 mg/ml" post-dilution concentration is not a separate choice, but is just what happens when the other choices are implemented.

The court, however, did not complete an analysis of this issue because it found that the 50 ml volume of diluent would not have been obvious. Appx86 ("[B]ecause I find that the claimed volumes are not obvious, it does not follow that the claimed concentrations are obvious as inherent."). But, as already explained, that volume follows from the pre-dilution bendamustine concentration in Palepu 2011 that is ten times greater than what is in the Treanda® label. Appx18428-18429 (550:25-551:15; 553:15-20; 554:2-9). Accordingly, in view

of the evidence and the parties' stipulation, this Court should hold that the claimed post-dilution bendamustine concentration parameter adds nothing patentable. Therefore, the district court's holding that the administration claims are not invalid for obviousness should be reversed. Alternatively, this case should be remanded for findings on this issue.

CONCLUSION

The district court's judgment of non-obviousness of the formulation patents and the administration patents should be reversed. Alternatively, with respect to the formulation patents, the district court's judgment of lack of enablement should be reversed. If the Court determines that additional findings are necessary, the case should be remanded.

Respectfully Submitted,

Date: April 27, 2021

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ADDENDUM

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

CEPHALON, INC., *et al.*,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	C.A. No. 17-1154-CFC
	)	
SLAYBACK PHARMA LLC, *et al.*,	)	**CONSOLIDATED**
	)	
Defendants.	)	
	)	

~~**PROPOSED**~~ **FINAL JUDGMENT ORDER**

WHEREAS, in September 2019, the Court held a seven-day bench trial in the above-captioned matter. For the reasons set forth in the Court's Opinion of April 27, 2020 (D.I. 394) and the Parties' Stipulations (D.I. 318 ¶ 4, 320 ¶ 8),[1] the Court hereby enters the following judgment for Plaintiffs Teva Pharmaceuticals International GmbH, Cephalon, Inc., and Eagle Pharmaceuticals, Inc. (collectively, "Plaintiffs") and against Defendants Apotex Inc., Apotex Corp. (collectively, "Apotex"), Fresenius Kabi USA, LLC ("Fresenius Kabi"), Mylan Laboratories Ltd. ("Mylan"), and Slayback Pharma LLC ("Slayback"):

[1] To narrow the issues in dispute for purposes of trial, the Parties stipulated that a determination as to non-infringement (in the case of Apotex, Fresenius Kabi, and Mylan) and/or invalidity (in the case of all Defendants) of the claims asserted at trial would result in a final judgment as to each Defendant of all patents that had been asserted by Plaintiffs in this case as to each such Defendant, respectively, with the exception of U.S. Patent No. 8,791,270, which had been resolved by the granting of covenants not to sue and/or consent judgments. (D.I. 318 ¶ 4; 320 ¶ 8.) The parties have further agreed that a decision by the U.S. Court of Appeals for the Federal Circuit in an appeal from this judgment as to all of the claims advanced at trial against a Defendant will govern the judgment as to the remainder of the claims that were asserted against that same Defendant. Thus, for Apotex, Fresenius Kabi, and Mylan, an appellate decision as to non-infringement or invalidity of all claims asserted against those Defendants at trial will govern the judgment as to the claims set forth in Paragraphs ¶¶ 2, 4, and 6, respectively. For Slayback, an appellate decision as to invalidity will govern the judgment as to claims 3, 12, 13, 18, 21, 22, 25, 29 of U.S. Patent No. 9,572,887 (the "#887 patent").

1. Apotex's filing of Abbreviated New Drug Application ("ANDA") No. 210601 ("Apotex's ANDA") infringes claims 2, 3, 5 of U.S. Patent No. 9,265,831 (the "#831 patent"); claims 9, 11 of U.S. Patent No. 9,572,797 (the "#797 patent"); claims 11, 18, 22 of U.S. Patent No. 9,144,568 (the "#568 patent"); and claims 13, 15 of U.S. Patent No. 9,597,399 (the "#399 patent"). The manufacture, use, sale, or offer for sale within the United States, or importation into the United States, of the product that is the subject of Apotex's ANDA ("Apotex's ANDA Product"), in accordance with Apotex's proposed labeling, would infringe or induce infringement of the same claims.[2]

2. Based on the Parties' Stipulation, D.I. 320 ¶ 8, and the record at trial with respect to the claims in the preceding paragraph, Apotex's filing of Apotex's ANDA also infringes claims 7, 12, 14, 18, 20 of U.S. Patent No. 8,609,707 (the "#707 patent"); claims 5, 7, 18, 20, 24 of U.S. Patent No. 9,572,796 (the "#796 patent"); claims 2, 3, 5, 7, 8, 10, 20, 21 of the #797 patent; claims 1, 5, 8-10, 14, 19, 22, 23 of U.S. Patent No. 9,034,908 (the "#908 patent"); claims 6, 8, 15, 21 of the #568 patent; claims 3, 12, 13, 18, 21, 22, 25, 29 of the #887 patent; claims 3-7 of U.S. Patent No. 9,597,397 (the "#397 patent"); claims 2, 3 of U.S. Patent No. 9,597,398 (the "#398 patent"); claims 2, 4, 17 of the #399 patent; claims 3-5, 9, 11, 14, 15, 17, 19, 21, 24, 26, 28, 29 of U.S. Patent No. 9,000,021 (the "#021 patent"); and claims 7, 12, 13, 18, 19, 23 of U.S. Patent No. 9,579,384 (the "#384 patent"). The manufacture, use, sale, or offer for sale within the United States, or importation into the United States, of Apotex's ANDA Product, in accordance with Apotex's proposed labeling, would also infringe or induce infringement of the same claims.

3. Fresenius Kabi's filing of ANDA No. 210410 ("Fresenius Kabi's ANDA")

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[2] For clarity, nothing in this Order precludes Defendants from conducting activities that are protected under 35 U.S.C. § 271(e)(1). In addition, nothing in this Order precludes Defendants from seeking relief from this Judgment under Rule 60, if warranted.

infringes claims 2, 3, 5 of the #831 patent; claims 9, 11 of the #797 patent; claims 11, 18, 22 of the #568 patent; and claim 15 of the #399 patent. The manufacture, use, sale, or offer for sale within the United States, or importation into the United States, of the product that is the subject of Fresenius Kabi's ANDA ("Fresenius Kabi's ANDA Product"), in accordance with Fresenius Kabi's proposed labeling, would infringe or induce infringement of the same claims.

4. Based on the Parties' Stipulation, D.I. 320 ¶ 8, and the record at trial with respect to the claims in the preceding paragraph, Fresenius Kabi's filing of Fresenius Kabi's ANDA also infringes claims 7, 12, 14, 18, 20 of the #707 patent; claims 5, 7, 18, 20, 24 of the #796 patent; claims 2, 3, 5, 7, 8, 10, 20, 21 of the #797 patent; claims 1, 5, 8-10, 14, 19, 22, 23 of the #908 patent; claims 6, 8, 15, 21 of the #568 patent; claims 3, 12, 13, 18, 21, 22, 25, 29 of the #887 patent; claims 3-7 of the #397 patent; claims 2, 3 the #398 patent; claims 2, 4, 17 of the #399 patent; claims 3-5, 9, 11, 14, 15, 17, 19, 21, 24, 26, 28, 29 of the #021 patent; claims 7, 12, 13, 18, 19, 23 of the #384 patent; claims 2, 3, 5, 8-12, 14, 17-19, 25, 26 of U.S. Patent No. 10,010,533 (the "#533 patent"); and claims 3, 4, 6, 7 of U.S. Patent No. 10,052,385 (the "#385 patent"). The manufacture, use, sale, or offer for sale within the United States, or importation into the United States, of Fresenius Kabi's ANDA Product, in accordance with Fresenius Kabi's proposed labeling, would also infringe or induce infringement of the same claims.

5. Mylan's filing of ANDA No. 210827 ("Mylan's ANDA") infringes claims 2, 3, 5 of the #831 patent; claims 9, 11 of the #797 patent; claims 11, 18, 22 of the #568 patent; and claim 15 of the #399 patent. The manufacture, use, sale, or offer for sale within the United States, or importation into the United States, of the product that is the subject of Mylan's ANDA ("Mylan's ANDA Product"), in accordance with Mylan's proposed labeling, would infringe or induce infringement of the same claims.

6. Based on the Parties' Stipulation, D.I. 320 ¶ 8, and the record at trial with respect to the claims in the preceding paragraph, Mylan's filing of Mylan's ANDA also infringes claims 7, 12, 14, 18, 20 of the #707 patent; claims 5, 7, 18, 20, 24 of the #796 patent; claims 2, 3, 5, 7, 8, 10, 20, 21 of the #797 patent; claims 1, 5, 8-10, 14, 19, 22, 23 of the #908 patent; claims 6, 8, 15, 21 of the #568 patent; claims 3, 12, 13, 18, 21, 22, 25, 29 of the #887 patent; claims 3-7 of the #397 patent; claims 2, 3 the #398 patent; claims 2, 4, 17 of the #399 patent; claims 3-5, 9, 11, 14, 15, 17, 19, 21, 24, 26, 28, 29 of the #021 patent; claims 7, 12, 13, 18, 19, 23 of the #384 patent; claims 2, 3, 5, 8-12, 14, 17-19, 25, 26 of the #533 patent; and claims 3, 4, 6, 7 of the #385 patent. The manufacture, use, sale, or offer for sale within the United States, or importation into the United States, of Mylan's ANDA Product, in accordance with Mylan's proposed labeling, would also infringe or induce infringement of the same claims.

7. Slayback's filing of ANDA No. 210617 ("Slayback's ANDA") infringes claim 13 of the #887 patent. The manufacture, use, sale, or offer for sale within the United States, or importation into the United States of the product that is the subject of Slayback's ANDA ("Slayback's ANDA Product"), in accordance with Slayback's proposed labeling, would induce infringement of the same claims.

8. Claims 7, 12, 14, 18, 20 of the #707 patent, claims 2, 3, 5 of the #831 patent; claims 5, 7, 18, 20, 24 of the #796 patent; claims 2, 3, 5, 7-11, 20, 21 of the #797 patent; claims 1, 5, 8-10, 14, 19, 22, 23 of the #908 patent; claims 6, 8, 11, 15, 18, 21, 22 of the #568 patent; claims 3, 12, 13, 18, 21, 22, 25, 29 of the #887 patent; claims 3-7 of the #397 patent; claims 2, 3 of the #398 patent; claims 2, 4, 13, 15, 17 of the #399 patent; claims 3-5, 9, 11, 14, 15, 17, 19, 21, 24, 26, 28, 29 of the #021 patent; claims 7, 12, 13, 18, 19, 23 of the #384 patent; claims 2, 3, 5, 8-12, 14, 17-19, 25, 26 of the #533 patent; and claims 3, 4, 6, 7 of the #385 patent are not

invalid.

9. Pursuant to 35 U.S.C. § 271(e)(4)(A), the U.S. Food & Drug Administration shall not approve Apotex's, Fresenius Kabi's, Mylan's, Slayback's ANDA Products on a date which is earlier than the expiration date of the latest-expiring claim that such Defendant has been adjudged to infringe (in all cases, January 28, 2031) (D.I. 315-1 ¶¶ 14, 23, 33, 42, 53, 62, 72, 82, 91, 102, 111, 123, 131, 142), including any extensions and market exclusivities.

10. Pursuant to 35 U.S.C. § 271(e)(4)(B), Apotex, Fresenius Kabi, Mylan, and Slayback; their officers, agents, servants, employees, and attorneys; and any other persons who are in active concert or participation with anyone described above are hereby enjoined from commercially manufacturing, using, offering to sell, or selling within the United States, or importing into the United States, their ANDA Products before the expiration date of the latest-expiring claim that such Defendant has been adjudged to infringe (in all cases, January 28, 2031) (D.I. 315-1 ¶¶ 14, 23, 33, 42, 53, 62, 72, 82, 91, 102, 111, 123, 131, 142), including any extensions and market exclusivities.

11. Judgment is hereby entered (a) in favor of Plaintiffs and against Apotex, Fresenius Kabi, Mylan, and Slayback on Plaintiffs' claims for infringement of claims 3, 12, 13, 18, 21, 22, 25, 29 of the #887 patent; (b) in favor of Plaintiffs and against Apotex, Fresenius Kabi, and Mylan on Plaintiffs claims for infringement of claims 7, 12, 14, 18, 20 of the #707 patent, claims 2, 3, 5 of the #831 patent; claims 5, 7, 18, 20, 24 of the #796 patent; claims 2, 3, 5, 7-11, 20, 21 of the #797 patent; claims 1, 5, 8-10, 14, 19, 22, 23 of the #908 patent; claims 6, 8, 11, 15, 18, 21, 22 of the #568 patent; claims 3-7 of the #397 patent; claims 2, 3 of the #398 patent; claims 2, 4, 13, 15, 17 of the #399 patent; claims 3-5, 9, 11, 14, 15, 17, 19, 21, 24, 26, 28, 29 of the #021 patent; and claims 7, 12, 13, 18, 19, 23 of the #384 patent; (c) in favor of

Plaintiffs and against Fresenius Kabi and Mylan on Plaintiffs' claims for infringement of claims 2, 3, 5, 8-12, 14, 17-19, 25, 26 of the #533 patent; and claims 3, 4, 6, 7 of the #385 patent; and (d) in favor of Plaintiffs and against Defendants on Defendants' counterclaims and defenses.

12. All other claims, counterclaims, and defenses of Plaintiffs, Apotex, Fresenius Kabi, Mylan, and Slayback in their respective Complaints and Answers are dismissed without prejudice.

IT IS SO ORDERED this 6th day of July, 2020

The Honorable Colm F. Connolly

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CEPHALON, INC., *et al.*, Plaintiffs, v. SLAYBACK PHARMA LIMITED LIABILITY CO., *et al.*, Defendants.	Civil Action No. 17-1154-CFC CONSOLIDATED

MEMORANDUM

On April 27, 2020, after a seven-day bench trial in this Hatch-Waxman patent case, I issued pursuant to Federal Rule of Civil Procedure 52(a) an Opinion in which I set forth my findings of fact and conclusions of law. D.I. 394. I held in the Opinion that the 11 patent claims asserted by the Plaintiff at trial were not invalid and that Defendants infringed and induced the infringement of those claims. D.I. 394 at 68. I then asked the parties to submit a proposed order of final judgment consistent with my Opinion. D.I. 395.

The parties are unable to agree on a proposed final judgment order because they dispute which claims should be included in the judgment. D.I. 401 at 1. Defendants argue that the judgment should be limited to the 11 claims asserted at trial. D.I. 404 at 1; D.I. 401-2 ¶¶ 1–8. Plaintiffs propose a judgment that covers those 11 claims plus 86 claims they had asserted earlier in the litigation. D.I. 402

at 2; D.I. 401-1 ¶ 11.

The parties agree that resolution of their dispute turns on the meaning of two paragraphs in two stipulated orders I signed before trial. *See* D.I. 402 at 1; D.I. 404 at 1–2. Paragraph 8 of the first Stipulation and Order, which applies to all parties save Defendant Slayback Pharma LLC, reads: "The parties stipulate that a determination as to non-infringement and/or invalidity of the asserted claims at trial will result in a final judgment as to each Defendant of all patents that have been asserted by Plaintiffs in this case as to each such Defendant, respectively, with the exception of U.S. Patent No. 8,791,270, which has been resolved by the granting of covenants not to sue and/or consent judgments." D.I. 320 ¶ 8. Paragraph 4 of the second Stipulation and Order reads: "Plaintiffs and Slayback stipulate that a determination as to invalidity of the asserted claim at trial will result in a final judgment as to Slayback of all claims of the patent that has been asserted by Slayback in this case, with the exception of U.S. Patent No. 8,791,270, which has been resolved by the granting of a consent judgment." D.I. 319 ¶ 4.

Defendants argue that the stipulations apply "only to a situation in which ***Defendants*** won"—i.e., a situation in which I found that the asserted claims were invalid and/or not infringed—because the stipulations apply only to a "determination as to ***non***-infringement and/or ***in***validity." D.I. 404 at 1–2. (emphasis in original). Plaintiffs counter that "Defendants misread the stipulations

to apply only to determinations ***of*** non-infringement or invalidity—not as they actually provide, to determinations '***as to*** non-infringement and/or invalidity.'" D.I. 402 at 3 (emphasis in original) (citation omitted).

At the outset, "it must be said that *as to* is an all-purpose preposition to be avoided whenever a more specific preposition will do." Bryan A. Garner, *Garner's Modern English Usage* 79 (4th ed. 2016). The phrase is typically used as "a passable shorthand form of *regarding*, *with regard to*, or *on the question of*, and it "is also (minimally) defensible when used for *about*." *Id.* at 80. It is clear to me now, and it was clear to me at the time I signed the stipulated orders, that the parties used "as to" in their stipulations in these "passable shorthand" and "defensible" (even if minimally) ways. Thus, the stipulations apply to any determination I made regarding, about, or on the questions of noninfringement and invalidity of the asserted claims.

It is equally clear that the stipulations do not apply only to "a situation in which Defendants won." My determination that Plaintiffs had established that the Defendants' proposed products infringe the asserted claims necessarily entailed a determination that Defendants had failed to prevail on their claim that the proposed products were noninfringing. Defendants' contention that a "determination as to non-infringement" differs from a "determination as to infringement" makes no sense in a case like this one where Plaintiffs seek a declaratory judgment of

infringement and Defendants seek a declaratory judgment of noninfringement. The accused products in such a case either infringe the asserted patents or don't infringe the asserted patents. I note in this regard that even though all the Defendants accused by Plaintiffs of infringement filed counterclaims seeking declaratory judgments of noninfringement, those Defendants never distinguished Plaintiffs' infringement claims from Defendants' noninfringement counterclaims until I asked the parties to meet and confer about a final judgment order. For example, in the jointly-filed Pretrial Order, the Defendants proposed the following order of presentation of evidence at trial:

Phase I	Plaintiffs' presentation of asserted patents and case-in-chief on infringement
Phase II	Defendants' response on infringement, and case-in-chief on invalidity
Phase III	Plaintiffs' rebuttal on infringement and response on invalidity
Phase IV	Defendants' rebuttal on invalidity

D.I. 307 at 19. Defendants made no mention of "non-infringement" because it would have been redundant of "infringement."

In the same vein, "invalid" and "not invalid" are inseparable concepts in a patent case. My determination that the asserted claims were not invalid constitutes a determination on the question of invalidity.

Defendants argue that the stipulated orders apply only to findings of "***in***validity" as opposed to findings of "validity." D.I. 404 at 1 (emphasis in

original); *see also id.* at 3 (arguing that "[t]he stipulation does not provide automatic judgment to Plaintiffs for infringement and validity."). But it is not the role of the court (or jury) to declare a patent valid. When a patent's validity is challenged, the court (or jury) is tasked with deciding if the challenger has proven that the patent is invalid. The "determination" to be made in such cases is whether the patent is invalid or not invalid. Under 35 U.S.C. § 282, "[a] patent shall be presumed valid." Thus, "[a] suit brought only for a declaration that a patent is valid would be an anomaly, and a patentee who in an infringement suit asks the court to hold his or her patent valid states a redundancy . . . ." Robert L. Harmon, Cynthia A. Homan & Laura A. Lydigsen, *Patents and the Federal Circuit*, §1.5(b)(i), at 40 (13th ed. 2017). In this case, I determined that the asserted claims were "not invalid." D.I. 394 at 68. That determination is clearly "a determination as to invalidity."

Because the stipulated orders apply to my determinations that the asserted claims are infringed and not invalid, the judgment in this case should extend to all the claims of all the patents that were asserted in the case by Plaintiffs except for U.S. Patent No. 8,791,270. The first Stipulation and Order provides in relevant part that "a determination as to non-infringement and/or invalidity of the asserted claims at trial will result in a final judgment as to each Defendant *of all patents that have been asserted by Plaintiffs in this case* as to each such Defendant,

respectively." D.I. 320 ¶ 8 (emphasis added). The phrase "all patents that have been asserted by Plaintiffs in this case" is unambiguous. It clearly covers every claim of every patent asserted by Plaintiffs at any time in the case before the date of the Stipulation and Order. The language of the second Stipulation and Order is also unambiguous. It provides in relevant part that "a determination as to invalidity of the asserted claim at trial will result in a final judgment as to Slayback of *all claims of the patent that has been asserted by Slayback in this case*." D.I. 318 ¶ 4 (emphasis added). Thus, pursuant to the second stipulated order, my determination that claim 13 of U.S. Patent No. 9,572,887 is not invalid requires a judgment against Slayback that covers all claims of that patent.

For these reasons, I will enter the Order proposed by Plaintiffs.

July 6, 2020

United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CEPHALON, INC., *et al.*,

Plaintiffs,

v.

SLAYBACK PHARMA LIMITED LIABILITY CO., *et al.*,

Defendants.

Civil Action No. 17-1154-CFC
CONSOLIDATED

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OPINION

April 27, 2020
Wilmington, Delaware

COLM F. CONNOLLY
UNITED STATES DISTRICT JUDGE

Plaintiffs Teva Pharmaceuticals International GmbH, Cephalon, Inc., and Eagle Pharmaceuticals, Inc. have sued Defendants Apotex Inc. and Apotex Corp., Fresenius Kabi USA, LLC, Mylan Laboratories Ltd., and Slayback Pharma LLC under the Hatch-Waxman Act, 35 U.S.C. § 271(e)(2)(A). Defendants seek to bring to market generic versions of Plaintiffs' Bendeka®, a drug indicated for the treatment of chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin lymphoma (NHL). D.I. 1 ¶¶ 1, 12.[1] Plaintiffs allege infringement of U.S. Patent Nos. 9,265,831 (the #831 patent), 9,572,797 (the #797 patent), 9,144,568 (the #568 patent) and 9,597,399 (the #399 patent) by all defendants and infringement of U.S. Patent No. 9,572,887 (the #887 patent) by Slayback. Defendants have stipulated to infringement of the asserted claims with two exceptions outlined below. Defendants argue that all asserted claims of the asserted patents are invalid.

I held a seven-day bench trial, and, as required by Federal Rule of Civil Procedure 52(a)(1), I have set forth separately below my findings of fact and conclusions of law.

[1] All docket citations are to the docket for C.A. No. 17-1154 unless stated otherwise.

I. BACKGROUND

Plaintiffs sell Bendeka® under New Drug Application No. 208194. D.I. 1 ¶ 13. Eagle is the owner and assignee of the asserted patents and has listed them in connection with Bendeka® in the Orange Book maintained by the Food and Drug Administration (FDA). *Teva Pharms. Int'l GmbH v. Apotex Inc.*, No. 17-1164 (D. Del. 2017), D.I. 1 ¶¶ 27–35. Cephalon holds an exclusive license to the asserted patents and has assigned to Teva its rights under the license, including the right to sue for infringement. *Id.*, D.I. 1 ¶¶ 38–39.

Bendeka®'s active ingredient is bendamustine hydrochloride (referred to by the parties as bendamustine), a nitrogen mustard chemotherapy drug that was first developed in East Germany in the 1960s. D.I. 334 at 2; D.I. 364 ¶ 1.

In 2008, Cephalon launched the first U.S. bendamustine product, Treanda®. Tr. 403:18–22. Cephalon initially sold Treanda® in a lyophilized, or freeze-dried, form. Tr. 404:7–11, 1357:13–19. Lyophilized drugs must be reconstituted into an injectable liquid before they can be administered to patients. Tr. 404:7–18, 405:8–06:4. Aware that bendamustine's toxicity makes it potentially dangerous for medical staff to reconstitute the drug, Eagle began in 2009 to develop a liquid bendamustine formulation that ultimately became Bendeka®. Tr. 83:7–84:13, 86:3–19.

In November 2014, Cephalon launched its own liquid version of Treanda®. Tr. 981:25–82:2, 1657:10–11.

In 2015, Teva acquired Cephalon, Tr. 1660:10–14, and Cephalon thereafter commercialized Bendeka® as permitted by its exclusive license agreement with Eagle, PTX-0408; Tr. 1660:10–24, 1795:4–9.

On December 7, 2015, the FDA approved Bendeka®, D.I. 307-1 ¶ 152, and on January 27, 2016, Teva launched Bendeka®, DTX-0500; Tr. 984:17–85:23, 1006:6–07:5. Bendeka® subsequently received orphan drug exclusivity, a seven-year period during which the FDA is precluded from approving any other manufacturer's application to market the same drug to treat the same rare disease. *Eagle Pharm., Inc. v. Azar*, 2018 WL 3838265, at *1 (D.D.C. June 8, 2018), *aff'd,* 952 F.3d 323 (D.C. Cir. 2020); Tr. 1725:15–19.

In March of 2016, Teva stopped selling liquid Treanda®. DTX-0500_0001; Tr. 1623:7–8.

In July and August of 2017, Defendants each filed an Abbreviated New Drug Application (ANDA) with Paragraph IV certifications under § 505(j) of the Federal Food, Drug and Cosmetic Act to gain FDA-approval for the commercial manufacture, use, and sale of a generic version of Bendeka®. *E.g.*, D.I. 1 ¶ 15. In August of 2017, Plaintiffs filed these suits alleging that Defendants' ANDA filings with Paragraph IV certifications constituted acts of infringement. *E.g.*, D.I. 1.

These cases were consolidated for all purposes. *See* December 13, 2017 Order.

At trial, Plaintiffs accused all Defendants other than Slayback of infringing six formulation claims in two of the asserted patents: claims 2, 3, and 5 of the #831 patent; and claims 9 and 11 of the #797 patent. Plaintiffs also alleged infringement of six administration claims in four of the asserted patents: claims 11, 18, and 22 of the #568 patent and claim 15 of the #399 patent (by all Defendants); claim 13 of the #399 patent (by Apotex only); and claim 13 of the #887 patent (by Slayback only). Defendants countered that (1) the asserted formulation and administration claims are invalid for obviousness under 35 U.S.C. § 103; (2) the asserted formulation claims are invalid for indefiniteness under 35 U.S.C. § 112; (3) the asserted formulation claims are invalid for lack of enablement under 35 U.S.C. § 112; and (4) claim 9 of the #797 patent is invalid for lack of written description. Defendants stipulated that they infringe or induce infringement of each of the asserted claims with two exceptions: Apotex, Fresenius Kabi, and Mylan argue that (1) their ANDA products do not contain "a stabilizing amount of an antioxidant" as the asserted formulation claims require; and (2) they do not induce infringement of claim 9 of the #797 patent.

II. OBVIOUSNESS

A. Legal Standards for Obviousness

Under § 103 of the Patent Act, codified at 35 U.S.C. § 1 *et seq.*, a patent

"may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art [POSITA] to which said subject matter pertains." 35 U.S.C. § 103. As the Supreme Court explained in the seminal case, *Graham v. John Deere Co.*, 383 U.S. 1 (1966), under § 103, "[a]n invention which has been made, and which is new in the sense that the same thing has not been made before, may still not be patentable if the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent." *Id.* at 14. Section 103 ensures that "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007). "Were it otherwise patents might stifle rather than promote, the progress of useful arts." *Id.* (citing U.S. Const. art. I, § 8, cl. 8).

The Court reaffirmed in *KSR* that the "framework" set out in the following paragraph from *Graham* governs the application of § 103, *id.* at 406:

> While the ultimate question of patent validity is one of law, the [§] 103 condition [of patentability], . . . lends itself to several basic factual inquiries. Under [§] 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but

> unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Graham, 383 U.S. at 14–15 (citations omitted).

It is clear that under this framework, a district court must consider in an obviousness inquiry the three primary factors identified by the Court in *Graham*: (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, and (3) the level of ordinary skill in the pertinent art. Less clear is the role, if any, secondary considerations should play in the analysis.

The logical—some would say necessary—implication of the Court's use of the word "secondary" in *Graham* and its holding that the secondary considerations "*might* be utilized" and "*may* have relevancy" is that a district court is permitted—but not required in all cases—to examine such considerations in evaluating an obviousness-based invalidity challenge. The Court seemed to confirm as much in *KSR*, when it noted that "*Graham* set forth a broad inquiry and *invited* courts, *where appropriate*, to look at any *secondary considerations* that would prove instructive." *KSR*, 550 U.S. at 415 (emphasis added).

But a district court ignores *Graham*'s "invitation" to examine secondary considerations at its peril. One legal scholar, Harmon, has observed that under Federal Circuit law "[w]e are able now safely to strike the 'may' in the . . .

sentence" in *Graham* in which the Court stated that secondary "indicia of obviousness and nonobviousness . . . may have relevancy." Robert Harmon, Cynthia Homan, Laura Lydigsen, *Patents and the Federal Circuit* 245 (13th ed. 2017). Harmon correctly notes that "[t]he Federal Circuit has emphatically and repeatedly held that objective evidence of non-obviousness [i.e., the "secondary considerations" identified in *Graham*] must be taken into account always and not just when the decisionmaker is in doubt." *Id.* In *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983), for example, the Federal Circuit held that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *Id.* at 1538. And in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063 (Fed. Cir. 2012), the Federal Circuit reaffirmed that holding, *id.* at 1079, and went on to say that the Supreme Court in *Graham* "did not relegate . . . to 'secondary status'" the "objective factors" the Supreme Court had explicitly identified in *Graham* as "secondary considerations," *id.* at 1078.

It is true that less than a month after *In re Cyclobenzaprine*, a different Federal Circuit panel held in *Otsuka Pharmaceutical Co. v. Sandoz, Inc.*, 678 F.3d 1280 (Fed. Cir. 2012) that because it found that the defendants had "failed to prove that [the challenged patent claim] would have been *prima facie* obvious over the asserted prior art," it "need not address" the "objective evidence" of commercial

success, long-felt need, and the failure of others. *Id.* at 1296. But the safer course for a district court faced with an obviousness challenge (and looking to avoid reversal by the Federal Circuit) is to treat *Graham*'s "invitation" to look at secondary considerations like a subpoena.

Obviousness is assessed based on the perspective of a POSITA at the time of the invention. *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). The court therefore needs to guard against "hindsight bias" that infers from the inventor's success in making the patented invention that the invention was obvious. *In re Cyclobenzaprine*, 676 F.3d at 1079. The ultimate question in the obviousness analysis is "whether there was an apparent reason [for a POSITA] to combine [at the time of the invention] the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. "The analysis is objective." *Id.* at 406. Thus, a court must determine whether a POSITA "would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine*, 676 F.3d at 1069.

The party challenging the patent's validity bears the burden of proving obviousness by clear and convincing evidence. *Id.* at 1068–69. In weighing the *Graham* factors to decide whether the party has met that burden, the district court must be guided by common sense. *Wyers v. Master Lock Co.*, 616 F.3d 1231,

1238 (Fed. Cir. 2010). Indeed, "the legal determination of obviousness may include recourse to logic, judgment, and common sense, in lieu of expert testimony." *Id.* at 1239. In *KSR*, the Supreme Court warned lower courts to avoid "[r]igid preventative rules that deny factfinders common sense" and to employ instead "an expansive and flexible approach" under the *Graham* framework. *KSR*, 550 U.S. at 415. Thus, the district court may "reorder[ ] in any particular case" the "sequence" in which it considers the *Graham* factors. *Id.* at 407. And although a court should consider carefully the published prior art, "[t]he obviousness analysis cannot be confined by . . . overemphasis on the importance of published articles and the explicit content of patents." *Id.* at 419.

"[A]ny need or problem known in the field of endeavor at the time of the invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *KSR*, 550 U.S. at 420. And "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. "[T]he fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* at 421. But a combination is obvious to try only "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions" in the prior art at the time of the invention. *Id.* And the court must also be mindful that "when the prior art teaches away from combing

certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 416.

B. Obviousness of the Asserted Formulation Claims

1. Findings of Fact

a. The Priority Date

The parties agree that the date of invention (i.e., the priority date) for the asserted formulation claims is January 28, 2010. Tr. 403:4–6, 1352:16–21, 2015:3–16; #831 patent at (60); #797 patent at (60).

b. Definition of the Relevant POSITA

The parties agree that a POSITA would have had the skills, education, and expertise of a team of individuals working together to formulate a liquid injectable drug product. Such a team would have included individuals with doctoral degrees in chemistry, biochemistry, pharmaceutics, pharmaceutical sciences, chemical engineering, biochemical engineering or related fields, with at least two years of post-graduate experience in developing liquid injectable drug products, or master's or bachelor's degrees in similar fields of study, with a commensurate increase in their years of postgraduate experience. Such a team also would have been familiar with a variety of issues relevant to developing liquid injectable drug formulations, including, among other things, solubility, stability, pharmacokinetics, pharmacodynamics, and other pharmaceutical characteristics. Such a team also

would have included persons with expertise in analytical chemistry, including the detection and measurement of chemical degradants. The team also would have had access to an individual with a medical degree with experience in treating patients with CLL and NHL. PDX-4-2; Tr. 562:1–63:6, 1036:7–37:11, 1353:6–20, 2014:22–15:2.

c. Content of the Asserted Formulation Claims

The asserted formulation claims teach a non-aqueous liquid composition that contains (1) bendamustine (or a pharmaceutically acceptable salt thereof); (2) about 5% to about 10% by volume of the solvent propylene glycol (PG); (3) the solvent polyethylene glycol (PEG); (4) one of the following ratios of PEG to PG: about 95:5, about 90:10, about 85:15, about 80:20, and about 75:25; and (5) a stabilizing amount of an antioxidant. #831 patent at claims 2, 3, 5; #797 patent at claims 9, 11. Two claims also specify components and quantities: (1) claim 11 of the #797 patent requires that "the antioxidant is thioglycerol or monothioglycerol,"[2] and (2) claim 5 of the #831 patent requires that "the bendamustine concentration is from about 25 mg/mL to about 50 mg/mL." Certain claims also recite stability limitations such as "less than or equal to 0.11% PG esters at about 1 month of storage at about 5°C." #831 patent at claims 2, 3, 5; #797 patent at claims 9, 11.

[2] Thioglycerol or monothioglycerol are used synonymously. Tr. 519:10–15.

d. Bendamustine, PEG, and PG

Bendamustine has two relevant functional groups at opposing ends of its chemical structure: a nitrogen mustard group and a carboxylic acid group. Tr. 422:23–23:13, 430:19–31:6, 1038:5–7.

Nucleophiles—such as water, PG, and PEG—degrade bendamustine at its nitrogen mustard group through reactions in which an aziridinium ring forms. Tr. 407:12–19, 564:10–66:12, 1038:13–21, 1043:23–46:12, 1381:11–18; DTX-0073 at 4:33–37; PTX-1010 at TEVABEND00296748. Compounds like PEG and PG that have hydroxyl (OH) groups also degrade bendamustine at its carboxylic acid group through a process called esterification where the carboxylic acid group reacts with the OH groups to form degradants called esters. Tr. 431:4–13.

When PEG is combined with bendamustine, a process called PEG oxidation accelerates the esterification reaction. Tr. 484:15–85:11, 1416:11–18:12; PTX-0669 at TEVABEND00294275; PTX-0623 at TEVABEND00289470. PEG thus causes more degradation at bendamustine's carboxylic acid group than the same amount of PG would cause. Tr. 1054:5–59:11; PTX-0999 at TEVAVEND00292131; PTX-0997 at TEVABEND00291955.

Because water causes bendamustine to degrade at its nitrogen mustard group, the prior art bendamustine formulations used a lyophilized (freeze-dried) form of bendamustine that required a human operator to reconstitute it using water

shortly before administering it to a patient. DTX-0094_0010; Tr. 404:7–18, 405:8–06:4, 408:17–09:1, 410:4–5, 1357:13–19. Reconstitution by human manipulation had two known disadvantages in 2010: it increased the risk of contamination, Tr. 406:16–20; and, because bendamustine is a cytotoxic compound, it posed a potential danger to the operator, Tr. 84:2–13, 406:23–07:3; DTX-0056_0001; DTX-0056 at 2:33–67; DTX-0094_0011.

e. Content of the Prior Art

Defendants argue that five prior art references would have motivated a POSITA to arrive at the asserted formulation claims with a reasonable expectation of success: Olthoff, Drager, Alam, Rowe, and Boylan. D.I. 378 at 31.

1) Olthoff (DTX-0094)

Olthoff, a 1983 East German patent, claimed a stable, non-aqueous liquid injection solution of between 25 and 100 mg/mL bendamustine dissolved in a solvent consisting of 100% PG. DTX-0094_0016; Tr. 448:20–25. Olthoff's objective was to "produce a stable and ready-to-use injection solution out of N[itrogen]-mustard compounds, avoiding the technical solution of a dry ampoule [i.e., lyophilization]." DTX-0094_0012; Tr. 409:18–10:5. Olthoff disclosed that bendamustine has "a[n] extraordinarily high chemical stability for the production of injection solutions in" monovalent alcohols, glycols and polyols. DTX-0094_0012; Tr. 410:6–11:8. Olthoff specifically proposed dissolving

bendamustine in "polyols, particularly 1,2-propylene glycol [i.e., PG]." DTX-0094_0014; Tr. 412:6–14. Polyols are another name for compounds that have multiple OH groups. Tr. 412:17–18, 413:11–13. Both PEG and PG are polyols. *Id.*

Olthoff's examples did not use an antioxidant. DTX-0094_0013, _0015; Tr. 1457:5–12.

In the decades between Olthoff's publication and the priority date, its formulations were never used. DTX-0073 at 2:19–29.

2) Drager (DTX-0073)

About 30 years after Olthoff was published, Drager, a U.S. patent, issued in 2013. Tr. 434:6–20; D.I. 307-1 ¶ 223. (Drager's priority date is September 25, 2008 making it prior art to the asserted formulation claims.) Like Olthoff, Drager described stable "liquid pharmaceutical formulations comprising bendamustine." DTX-0073 at 2:33–35, Abstract; Tr. 433:23–25. But Drager determined that the "results described in [Olthoff] were not reproducible." DTX-0073 at 2:62–64. Drager's data showed that bendamustine in 99% PG degraded almost completely after eight weeks at 25°C and more than 20% at 5°C after one year. DTX-0073 at Fig. 3; Tr. 1378:9–80:5. The reason for that degradation, according to Drager, was that (1) PG causes bendamustine to degrade at the nitrogen mustard group, DTX-0073 at 4:19–24, 4:33–37; Tr. 602:13–15, and (2) PG's OH groups cause

bendamustine to degrade at the carboxylic acid group through esterification, DTX-0073 at 5:12–14; Tr. 602:3–6.

As a solution to the degradation problem, Drager disclosed the use of aprotic solvents, i.e., solvents containing no OH groups, in a liquid bendamustine formulation. DTX-0073 at 3:21–25; Tr. 581:19–82:12. Drager showed that dissolving bendamustine in 100% DMA, an aprotic solvent, results in no degradation of bendamustine at the carboxylic acid group. DTX-0073 at Table II; Tr. 432:22–33:7, 435:11–36:9.

Drager also taught that protic solvents—i.e., solvents, including PEG and PG, that have OH groups—are acceptable to use with bendamustine but only when combined with aprotic solvents. DTX-0073 at 3:3–10, 3:36–48, 4:18–24; Tr. 601:11–17. Drager showed that the formulation containing 66% DMA and 34% PG is stable. DTX-0073 at Table II; Tr. 436:16–37:15.

3) Alam (DTX-0056)

Alam, a U.S. Patent issued on November 7, 1989, disclosed stable liquid formulations of cyclophosphamide, a compound that, like bendamustine, has a nitrogen mustard group. DTX-0056 at Abstract, 1:5–8; Tr. 422:3–9, 424:6–12. Alam tested cyclophosphamide's stability in mixtures of three polyols—PG, PEG and glycerol—and found that the formulation containing PEG and PG had "less degradation than the others." Tr. 424:2–25:5, 428:6–12, 1421:18–24; DTX-0056

at Tables 1–5. Alam disclosed using PG at a ratio of from about 10% to about 90% and PEG at a ratio of from about 90% to about 10%. DTX-0056 at 4:6–12; Tr. 425:6–14.

Bendamustine and cyclophosphamide have two structural differences that bear on how they degrade when they are mixed with PEG and PG. First, because cyclophosphamide does not have a carboxylic acid group, cyclophosphamide does not experience esterification, i.e., it does not react with compounds such as PEG and PG that have OH groups to form esters. Tr. 430:22–31:1, 1077:25–78:6. Second, in bendamustine, the nitrogen mustard group is attached to a benzene ring, while in cyclophosphamide, the group is attached to a phosphoramide. Tr. 1075:4–25. Because it is attached to a benzene ring in bendamustine, a POSITA would have expected nucleophiles such as PEG and PG to accelerate degradation at the nitrogen mustard group via the formation of an unstable aziridinium ring. Tr. 1037:19–41:16, 1058:12–17, 1060:2–9; PTX-0376 at JDG_BENDA_00002265; PTX-1010 at TEVABEND00296748. But in cyclophosphamide, the phosphoramide deactivates the nitrogen mustard group and cyclophosphamide consequently does not degrade by forming the aziridinium ring in a liquid formulation before administration. Tr. 1076:1–77:24; PTX-0991 at TEVABEND00290978; PTX-0993 at TEVABEND00291516.

Neither Alam nor Drager used an antioxidant in their exemplary or preferred

formulations. Tr. 1458:2–58:23.

4) Rowe, Handbook of Pharmaceutical Excipients (DTX-0160)

Rowe's Handbook of Pharmaceutical Excipients disclosed that PEG is susceptible to oxidation and that one can use an antioxidant to prevent such oxidation. DTX-0160_0011; Tr. 486:7–24.

5) Boylan (DTX-0063)

Boylan disclosed a list of "some of the most commonly used antioxidants in pharmaceutical injectable formulations" including monothioglycerol. DTX-0063_0019, 0020; Tr. 487:12–18. Boylan also disclosed usual concentrations for each of the listed antioxidants. DTX-0063_0020; Tr. 487:18–19. Monothioglycerol is FDA-approved. Tr. 340:20–23.

2. Conclusions of Law

I find that Defendants have not established by clear and convincing evidence that a POSITA would have had reason to combine the limitations recited in the asserted patents' formulation claims. Although Defendants persuaded me that a POSITA would have had reason to try to develop a non-aqueous liquid bendamustine formulation, they failed to establish by clear and convincing evidence that a POSITA would have used in that formulation the PEG and PG solvents, PEG:PG ratios, antioxidant, concentrations of bendamustine, or PG ester stability limitations recited in the asserted claims. I do not find Plaintiffs' evidence

of secondary considerations to establish nonobviousness, but I find Defendants' failure of proof with respect to *Graham*'s primary factors in this case to be dispositive and that therefore the formulation claims are not invalid under § 103.

a. Non-Aqueous Liquid Bendamustine Formulation

Every asserted formulation claim requires a non-aqueous liquid formulation. Due to bendamustine's instability in water, the prior art used a lyophilized form of bendamustine. Tr. 404:9–18, 1357:13–19. But, as discussed above, lyophilization had known disadvantages. To avoid lyophilization while still avoiding the use of water, a POSITA would have been motivated to create a non-aqueous liquid bendamustine product. In fact, as can be seen in Olthoff and Drager, other inventors sought to create non-aqueous liquid bendamustine formulations before the priority date.

b. Use of PEG and PG

The claimed non-aqueous liquid bendamustine formulations contain the solvents PEG and PG. Defendants argue that Olthoff, Drager, and Alam would have motivated a POSITA to use PEG and PG with bendamustine. D.I. 378 at 13, 16.

1) Olthoff and Drager

Viewed in isolation, Olthoff would have led a POSITA to use PEG and PG in a liquid bendamustine formulation. D.I. 378 at 13; DTX-0094_0014; Tr.

412:3–18, 413:4–13. Olthoff provided a short, finite list of solvent options that included PEG and PG. Specifically, Olthoff reported that bendamustine is stable in monovalent alcohols and polyols, DTX-0094_0012–13; Tr. 410:6–11:8, 1084:13–86:11; and the disclosure of "polyols" would have given a POSITA just three polyol options: PEG, PG, and glycerol, Tr. 413:4–13. Plaintiffs dispute that assertion, D.I. 371 at 20–23, but Plaintiffs' expert himself limited polyols to those three options in a patent application that he submitted in 2009, *see* DTX-0764_0011 ("Preferably the water soluble plasticizer is selected from the group consisting of polyols (glycerin [i.e., glycerol], propylene glycol, polyethylene glycols) . . . ."). His response when confronted with that disclosure at trial was: "Yes, but I didn't -- at that time I didn't know that I would be sitting here today." Tr. 1575:2–76:1. Moreover, while I agree with Plaintiffs that Olthoff would have taught a POSITA also to consider monovalent alcohols, D.I. 371 at 21, Plaintiffs only list four monovalent alcohols that a POSITA would have considered using with bendamustine, D.I. 361 ¶ 73. Olthoff thus would have left a POSITA with three polyols and four monovalent alcohols as options. By providing a finite list, Olthoff would have made using PEG and PG obvious to try because a POSITA would face only "a finite number of identified, predictable solutions." *KSR*, 550 U.S. 398 at 421.

Drager, however, teaches away from Olthoff's teaching of using polyols

such as PEG and PG alone with bendamustine. As noted, Drager determined that the "results described in [Olthoff] were not reproducible." DTX-0073 at 2:62–64, 3:1–2. And Drager's data showed that bendamustine in 99% PG degraded almost completely after eight weeks at 25°C and more than 20% at 5°C after one year. DTX-0073 at Fig. 3; Tr. 1378:9–80:5. As Plaintiffs' expert, Dr. Siepmann, credibly testified, a POSITA would have considered 20% degradation after just one year at 5°C to be "not good." Tr. 1379:25–80:5.

Drager disclosed combining bendamustine with aprotic solvents as a means of reducing such degradation. DTX-0073 at 3:3–10, 3:21–25; Tr. 581:19–82:12. Drager also allowed for combining bendamustine with a mixture of aprotic solvents and protic solvents, including PEG and PG. DTX-0073 at 3:3–10, 3:36–48, 4:18–24; Tr. 601:11–17. But Drager stated that the concentration of protic solvents should be kept at 90%—and preferably lower—to limit degradation. DTX-0073 at 3:49–4:25; Tr. 1393:3–22. Drager specifically showed that a formulation containing 66% DMA and 34% PG is stable. DTX-0073 at Table II; Tr. 436:16–37:15.

Defendants assert that Drager taught the use of aprotic solvents because they have no OH groups and that, therefore, Drager would have motivated a POSITA to use solvents with a low number of OH-groups. Tr. 431:20–23, 437:8–15. They argue that "[w]hile Drager claimed a formulation containing a polar aprotic solvent

(DMA) and a polar protic solvent (PG), a POS[IT]A would be motivated to remove DMA from the formulation because DMA has been known to cause problems in formulations." D.I. 379 ¶ 65; D.I. 378 at 14–15. According to Defendants, because DMA was the only aprotic solvent listed by Drager that is "used in FDA products," D.I. 378 at 15, a POSITA would turn to protic solvents like PEG that have a relatively low number of OH groups. D.I. 379 ¶ 67; D.I. 378 at 21.

Drager, however, teaches away from the use of only protic solvents. Therefore, Drager would not have motivated a POSITA to replace DMA with a low-OH protic solvent. Defendants and their expert conceded that neither Drager's disclosures nor its examples taught using exclusively protic solvents. Tr. 583:1–83:10, 1886:17–19. Instead, Drager taught the use of an *aprotic* solvent with bendamustine to avoid degradation by nucleophiles like PEG and PG. Moreover, Drager disclosed numerous alternative aprotic solvents that could potentially replace DMA. DTX-0073 at 3:9–14; Tr. 1395:7–14. And DMA was *not* the only aprotic solvent in an FDA-approved product. The prior art reference Strickley, for example, disclosed that the aprotic solvents NMP and DMSO had been commercially used. PTX-0569 at JDG_BENDA_00003311–14; Tr. 1390:19–24.

A POSITA in 2010 reading Olthoff and Drager thus would have found that Olthoff taught combining bendamustine with polyols including PEG and PG, but

that Drager taught away from using protic solvents, such as PEG and PG, alone with bendamustine. "Where the prior art contains apparently conflicting teachings (i.e., where some references teach the combination and others teach away from it) each reference must be considered for its power to suggest solutions to an artisan of ordinary skill . . . consider[ing] the degree to which one reference might accurately discredit another." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (internal quotation marks and citation omitted).

After considering the two references, I find that a POSITA would have credited Drager's data and conclusions over those in Olthoff. Drager expressly asserted that the "results described in [Olthoff] were not reproducible." DTX-0073 at 2:62–64. And Drager used high-performance liquid chromatography (HPLC) to make its determinations while Olthoff used thin-layer-chromatography (TLC). Plaintiffs assert, and Defendants do not dispute, that HPLC is more reliable than TLC because of its superior sensitivity and ability to resolve impurities. Tr. 1074:4–75:3, 1086:17–20, 1380:14–25, 1511:5–11. Moreover, in the decades between Olthoff's publication in 1983 and the priority date in 2010, Olthoff's formulations were never used, suggesting that POSITAs generally did not rely on Olthoff. DTX-0073 at 2:19–29. "The elapsed time between [Olthoff] and the [asserted] patent's filing date evinces that the [asserted] patent's claimed invention was not obvious to try." *Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346, 1356 (Fed.

Cir. 2013). Thus, a POSITA looking at Olthoff and Drager would have followed Drager's teaching not to use protic solvents such as PG and PEG alone with bendamustine.

2) Alam

Defendants also argue that Alam's disclosure of mixing cyclophosphamide with PEG and PG would have motivated a POSITA to use those solvents with bendamustine because both bendamustine and cyclophosphamide have nitrogen mustard groups. D.I. 378 at 16. But two structural differences between cyclophosphamide and bendamustine that effect how they degrade when they are combined with PEG and PG would have discouraged a POSITA from relying on Alam in formulating bendamustine. First, unlike bendamustine, cyclophosphamide does not have a carboxylic acid group and thus does not undergo an esterification reaction when it is combined with PEG or PG. Tr. 1077:25–78:6, 1421:1–5. Second, because the nitrogen mustard group in bendamustine is attached to a benzene ring, while in cyclophosphamide it is attached to a phosphoramide, cyclophosphamide degrades differently at the nitrogen mustard group than bendamustine does. Tr. 1077:4-1077:24; PTX-0991 at TEVABEND00290978; PTX-0993 at TEVABEND00291516. Defendants' expert, Dr. Pinal, did not point to any prior art references to support his contrary conclusion that "the nitrogen group in the two molecules are exactly the same." Tr. 423:7–13, 504:21–05:5.

I find therefore that a POSITA in 2010 would not have viewed cyclophosphamide as a relevant comparator for bendamustine reactions, Tr. 1078:7–11, and would not have considered Alam in formulating a stable bendamustine formulation, Tr. 1420:10–21:5.

* * * *

In sum, Defendants have not proven by clear and convincing evidence that Olthoff, Drager, and Alam would have motivated a POSITA to use PEG and PG to create a non-aqueous liquid bendamustine formulation. Although Olthoff taught using polyols such as PEG and PG with bendamustine, Drager teaches away from the use of protic solvents such as PEG and PG alone with bendamustine and a POSITA would credit Drager's teaching over Olthoff's. Moreover, a POSITA looking to solve the degradation problem in bendamustine would not have considered Alam in formulating a liquid bendamustine product because Alam concerned a compound that degrades differently than bendamustine when combined with PEG and PG.

c. Use of Claimed PEG:PG Ratios

Every asserted formulation claim requires a PEG:PG ratio that falls between 95:5 and 75:25. Defendants argue that the claimed PEG:PG ratios would have been obvious "in light of Alam's express disclosure of the entire range from 10:90 to 90:10." D.I. 378 at 19–20. But as explained above, the prior art would not have

motivated a POSITA to use PEG and PG in the first place. Also, even if a POSITA had chosen to use PEG and PG, it would not have relied on Alam because Alam concerned a compound that degrades differently than bendamustine in reaction to PEG and PG. Finally, the claimed formulations use more PEG than PG whereas Alam preferred using more PG than PEG, DTX-0056 at 4:6–12, and a POSITA in 2010 would have known that PEG would cause more degradation at bendamustine's nitrogen mustard group than PG due to PEG oxidation. Tr. 1054:5–59:11; PTX-0999 at TEVAVEND00292131; PTX-0997 at TEVABEND00291955. Thus, Alam did not make obvious the PEG:PG ratios recited in the asserted formulation claims.

d. Use of An Antioxidant

Every asserted claim requires an antioxidant and one asserted claim requires that the antioxidant be monothioglycerol. Assuming a POSITA had chosen to use a 90% PEG and 10% PG bendamustine formulation, that POSITA would have been motivated to curb PEG oxidation: a process in which PEG accelerates the esterification reaction. Tr. 484:15–85:11, 1416:11–18:12; PTX-0669 at TEVABEND00294275; PTX-0623 at TEVABEND00289470.

Defendants argue that Boylan and Rowe would have motivated a POSITA to solve the oxidation problem with an antioxidant. D.I. 378 at 22–23. They assert that Rowe taught a POSITA to inhibit the oxidation of PEG with the inclusion of a

suitable antioxidant and that Boylan taught using specific antioxidants, including monothioglycerol. D.I. 378 at 23; Tr. 486:7–24, 488:7–9, 505:11–06:7, 543:2–5; DTX-0160_0011; DTX-0063_0020. Defendants also note that monothioglycerol is "very commonly used," and is FDA-approved for injectable products. D.I. 378 at 23.[3]

Other prior art references, however, teach away from the use of antioxidants. *See* Tr. 1452:20–53:21; *Note for Guidance*, European Agency for the Evaluation of Medicinal Products, PTX-0629 at TEVABEND00290713, TEVABEND00290720 ("Antioxidants should only be included in a formulation if it has been proven [t]hat their use cannot be avoided."); *Pharmaceutical Preformulation and Formulation*, Interpharm, PTX-0391 at JDG_BENDA_00000415 (stating that antioxidant use "is now in decline" and that "[a] preferred method of preventing oxidation [over antioxidants] is simply to exclude oxygen"). Moreover, none of the four approved injectable products in the prior art that contained PEG included an antioxidant. Tr. 600:4–6, 1454:24–55:17; PTX-0722 (Ativan); PTX-0718 (Busulfex); PTX-0720 (Robaxin); PTX-0569 at JDG_BENDA_00003308 (VePesid). In addition, the

[3] Defendants also assert that Drager taught "the use of antioxidants in the formulation." D.I. 378 at 22. They did not, however, request a finding of fact on this point and none of Drager's preferred or exemplary formulations contained an antioxidant. Drager mentioned that the invention may include other excipients such as an antioxidant, DTX-0073 at 7:1−18, claim 5, but it did not encourage a POSITA to use an antioxidant.

liquid bendamustine examples in Defendants' prior art references do not include antioxidants: Olthoff's liquid bendamustine formulation with PG had no antioxidant, DTX-0094 at JDG_BENDA_00002313; Tr. 1457:5–12, and neither Alam nor Drager used an antioxidant in their exemplary formulations, Tr. 1458:2–58:23. Accordingly, I find that Defendants did not establish by clear and convincing evidence that the combination of Boylan and Rowe would have motivated a POSITA to use an antioxidant.

e. Use of the Claimed Bendamustine Concentrations

Claim 5 of the #831 patent requires a bendamustine concentration of "from about 25 mg/mL to about 50 mg/mL." DTX-0006_0009. Defendants argue that "[t]here was nothing special or unobvious about [that] concentration range" in view of the Treanda® Label and Olthoff. D.I. 378 at 25.

First, Defendants assert that the lyophilized Treanda® Label would have motivated a POSITA to use the claimed concentrations because a POSITA would have multiplied the 120 mg/m^2 dose for NHL patients disclosed in the lyophilized Treanda® Label, DTX-0848_0001, by the average body-surface-area of a human, 2.0 m^2, to get a 240 mg total dosage, D.I. 378 at 25–26. According to Defendants, the POSITA then would have placed that dose in a common vial size of either 5 mL or 10 mL to arrive at a concentration of either 24 or 48 mg/mL. D.I. 378 at 26. Defendants, however, offered no evidence establishing why a POSITA would have

combined a dosage for a lyophilized bendamustine formulation with a particular vial size when making a liquid bendamustine formulation.

Second, Defendants argue that Olthoff would have motivated a POSITA to reach the claimed concentration because "Olthoff disclosed and claimed [PG-only] liquid bendamustine formulations containing 'concentrations of 25 mg/m[L] to 100 mg/m[L],'" D.I. 378 at 25, and Olthoff disclosed that bendamustine's solubility in PG was very high, 125 mg/mL, D.I. 378 at 26. Defendants assert that "[w]hile the prior art did not disclose bendamustine's solubility in PEG, . . . solubility is an inherent (i.e. intrinsic) property" that can be discovered through routine testing, and given the high 125 mg/mL solubility in PG, a POSITA "would understand that by adding PEG to PG, the solubility would drop from 125 to a lower value, and that at ten percent PG and 90 percent PEG, it would be possible to make a solution with a concentration of 25 milligrams per milliliter." D.I. 378 at 26–27.

But as explained above, Defendants have not established a motivation to use PEG and PG in the first place. Thus, even assuming that a POSITA could have found bendamustine's solubility in PEG through routine testing, Defendants did not establish by clear and convincing evidence that a POSITA would have been motivated to conduct such testing. As Plaintiffs note, Defendants' expert "testified only that the POS[IT]A would have considered it 'possible' to dissolve 25 mg/mL bendamustine in 90:10 PEG:PG at room temperature, far short of establishing

motivation" to use PEG. D.I. 371 at 43.

Moreover, Defendants fail to explain why a POSITA would believe that bendamustine would have a lower solubility in PEG and PG as opposed to in PG alone based only on bendamustine's high solubility in PG. In choosing a concentration, a POSITA would have required that the bendamustine concentration remain below the formulation's bendamustine solubility limit so that the bendamustine would completely dissolve and dangerous precipitation would not occur. Tr. 591:19–92:7, 593:23–94:4, 1434:13–35:9, 1435:10–25, 1472:12–14; PTX-0667 at TEVABEND00293319. Because a POSITA would want to avoid such precipitation, it would likely not combine bendamustine with a 90% PEG and 10% PG formulation based on bendamustine's solubility in PG alone.

f. PG Ester Stability Limitations

Finally, certain asserted formulation claims contain a stability limitation, i.e., a maximum amount of degradants called PG esters that the composition can have after storage for a set time period at a set temperature. For example, claims 2, 3, and 5 of the #831 patent recite compositions having "less than or equal to 0.11% PG esters at about 1 month of storage at about 5°C." #831 patent at claims 2, 3, 5.

Defendants argue that the stability limitations are an inherent property because at least one obvious formulation in the asserted claims would naturally result in the required PG ester levels. D.I. 378 at 27. But "[t]o prove that a claim

limitation is inherent in the prior art, [the challenger] must show . . . [not only] that the limitation at issue is necessarily present, or the natural result of the combination of elements," but also that the combination of elements that naturally result in the limitation is "*explicitly disclosed by the prior art.*" *Par Pharm., Inc. v. Twi Pharm., Inc.*, 120 F. Supp. 3d 468, 473 (D. Md.), *aff'd,* 624 F. App'x 756 (Fed. Cir. 2015) (emphasis added) (internal quotation marks omitted); *see also* D.I. 378 at 28 ("*Once an embodiment is shown to be obvious*, any corresponding data can be used to show that the stability property is inherent." (emphasis added)). Because I find that the combination of elements that Defendants allege inherently result in the stability limitations is not obvious, such limitations are not obvious through inherency.

g. Secondary Considerations

The parties adduced at trial evidence of only one secondary consideration that bears on the formulation claims—commercial success. D.I. 371 at 79–80. Plaintiffs argue that "[s]ales of Bendeka® exceed $2 billion," and that "Bendeka® halted the downward trend in bendamustine sales, despite increasing competition." D.I. 371 at 79. But such evidence does not support a finding of nonobviousness. First, Bendeka® sells at a lower price than the prior art lyophilized Treanda® product. Tr. 1641:25–42:3, 1680:2–12, 1798:8–99:2. Second, Plaintiffs' cluster

of exclusivities has blocked others from entering the market.[4] Tr. 1723:24–26:1, 1730:3–7. "Where market entry by others was precluded . . . the inference of nonobviousness of the asserted claims, from evidence of commercial success, is weak." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) (internal quotation marks, alterations, and citations omitted).

* * * *

Although the evidence of commercial success does not support a finding of nonobviousness, I still find that Defendants have not shown by clear and convincing evidence that the prior art they cited would have motivated a POSITA to reach the claimed formulations. As discussed above, a POSITA would have credited Drager over Olthoff, and Drager teaches away from the use of protic solvents such as PG and PEG alone with bendamustine. Moreover, a POSITA would not have relied on Alam in formulating bendamustine. Finally, clear and convincing evidence does not show that a POSITA would have relied on Boylan and Rowe as motivation to use an antioxidant because of the references that teach

[4] Cephalon had an exclusive license from Fujisawa to develop bendamustine in the U.S. DTX-1230_0001, _0002, _0019; Tr. 1226:24–27:1, 1263:21–25, 1233:18–34:25. Also, in 2008, lyophilized Treanda® obtained seven years of orphan drug exclusivity (ODE) and an additional six months of pediatric exclusivity. Tr. 1723:24–26:1. Bendeka® also received ODE. *Eagle Pharm.*, 2018 WL 3838265, at *1. Thus, Bendeka® received seven years of exclusivity that would prevent generics from entering the market until 2022. Tr. 1723:24–26:1.

away from the use of antioxidants in injectable formulations. And the Treanda® Label and Olthoff would not have motivated a POSITA to reach the claimed concentrations.

C. Obviousness of the Asserted Administration Claims

1. Findings of Fact

a. The Priority Date

The parties agree that the priority dates for the asserted administrations claims are (1) March 20, 2012 for claim 22 of the #568 patent, and (2) July 10, 2012 for the remaining administration claims. D.I. 332; Tr. 2015:10-16.

b. Definition of the Relevant POSITA

The parties agree that a POSITA would have had the skills, education, and expertise of a team of individuals working together to develop a safe and effective administration protocol for a cytotoxic parenteral[5] drug product. Such a team would have included individuals with doctoral degrees in pharmaceutics, pharmaceutical sciences, pharmacology, pharmacokinetics, pharmacodynamics, or related fields, with at least two years of post-graduate experience in developing protocols for pharmaceutical administration, or master's or bachelor's degrees in similar fields of study, with a commensurate increase in their years of post-

[5] In the pharmaceutical field, "parenteral" typically refers to products that are administered by injection. Tr. 407:6–8.

graduate experience. Such a team would have been familiar with a variety of issues relevant to administering liquid injectable drug products, including, among other things, toxicity, solubility, pharmacokinetics, and pharmacodynamics. Such a team would have included at least one individual with a medical degree with experience in treating patients with CLL and NHL. PDX-2-4; Tr. 1112:4-20, 1293:22–94:9, 1233:1–17, 2014:22–15:2.

c. Content of the Asserted Administration Claims

The asserted administration claims recite methods of treating CLL or NHL[6] with a liquid bendamustine composition. #568 patent at claims 11, 18, 22; #887 patent at claim 13. Certain claims require administering the bendamustine composition on days one and two of a 21-day cycle for NHL, #568 patent at claim 18, or on days one and two of a 28-day cycle for CLL, #568 patent at claim 11. One claim requires a bendamustine dose of "about 25 mg/m^2 to about 120 mg/m^2." #887 patent at claim 13.

The asserted administration claims also specify administration times, the longest time being "about 15 minutes or less." *See e.g.,* #568 patent at claim 22; #887 patent at claim 13. They also specify administration volumes that are all 100 mL or less. *See e.g.*, #399 patent at claim 13. Finally, certain claims specify post-

[6] Two claims recite, more generally, a "method of treating cancer or malignant disease." #399 patent at claims 13, 15.

dilution bendamustine concentrations ranging from 0.05 mg/mL to 12.5 mg/mL. *See e.g.*, #568 patent at claims 11, 18.

d. Content of the Prior Art

Defendants argue that eight prior art references would have motivated a POSITA to combine the elements of the claimed administration with a reasonable expectation of success: Palepu 2011, the Treanda® Label, Preiss 1985, Preiss 1998, Schöffski 2000a, Schöffski 2000b, Barth, and Glimelius.[7] D.I. 378 at 53.

1) Palepu 2011 (DTX-0984)

Palepu 2011 is the published application that led to the asserted formulation patents. Tr. 546:25–47:17. The parties have stipulated that Palepu 2011 disclosed the formulations claimed in the asserted formulation and administration claims. D.I. 320 ¶ 6.

2) Treanda® Label (DTX-0993 and DTX-1202)

The Treanda® Label, published in April 2009, D.I. 307-1 ¶ 247, disclosed two FDA-approved liquid bendamustine composition dosing schedules: (1) for CLL, intravenous (IV) infusion at a dose of 100 mg/m^2 over 30 minutes on days

[7] Defendants also cite Olthoff to argue that the asserted administration claims were obvious, but the arguments regarding Olthoff were advanced only by Dr. Yates, an admitted non-formulator, and an expert that all Defendants but Apotex rejected. Tr. 918:11–17, 920:19–22:13. Dr. Yates is a professional witness with limited relevant experience who has testified repeatedly for Apotex. Tr. 908:17–13:12. I did not find his testimony credible and do not rely on it.

one and two of a 28-day cycle for up to six cycles, Tr. 648:3–9; DTX-0993_0001; DTX-1202_001; and (2) for NHL, IV infusion at a dose of 120 mg/m^2 over 60 minutes on days one and two of a 21-day cycle for up to eight cycles, DTX-0993_0001; DTX-1202_001; Tr. 648:3–9.

The Treanda® Label required the administration of Treanda® in a volume of 500 mL, Tr. 652:13–16; DTX-1202_002, with a post-dilution bendamustine concentration of 0.2–0.6 mg/mL bendamustine, DTX-0993_0002; DTX-1202_003; Tr. 652:21–23.

3) Preiss 1985 (DTX-0320; DTX-0985)

Preiss 1985 disclosed the results of a pharmacokinetic analysis of bendamustine. DTX-0320_0002; Tr. 658:25–59:2, 1119:18–20. A pharmacokinetic analysis is a preliminary study in which a new drug is administered to a small number of patients to determine the Cmax and area under the curve (AUC). The Cmax is the peak concentration of the drug in the bloodstream; the AUC is the patient's total exposure to the drug. Tr. 659:3–15, 847:8–24, 1114:2–7, 1120:18–25. Pharmacokinetic studies are not designed to assess a drug's safety. Tr. 724:7–12, 1120:8–25.

Preiss 1985 administered bendamustine intravenously for three minutes to seven patients with various cancers. DTX-0320_0002; Tr. 659:23–60:2, 723:16–24:3. Preiss 1985 administered an average total dose of 280 to 375 mg.

Preiss 1985 reported "only rather mild side effects" at those doses. DTX-0320_0006; Tr. 664:6–20, 1123:9–22.

4) Preiss 1998 (DTX-0991)

Preiss 1998 investigated bendamustine's clinical pharmacology and defined bendamustine's maximum tolerated dose (MTD) and dose limiting toxicities (DLT). DTX-0991_0002; Tr. 674:16–25. The MTD of a drug is a tolerable dose without severe or life-threatening toxicities; it differs from a recommended dose for clinical use. Tr. 1126: 9–11. DLTs are severe or life-threatening side effects. Tr. 674:23–75:1, 1126:12–23. Preiss 1998 administered bendamustine to more than 50 patients with various cancers. DTX-0991_002. Preiss 1998 was not designed to evaluate the safety of an infusion protocol. Tr. 730:22–31:1, 731:8–21.

Preiss 1998 administered three-to-ten-minute one-time infusions of bendamustine in doses ranging from 54 to 226 mg/m^2. It also administered three-to-ten-minute infusions on four consecutive days in doses ranging from 20 to 88 mg/m^2. DTX-0987_005. Preiss 1998 concluded that "only mild toxicity occurred even at high doses (> 200mg/m^2 b-hydrochloride per cycle)." DTX-0991_0004; Tr. 676:19–25. Preiss 1998 reported "disorientation" and a "vegetative neurotoxic effect" after the one-time infusions of 175 mg/m^2 and 215 mg/m^2 doses. DTX-991_0004, _0005.

5) Schöffski 2000a (DTX-0987)

Schöffski 2000a administered bendamustine over 30 minutes and compared its results to the three-to-ten-minute infusions disclosed in Preiss 1998. DTX-0987_0002,_0005; Tr. 678:4–14. Schöffski 2000a reported that some side effects from its 30-minute infusions were comparable to those observed with the three-to-ten-minute infusions in Preiss 1998. DTX-0987_0005,_0006; Tr. 678:10–79:5.

6) Schöffski 2000b (DTX-0988)

Schöffski 2000b administered 60 to 80 mg/m^2 of bendamustine in 30 minutes. DTX-0988_0001–03; Tr. 679:20–22. Schöffski 2000b observed side effects that were comparable to those observed in Schöffski 2000a. DTX-0988_0005. Schöffski 2000b's authors did not "observe confusion or other signs of neurotoxicity when giving the drug as a repeated 30-min i.v. infusion." DTX-0988_0005.

7) Barth 2010 (DTX-1004)

Barth suggested administering bendamustine in a solvent volume of 100 to 250 mL. DTX-1004_0005; Tr. 658:12–20, 681:21–83:8. Barth explained that

> [t]he 30-minute short infusion [of bendamustine] that is practiced in Germany can be readily achieved with infusion volumes of 100 to 250 m[L] 0.9% NaCl.
>
> It is unclear why the American prescribing information specifies 500 m[L] 0.9% NaCl or a final concentration of 0.2-0.6 mg/m[L] . . . . A short infusion with such volume is difficult to implement.

DTX-1004_0005; Tr. 682:9–83:2. Barth did not disclose any study or data. DTX-1004_0005; Tr. 1157:22–59:18.

8) Glimelius (DTX-0079)

Glimelius disclosed the administration of 5-Fluorouracil to treat colorectal cancer as an infusion lasting ten to 20 minutes using a 50 to 100 mL mini-bag. DTX-0079_0001, _0002. Mini-bags are small standard size bags. Tr. 554:2–9.

2. Conclusions of Law

Defendants did not establish by clear and convincing evidence that a POSITA would have been motivated to combine the prior art references to arrive at the claimed administrations with a reasonable expectation of success. Although the prior art would have motivated a POSITA to reach the claimed formulation, dose, and dosing schedule, and although Plaintiffs' proffered secondary indicia of nonobviousness were of little or no probative value, I find that the prior art would not have motivated a POSITA to reach the remaining claim limitations, and thus the claims as a whole are not obvious.

a. Formulation, Dose, and Dosing Schedule

The parties agree that Palepu 2011, the published application that led to the asserted formulation patents, disclosed before the priority date the formulations found in the asserted administration claims. D.I. 320 ¶ 6. But Plaintiffs argue that Defendants have not shown that a POSITA would have been motivated to select

Palepu 2011's formulations for the administrations recited in the asserted claims. D.I. 371 at 48. Palepu 2011 itself, however, established a motivation to use its formulations: it touted advantages of its disclosed formulations including "that they have substantially improved long term stability when compared to currently available formulations" and that they "are advantageously ready to use or ready for further dilution" and thus "[r]econstitution of lyophilized powder is not required." DTX-0984_0002 at [0007]; Tr. 889:8–90:3. It is undisputed that a POSITA would have wanted to use a stable and ready-to-use formulation as part of an improved administration method.

A POSITA also would have been motivated to combine Palepu 2011 with the Treanda® Label to come up with the claimed doses and dosing schedule. Palepu 2011 instructed administering its formulations in accordance with the Treanda® dosing schedule. DTX-0984_0004 at [0044]; Tr. 856:8–9. And the Treanda® Label taught similar doses and the same dosing schedules as those in the asserted administration claims. DTX-0993_0001; DTX-1202_0001; Tr. 654:18–21, 695:10–20. The required dose found in the claims is about 25 mg/m^2 to about 120 mg/m^2 and the Treanda® Label requires doses of 100 mg/m^2 or 120 mg/m^2. #887 patent at claim 13; DTX-0993_0001; DTX-1202_0001. Also, the dosing schedule recited in the claims is the same as the Treanda® Label's schedule: (1) for CLL, infusion on days one and two of a 28-day cycle, #568 patent

at claim 18; DTX-0993_0001; DTX-1202_001; Tr. 648:3–9; and (2) for NHL, IV infusion on days one and two of a 21-day cycle, #568 patent at claim 11; DTX-0993_0001; DTX-1202_001; Tr. 648:3–9.

That said, the asserted administration claims require administering each bendamustine dose in faster times, in lower volumes, and at higher post-dilution concentrations than the Treanda® Label requires. The question thus remains whether a POSITA would have been motivated to reach the claimed administration times, volumes, and concentrations.

b. Administration Times, Volumes, and Post-Dilution Concentrations

All asserted claims require administering bendamustine in 15 minutes or less, with some requiring ten minutes or less. All asserted claims also require administering bendamustine in a volume of 100 mL or less, with some claims requiring about 50 mL. Finally, all but one of the asserted administration claims require post-dilution bendamustine concentrations ranging from 0.05 to 12.5 mg/mL.[8]

Defendants argue that the claimed administration times were obvious under the Preiss and Schöffski studies; that the claimed administration volumes are

[8] Claim 13 of the #887 patent, the only claim asserted against Slayback, does not have a concentration limitation. D.I. 362 at 3.

obvious under the Preiss studies, Barth, and Glimelius;[9] and that the claimed post-dilution concentrations are obvious under the Preiss studies and the Treanda® Label. Defendants also contend that Eagle's post-invention statements corroborate Defendants' assertion that the Preiss studies would have motivated a POSITA to use shorter administration times, lower volumes, and higher concentrations.

1) The Preiss Studies

Defendants argue that the Preiss studies support a finding that the claimed administration times, volumes, and concentrations are obvious. First, Defendants argue that a POSITA would have been motivated to administer bendamustine in 15 minutes or less because Preiss 1985 and Preiss 1998 disclosed that administration of bendamustine in three-to-ten minutes was well-tolerated in humans and Schöffski 2000a and 2000b disclosed that the safety results of 30-minute bendamustine administrations were consistent with Preiss's three-to-ten-minute infusions. D.I. 378 at 39–40. Second, Defendants assert that the Preiss studies render the claimed volumes of 100 mL or less obvious because, although the Preiss references did not disclose a volume, a POSITA would have known based on Preiss's three-to-ten-minute time constraint and typical infusion rates that the

[9] Relying on the testimony of Dr. Yates, Defendants also cite Olthoff to argue that the claimed volumes were obvious. D.I. 378 at 43. As noted above, I did not find Dr. Yates's testimony to be credible and will not rely on it. Moreover, Olthoff's example bendamustine formulation did not use PEG and, as explained above, Drager discredited Olthoff's data. DTX-0094_0015; Tr. 923:14–24.

studies infused similar volumes. D.I. 378 at 42. Third, Defendants contend that Preiss rendered the claimed concentrations of 0.05 to 12.5 mg/mL obvious because Preiss 1985 likely used a concentration of 5.6 mg/mL. D.I. 378 at 46.

I find, however, that the Preiss studies would not have motivated a POSITA to reach the claimed administration times, volumes, or concentrations because (1) a POSITA would not have relied on the Preiss studies to determine a safe and effective infusion time, volume, or concentration for bendamustine, (2) subsequent prior art taught away from Preiss's three-to-ten-minute infusions, and (3) Defendants only hypothesize that the Preiss studies used volumes and concentrations similar to those in the claimed administrations.

a) A POSITA would not have relied on the Preiss studies to determine a safe administration.

As an initial matter, Preiss 1985 and Preiss 1988 were not designed to evaluate safety, and thus a POSITA would not have relied on the Preiss studies to determine a safe infusion time, volume, or concentration. Tr. 724:7–12, 730:22–31:1, 731:8–21. Moreover, the Preiss studies did not provide enough data points or information to allow a POSITA to rely on them for safety information. Preiss 1985 tested only seven patients with various cancers, DTX-320_0002; Tr. 723:16–24:3, 1122:20–22; it did not discuss how it collected side effect information, including the number or timing of observations, the side effects being

observed, or a grading system, Tr. 724:14–28:16; and it neither specified which of the seven patients in the study had side effects nor distinguished between IV and oral side effects, Tr. 728:8–20. A POSITA would not have concluded that side effects would not be present in a larger population, Tr. 1121:1–5, let alone the relevant population, Tr. 1122:20–23:8, based on a study that covered only seven patients with various cancers and offered no explanation of how the side effects were studied or which patients experienced the side effects. Preiss 1998 similarly tested patients with various cancers, Tr. 1125:24–26:1, and it did not disclose when the side effects it reported were monitored or how many times side effect information was collected from patients. Thus, a POSITA would not have relied on either Preiss study to determine the safety of a short bendamustine infusion. Tr. 1122:14–19, 1123:9–22.

In addition, the parties agree that the claimed administrations require repeated cycles, D.I. 378 at 38; D.I. 371 at 59, but the Preiss studies did not administer bendamustine in repeated cycles.[10] And according to Defendants' expert, "bendamustine therapy side effects result from . . . the number of cycles given" and "these side effects are typically more severe in subsequent cycles

[10] Defendants cited no reference that administered bendamustine in ten minutes or less in repeated cycles. Tellingly, Defendants' references that did administer bendamustine in repeated cycles all used 30-minute infusions. DTX-0987_0001; DTX-0988_0001; DTX-1004_0002, _0005; DTX-0848; PTX-0268.

because there are cumulative effects on bone marrow." Tr. 736:11–37:20. A POSITA would therefore not have relied on the Preiss studies to determine the safety of a short infusion of bendamustine administered in multiple cycles. Tr. 1133:7–11. Moreover, neither Preiss study administered bendamustine over two consecutive days as the claims require. Tr. 1129:12–20.

The Schöffski articles also would not have motivated a POSITA to rely on the Preiss studies to determine the safety of a short infusion time, lower infusion volume, or higher infusion concentration. Schöffski 2000a reported that it observed *some* side effects like those in Preiss 1998, but did not compare the overall incidence or severity of side effects in the two infusion protocols. DTX_0987_0006,_0007; Tr. 1138:21–39:19. Also, Schöffski 2000b stated that it observed similar side effects to those observed in Schöffski 2000a, not that it observed the same side effects as Preiss. And Schöffski 2000b stated that it did not "observe confusion or other signs of neurotoxicity when giving the drug as a repeated 30-min i.v. infusion," DTX-0988_005, while Preiss 1998 reported "disorientation" and a "vegetative neurotoxic effect," DTX-0991 at JDG_BENDA_00006920–21.

b) Subsequent prior art taught away from the Preiss infusions.

Subsequent prior art also would have dissuaded a POSITA from relying on the Preiss studies. A POSITA would not have stopped with Preiss 1985 and Preiss

1998; instead, it would have also considered later prior art references that used 30 to 60 minute infusions and a 500 mL volume. "Too often the obviousness analysis is framed as an inquiry into whether a person of skill, with two (and only two) references sitting on the table in front of him, would have been motivated to combine . . . the references in a way that renders the claimed invention obvious. The real question is whether that skilled artisan would have plucked [those references] out of the sea of prior art and combined [them]." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1337 (Fed. Cir. 2016).

The Preiss researchers themselves conducted later studies and recommended in subsequent papers an infusion of at least 30 minutes in 500 mL. DTX-0987_0001; DTX-0988_0001; PTX-0268; DTX-0982_0009; Tr. 1145:13–46:7. Preiss 2003—conducted by the same research group as Preiss 1985 and 1998—reported administration over 30 minutes in repeated cycles. PTX-0268; Tr. 1141:21–43:15. Moreover, the Ribomustin Monograph—which set forth the prescription information for the German bendamustine product Ribomustin and was developed by a company that employed scientists involved in the Preiss and Schöffski studies—recommended a 30 to 60 minute infusion in 500 mL because of local toxicity concerns. DTX-0982_009; Tr. 1143:17–44:13, 1144:14–45:5, 1146:8–54:4.

c) Defendants only hypothesize that the Preiss studies used the claimed volumes and concentrations.

Finally, Defendants only hypothesize that the Preiss studies used similar volumes and concentrations as those recited in the asserted claims. With respect to volume, Defendants assert that although the Preiss references did not disclose a volume, "[b]ecause administration time and volume are related," a POSITA would have known based on Preiss's three-to-ten-minute time constraint and typical infusion rates that the studies infused small volumes. D.I. 378 at 42 (citations omitted). With respect to concentration, Defendants contend that "Preiss 1985 administered bendamustine in a dose of 280-375 mg in a bolus, [i.e., a volume that the] evidence showed likely meant 50 or 100 mL," and diluting 280 mg in 50 mL would result in a concentration of 5.6 mg/mL. D.I. 378 at 46. Such speculations about Preiss's infusion rate and volume, however, are only based on "conclusory and unsupported expert testimony" and they do not support a finding of obviousness by clear and convincing evidence. *See TQ Delta, LLC v. CISCO Sys., Inc.*, 942 F.3d 1352, 1361 (Fed. Cir. 2019) ("In cases like *InTouch*, *ActiveVideo*, and *DSS*, we rejected obviousness determinations based on conclusory and unsupported expert testimony.").

Defendants have thus failed to establish by clear and convincing evidence that the Preiss studies support a finding that the claimed infusion times, volumes,

and concentrations were obvious. "Whether a skilled artisan would be motivated to make a combination includes whether he would select particular references in order to combine their elements," *WBIP*, 829 F.3d at 1337, and a POSITA in 2010 would not have selected the Preiss studies to determine a safe and effective infusion for a bendamustine formulation.

2) Barth and Glimelius

Defendants also argue that the administration volumes are obvious under Barth and Glimelius. They note that Barth recommended a 100 to 250 mL bendamustine infusion, D.I. 378 at 43, and that a "POS[IT]A would have known from Glimelius (DTX-0079) that minibags, [standard infusion bag sizes of 50 or 100 mL], were typically used for infusions of 10-20 min," D.I. 378 at 44 (citations omitted).

Barth and Glimelius, however, would not have motivated a POSITA to use the claimed volumes. First, Barth did not disclose any study or data; it only suggested hypothetical smaller volumes. DTX-1004_0005; Tr. 1159:10–18. And Barth's 100 to 250 mL suggestion did not cover the claimed volumes (all claims require 100 mL or less). DTX-1004_0005; Tr. 1159:3–16. Second, Glimelius did not disclose any bendamustine administration, Tr. 841:3–42:22, and the mere availability of a standard IV bag would not have given a POSITA motivation to use a bag that size. IV bags of 50 mL were available before the priority date, but

had never been used to deliver bendamustine. D.I. 371 at 58.

3) The Treanda® Label

Defendants also assert that the Treanda® Label would have motivated a POSITA to use the claimed post-dilution concentrations. They argue that the claimed concentrations are obvious as inherent because diluting the claimed doses disclosed in the Treanda® Label in the claimed volume of liquid necessarily would have resulted in the claimed concentrations of bendamustine, PG, and PEG. D.I. 378 at 44. But because I find that the claimed volumes are not obvious, it does not follow that the claimed concentrations are obvious as inherent. Defendants also state that "on the lower end of the spectrum, the [claimed] concentration falls within the 0.2-0.6 mg/mL concentration of the Treanda® Label." D.I. 378 at 45. But the Treanda® concentrations only cover a small portion of the claimed range of 0.05 to 12.5 mg/mL and thus they do not render the claimed concentrations obvious.

4) Eagle's Post-Invention Statements

Defendants further argue that, through post-invention statements, Plaintiffs admitted that the prior art taught that short infusions in lower volumes were safe and effective. Defendants point to the fact that Eagle relied on the conclusions from the Preiss studies when it told the FDA that its Bendeka® protocol was safe. D.I. 378 at 51.

It is true that, in support of its request for permission to test Bendeka®, Eagle submitted to the FDA a Detailed Review of Literature that relied in part on data from the Preiss and Schöffski references. DTX-1041_0175. The literature review stated: "Thus, the short duration infusion of bendamustine appears to be well tolerated in this study and a dose of 215 milligrams has been reported in the literature as the clinically tolerated dose for bolus administration of bendamustine." DTX-1041_0175. Later, Eagle made similar statements to the FDA when drafting its Investigator's Brochure to support its requested study that required administering the Bendeka® formulation in ten minutes. DTX-1061 at 14.

Eagle's submissions to the FDA, however, also contained non-public, non-prior-art tests and analysis Eagle had conducted to show those short-infusion protocols were safe to test in humans. DTX-1041_0025–26. And I find that Eagle's post-invention discussion of the prior art that is intermingled with its own non-public data that it developed in inventing the claimed administration does not show that a POSITA who did not have Eagle's non-public data would have relied on the Preiss studies. Conclusions drawn from a patentee's "disclosures to the FDA" risk being "distorted by hind-sight bias," especially here where the FDA submission was dated after the priority dates and thus was written "through the lens of what [the inventor] had invented." *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1377 (Fed. Cir. 2019).

In sum, Defendants failed to prove by clear and convincing evidence that a POSITA reading the Preiss and Schöffski studies, Barth, Glimelius, and the Treanda® Label would have found the claimed infusion times, volumes, and concentrations obvious.

c. Secondary Considerations

Plaintiffs offered at trial evidence of four secondary considerations that bear on the administration claims: skepticism, long-felt need, commercial success, and industry praise. I did not, however, find this evidence to be probative indicia of nonobviousness for the following reasons.

1) Skepticism

Plaintiffs argue that "industry participants" were skeptical of the claimed invention. D.I. 371 at 77. But the skepticism they cite was apparently held by a "couple of nurses, a pharmacist[,] and an oncology medical resident," DTX-0959_0001, and investors, D.I. 371 at 78. Such "lack of enthusiasm by a few is not equivalent to skepticism." *BTG Int'l Ltd. v. Amneal Pharm. LLC*, 923 F.3d 1063, 1076 (Fed. Cir. 2019).

Plaintiffs also contend that the FDA declined to allow testing of Eagle's IV push method of administration because of safety concerns. D.I. 371 at 78. But the IV push method is not the claimed invention; the invention is the ten-minute infusion and the FDA told Eagle to proceed with its ten-minute infusion study.

PTX-0746 at EGL-BENDEKA_00146354; Tr. 1691:3–14; *see also* PTX-0747 at EGL-BENDEKA_00146355 ("[Eagle] stated that they have decided not to evaluate the IV push method administration. [Eagle] will use 120 mg/m^2 over 10 minutes in their bridging study.").

2) Long-Felt Need

Plaintiffs also argue that Bendeka®'s shorter infusion addressed a "long-felt need to reduce chair time for chemotherapy, improving patient experience and allowing more patients to be treated." D.I. 371 at 79. The parties offered competing expert testimony on this point. I found credible only Defendant's expert, Dr. Thirman, who testified that Bendeka® does not meaningfully reduce chair time because patients receive IV fluids and other drugs simultaneously with the administration of Bendeka® and the administration of those fluids and other drugs lasts for much longer than 15 minutes. Tr. 188:20–89:9, 189:22–24, 1744:14–51:20, 1745:20–46:6, 1751:3–51:8, 1765:18–66:6, 1779:11–18; DTX-0968_0001. For example, Bendamustine is frequently administered with a drug called Rituxan that has an administration time of four to eight hours. Tr. 190:24–91:6, 191:2–6, 713:14–22, 1746:11–17, 1781:14–22.[11]

[11] Plaintiffs' expert, Dr. Agarwal, was not credible. He testified that, based on his experience in a "community-based cancer center," Tr. 1288:19, there were "always issues with the chair time" in the oncology field and that Bendeka® resolved the chair time need, Tr. 1304:7–05:19. My assessment of his lack of credibility was informed by the logic and credible nature of Dr. Thirman's testimony and also by

Dr. Agarwal's dissembling with respect to his billing practices (which might explain why he favored shorter chair times). Dr. Agarwal initially denied having any idea how his patients are billed for his work: "I mean, I'm not, I'm not the biller and I don't get paid by the amount I bill or anything. . . . My only concern is the patient's safety and that's all I care about. . . . I have no clue honestly about billing, billing procedures." Tr. 1339:15–21. He volunteered that "billing, which is a totally different department, I have no clue how they do it and I don't take a look at it. I don't even know how to look at it." Tr. 1340:15–17. And when asked how billing relates to infusion time, Dr. Agarwal claimed to have "no idea how the billing codes work with the infusion." Tr. 1344:13–17. But when asked by the Court if he was "paid by salary," Dr. Agarwal responded: "So the way it works is, what they [his practice group] wanted is eat what you kill. Basically, if I see more patients, I get paid more. If I work harder, I get more. If I work less, I get paid less." Tr. 1345:7–11. He then continued to explain the billing process in detail:

> So the way it works is, so we have like repeated billing codes for repeated business, which are from level one to level four, and that's very small. You just mark what billing code you want to put. These are being audited by McKesson and auditors, that you are not -- they look at our notes. They decide if the doctor is overbilling or underbilling with the code. We have another code for the new patient.
>
> * * * *
>
> So they have like one to four levels of visit. Depending on how much time I spend with a patient, either from 15 minutes to 30 minutes, I can go from a level one visit to a level four visit and that's what I mark on that. I think it's level one to level five. Level five is a very complex visit where I spend an hour or more with a patient, and most of the visits are about level three or level four, but these patients that are going to see me, I just bill level 3 or 4 and then I submit the payment and that is taken care of by the billing and coding department.

Tr. 1345:19–46:1, 1346:13–23. Also, when Dr. Agarwal was asked if he was "familiar with a term called infusion billing," he responded "Yes." Tr. 1338:2–4.

3) Commercial Success

Plaintiffs further argue that Bendeka®'s commercial success is demonstrated by (1) the fact that "Bendeka® halted the downward trend in bendamustine sales, despite increasing competition," D.I. 371 at 79, and (2) "Teva's choice to license Bendeka® and pay Eagle a portion of the profit for each Bendeka® sale, when it could keep all profits from Treanda®," D.I. 361 ¶ 222. But such evidence does not support a finding of nonobviousness. Plaintiffs have not provided evidence to establish that Bendeka®'s sales and Teva's decision to license Bendeka® were linked to Bendeka®'s patented advantages as opposed to Bendeka®'s exclusivities. *See* D.I. 371 at 80 ("Eagle's patents expire shortly after Teva's pre-existing patents."); Tr. 1725:25–26:2 (stating that with the Bendeka® license, Teva has FDA exclusivity until 2022). Also, the "competition" that Plaintiffs cite consists only of Eagle's Belrapzo®—a drug that shares Bendeka®'s formulation, but lacks the short-infusion protocol. D.I. 361 ¶ 219. Because Eagle benefits from the sales of both Belrapzo® and Bendeka®, it may have an incentive to market Bendeka® over Belrapzo®, Tr. 1652:19–53:2, and thus any evidence that Bendeka® has higher sales has little if any probative value.

4) Praise

Finally, Plaintiffs argue that "Bendeka®'s patented advantages . . . have received industry praise." D.I. 371 at 81. In support of this assertion, they cite (1)

Veteran's Administration (VA) newsletter that highlighted the advantages of Bendeka® as compared to Treanda®, (2) a study that noted attributes of Bendeka® that drive Bendeka®'s usage, and (3) Fresenius Kabi's pre-litigation statement that Bendeka® reduced "[p]atient chair time" and that Bendeka® could "have higher pricing and still retain volume due to the benefits it offers." D.I. 371 at 81; D.I. 361 ¶ 226. Here again, I find such evidence to have at best marginal probative value. As an initial matter, the VA does not even use Bendeka®. Tr. 1777:1–78:16. Second, the study Plaintiffs cite was funded by Teva and provides no connection between the claimed limitations and industry praise. Tr. 1305:25–07:4. Third, Fresenius Kabi's statement merely lists reduced chair time as a fact and does not exhibit any praise related to the asserted claims.

* * * *

In sum, the secondary consideration evidence does not support a finding of nonobviousness. I still find, however, that the asserted administration claims are not obvious. Defendants have not shown by clear and convincing evidence that Palepu 2011, the Treanda® Label, Preiss 1985, Preiss 1998, Schöffski 2000a, Schöffski 2000b, Barth, and Glimelius would have motivated a POSITA to arrive at the claimed administrations with a reasonable expectation of success. A POSITA would not have been motivated to follow Preiss's three-to-ten-minute (and potentially lower volume and higher concentration) infusions because (1) a

POSITA would not have relied on the Preiss studies to determine a safe bendamustine infusion protocol, (2) subsequent prior art taught away from the three-to-ten-minute infusions, and (3) Defendants only guess that Preiss used similar volumes and concentrations to those claimed. Moreover, Barth and Glimelius would not have motivated a POSITA to administer bendamustine at lower volumes because (1) Barth only disclosed hypothetical volumes that did not even include the claimed volumes of 100 mL or less and (2) Glimelius did not involve bendamustine. Finally, the claimed concentrations are not obvious as inherent or under the prior art.

III. INDEFINITENESS

Defendants argue that the asserted formulation claims are invalid because they each require "a stabilizing amount of antioxidant"—a requirement Defendants contend is indefinite. D.I. 371 at 2.

A. Legal Standards for Indefiniteness

"[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014). "Indefiniteness is a matter of claim construction, and the same principles that generally govern claim construction are applicable to determining whether

allegedly indefinite claim language is subject to construction." *Praxair, Inc. v. ATMI, Inc.*, 543 F.3d 1306, 1319 (Fed. Cir. 2008), *abrogated on other grounds by Nautilus*, 572 U.S. at 901 (rejecting Federal Circuit's "insolubly ambiguous" standard for indefiniteness). As in claim construction, in making an indefiniteness determination, the district court may make "any factual findings about extrinsic evidence relevant to the question, such as evidence about knowledge of those skilled in the art." *See BASF Corp. v. Johnson Matthey Inc.*, 875 F.3d 1360, 1365 (Fed. Cir. 2017). "Any fact critical to a holding on indefiniteness . . . must be proven by the challenger by clear and convincing evidence." *Cox Commc'ns, Inc. v. Sprint Commc'n Co. LP*, 838 F.3d 1224, 1228 (Fed. Cir. 2016) (alteration in original)).

B. Discussion

Defendants argue that "the claims recite a 'stabilizing amount' [of antioxidant] with no guidance, functional or otherwise, on what degree of stability is required to obtain some unnamed objective." D.I. 380 at 3. But this argument conflates (1) whether a given antioxidant amount improves bendamustine's stability with (2) the extent to which that given antioxidant amount improves stability. The written description defines a "stabilizing amount of antioxidant" as an amount that "increase[s] or enhance[s] the stability of the bendamustine in the compositions described herein," #831 patent at 3:49–54; Tr. 370:25–71:9. Thus,

the "objective" of the antioxidant amount is not "unnamed" but is instead "to increase or enhance the stability of the bendamustine in the compositions" described in the specification.[12]

Defendants argue that the term is indefinite because "[t]he specification does not explain how to determine whether stability has been 'increased' or 'enhanced.'" D.I. 378 at 3. But as Plaintiffs' expert, Dr. Siepmann, credibly testified, a POSITA would understand that a stabilizing amount of an antioxidant includes any amount that decreases the amount of bendamustine degradation after any time period and at any temperature. Tr. 1485:4–87:10, 1502:8–12. And the patents provide a POSITA with a method for measuring stability: using HPLC to compare the amount of overall bendamustine degradation with and without the antioxidant. Tr. 1485:14–86:11. Example 3 demonstrates that a POSITA would compare the amount of bendamustine remaining in the same formulation, stored under the same conditions, with and without the antioxidant, #831 patent at

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[12] Section 112(b) of Title 35 provides that "[t]he specification shall conclude with one or more claims[.]" This language makes clear that the specification includes the claims asserted in the patent, and the Federal Circuit has so held. *See Markman*, 52 F.3d at 979 ("Claims must be read in view of the specification, of which they are part"). The Federal Circuit and other courts, however, have also used "specification" on occasion to refer to the written description of the patent as distinct from the claims. *See, e.g., id.* ("To ascertain the meaning of claims, we consider three sources: The claims, the specification, and the prosecution history."). To avoid confusion, I refer to the portions of the specification that are not claims as "the written description."

7:59–8:27; and the specifications describe measuring the remaining bendamustine using HPLC, *id.* at 2:26–44, 2:57–3:4, 4:22–26; Tr. 1487:11–89:11. In addition to providing exemplary test methods, the specification also lists "suitable antioxidant amounts" and "antioxidants," and provides examples of "stabilizing" amounts. #831 patent at 3:57–4:8, 7:59–9:2; Tr. 371:15–72:18, 1489:23–90:4.

In *BASF*, the Federal Circuit held the term "composition . . . effective to catalyze" not indefinite, even though the patent did not "recite a minimum level of function needed to meet this 'effective' limitation" or "a particular measurement method," because tests for determining whether a composition was catalyzing were well-known. 875 F.3d at 1366–68. Here, the term "stabilizing amount of antioxidant" is like the term "composition . . . effective to catalyze" and Plaintiffs' expert, like the expert in *BASF*, persuasively testified that a POSITA would know how to determine whether an amount of antioxidant is stabilizing. Moreover, unlike in *BASF*, the asserted patents here provide a test method.

Finally, Defendants cite the patentee's removal of antioxidant and stability limitations during prosecution as support for their indefiniteness argument. D.I. 378 at 5–6. But the removal of those limitations undercuts Defendants' argument because it confirms that the "examiner understood" the claims without those limitations. *See Sonix Tech. Co. v. Publ'ns Int'l, Ltd.*, 844 F.3d 1370, 1379–80 (Fed. Cir. 2017).

I thus find that the term "stabilizing amount of antioxidant" is not indefinite and I construe it as: any amount of an antioxidant that decreases the amount of bendamustine degradation after any time period and at any temperature.

IV. ENABLEMENT

Defendants assert that the asserted formulation claims are invalid for lack of enablement because the formulation patents disclosed neither the use of sodium hydroxide (NaOH) or of "other undisclosed variables." D.I. 378 at 59.

A. Legal Standards for Enablement

"Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation." *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013) (citation omitted). "That some experimentation is necessary does not preclude enablement; the amount of experimentation, however, must not be unduly extensive." *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984) (citations omitted). A challenger must prove invalidity based on non-enablement by clear and convincing evidence. *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012). Enablement is a question of law based on underlying facts. *Abbott Labs.*, 720 F.3d at 1384 (citations omitted).

B. Discussion

Defendants argue that the asserted formulation claims are not enabled because the claims do not contain NaOH and "a pH adjuster like NaOH is necessary to obtain the PG ester levels claimed in the [a]sserted [f]ormulation [c]laims." D.I. 378 at 59. Defendants note that "Eagle's later-filed [#]879 application . . . explains [that] 'the control samples, which did not include NaOH did not provide long term storage stability,' and 'exhibited more than 28% total esters compared to initial after six months of storage at 25° C.'" D.I. 378 at 60 (citation omitted).

Evidence that some claimed formulations did not result in the PG ester limitations, however, does not establish that the claims are not enabled. Defendants have not presented any evidence to show that a POSITA would have had to undertake undue experimentation to alter the formulation to obtain the PG ester limitations. That some formulations with the claimed ingredients do not satisfy the PG ester limitations does not support non-enablement unless the number of such formulations is significant enough to have required a POSITA to experiment unduly. *See Atlas Powder*, 750 F.2d at 1576–77 ("Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. . . . Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to

practice the claimed invention, the claims might indeed be invalid. That, however, has not been shown to be the case here." (citations omitted)). Defendants presented no evidence showing that the number of unsuccessful formulations is significant enough to require undue experimentation. Accordingly, they failed to establish by clear and convincing evidence that the asserted claims are invalid for lack of enablement.

V. WRITTEN DESCRIPTION

Apotex argues that claim 9 of the #797 patent is invalid for lack of written description. D.I. 378 at 60. It asserts that "the absence of any mention of a pH adjuster like NaOH in the [#]797 patent demonstrates that the inventors did not have possession of it at that time, as confirmed by their later filing of another patent application that discloses and claims it." D.I. 378 at 61 (citations omitted). "But written description is about whether the skilled reader of the patent disclosure can recognize that what was claimed corresponds to what was described . . . . " *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1191 (Fed. Cir. 2014). And Apotex never cites the intrinsic record to show that the asserted formulation patents claim something that they do not describe in their written descriptions. Instead, Apotex improperly cites extrinsic evidence—the later-filed Eagle patent application. Apotex has thus failed to establish that claim 9 is invalid for lack of written description.

VI. INFRINGEMENT

Defendants stipulated to infringement of the asserted claims with two exceptions. Apotex, Fresenius Kabi, and Mylan argue that (1) they do not infringe the asserted formulation claims because their ANDA products do not contain "a stabilizing amount of an antioxidant" as the asserted formulation claims require, D.I. 369 at 2; and (2) they do not directly infringe or induce infringement of claim 9 of the #797 patent, which requires that the "bendamustine-containing composition ha[ve] less than or equal to 0.43 % total PG esters at about 3 months of storage at a temperature of about 25°C," because their proposed labeling does not direct physicians to store their ANDA products for about 3 months at about 25°C, D.I. 369 at 4–5.

A. Legal Standards for Infringement

A defendant is liable for patent infringement if it files an ANDA "for a drug claimed in a patent or the use of which is claimed in a patent." 35 U.S.C. § 271(e)(2)(A). To establish infringement based on the filing of an ANDA under § 271(e)(2)(A), a patentee must show that "if the drug were approved based upon the ANDA, the manufacture, use, or sale of that drug would infringe the patent in the conventional sense." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997).

"Conventional" infringement includes direct infringement and inducement.

35 U.S.C. § 271 (a), (b). Direct infringement requires that "every limitation set forth in a claim . . . be found in an accused product, exactly." *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995) (citation omitted). Inducement requires a showing "that the accused inducer took an affirmative act to encourage infringement with the knowledge that the induced acts constitute patent infringement." *Microsoft Corp. v. DataTern, Inc.*, 755 F.3d 899, 904 (Fed. Cir. 2014) (citation omitted). A plaintiff can prevail on a claim of inducement only if it establishes direct infringement. *See Limelight Networks, Inc. v. Akamai Techs., Inc.*, 572 U.S. 915, 921 (2014) ("[I]nducement liability may arise if, but only if, there is direct infringement." (internal quotation marks, alterations, and citation omitted)).

A patentee must prove infringement by a preponderance of the evidence. *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984). "A patentee may prove infringement by any method of analysis that is probative of the fact of infringement, and circumstantial evidence may be sufficient." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009) (internal quotation marks and citations omitted).

B. Direct Infringement of the "Stabilizing Amount of Antioxidant" Limitation

The asserted formulation claims require a "stabilizing amount of an antioxidant," a term that I construed as any amount of an antioxidant that decreases

the amount of bendamustine degradation after any time period and at any temperature.

Defendants' ANDA products each contain 5 mg/mL of the antioxidant monothioglycerol, *see* PTX-0474 at APOLIQBENDA_ANDA_0005427 (Apotex); PTX-0486 at FK_BENDA_00003243, 3245 (Fresenius Kabi); PTX-0007 at MYLBEN_000248 (Mylan); Tr. 372:19–74:13, and the formulation patents' written description shows that 5 mg/mL of monothioglycerol is a stabilizing amount. The written description identifies "5 mg/mL to about 20 mg/mL" as a "preferable" stabilizing amount of antioxidant. #831 patent at 3:49–68; #797 patent at 3:55–66. The written description also identifies "thioglycerol (also known as monothioglycerol)" as a preferred antioxidant. #831 patent at 4:1–8; #797 patent at 4:6–16. Moreover, Example 3 demonstrates that adding "5 mg/m[L] of lipoic acid . . . as a stabilizing antioxidant" to 20 mg/mL of bendamustine in PEG decreased the amount of bendamustine degradation after 15 days at 25°C and 40°C as compared to the same formulation without an antioxidant. #831 patent at 7:59–8:27; #797 patent at 7:61–8:29; Tr. 371:15–72:18. Example 4 recites dissolving 50 mg/mL bendamustine in 90% PEG and 10% PG, and adding "5 mg/m[L] of [mono]thioglycerol, α-lipoic acid or dihydrolipoic acid," an amount that it describes as "a stabilizing amount of an antioxidant." #831 patent at 8:29–65; #797 patent at 8:32–66.

Circumstantial evidence can establish infringement; and here, the asserted formulation patents' disclosures that 5 mg/mL of an antioxidant (and specifically monothioglycerol) is stabilizing shows that the 5 mg/mL of monothioglycerol that Defendants use in their ANDA products decreases the amount of bendamustine degradation as compared to the same formulation without an antioxidant. Finally, Fresenius Kabi and Mylan represented to the FDA that 5 mg/mL monothioglycerol was sufficient to ensure that the amount of bendamustine in their ANDA products did not fall below specification limits. *See* PTX-0054 at FK_BENDA_00000543 (Fresenius Kabi); PTX-0201 at MYL-BEN_005258 (Mylan); Tr. 374:14–77:1.

C. Direct and Induced Infringement of Claim 9 of the #797 Patent

Claim 1 of the #797 patent recites a "method of treating leukemia, Hodgkin's disease, or multiple myeloma" comprising "administering" the specified "liquid bendamustine-containing composition." #797 patent at 12:43–46 (claim 1). Claim 9 recites the method of claim 1, wherein the "bendamustine-containing composition has less than or equal to 0.43% total PG esters at about 3 months of storage at a temperature of about 25° C." #797 patent at claim 9. Defendants stipulate that their ANDA Products have "less than or equal to 0.43% total PG esters at about 3 months of storage at a temperature of about 25° C," but contend that they do not directly infringe or induce infringement of claim 9 because their

proposed labeling does not recommend storing their ANDA Products for "about 3 months" at "a temperature of about 25° C." D.I. 307-4 ¶ I.a; D.I. 320 ¶ 3.

I find, however, that even though Defendants' labeling does not mention storage, Defendants' ANDA products directly and indirectly infringe claim 9 because the PG ester limitation does not require the user to store the products for three months at 25°C. Claim 9's PG ester limitation describes a characteristic of the claimed formula; it is not a method step and thus, does not require action to infringe. The claim does not recite testing for the PG ester limitation; it just describes a composition that would have less than 0.43% PG esters if one were to test for them after storing the composition for three months at 25°C.

Defendants' proposal to construe the PG ester limitation as a method step that requires actual storage under the specified conditions also fails because it "renders [claim 9] nonsensical." *See Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1255 (Fed. Cir. 2010) ("A claim construction that renders asserted claims facially nonsensical cannot be correct." (internal quotation marks and citations omitted)). Although claim 1 of the #797 patent requires the composition to have "less than or equal to 0.11% total PG esters at about 1 month of storage *at a temperature of about 5° C*," claim 9 requires the same composition to have "less than or equal to 0.43% total PG esters at about 3 months of storage *at a temperature of about 25° C*." #797 patent at 12:61–63 (claim 1), 13:22–25

(claim 9). Under Defendants' proposed construction, to infringe, the user would need to store the composition simultaneously at different temperatures, which is impossible.

Defendants therefore directly infringe and induce infringement of claim 9 of the #797 patent. With respect to direct infringement, Defendants agree that their products have less than or equal to 0.43% total PG esters after storing them for three months at a temperature of about 25°C and, other than with respect to a stabilizing amount of an antioxidant, they stipulated to direct infringement of the remaining limitations. D.I. 320 ¶ 3. With respect to induced infringement, Defendants will encourage others to administer their ANDA products through their proposed labels. Although Defendants' proposed labeling does not mention the claimed PG ester limitations, Defendants know "that [their ANDA products] meet all of the claim limitations and, through [their] proposed label[s], encourage[] patients to administer [their ANDA products] in a manner that infringes the claimed method." *Orexigen Therapeutics, Inc. v. Actavis Labs. FL, Inc.*, 282 F. Supp. 3d 793, 816 (D. Del. 2017), *rev'd in part on other grounds sub nom. Nalpropion Pharm., Inc. v. Actavis Labs. FL, Inc.*, 934 F.3d 1334 (Fed. Cir. 2019). "Whether the [user] who performs the method by administering the [products] knows that the [products] meet the [PG ester limitations] is irrelevant for the purposes of infringement." *Id.*

VII. CONCLUSION

For the foregoing reasons, I find that all asserted claims of the asserted patents are not invalid and that Defendants infringe and induce infringement of each of the asserted claims.

The parties will be directed to submit a proposed order by which the Court may enter final judgment consistent with this Opinion.

IW 7647896

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

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United States Patent and Trademark Office

August 31, 2017

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *15/008,827*
FILING DATE: *January 28, 2016*
PATENT NUMBER: *9,597,399*
ISSUE DATE: *March 21, 2017*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

W. MONTGOMERY
Certifying Officer

DEFENDANTS' TRIAL EXHIBIT
DTX-0013
Case No 17-cv-1154


US009597399B2

(12) **United States Patent**
Sundaram

(10) **Patent No.: US 9,597,399 B2**
(45) **Date of Patent: *Mar. 21, 2017**

(54) **FORMULATIONS OF BENDAMUSTINE**

(71) Applicant: **Eagle Pharmaceuticals, Inc.**, Woodcliff Lake, NJ (US)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/008,827**

(22) Filed: **Jan. 28, 2016**

(65) **Prior Publication Data**

US 2016/0144035 A1 May 26, 2016

Related U.S. Application Data

(63) Continuation of application No. 14/857,064, filed on Sep. 17, 2015, which is a continuation of application No. 14/714,578, filed on May 18, 2015, now Pat. No. 9,144,568, which is a continuation of application No. 13/838,090, filed on Mar. 15, 2013, now Pat. No. 9,034,908.

(60) Provisional application No. 61/613,173, filed on Mar. 20, 2012, provisional application No. 61/669,889, filed on Jul. 10, 2012.

(51) **Int. Cl.**

A61K 31/4184	(2006.01)
A61K 47/10	(2006.01)
A61K 9/00	(2006.01)
A61K 47/20	(2006.01)
A61K 47/02	(2006.01)
A61K 47/22	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 47/10*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 31/4184*** (2013.01); ***A61K 47/02*** (2013.01); ***A61K 47/20*** (2013.01); ***A61K 47/22*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Methods of treatment using bendamustine formulations designed for small volume intravenous administration are disclosed. The methods conveniently allow shorter administration time without the active ingredient coming out of solution as compared to presently available formulations.

17 Claims, No Drawings

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FORMULATIONS OF BENDAMUSTINE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 14/857,064, filed Sep. 17, 2015, which is a continuation of U.S. application Ser. No. 14/714,578, filed May 18, 2015, now U.S. Pat. No. 9,144,568, issued Sep. 29, 2015 which is a continuation of U.S. application Ser. No. 13/838,090, filed Mar. 15, 2013, now U.S. Pat. No. 9,034,908, issued May 19, 2015, which in turn claims the benefit of priority from U.S. Provisional Patent Application Ser. No. 61/613,173, filed Mar. 20, 2012, and 61/669,889, filed Jul. 10, 2012, the disclosure of each of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

Bendamustine is used in the treatment of a number of cancers including leukemias, Hodgkin's disease and multiple myelomas. Bendamustine (present as the HCl salt) is the active ingredient of the commercial product Treanda™, a lyophilized powder for reconstitution. Current labeling requirements call for the reconstituted product to be immediately (within 30 minutes) diluted into 500 mL of parenterally acceptable diluents such as 0.9% saline (normal saline) or 2.5% dextrose/0.45% saline and administered as part of an intravenous infusion delivering 100 mg/m^2 over 30 minutes or 120 mg/m^2 over 60 minutes. The diluted admixture may be stored at 2-8° C. for up to 24 hours, or 3 hours at room temperature (15-30° C.); administration must be completed within this period due to limited chemical stability in aqueous solutions.

Solubility limitations at 2-8° C. with currently approved and/or available formulations are believed to prevent current formulations from being administered in smaller more concentrated infusion volumes up to about 150 ml; at volumes below 150 ml, solubility is not sufficient even at 25° C. Side effects associated with extravasation and local erythema, swelling and pain at the injection site also dictate that the infusion be as dilute as possible. Therefore, precautions are taken to avoid extravasation, including monitoring of the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of bendamustine. Higher infusion volume and longer infusion times, however, are associated with many drawbacks. For example, after reconstitution, the current product has a short period of stability, degradation of the drug occurs from the time of reconstitution until the entire large volume infusion has been completely administered. The current label for Treanda™ therefore instructs that the admixture should be prepared as close as possible to the time of patient administration, and that administration of Treanda™ must be completed within the durations indicated above. From patient comfort and nursing administration points of view, higher infusion volumes and long infusion times are undesirable. Higher infusion volumes may be associated with higher likelihood of weight gain and edema. Shorter infusion times and smaller infusion volumes result in a better quality of life experience for the patient by reducing the overall "stress" to the patient and reducing the time spent in the infusion clinic. Shorter infusion times (and smaller volumes) also reduce the potential extravasation (and shorten the patient monitoring time required). It would be advantageous if the drug could be administered in smaller volumes and over shorter times. The present invention addresses these needs.

SUMMARY OF THE INVENTION

In a first aspect of the invention there are provided methods of treating or preventing cancer or malignant disease in a subject such as a human. The methods include parenterally administering a volume of about 325 ml or less of a liquid composition containing:

a) from about 0.05 to about 12.5 mg/ml of bendamustine or a pharmaceutically acceptable salt thereof;

b) a solubilizer comprising polyethylene glycol and propylene glycol; and optionally

c) a parenterally acceptable diluent;

over a substantially continuous period of less than or equal to about 30 minutes to a subject in need thereof.

In alternative aspects of the invention there are provided methods of treating or preventing a bendamustine-responsive condition in a subject such as a human. In a first embodiment the methods include administering less than or equal to 325 ml of a liquid composition which contains

Ingredient	Concentration Range (mg/ml)
Bendamustine HCl	0.05 to 1.6
Solubilizer 1 propylene glycol	0.30 to 6.5
Solubilizer 2 PEG 400	3.3 to 65
Monothioglycerol	0.02 to 0.35
NaOH	0.0 to 0.01

over a substantially continuous period of less than or equal to about 30 minutes to a subject in need thereof.

In a related second embodiment of this aspect of the invention, the methods include administering less than or equal to 325 ml of a liquid composition which contains

Ingredient	Concentration Range (mg/ml)
Bendamustine HCl	1.1 to 12.5
Solubilizer 1 propylene glycol	4.5 to 51
Solubilizer 2 PEG 400	45 to 500
Monothioglycerol	0.2 to 2.5
NaOH	0.0 to 0.04

over a substantially continuous period of less than or equal to about 30 minutes to a subject in need thereof.

The methods of the present invention take advantage of the fact that the concentration of the bendamustine HCl is below the room temperature solubility limit of the vehicle into which it is placed. As a result, the bendamustine does not precipitate during administration to the patient thereby substantially avoiding the side effects which would otherwise occur during small volume administration of therapeutic doses of the drug. In addition, patients or subjects with bendamustine-responsive conditions can be treated using substantially smaller parenteral volumes which are well below the standard 500 ml administration volume.

DETAILED DESCRIPTION OF THE INVENTION

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this

invention belongs. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

In a first aspect of the invention there are provided methods of treating or preventing cancer or malignant disease in a subject or patient who is preferably a human. The methods generally include parenterally administering a volume of about 325 ml or less of a liquid composition containing:

a) from about 0.05 to about 12.5 mg/ml of bendamustine HCl or a pharmaceutically acceptable salt thereof, the HCl salt being preferred;

b) a solubilizer comprising polyethylene glycol and propylene glycol; and optionally

c) a parenterally acceptable diluent;

over a substantially continuous period of less than or equal to about 30 minutes to a subject in need thereof.

The solubilizer portion of the formulation preferably includes from about 0.3 to about 45% volume polyethylene glycol (PEG) and from about 0.03 to about 5% volume propylene glycol (PG), as calculated on the basis of the total or final volume administered. Stated alternatively, the final concentration of the PEG generally ranges from about 3 to about 500 mg/ml, while the final concentration of the PG generally ranges from about 0.5 to about 51 mg/ml. Within these general ranges, certain aspects of the invention include concentration ranges for the PEG of from about 45 to about 500 mg/ml or from about 3.3 to about 63.3 mg/ml; and for the PG ranges of from about 4.7 to about 50.6; or from about 0.02 to about 6.5 mg/ml.

In some aspects of the invention, the bendamustine is administered intravenously as part of an intravenous infusion. Contemplated infusion volumes are preferably less than 325 ml with volumes such as about 250 ml, 100 ml, and 50 ml, with each volume varying about +/−10% or +/−15% being preferred in some embodiments. In alternative aspects of the invention, the intravenous administration volume is suitable for IV bolus administration and may also include an amount of pharmaceutically acceptable diluent such as normal saline or one of the other diluents described herein which does not cause the solubility of the vehicle to fall below the concentration of the bendamustine. Stated alternatively, the final concentration of the bendamustine will be below the solubility of the combination vehicle containing the mixture of propylene glycol and PEG and diluent. While most aspects of the invention are described in the context of administering less than about 325 ml including all vehicle ingredients, excipients, etc., it should be appreciated that volumes as low as a few milliliters, e.g. about 2, can be used so long as the vehicle includes sufficient solubilizers to preserve the solubility of the bendamustine therein during administration to the patient.

For purposes of the present invention, the word "about" when used to modify infusion volumes or concentrations shall be understood to include values which may vary by amounts of about +/−10% or 15%. In certain embodiments where the infusion volume is about 50 ml, the concentration of the bendamustine HCl or other pharmaceutically acceptable salt thereof is preferably from about 0.5 to about 5.6 mg/ml. In embodiments where the infusion volume is about 100 ml, the concentration of the bendamustine HCl or other pharmaceutically acceptable salt thereof can be preferably from about 0.1 to about 3.2 mg/ml. Similarly, in some aspects of the invention where the infusion volume is about 250 ml, the concentration of the bendamustine HCl or other pharmaceutically acceptable salt thereof is from about 0.05 to about 1.4 mg/ml.

The solubilizer is preferably a mixture of polyethylene glycol, hereinafter "PEG" and propylene glycol, hereinafter "PG". The solubilizer can also optionally include an antioxidant such as monothioglycerol. The amount of antioxidant included is a formulation stabilizing amount, which, in the case of monothioglycerol ranges from about 2 to about 10 mg/ml. The PEG preferably has a molecular weight of about 400, i.e. PEG 400. Other molecular weight PEG's known to those of ordinary skill can be included if desired in alternative embodiments.

Certain aspects of the invention call for the ratio of the PEG to PG found in the solubilizer to be about 90:10. In alternative aspects, the ratio of the PEG to PG is about 85:15.

In some aspects of the invention, the total amount of solubilizer, i.e. blend of PEG and PG, included in infusion volumes of about 100-115 ml is from about 0.5 to about 26.5% vol.; while amounts of from about 0.2 to about 5% vol. for the solubilizer are preferably included in infusion volumes of about 250-265 ml; with solubilizer amounts of from about 2.0 to about 22.4% vol. included in infusion volumes of about 50-65 ml.

Since the solubilizer is a blend, the amount of PEG and PG in various volumes (calculated as % vol.) can be as follows:

Solubilizer	50 ml	100 ml	250 ml
PEG	20.12	11.33	4.9
PG	2.24	1.26	0.54

In some preferred embodiments, the methods of the invention are advantageously carried out using bendamustine HCl containing compositions administered as small volume infusions with volumes of about 50 ml or about 100 ml or about 250 ml. Such smaller volumes allow the drug to be administered over a time period of about 10 minutes or less as part of an intravenous infusions containing a volume of about 50 ml; about 15 minutes or less as part of an intravenous infusions containing a volume of about 100 ml or when volumes of about 250 ml are infused, the IV infusion is administered over a time period of about 30 minutes or less. Depending upon the amount of drug administered, the IV bolus volumes containing sufficient amount of the drug will be less than 50 ml, with amounts of about 10 or 15 to 30 ml being sufficient.

The infusible compositions in many aspects of the invention will also preferably include the parenterally acceptable diluents such as water for injection (WFI), 0.9% saline (normal saline, preferred), 0.45% saline (half normal saline) or 2.5% dextrose/0.45% saline. Formulations well suited for carrying out the methods described herein are also described in commonly assigned U.S. patent application Ser. No. 13/016,473, filed Jan. 28, 2011, and Ser. No. 13/767,672 filed Feb. 14, 2013, the contents of which are incorporated herein by reference. As reviewed in the '672 patent application, some preferred bendamustine formulations can also include a minor amount of a pH adjuster such as sodium formate, sodium phosphate, potassium hydroxide, phosphoric acid or, preferably, sodium hydroxide.

In an alternative embodiment of the invention, the bendamustine formulations used in the methods described herein can be one or more of those described in U.S. Pat. Nos. 8,344,006 and 8,076,366; and US Patent Application Nos. 2013/0041004; 2012/0071532; 2010/0216858; 2006/0159713; and 2013/0041003, the contents of each of which

are incorporated herein by reference. It being understood that the vehicle into which the bendamustine HCl is placed will have sufficient bendamustine solubility which exceeds the concentration of the drug included therein.

If desired, a sufficient amount of a concentrated, ready to use liquid formulation such one containing 25 mg/ml bendamustine HCl and already admixed with sufficient solubilizers can be transferred to a suitable fixed volume diluent container such as a bag containing 50, 100, 250 ml normal saline or the like. Alternatively, lyophilized bendamustine HCl can be reconstituted, combined with sufficient solubilizer blends as described herein and administered in accordance with the inventive methods. In such embodiments, the actual amount delivered to the patient will be slightly more than the diluent amount so as to allow for the addition of the drug/solubilizer vehicle.

In some aspects of the invention, there are provided methods of treating or preventing chronic lymphocytic leukemia (CLL). The small volume infusions can be given as part of any treatment protocol for which bendamustine is included. Thus, the compositions described herein can be administered as part of a poly-pharmaceutical treatment regimen according to known protocols with the exception that the concentrated bendamustine compositions described herein are administered in smaller infusion volumes over significantly shorter administration periods. For example, some CLL treatment regimens can include administering the compositions described herein intravenously as part of about 100 ml infusions in about 20 minutes or less and more preferably in about 15 minutes or less on days 1 and 2 of a 28 day cycle and repeating the cycle up to 6 times or longer if clinically appropriate. If 250 ml volumes are used to deliver the bendamustine, the time of administration is preferably about 30 minutes or less. If 50 ml volumes are used to deliver the bendamustine, the time of administration is preferably about 10 minutes or less.

In spite of the smaller volumes, the amount of bendamustine HCl administered to the patient in need thereof per dose (infusion or otherwise) in some preferred embodiments is about 100 mg/m^2. In some alternative aspects of the invention, the amount of bendamustine HCl administered to the patient in need thereof as part of the 50, 100 or 250 ml infusion is an amount sufficient to provide a dosage of 50 or 25 mg/m^2. Additional administration dosages will be apparent to those of ordinary skill based upon clinical experience, patient need without undue experimentation.

In other aspects of the invention, there are methods of treating or preventing the malignant disease of indolent B-cell non-Hodgkin's lymphoma. In these aspects, the composition is administered intravenously as a 100 ml infusion in less than 20 minutes and more preferably in about 15 minutes or less on days 1 and 2 of a 21 day cycle for up to 8 cycles or longer if clinically appropriate. If 250 ml volumes are used to deliver the bendamustine, the time of administration is preferably about 30 minutes or less. If 50 ml volumes are used to deliver the bendamustine, the time of administration is preferably about 10 minutes or less. The amount of bendamustine administered to the subject is preferably about 120 mg/m^2, although in alternative embodiments, the amount administered ranges from about 90 or 60 mg/m^2. As will be appreciated, further alternative dosage amounts will be apparent to those of ordinary skill based upon clinical experience, patient need without undue experimentation.

It will be appreciated by those skilled in the art that the above-mentioned dosages calculated in mg/m^2 for purposes of body surface area (BSA) are consistent with the bendamustine HCl concentrations also described herein, e.g. 0.5 to 5.6 mg/ml. In the alternative, the invention also contemplates IV bolus administration of bendamustine-containing formulations in volumes which can be administered via syringe, e.g. from a few milliliters up to about 50 milliliters, with therapeutic amounts of the drug in a concentration which does not exceed the vehicle solubility for the drug therein.

Further embodiments of the invention include methods of treating or preventing a bendamustine-responsive condition in a subject such as a human. In a first embodiment, the methods include administering less than or equal to 325 ml of a liquid composition which contains

Ingredient	Concentration Range (mg/ml)
Bendamustine HCl	0.05 to 1.6
Solubilizer 1 propylene glycol	0.30 to 6.5
Solubilizer 2 PEG 400	3.3 to 65
Monothioglycerol	0.02 to 0.35
NaOH	0.0 to 0.01

over a substantially continuous period of less than or equal to about 30 minutes to a subject in need thereof. More preferably, the administration time is well below 30 minutes and the administration time will decrease as the volume administered decreases.

Bendamustine formulations containing the above ingredients are capable of delivering approximately 25 mg of the drug as the HCl salt in volumes of pharmaceutically acceptable diluent ranging from about 325 ml down to about 15 ml. For example, 1 ml of a bendamustine HCl ready to use liquid available from Eagle Pharmaceuticals containing

Ingredient	Concentration (mg/ml)
Bendamustine HCl	25
PG	103.2
PEG 400	1013.4
Monothioglycerol	5
NaOH	0.08

is combined with 300 ml of a normal saline diluent to provide a final IV infusion containing 301 ml and a bendamustine final concentration of 0.08 mg/ml.

One ml of the 25 mg/ml Eagle bendamustine HCl is diluted into additional diluent volumes as shown below:

Diluent Volume (ml)	Final Volume (ml)	Final Bendamustine Conc. (mg/ml)
200	201	0.12
100	101	0.25
50	51	0.49
30	31	0.81
15	16	1.56

The measured solubility of the bendamustine HCl in the diluent/solubilizer combination (50 ml diluent plus 1 ml of 25 mg/ml bendamustine HCl and solubilizers, etc.) at room temperature was 10.5 mg/ml using normal saline and 14.2 mg/ml using half normal saline/dextrose. The solubility of the diluent/solubilizer combination far exceeded the bendamustine concentration, thus assuring the avoidance of precipitated drug prior to or during administration. As will be appreciated by those of ordinary skill, as the concentration

of solubilizers increases with respect to the total volume in small administration doses, the solubility of the bendamustine is maintained.

In a related second embodiment of this aspect of the invention, the methods include administering less than or equal to 325 ml of a liquid composition which contains

Ingredient	Concentration Range (mg/ml)
Bendamustine HCl	1.1 to 12.5
Solubilizer 1 propylene glycol	4.5 to 51
Solubilizer 2 PEG 400	45 to 500
Monothioglycerol	0.2 to 2.5
NaOH	0.0 to 0.04

over a substantially continuous period of less than or equal to about 30 minutes to a subject in need thereof. As was the case above, the administration time will decrease with the decrease in volume administered.

Bendamustine formulations containing the above ingredients are capable of delivering approximately 360 mg of the drug as the HCl salt in volumes of pharmaceutically acceptable diluent ranging from about 325 ml down to about 15 ml. As was the case above, the measured solubility of the bendamustine HCl in the diluent/solubilizer combination (1 ml drug+solubilizers, etc. and 50 ml diluent) at room temperature was 10.5 mg/ml using normal saline and 14.2 mg/ml using half normal saline/dextrose.

Instead of using only 1 ml of the above described Eagle 25 mg/ml bendamustine HCl ready to use liquid, 14.4 ml is combined with various amounts of diluent.

Diluent Volume (ml)	Final Volume (ml)	Final Bendamustine Conc. (mg/ml)
300	314.4	1.15
200	214.4	1.68
100	114.4	3.15
50	64.4	5.59
30	44.4	8.11
15	29.4	12.24

In each case, the solubility of the diluent/solubilizer combination exceeds the bendamustine concentration, thus assuring the avoidance of precipitated drug prior to or during administration.

EXAMPLES

The following examples serve to provide further appreciation of the invention but are not meant in any way to restrict the effective scope of the invention.

Example 1

The solubility of bendamustine HCl, obtained from two different sources, in 0.9% saline and 0.9% saline containing from different amounts of a non-aqueous solubilizer comprising a mixture of polyethylene glycol 400 and propylene glycol (in the volume proportion of 90:10) with and without 5 mg/ml monothioglycerol was determined at both room temperature (22-23° C.) and at refrigerated temperature (5° C.). Essentially, an excess of bendamustine HCl was added to solvents comprising of various volume percent of the non-aqueous solubilizer in 0.9% saline, and allowed to equilibrate with shaking for 30 minutes at room temperature, or for 24 hours at refrigerated temperature. At the end of the equilibration step, the suspensions were filtered through a 0.2 micron filter to remove undissolved bendamustine, and the filtrate solutions analyzed for bendamustine HCl content using a HPLC assay; quantification was performed against a bendamustine HCl reference standard. The solubility data are presented in Table 1.

TABLE 1

Solubility of bendamustine HCl in 0.9% saline with various amounts of non-aqueous solubilizer (90:10 PEG400:PG with and without 5 mg/mL monothioglycerol (MTG))

	Volume % of Normal Saline	Volume % of Non-aqueous Solubilizer	Solubility of bendamustine HCl (mg/mL) in 90:10 PEG 400/PG Room temperature API Source A	API Source B* B	5° C. API Source A
Dilution Fold					
n/a	100.0	0.0	3.461	3.304	1.175
40	97.5	2.5	3.987	3.889	nd
20	95.0	5.0	4.429	4.204	2.022
13.3	92.5	7.5	nd	4.742	nd
10	90.0	10.0	5.626	5.351	2.431
8	87.5	12.5	nd	5.825	nd
6.7	85.0	15.0	7.012	6.554	2.900
5.7	82.5	17.5	nd	7.641	3.328
5	80.0	20.0	8.642	8.492	3.824
3.3	70.0	30.0	12.006	11.407	nd

*solvent also contained 5 mg/ml monothioglycerol
nd = not determined;
API = active pharmaceutical ingredient

Example 2

Bendamustine-containing compositions are prepared by adding 5 mg/ml of thioglycerol to a mixture containing 90% polyethylene glycol 400 and 10% propylene glycol. As indicated in the Table 2 below, NaOH may be added to the PEG in an amount sufficient to get apparent pH of greater than or equal to 6.5 as measured using the pH method outlined in the USP monograph for polyethylene glycol (PEG). Bendamustine (BDM) is then added to the sample to a concentration of 10 mg/ml.

TABLE 2

Formulation
BDM - 10 mg/mL Thioglycerol - 5 mg/mL PEG 400:PG (90:10) qs to 1 mL
BDM - 10 mg/mL Thioglycerol - 5 mg/mL PEG 400:PG (90:10) qs to 1 mL (PEG 400 Treated with NaOH)

The compositions are then admixed with normal saline based on the total dose of bendamustine HCl, which in turn is based on the patient body surface area (BSA) and the dosing regimen (100 mg/m^2 for CLL and 120 mg/m^2 for NLL; although dose modifications of 90, 60, 50, and 25 mg/m^2 are possible, only the highest two dosing regimens are considered for illustrative purposes, as these result in the highest concentration of bendamustine during infusion). The 100 ml infusion is then made by admixing the dose appropriate volume of the 10 mg/ml solution with a 100 ml portion of normal saline to provide an infusible composition

containing the appropriate dose of bendamustine (as the HCl salt) in the final admixture, which can be administered intravenously over about 15 minutes to a patient in need thereof.

As seen in Table 3, the concentrations of bendamustine (as HCl salt) and the corresponding volume percent of non-aqueous component are well below the corresponding solubilities at both room temperature and refrigerated temperature as detailed in Table 1. For example, for a 2.0 m^2 (average) patient dosed at 120 mg/m2, the final concentration of bendamustine HCl in a 100 ml admixture is 1.94 mg/mL. This is above the solubility of bendamustine HCl at refrigerated storage conditions in the absence of any non-aqueous components (1.175 mg/ml as shown in Table 1 for 100% normal saline), as would be the case with the currently approved Treanda™ product, thereby precluding preparation and storage of a 100 ml admixture volume at refrigerated conditions. However, the use of the non-aqueous bendamustine formulation described in this example results in the presence of 19.4% of the non-aqueous component in the final admixture, which improves the solubility to about 3.8 mg/mL (solubility of 3.824 mg/mL at 2-8° C. with 20% non-aqueous component, as shown in Table 1). Therefore, the solubility with the non-aqueous formulation is well above the final concentration (of bendamustine HCl) of 1.94 mg/mL, allowing preparation and storage of the 100 ml admixture at refrigerated conditions. In this example, the room temperature solubilities in 100% normal saline and 80% normal saline (with 20% non-aqueous component) are about 3.3 mg/ml and 8.5 mg/ml, respectively (see Table 1), which are also well above the final concentration of 1.94 mg/ml. Therefore, 100 ml admixtures of the non-aqueous formulation described in the example may also be prepared and stored at room temperature. In addition, the non-aqueous formulation of bendamustine described in this example at Table 2 may be diluted into smaller infusion volumes ranging from 250 ml or less, and stored at either room temperature or refrigerated temperature, with bendamustine continuing to remain in solution for extended periods of time as compared to currently available formulations.

TABLE 3

Concentrations of bendamustine (BDM, as HCl salt) and corresponding volume % of non-aqueous (NA) component in the final admixture, for volumes ranging from 100 ml to 250 ml For 10 mg/mL Formulation

	Admix. Volume 250 mL				Admix. Volume 200 mL			
	100 mg/m² dose		120 mg/m² dose		100 mg/m² dose		120 mg/m² dose	
BSA (m^2)	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.
1.00	0.38	3.8	0.46	4.6	0.48	4.8	0.57	5.7
1.25	0.48	4.8	0.57	5.7	0.59	5.9	0.70	7.0
1.50	0.57	5.7	0.67	6.7	0.70	7.0	0.83	8.3
1.75	0.65	6.5	0.77	7.7	0.80	8.0	0.95	9.5
2.00	0.74	7.4	0.88	8.8	0.91	9.1	1.07	10.7
2.25	0.83	8.3	0.97	9.7	1.01	10.1	1.19	11.9
2.50	0.91	9.1	1.07	10.7	1.11	11.1	1.30	13.0
2.75	0.99	9.9	1.17	11.7	1.21	12.1	1.42	14.2
3.00	1.07	10.7	1.26	12.6	1.30	13.0	1.53	15.3
1.00	0.63	6.3	0.74	7.4	0.91	9.1	1.07	10.7
1.25	0.77	7.7	0.91	9.1	1.11	11.1	1.30	13.0
1.50	0.91	9.1	1.07	10.7	1.30	13.0	1.53	15.3
1.75	1.04	10.4	1.23	12.3	1.49	14.9	1.74	17.4
2.00	1.18	11.8	1.38	13.8	1.67	16.7	1.94	19.4
2.25	1.30	13.0	1.53	15.3	1.84	18.4	2.13	21.3

TABLE 3-continued

Concentrations of bendamustine (BDM, as HCl salt) and corresponding volume % of non-aqueous (NA) component in the final admixture, for volumes ranging from 100 ml to 250 ml For 10 mg/mL Formulation

	Admix. Volume 250 mL				Admix. Volume 200 mL			
	100 mg/m² dose		120 mg/m² dose		100 mg/m² dose		120 mg/m² dose	
BSA (m^2)	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.
2.50	1.43	14.3	1.67	16.7	2.00	20.0	2.31	23.1
2.75	1.55	15.5	1.80	18.0	2.16	21.6	2.48	24.8
3.00	1.67	16.7	1.94	19.4	2.31	23.1	2.65	26.5

Example 3

The procedures of Example 2 are repeated except that the dose appropriate volume of the 10 mg/ml bendamustine solution is diluted into 250 ml of normal saline. The final concentration of bendamustine in the 250 ml volume container ranges from about 0.05 mg/ml to about 1.3 mg/ml.

Example 4

The approximately 100 ml bendamustine HCl infusion of Example 2 is administered to a patient in about 15 minutes.

Example 5

Bendamustine-containing compositions may be prepared by adding 5 mg/ml of thioglycerol to 90% polyethylene glycol 400 and 10% propylene glycol. As indicated in the Table 4 below, NaOH may be added in an amount sufficient to get apparent pH of greater than or equal to 6.5 as measured using the pH method outlined in the USP monograph for polyethylene glycol (PEG). Bendamustine is then added to the sample to a concentration of 25 mg/ml as indicated in Table 4 below.

TABLE 4

Formulation
BDM - 25 mg/mL Thioglycerol - 5 mg/mL PEG 400:PG (90:10) qs to 1 mL BDM - 25 mg/mL Thioglycerol - 5 mg/mL PEG 400:PG (90:10) qs to 1 mL (PEG 400 Treated with NaOH)

The compositions are then admixed with normal saline based on the total dose of bendamustine HCl, which in turn is based on the patient body surface area (BSA) and the dosing regimen (100 mg/m^2 for CLL and 120 mg/m2 for NLL; although dose modifications of 90, 60, 50, and 25 mg/m^2 are possible, only the highest two dosing regimens are considered for illustrative purposes, as these result in the highest concentration of bendamustine during infusion). Table 5 below provides the final concentration of bendamustine (as the HCl salt) in the final admixture, for volumes ranging from 250 ml to 50 ml.

As seen in Table 5, the concentrations of bendamustine (as HCl salt) and the corresponding volume percent of non-aqueous component are well below the corresponding solubilities at room temperature as detailed in Table 1, for all admixture volumes up to 50 ml. For example, for a 2.0 m^2 (average) patient dosed at 120 mg/m^2, the final concentration of bendamustine HCl in a 50 ml admixture is 4.03 mg/ml. This is above the solubility of bendamustine HCl at both refrigerated and room temperature conditions in the absence of any non-aqueous components (1.175 mg/ml at 2-8° C. and 3.304-3.461 mg/ml at room temperature, as shown in Table 1 for 100% normal saline), as would be the case with the currently approved Treanda product, thereby precluding preparation and storage of a 50 ml admixture volume. However, the use of the non-aqueous bendamustine formulation described in this example results in the presence of 16.1% of the non-aqueous component in the final admixture, which improves the room temperature solubility to about 6.5 mg/ml (solubility of 6.554 mg/ml and 7.012 mg/ml with 15% non-aqueous component, as shown in Table 1). Therefore, the solubility with the non-aqueous formulation is well above the final concentration (of bendamustine HCl) of 4.03 mg/mL, allowing preparation and storage of the 100 ml admixture at room temperature conditions. Therefore, the

non-aqueous formulation of bendamustine described in this example may be diluted into smaller infusion volumes ranging from 250 ml or less, with bendamustine continuing to remain in solution if maintained at room temperature. However, at refrigerated temperatures, the concentrations of bendamustine (as HCl salt) and the corresponding volume percent of non-aqueous component exceed the corresponding solubilities as detailed in Table 1, for all admixture volumes equal to or below 150 ml. In the scenario above, the solubility at refrigerated conditions with 15% non-aqueous component has improved to 2.9 mg/ml but is still below the final concentration of 4.03 mg/ml. Therefore, 50 ml admixtures of the non-aqueous formulation described in the example cannot be prepared and stored at refrigerated temperatures. However, for a 150 ml admixture, the final concentration of bendamustine HCl in this scenario is 1.5 mg/ml with about 6.0% non-aqueous component, which is below the solubility limit (of 2.022 mg/ml at 5% non-aqueous at 2-8° C.). Therefore, the non-aqueous formulation of bendamustine described in this example may be diluted into smaller infusion volumes ranging from 250 ml to 50 ml, and stored at only room temperature (but not refrigerated temperature), with bendamustine continuing to remain in solution. For storage at refrigerated temperatures, the minimum admixture volume that can be used is 150 ml or higher.

TABLE 5

Concentrations of bendamustine (BDM, as HCl salt) and corresponding volume % of non-aqueous (NA) component in the final admixture, for volumes ranging from 100 ml to 250 ml For 25 mg/mL Formulation

	Admix. Volume 250 mL				Admix. Volume 200 mL			
	100 mg/m^2 dose		120 mg/m^2 dose		100 mg/m^2 dose		120 mg/m^2 dose	
BSA (m^2)	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.
1.00	0.39	1.6	0.47	1.9	0.49	2.0	0.59	2.3
1.25	0.49	2.0	0.59	2.3	0.61	2.4	0.73	2.9
1.50	0.59	2.3	0.70	2.8	0.73	2.9	0.87	3.5
1.75	0.68	2.7	0.81	3.3	0.85	3.4	1.01	4.0
2.00	0.78	3.1	0.92	3.7	0.96	3.8	1.15	4.6
2.25	0.87	3.5	1.04	4.1	1.08	4.3	1.28	5.1
2.50	0.96	3.8	1.15	4.6	1.19	4.8	1.42	5.7
2.75	1.05	4.2	1.25	5.0	1.30	5.2	1.55	6.2
3.00	1.15	4.6	1.36	5.4	1.42	5.7	1.68	6.7
	Admix. Volume 150 mL				Admix. Volume 100 mL			
	100 mg/m^2 dose		120 mg/m^2 dose		100 mg/m^2 dose		120 mg/m^2 dose	
BSA (m^2)	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.
1.00	0.65	2.6	0.78	3.1	0.96	3.8	1.15	4.6
1.25	0.81	3.2	0.96	3.8	1.19	4.8	1.42	5.7
1.50	0.96	3.8	1.15	4.6	1.42	5.7	1.68	6.7
1.75	1.11	4.5	1.33	5.3	1.64	6.5	1.94	7.7
2.00	1.27	5.1	1.50	6.0	1.85	7.4	2.19	8.8
2.25	1.42	5.7	1.68	6.7	2.06	8.3	2.44	9.7
2.50	1.56	6.3	1.85	7.4	2.27	9.1	2.68	10.7

TABLE 5-continued

Concentrations of bendamustine (BDM, as HCl salt) and corresponding volume % of non-aqueous (NA) component in the final admixture, for volumes ranging from 100 ml to 250 ml For 25 mg/mL Formulation

2.75	1.71	6.8	2.02	8.1	2.48	9.9	2.92	11.7
3.00	1.85	7.4	2.19	8.8	2.68	10.7	3.15	12.6

	Admix. Volume 50 mL			
	100 mg/m^2 dose		120 mg/m^2 dose	
BSA (m^2)	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.
1.00	1.85	7.4	2.19	8.8
1.25	2.27	9.1	2.68	10.7
1.50	2.68	10.7	3.15	12.6
1.75	3.07	12.3	3.60	14.4
2.00	3.45	13.8	4.03	16.1
2.25	3.81	15.3	4.44	17.8
2.50	4.17	16.7	4.84	19.4
2.75	4.51	18.0	5.22	20.9
3.00	4.84	19.4	5.59	22.4

Example 6

The hemolytic potential of the non-aqueous bendamustine formulation indicated in Table 4 (Example 5), when admixed with 250 ml and 100 ml of normal saline, was assessed. The hemolysis study was conducted at the highest final bendamustine HCl concentrations expected at these admixture volumes, namely, for a 3.0 m^2 patient dosed at 120 mg/m^2. At this dosing, the final bendamustine HCl concentration for 250 ml and 100 ml admixture volumes is 1.36 mg/ml and 3.15 mg/ml, respectively (Table 5). Human whole blood (1 ml) was incubated at 37° C. for approximately 30 minutes with admixed bendamustine HCl solutions at 1.4 mg/ml or 3.2 mg/ml at blood to drug solution volumetric ratios of 1:2 and 1:1, respectively. These volumetric ratios correspond to infusion times of 15 minutes and 10 minutes, respectively, for the 250 ml and 100 ml admixture volumes. A placebo of the bendamustine formulation (without the active ingredient) was also evaluated at these concentrations and volumetric ratios. A positive control (1% saponin solution), a negative control (normal saline), and Treanda™ diluted in normal saline to the highest concentration stated in the prescribing information (0.6 mg/ml) were included in the study. Following incubation and centrifugation of the samples, the plasma was harvested and hemolysis was evaluated by spectrophotometric analysis for hemoglobin in the supernatant. The results are summarized in Table 6. No hemolysis was observed with the non-aqueous bendamustine formulation when diluted with saline at either concentration or volumetric (blood:drug solution) ratios, or with the corresponding placebo at comparable sample volumes; supernatants from all samples were light yellow. In conclusion, no hemolytic effects are observed with non-aqueous bendamustine formulations when diluted to smaller volumes (100 to 250 ml) and infused in shorter times (10-15 minutes) than current practice.

TABLE 6

Hemolytic Potential test results

Mixture	Hemoglobin[a] (mg/dL)	Test Result	Supernatant Color[b]	Tube No.
Human blood plus: Test Article A (25 mg/mL, diluted to 3.2 mg/mL with saline) - 100 ml admixture				
	1	N	Light yellow	1
	0	N	Light yellow	2
	1	N	Light yellow	3
Test Article A (25 mg/mL, diluted to 1.4 mg/mL with saline) - 250 ml admixture				
	2	N	Light yellow	4
	1	N	Light yellow	5
	1	N	Light yellow	6
Test Article A Vehicle (Placebo, diluted with 100 ml saline)				
	0	N	Light yellow	7
	1	N	Light yellow	8
	0	N	Light yellow	9
Test Article A Vehicle (Placebo, diluted with 250 ml saline)				
	1	N	Light yellow	10
	4	N	Light yellow	11
	1	N	Light yellow	12
Treanda ™ (5 mg/mL, diluted to 0.6 mg/mL with saline)				
	3	N	Light yellow	43
	4	N	Light yellow	44
	2	N	Light yellow	45
Negative Control (normal saline)				
	9	N	Yellow	55
	5	N	Yellow	56
	3	N	Yellow	57
Positive Control (1% Saponin)[c]				
	5949	P	Red	58
	5974	P	Red	59
	6386	P	Red	60

N = Negative, no hemolysis.
NA = Not applicable.
P = Positive, hemolysis.
[a]Hemoglobin index of the mixture supernatants.
[b]Plasma separated from whole blood plasma.
[c]1% Saponin. Saponin is a hemolytic agent used to lyse erythrocytes.

Example 7

The local tolerance (intravenous (IV) and perivascular (PV)) of the non-aqueous bendamustine-containing composition indicated in Table 4 (Example 5), when admixed with 100 ml of normal saline and infused over 10 minutes, was assessed. New Zealand White rabbits (3 males [IV] and 2 males [PV]) received a single dose of bendamustine formulation (admixed with 100 ml saline to a final concentration of 3.2 mg/ml bendamustine HCl) and corresponding placebo in the left and right ear, respectively. The formulation was administered as either intravenous infusion (5 mg/kg in 10 minutes), or perivascular injection (250 μl) to determine local tolerance. Treanda™ reconstituted and admixed with normal saline to a final concentration of 0.6 mg/ml (the highest concentration stated in the label) was also studied either as a 30 minute IV infusion (the shortest infusion time stated in the label), as well as perivascular injection (250 μl). Animals were held for a 96 hour (post-dose) observation period. During the observation period, dermal scores were recorded for all administration sites. At the end of the observation periods, animals were euthanized and a macroscopic and microscopic examination of both ears was performed. Parameters evaluated during the study were: viability, clinical observations, body weights, macroscopic observations and microscopic pathology.

The results of the local tolerance study are summarized in Table 7 (in life dermal observations) and Table 8 (microscopic pathology for perivascular administration).

In Life Dermal Observations:

As seen in Table 7, there was transient, dermal irritation in the form of slight to moderate erythema and moderate edema noted between 24 and 72 hours post dose, in each of the groups receiving either bendamustine-containing formulations or placebo material intravenously. At 96 hours, irritation was limited to a few individual sites treated with test or placebo articles. Only a limited number of animals were affected, and there was no consistent pattern of irritation within a dose group (either for test article or placebo). The bendamustine formulations were considered not to produce dermal irritation when administered intravenously.

Perivascular administration of bendamustine formulations (0.25 ml injection volume) produced dermal irritation in all groups. Local signs of dermal irritation following perivascular administration were mostly characterized by slight (group 6—Treanda™) or slight to moderate (group 7—non aqueous bendamustine formulation of example 5) erythema, and slight edema (groups 7). The severity of the irritation observed correlated with the dose and/or concentration of the test article administered, with placebo groups generally showing a lesser level of irritation than the corresponding test-article formulation.

TABLE 7

Summary of in life dermal observations

Material - Left ear/Right ear	Dermal observations during 96 hour post dose period (incidence and most severe level of erythema and edema noted)	
	Left ear (Bendamustine-containing formulation)	Right ear (Placebo material)
Intravenous administration		
Group 1: Treanda ™ diluted to 0.6 mg/ml in saline/Treanda	—	(2/3) Slight

TABLE 7-continued

Summary of in life dermal observations

Material - Left ear/Right ear	Dermal observations during 96 hour post dose period (incidence and most severe level of erythema and edema noted)	
	Left ear (Bendamustine-containing formulation)	Right ear (Placebo material)
Placebo - 500 ml admixture		
Group 2: Non-aqueous bendamustine formulation 25 mg/ml diluted to 3.2 mg/ml in saline/placebo (+saline) - 100 ml admixture	—	(1/3) Moderate
Perivascular administration		
Group 6: Treanda ™ diluted to 0.6 mg/ml in saline/Treanda ™	(1/2) Slight	(1/2) Slight
Placebo - 500 ml admixture		
Group 7: Non-aqueous bendamustine formulation 25 mg/ml diluted to 3.2 mg/ml in saline/placebo (+saline) - 100 ml admixture	(2/2) Moderate	(2/2) Slight

Microscopic Pathology:

Intravenous administration of test articles/placebos was generally well tolerated; no test article related effects were observed. Perivascular administration of bendamustine-containing formulations (including Treanda™) was associated with dose and/or concentration related minimal to marked edema/collagen degeneration and mixed inflammation in perivascular tissues. The non-aqueous formulation of bendamustine (Group 7) was nominally more severe in grade than Treanda™ (Group 6).

TABLE 8

Incidence and Average Severity of Microscopic Findings at Perivascular Sites

Formulation	Treanda ™ (diluted to 0.6 mg/ml)/ Treanda ™ Placebo	Non Aqueous Bendamustine (diluted to 3.2 mg/ml)/ Placebo
Group number	6	7
No. Animals examined	2	2
RIGHT EAR (RE) - Placebo	Incidence (Average Severity)*	
RE Injection site		
Hemorrhage	0 (0.0)	0 (0.0)
Mixed Inflammation	0 (0.0)	0 (0.0)
Edema/Collagen Degeneration	1 (0.5)	0 (0.0)
Degeneration/Inflammation, Vascular	0 (0.0)	0 (0.0)
RE 2 cm distal		
Edema/Collagen Degeneration	0 (0.0)	0 (0.0)
Degeneration/Inflammation, Vascular	0 (0.0)	0 (0.0)
RE 4 cm distal		
Degeneration/Inflammation, Vascular	0 (0.0)	0 (0.0)
LEFT EAR (LE) - Test Article	Incidence (Average Severity)	
LE Injection site		
Hemorrhage	0 (0.0)	0 (0.0)
Mixed inflammation	0 (0.0)	2 (2.0)

TABLE 8-continued

Incidence and Average Severity of Microscopic Findings at Perivascular Sites

Formulation	Treanda ™ (diluted to 0.6 mg/ml)/ Treanda ™ Placebo	Non Aqueous Bendamustine (diluted to 3.2 mg/ml)/ Placebo
Edema/Collagen Degeneration	1 (1.0)	2 (1.5)
Epidermis, Crust/Pustule, Erosion/Ulceration	0 (0.0)	0 (0.0)
Degeneration/Inflammation, Vascular LE 2 cm distal	1 (1.5)	1 (1.5)
Hemorrhage	0 (0.0)	0 (0.0)
Mixed Inflammation	1 (0.5)	1 (1.0)
Edema/Collagen Degeneration	0 (0.0)	2 (2.0)
Epidermis, Crust/Pustule, Erosion/Ulceration	0 (0.0)	0 (0.0)
Degeneration/Inflammation, Vascular LE 4 cm distal	0 (0.0)	0 (0.0)
Hemorrhage	0 (0.0)	0 (0.0)
Mixed inflammation	0 (0.0)	1 (1.5)
Edema/Collagen Degeneration	0 (0.0)	1 (2.0)
Epidermis, Crust/Pustule, Erosion/Ulceration	0 (0.0)	0 (0.0)
Degeneration/Inflammation, Vascular	0 (0.0)	0 (0.0)

*The number in parentheses represents the average severity score; the total of severity scores of the findings divided by the number of animals in the group.

CONCLUSION

No test-article related irritation effects were observed for the non-aqueous formulation of bendamustine via the IV route, indicating that proper administration of this formulation did not result in any adverse local reaction. Perivascular administration of the non-aqueous bendamustine formulation, which is primarily related to effects that may occur if extravasation should occur, resulted in irritation that was generally comparable to Treanda. Therefore, the non-aqueous formulation of bendamustine described herein is well tolerated, despite the higher concentration of the smaller infusion volume preparation.

Example 8

The chemical stability of the non-aqueous bendamustine formulation (25 mg/ml) indicated in Table 4 (Example 5), when admixed with 50 ml and 100 ml of normal saline, was assessed. For each admixture volume, the admixture solutions were prepared at the expected lowest concentration (corresponding to a 1.0 m^2 patient dosed at 25 mg/m^2) and the highest concentration (corresponding to a 3.0 m^2 patient dosed at 120 mg/m^2) of bendamustine HCl in the final admixture. For the 50 ml admixture volume, the tested minimum and maximum concentrations are about 0.5 mg/ml and 6.0 mg/ml, respectively. For the 100 ml admixture volume, the tested minimum and maximum concentrations are about 0.25 mg/ml and 3.2 mg/ml, respectively. The chemical stability of Treanda™ was also determined at the lowest (0.2 mg/ml) and the highest (0.6 mg/ml) admixed concentrations stated in the label. The chemical stability was monitored at room temperature at periodic intervals up to 24 hours using a validated HPLC assay. The results are summarized in Table 9.

TABLE 9

Dilution (Admixed) Stability of Bendamustine Formulations in Normal Saline at Room Temperature

	Attribute									
	Highest Concentration (3.2 mg/ml)					Lowest Concentration (0.25 mg/ml)				
	Time									
	Initial	1 hr	3 hrs	6 hrs	24 hrs	Initial	1 hr	3 hrs	6 hrs	24 hrs
	Formulation									
	Non Aqueous Bendamustine Formulation 25 mg/ml admixed with 100 ml normal saline									
Assay (mg/ml)	3.155	3.090	3.060	3.085	2.895	0.240	0.234	0.229	0.224	0.196
Assay (% Initial)	100.0	97.9	97.0	97.8	91.8	100.0	97.5	95.4	93.3	81.7
Impurity—MCE (%)	BLQ	BLQ	BLQ	BLQ	BLQ	ND	ND	ND	ND	ND
Impurity—HP1 (%)	0.244	0.606	1.237	2.236	6.707	0.525	1.449	3.495	5.529	13.424
Impurity—Dimer (%)	BLQ	BLQ	BLQ	0.068	0.158	ND	ND	ND	BLQ	0.063
Single unknown (%)	0.086	0.061	BLQ	BLQ	0.098	ND	ND	ND	ND	BLQ
Total (%)	0.33	0.67	1.24	2.30	6.96	0.58	1.45	3.50	5.53	13.49
	Attribute									
	Highest Concentration (6.4 mg/ml)					Lowest Concentration (0.5 mg/ml)				
	Time									
	Initial	1 hr	hrs	6 hrs	24 hrs	Initial	1 hr	3 hrs	6 hrs	24 hrs
	Formulation									
	Non Aqueous Bendamustine Formulation 25 mg/ml admixed with 50 ml normal saline									
Assay (mg/ml)	6.62	6.60	6.60	6.54	6.46	0.475	0.470	0.455	0.445	0.394
Assay (% Initial)	100.0	99.7	99.7	98.8	97.8	100.0	98.9	95.8	93.7	82.9
Impurity—MCE (%)	BLQ	BLQ	BLQ	BLQ	0.074	BLQ	BLQ	BLQ	BLQ	BLQ
Impurity—HP1 (%)	0.137	0.265	0.528	0.945	2.967	0.567	1.618	3.719	5.892	14.427

TABLE 9-continued

Dilution (Admixed) Stability of Bendamustine Formulations in Normal Saline at Room Temperature										
Impurity—Dimer (%)	BLQ	BLQ	BLQ	0.050	0.110	BLQ	BLQ	BLQ	0.065	0.115
Single unknown (%)	0.112	0.105	0.086	0.054	0.112	0.057	BLQ	ND	ND	ND
Total (%)	0.25	0.37	0.61	1.05	3.36	0.67	1.62	3.72	5.96	14.54
	Attribute									
	Highest Concentration (0.6 mg/ml)					Lowest Concentration (0.2 mg/ml)				
	Time									
	Initial	1 hr	3 hrs	6 hrs	24 hrs	Initial	1 hr	3 hrs	6 hrs	24 hrs
	Formulation									
	Treanda ™ 5 mg/ml admixed with 500 ml normal saline									
Assay (mg/ml)	0.566	0.558	0.544	0.527	0.454	0.193	0.191	0.185	0.178	0.154
Assay (% Initial)	100.0	98.6	96.1	93.1	80.2	100.0	99.0	95.9	92.2	79.8
Impurity—MCE (%)	0.263	0.261	0.268	0.262	0.263	0.261	0.288	0.277	0.250	0.276
Impurity—HP1 (%)	1.250	2.248	4.730	7.287	16.887	1.231	2.241	4.770	7.462	17.504
Impurity—Dimer (%)	0.223	0.229	0.269	0.279	0.326	0.188	0.185	0.178	0.176	0.252
Single unknown (%)	0.103	0.103	0.101	0.097	0.081	0.077	0.079	0.103	0.083	0.066
Total (%)	1.97	2.97	5.50	8.04	17.66	1.85	3.01	5.41	8.07	18.27

MCE—monochloroethyl derivative;
HP1—mono hydroxyl bendamustine

As shown in Table 9, Treanda™ when prepared as directed in the label (final concentration between 0.2-0.6 mg/ml) shows total degradation of about 5-6% in 3 hours at room temperature (corresponding to the room temperature stability claim in the label); monohydroxy bendamustine is the main degradant. In contrast, the non-aqueous bendamustine formulations admixed in either 50 ml or 100 ml saline show total degradation of less than 5-6% over 6 hours at the lowest concentrations tested, indicating that these admixtures are significantly less prone to degradation. This stabilizing effect is particularly pronounced at the higher concentrations (which are more typical), with chemical stability evident for 24 hours at these concentrations. The non-aqueous formulations of bendamustine thus offer better chemical stability than Treanda™ when admixed into smaller volumes.

I claim:

1. A method of treating cancer or malignant disease in a subject, comprising parenterally administering a volume of about 100 ml or less of a liquid composition comprising:

a) from about 0.05 to about 12.5 mg/ml of bendamustine or a pharmaceutically acceptable salt thereof;

b) a solubilizer comprising propylene glycol in an amount of from about 4.5 mg/ml to about 51 mg/ml and polyethylene glycol;

c) a parenterally acceptable diluent; and optionally

d) an antioxidant;

over a period of less than or equal to about 15 minutes to a subject in need thereof.

2. The method of claim **1**, wherein the composition is administered over a time period of less than or equal to about 10 minutes.

3. The method of claim **1**, wherein the volume administered is from about 50 ml to about 65 ml.

4. The method of claim **1**, wherein the volume administered is about 50 ml.

5. The method of claim **1**, wherein the concentration of bendamustine or pharmaceutically acceptable salt thereof is from about 0.05 mg/ml to about 10 mg/ml.

6. The method of claim **1**, wherein the concentration of bendamustine or pharmaceutically acceptable salt thereof is from about 0.1 mg/ml to about 7.0 mg/ml.

7. The method of claim **1**, wherein the concentration of bendamustine or pharmaceutically acceptable salt thereof is from about 0.5 mg/ml to about 3.2 mg/ml.

8. The method of claim **1**, wherein the concentration of bendamustine or pharmaceutically acceptable salt thereof is about 10 mg/ml.

9. The method of claim **1** wherein the concentration of bendamustine or pharmaceutically acceptable salt thereof is about 5.6 mg/ml.

10. The method of claim **8**, wherein the composition is administered intravenously.

11. The method of claim **10**, wherein the composition is administered intravenously over a time period of about 10 minutes or less.

12. The method of claim **9**, wherein the composition is administered intravenously.

13. The method of claim **12**, wherein the composition is administered intravenously over a time period of about 10 minutes or less.

14. The method of claim **3**, wherein the composition is administered intravenously.

15. The method of claim **14**, wherein the composition is administered intravenously over a time period of about 10 minutes or less.

16. The method of claim **4**, wherein the composition is administered intravenously.

17. The method of claim **16**, wherein the composition is administered intravenously over a time period of about 10 minutes or less.

* * * * *

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APPLICATION NUMBER: *14/031,879*
FILING DATE: *September 19, 2013*
PATENT NUMBER: *9,265,831*
ISSUE DATE: *February 23, 2016*

Dist. Delaware
No. 17-1154-CFC
PTX-0308

By Authority of the
Under Secretary of Commerce for Intellectual Property
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US009265831B2

(12) **United States Patent**
Palepu et al.

(10) **Patent No.: US 9,265,831 B2**
(45) **Date of Patent: *Feb. 23, 2016**

(54) **FORMULATIONS OF BENDAMUSTINE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/031,879**

(22) Filed: **Sep. 19, 2013**

(65) **Prior Publication Data**

US 2014/0024691 A1 Jan. 23, 2014

Related U.S. Application Data

(63) Continuation of application No. 13/016,473, filed on Jan. 28, 2011, now Pat. No. 8,609,707.

(60) Provisional application No. 61/299,100, filed on Jan. 28, 2010.

(51) **Int. Cl.**

A61K 47/10	(2006.01)
A61K 9/08	(2006.01)
A61K 9/00	(2006.01)
A61K 31/4184	(2006.01)
A61K 31/25	(2006.01)
A61K 47/18	(2006.01)
A61K 47/20	(2006.01)
A61K 47/12	(2006.01)

(52) **U.S. Cl.**

CPC . ***A61K 47/18*** (2013.01); ***A61K 9/08*** (2013.01); ***A61K 31/4184*** (2013.01); ***A61K 47/10*** (2013.01); ***A61K 47/12*** (2013.01); ***A61K 47/20*** (2013.01); *A61K 9/0019* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Long term storage stable bendamustine-containing compositions are disclosed. The compositions can include bendamustine or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable fluid which can include in some embodiments PEG, PG or mixtures thereof and an antioxidant or chloride ion source. The bendamustine-containing compositions have less than about 5% total impurities, on a normalized peak area response ("PAR") basis as determined by high performance liquid chromatography ("HPLC") at a wavelength of 223 nm, after at least about 15 months of storage at a temperature of from about 5° C. to about 25° C.

6 Claims, No Drawings

FORMULATIONS OF BENDAMUSTINE

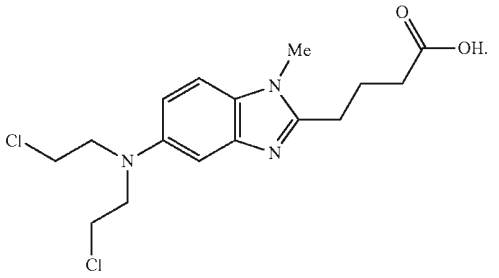
CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 13/016,473, filed Jan. 28, 2011, issued as U.S. Pat. No. 8,609,707 which claims the benefit of U.S. Provisional Patent Application No. 61/299,100, filed Jan. 28, 2010, the contents of each of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Bendamustine free base is represented by the following structural formula (I)

(I)



Bendamustine is used in the treatment of a number of cancers including leukemias, Hodgkins disease and multiple myelomas. Bendamustine is the active ingredient of the commercial product Treanda™, a lyophilized powder for reconstitution.

Bendamustine exhibits rapid degradation upon reconstitution of the lyophilized product. Bendamustine undergoes hydrolysis by direct substitution rather than an addition elimination process due to the presence of the highly labile aliphatic chlorine atoms. Some of the main degradants of bendamustine are the monohydroxy compound known as HP1 (hydrolysis product 1) and dihydroxy compound HP2 (hydrolysis product 2). The monohydroxy compound appears as the main impurity at Relative Retention Time (RRT) 0.6 and the dihydroxy compound appears as the main impurity at RRT 0.27. Minor peaks appear at RRT 1.2, which are presently unknown.

The stability of bendamustine in water is measured in hours, and is therefore, not suitable for long-term storage in liquid form. The lyophile possesses good chemical stability. However, reconstitution of the lyophile is clinically inconvenient, taking 15-30 mins with implications of chemical instability. There is a need for ready to use (RTU) bendamustine formulations having enhanced stability.

SUMMARY OF THE INVENTION

In other aspects of the invention, the bendamustine-containing compositions include a) a pharmaceutically acceptable fluid which contains one or more of propylene glycol, ethanol, polyethylene glycol, benzyl alcohol and glycofurol, and b) a stabilizing amount of a chloride salt. In other aspects of the invention, the bendamustine-containing compositions include DMSO (dimethyl sulfoxide) as part of the pharmaceutically acceptable fluid included therein. Regardless of the pharmaceutically acceptable fluid included, the amount of bendamustine included in the composition is preferably from about 20 mg/mL to about 60 mg/mL. Still further aspects of the invention include methods of treatment using bendamustine-containing compositions and kits containing the same.

One of the advantages of the inventive liquid compositions is that they have substantially improved long term stability when compared to currently available formulations. For example, the inventive bendamustine compositions are substantially free of impurities after at least about 15 months at a temperature of from about 5° C. to about 25° C. The inventive formulations are advantageously ready to use or ready for further dilution. Reconstitution of lyophilized powders is not required.

DETAILED DESCRIPTION OF THE INVENTION

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein, RRT is calculated by dividing the retention time of the peak of interest by the retention time of the main peak. Any peak with an RRT<1 elutes before the main peak, and any peak with an RRT>1 elutes after the main peak.

For purposes of the present invention, "substantially free of impurities" shall be understood to include bendamustine-containing compositions in which the amount of total impurities is less than about 5%, as calculated on a normalized peak area response ("PAR") basis as determined by high performance liquid chromatography ("HPLC") at a wavelength of 223 nm, after a period of about 15 months at a temperature of from about 5° C. to about 25° C. The amount of impurities is further calculated as being based upon the original amount bendamustine (or salt thereof) being present in the composition or formulation.

For purposes of the present invention, a pharmaceutically acceptable fluid is a fluid which is suitable for pharmaceutical use.

Preferably, the amount of any individual degradant in the inventive compositions does not exceed 2% PAR as determined by HPLC at a wavelength of 223 nm after storage periods of at least about 15 months at a temperature of from about 5° C. to about 25° C. In some aspects, the amount of time the inventive compositions demonstrate long term storage stability is at least about 18 months and preferably at least about 2 years when stored under the conditions described herein.

In accordance with one aspect of the invention there are provided long term storage stable bendamustine-containing compositions including:

a) bendamustine or a pharmaceutically acceptable salt thereof; and

b) a pharmaceutically acceptable fluid including

i) PEG, PG or mixtures thereof; and

ii) a stabilizing amount of an antioxidant.

The total impurities in the inventive compositions resulting from the degradation of the bendamustine in the compositions is less than about 5% PAR as determined by HPLC at a wavelength of 223 nm after at least about 15 months at a temperature of from about 5° C. to about 25° C., and thus have long term stability for at least the same period of time or longer. Preferably, the bendamustine-containing compositions demonstrate long term storage stability for at least about 2 years, especially when stored at the lower (refrigerated) temperatures. In one embodiment, the amount of total impurities in the inventive compositions resulting from the degra-

dation of the bendamustine is less than about 3% PAR as determined by HPLC at a wavelength of 223 nm after at least about 2 years at a temperature of from about 5° C. to about 25° C.

In some aspects of the invention, the bendamustine concentration in the inventive compositions is from about 10 mg/mL to about 100 mg/mL, preferably 20 mg/mL to about 60 mg/mL. Preferably the bendamustine concentration in the inventive compositions is from about 25 mg/mL to about 50 mg/mL, and more preferably from about 30 mg/mL to about 50 mg/mL. It will be understood that compositions containing any useful concentration within the ranges, i.e. 10, 20, 25, 30, 35, 40, 45, 50, 55, 60 . . . 100 are contemplated. In other embodiments, the bendamustine concentration in the composition is about 50 mg/mL. In alternative aspects, the amount of bendamustine is outside these ranges but the amounts will be sufficient for single or multiple administrations of dosages generally regarded as effective amounts.

In several embodiments of the invention, pharmaceutically acceptable fluid is non-aqueous and may be, but is not necessarily, a solvent for the bendamustine or salt thereof. Within this aspect, the pharmaceutically acceptable fluid is propylene glycol (PG) or polyethylene glycol (PEG). In other embodiments of the invention however, the pharmaceutically acceptable fluid is a mixture of PEG and PG. For example, the pharmaceutically acceptable fluid can include about 50% PEG and about 50% PG. Alternatively, pharmaceutically acceptable fluid includes about 95% PEG and about 5% PG. The amount of PEG and PG can also be varied within the ranges, i.e. the ratio of PEG:PG in the pharmaceutically acceptable fluid can range from about 95:5 to about 50:50. Within this range, is a pharmaceutically acceptable fluid containing about 75% PEG and about 25% PG, and preferably 80% PEG and 20% PG. In another embodiment, a pharmaceutically acceptable fluid can include about 85% PEG and about 15% PG while another preferred pharmaceutically acceptable fluid includes about 90% PEG and about 10% PG. The molecular weight of the PEG will be within the range of pharmaceutically acceptable weights although PEG 400 is preferred in many aspects of the invention.

Without meaning to be bound by any theory or hypothesis, the hydroxide of the polyethylene glycol molecule is less reactive than the hydroxides of propylene glycol. As a result, the ester forms at a slower rate in polyethylene glycol than propylene glycol and the resulting bendamustine degradants are unexpectedly and substantially reduced over extended periods of time when PEG is a substantial part of the pharmaceutically acceptable fluid.

The bendamustine-containing compositions according to several preferred aspects of the invention include a stabilizing amount of an antioxidant. For purposes of the present invention, "stabilizing amount" shall be understood to include those amounts which increase or enhance the stability of the bendamustine in the compositions described herein. The presence of one or more antioxidants described herein thus contributes, at least in part to the long term stability of the composition. Within this guideline, suitable antioxidant concentrations in the compositions can range from about 2.5 mg/mL to about 35 mg/mL, and preferably from about 5 mg/mL to about 20 mg/mL or from about 10 mg/mL to about 15 mg/mL. In some other embodiments, the concentration of the antioxidant in the bendamustine-containing composition is about 5 mg/mL.

Suitable antioxidants for inclusion include those which are pharmaceutically acceptable for use in human and veterinary formulations although not limited to those currently regarded as safe by any regulatory authority. For example, the antioxidant can be selected from among lipoic acid, thioglycerol (also known as monothioglycerol) and analogs thereof, propyl gallate, methionine, cysteine, metabisulfites, sodium formaldehyde sulfoxylate, phenol-containing aromatic and aliphatic compounds, dihydrolipoic acid and mixtures of the foregoing. Preferably, the antioxidant is thioglycerol, lipoic acid or a mixture thereof. Some particularly preferred embodiments of the invention include thioglycerol.

In view of the foregoing, some preferred long term storage stable bendamustine-containing compositions in accordance with the invention compositions include:

I. a) bendamustine or a pharmaceutically acceptable salt thereof; and
   b) a pharmaceutically acceptable fluid including
      i) polyethylene glycol and propylene glycol; and
      ii) a stabilizing amount of thioglycerol; or

II. a) about 50 mg/mL bendamustine or a pharmaceutically acceptable salt thereof; and
   b) a pharmaceutically acceptable fluid including
      i) about 90% PEG and about 10% PG; and
      ii) about 2.5 mg/mL thioglycerol.

Each of these compositions have the same stability profiles already described, i.e. having less than about 5% total impurities, PAR as determined by HPLC at a wavelength of 223 nm, after at least about 15 months of storage at a temperature of from about 5° C. to about 25° C.

In accordance with other aspects of the invention, there are provided long term storage stable bendamustine-containing compositions, including:

a) bendamustine or a pharmaceutically acceptable salt thereof;
b) a pharmaceutically acceptable fluid including one or more of the following: PG, ethanol, PEG, benzyl alcohol and glycofurol; and
c) a stabilizing amount of a chloride salt.

These compositions also have the low levels of impurities and long term stability mentioned herein. Preferred pharmaceutically acceptable fluids include PG, PEG or ethanol in this embodiment of the invention. Preferably, the PEG is PEG 400. If desired, glycerin and/or 88% (w/w) lactic acid can be added to the pharmaceutically acceptable fluid.

Suitable chloride salts include but are not limited to organic chloride salts, sodium chloride, choline chloride, hydrochloride salts of amino acids and mixtures thereof. Thus, as will be appreciated by those of ordinary skill, one can select from among a number of suitable chloride salts and it is Applicants' intention that the scope of the invention includes all such chloride salts that are capable of being included in bendamustine-containing formulations for extended periods without having a deleterious effect on the drug. In one embodiment of the invention, the chloride salt concentration is from about 10 to about 300 mg/mL. In another embodiment, the chloride salt concentration is from about 50 to about 215 mg/mL. In one preferred embodiment, the chloride salt concentration is about 215 mg/mL.

In accordance with another aspect of the invention, there is provided long term storage stable bendamustine-containing compositions, including:

a) bendamustine or a pharmaceutically acceptable salt thereof; and
b) a pharmaceutically acceptable fluid including DMSO.

These compositions also have the low levels of impurities and long term stability mentioned herein. In some aspects, the bendamustine concentration in these compositions is from about 10 mg/mL to about 100 mg/mL. Preferably, the bendamustine concentration is from about 20 mg/mL to about 50 mg/mL, more preferably from about 25 mg/mL to about 50

mg/mL. In an alternative embodiment, the bendamustine concentration is about 50 mg/mL.

Another embodiment of the invention provides methods of treating cancer in mammals. The methods include administering to a mammal in need thereof an effective amount of one of the bendamustine-containing compositions described herein. Since the active ingredient portion of the inventive composition is an FDA-approved drug, those of ordinary skill will recognize that the doses of bendamustine employed in this aspect of the invention will be similar to those employed in any treatment regimens designed for bendamustine as marketed under the trade name TREANDA. The patient package insert containing dosing information is incorporated herein by reference. The methods of treatment also include administering the inventive formulations for any purpose or physical condition for which bendamustine has been indicated as being useful.

Another embodiment of the invention includes methods of preparing bendamustine-containing compositions described herein. The methods include reconstituting lyophilized bendamustine in a pharmaceutically acceptable fluid containing one of the following:

A) i) PEG, PG or mixtures thereof; and
ii) a stabilizing amount of an antioxidant;
B) i) one or more of PG, ethanol, PEG, benzyl alcohol and glycofurol; and
ii) a stabilizing amount of a chloride salt; or
C) DMSO.

The steps are carried out under pharmaceutically acceptable conditions for sterility and manufacturing.

In a further aspect of the invention, there are provided methods of controlling or preventing the formation of impurities in bendamustine-containing compositions during long term storage. The methods include combining an amount of bendamustine or a pharmaceutically acceptable salt thereof with a sufficient amount of a pharmaceutically acceptable fluid containing one of the following:

A) i) PEG, PG or mixtures thereof; and
ii) a stabilizing amount of an antioxidant;
B) i) one or more of PG, ethanol, PEG, glycofurol and benzyl alcohol; and
ii) a stabilizing amount of a chloride salt; or
C) DMSO.

Further optional steps in accordance therewith include transferring one or more pharmaceutically acceptable doses of the formulations into a suitable sealable container and storing the sealed container at a temperature of from about 5° C. to about 25° C. As a result of carrying out these steps, it is possible to control or substantially prevent the formation of impurities which otherwise occur with bendamustine-containing compositions during long term storage so that the artisan is provided with bendamustine-containing formulations having less than about 5% total impurities PAR as determined by HPLC at a wavelength of 223 nm, after at least about 15 months of storage at a temperature of from about 5° C. to about 25° C.

The compositions of the present invention can be packaged in any suitable sterile vial or container fit for the sterile storage of a pharmaceutical such as bendamustine. Suitable containers can be glass vials, polypropylene or polyethylene vials or other special purpose containers and be of a size sufficient to hold one or more doses of bendamustine.

A further aspect of the invention includes kits containing lyophilized bendamustine or a pharmaceutically acceptable salt thereof in a first container or vial; and, in a second container, a sufficient amount of a pharmaceutically acceptable fluid such as those described herein, i.e. one of the following:

A) i) PEG, PG or mixtures thereof; and
ii) a stabilizing amount of an antioxidant;
B) i) one or more of PG, ethanol, PEG, glycofurol and benzyl alcohol; and
ii) a stabilizing amount of a chloride salt; or
C) DMSO.

For purposes of this embodiment, the amount of fluid which is sufficient is an amount which allows the bendamustine to be dissolved or dispersed to a degree which renders the liquid composition ready for use.

As will be appreciated by those of ordinary skill, the kit will contain other pharmaceutically necessary materials for storing and/or administering the drug, including instructions for storage and use, additional diluents, if desired, etc.

EXAMPLES

The following examples serve to provide further appreciation of the invention but are not meant in any way to restrict the effective scope of the invention.

Example 1

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 10 mg/ml in one of ethanol, propylene glycol and benzyl alcohol as indicated in Table 1 below. 215 mg/ml of choline chloride was added in half of the samples as a source of soluble chloride ions. The samples were maintained at 40° C. and analyzed periodically for drug content and total impurities. The results obtained are presented in Table 1.

TABLE 1

Stability of Bendamustine HCl

Formulation	Temp	Time	BDM mg/ml	% Total Impurities
BDM - 10 mg/mL	Initial		10.43	0.27
Choline chloride -	40° C.	48 hrs	10.48	1.27
215 mg/mL		7 day	10.26	2.11
Ethanol qs to 1 mL				
BDM - 10 mg/mL	Initial		10.55	0.27
Ethanol qs to 1 mL	40° C.	48 hrs	10.30	2.39
		7 day	9.55	6.66
BDM - 10 mg/mL	Initial		9.99	0.21
Choline chloride -	40° C.	48 hrs	9.95	0.60
215 mg/mL		7 day	9.43	2.31
Propylene glycol qs to 1 mL				
BDM - 10 mg/mL	Initial		9.68	0.21
Propylene glycol qs to	40° C.	48 hrs	9.45	0.88
1 mL		7 day	9.00	3.44
BDM - 10 mg/mL	Initial		9.95	1.19
Choline Chloride -	40° C.	48 hrs	9.89	3.51
215 mg/mL		7 day	8.97	4.24
Benzyl alcohol qs to 1 mL				
BDM - 10 mg/mL	Initial		9.52	0.33
Benzyl alcohol qs to	40° C.	48 hrs	8.67	4.18
1 mL		7 day	7.49	7.84

Note:
In Table 1 the total % impurities include total contributions from peaks at various RRTs.

As shown in Table 1, the bendamustine formulations are very stable in solutions containing solvent and chloride salt. Table 1 shows that bendamustine, when dissolved at a concentration of about 10 mg/mL, in a pharmaceutically acceptable fluid, such as ethanol and propylene glycol, and containing a stabilizing amount of a chloride salt, such as choline chloride, had less than about 5% after at least 7 days storage at 40° C.

The data presented in Table 1 translates to bendamustine-containing compositions including a pharmaceutically acceptable fluid and a stabilizing amount of a chloride salt having a shelf life of at least about 15 months at 5° C. and 25° C.

The sample including ethanol alone exhibited more than 6.5 total degradants after 7 days storage at 40° C. The sample including benzyl alcohol alone exhibited more than 7.5% total degradants after 7 days storage at 40° C. Bendamustine-containing compositions with such high levels of degradation would not be suitable for long-term storage.

Example 2

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 10 mg/ml in DMSO. The samples were maintained at 40° C. and analyzed periodically for drug content and impurity profile. The results obtained are presented in Table 2.

TABLE 2

Stability of Bendamustine HCl in DMSO

Formulation	Temp	Time	Content (mg/mL)	% Total Imp
BDM - 10 mg/mL	Initial		10.2	0.23
DMSO qs to 1 mL	40° C.	48 hrs	9.80	0.30
		1 week	10.0	0.56

Note:
In Table 2 the total % impurities inelude total contributions from peaks at various RRTs.

Table 2 shows that bendamustine, when dissolved in DMSO, had substantially no increase in total degradants. The data presented in Table 2 translates to bendamustine-containing compositions including DMSO having a shelf life of at least about 15 months at 5° C. and 25° C. In fact, such compositions are expected to have long term stability for periods beyond 15 months, i.e. up to 2 years or greater.

Example 3

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 20 mg/ml in polyethylene glycol 400 and 5 mg/ml of lipoic acid was added as a stabilizing antioxidant as indicated in Table 3 below. The samples were maintained at 40° C. or 25° C. and analyzed after 15 days for drug content and impurities. The results obtained are presented in Table 3.

TABLE 3

Stability of Bendamustine (20 mg/ml) in PEG 400 and Antioxidants

Antioxidant	T° C.	Time days	% Initial	% Imp RRT 0.58	% Total Imps
None	25	15	97.6	2.08	2.28
	40	15	56.3	2.17	41.9
Lipoic Acid 5 mg/ml	25	15	98.5	<LD	0.23
	40	15	97.5	0.33	0.53

<LD = Below Level of Deteetion

As shown in Table 3, bendamustine, when dissolved in a pharmaceutically acceptable fluid, such as polyethylene glycol, in the presence of a stabilizing amount of an antioxidant, such as lipoic acid, had substantially no increase in total degradants after a period of 15 days. The data presented in Table 3 translates to bendamustine-containing compositions including a pharmaceutically acceptable fluid and a stabilizing amount of an antioxidant having a shelf life of at least about 15 months at 5° C. and 25° C.

The sample including PEG alone, on the other hand, which did not contain an antioxidant, did not exhibit stabilizing effects at 40° C. This sample had more than 40% more total impurities than the sample including lipoic acid. Bendamustine-containing compositions with such high levels of total impurities would not be suitable for long-term storage.

Example 4

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in 90% polyethylene glycol 400 and 10% propylene glycol. 5 mg/ml of thioglycerol, α-lipoic acid or dihydrolipoic acid was added as a stabilizing antioxidant as indicated in Table 4 below. The samples were maintained at 40° C. and analyzed after 15 days or one month for drug content and impurity profile as indicated in Table 4 below. The results obtained are presented in Table 4.

TABLE 4

Stability of Bendamustine (50 mg/ml) in 90% PEG 400, 10% Propylene Glycol and Antioxidant

					% Impurities RRT		
Antioxidant	T (° C.)	Time	Content (mg/mL)	% Initial	HP1 0.59	PG ester 1.10	% Total Imps
Thioglycerol	40	initial	48.8	100	<LD	<LD	0
	40	1 month	48.5	99.4	0.06	0.20	0.71
α-lipoic acid	40	initial	49	100	<LD	<LD	0
	40	15 days	48.8	99.6	0.19	0.13	0.32
	40	1 month	48.7	99.4	0.34	0.26	0.79
Dihydrolipoic acid	40	initial	49.3	100	<LD	<LD	0
	40	1 month	47.7	97.4	0.63	0.12	1.84

<LD = Below Level of Deteetion

As shown in Table 4, bendamustine, when dissolved in a pharmaceutically acceptable fluid, such as a combination of polyethylene glycol and propylene glycol, in the presence of a stabilizing amount of an antioxidant, such as thioglycerol, α-lipoic acid or dihydrolipoic acid, had substantially no increase in total degradants after a period of 1 month. This data supports the position that bendamustine-containing compositions according to the invention have a shelf life of at

least about 2 years when stored at temperatures between 5° C. and 25° C.

Example 5

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in a mixture of polyethylene glycol 400 and propylene glycol as indicated in Table 5 below. 5 mg/ml of lipoic acid was added as a stabilizing antioxidant. The samples were maintained at 40° C., 25° C. and 5° C. and analyzed after 1 week, 15 days or one month for drug content and impurity profile as indicated in Table 5 below. The results obtained are presented in Table 5.

TABLE 5

Stability of Bendamustine (50 mg/ml) and Lipoic Acid (5 mg/ml) in PEG400 and Propylene glycol

					% Area of degradants			%
Formulation	Temp.	Time Peiriod	Content (mg/mL)	% of Initial	HP1 0.58	PG ester 1.10	PG ester 1.13	Total Imp.
BDM -	Initial		49.6	100	BDL	BDL	BDL	0.18
50 mg/mL	40° C.	1 W	49.0	98.8	0.05	0.13	BDL	0.38
Lipoic acid -		15 d	48.3	97.4	0.08	0.26	BDL	0.55
5 mg/mL		1 M	48.0	96.8	0.11	0.43	0.13	1.03
PEG 400:PG	25° C.	15 d	49.6	100.0	BDL	0.10	BDL	0.30
(75:25) qs to		1 M	48.4	97.6	0.05	0.19	BDL	0.43
1 mL	5° C.	1 M	49.6	100.0	BDL	0.07	BDL	0.27
BDM -	Initial		50.2	100	BDL	BDL	BDL	0.21
50 mg/mL	40° C.	1 W	49.9	99.4	BDL	0.15	BDL	0.30
Lipoic acid -		15 d	49.1	97.8	0.06	0.35	BDL	0.73
5 mg/mL		1 M	49.0	97.6	0.09	0.90	0.25	1.82
PEG 400:PG	25° C.	15 d	49.9	99.4	BDL	0.12	BDL	0.32
(50:50) qs to		1 M	49.7	99.0	BDL	0.25	BDL	0.59
1 mL	5° C.	1 M	50.0	99.6	BDL	0.11	BDL	0.33
BDM -	Initial		50.8	100	BDL	BDL	BDL	0.21
50 mg/mL	40° C.	1 W	50.4	99.2	BDL	0.11	BDL	0.30
Lipoic acid -		15 d	49.7	97.8	0.07	0.17	BDL	0.43
5 mg/mL		1 M	49.7	97.8	0.13	0.27	0.09	0.84
PEG 400:PG	25° C.	15 d	50.8	100.0	BDL	0.10	BDL	0.26
(90:10) qs to		1 M	50.8	100.0	0.05	0.14	BDL	0.39
1 mL	5° C.	1 M	50.8	100.0	BDL	0.06	BDL	0.34

BDL = Below Detectable Limit

As shown in Table 5, bendamustine, when dissolved in certain mixtures of polyethylene glycol and propylene glycol and a stabilizing amount of lipoic acid, had substantially no increase in total degradants after a period of 1 month. The data presented in Table 5 translates to bendamustine-containing compositions having a shelf life of at least about 2 years when stored at temperatures between 5° C. and at 25° C.

Example 6

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in 90% polyethylene glycol 400 and 10% propylene glycol and α-lipoic acid was added as a stabilizing antioxidant as indicated in Table 6 below. The samples were maintained at 40° C., 25° C. and 5° C. and analyzed for drug content and impurity profile as indicated in Table 6 below. The results obtained are presented in Table 6.

TABLE 6

Stability of Bendamustine in 90% PEG 400, 10% PG and α-lipoic acid

					% Area of degradants								% Total
Formulation	Temp	Time Per.	Amt. mg/ml	% of Initial	0.59	1.10	1.13	1.15	1.17	1.20	1.22	1.30	Imp.
BDM -	Initial		51.0	100	0.20	0.06	<LD	<LD	<LD	<LD	<LD	<LD	0.26
50 mg/mL	40° C.	1 M	50.5	99.0	0.21	0.31	0.13	0.07	0.13	0.10	<LD	<LD	0.95
α-lipoic		2 M	49.7	97.5	0.22	0.71	0.28	0.14	0.12	0.21	0.12	<LD	2.02
acid -		3 M	48.7	95.5	0.22	1.01	0.45	0.21	0.14	0.37	0.16	0.05	2.96
10 mg/mL	25° C.	3 M	50.5	99.0	0.20	0.36	0.07	<LD	<LD	0.10	<LD	<LD	0.73
PEG		6 M	50.4	98.8	0.22	0.60	0.17	0.06	0.06	0.09	0.10	0.08	1.44
400:PG	5° C.	6 M	50.9	99.8	0.16	0.05	<LD	<LD	<LD	<LD	<LD	<LD	0.21
(90:10) qs		12 M	50.6	99.2	0.20	0.18	<LD	<LD	<LD	<LD	<LD	<LD	0.38
to 1 mL													

TABLE 6-continued

Stability of Bendamustine in 90% PEG 400, 10% PG and α-lipoic acid

Formulation	Temp	Time Per.	Amt. mg/ml	% of Initial	% Area of degradants 0.59	1.10	1.13	1.15	1.17	1.20	1.22	1.30	% Total Imp.
BDM -	Initial		50.3	100	0.18	<LD	<LD	<LD	<LD	<LD	<LD	<LD	0.18
50 mg/mL	40° C.	1 M	50.0	99.4	0.19	0.32	0.08	0.06	0.08	0.06	0.06	<LD	0.85
α-lipoic		2 M	49.8	99.0	0.19	0.65	0.21	0.12	0.13	0.23	0.14	0.06	1.85
acid -		3 M	49.5	98.4	0.15	0.89	0.37	0.17	0.13	0.32	0.10	<LD	2.40
15 mg/mL		6 M	47.0	93.4	0.20	1.76	0.66	0.19	0.31	0.47	0.33	0.17	4.93
PEG	25° C.	3 M	50.0	99.4	0.20	0.35	0.08	<LD	<LD	<LD	0.11	<LD	0.79
400:PG		6 M	49.5	98.4	0.19	0.58	0.15	0.06	0.07	0.09	0.08	0.10	1.38
(90:10) qs	5° C.	6 M	50.3	100	0.17	0.06	<LD	<LD	<LD	<LD	<LD	<LD	0.23
to 1 mL		12 M	50.2	99.8	0.19	0.15	<LD	<LD	<LD	<LD	<LD	<LD	0.34

<LD = Below Level of Deteetion

The data reported in Table 6 along with the data in Table 5 demonstrates that bendamustine solutions are stable when dissolved in mixtures of PEG and PG and 5-15 mg/mL α-lipoic acid. As shown in Table 6, bendamustine, when dissolved in combinations of polyethylene glycol and propylene glycol, in the presence of a stabilizing amount of lipoic acid, had less than 3% increase in total degradants after a period of 3 months at 40° C. Additionally, the same compounds had substantially no increase in total degradants after a period of 6-12 months at 5° C. and 25° C. The data corresponds to bendamustine solutions being stable under ambient or refrigerated storage conditions for well in excess of 2 years, and thus long term stable.

Example 7

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in 90% polyethylene glycol 400 and 10% propylene glycol. 2.5 mg/ml of thioglycerol was added as an antioxidizing agent. The samples were maintained at 40° C. and 25° C. and analyzed for drug content and impurity profile as indicated in Table 7 below. The results obtained are presented in Table 7.

The stability is similar to that of α-lipoic acid samples in Example 6 above. As shown in Table 7, bendamustine, when dissolved in a combination of polyethylene glycol and propylene glycol, and a stabilizing amount of thioglycerol, had less than 3% increase in total degradants after a period of 3 months at 40° C. Additionally, the same compounds had substantially no increase in total degradants after a period of 6 months at 25° C. The data reported supports the conclusion that these bendamustine solutions are stable under ambient or refrigerated storage conditions for about 2 years.

Example 8

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in 85% PEG 400 and 15% PG in the presence of 5 mg/ml of thioglycerol. The samples were maintained at 40° C. and 25° C. and analyzed for drug content and impurity profile as indicated in Table 8 below. The results obtained are presented in Table 8.

TABLE 7

Stability of Bendamustine in 90% PEG 400, 10% PG and Thioglycerol

Formulation	Temp	Time Per.	Amt. mg/ml	% of Initial	RRTs of degradants 0.15	0.37	1.10	1.13	1.15	1.17	1.18	1.20	1.22	% Total Imp.
BDM -	Initial		50.3	100	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	0.00
50 mg/mL	40° C.	15 d	50.2	99.8	BDL	BDL	0.18	BDL	BDL	BDL	0.05	0.08	BDL	0.31
Thio		1 M	49.9	99.2	BDL	0.12	0.32	0.07	BDL	BDL	0.09	0.08	BDL	0.75
glycerol -		2 M	49.1	97.6	BDL	0.18	0.56	0.24	0.09	0.17	0.19	0.12	0.11	1.76
2.5 mg/mL		3 M	48.8	97.0	BDL	0.23	0.85	0.34	0.16	0.30	0.34	0.29	0.19	2.94
PEG	25° C.	3 M	49.9	99.2	0.06	0.12	0.23	0.07	BDL	0.06	0.07	0.06	BDL	0.67
400:PG		6 M	49.3	98.0	BDL	0.23	0.53	0.22	0.11	BDL	0.21	0.22	0.20	2.07
(90:10) qs														
to 1 mL														

BDL = Below Deteetable Limit

TABLE 8

Stability of Bendamustine in 85% PEG 400, 15% PG and Thioglycerol

Formulation	Temp.	Time Period	Content (mg/mL)	% of Initial	% Total Imp.
BDM—50 mg/mL	Initial		51.5	100	0.12
Thioglycerol—5 mg/mL	40° C.	1 M	50.4	97.9	1.18
PEG 400:PG (85:15) qs to 1 mL	25° C.	1 M	51.4	99.8	0.41
		3 M	50.4	97.9	1.21
	5° C.	3 M	51.0	99.0	0.26

The stability is similar to that of thioglycerol samples in Example 7 above. As reported in Table 8, total impurities did not exceed 2% at 40° C. or 25° C. storage over one month, or at 25° C. and 5° C. storage after three months. The data reported in Table 8 supports the conclusion that these bendamustine solutions are stable under ambient or refrigerated storage conditions for at least about 2 years if not longer.

We claim:

1. A non-aqueous liquid bendamustine-containing composition, comprising:

a) bendamustine or a pharmaceutically acceptable salt thereof; and

b) a pharmaceutically acceptable fluid comprising;

i) about 5% to about 10% by volume propylene glycol,

ii) polyethylene glycol, and

iii) a stabilizing amount of an antioxidant selected from the group consisting of thioglycerol, monothioglycerol, lipoic acid, propyl gallate, methionine, cysteine, metabisulfites, sodium formaldehyde sulfoxylate, phenol-containing aromatic and aliphatic compounds and dihydrolipoic acid;

the bendamustine-containing composition having less than or equal to 0.11% total PG esters at about 1 month of storage at a temperature of about 5° C.;

wherein the ratio of polyethylene glycol to propylene glycol is selected from the group consisting of: about 95:5, about 90:10, about 85:15, about 80:20 and about 75:25.

2. The liquid bendamustine-containing composition of claim **1**, wherein said bendamustine-containing composition has less than or equal to 0.18% total PG esters at about 12 months of storage at a temperature of about 5° C.

3. The liquid bendamustine-containing composition of claim **1**, wherein the amount of propylene glycol in the pharmaceutically acceptable fluid is about 10%.

4. The liquid bendamustine-containing composition of claim **1**, wherein the bendamustine concentration is from about 20 mg/mL to about 60 mg/mL.

5. The liquid bendamustine-containing composition of claim **4**, wherein the bendamustine concentration is from about 25 mg/mL to about 50 mg/mL.

6. The liquid bendamustine-containing composition of claim **5**, wherein the bendamustine concentration is about 50 mg/mL.

* * * * *

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APPLICATION NUMBER: *15/013,436*
FILING DATE: *February 02, 2016*
PATENT NUMBER: *9,572,797*
ISSUE DATE: *February 21, 2017*

Dist. Delaware
No. 17-1154-CFC
PTX-0310

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W. MONTGOMERY
Certifying Officer

(12) **United States Patent**
Palepu et al.

(10) **Patent No.: US 9,572,797 B2**
(45) **Date of Patent: *Feb. 21, 2017**

(54) **FORMULATIONS OF BENDAMUSTINE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/013,436**

(22) Filed: **Feb. 2, 2016**

(65) **Prior Publication Data**

US 2016/0143888 A1 May 26, 2016

Related U.S. Application Data

(63) Continuation of application No. 14/031,879, filed on Sep. 19, 2013, now Pat. No. 9,265,831, which is a continuation of application No. 13/016,473, filed on Jan. 28, 2011, now Pat. No. 8,609,707.

(60) Provisional application No. 61/299,100, filed on Jan. 28, 2010.

(51) **Int. Cl.**

A61K 31/4184	(2006.01)
A61K 47/10	(2006.01)
A61K 47/12	(2006.01)
A61K 47/18	(2006.01)
A61K 47/20	(2006.01)
A61K 47/22	(2006.01)
A61K 9/08	(2006.01)
A61K 9/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/4184*** (2013.01); ***A61K 9/08*** (2013.01); ***A61K 47/10*** (2013.01); ***A61K 47/12*** (2013.01); ***A61K 47/18*** (2013.01); ***A61K 47/186*** (2013.01); ***A61K 47/20*** (2013.01); ***A61K 47/22*** (2013.01); *A61K 9/0019* (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/4184; A61K 47/10; A61K 47/12; A61K 47/18; A61K 47/186; A61K 47/20; A61K 47/22; A61K 9/0019; A61K 9/08

See application file for complete search history.

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(57) **ABSTRACT**

Long term storage stable bendamustine-containing compositions are disclosed. The compositions can include bendamustine or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable fluid which can include in some embodiments PEG, PG or mixtures thereof and an antioxidant or chloride ion source. The bendamustine-containing compositions have less than about 5% total impurities, on a normalized peak area response ("PAR") basis as determined by high performance liquid chromatography ("HPLC") at a wavelength of 223 nm, after at least about 15 months of storage at a temperature of from about 5° C. to about 25° C.

27 Claims, No Drawings

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FORMULATIONS OF BENDAMUSTINE

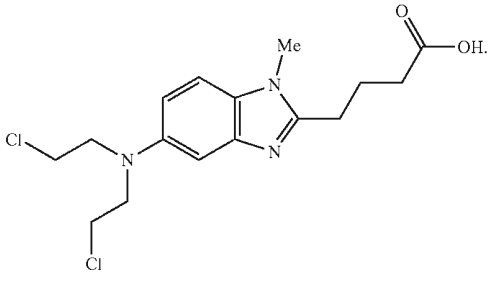
CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 14/031,879, filed Sep. 19, 2013, which is a continuation of application Ser. No. 13/016,473, filed Jan. 28, 2011, now U.S. Pat. No. 8,609,707, issued Dec. 17, 2013, which claims the benefit of U.S. Provisional Patent Application No. 61/299,100, filed Jan. 28, 2010, the contents of each of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Bendamustine free base is represented by the following structural formula (I)

(I)



Bendamustine is used in the treatment of a number of cancers including leukemias, Hodgkins disease and multiple myelomas. Bendamustine is the active ingredient of the commercial product TreandaTM, a lyophilized powder for reconstitution.

Bendamustine exhibits rapid degradation upon reconstitution of the lyophilized product. Bendamustine undergoes hydrolysis by direct substitution rather than an addition elimination process due to the presence of the highly labile aliphatic chlorine atoms. Some of the main degradants of bendamustine are the monohydroxy compound known as HP1 (hydrolysis product 1) and dihydroxy compound HP2 (hydrolysis product 2). The monohydroxy compound appears as the main impurity at Relative Retention Time (RRT) 0.6 and the dihydroxy compound appears as the main impurity at RRT 0.27. Minor peaks appear at RRT 1.2, which are presently unknown.

The stability of bendamustine in water is measured in hours, and is therefore, not suitable for long-term storage in liquid form. The lyophile possesses good chemical stability. However, reconstitution of the lyophile is clinically inconvenient, taking 15-30 mins with implications of chemical instability. There is a need for ready to use (RTU) bendamustine formulations having enhanced stability.

SUMMARY OF THE INVENTION

In other aspects of the invention, the bendamustine-containing compositions include a) a pharmaceutically acceptable fluid which contains one or more of propylene glycol, ethanol, polyethylene glycol, benzyl alcohol and glycofurol, and b) a stabilizing amount of a chloride salt. In other aspects of the invention, the bendamustine-containing compositions include DMSO (dimethyl sulfoxide) as part of the pharmaceutically acceptable fluid included therein.

Regardless of the pharmaceutically acceptable fluid included, the amount of bendamustine included in the composition is preferably from about 20 mg/mL to about 60 mg/mL. Still further aspects of the invention include methods of treatment using bendamustine-containing compositions and kits containing the same.

One of the advantages of the inventive liquid compositions is that they have substantially improved long term stability when compared to currently available formulations. For example, the inventive bendamustine compositions are substantially free of impurities after at least about 15 months at a temperature of from about 5° C. to about 25° C. The inventive formulations are advantageously ready to use or ready for further dilution. Reconstitution of lyophilized powders is not required.

DETAILED DESCRIPTION OF THE INVENTION

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein, RRT is calculated by dividing the retention time of the peak of interest by the retention time of the main peak. Any peak with an RRT<1 elutes before the main peak, and any peak with an RRT>1 elutes after the main peak.

For purposes of the present invention, "substantially free of impurities" shall be understood to include bendamustine-containing compositions in which the amount of total impurities is less than about 5%, as calculated on a normalized peak area response ("PAR") basis as determined by high performance liquid chromatography ("HPLC") at a wavelength of 223 nm, after a period of about 15 months at a temperature of from about 5° C. to about 25° C. The amount of impurities is further calculated as being based upon the original amount bendamustine (or salt thereof) being present in the composition or formulation.

For purposes of the present invention, a pharmaceutically acceptable fluid is a fluid which is suitable for pharmaceutical use.

Preferably, the amount of any individual degradant in the inventive compositions does not exceed 2% PAR as determined by HPLC at a wavelength of 223 nm after storage periods of at least about 15 months at a temperature of from about 5° C. to about 25° C. In some aspects, the amount of time the inventive compositions demonstrate long term storage stability is at least about 18 months and preferably at least about 2 years when stored under the conditions described herein.

In accordance with one aspect of the invention there are provided long term storage stable bendamustine-containing compositions including:

a) bendamustine or a pharmaceutically acceptable salt thereof; and

b) a pharmaceutically acceptable fluid including

i) PEG, PG or mixtures thereof; and

ii) a stabilizing amount of an antioxidant.

The total impurities in the inventive compositions resulting from the degradation of the bendamustine in the compositions is less than about 5% PAR as determined by HPLC at a wavelength of 223 nm after at least about 15 months at a temperature of from about 5° C. to about 25° C., and thus have long term stability for at least the same period of time

or longer. Preferably, the bendamustine-containing compositions demonstrate long term storage stability for at least about 2 years, especially when stored at the lower (refrigerated) temperatures. In one embodiment, the amount of total impurities in the inventive compositions resulting from the degradation of the bendamustine is less than about 3% PAR as determined by HPLC at a wavelength of 223 nm after at least about 2 years at a temperature of from about 5° C. to about 25° C.

In some aspects of the invention, the bendamustine concentration in the inventive compositions is from about 10 mg/mL to about 100 mg/mL, preferably 20 mg/mL to about 60 mg/mL. Preferably the bendamustine concentration in the inventive compositions is from about 25 mg/mL to about 50 mg/mL, and more preferably from about 30 mg/mL to about 50 mg/mL. It will be understood that compositions containing any useful concentration within the ranges, i.e. 10, 20, 25, 30, 35, 40, 45, 50, 55, 60 . . . 100 are contemplated. In other embodiments, the bendamustine concentration in the composition is about 50 mg/mL. In alternative aspects, the amount of bendamustine is outside these ranges but the amounts will be sufficient for single or multiple administrations of dosages generally regarded as effective amounts.

In several embodiments of the invention, pharmaceutically acceptable fluid is non-aqueous and may be, but is not necessarily, a solvent for the bendamustine or salt thereof. Within this aspect, the pharmaceutically acceptable fluid is propylene glycol (PG) or polyethylene glycol (PEG). In other embodiments of the invention however, the pharmaceutically acceptable fluid is a mixture of PEG and PG. For example, the pharmaceutically acceptable fluid can include about 50% PEG and about 50% PG. Alternatively, pharmaceutically acceptable fluid includes about 95% PEG and about 5% PG. The amount of PEG and PG can also be varied within the ranges, i.e. the ratio of PEG:PG in the pharmaceutically acceptable fluid can range from about 95:5 to about 50:50. Within this range, is a pharmaceutically acceptable fluid containing about 75% PEG and about 25% PG, and preferably 80% PEG and 20% PG. In another embodiment, a pharmaceutically acceptable fluid can include about 85% PEG and about 15% PG while another preferred pharmaceutically acceptable fluid includes about 90% PEG and about 10% PG. The molecular weight of the PEG will be within the range of pharmaceutically acceptable weights although PEG 400 is preferred in many aspects of the invention.

Without meaning to be bound by any theory or hypothesis, the hydroxide of the polyethylene glycol molecule is less reactive than the hydroxides of propylene glycol. As a result, the ester forms at a slower rate in polyethylene glycol than propylene glycol and the resulting bendamustine degradants are unexpectedly and substantially reduced over extended periods of time when PEG is a substantial part of the pharmaceutically acceptable fluid.

The bendamustine-containing compositions according to several preferred aspects of the invention include a stabilizing amount of an antioxidant. For purposes of the present invention, "stabilizing amount" shall be understood to include those amounts which increase or enhance the stability of the bendamustine in the compositions described herein. The presence of one or more antioxidants described herein thus contributes, at least in part to the long term stability of the composition. Within this guideline, suitable antioxidant concentrations in the compositions can range from about 2.5 mg/mL to about 35 mg/mL, and preferably from about 5 mg/mL to about 20 mg/mL or from about 10 mg/mL to about 15 mg/mL. In some other embodiments, the concentration of the antioxidant in the bendamustine-containing composition is about 5 mg/mL.

Suitable antioxidants for inclusion include those which are pharmaceutically acceptable for use in human and veterinary formulations although not limited to those currently regarded as safe by any regulatory authority. For example, the antioxidant can be selected from among lipoic acid, thioglycerol (also known as monothioglycerol) and analogs thereof, propyl gallate, methionine, cysteine, metabisulfites, sodium formaldehyde sulfoxylate, phenol-containing aromatic and aliphatic compounds, dihydrolipoic acid and mixtures of the foregoing. Preferably, the antioxidant is thioglycerol, lipoic acid or a mixture thereof. Some particularly preferred embodiments of the invention include thioglycerol.

In view of the foregoing, some preferred long term storage stable bendamustine-containing compositions in accordance with the invention compositions include:

I. a) bendamustine or a pharmaceutically acceptable salt thereof; and
   b) a pharmaceutically acceptable fluid including
      i) polyethylene glycol and propylene glycol; and
      ii) a stabilizing amount of thioglycerol; or

II. a) about 50 mg/mL bendamustine or a pharmaceutically acceptable salt thereof;

and

   b) a pharmaceutically acceptable fluid including
      i) about 90% PEG and about 10% PG; and
      ii) about 2.5 mg/mL thioglycerol.

Each of these compositions have the same stability profiles already described, i.e. having less than about 5% total impurities, PAR as determined by HPLC at a wavelength of 223 nm, after at least about 15 months of storage at a temperature of from about 5° C. to about 25° C.

In accordance with other aspects of the invention, there are provided long term storage stable bendamustine-containing compositions, including:

a) bendamustine or a pharmaceutically acceptable salt thereof;
b) a pharmaceutically acceptable fluid including one or more of the following: PG, ethanol, PEG, benzyl alcohol and glycofurol; and
c) a stabilizing amount of a chloride salt.

These compositions also have the low levels of impurities and long term stability mentioned herein. Preferred pharmaceutically acceptable fluids include PG, PEG or ethanol in this embodiment of the invention. Preferably, the PEG is PEG 400. If desired, glycerin and/or 88% (w/w) lactic acid can be added to the pharmaceutically acceptable fluid.

Suitable chloride salts include but are not limited to organic chloride salts, sodium chloride, choline chloride, hydrochloride salts of amino acids and mixtures thereof. Thus, as will be appreciated by those of ordinary skill, one can select from among a number of suitable chloride salts and it is Applicants' intention that the scope of the invention includes all such chloride salts that are capable of being included in bendamustine-containing formulations for extended periods without having a deleterious effect on the drug. In one embodiment of the invention, the chloride salt concentration is from about 10 to about 300 mg/mL. In another embodiment, the chloride salt concentration is from about 50 to about 215 mg/mL. In one preferred embodiment, the chloride salt concentration is about 215 mg/mL.

In accordance with another aspect of the invention, there is provided long term storage stable bendamustine-containing compositions, including:

a) bendamustine or a pharmaceutically acceptable salt thereof; and

b) a pharmaceutically acceptable fluid including DMSO.

These compositions also have the low levels of impurities and long term stability mentioned herein. In some aspects, the bendamustine concentration in these compositions is from about 10 mg/mL to about 100 mg/mL. Preferably, the bendamustine concentration is from about 20 mg/mL to about 50 mg/mL, more preferably from about 25 mg/mL to about 50 mg/mL. In an alternative embodiment, the bendamustine concentration is about 50 mg/mL.

Another embodiment of the invention provides methods of treating cancer in mammals. The methods include administering to a mammal in need thereof an effective amount of one of the bendamustine-containing compositions described herein. Since the active ingredient portion of the inventive composition is an FDA-approved drug, those of ordinary skill will recognize that the doses of bendamustine employed in this aspect of the invention will be similar to those employed in any treatment regimens designed for bendamustine as marketed under the trade name TREANDA. The patient package insert containing dosing information is incorporated herein by reference. The methods of treatment also include administering the inventive formulations for any purpose or physical condition for which bendamustine has been indicated as being useful.

Another embodiment of the invention includes methods of preparing bendamustine-containing compositions described herein. The methods include reconstituting lyophilized bendamustine in a pharmaceutically acceptable fluid containing one of the following:

A) i) PEG, PG or mixtures thereof; and
ii) a stabilizing amount of an antioxidant;

B) i) one or more of PG, ethanol, PEG, benzyl alcohol and glycofurol; and
ii) a stabilizing amount of a chloride salt; or

C) DMSO.

The steps are carried out under pharmaceutically acceptable conditions for sterility and manufacturing.

In a further aspect of the invention, there are provided methods of controlling or preventing the formation of impurities in bendamustine-containing compositions during long term storage. The methods include combining an amount of bendamustine or a pharmaceutically acceptable salt thereof with a sufficient amount of a pharmaceutically acceptable fluid containing one of the following:

A) i) PEG, PG or mixtures thereof; and
ii) a stabilizing amount of an antioxidant;

B) i) one or more of PG, ethanol, PEG, glycofurol and benzyl alcohol; and
ii) a stabilizing amount of a chloride salt; or

C) DMSO.

Further optional steps in accordance therewith include transferring one or more pharmaceutically acceptable doses of the formulations into a suitable sealable container and storing the sealed container at a temperature of from about 5° C. to about 25° C. As a result of carrying out these steps, it is possible to control or substantially prevent the formation of impurities which otherwise occur with bendamustine-containing compositions during long term storage so that the artisan is provided with bendamustine-containing formulations having less than about 5% total impurities PAR as determined by HPLC at a wavelength of 223 nm, after at least about 15 months of storage at a temperature of from about 5° C. to about 25° C.

The compositions of the present invention can be packaged in any suitable sterile vial or container fit for the sterile storage of a pharmaceutical such as bendamustine. Suitable containers can be glass vials, polypropylene or polyethylene vials or other special purpose containers and be of a size sufficient to hold one or more doses of bendamustine.

A further aspect of the invention includes kits containing lyophilized bendamustine or a pharmaceutically acceptable salt thereof in a first container or vial; and, in a second container, a sufficient amount of a pharmaceutically acceptable fluid such as those described herein, i.e. one of the following:

A) i) PEG, PG or mixtures thereof; and
ii) a stabilizing amount of an antioxidant;

B) i) one or more of PG, ethanol, PEG, glycofurol and benzyl alcohol; and
ii) a stabilizing amount of a chloride salt; or

C) DMSO.

For purposes of this embodiment, the amount of fluid which is sufficient is an amount which allows the bendamustine to be dissolved or dispersed to a degree which renders the liquid composition ready for use.

As will be appreciated by those of ordinary skill, the kit will contain other pharmaceutically necessary materials for storing and/or administering the drug, including instructions for storage and use, additional diluents, if desired, etc.

EXAMPLES

The following examples serve to provide further appreciation of the invention but are not meant in any way to restrict the effective scope of the invention.

Example 1

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 10mg/m1 in one of ethanol, propylene glycol and benzyl alcohol as indicated in Table 1 below. 215 mg/ml of choline chloride was added in half of the samples as a source of soluble chloride ions. The samples were maintained at 40° C. and analyzed periodically for drug content and total impurities. The results obtained are presented in Table 1.

TABLE 1

Stability of Bendamustine HCl

Formulation	Temp	Time	BDM mg/ml	% Total Impurities
BDM - 10 mg/mL		Initial	10.43	0.27
Choline chloride -	40° C.	48 hrs	10.48	1.27
215 mg/mL		7 day	10.26	2.11
Ethanol qs to 1 mL				
BDM - 10 mg/mL		Initial	10.55	0.27
Ethanol qs to 1 mL	40° C.	48 hrs	10.30	2.39
		7 day	9.55	6.66
BDM - 10 mg/mL		Initial	9.99	0.21
Choline chloride -	40° C.	48 hrs	9.95	0.60
215 mg/mL		7 day	9.43	2.31
Propylene glycol qs to 1 mL				
BDM - 10 mg/mL		Initial	9.68	0.21
Propylene glycol qs to	40° C.	48 hrs	9.45	0.88
1mL		7 day	9.00	3.44
BDM - 10 mg/mL		Initial	9.95	1.19
Choline Chloride -	40° C.	48 hrs	9.89	3.51
215 mg/mL		7 day	8.97	4.24
Benzyl alcohol qs to 1 mL				
BDM - 10 mg/mL		Initial	9.52	0.33

TABLE 1-continued

Stability of Bendamustine HCl

Formulation	Temp	Time	BDM mg/ml	% Total Impurities
Benzyl alcohol qs to 1 mL	40° C.	48 hrs	8.67	4.18
		7 day	7.49	7.84

Note:
In Table 1 the total % impurities include total contributions from peaks at various RRTs.

As shown in Table 1, the bendamustine formulations are very stable in solutions containing solvent and chloride salt. Table 1 shows that bendamustine, when dissolved at a concentration of about 10 mg/mL, in a pharmaceutically acceptable fluid, such as ethanol and propylene glycol, and containing a stabilizing amount of a chloride salt, such as choline chloride, had less than about 5% after at least 7 days storage at 40° C.

The data presented in Table 1 translates to bendamustine-containing compositions including a pharmaceutically acceptable fluid and a stabilizing amount of a chloride salt having a shelf life of at least about 15 months at 5° C. and 25° C.

The sample including ethanol alone exhibited more than 6.5 total degradants after 7 days storage at 40° C. The sample including benzyl alcohol alone exhibited more than 7.5% total degradants after 7 days storage at 40° C. Bendamustine-containing compositions with such high levels of degradation would not be suitable for long-term storage.

Example 2

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 10mg/m1 in DMSO. The samples were maintained at 40° C. and analyzed periodically for drug content and impurity profile. The results obtained are presented in Table 2.

TABLE 2

Stability of Bendamustine HCl in DMSO

Formulation	Temp	Time	Content (mg/mL)	% Total Imp
BDM - 10 mg/mL	Initial		10.2	0.23
DMSO qs to 1 mL	40° C.	48 hrs	9.80	0.30
		1 week	10.0	0.56

Note:
In Table 2 the total % impurities include total contributions from peaks at various RRTs.

Table 2 shows that bendamustine, when dissolved in DMSO, had substantially no increase in total degradants. The data presented in Table 2 translates to bendamustine-containing compositions including DMSO having a shelf life of at least about 15 months at 5° C. and 25° C. In fact, such compositions are expected to have long term stability for periods beyond 15 months, i.e. up to 2 years or greater.

Example 3

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 20 mg/ml in polyethylene glycol 400 and 5 mg/ml of lipoic acid was added as a stabilizing antioxidant as indicated in Table 3 below. The samples were maintained at 40° C. or 25° C. and analyzed after 15 days for drug content and impurities. The results obtained are presented in Table 3.

TABLE 3

Stability of Bendamustine (20 mg/ml) in PEG 400 and Antioxidants

Antioxidant	T° C.	Time days	% Initial	% Imp RRT 0.58	% Total Imps
None	25	15	97.6	2.08	2.28
	40	15	56.3	2.17	41.9
Lipoic Acid 5 mg/ml	25	15	98.5	<LD	0.23
	40	15	97.5	0.33	0.53

<LD = Below Level of Detection

As shown in Table 3, bendamustine, when dissolved in a pharmaceutically acceptable fluid, such as polyethylene glycol, in the presence of a stabilizing amount of an antioxidant, such as lipoic acid, had substantially no increase in total degradants after a period of 15 days. The data presented in Table 3 translates to bendamustine-containing compositions including a pharmaceutically acceptable fluid and a stabilizing amount of an antioxidant having a shelf life of at least about 15 months at 5° C. and 25° C.

The sample including PEG alone, on the other hand, which did not contain an antioxidant, did not exhibit stabilizing effects at 40° C. This sample had more than 40% more total impurities than the sample including lipoic acid. Bendamustine-containing compositions with such high levels of total impurities would not be suitable for long-term storage.

Example 4

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in 90% polyethylene glycol 400 and 10% propylene glycol. 5 mg/ml of thioglycerol, a-lipoic acid or dihydrolipoic acid was added as a stabilizing antioxidant as indicated in Table 4 below. The samples were maintained at 40° C. and analyzed after 15 days or one month for drug content and impurity profile as indicated in Table 4 below. The results obtained are presented in Table 4.

TABLE 4

Stability of Bendamustine (50 mg/ml) in 90% PEG 400, 10% Propylene Glycol and Antioxidant

Antioxidant	T (° C.)	Time	Content (mg/mL)	% Initial	% Impurities RRT HP1 0.59	PG ester 1.10	% Total Imps
Thioglycerol	40	initial	48.8	100	<LD	<LD	0
	40	1 month	48.5	99.4	0.06	0.20	0.71
α-lipoic acid	40	initial	49	100	<LD	<LD	0
	40	15 days	48.8	99.6	0.19	0.13	0.32
	40	1 month	48.7	99.4	0.34	0.26	0.79
Dihydrolipoic acid	40	initial	49.3	100	<LD	<LD	0
	40	1 month	47.7	97.4	0.63	0.12	1.84

<LD = Below Level of Detection

As shown in Table 4, bendamustine, when dissolved in a pharmaceutically acceptable fluid, such as a combination of polyethylene glycol and propylene glycol, in the presence of a stabilizing amount of an antioxidant, such as thioglycerol, a-lipoic acid or dihydrolipoic acid, had substantially no increase in total degradants after a period of 1 month. This data supports the position that bendamustine-containing

compositions according to the invention have a shelf life of at least about 2 years when stored at temperatures between 5° C. and 25° C.

Example 5

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in a mixture of polyethylene glycol 400 and propylene glycol as indicated in Table 5 below. 5 mg/ml of lipoic acid was added as a stabilizing antioxidant. The samples were maintained at 40° C., 25° C. and 5° C. and analyzed after 1 week, 15 days or one month for drug content and impurity profile as indicated in Table 5 below. The results obtained are presented in Table 5.

TABLE 5

Stability of Bendamustine (50 mg/ml) and Lipoic Acid (5 mg/ml) in PEG400 and Propylene glycol

Formulation	Temp.	Time Period	Content (mg/mL)	% of Initial	% Area of degradants HP1 0.58	PG ester 1.10	PG ester 1.13	% Total Imp.
BDM-	Initial		49.6	100	BDL	BDL	BDL	0.18
50 mg/mL	40° C.	1 W	49.0	98.8	0.05	0.13	BDL	0.38
Lipoic acid-		15 d	48.3	97.4	0.08	0.26	BDL	0.55
5 mg/mL		1 M	48.0	96.8	0.11	0.43	0.13	1.03
PEG 400:PG	25° C.	15 d	49.6	100.0	BDL	0.10	BDL	0.30
(75:25)		1 M	48.4	97.6	0.05	0.19	BDL	0.43
qs to 1 mL	5° C.	1 M	49.6	100.0	BDL	0.07	BDL	0.27
BDM-	Initial		50.2	100	BDL	BDL	BDL	0.21
50 mg/mL	40° C.	1 W	49.9	99.4	BDL	0.15	BDL	0.30
Lipoic acid-		15 d	49.1	97.8	0.06	0.35	BDL	0.73
5 mg/mL		1 M	49.0	97.6	0.09	0.90	0.25	1.82
PEG 400:PG	25° C.	15 d	49.9	99.4	BDL	0.12	BDL	0.32
(50:50)		1 M	49.7	99.0	BDL	0.25	BDL	0.59
qs to 1 mL	5° C.	1 M	50.0	99.6	BDL	0.11	BDL	0.33
BDM-	Initial		50.8	100	BDL	BDL	BDL	0.21
50 mg/mL	40° C.	1 W	50.4	99.2	BDL	0.11	BDL	0.30
Lipoic acid-		15 d	49.7	97.8	0.07	0.17	BDL	0.43
5 mg/mL		1 M	49.7	97.8	0.13	0.27	0.09	0.84
PEG 400:PG	25° C.	15 d	50.8	100.0	BDL	0.10	BDL	0.26
(90:10)		1 M	50.8	100.0	0.05	0.14	BDL	0.39
qs to 1 mL	5° C.	1 M	50.8	100.0	BDL	0.06	BDL	0.34

BDL = Below Deteetable Limit

As shown in Table 5, bendamustine, when dissolved in certain mixtures of polyethylene glycol and propylene glycol and a stabilizing amount of lipoic acid, had substantially no increase in total degradants after a period of 1 month. The data presented in Table 5 translates to bendamustine-containing compositions having a shelf life of at least about 2 years when stored at temperatures between 5° C. and at 25° C.

Example 6

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in 90% polyethylene glycol 400 and 10% propylene glycol and a-lipoic acid was added as a stabilizing antioxidant as indicated in Table 6 below. The samples were maintained at 40° C., 25° C. and 5° C. and analyzed for drug content and impurity profile as indicated in Table 6 below. The results obtained are presented in Table 6.

TABLE 6

Stability of Bendamustine in 90% PEG 400, 10% PG and α-lipoic acid

Formulation	Temp	Time Per.	Amt. mg/ml	% of Ini-tial	% Area of degradants 0.59	1.10	1.13	1.15	1.17	1.20	1.22	1.30	% Total Imp.
BDM-	Initial		51.0	100	0.20	0.06	<LD	<LD	<LD	<LD	<LD	<LD	0.26
50 mg/mL	40° C.	1 M	50.5	99.0	0.21	0.31	0.13	0.07	0.13	0.10	<LD	<LD	0.95
α-lipoic acid-		2 M	49.7	97.5	0.22	0.71	0.28	0.14	0.12	0.21	0.12	<LD	2.02
10 mg/mL		3 M	48.7	95.5	0.22	1.01	0.45	0.21	0.14	0.37	0.16	0.05	2.96
PEG 400:PG	25° C.	3 M	50.5	99.0	0.20	0.36	0.07	<LD	<LD	0.10	<LD	<LD	0.73
(90:10)		6 M	50.4	98.8	0.22	0.60	0.17	0.06	0.06	0.09	0.10	0.08	1.44
qs to 1 mL	5° C.	6 M	50.9	99.8	0.16	0.05	<LD	<LD	<LD	<LD	<LD	<LD	0.21
		12 M	50.6	99.2	0.20	0.18	<LD	<LD	<LD	<LD	<LD	<LD	0.38
BDM-	Initial		50.3	100	0.18	<LD	<LD	<LD	<LD	<LD	<LD	<LD	0.18
50 mg/mL	40° C.	1 M	50.0	99.4	0.19	0.32	0.08	0.06	0.08	0.06	0.06	<LD	0.85
α-lipoic acid-		2 M	49.8	99.0	0.19	0.65	0.21	0.12	0.13	0.23	0.14	0.06	1.85
15 mg/mL		3 M	49.5	98.4	0.15	0.89	0.37	0.17	0.13	0.32	0.10	<LD	2.40
PEG 400:PG		6 M	47.0	93.4	0.20	1.76	0.66	0.19	0.31	0.47	0.33	0.17	4.93
(90:10)	25° C.	3 M	50.0	99.4	0.20	0.35	0.08	<LD	<LD	<LD	0.11	<LD	0.79
qs to 1 mL		6 M	49.5	98.4	0.19	0.58	0.15	0.06	0.07	0.09	0.08	0.10	1.38
	5° C.	6 M	50.3	100	0.17	0.06	<LD	<LD	<LD	<LD	<LD	<LD	0.23
		12 M	50.2	99.8	0.19	0.15	<LD	<LD	<LD	<LD	<LD	<LD	0.34

<LD = Below Level of Detection

The data reported in Table 6 along with the data in Table 5 demonstrates that bendamustine solutions are stable when dissolved in mixtures of PEG and PG and 5-15mg/mL a-lipoic acid. As shown in Table 6, bendamustine, when dissolved in combinations of polyethylene glycol and propylene glycol, in the presence of a stabilizing amount of lipoic acid, had less than 3% increase in total degradants after a period of 3 months at 40° C. Additionally, the same compounds had substantially no increase in total degradants after a period of 6-12 months at 5° C. and 25° C. The data corresponds to bendamustine solutions being stable under ambient or refrigerated storage conditions for well in excess of 2 years, and thus long term stable.

Example 7

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in 90% polyethylene glycol 400 and 10% propylene glycol. 2.5 mg/ml of thioglycerol was added as an antioxidizing agent. The samples were maintained at 40° C. and 25° C. and analyzed for drug content and impurity profile as indicated in Table? below. The results obtained are presented in Table 7.

TABLE 7

Stability of Bendamustine in 90% PEG 400, 10% PG and Thioglycerol

Formulation	Temp	Time Per.	Amt mg/ml	% of Initial	RRTs of degradants 0.15	0.37	1.10	1.13	1.15	1.17	1.18	1.20	1.22	% Total Imp.
BDM-	Initial		50.3	100	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	0.00
50 mg/mL	40° C.	15 d	50.2	99.8	BDL	BDL	0.18	BDL	BDL	BDL	0.05	0.08	BDL	0.31
Thio		1 M	49.9	99.2	BDL	0.12	0.32	0.07	BDL	BDL	0.09	0.08	BDL	0.75
glycerol-		2 M	49.1	97.6	BDL	0.18	0.56	0.24	0.09	0.17	0.19	0.12	0.11	1.76
2.5 mg/mL		3 M	48.8	97.0	BDL	0.23	0.85	0.34	0.16	0.30	0.34	0.29	0.19	2.94
PEG 400:PG	25° C.	3 M	49.9	99.2	0.06	0.12	0.23	0.07	BDL	0.06	0.07	0.06	BDL	0.67
(90:10)		6 M	49.3	98.0	BDL	0.23	0.53	0.22	0.11	BDL	0.21	0.22	0.20	2.07
qs to 1 mL														

BDL = Below Detectable Limit

The stability is similar to that of a-lipoic acid samples in Example 6 above. As shown in Table 7, bendamustine, when dissolved in a combination of polyethylene glycol and propylene glycol, and a stabilizing amount of thioglycerol, had less than 3% increase in total degradants after a period of 3 months at 40° C. Additionally, the same compounds had substantially no increase in total degradants after a period of 6 months at 25° C. The data reported supports the conclusion that these bendamustine solutions are stable under ambient or refrigerated storage conditions for about 2 years.

Example 8

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in 85% PEG 400 and 15% PG in the presence of 5 mg/ml of thioglycerol. The samples were maintained at 40° C. and 25° C. and analyzed for drug content and impurity profile as indicated in Table 8 below. The results obtained are presented in Table 8.

TABLE 8

Stability of Bendamustine in 85% PEG 400, 15% PG and Thioglycerol

Formulation	Temp.	Time Period	Content (mg/mL)	% of Initial	% Total Imp.
BDM - 50 mg/mL	Initial		51.5	100	0.12
Thioglycerol - 5 mg/mL	40° C.	1 M	50.4	97.9	1.18
PEG 400:PG (85:15) qs to	25° C.	1 M	51.4	99.8	0.41
1 mL		3 M	50.4	97.9	1.21
	5° C.	3 M	51.0	99.0	0.26

The stability is similar to that of thioglycerol samples in Example 7 above. As reported in Table 8, total impurities did not exceed 2% at 40° C. or 25° C. storage over one month, or at 25° C. and 5 ° C. storage after three months. The data reported in Table 8 supports the conclusion that these bendamustine solutions are stable under ambient or refrigerated storage conditions for at least about 2 years if not longer.

We claim:

1. A method of treating leukemia, Hodgkin's disease, or multiple myeloma in a mammal, comprising administering to the mammal, a liquid bendamustine-containing composition comprising:

a) bendamustine or a pharmaceutically acceptable salt thereof; and

b) a non-aqueous pharmaceutically acceptable fluid comprising

about 5% to about 10%, based on the volume of the pharmaceutically acceptable fluid, of propylene glycol,

polyethylene glycol,

and a stabilizing amount of an antioxidant selected from the group consisting of thioglycerol, monothioglycerol, lipoic acid, propyl gallate, methionine, cysteine, metabisulfites, sodium formaldehyde sulfoxylate, phenol-containing aromatic and aliphatic compounds and dihydrolipoic acid;

the bendamustine-containing composition having less than or equal to 0.11% total PG esters at about 1 month of storage at a temperature of about 5° C.;

wherein the ratio of polyethylene glycol to propylene glycol is selected from the group consisting of: about 95:5, about 90:10, about 85:15, about 80:20, and about 75:25.

2. The method of claim 1, wherein the bendamustine-containing composition has less than or equal to 0.18% total PG esters at about 12 months of storage at a temperature of about 5° C.

3. The method of claim 1, wherein the amount of propylene glycol in the pharmaceutically acceptable fluid is about 10%.

4. The method of claim 1, wherein the bendamustine concentration is from about 20 mg/mL to about 60 mg/mL.

5. The method of claim 4, wherein the bendamustine concentration is from about 25 mg/mL to about 50 mg/mL.

6. The method of claim 5, wherein the bendamustine concentration is about 50 mg/mL.

7. The method of claim 1, wherein said bendamustine-containing composition has less than or equal to 0.12% total PG esters at about 15 days of storage at a temperature of about 25° C.

8. The method of claim 1, wherein said bendamustine-containing composition has less than or equal to 0.25% total PG esters at about 1 month of storage at a temperature of about 25° C.

9. The method of claim 1, wherein said bendamustine-containing composition has less than or equal to 0.43% total PG esters at about 3 months of storage at a temperature of about 25° C.

10. The method of claim 1, wherein said bendamustine-containing composition has less than or equal to 0.77% total PG esters at about 6 months of storage at a temperature of about 25° C.

11. The method of claim 1, wherein the antioxidant is thioglycerol or monothioglycerol.

12. The method of claim 1, wherein the antioxidant concentration is from about 2.5 mg/mL to about 35 mg/mL.

13. The method of claim 1, for the treatment of leukemia.

14. The method of claim 1, for the treatment of Hodgkin's disease.

15. The method of claim 1, for the treatment of multiple myeloma.

16. A method of treating leukemia, Hodgkin's disease, or multiple myeloma in a mammal, comprising administering to the mammal, a liquid bendamustine-containing composition, comprising:

a) bendamustine or a pharmaceutically acceptable salt thereof; and

b) a non-aqueous pharmaceutically acceptable fluid comprising propylene glycol, polyethylene glycol, and a stabilizing amount of an antioxidant selected from the group consisting of thioglycerol, monothioglycerol, lipoic acid, propyl gallate, methionine, cysteine, metabisulfites, sodium formaldehyde sulfoxylate, phenol-containing aromatic and aliphatic compounds and dihydrolipoic acid;

the bendamustine-containing composition having less than or equal to 0.12% total PG esters at about 15 days of storage at a temperature of about 25° C.;

wherein the ratio of polyethylene glycol to propylene glycol is selected from the group consisting of: about 95:5, about 90:10, about 85:15, about 80:20, and about 75:25.

17. The method of claim 16, wherein said bendamustine-containing composition has less than or equal to 0.25% total PG esters at about 1 month of storage at a temperature of about 25° C.

18. The method of claim 16, wherein said bendamustine-containing composition has less than or equal to 0.43% total PG esters at about 3 months of storage at a temperature of about 25° C.

19. The method of claim 16, wherein said bendamustine-containing composition has less than or equal to 0.77% total PG esters at about 6 months of storage at a temperature of about 25° C.

20. The method of claim 16, wherein the bendamustine-containing composition has less than or equal to 0.25% total PG esters at about 1 month of storage at a temperature of about 25° C., has less than or equal to 0.43% total PG esters at about 3 months of storage at a temperature of about 25° C., and has less than or equal to 0.77% total PG esters at about 6 months of storage at a temperature of about 25° C.

21. The method of claim 16, wherein the amount of propylene glycol in the pharmaceutically acceptable fluid is about 10%.

22. The method of claim 16, wherein the bendamustine concentration is from about 20 mg/mL to about 60 mg/mL.

23. The method of claim 16, wherein the bendamustine concentration is from about 25 mg/mL to about 50 mg/mL.

24. The method of claim 23, wherein the bendamustine concentration is about 50 mg/mL.

25. The method of claim 16, for the treatment of leukemia.

26. The method of claim 16, for the treatment of Hodgkin's disease.

27. The method of claim 16, for the treatment of multiple myeloma.

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APPLICATION NUMBER: *14/714,578*
FILING DATE: *May 18, 2015*
PATENT NUMBER: *9,144,568*
ISSUE DATE: *September 29, 2015*

Dist. Delaware
No. 17-1154-CFC
PTX-0312

By Authority of the
Under Secretary of Commerce for Intellectual Property
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W. MONTGOMERY
Certifying Officer

(12) **United States Patent**
Sundaram

(10) **Patent No.: US 9,144,568 B1**
(45) **Date of Patent: *Sep. 29, 2015**

(54) **FORMULATIONS OF BENDAMUSTINE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/714,578**

(22) Filed: **May 18, 2015**

Related U.S. Application Data

(63) Continuation of application No. 13/838,090, filed on Mar. 15, 2013, now Pat. No. 9,034,908.

(60) Provisional application No. 61/613,173, filed on Mar. 20, 2012, provisional application No. 61/669,889, filed on Jul. 10, 2012.

(51) **Int. Cl.**

A61K 31/4184	(2006.01)
A61K 47/12	(2006.01)
A61K 47/10	(2006.01)
A61K 47/20	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/4184*** (2013.01); ***A61K 47/10*** (2013.01); ***A61K 47/20*** (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

Methods of treatment using bendamustine formulations designed for small volume intravenous administration are disclosed. The methods conveniently allow shorter administration time without the active ingredient coming out of solution as compared to presently available formulations.

23 Claims, No Drawings

FORMULATIONS OF BENDAMUSTINE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 13/838,090, filed Mar. 15, 2013, which claims the benefit of priority from U.S. Provisional Patent Application Ser. Nos. 61/613,173, filed Mar. 20, 2012, and 61/669,889, filed Jul. 10, 2012, the disclosure of each of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

Bendamustine is used in the treatment of a number of cancers including leukemias, Hodgkin's disease and multiple myelomas. Bendamustine (present as the HCl salt) is the active ingredient of the commercial product Treanda™, a lyophilized powder for reconstitution. Current labeling requirements call for the reconstituted product to be immediately (within 30 minutes) diluted into 500 mL of parenterally acceptable diluents such as 0.9% saline (normal saline) or 2.5% dextrose/0.45% saline and administered as part of an intravenous infusion delivering 100 mg/m^2 over 30 minutes or 120 mg/m^2 over 60 minutes. The diluted admixture may be stored at 2-8° C. for up to 24 hours, or 3 hours at room temperature (15-30° C.); administration must be completed within this period due to limited chemical stability in aqueous solutions.

Solubility limitations at 2-8° C. with currently approved and/or available formulations are believed to prevent current formulations from being administered in smaller more concentrated infusion volumes up to about 150 ml; at volumes below 150 ml, solubility is not sufficient even at 25° C. Side effects associated with extravasation and local erythema, swelling and pain at the injection site also dictate that the infusion be as dilute as possible. Therefore, precautions are taken to avoid extravasation, including monitoring of the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of bendamustine. Higher infusion volume and longer infusion times, however, are associated with many drawbacks. For example, after reconstitution, the current product has a short period of stability, degradation of the drug occurs from the time of reconstitution until the entire large volume infusion has been completely administered. The current label for Treanda™ therefore instructs that the admixture should be prepared as close as possible to the time of patient administration, and that administration of Treanda™ must be completed within the durations indicated above. From patient comfort and nursing administration points of view, higher infusion volumes and long infusion times are undesirable. Higher infusion volumes may be associated with higher likelihood of weight gain and edema. Shorter infusion times and smaller infusion volumes result in a better quality of life experience for the patient by reducing the overall "stress" to the patient and reducing the time spent in the infusion clinic. Shorter infusion times (and smaller volumes) also reduce the potential extravasation (and shorten the patient monitoring time required). It would be advantageous if the drug could be administered in smaller volumes and over shorter times. The present invention addresses these needs.

SUMMARY OF THE INVENTION

In a first aspect of the invention there are provided methods of treating or preventing cancer or malignant disease in a subject such as a human. The methods include parenterally administering a volume of about 325 ml or less of a liquid composition containing:

a) from about 0.05 to about 12.5 mg/ml of bendamustine or a pharmaceutically acceptable salt thereof;

b) a solubilizer comprising polyethylene glycol and propylene glycol; and optionally

c) a parenterally acceptable diluent;

over a substantially continuous period of less than or equal to about 30 minutes to a subject in need thereof.

In alternative aspects of the invention there are provided methods of treating or preventing a bendamustine-responsive condition in a subject such as a human. In a first embodiment the methods include administering less than or equal to 325 ml of a liquid composition which contains

Ingredient	Concentration Range (mg/ml)
Bendamustine HCl	0.05 to 1.6
Solubilizer 1 propylene glycol	0.30 to 6.5
Solubilizer 2 PEG 400	3.3 to 65
Monothioglycerol	0.02 to 0.35
NaOH	0.0 to 0.01

over a substantially continuous period of less than or equal to about 30 minutes to a subject in need thereof.

In a related second embodiment of this aspect of the invention, the methods include administering less than or equal to 325 ml of a liquid composition which contains

Ingredient	Concentration Range (mg/ml)
Bendamustine HCl	1.1 to 12.5
Solubilizer 1 propylene glycol	4.5 to 51
Solubilizer 2 PEG 400	45 to 500
Monothioglycerol	0.2 to 2.5
NaOH	0.0 to 0.04

over a substantially continuous period of less than or equal to about 30 minutes to a subject in need thereof.

The methods of the present invention take advantage of the fact that the concentration of the bendamustine HCl is below the room temperature solubility limit of the vehicle into which it is placed. As a result, the bendamustine does not precipitate during administration to the patient thereby substantially avoiding the side effects which would otherwise occur during small volume administration of therapeutic doses of the drug. In addition, patients or subjects with bendamustine-responsive conditions can be treated using substantially smaller parenteral volumes which are well below the standard 500 ml administration volume.

DETAILED DESCRIPTION OF THE INVENTION

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

In a first aspect of the invention there are provided methods of treating or preventing cancer or malignant disease in a subject or patient who is preferably a human. The methods generally include parenterally administering a volume of about 325 ml or less of a liquid composition containing:

a) from about 0.05 to about 12.5 mg/ml of bendamustine HCl or a pharmaceutically acceptable salt thereof, the HCl salt being preferred;

b) a solubilizer comprising polyethylene glycol and propylene glycol; and optionally

c) a parenterally acceptable diluent;

over a substantially continuous period of less than or equal to about 30 minutes to a subject in need thereof.

The solubilizer portion of the formulation preferably includes from about 0.3 to about 45% volume polyethylene glycol (PEG) and from about 0.03 to about 5% volume propylene glycol (PG), as calculated on the basis of the total or final volume administered. Stated alternatively, the final concentration of the PEG generally ranges from about 3 to about 500 mg/ml, while the final concentration of the PG generally ranges from about 0.5 to about 51 mg/ml. Within these general ranges, certain aspects of the invention include concentration ranges for the PEG of from about 45 to about 500 mg/ml or from about 3.3 to about 63.3 mg/ml; and for the PG ranges of from about 4.7 to about 50.6; or from about 0.02 to about 6.5 mg/ml.

In some aspects of the invention, the bendamustine is administered intravenously as part of an intravenous infusion. Contemplated infusion volumes are preferably less than 325 ml with volumes such as about 250 ml, 100 ml, and 50 ml, with each volume varying about +/−10% or +/−15% being preferred in some embodiments. In alternative aspects of the invention, the intravenous administration volume is suitable for IV bolus administration and may also include an amount of pharmaceutically acceptable diluent such as normal saline or one of the other diluents described herein which does not cause the solubility of the vehicle to fall below the concentration of the bendamustine. Stated alternatively, the final concentration of the bendamustine will be below the solubility of the combination vehicle containing the mixture of propylene glycol and PEG and diluent. While most aspects of the invention are described in the context of administering less than about 325 ml including all vehicle ingredients, excipients, etc., it should be appreciated that volumes as low as a few milliliters, e.g. about 2, can be used so long as the vehicle includes sufficient solubilizers to preserve the solubility of the bendamustine therein during administration to the patient.

For purposes of the present invention, the word "about" when used to modify infusion volumes or concentrations shall be understood to include values which may vary by amounts of about +/−10% or 15%. In certain embodiments where the infusion volume is about 50 ml, the concentration of the bendamustine HCl or other pharmaceutically acceptable salt thereof is preferably from about 0.5 to about 5.6 mg/ml. In embodiments where the infusion volume is about 100 ml, the concentration of the bendamustine HCl or other pharmaceutically acceptable salt thereof can be preferably from about 0.1 to about 3.2 mg/ml. Similarly, in some aspects of the invention where the infusion volume is about 250 ml, the concentration of the bendamustine HCl or other pharmaceutically acceptable salt thereof is from about 0.05 to about 1.4 mg/ml.

The solubilizer is preferably a mixture of polyethylene glycol, hereinafter "PEG" and propylene glycol, hereinafter "PG". The solubilizer can also optionally include an antioxidant such as monothioglycerol. The amount of antioxidant included is a formulation stabilizing amount, which, in the case of monothioglycerol ranges from about 2 to about 10 mg/ml. The PEG preferably has a molecular weight of about 400, i.e. PEG 400. Other molecular weight PEG's known to those of ordinary skill can be included if desired in alternative embodiments.

Certain aspects of the invention call for the ratio of the PEG to PG found in the solubilizer to be about 90:10. In alternative aspects, the ratio of the PEG to PG is about 85:15.

In some aspects of the invention, the total amount of solubilizer, i.e. blend of PEG and PG, included in infusion volumes of about 100-115 ml is from about 0.5 to about 26.5% vol.; while amounts of from about 0.2 to about 5% vol. for the solubilizer are preferably included in infusion volumes of about 250-265 ml; with solubilizer amounts of from about 2.0 to about 22.4% vol. included in infusion volumes of about 50-65 ml.

Since the solubilizer is a blend, the amount of PEG and PG in various volumes (calculated as % vol.) can be as follows:

Solubilizer	50 ml	100 ml	250 ml
PEG	20.12	11.33	4.9
PG	2.24	1.26	0.54

In some preferred embodiments, the methods of the invention are advantageously carried out using bendamustine HCl containing compositions administered as small volume infusions with volumes of about 50 ml or about 100 ml or about 250 ml. Such smaller volumes allow the drug to be administered over a time period of about 10 minutes or less as part of an intravenous infusions containing a volume of about 50 ml; about 15 minutes or less as part of an intravenous infusions containing a volume of about 100 ml or when volumes of about 250 ml are infused, the IV infusion is administered over a time period of about 30 minutes or less. Depending upon the amount of drug administered, the IV bolus volumes containing sufficient amount of the drug will be less than 50 ml, with amounts of about 10 or 15 to 30 ml being sufficient.

The infusible compositions in many aspects of the invention will also preferably include the parenterally acceptable diluents such as water for injection (WFI), 0.9% saline (normal saline, preferred), 0.45% saline (half normal saline) or 2.5% dextrose/0.45% saline. Formulations well suited for carrying out the methods described herein are also described in commonly assigned U.S. patent application Ser. No. 13/016,473 (U.S. Published Application No. 2011/0184036), filed Jan. 28, 2011, and Ser. No. 13/767,672 (U.S. Published Application No. 2013/0210879), filed Feb. 14, 2013, the contents of which are incorporated herein by reference. As reviewed in the '672 patent application, some preferred bendamustine formulations can also include a minor amount of a pH adjuster such as sodium formate, sodium phosphate, potassium hydroxide, phosphoric acid or, preferably, sodium hydroxide.

In an alternative embodiment of the invention, the bendamustine formulations used in the methods described herein can be one or more of those described in U.S. Pat. Nos. 8,344,006 and 8,076,366; and US Patent Application Nos. 2013/0041004; 2012/0071532; 2010/0216858; 2006/0159713; and 2013/0041003, the contents of each of which are incorporated herein by reference. It being understood that the vehicle into which the bendamustine HCl is placed will have sufficient bendamustine solubility which exceeds the concentration of the drug included therein.

If desired, a sufficient amount of a concentrated, ready to use liquid formulation such one containing 25 mg/ml bendamustine HCl and already admixed with sufficient solubilizers can be transferred to a suitable fixed volume diluent container such as a bag containing 50, 100, 250 ml normal saline or the like. Alternatively, lyophilized bendamustine HCl can be reconstituted, combined with sufficient solubilizer blends as

described herein and administered in accordance with the inventive methods. In such embodiments, the actual amount delivered to the patient will be slightly more than the diluent amount so as to allow for the addition of the drug/solubilizer vehicle.

In some aspects of the invention, there are provided methods of treating or preventing chronic lymphocytic leukemia (CLL). The small volume infusions can be given as part of any treatment protocol for which bendamustine is included. Thus, the compositions described herein can be administered as part of a poly-pharmaceutical treatment regimen according to known protocols with the exception that the concentrated bendamustine compositions described herein are administered in smaller infusion volumes over significantly shorter administration periods. For example, some CLL treatment regimens can include administering the compositions described herein intravenously as part of about 100 ml infusions in about 20 minutes or less and more preferably in about 15 minutes or less on days 1 and 2 of a 28 day cycle and repeating the cycle up to 6 times or longer if clinically appropriate. If 250 ml volumes are used to deliver the bendamustine, the time of administration is preferably about 30 minutes or less. If 50 ml volumes are used to deliver the bendamustine, the time of administration is preferably about 10 minutes or less.

In spite of the smaller volumes, the amount of bendamustine HCl administered to the patient in need thereof per dose (infusion or otherwise) in some preferred embodiments is about 100 mg/m^2. In some alternative aspects of the invention, the amount of bendamustine HCl administered to the patient in need thereof as part of the 50, 100 or 250 ml infusion is an amount sufficient to provide a dosage of 50 or 25 mg/m^2. Additional administration dosages will be apparent to those of ordinary skill based upon clinical experience, patient need without undue experimentation.

In other aspects of the invention, there are methods of treating or preventing the malignant disease of indolent B-cell non-Hodgkin's lymphoma. In these aspects, the composition is administered intravenously as a 100 ml infusion in less than 20 minutes and more preferably in about 15 minutes or less on days 1 and 2 of a 21 day cycle for up to 8 cycles or longer if clinically appropriate. If 250 ml volumes are used to deliver the bendamustine, the time of administration is preferably about 30 minutes or less. If 50 ml volumes are used to deliver the bendamustine, the time of administration is preferably about 10 minutes or less. The amount of bendamustine administered to the subject is preferably about 120 mg/m^2, although in alternative embodiments, the amount administered ranges from about 90 or 60 mg/m^2. As will be appreciated, further alternative dosage amounts will be apparent to those of ordinary skill based upon clinical experience, patient need without undue experimentation.

It will be appreciated by those skilled in the art that the above-mentioned dosages calculated in mg/m^2 for purposes of body surface area (BSA) are consistent with the bendamustine HCl concentrations also described herein, e.g. 0.5 to 5.6 mg/ml. In the alternative, the invention also contemplates IV bolus administration of bendamustine-containing formulations in volumes which can be administered via syringe, e.g. from a few milliliters up to about 50 milliliters, with therapeutic amounts of the drug in a concentration which does not exceed the vehicle solubility for the drug therein.

Further embodiments of the invention include methods of treating or preventing a bendamustine-responsive condition in a subject such as a human. In a first embodiment, the methods include administering less than or equal to 325 ml of a liquid composition which contains

Ingredient	Concentration Range (mg/ml)
Bendamustine HCl	0.05 to 1.6
Solubilizer 1 propylene glycol	0.30 to 6.5
Solubilizer 2 PEG 400	3.3 to 65
Monothioglycerol	0.02 to 0.35
NaOH	0.0 to 0.01

over a substantially continuous period of less than or equal to about 30 minutes to a subject in need thereof. More preferably, the administration time is well below 30 minutes and the administration time will decrease as the volume administered decreases.

Bendamustine formulations containing the above ingredients are capable of delivering approximately 25 mg of the drug as the HCl salt in volumes of pharmaceutically acceptable diluent ranging from about 325 ml down to about 15 ml. For example, 1 ml of a bendamustine HCl ready to use liquid available from Eagle Pharmaceuticals containing

Ingredient	Concentration (mg/ml)
Bendamustine HCl	25
PG	103.2
PEG 400	1013.4
Monothioglycerol	5
NaOH	0.08

is combined with 300 ml of a normal saline diluent to provide a final IV infusion containing 301 ml and a bendamustine final concentration of 0.08 mg/ml.

One ml of the 25 mg/ml Eagle bendamustine HCl is diluted into additional diluent volumes as shown below:

Diluent Volume (ml)	Final Volume (ml)	Final Bendamustine Conc. (mg/ml)
200	201	0.12
100	101	0.25
50	51	0.49
30	31	0.81
15	16	1.56

The measured solubility of the bendamustine HCl in the diluent/solubilizer combination (50 ml diluent plus 1 ml of 25 mg/ml bendamustine HCl and solubilizers, etc.) at room temperature was 10.5 mg/ml using normal saline and 14.2 mg/ml using half normal saline/dextrose. The solubility of the diluent/solubilizer combination far exceeded the bendamustine concentration, thus assuring the avoidance of precipitated drug prior to or during administration. As will be appreciated by those of ordinary skill, as the concentration of solubilizers increases with respect to the total volume in small administration doses, the solubility of the bendamustine is maintained.

In a related second embodiment of this aspect of the invention, the methods include administering less than or equal to 325 ml of a liquid composition which contains

Ingredient	Concentration Range (mg/ml)
Bendamustine HCl	1.1 to 12.5
Solubilizer 1 propylene glycol	4.5 to 51
Solubilizer 2 PEG 400	45 to 500
Monothioglycerol	0.2 to 2.5
NaOH	0.0 to 0.04

over a substantially continuous period of less than or equal to about 30 minutes to a subject in need thereof. As was the case above, the administration time will decrease with the decrease in volume administered.

Bendamustine formulations containing the above ingredients are capable of delivering approximately 360 mg of the drug as the HCl salt in volumes of pharmaceutically acceptable diluent ranging from about 325 ml down to about 15 ml. As was the case above, the measured solubility of the bendamustine HCl in the diluent/solubilizer combination (1 ml drug+solubilizers, etc. and 50 ml diluent) at room temperature was 10.5 mg/ml using normal saline and 14.2 mg/ml using half normal saline/dextrose.

Instead of using only 1 ml of the above described Eagle 25 mg/ml bendamustine HCl ready to use liquid, 14.4 ml is combined with various amounts of diluent.

Diluent Volume (ml)	Final Volume (ml)	Final Bendamustine Conc. (mg/ml)
300	314.4	1.15
200	214.4	1.68
100	114.4	3.15
50	64.4	5.59
30	44.4	8.11
15	29.4	12.24

In each case, the solubility of the diluent/solubilizer combination exceeds the bendamustine concentration, thus assuring the avoidance of precipitated drug prior to or during administration.

EXAMPLES

The following examples serve to provide further appreciation of the invention but are not meant in any way to restrict the effective scope of the invention.

Example 1

The solubility of bendamustine HCl, obtained from two different sources, in 0.9% saline and 0.9% saline containing from different amounts of a non-aqueous solubilizer comprising a mixture of polyethylene glycol 400 and propylene glycol (in the volume proportion of 90:10) with and without 5 mg/ml monothioglycerol was determined at both room temperature (22-23° C.) and at refrigerated temperature (5° C.). Essentially, an excess of bendamustine HCl was added to solvents comprising of various volume percent of the non-aqueous solubilizer in 0.9% saline, and allowed to equilibrate with shaking for 30 minutes at room temperature, or for 24 hours at refrigerated temperature. At the end of the equilibration step, the suspensions were filtered through a 0.2 micron filter to remove undissolved bendamustine, and the filtrate solutions analyzed for bendamustine HCl content using a HPLC assay; quantification was performed against a bendamustine HCl reference standard. The solubility data are presented in Table 1.

TABLE 1

Solubility of bendamustine HCl in 0.9% saline with various amounts of non-aqueous solubilizer (90:10 PEG400:PG with and without 5 mg/mL monothioglycerol (MTG))

Dilution Fold	Volume % of Normal Saline	Volume % of Non-aqueous Solubilizer	Solubility of bendamustine HCl (mg/mL) in 90:10 PEG 400/PG — Room temperature: API Source A	Room temperature: API Source B* B	5° C.: API Source A
n/a	100.0	0.0	3.461	3.304	1.175
40	97.5	2.5	3.987	3.889	nd
20	95.0	5.0	4.429	4.204	2.022
13.3	92.5	7.5	nd	4.742	nd
10	90.0	10.0	5.626	5.351	2.431
8	87.5	12.5	nd	5.825	nd
6.7	85.0	15.0	7.012	6.554	2.900
5.7	82.5	17.5	nd	7.641	3.328
5	80.0	20.0	8.642	8.492	3.824
3.3	70.0	30.0	12.006	11.407	nd

*solvent also contained 5 mg/ml monothioglycerol
nd = not determined;
API = active pharmaceutical ingredient

Example 2

Bendamustine-containing compositions are prepared by adding 5 mg/ml of thioglycerol to a mixture containing 90% polyethylene glycol 400 and 10% propylene glycol. As indicated in the Table 2 below, NaOH may be added to the PEG in an amount sufficient to get apparent pH of greater than or equal to 6.5 as measured using the pH method outlined in the USP monograph for polyethylene glycol (PEG). Bendamustine (BDM) is then added to the sample to a concentration of 10 mg/ml.

TABLE 2

Formulation
BDM - 10 mg/mL Thioglycerol - 5 mg/mL PEG 400:PG (90:10)

TABLE 2-continued

Formulation
qs to 1 mL
BDM - 10 mg/mL
Thioglycerol - 5 mg/mL
PEG 400:PG (90:10)
qs to 1 mL
(PEG 400 Treated with NaOH)

The compositions are then admixed with normal saline based on the total dose of bendamustine HCl, which in turn is based on the patient body surface area (BSA) and the dosing regimen (100 mg/m^2 for CLL and 120 mg/m^2 for NHL; although dose modifications of 90, 60, 50, and 25 mg/m^2 are possible, only the highest two dosing regimens are considered for illustrative purposes, as these result in the highest concentration of bendamustine during infusion). The 100 ml infusion is then made by admixing the dose appropriate volume of the 10 mg/ml solution with a 100 ml portion of normal saline to provide an infusible composition containing the appropriate dose of bendamustine (as the HCl salt) in the final admixture, which can be administered intravenously over about 15 minutes to a patient in need thereof.

As seen in Table 3, the concentrations of bendamustine (as HCl salt) and the corresponding volume percent of non-aqueous component are well below the corresponding solubilities at both room temperature and refrigerated temperature as detailed in Table 1. For example, for a 2.0 m^2 (average) patient dosed at 120 mg/m2, the final concentration of bendamustine HCl in a 100 ml admixture is 1.94 mg/mL. This is above the solubility of bendamustine HCl at refrigerated storage conditions in the absence of any non-aqueous components (1.175 mg/ml as shown in Table 1 for 100% normal saline), as would be the case with the currently approved Treanda™ product, thereby precluding preparation and storage of a 100 ml admixture volume at refrigerated conditions. However, the use of the non-aqueous bendamustine formulation described in this example results in the presence of 19.4% of the non-aqueous component in the final admixture, which improves the solubility to about 3.8 mg/mL (solubility of 3.824 mg/mL at 2-8° C. with 20% non-aqueous component, as shown in Table 1). Therefore, the solubility with the non-aqueous formulation is well above the final concentration (of bendamustine HCl) of 1.94 mg/mL, allowing preparation and storage of the 100 ml admixture at refrigerated conditions. In this example, the room temperature solubilities in 100% normal saline and 80% normal saline (with 20% non-aqueous component) are about 3.3 mg/ml and 8.5 mg/ml, respectively (see Table 1), which are also well above the final concentration of 1.94 mg/ml. Therefore, 100 ml admixtures of the non-aqueous formulation described in the example may also be prepared and stored at room temperature. In addition, the non-aqueous formulation of bendamustine described in this example at Table 2 may be diluted into smaller infusion volumes ranging from 250 ml or less, and stored at either room temperature or refrigerated temperature, with bendamustine continuing to remain in solution for extended periods of time as compared to currently available formulations.

TABLE 3

Concentrations of bendamustine (BDM, as HCl salt) and corresponding volume % of non-aqueous (NA) component in the final admixture, for volumes ranging from 100 ml to 250 ml For 10 mg/mL Formulation

	100 mg/m^2 dose		120 mg/m^2 dose		100 mg/m^2 dose		120 mg/m^2 dose	
BSA (m^2)	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.
	Admix. Volume 250 mL				Admix. Volume 200 mL			
1.00	0.38	3.8	0.46	4.6	0.48	4.8	0.57	5.7
1.25	0.48	4.8	0.57	5.7	0.59	5.9	0.70	7.0
1.50	0.57	5.7	0.67	6.7	0.70	7.0	0.83	8.3
1.75	0.65	6.5	0.77	7.7	0.80	8.0	0.95	9.5
2.00	0.74	7.4	0.88	8.8	0.91	9.1	1.07	10.7
2.25	0.83	8.3	0.97	9.7	1.01	10.1	1.19	11.9
2.50	0.91	9.1	1.07	10.7	1.11	11.1	1.30	13.0
2.75	0.99	9.9	1.17	11.7	1.21	12.1	1.42	14.2
3.00	1.07	10.7	1.26	12.6	1.30	13.0	1.53	15.3
	Admix. Volume 150 mL				Admix. Volume 100 mL			
1.00	0.63	6.3	0.74	7.4	0.91	9.1	1.07	10.7
1.25	0.77	7.7	0.91	9.1	1.11	11.1	1.30	13.0
1.50	0.91	9.1	1.07	10.7	1.30	13.0	1.53	15.3
1.75	1.04	10.4	1.23	12.3	1.49	14.9	1.74	17.4
2.00	1.18	11.8	1.38	13.8	1.67	16.7	1.94	19.4
2.25	1.30	13.0	1.53	15.3	1.84	18.4	2.13	21.3
2.50	1.43	14.3	1.67	16.7	2.00	20.0	2.31	23.1
2.75	1.55	15.5	1.80	18.0	2.16	21.6	2.48	24.8
3.00	1.67	16.7	1.94	19.4	2.31	23.1	2.65	26.5

Example 3

The procedures of Example 2 are repeated except that the dose appropriate volume of the 10 mg/ml bendamustine solution is diluted into 250 ml of normal saline. The final concentration of bendamustine in the 250 ml volume container ranges from about 0.05 mg/ml to about 1.3 mg/ml.

Example 4

The approximately 100 ml bendamustine HCl infusion of Example 2 is administered to a patient in about 15 minutes.

Example 5

Bendamustine-containing compositions may be prepared by adding 5 mg/ml of thioglycerol to 90% polyethylene glycol 400 and 10% propylene glycol. As indicated in the Table 4 below, NaOH may be added in an amount sufficient to get apparent pH of greater than or equal to 6.5 as measured using the pH method outlined in the USP monograph for polyethylene glycol (PEG). Bendamustine is then added to the sample to a concentration of 25 mg/ml as indicated in Table 4 below.

TABLE 4

Formulation
BDM - 25 mg/mL
Thioglycerol - 5 mg/mL
PEG 400:PG (90:10)
qs to 1 mL
BDM - 25 mg/mL
Thioglycerol - 5 mg/mL

TABLE 4-continued

Formulation
PEG 400:PG (90:10) qs to 1 mL (PEG 400 Treated with NaOH)

The compositions are then admixed with normal saline based on the total dose of bendamustine HCl, which in turn is based on the patient body surface area (BSA) and the dosing regimen (100 mg/m^2 for CLL and 120 mg/m2 for NHL; although dose modifications of 90, 60, 50, and 25 mg/m^2 are possible, only the highest two dosing regimens are considered for illustrative purposes, as these result in the highest concentration of bendamustine during infusion). Table 5 below provides the final concentration of bendamustine (as the HCl salt) in the final admixture, for volumes ranging from 250 ml to 50 ml.

As seen in Table 5, the concentrations of bendamustine (as HCl salt) and the corresponding volume percent of non-aqueous component are well below the corresponding solubilities at room temperature as detailed in Table 1, for all admixture volumes up to 50 ml. For example, for a 2.0 m^2 (average) patient dosed at 120 mg/m^2, the final concentration of bendamustine HCl in a 50 ml admixture is 4.03 mg/ml. This is above the solubility of bendamustine HCl at both refrigerated and room temperature conditions in the absence of any non-aqueous components (1.175 mg/ml at 2-8° C. and 3.304-3.461 mg/ml at room temperature, as shown in Table 1 for 100% normal saline), as would be the case with the currently approved Treanda product, thereby precluding preparation and storage of a 50 ml admixture volume. However, the use of the non-aqueous bendamustine formulation described in this example results in the presence of 16.1% of the non-aqueous component in the final admixture, which improves the room temperature solubility to about 6.5 mg/ml (solubility of 6.554 mg/ml and 7.012 mg/ml with 15% non-aqueous component, as shown in Table 1). Therefore, the solubility with the non-aqueous formulation is well above the final concentration (of bendamustine HCl) of 4.03 mg/mL, allowing preparation and storage of the 100 ml admixture at room temperature conditions. Therefore, the non-aqueous formulation of bendamustine described in this example may be diluted into smaller infusion volumes ranging from 250 ml or less, with bendamustine continuing to remain in solution if maintained at room temperature. However, at refrigerated temperatures, the concentrations of bendamustine (as HCl salt) and the corresponding volume percent of non-aqueous component exceed the corresponding solubilities as detailed in Table 1, for all admixture volumes equal to or below 150 ml. In the scenario above, the solubility at refrigerated conditions with 15% non-aqueous component has improved to 2.9 mg/ml but is still below the final concentration of 4.03 mg/ml. Therefore, 50 ml admixtures of the non-aqueous formulation described in the example cannot be prepared and stored at refrigerated temperatures. However, for a 150 ml admixture, the final concentration of bendamustine HCl in this scenario is 1.5 mg/ml with about 6.0% non-aqueous component, which is below the solubility limit (of 2.022 mg/ml at 5% non-aqueous at 2-8° C.). Therefore, the non-aqueous formulation of bendamustine described in this example may be diluted into smaller infusion volumes ranging from 250 ml to 50 ml, and stored at only room temperature (but not refrigerated temperature), with bendamustine continuing to remain in solution. For storage at refrigerated temperatures, the minimum admixture volume that can be used is 150 ml or higher.

Concentrations of bendamustine (BDM, as HCl salt) and corresponding volume % of non-aqueous (NA) component in the final admixture, for volumes ranging from 100 ml to 250 ml For 25 mg/mL Formulation

	100 mg/m^2 dose		120 mg/m^2 dose		100 mg/m^2 dose		120 mg/m^2 dose	
BSA (m^2)	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.
	Admix. Volume 250 mL				Admix. Volume 200 mL			
1.00	0.39	1.6	0.47	1.9	0.49	2.0	0.59	2.3
1.25	0.49	2.0	0.59	2.3	0.61	2.4	0.73	2.9
1.50	0.59	2.3	0.70	2.8	0.73	2.9	0.87	3.5
1.75	0.68	2.7	0.81	3.3	0.85	3.4	1.01	4.0
2.00	0.78	3.1	0.92	3.7	0.96	3.8	1.15	4.6
2.25	0.87	3.5	1.04	4.1	1.08	4.3	1.28	5.1
2.50	0.96	3.8	1.15	4.6	1.19	4.8	1.42	5.7
2.75	1.05	4.2	1.25	5.0	1.30	5.2	1.55	6.2
3.00	1.15	4.6	1.36	5.4	1.42	5.7	1.68	6.7
	Admix. Volume 150 mL				Admix. Volume 100 mL			
1.00	0.65	2.6	0.78	3.1	0.96	3.8	1.15	4.6
1.25	0.81	3.2	0.96	3.8	1.19	4.8	1.42	5.7
1.50	0.96	3.8	1.15	4.6	1.42	5.7	1.68	6.7
1.75	1.11	4.5	1.33	5.3	1.64	6.5	1.94	7.7
2.00	1.27	5.1	1.50	6.0	1.85	7.4	2.19	8.8
2.25	1.42	5.7	1.68	6.7	2.06	8.3	2.44	9.7
2.50	1.56	6.3	1.85	7.4	2.27	9.1	2.68	10.7
2.75	1.71	6.8	2.02	8.1	2.48	9.9	2.92	11.7
3.00	1.85	7.4	2.19	8.8	2.68	10.7	3.15	12.6

	Admix. Volume 50 mL			
	100 mg/m^2 dose		120 mg/m^2 dose	
BSA (m^2)	BDM Conc (mg/ml)	% NA comp.	BDM Conc (mg/ml)	% NA comp.
1.00	1.85	7.4	2.19	8.8
1.25	2.27	9.1	2.68	10.7
1.50	2.68	10.7	3.15	12.6
1.75	3.07	12.3	3.60	14.4
2.00	3.45	13.8	4.03	16.1
2.25	3.81	15.3	4.44	17.8
2.50	4.17	16.7	4.84	19.4
2.75	4.51	18.0	5.22	20.9
3.00	4.84	19.4	5.59	22.4

Example 6

The hemolytic potential of the non-aqueous bendamustine formulation indicated in Table 4 (Example 5), when admixed with 250 ml and 100 ml of normal saline, was assessed. The hemolysis study was conducted at the highest final bendamustine HCl concentrations expected at these admixture volumes, namely, for a 3.0 m^2 patient dosed at 120 mg/m^2. At this dosing, the final bendamustine HCl concentration for 250 ml and 100 ml admixture volumes is 1.36 mg/ml and 3.15 mg/ml, respectively (Table 5). Human whole blood (1 ml) was incubated at 37° C. for approximately 30 minutes with admixed bendamustine HCl solutions at 1.4 mg/ml or 3.2 mg/ml at blood to drug solution volumetric ratios of 1:2 and 1:1, respectively. These volumetric ratios correspond to infusion times of 15 minutes and 10 minutes, respectively, for the 250 ml and 100 ml admixture volumes. A placebo of the bendamustine formulation (without the active ingredient) was also evaluated at these concentrations and volumetric ratios. A positive control (1% saponin solution), a negative

control (normal saline), and Treanda™ diluted in normal saline to the highest concentration stated in the prescribing information (0.6 mg/ml) were included in the study. Following incubation and centrifugation of the samples, the plasma was harvested and hemolysis was evaluated by spectrophotometric analysis for hemoglobin in the supernatant. The results are summarized in Table 6. No hemolysis was observed with the non-aqueous bendamustine formulation when diluted with saline at either concentration or volumetric (blood:drug solution) ratios, or with the corresponding placebo at comparable sample volumes; supernatants from all samples were light yellow. In conclusion, no hemolytic effects are observed with non-aqueous bendamustine formulations when diluted to smaller volumes (100 to 250 ml) and infused in shorter times (10-15 minutes) than current practice.

TABLE 6

Hemolytic Potential test results

Mixture	Hemoglobin[a] (mg/dL)	Test Result	Supernatant Color[b]	Tube No.
Human blood plus:				
Test Article A (25 mg/mL, diluted to 3.2 mg/mL with saline) - 100 ml admixture				
	1	N	Light yellow	1
	0	N	Light yellow	2
	1	N	Light yellow	3
Test Article A (25 mg/mL, diluted to 1.4 mg/mL with saline) - 250 ml admixture				
	2	N	Light yellow	4
	1	N	Light yellow	5
	1	N	Light yellow	6
Test Article A Vehicle (Placebo, diluted with 100 ml saline)				
	0	N	Light yellow	7
	1	N	Light yellow	8
	0	N	Light yellow	9
Test Article A Vehicle (Placebo, diluted with 250 ml saline)				
	1	N	Light yellow	10
	4	N	Light yellow	11
	1	N	Light yellow	12
Treanda ™ (5 mg/mL, diluted to 0.6 mg/mL with saline)				
	3	N	Light yellow	43
	4	N	Light yellow	44
	2	N	Light yellow	45
Negative Control (normal saline)				
	9	N	Yellow	55
	5	N	Yellow	56
	3	N	Yellow	57
Positive Control (1% Saponin)[c]				
	5949	P	Red	58
	5974	P	Red	59
	6386	P	Red	60

N = Negative, no hemolysis.
NA = Not applicable.
P = Positive, hemolysis.
[a]Hemoglobin index of the mixture supernatants.
[b]Plasma separated from whole blood plasma.
[c]1% Saponin. Saponin is a hemolytic agent used to lyse erythrocytes.

Example 7

The local tolerance (intravenous (IV) and perivascular (PV)) of the non-aqueous bendamustine-containing composition indicated in Table 4 (Example 5), when admixed with 100 ml of normal saline and infused over 10 minutes, was assessed. New Zealand White rabbits (3 males [IV] and 2 males [PV]) received a single dose of bendamustine formulation (admixed with 100 ml saline to a final concentration of 3.2 mg/ml bendamustine HCl) and corresponding placebo in the left and right ear, respectively. The formulation was administered as either intravenous infusion (5 mg/kg in 10 minutes), or perivascular injection (250 μl) to determine local tolerance. Treanda™ reconstituted and admixed with normal saline to a final concentration of 0.6 mg/ml (the highest concentration stated in the label) was also studied either as a 30 minute IV infusion (the shortest infusion time stated in the label), as well as perivascular injection (250 μl). Animals were held for a 96 hour (post-dose) observation period. During the observation period, dermal scores were recorded for all administration sites. At the end of the observation periods, animals were euthanized and a macroscopic and microscopic examination of both ears was performed. Parameters evaluated during the study were: viability, clinical observations, body weights, macroscopic observations and microscopic pathology.

The results of the local tolerance study are summarized in Table 7 (in life dermal observations) and Table 8 (microscopic pathology for perivascular administration).

In Life Dermal Observations:

As seen in Table 7, there was transient, dermal irritation in the form of slight to moderate erythema and moderate edema noted between 24 and 72 hours post dose, in each of the groups receiving either bendamustine-containing formulations or placebo material intravenously. At 96 hours, irritation was limited to a few individual sites treated with test or placebo articles. Only a limited number of animals were affected, and there was no consistent pattern of irritation within a dose group (either for test article or placebo). The bendamustine formulations were considered not to produce dermal irritation when administered intravenously.

Perivascular administration of bendamustine formulations (0.25 ml injection volume) produced dermal irritation in all groups. Local signs of dermal irritation following perivascular administration were mostly characterized by slight (group 6—Treanda™) or slight to moderate (group 7—non aqueous bendamustine formulation of example 5) erythema, and slight edema (groups 7). The severity of the irritation observed correlated with the dose and/or concentration of the test article administered, with placebo groups generally showing a lesser level of irritation than the corresponding test-article formulation.

TABLE 7

Summary of in life dermal observations

Material - Left ear/Right ear	Dermal observations during 96 hour post dose period (incidence and most severe level of erythema and edema noted)	
	Left ear (Bendamustine-containing formulation)	Right ear (Placebo material)
Intravenous administration		
Group 1: Treanda ™ diluted to 0.6 mg/ml in saline/Treanda Placebo - 500 ml admixture	—	(2/3) Slight

TABLE 7-continued

Summary of in life dermal observations		
	Dermal observations during 96 hour post dose period (incidence and most severe level of erythema and edema noted)	
Material - Left ear/Right ear	Left ear (Bendamustine-containing formulation)	Right ear (Placebo material)
Group 2: Non-aqueous bendamustine formulation 25 mg/ml diluted to 3.2 mg/ml in saline/placebo (+saline) - 100 ml admixture	—	(1/3) Moderate
Perivascular administration		
Group 6: Treanda ™ diluted to 0.6 mg/ml in saline/Treanda ™ Placebo - 500 ml admixture	(1/2) Slight	(1/2) Slight

TABLE 7-continued

Summary of in life dermal observations		
	Dermal observations during 96 hour post dose period (incidence and most severe level of erythema and edema noted)	
Material - Left ear/Right ear	Left ear (Bendamustine-containing formulation)	Right ear (Placebo material)
Group 7: Non-aqueous bendamustine formulation 25 mg/ml diluted to 3.2 mg/ml in saline/placebo (+saline) - 100 ml admixture	(2/2) Moderate	(2/2) Slight

Microscopic Pathology:

Intravenous administration of test articles/placebos was generally well tolerated; no test article related effects were observed. Perivascular administration of bendamustine-containing formulations (including Treanda™) was associated with dose and/or concentration related minimal to marked edema/collagen degeneration and mixed inflammation in perivascular tissues. The non-aqueous formulation of bendamustine (Group 7) was nominally more severe in grade than Treanda™ (Group 6).

TABLE 8

Incidence and Average Severity of Microscopic Findings at Perivascular Sites		
Formulation	Treanda ™ (diluted to 0.6 mg/ml)/ Treanda ™ Placebo	Non Aqueous Bendamustine (diluted to 3.2 mg/ml)/Placebo
Group number	6	7
No. Animals examined	2	2
RIGHT EAR (RE) - Placebo	Incidence (Average Severity)*	
RE Injection site		
Hemorrhage	0 (0.0)	0 (0.0)
Mixed Inflammation	0 (0.0)	0 (0.0)
Edema/Collagen Degeneration	1 (0.5)	0 (0.0)
Degeneration/Inflammation, Vascular	0 (0.0)	0 (0.0)
RE 2 cm distal		
Edema/Collagen Degeneration	0 (0.0)	0 (0.0)
Degeneration/Inflammation, Vascular	0 (0.0)	0 (0.0)
RE 4 cm distal		
Degeneration/Inflammation, Vascular	0 (0.0)	0 (0.0)
LEFT EAR (LE) - Test Article	Incidence (Average Severity)	
LE Injection site		
Hemorrhage	0 (0.0)	0 (0.0)
Mixed inflammation	0 (0.0)	2 (2.0)
Edema/Collagen Degeneration	1 (1.0)	2 (1.5)
Epidermis, Crust/Pustule, Erosion/Ulceration	0 (0.0)	0 (0.0)
Degeneration/Inflammation, Vascular	1 (1.5)	1 (1.5)
LE 2 cm distal		
Hemorrhage	0 (0.0)	0 (0.0)
Mixed Inflammation	1 (0.5)	1 (1.0)
Edema/Collagen Degeneration	0 (0.0)	2 (2.0)
Epidermis, Crust/Pustule, Erosion/Ulceration	0 (0.0)	0 (0.0)
Degeneration/Inflammation, Vascular	0 (0.0)	0 (0.0)
LE 4 cm distal		
Hemorrhage	0 (0.0)	0 (0.0)
Mixed inflammation	0 (0.0)	1 (1.5)
Edema/Collagen Degeneration	0 (0.0)	1 (2.0)
Epidermis,Crust/Pustule, Erosion/Ulceration	0 (0.0)	0 (0.0)
Degeneration/Inflammation, Vascular	0 (0.0)	0 (0.0)

*The number in parentheses represents the average severity score; the total of severity scores of the findings divided by the number of animals in the group.

Conclusion:

No test-article related irritation effects were observed for the non-aqueous formulation of bendamustine via the IV route, indicating that proper administration of this formulation did not result in any adverse local reaction. Perivascular administration of the non-aqueous bendamustine formulation, which is primarily related to effects that may occur if extravasation should occur, resulted in irritation that was generally comparable to Treanda. Therefore, the non-aqueous formulation of bendamustine described herein is well tolerated, despite the higher concentration of the smaller infusion volume preparation.

Example 8

The chemical stability of the non-aqueous bendamustine formulation (25 mg/ml) indicated in Table 4 (Example 5), when admixed with 50 ml and 100 ml of normal saline, was assessed. For each admixture volume, the admixture solutions were prepared at the expected lowest concentration (corresponding to a 1.0 m^2 patient dosed at 25 mg/m^2) and the highest concentration (corresponding to a 3.0 m^2 patient dosed at 120 mg/m^2) of bendamustine HCl in the final admixture. For the 50 ml admixture volume, the tested minimum and maximum concentrations are about 0.5 mg/ml and 6.0 mg/ml, respectively. For the 100 ml admixture volume, the tested minimum and maximum concentrations are about 0.25 mg/ml and 3.2 mg/ml, respectively. The chemical stability of Treanda™ was also determined at the lowest (0.2 mg/ml) and the highest (0.6 mg/ml) admixed concentrations stated in the label. The chemical stability was monitored at room temperature at periodic intervals up to 24 hours using a validated HPLC assay. The results are summarized in Table 9.

TABLE 9

Dilution (Admixed) Stability of Bendamustine Formulations in Normal Saline at Room Temperature

	Attribute									
	Highest Concentration (3.2 mg/ml)					Lowest Concentration (0.25 mg/ml)				
	Time									
	Initial	1 hr	3 hrs	6 hrs	24 hrs	Initial	1 hr	3 hrs	6 hrs	24 hrs
	Formulation									
	Non Aqueous Bendamustine Formulation 25 mg/ml admixed with 100 ml normal saline									
Assay (mg/ml)	3.155	3.090	3.060	3.085	2.895	0.240	0.234	0.229	0.224	0.196
Assay (% Initial)	100.0	97.9	97.0	97.8	91.8	100.0	97.5	95.4	93.3	81.7
Impurity - MCE (%)	BLQ	BLQ	BLQ	BLQ	BLQ	ND	ND	ND	ND	ND
Impurity - HP1 (%)	0.244	0.606	1.237	2.236	6.707	0.525	1.449	3.495	5.529	13.424
Impurity - Dimer (%)	BLQ	BLQ	BLQ	0.068	0.158	ND	ND	ND	BLQ	0.063
Single unknown (%)	0.086	0.061	BLQ	BLQ	0.098	ND	ND	ND	ND	BLQ
Total (%)	0.33	0.67	1.24	2.30	6.96	0.58	1.45	3.50	5.53	13.49
	Attribute									
	Highest Concentration (6.4 mg/ml)					Lowest Concentration (0.5 mg/ml)				
	Time									
	Initial	1 hr	hrs	6 hrs	24 hrs	Initial	1 hr	3 hrs	6 hrs	24 hrs
	Formulation									
	Non Aqueous Bendamustine Formulation 25 mg/ml admixed with 50 ml normal saline									
Assay (mg/ml)	6.62	6.60	6.60	6.54	6.46	0.475	0.470	0.455	0.445	0.394
Assay (% Initial)	100.0	99.7	99.7	98.8	97.8	100.0	98.9	95.8	93.7	82.9
Impurity - MCE (%)	BLQ	BLQ	BLQ	BLQ	0.074	BLQ	BLQ	BLQ	BLQ	BLQ
Impurity - HP1 (%)	0.137	0.265	0.528	0.945	2.967	0.567	1.618	3.719	5.892	14.427
Impurity - Dimer (%)	BLQ	BLQ	BLQ	0.050	0.110	BLQ	BLQ	BLQ	0.065	0.115
Single unknown (%)	0.112	0.105	0.086	0.054	0.112	0.057	BLQ	ND	ND	ND
Total (%)	0.25	0.37	0.61	1.05	3.36	0.67	1.62	3.72	5.96	14.54
	Attribute									
	Highest Concentration (0.6 mg/ml)					Lowest Concentration (0.2 mg/ml)				
	Time									
	Initial	1 hr	3 hrs	6 hrs	24 hrs	Initial	1 hr	3 hrs	6 hrs	24 hrs
	Formulation									
	Treanda ™ 5 mg/ml admixed with 500 ml normal saline									
Assay (mg/ml)	0.566	0.558	0.544	0.527	0.454	0.193	0.191	0.185	0.178	0.154
Assay (% Initial)	100.0	98.6	96.1	93.1	80.2	100.0	99.0	95.9	92.2	79.8
Impurity - MCE (%)	0.263	0.261	0.268	0.262	0.263	0.261	0.288	0.277	0.250	0.276
Impurity - HP1 (%)	1.250	2.248	4.730	7.287	16.887	1.231	2.241	4.770	7.462	17.504
Impurity - Dimer (%)	0.223	0.229	0.269	0.279	0.326	0.188	0.185	0.178	0.176	0.252
Single unknown (%)	0.103	0.103	0.101	0.097	0.081	0.077	0.079	0.103	0.083	0.066
Total (%)	1.97	2.97	5.50	8.04	17.66	1.85	3.01	5.41	8.07	18.27

MCE—monochloroethyl derivative;

HP1—mono hydroxyl bendamustine

As shown in Table 9, Treanda™ when prepared as directed in the label (final concentration between 0.2-0.6 mg/ml) shows total degradation of about 5-6% in 3 hours at room temperature (corresponding to the room temperature stability claim in the label); monohydroxy bendamustine is the main degradant. In contrast, the non-aqueous bendamustine formulations admixed in either 50 ml or 100 ml saline show total degradation of less than 5-6% over 6 hours at the lowest concentrations tested, indicating that these admixtures are significantly less prone to degradation. This stabilizing effect is particularly pronounced at the higher concentrations (which are more typical), with chemical stability evident for 24 hours at these concentrations. The non-aqueous formulations of bendamustine thus offer better chemical stability than Treanda™ when admixed into smaller volumes.

I claim:

1. A method of treating chronic lymphocytic leukemia or indolent B cell non-Hodgkin's lymphoma comprising parenterally administering to a subject a volume of about 100 ml or less of a liquid composition comprising:

a) from about 0.5 to about 5.6 mg/ml of bendamustine or a pharmaceutically acceptable salt thereof;

b) a solubilizer comprising polyethylene glycol and propylene glycol, wherein the amount of solubilizer is from about 0.5 to about 26.5% vol;

c) a parenterally acceptable diluent; and optionally

d) an antioxidant;

over a period of less than or equal to about 15 minutes to the subject.

2. The method of claim **1**, wherein the subject is human.

3. The method of claim **1**, wherein the amount of solubilizer is from about 2.0 to about 22.4% vol.

4. The method of claim **1**, where the polyethylene glycol is PEG 400.

5. The method of claim **1**, wherein the weight ratio of polyethylene glycol to propylene glycol is about 90:10.

6. The method of claim **5**, wherein the volume administered is about 50 ml.

7. The method of claim **1**, wherein the antioxidant is monothioglycerol.

8. The method of claim **1**, wherein the volume administered is about 50 ml.

9. The method of claim **1**, wherein the bendamustine is administered to treat chronic lymphocytic leukemia.

10. The method of claim **9**, wherein the composition is administered intravenously in a volume of about 50 ml in 10 minutes or less on days 1 and 2 of a 28 day cycle.

11. The method of claim **10**, wherein the composition is administered in about 10 minutes.

12. The method of claim **10**, wherein the composition is administered for up to 6 cycles.

13. The method of claim **9**, wherein the volume of the composition administered to the subject provides a bendamustine dosage amount ranging from about 25 mg/m^2 to about 100 mg/m^2 to the subject.

14. The method of claim **13**, wherein the composition provides a bendamustine dosage of about 100 mg/m^2.

15. The method of claim **9**, wherein the liquid composition comprises from about 1.85 mg/ml to about 4.84 mg/ml of bendamustine or a pharmaceutically acceptable salt thereof.

16. The method of claim **1**, wherein the bendamustine is administered to treat indolent B cell non-Hodgkin's lymphoma.

17. The method of claim **16**, wherein the composition is administered intravenously in a volume of about 50 ml in about 10 minutes or less on days 1 and 2 of as 21 day cycle.

18. The method of claim **17**, wherein the composition is administered in about 10 minutes.

19. The method of claim **17**, wherein the composition is administered for up to 8 cycles.

20. The method of claim **16**, wherein the volume of the composition administered to the subject provides a bendamustine dosage amount ranging from about 60 mg/m^2 to about 120 mg/m^2 to the subject.

21. The method of claim **20**, wherein the composition provides a bendamustine dosage of about 120 mg/m^2.

22. The method of claim **16**, wherein the liquid composition comprises from about 2.19 mg/ml to about 5.59 mg/ml of bendamustine or a pharmaceutically acceptable salt thereof.

23. The method according to claim **1**, wherein the bendamustine is present as the hydrochloride salt.

* * * * *

FORM 19. Certificate of Compliance with Type-Volume Limitations **Form 19**
July 2020

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATIONS

Case Number: 2020-2134, -2136, -2137

Short Case Caption: Cephalon, Inc. V. Slayback Pharma Limited

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