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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS IRELAND LIMITED and PHARMA MAR, S.A., Plaintiffs, v. INVAGEN PHARMACEUTICALS, INC., CIPLA USA, INC., CIPLA (EU) LIMITED, CIPLA LIMITED, SANDOZ, INC., ZYDUS LIFESCIENCES GLOBAL FZE, ZYDUS PHARMACEUTICALS (USA) INC., ZYDUS LIFESCIENCES LIMITED, RK PHARMA, INC., APICORE US LLC, ARCHIS PHARMA LLC, VGYAAN PHARMACEUTICALS LLC, DR. REDDY'S LABORATORIES, INC., MSN PHARMACEUTICALS INC., and MSN LABORATORIES PVT. LTD., Defendants.	Civil Action No. _____ (Filed Electronically) **HIGHLY CONFIDENTIAL – ATTORNEYS' EYES ONLY** **FILED UNDER SEAL PURSUANT TO L. CIV. R. 5.3**

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Jazz Pharmaceuticals Ireland Limited ("Jazz") and Pharma Mar, S.A. ("Pharma Mar") (collectively, "Plaintiffs"), for their Complaint against Defendants InvaGen Pharmaceuticals, Inc. ("InvaGen"), Cipla USA, Inc. ("Cipla USA"), Cipla (EU) Limited ("Cipla

EU"), and Cipla Limited ("Cipla Limited") (collectively, "InvaGen Defendants"); Sandoz, Inc. ("Sandoz"); Zydus Lifesciences Global FZE ("Zydus FZE"), Zydus Pharmaceuticals (USA) Inc. ("Zydus USA"), and Zydus Lifesciences Limited ("Zydus Limited") (collectively, "Zydus Defendants"); RK Pharma, Inc. ("RK"), Apicore US LLC ("Apicore"), Archis Pharma LLC ("Archis"), Vgyaan Pharmaceuticals LLC ("Vgyaan"), and Dr. Reddy's Laboratories, Inc. ("DRL") (collectively, "RK Defendants"); and MSN Pharmaceuticals, Inc. ("MSNPI") and MSN Laboratories Pvt. Ltd. ("MSN Labs") (collectively, "MSN Defendants") (all collectively, "Defendants"), hereby allege as follows:

THE PARTIES

Plaintiffs

1. Plaintiff Jazz is a corporation organized and existing under the laws of Ireland, having a principal place of business at Fifth Floor, Waterloo Exchange, Waterloo Road, Dublin, N37 AX84, Ireland.

2. Plaintiff Pharma Mar is a corporation organized and existing under the laws of Spain, having a principal place of business at Avenida De Los Reyes, 1, 28770 - Colmenar Viejo, Madrid, Spain.

InvaGen Defendants

3. On information and belief, Defendant InvaGen is a corporation organized and existing under the laws of New York, having a principal place of business at 7 Oser Avenue, Hauppauge, New York 11788, United States.

4. On information and belief, Defendant InvaGen, by itself and/or through its affiliates and agents, is in the business of, *inter alia,* manufacturing, marketing, importing, preparing, and selling generic pharmaceutical products that it distributes in the State of New Jersey and throughout the United States.

5. On information and belief, Defendant Cipla USA is a corporation organized and existing under the laws of Delaware, having a principal place of business at 10 Independence Boulevard, Suite 300, Warren, New Jersey 07059, United States.

6. On information and belief, Cipla USA, by itself and/or through its affiliates and agents, is in the business of, *inter alia,* manufacturing, marketing, importing, preparing, and selling generic pharmaceutical products that it distributes in the State of New Jersey and throughout the United States.

7. On information and belief, Defendant Cipla EU is a corporation organized and existing under the laws of United Kingdom, having a principal place of business at 3rd Floor, 364-366 Kensington High Street, London, W14 8NS, United Kingdom.

8. On information and belief, Cipla EU, by itself and/or through its affiliates and agents, is in the business of, *inter alia,* manufacturing, marketing, importing, preparing, and selling generic pharmaceutical products that it distributes in the State of New Jersey and throughout the United States.

9. On information and belief, Defendant Cipla Limited is a corporation organized and existing under the laws of India, having a principal place of business at Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400013, India.

10. On information and belief, Cipla Limited, by itself and/or through its affiliates and agents, is in the business of, *inter alia,* manufacturing, marketing, importing, preparing, and selling generic pharmaceutical products that it distributes in the State of New Jersey and throughout the United States.

11. On information and belief, InvaGen is a wholly owned subsidiary of Cipla EU, which is a wholly owned subsidiary of Cipla Limited.

12. On information and belief, Cipla USA is a wholly owned subsidiary of InvaGen. In an IPR petition to the PTAB, InvaGen represented that it "has a 100% fully owned subsidiary named Cipla USA Inc." *See* Petition for *Inter Partes* Review of U.S. Patent No. 10,828,310, *InvaGen Pharmaceuticals, Inc. v. Bayer Pharma*, Case IPR2022-01515 (P.T.A.B. Sept. 8, 2022).

13. On information and belief, the InvaGen Defendants are agents of each other with respect to the development, regulatory approval, marketing, sale, and/or distribution of generic products within the United States. On information and belief, the acts of the InvaGen Defendants complained of herein were done with the cooperation, participation, and assistance of, and at least in part for the benefit of, each other.

14. On information and belief, the InvaGen Defendants have cooperated and assisted in the preparation and filing of Abbreviated New Drug Application ("ANDA") No. 219605 ("InvaGen ANDA") and will be involved in the manufacture, importation, marketing, and/or sale of the drug that is the subject of the InvaGen ANDA, if approved by the United States Food and Drug Administration ("FDA").

Sandoz

15. On information and belief, Defendant Sandoz is a corporation organized and existing under the laws of Delaware, having a principal place of business at 100 College Road West, Princeton, New Jersey 08540, United States.

16. On information and belief, Sandoz, by itself and/or through its affiliates and agents, is in the business of, *inter alia*, manufacturing, marketing, importing, preparing, and selling generic pharmaceutical products that it distributes in the State of New Jersey and throughout the United States.

17. On information and belief, Sandoz has prepared and filed ANDA No. 219515 ("Sandoz ANDA") and will be involved in the manufacture, importation, marketing, and/or sale of the drug that is the subject of the Sandoz ANDA, if approved by the FDA.

Zydus Defendants

18. On information and belief, Defendant Zydus FZE is a corporation organized and existing under the laws of Dubai, United Arab Emirates, having a principal place of business at Fzjo B2601, Jebel Ali Free Zone Dubai, Dubai, United Arab Emirates.

19. On information and belief, Zydus FZE, by itself and/or through its affiliates and agents, is in the business of, *inter alia*, manufacturing, marketing, importing, preparing, and selling generic pharmaceutical products that it distributes in the State of New Jersey and throughout the United States.

20. On information and belief, Defendant Zydus USA is a corporation organized and existing under the laws of New Jersey, having a principal place of business at 73 Route 31 North, Pennington, New Jersey 08534, United States.

21. On information and belief, Zydus USA, by itself and/or through its affiliates and agents, is in the business of, *inter alia,* manufacturing, marketing, importing, preparing, and selling generic pharmaceutical products that it distributes in the State of New Jersey and throughout the United States.

22. On information and belief, Defendant Zydus Limited is a corporation organized and existing under the laws of India, having a principal place of business at Zydus Corporate Park Scheme No. 63, Survey No. 536, Khoraj (Gandhinagar) Nr. Vaishnodevi Circle, Ahmedabad, Gujarat 382481, India.

23. On information and belief, Zydus Limited, by itself and/or through its affiliates and agents, is in the business of, *inter alia*, manufacturing, marketing, importing, preparing, and selling

generic pharmaceutical products that it distributes in the State of New Jersey and throughout the United States.

24. On information and belief, Zydus FZE and Zydus USA are wholly owned subsidiaries of Zydus Limited.

25. On information and belief, the Zydus Defendants are agents of each other with respect to the development, regulatory approval, marketing, sale, and/or distribution of generic products within the United States. On information and belief, the acts of the Zydus Defendants complained of herein were done with the cooperation, participation, and assistance of, and at least in part for the benefit of, each other.

26. On information and belief, the Zydus Defendants have cooperated and assisted in the preparation and filing of ANDA No. 219582 ("Zydus ANDA") and will be involved in the manufacture, importation, marketing, and/or sale of the drug that is the subject of the Zydus ANDA, if approved by the FDA.

RK Defendants

27. On information and belief, Defendant RK is a corporation organized and existing under the laws of Delaware, having a principal place of business at 401 North Middletown Road, Building 215/215A, Pearl River, New York 10965, United States.

28. On information and belief, RK, by itself and/or through its affiliates and agents, is in the business of, *inter alia*, manufacturing, marketing, importing, preparing, and selling generic pharmaceutical products that it distributes in the State of New Jersey and throughout the United States.

29. On information and belief, Defendant Apicore is a corporation organized and existing under the laws of Delaware, having a principal place of business at 49 Napoleon Court, Somerset, New Jersey 08873.

30. On information and belief, Apicore, by itself and/or through its affiliates and agents, is in the business of, inter alia, manufacturing, marketing, importing, preparing, and selling generic pharmaceutical products that it distributes in the State of New Jersey and throughout the United States.

31. On information and belief, Defendant Archis is a corporation organized and existing under the laws of Delaware, having a principal place of business at 15 Corporate Place South, Suite 108, Piscataway, New Jersey 08854, United States.

32. On information and belief, Archis, by itself and/or through its affiliates and agents, is in the business of, inter alia, manufacturing, marketing, importing, preparing, and selling generic pharmaceutical products that it distributes in the State of New Jersey and throughout the United States.

33. On information and belief, Defendant Vgyaan is a corporation organized and existing under the laws of New Jersey, having a principal place of business at 23 Orchard Road, Suite 180, Skillman, New Jersey 08558, United States.

34. On information and belief, Vgyaan, by itself and/or through its affiliates and agents, is in the business of, *inter alia*, manufacturing, marketing, importing, preparing, and selling generic pharmaceutical products that it distributes in the State of New Jersey and throughout the United States.

35. On information and belief, Defendant DRL is a corporation organized and existing under the laws of the State of New Jersey, having a principal place of business at 600 College Road East, Princeton, New Jersey 08540, United States.

36. On information and belief, DRL, by itself and/or through its affiliates and agents, is in the business of, *inter alia*, manufacturing, marketing, importing, preparing, and selling generic

pharmaceutical products that it distributes in the State of New Jersey and throughout the United States.

37. On information and belief, Apicore, Archis, and Vgyaan are wholly owned subsidiaries of RK.

38. On information and belief, the RK Defendants are agents of each other with respect to the development, regulatory approval, marketing, sale, and/or distribution of generic products within the United States. On information and belief, the acts of the RK Defendants complained of herein were done with the cooperation, participation, and assistance of, and at least in part for the benefit of, each other.

39. On information and belief, the RK Defendants have cooperated and assisted in the preparation and filing of ANDA No. 219731 ("RK ANDA") and will be involved in the manufacture, importation, marketing, and/or sale of the drug that is the subject of the RK ANDA, if approved by the FDA.

40. [redacted]

MSN Defendants

41. On information and belief, Defendant MSNPI is a corporation organized and existing under the laws of Delaware, having a principal place of business at 20 Duke Road, Piscataway, New Jersey 08854, United States.

42. On information and belief, MSNPI, by itself and/or through its affiliates and agents, is in the business of, *inter alia*, manufacturing, marketing, importing, preparing, and selling generic pharmaceutical products that it distributes in the State of New Jersey and throughout the United States.

43. On information and belief, Defendant MSN Labs is a corporation organized and existing under the laws of India, having a principal place of business at MSN House, Plot No. C-24, SanathNagar Industrial Estate, SanathNagar, Hyderabad, Telangana 500018, India.

44. On information and belief, MSN Labs, by itself and/or through its affiliates and agents, is in the business of, *inter alia*, manufacturing, marketing, importing, preparing, and selling generic pharmaceutical products that it distributes in the State of New Jersey and throughout the United States.

45. On information and belief, MSNPI is a wholly owned subsidiary of MSN Labs.

46. On information and belief, the MSN Defendants are agents of each other with respect to the development, regulatory approval, marketing, sale, and/or distribution of generic products within the United States. On information and belief, the acts of the MSN Defendants complained of herein were done with the cooperation, participation, and assistance of, and at least in part for the benefit of, each other.

47. On information and belief, the MSN Defendants have cooperated and assisted in the preparation and filing of ANDA No. 219771 ("MSN ANDA") and will be involved in the manufacture, importation, marketing, and/or sale of the drug that is the subject of the MSN ANDA, if approved by the FDA.

NATURE OF THE ACTION

48. This is a civil action for the infringement of United States Patent No. 12,324,806 ("the '806 Patent") under the Patent Laws of the United States, 35 U.S.C. § 100 et seq., arising from Defendants' filing of ANDA Nos. 219605, 219515, 219582, 219731, and 219771 with the FDA seeking approval to market generic versions of the pharmaceutical product Zepzelca® (lurbinectedin) for injection, for intravenous use, 4 mg/vial, before the expiration of the '806 Patent covering Zepzelca®'s use.

JURISDICTION AND VENUE

49. This Court has jurisdiction over the subject matter of this action, including Counts I – IX against the Defendants, pursuant to 28 U.S.C. §§ 1331, 1338, 2201, and 2202.

InvaGen Defendants

50. This Court has personal jurisdiction over the InvaGen Defendants by virtue of the fact that, *inter alia*, the InvaGen Defendants have committed the tortious act of patent infringement pursuant to 35 U.S.C. § 271(e)(2)(A) that has led to foreseeable harm and injury to Plaintiffs in the State of New Jersey and throughout the United States.

51. This Court has personal jurisdiction over the InvaGen Defendants by virtue of the fact that, on information and belief, the InvaGen Defendants, either directly or through their affiliates, regularly and continuously do or solicit business in New Jersey, engage in other persistent courses of conduct in New Jersey, and/or derive substantial revenue from services or things used or consumed in New Jersey, including by selling their pharmaceutical products in New Jersey and, therefore, can reasonably expect to be subject to jurisdiction in the New Jersey courts. On information and belief, the InvaGen Defendants conduct marketing and sales activities in the State of New Jersey, including, but not limited to, distribution, marketing, and sales of pharmaceutical products to New Jersey residents that are continuous and systematic. On information and belief, if the InvaGen ANDA is approved, the InvaGen Defendants will market and sell their generic version of Zepzelca® in New Jersey.

52. This Court further has personal jurisdiction over the InvaGen Defendants by virtue of the fact that the InvaGen Defendants have previously submitted to the jurisdiction of this Court and purposefully availed themselves of this Court by consenting to this Court's jurisdiction in a patent infringement action initiated in this jurisdiction involving the same InvaGen ANDA. *See*

Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al., CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 29 (InvaGen Defendants' Answer).

53. This Court has personal jurisdiction over InvaGen. On information and belief, InvaGen regularly and continuously conducts business in New Jersey. InvaGen has an active business entity status registered with the state of New Jersey under the business entity identification number 0450360045 and has a corporate agent for service of process at 208 West State Street, Trenton, New Jersey 08608. InvaGen's New Jersey business entity registration also identifies its officers and directors as having the address 10 Independence Boulevard, Suite 300, Warren, New Jersey 07059, which is the address of its wholly owned subsidiary Cipla USA.

54. This Court further has personal jurisdiction over InvaGen by virtue of the fact that InvaGen has previously submitted to the jurisdiction of this Court and purposefully availed itself of this Court by consenting to this Court's jurisdiction and asserting counterclaims in civil actions initiated in this jurisdiction, including, but not limited to, *e.g.*, *Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024); *Jazz Pharm. Research UK Ltd. f/k/a GW Research Ltd. v. Apotex Inc.*, *et al.*, CA. No. 23-cv-23141 (D.N.J. *filed* Dec. 15, 2023); *Sumitomo Dainippon Pharma Co., Ltd. v. Aurobindo Pharma Ltd.*, *et al.*, CA. No. 18-cv-2620 (D.N.J. *filed* Feb. 23, 2018); *Mitsubishi Tanabe Pharma Corp.*, *et al. v. InvaGen Pharm., Inc.*, CA. No. 17-cv-06375 (D.N.J. *filed* Aug. 23, 2017); *Sumitomo Dainippon Pharma Co., Ltd.*, *et al. v. InvaGen Pharm., Inc.*, CA. No. 15-cv-00281 (D.N.J. *filed* Jan. 14, 2015); *Shire Development LLC*, *et al v. InvaGen Pharm., Inc.*, CA. No. 15-cv-00367 (D.N.J. *filed* Dec. 12, 2014).

55. This Court has personal jurisdiction over Cipla USA. On information and belief, Cipla USA regularly and continuously conducts business in New Jersey and has a principal place

of business at 10 Independence Boulevard, Suite 300, Warren, New Jersey 07059. Cipla USA has an active business entity status registered with the state of New Jersey under the business entity identification number 0450318628 and has a corporate agent for service of process at 208 West State Street, Trenton, New Jersey 08608.

56. This Court further has personal jurisdiction over Cipla USA by virtue of the fact that Cipla USA has previously submitted to the jurisdiction of this Court and purposefully availed itself of this Court by consenting to this Court's jurisdiction and asserting counterclaims in civil actions initiated in this jurisdiction, including, but not limited to, *e.g.*, *Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024); *Teva Branded Pharmaceutical Products R&D, Inc.*, *et al. v. Cipla USA, Inc.*, *et al.*, CA. No. 24-cv-00909 (D.N.J. *filed* Feb. 16, 2024); *Jazz Pharm. Research UK Ltd. f/k/a GW Research Ltd. v. Apotex Inc.*, *et al.*, CA. No. 23-cv-23141 (D.N.J. *filed* Dec. 15, 2023); *Cubist Pharm. LLC f/k/a Cubist Pharm., Inc. v. Cipla USA, Inc.*, *et al.*, CA. No. 19-cv-12920 (D.N.J. *filed* May. 24, 2019).

57. Additionally, on information and belief, InvaGen's online presence resides within Cipla USA's website, and all the manufacturing sites identified on Cipla USA's website are InvaGen units. On information and belief, InvaGen and Cipla USA work in concert to market and sell generic pharmaceutical products throughout the United States, including in New Jersey. On information and belief, Cipla USA and InvaGen share officers and employees. On information and belief, InvaGen and Cipla USA are alter egos.

58. This Court has personal jurisdiction over Cipla EU. On information and belief, Cipla EU regularly and continuously transacts business within New Jersey, either directly or through its subsidiaries—InvaGen and Cipla USA, companies having active business entity statuses registered with New Jersey—including by selling pharmaceutical products in New Jersey.

59. This Court further has personal jurisdiction over Cipla EU by virtue of the fact that Cipla EU has previously submitted to the jurisdiction of this Court and purposefully availed itself of this Court by consenting to this Court's jurisdiction in a civil action initiated in this jurisdiction, *e.g.*, *Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024).

60. Alternatively, this Court may exercise jurisdiction over Cipla EU pursuant to Federal Rule of Civil Procedure 4(k)(2) because (a) Plaintiffs' claims arise under federal law; (b) Cipla EU is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Cipla EU has sufficient contacts with the United States as a whole, including, but not limited to manufacturing and/or selling pharmaceutical products distributed throughout the United States, such that this Court's exercise of jurisdiction over Cipla EU satisfies due process.

61. This Court has personal jurisdiction over Cipla Limited. On information and belief, Cipla Limited regularly and continuously transacts business within New Jersey, either directly or through its subsidiaries—InvaGen and Cipla USA, companies having active business entity statuses registered with New Jersey—including by selling pharmaceutical products in New Jersey.

62. This Court further has personal jurisdiction over Cipla Limited by virtue of the fact that Cipla Limited has previously submitted to the jurisdiction of this Court and purposefully availed itself of this Court by consenting to this Court's jurisdiction and asserting counterclaims in civil actions initiated in this jurisdiction, including, but not limited to, *e.g.*, *Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024); *Teva Branded Pharm. Products R&D, Inc.*, *et al v. Cipla USA, Inc.*, *et al.*, CA. No. 24-cv-05856 (D.N.J. *filed* May. 06, 2024); *Jazz Pharm. Research UK Ltd. f/k/a GW Research Ltd. v. Apotex*

Inc., *et al.*, CA. No. 23-cv-23141 (D.N.J. *filed* Dec. 15, 2023); *Celgene Corp.*, *v. Cipla Ltd.*, CA. No. 19-cv-14731 (D.N.J. *filed* Jul. 03, 2019).

63. Alternatively, this Court may exercise jurisdiction over Cipla Limited pursuant to Federal Rule of Civil Procedure 4(k)(2) because (a) Plaintiffs' claims arise under federal law; (b) Cipla Limited is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Cipla Limited has sufficient contacts with the United States as a whole, including, but not limited to, manufacturing and/or selling pharmaceutical products distributed throughout the United States, such that this Court's exercise of jurisdiction over Cipla Limited satisfies due process.

64. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

65. The InvaGen Defendants have previously consented to venue in this Judicial District in a patent infringement action involving the same InvaGen ANDA. *See Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 29 (InvaGen Defendants' Answer).

66. Venue is proper in this Judicial District for InvaGen. On information and belief, InvaGen has an active business entity identification number in the State of New Jersey (0450360045), has employees in New Jersey, and maintains a regular and established place of business in New Jersey at 10 Independence Boulevard, Suite 300, Warren New Jersey 07059. In InvaGen's business registrations for New Jersey (as well as for California, Florida, Massachusetts, and Vermont), the "Principals" and "Officers and Directors" of InvaGen are identified as Arunesh Verma (President, CEO, Director), Deepak Agarwal (CFO, Treasurer, Director), Umang Vohra (Director), Srinivas Mallavarapu (Director), Robert Stewart (Independent Director), Anup Dad (Secretary, Treasurer), and Marc Falkin (CEO), and the address provided for all these individuals

is Cipla USA's principal address, *i.e.*, 10 Independence Boulevard, Suite 300, Warren, New Jersey 07059. Online third-party company profiles (*e.g.*, Moody's Analytics) also give the "contact information" for InvaGen as the above Warren, New Jersey address. Furthermore, on information and belief, based on InvaGen's connections to New Jersey, discoverable information in its possession, custody, or control regarding the InvaGen ANDA will likely show that InvaGen engaged in activities in New Jersey relevant to the preparation and/or submission of the InvaGen ANDA and therefore committed acts of infringement within this Judicial District.

67. Venue is proper in this Judicial District for Cipla USA. On information and belief, Cipla USA has its principal place of business at 10 Independence Boulevard, Suite 300, Warren, New Jersey 07059. On information and belief, Cipla USA has an active business entity identification number in the State of New Jersey (0450318628), has employees in New Jersey, and maintains a regular and established place of business in New Jersey at 10 Independence Boulevard, Suite 300, Warren, New Jersey 07059. In Cipla USA's business registration for New Jersey (as well as for New York), the "Principals" and "Officers and Directors" of Cipla USA are identified as Arunesh Verma (CEO, Director), Deepak Agarwal (CFO), Umang Vohra (President, Director), Robert Stewart (Director), Biplab Mazumdar (Secretary, Treasurer), and AS Kumar (Director), and the address provided for all these individuals is 10 Independence Boulevard, Suite 300, Warren, New Jersey 07059. Online third-party company profiles (*e.g.*, Moody's Analytics) also give the "contact information" for InvaGen as the above Warren, New Jersey address. Furthermore, on information and belief, based on Cipla USA's connections to New Jersey, discoverable information in its possession, custody, or control regarding the InvaGen ANDA will likely show that Cipla USA engaged in activities in New Jersey relevant to the preparation and/or

submission of the InvaGen ANDA and therefore committed acts of infringement within this Judicial District.

68. Venue is proper in this Judicial District for Cipla EU and Cipla Limited because, *inter alia*, they both are foreign corporations not residing in any United States district and may be sued in any judicial district.

69. Venue is further proper in this Court as to the InvaGen Defendants because, *inter alia*, they have committed, aided, abetted, contributed to, and/or participated in the commission of acts of patent infringement that will lead to foreseeable harm and injury to Plaintiffs, which manufacture Zepzelca® for sale and use throughout the United States, including within the State of New Jersey.

Sandoz

70. This Court has personal jurisdiction over Sandoz by virtue of the fact that, *inter alia*, Sandoz has committed the tortious act of patent infringement pursuant to 35 U.S.C. § 271(e)(2)(A) that has led to foreseeable harm and injury to Plaintiffs in the State of New Jersey and throughout the United States.

71. This Court has personal jurisdiction over Sandoz by virtue of the fact that, on information and belief, Sandoz, either directly or through its affiliates, regularly and continuously does or solicits business in New Jersey, engages in other persistent courses of conduct in New Jersey, and/or derives substantial revenue from services or things used or consumed in New Jersey, including by selling its pharmaceutical products in New Jersey and, therefore, can reasonably expect to be subject to jurisdiction in the New Jersey courts. On information and belief, the Sandoz conducts marketing and sales activities in the State of New Jersey, including, but not limited to, distribution, marketing, and sales of pharmaceutical products to New Jersey residents that are

continuous and systematic. On information and belief, if the Sandoz ANDA is approved, Sandoz will market and sell its generic version of Zepzelca® in New Jersey.

72. This Court further has personal jurisdiction over Sandoz by virtue of the fact that Sandoz has previously submitted to the jurisdiction of this Court and purposefully availed itself of this Court by consenting to this Court's jurisdiction and asserting counterclaims in a patent infringement action initiated in this jurisdiction involving the same Sandoz ANDA. *See Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 26 (Sandoz's Answer).

73. This Court has personal jurisdiction over Sandoz. On information and belief, Sandoz regularly and continuously conducts business in New Jersey. Sandoz has an active business entity status registered with the state of New Jersey under the business entity identification number 0101056767, a principal place of business at 100 College Road West, Princeton, New Jersey 08540, and a corporate agent for service of process at Princeton South Corporate Center, Suite 160, 100 Charles Ewing Blvd, Ewing, New Jersey 08628. Sandoz's New Jersey business entity registration also identifies its officers and directors as having the address 100 College Road West, Princeton, New Jersey 08540.

74. This Court further has personal jurisdiction over Sandoz by virtue of the fact that Sandoz has previously submitted to the jurisdiction of this Court and purposefully availed itself of this Court by consenting to this Court's jurisdiction and asserting counterclaims in civil actions initiated in this jurisdiction, including, but not limited to, *e.g.*, *Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024); *Merck Sharp & Dohme BV*, *et al. v. Sandoz, Inc.*, *et al.*, CA. No. 20-cv-03117 (D.N.J. *filed* Mar. 20, 2020); *Celgene Corp. v. Sandoz Inc.*, CA. No. 18-cv-11026 (D.N.J. *filed* Jun. 26, 2018); *Allergan*

Sales, LLC, *et al. v. Sandoz, Inc.*, *et al.*, CA. No. 17-cv-10129 (D.N.J. *filed* Oct. 30, 2017); *Boehringer Ingelheim Pharm., Inc.*, *et al. v. Sandoz Inc.*, CA. No. 17-cv-08825 (D.N.J. *filed* Oct. 20, 2017); *Mitsubishi Tanabe Pharma Corp.*, *et al. v. MSN Labs. Pvt. Ltd.*, *et al.*, CA. No. 17-cv-05302 (D.N.J. *filed* Jul. 20, 2017).

75. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

76. Sandoz has previously consented to venue in this Judicial District in a patent infringement action involving the same Sandoz ANDA. *See Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 26 (Sandoz's Answer).

77. Venue is proper in this Judicial District for Sandoz. On information and belief, Sandoz has active business entity identification number in the State of New Jersey (0101056767), has employees in New Jersey, and maintains a regular and established place of business in New Jersey at 100 College Road West, Princeton, New Jersey 08540. In Sandoz's business registrations for New Jersey (as well as for California, Florida, and Vermont), the "Principals" and "Officers and Directors" of Sandoz are identified as Keren Haruvi (President), Karen McDonnell (Secretary, Vice President), Mohammad Obeidat (COO), Edward Stueck (Vice President), and Martin Bischof (Director), and the address provided for all these individuals is 100 College Road West, Princeton, New Jersey 08540. Furthermore, on information and belief, based on Sandoz's connections to New Jersey, discoverable information in its possession, custody, or control regarding the Sandoz ANDA will likely show that Sandoz engaged in activities in New Jersey relevant to the preparation and/or submission of the Sandoz ANDA and therefore committed acts of infringement within this Judicial District. For example, Sandoz has previously identified Gregory Seitz, Head, U.S. Regulatory Affairs Generics as possessing knowledge and information "regarding the compilation and filing"

of the Sandoz ANDA. *See Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), Sandoz's Initial Disclosures Pursuant to Fed. R. Civ. P. 26(a)(1) (Jan. 29, 2025). On information and belief, Mr. Seitz is employed by Sandoz in New Jersey.

78. Venue is further proper in this Court as to Sandoz because, *inter alia*, Sandoz has committed, aided, abetted, contributed to, and/or participated in the commission of acts of patent infringement that will lead to foreseeable harm and injury to Plaintiffs, which manufacture Zepzelca® for sale and use throughout the United States, including within the State of New Jersey.

Zydus Defendants

79. This Court has personal jurisdiction over the Zydus Defendants by virtue of the fact that, *inter alia*, the Zydus Defendants have committed the tortious act of patent infringement pursuant to 35 U.S.C. § 271(e)(2)(A) that has led to foreseeable harm and injury to Plaintiffs in the State of New Jersey and throughout the United States.

80. This Court has personal jurisdiction over the Zydus Defendants by virtue of the fact that, on information and belief, the Zydus Defendants, either directly or through their affiliates, regularly and continuously do or solicit business in New Jersey, engage in other persistent courses of conduct in New Jersey, and/or derive substantial revenue from services or things used or consumed in New Jersey, including by selling their pharmaceutical products in New Jersey and, therefore, can reasonably expect to be subject to jurisdiction in the New Jersey courts. On information and belief, the Zydus Defendants conduct marketing and sales activities in the State of New Jersey, including, but not limited to, distribution, marketing, and sales of pharmaceutical products to New Jersey residents that are continuous and systematic. On information and belief, if the Zydus ANDA is approved, the Zydus Defendants will market and sell their generic version of Zepzelca® in New Jersey.

81. This Court further has personal jurisdiction over the Zydus Defendants by virtue of the fact that the Zydus Defendants have previously submitted to the jurisdiction of this Court and purposefully availed themselves of this Court by consenting to this Court's jurisdiction and asserting counterclaims in a patent infringement action initiated in this jurisdiction involving the same Zydus ANDA. *See Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 52 (Zydus Defendants' Answer).

82. This Court has personal jurisdiction over Zydus FZE. On information and belief, Zydus FZE regularly and continuously transacts business within New Jersey, either directly or through its affiliates—including Zydus USA, a New Jersey corporation—including selling pharmaceutical products in New Jersey. On information and belief, Zydus FZE and Zydus USA work in concert to market and sell generic pharmaceutical products throughout the United States, including in New Jersey. On information and belief, Zydus FZE and Zydus USA are alter egos.

83. Alternatively, this Court may exercise jurisdiction over Zydus FZE pursuant to Federal Rule of Civil Procedure 4(k)(2) because (a) Plaintiffs' claims arise under federal law; (b) Zydus FZE is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Zydus FZE has sufficient contacts with the United States as a whole, including, but not limited to manufacturing and/or selling pharmaceutical products distributed throughout the United States, directly or through related entities, such that this Court's exercise of jurisdiction over Zydus FZE satisfies due process.

84. This Court has personal jurisdiction over Zydus USA. On information and belief, Zydus USA is incorporated in and regularly and continuously conducts business in New Jersey. Zydus USA has an active business entity status registered with the state of New Jersey under the business entity identification number 0100915422 and has a principal place of business at 73 Route

31 North, Pennington, New Jersey, 08534. Zydus USA's New Jersey business entity registration also identifies its officers and directors as having the address 73 Route 31 North, Pennington, New Jersey 08534.

85. This Court further has personal jurisdiction over Zydus USA by virtue of the fact that Zydus USA has previously submitted to the jurisdiction of this Court and purposefully availed itself of this Court by consenting to this Court's jurisdiction and asserting counterclaims in civil actions initiated in this jurisdiction, including, but not limited to, *e.g.*, *Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024); *Astellas Pharma Inc.*, *et al. v. Zydus Pharm. (USA) Inc.*, *et al.*, CA. No. 22-cv-04499 (D.N.J. *filed* Jul. 08, 2022); *Merck Sharp & Dohme BV*, *et al. v. Aurobindo Pharma USA, Inc.*, *et al.*, CA. No. 20-cv-02576 (D.N.J. *filed* Mar. 10, 2020); *Sumitomo Dainippon Pharma Co., Ltd.*, *et al. v. Aurobindo Pharma Ltd.*, *et al*., CA. No. 18-cv-02620 (D.N.J. *filed* Feb. 23, 2018); *Impax Labs., Inc. v. Zydus Pharm. (USA) Inc.*, *et al.*, CA. No. 17-cv-13476 (D.N.J. *filed* Dec. 21, 2017); *Mitsubishi Tanabe Pharma Corp.*, *et al. v. Sandoz Inc.*, *et al.*, CA. No. 17-cv-05319 (D.N.J. *filed* Jul. 20, 2017); *Boehringer Ingelheim Pharm. Inc.*, *et al. v. Accord Healthcare, Inc. et al.*, CA. No. 16-cv-00852 (D.N.J. *filed* Feb. 17, 2016); *Otsuka Pharm. Co., Ltd. v. Zydus Pharm. USA Inc.*, CA. No. 14-cv-07252 (D.N.J. *filed* Nov. 20, 2014).

86. This Court has personal jurisdiction over Zydus Limited. On information and belief, Zydus Limited regularly and continuously transacts business within New Jersey, either directly or through its wholly owned subsidiaries—Zydus FZE and Zydus USA, the latter a New Jersey corporation—including by selling pharmaceutical products in New Jersey.

87. This Court further has personal jurisdiction over Zydus Limited by virtue of the fact that Zydus Limited has previously submitted to the jurisdiction of this Court and purposefully

availed itself of this Court by consenting to this Court's jurisdiction and asserting counterclaims in civil actions initiated in this jurisdiction, including, but not limited to, *e.g.*, *Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024); *Aragon Pharm., Inc.*, *et al. v. Zydus Worldwide DMCC*, *et al.*, CA. No. 23-cv-01685 (D.N.J. *filed* Mar. 24, 2023)*; Merck Sharp & Dohme BV*, *et al. v. Aurobindo Pharma USA, Inc.*, *et al.*, CA. No. 20-cv-02576 (D.N.J. *filed* Mar. 10, 2020).

88. Alternatively, this Court may exercise jurisdiction over Zydus Limited pursuant to Federal Rule of Civil Procedure 4(k)(2) because (a) Plaintiffs' claims arise under federal law; (b) Zydus Limited is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Zydus Limited has sufficient contacts with the United States as a whole, including, but not limited to manufacturing and/or selling pharmaceutical products distributed throughout the United States, such that this Court's exercise of jurisdiction over Zydus Limited satisfies due process.

89. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

90. The Zydus Defendants have previously consented to venue in this Judicial District in a patent infringement action involving the same Zydus ANDA. *See Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 52 (Zydus Defendants' Answer).

91. Venue is proper in this Judicial District for Zydus FZE and Zydus Limited because, *inter alia*, they both are foreign corporations not residing in any United States district and may be sued in any judicial district.

92. Venue is proper in this Judicial District for Zydus USA. On information and belief, Zydus USA is incorporated in, and therefore resides in, New Jersey.

93. Venue is proper in this Judicial District for the Zydus Defendants. On information and belief, based on the Zydus Defendants' connections to New Jersey, discoverable information in its possession, custody, or control regarding the Zydus ANDA will likely show that the Zydus Defendants engaged in activities in New Jersey relevant to the preparation and/or submission of the Zydus ANDA and therefore committed acts of infringement within this Judicial District. For example, the Zydus Defendants have previously identified Ashish Manjrekar as possessing knowledge and information about Zydus' decision to develop the product that is the subject of the Zydus ANDA. *See Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), Zydus' Objections and Responses to Plaintiffs' Interrogatory No. 3 (June 16, 2025). On information and belief, Mr. Manjrekar is a Director of Marketing employed by Zydus USA in New Jersey.

94. Venue is further proper in this Court as to the Zydus Defendants because, *inter alia*, they have committed, aided, abetted, contributed to, and/or participated in the commission of acts of patent infringement that will lead to foreseeable harm and injury to Plaintiffs, which manufacture Zepzelca® for sale and use throughout the United States, including within the State of New Jersey.

RK Defendants

95. This Court has personal jurisdiction over the RK Defendants by virtue of the fact that, *inter alia*, the RK Defendants have committed the tortious act of patent infringement pursuant to 35 U.S.C. § 271(e)(2)(A) that has led to foreseeable harm and injury to Plaintiffs in the State of New Jersey and throughout the United States.

96. This Court has personal jurisdiction over the RK Defendants by virtue of the fact that, on information and belief, the RK Defendants, either directly or through their affiliates, regularly and continuously do or solicit business in New Jersey, engage in other persistent courses

of conduct in New Jersey, and/or derive substantial revenue from services or things used or consumed in New Jersey, including by selling their pharmaceutical products in New Jersey and, therefore, can reasonably expect to be subject to jurisdiction in the New Jersey courts. On information and belief, the RK Defendants conduct marketing and sales activities in the State of New Jersey, including, but not limited to, distribution, marketing, and sales of pharmaceutical products to New Jersey residents that are continuous and systematic. On information and belief, if the RK ANDA is approved, the RK Defendants will market and sell their generic version of Zepzelca® in New Jersey.

97. This Court has personal jurisdiction over RK. On information and belief, RK regularly and continuously conducts business in New Jersey, either directly or through its subsidiaries—Apicore, Archis, and Vgyaan, companies incorporated and/or having principal places of business in New Jersey—including by selling pharmaceutical products in New Jersey. On information and belief, RK, Apicore, Archis, and Vgyaan work in concert to market and sell generic pharmaceutical products throughout the United States, including in New Jersey. On information and belief, RK, Apicore, Archis, and Vgyaan are alter egos.

98. This Court further has personal jurisdiction over RK virtue of the fact that RK has previously submitted to the jurisdiction of this Court and purposefully availed itself of this Court by consenting to this Court's jurisdiction and asserting counterclaims in a patent infringement action initiated in this jurisdiction involving the same RK ANDA. *See Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 36 (RK's Answer).

99. This Court further has personal jurisdiction over RK by virtue of the fact that RK has previously submitted to the jurisdiction of this Court and purposefully availed itself of this

Court by consenting to this Court's jurisdiction and asserting counterclaims in civil actions initiated in this jurisdiction, including, but not limited to, *e.g.*, *Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024); *American Regent, Inc. f/k/a Luitpold Pharm., Inc. v. RK Pharma, Inc.*, *et al.*, CA. No. 24-cv-01169 (D.N.J. *filed* Feb. 28, 2024); *American Regent, Inc. f/k/a Luitpold Pharm., Inc. v. Somerset Therapeutics, LLC*, *et al.*, CA. No. 24-cv-01022 (D.N.J. *filed* Feb. 22, 2024).

100. This Court has personal jurisdiction over Apicore. On information and belief, Apicore regularly and continuously conducts business in New Jersey and has a principal place of business at 49 Napoleon Court, Somerset, New Jersey 08873.

101. This Court further has personal jurisdiction over Apicore by virtue of the fact that Apicore has previously submitted to the jurisdiction of this Court and purposefully availed itself of this Court by consenting to this Court's jurisdiction and asserting counterclaims in a civil action initiated in this jurisdiction, including, *e.g.*, *Aurobindo Pharma USA, Inc.*, *et al. v. Apicore US LLC*, *et al.*, CA. No. 16-cv-03358 (D.N.J. *filed* Jun. 09, 2016). *See also Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 22 (Apicore's stipulation in case involving the same RK ANDA).

102. This Court has personal jurisdiction over Archis. On information and belief, Archis regularly and continuously conducts business in New Jersey and has a principal place of business at 15 Corporate Place South, Piscataway, New Jersey 08854. *See also Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 22 (Archis stipulation in case involving the same RK ANDA).

103. This Court has personal jurisdiction over Vgyaan. On information and belief, Vgyaan is incorporated in and regularly and continuously conducts business in New Jersey.

Vgyaan has an active business entity status registered with the state of New Jersey under the business entity identification number 0600406976, a principal place of business at 23 Orchard Road, Suite 180, Skillman, New Jersey 08558, and has a corporate agent for service of process at 23 Cornflower Court, Suite 200, Belle Mead, New Jersey 08502.

104. This Court further has personal jurisdiction over Vgyaan by virtue of the fact that Vgyaan has previously submitted to the jurisdiction of this Court and purposefully availed itself of this Court by consenting to this Court's jurisdiction and asserting counterclaims in a civil action initiated in this jurisdiction, including, *e.g.*, *Actelion Pharmaceuticals Ltd.*, *et al. v. MSN Pharmaceuticals Inc.*, *et al.*, C.A. No. 20-cv-03859 (D.N.J. *filed* Apr. 09, 2020). *See also Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 22 (Vgyaan stipulation in case involving the same RK ANDA).

105. This Court has personal jurisdiction over DRL. On information and belief, DRL is incorporated in and regularly and continuously conducts business in New Jersey. DRL has an active business entity status registered with the state of New Jersey under the business entity identification number 0100518911, a principal place of business at 600 College Road East, Princeton, New Jersey 08540, and has a corporate agent for service of process at 820 Bear Tavern Road, West Trenton, New Jersey 08628. DRL's New Jersey business entity registration also identifies its officers and directors as having the address 600 College Road East, Princeton, New Jersey 08540.

106. This court further has personal jurisdiction over DRL by virtue of the fact that DRL has previously submitted to the jurisdiction of this Court and purposefully availed itself of this Court by consenting to this Court's jurisdiction and asserting counterclaims in civil actions initiated in this jurisdiction, including, *e.g.*, *Pharmacosmos A/S, et al., v. Dr. Reddy's Labs., Inc.,*

et al., C.A. No. 25-cv-3967 (D.N.J. *filed* May 7, 2025); *Aurinia Pharmaceuticals Inc. v. Dr. Reddy's Labs. Inc.*, C.A. No. 25-cv-3693 (D.N.J. *filed* May 1, 2025); *Esperion Therapeutics, Inc. v. Re. Reddy's Labs. Inc.*, C.A. No. 24-cv-6391 (D.N.J. *filed* May 23, 2024); *Novo Nordisk Inc. et al. v. Dr. Reddy's Labs. Ltd. et al.*, C.A. No. 1:23-cv-22112 (D.N.J. *filed* Nov. 8, 2023).

107. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

108. Venue is proper in this Judicial District for RK. RK has previously consented to venue in this Judicial District in a patent infringement action involving the same RK ANDA. *See Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 36 (RK Defendants' Answer). On information and belief, RK has employees in New Jersey and maintains regular and established places of business in New Jersey at 49 Napoleon Court, Somerset, New Jersey 08873; 15 Corporate Place South, Piscataway, New Jersey 08854; and 23 Orchard Road, Suite 180, Skillman, New Jersey 08558. On information and belief, the identified "Principals" and "Officers and Directors" of RK are Ravishanker Kovi (Executive Chairman) and Naveen Paladugu (COO, Director), who are also on executive committees of Apicore and Archis, respectively, and the addresses provided for these individuals are the Somerset, New Jersey and Piscataway, New Jersey addresses of Apicore and Archis, above. The New York State Division of Corporations "Entity Information" registration form for RK states that the "Principal Executive Office Address" for RK is 1 Tower Center Blvd, 2300, East Brunswick, New Jersey 08816. Furthermore, on information and belief, based on RK's connections to New Jersey, discoverable information in its possession, custody, or control regarding the RK ANDA will likely show that RK engaged in activities in New Jersey relevant to the preparation and/or submission of the RK ANDA and therefore committed acts of infringement within this Judicial District.

109. Venue is proper in this Judicial District for Apicore. On information and belief, Apicore has employees in New Jersey and maintains a regular and established place of business in New Jersey at 49 Napoleon Court, Somerset, New Jersey 08873. Furthermore, on information and belief, based on Apicore's connections to New Jersey, discoverable information in its possession, custody, or control regarding the RK ANDA will likely show that Apicore engaged in activities in New Jersey relevant to the preparation and/or submission of the RK ANDA and therefore committed acts of infringement within this Judicial District.

110. Venue is proper in this Judicial District for Archis. On information and belief, Archis has employees in New Jersey and maintains a regular and established place of business in New Jersey at 15 Corporate Place South, Suite 108, Piscataway, New Jersey 08854. Furthermore, on information and belief, based on Archis's connections to New Jersey, discoverable information in its possession, custody, or control regarding the RK ANDA will likely show that Archis engaged in activities in New Jersey relevant to the preparation and/or submission of the RK ANDA and therefore committed acts of infringement within this Judicial District.

111. Venue is proper in this Judicial District for Vgyaan. On information and belief, Vgyaan is incorporated in, and therefore resides in, New Jersey.

112. Venue is proper in this Judicial District for DRL. On information and belief, DRL is incorporated in, and therefore resides in, New Jersey. On information and belief, DRL has employees in New Jersey and maintains a regular and established place of business in New Jersey at 600 College Road East, Princeton, New Jersey 08540. Furthermore, on information and belief, based on DRL's connections to New Jersey, discoverable information in its possession, custody, or control regarding the RK ANDA will likely show that DRL engaged in activities in New Jersey

relevant to the preparation and/or submission of the RK ANDA and therefore committed acts of infringement within this Judicial District.

113. Venue is proper in this Judicial District for the RK Defendants. On information and belief, based on the RK Defendants' connections to New Jersey, discoverable information in its possession, custody, or control regarding the RK ANDA will likely show that RK engaged in activities in New Jersey relevant to the preparation and/or submission of the RK ANDA and therefore committed acts of infringement within this Judicial District. For example, RK has previously identified Sonal Jagani and Raghu Kasu as possessing knowledge and information about the preparation and filing of the RK ANDA and the research and development of RK's Generic Product that is the subject of the RK ANDA. *See Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), RK's Objections and Responses to Plaintiffs' Interrogatory No. 1 (June 16, 2025). On information and belief, Ms. Jagani is a Director of Regulatory Affairs employed by Apicore (an RK subsidiary) in New Jersey. On information and belief, Mr. Kasu is a Chief Scientific Officer employed by RK in New Jersey.

114. Venue is further proper in this Court as to the RK Defendants because, *inter alia*, the RK Defendants have committed, aided, abetted, contributed to, and/or participated in the commission of acts of patent infringement that will lead to foreseeable harm and injury to Plaintiffs, which manufacture Zepzelca® for sale and use throughout the United States, including within the State of New Jersey.

MSN Defendants

115. This Court has personal jurisdiction over the MSN Defendants by virtue of the fact that, *inter alia*, the MSN Defendants have committed the tortious act of patent infringement pursuant to 35 U.S.C. § 271(e)(2)(A) that has led to foreseeable harm and injury to Plaintiffs in the State of New Jersey and throughout the United States.

116. This Court has personal jurisdiction over the MSN Defendants by virtue of the fact that, on information and belief, the MSN Defendants, either directly or through their affiliates, regularly and continuously do or solicit business in New Jersey, engage in other persistent courses of conduct in New Jersey, and/or derive substantial revenue from services or things used or consumed in New Jersey, including by selling their pharmaceutical products in New Jersey and, therefore, can reasonably expect to be subject to jurisdiction in the New Jersey courts. On information and belief, the MSN Defendants conduct marketing and sales activities in the State of New Jersey, including, but not limited to, distribution, marketing, and sales of pharmaceutical products to New Jersey residents that are continuous and systematic. On information and belief, if the MSN ANDA is approved, the MSN Defendants will market and sell their generic version of Zepzelca® in New Jersey.

117. This Court further has personal jurisdiction over the MSN Defendants by virtue of the fact that the MSN Defendants have previously submitted to the jurisdiction of this Court and purposefully availed themselves of this Court by consenting to this Court's jurisdiction and asserting counterclaims in a patent infringement action initiated in this jurisdiction involving the same MSN ANDA. *See Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 32 (MSN Defendants' Answer).

118. This Court further has personal jurisdiction over the MSN Defendants by virtue of the fact that both MSN Defendants have previously submitted to the jurisdiction of this Court and purposefully availed themselves of this Court by consenting to this Court's jurisdiction and asserting counterclaims in civil actions initiated in this jurisdiction, including, but not limited to, *e.g.*, *Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024); *Merck Sharp & Dohme BV*, *et al. v. Aurobindo Pharma USA, Inc.*,

et al., CA. No. 20-cv-2576 (D.N.J. *filed* Mar. 10, 2020); *Boehringer Ingelheim Pharm., Inc.*, *et al. v. HEC Pharm Group*, *et al.*, CA. No. 15-cv-5982 (D.N.J. *filed* Aug. 04, 2015).

119. This Court has personal jurisdiction over MSNPI. On information and belief, MSNPI regularly and continuously conducts business in New Jersey. On information and belief, MSNPI has its principal place of business at 20 Duke Road, Piscataway, New Jersey 08854. MSNPI has an active business entity status registered with the state of New Jersey under the business entity identification number 0400627791 and has a corporate agent for service of process at 20 Duke Road, Piscataway, New Jersey 08854.

120. This Court has personal jurisdiction over MSN Labs by virtue of the fact that, on information and belief, MSN Labs regularly and continuously transacts business within New Jersey, either directly or through its wholly owned subsidiary, MSNPI, a company having its principal place of business in New Jersey, including by selling pharmaceutical products in New Jersey.

121. Alternatively, this Court may exercise jurisdiction over MSN Labs pursuant to Federal Rule of Civil Procedure 4(k)(2) because (a) Plaintiffs' claims arise under federal law; (b) MSN Labs is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) MSN Labs has sufficient contacts with the United States as a whole, including, but not limited to manufacturing and/or selling pharmaceutical products distributed throughout the United States, such that this Court's exercise of jurisdiction over MSN Labs satisfies due process.

122. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

123. The MSN Defendants have previously consented to venue in this Judicial District in a patent infringement action involving the same MSN ANDA. *See Jazz Pharmaceuticals Ireland*

Limited, et al., v. Sandoz, Inc., et al., CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 32 (MSN Defendants' Answer).

124. Venue is proper in this Judicial District for MSNPI. On information and belief, MSNPI has active business entity identification number in the State of New Jersey (0400627791), has employees in New Jersey, and maintains a regular and established place of business in New Jersey at 20 Duke Road, Piscataway, New Jersey 08854. Furthermore, on information and belief, based on MSNPI's connections to New Jersey, discoverable information in its possession, custody, and/or control regarding the MSN ANDA will likely show that MSNPI engaged in activities in New Jersey relevant to the preparation and/or submission of the MSN ANDA and therefore committed acts of infringement within this Judicial District.

125. Venue is proper in this Judicial District for MSN Labs because, *inter alia*, MSN Labs is a foreign corporation not residing in any United States district and may be sued in any judicial district.

126. Venue is further proper in this Court as to both MSN Defendants because, *inter alia*, MSN Defendants have committed, aided, abetted, contributed to, and/or participated in the commission of acts of patent infringement that will lead to foreseeable harm and injury to Plaintiffs, which manufacture Zepzelca® for sale and use throughout the United States, including within the State of New Jersey.

THE ZEPZELCA® NDA

127. Pharma Mar USA, Inc., a wholly owned subsidiary of Pharma Mar, filed New Drug Application ("NDA") No. 213702 for "Zepzelca® (lurbinectedin) injection, 4 mg lyophilized powder in a single-dose vial." The FDA granted accelerated approval for NDA No. 213702 on June 15, 2020, for the treatment of adult patients with metastatic small cell lung cancer ("SCLC") with disease progression on or after platinum-based chemotherapy.

128. Pharma Mar USA, Inc. transferred and assigned NDA No. 213702 to Jazz.

129. Lurbinectedin is a compound that can be referred to by any of several chemical names, including (1'R,6R,6aR,7R,13S,14S,16R)-8,14-dihydroxy-6',9-dimethoxy-4,10,23-trimethyl-19-oxo-2',3',4',6,7,9',12,13,14,16-decahydro-6aH-spiro[7,13-azano-6,16-(epithiopropanooxymethano)[1,3]dioxolo[7,8]isoquinolino[3,2-b][3]benzazocine-20,1'-pyrido[3,4-b]indol]-5-yl acetate, and has the following chemical structure:

THE PATENT-IN-SUIT

130. On June 10, 2025, the ’806 Patent, entitled “Method of Treating SCLC and Managing Hepatotoxicity,” was duly and legally issued to Pharma Mar. A true and correct copy of the ’806 Patent is attached hereto as Exhibit A.

131. The ’806 Patent claims, *inter alia*, methods of treating metastatic SCLC in patients with disease progression after platinum-based chemotherapy, said method comprising administering, within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin by intravenous infusion as a monotherapy, a dose of 2.6 mg/m^2 lurbinectedin by intravenous infusion as a monotherapy to certain patients who previously experienced ≥ Grade 3 hepatotoxicity subsequent to receiving the dose of 3.2 mg/m^2 of lurbinectedin.

132. In accordance with 21 U.S.C. § 355(b)(1) and 21 C.F.R. § 314.53, the '806 Patent is listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (also known as the "Orange Book") for Zepzelca® for intravenous use, 4 mg/vial.

133. Pharma Mar owns the '806 Patent.

134. Pursuant to an agreement, as amended, entered into between Pharma Mar and Jazz, Jazz was granted an exclusive license to the '806 Patent, with the right to sue for infringement of the '806 Patent in the United States.

Claims for relief – patent infringement

InvaGen Defendants

135. The InvaGen Defendants previously submitted the InvaGen ANDA to the FDA, seeking approval to manufacture, use, and/or sell "Lurbinectedin for injection, 4 mg/vial" ("InvaGen's Generic Product") at or prior to the expiration of United States Patent No. 7,763,615 ("the '615 Patent"). *See Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 1. The '806 Patent will expire after the '615 Patent.

136. On information and belief, the InvaGen Defendants submitted the InvaGen ANDA to the FDA under § 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), seeking approval to engage in the commercial manufacture, use, and sale of InvaGen's Generic Product as a generic version of Zepzelca®.

137. On information and belief, the InvaGen ANDA seeks FDA approval of InvaGen's Generic Product for the indication of treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy.

138. By a letter dated July 22, 2025 ("InvaGen's '806 Notice Letter"), the InvaGen Defendants informed Plaintiffs that the InvaGen ANDA seeks approval to manufacture, use, and/or sell InvaGen's Generic Product prior to the expiration of the '806 Patent.

139. InvaGen's '806 Notice Letter also advised Plaintiffs that InvaGen's ANDA submissions include a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that, in the InvaGen Defendants' opinion, certain claims of the '806 Patent are invalid, unenforceable, and/or will not be infringed by the commercial manufacture, sale, and/or use of InvaGen's Generic Product.

140. InvaGen's '806 Notice Letter does not allege non-infringement of any claims of the '806 Patent.

141. By not identifying non-infringement defenses for any claims of the '806 Patent, the InvaGen Defendants admit InvaGen's Generic Product meets all limitations of those claims.

142. InvaGen's '806 Notice Letter does not allege invalidity under 35 U.S.C. §§ 101, 102, or 112, or unenforceability for any claim of the '806 Patent.

143. By not identifying invalidity defenses under 35 U.S.C. §§ 101, 102, or 112, or unenforceability for any claim of the '806 Patent, the InvaGen Defendants admit that the '806 Patent is valid under 35 U.S.C. §§ 101, 102, and 112 and enforceable.

144. There is an actual, real, immediate, and justiciable controversy between Plaintiffs and the InvaGen Defendants regarding the infringement, validity, and enforceability of the '806 Patent.

145. On information and belief, following FDA approval of the InvaGen ANDA, the InvaGen Defendants will act in concert to make, use, offer to sell, or sell InvaGen's Generic Product throughout the United States, or import such a generic product into the United States.

146. On information and belief, following FDA approval of the InvaGen ANDA, the InvaGen Defendants intend to directly benefit from sales of InvaGen's Generic Product.

147. Plaintiffs are commencing this action against the InvaGen Defendants within 45 days of receiving InvaGen's '806 Notice Letter pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

Sandoz

148. Sandoz previously submitted the Sandoz ANDA to the FDA, seeking approval to manufacture, use, and/or sell "Lurbinectedin for injection, 4 mg/vial" ("Sandoz's Generic Product") at or prior to the expiration of the '615 Patent. *See Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 1. The '806 Patent will expire after the '615 Patent.

149. On information and belief, Sandoz submitted the Sandoz ANDA to the FDA under § 505(j) of the FDCA, seeking approval to engage in the commercial manufacture, use, or sale of Sandoz's Generic Product as a generic version of Zepzelca®.

150. On information and belief, the Sandoz ANDA seeks FDA approval of Sandoz's Generic Product for the indication of treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy.

151. There is an actual, real, immediate, and justiciable controversy between Plaintiffs and Sandoz regarding the infringement, validity, and enforceability of the '806 Patent.

152. On information and belief, following FDA approval of the Sandoz ANDA, Sandoz will make, use, offer to sell, or sell Sandoz's Generic Product throughout the United States, and/or import such a generic product into the United States.

153. On information and belief, following FDA approval of the Sandoz ANDA, Sandoz intends to directly benefit from sales of Sandoz's Generic Product.

Zydus Defendants

154. The Zydus Defendants previously submitted the Zydus ANDA to the FDA, seeking approval to manufacture, use, and/or sell "Lurbinectedin powder, intravenous, 4 mg/vial" ("Zydus' Generic Product") at or prior to the expiration of the '615 Patent. *See Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 1. The '806 Patent will expire after the '615 Patent.

155. On information and belief, the Zydus Defendants submitted the Zydus ANDA to the FDA under § 505(j) of the FDCA, seeking approval to engage in the commercial manufacture, use, sale, or importation of Zydus' Generic Product as a generic version of Zepzelca®.

156. On information and belief, the Zydus ANDA seeks FDA approval of Zydus' Generic Product for the indication of treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy.

157. There is an actual, real, immediate, and justiciable controversy between Plaintiffs and the Zydus Defendants regarding the infringement, validity, and enforceability of the '806 Patent.

158. On information and belief, following FDA approval of the Zydus ANDA, the Zydus Defendants will act in concert to make, use, offer to sell, or sell Zydus' Generic Product throughout the United States, or import such a generic product into the United States.

159. On information and belief, following FDA approval of the Zydus ANDA, the Zydus Defendants intend to directly benefit from sales of Zydus' Generic Product.

RK Defendants

160. The RK Defendants previously submitted the RK ANDA to the FDA, seeking approval to manufacture, use, and/or sell "Lurbinectedin for injection (4 mg/vial) product" ("RK's Generic Product") at or prior to the expiration of the '615 Patent. *See Jazz Pharmaceuticals Ireland*

Limited, et al., v. Sandoz, Inc., et al., CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 1. The '806 Patent will expire after the '615 Patent.

161. On information and belief, the RK Defendants submitted the RK ANDA to the FDA under § 505(j) of the FDCA, seeking approval to engage in the commercial manufacture, use, and sale of RK's Generic Product as a generic version of Zepzelca®.

162. On information and belief, the RK ANDA seeks FDA approval of RK's Generic Product for the indication of treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy.

163. There is an actual, real, immediate, and justiciable controversy between Plaintiffs and the RK Defendants regarding the infringement, validity, and enforceability of the '806 Patent.

164. On information and belief, following FDA approval of the RK ANDA, the RK Defendants will act in concert to make, use, offer to sell, or sell RK's Generic Product throughout the United States, and/or import such a generic product into the United States.

165. On information and belief, following FDA approval of the RK ANDA, the RK Defendants intend to directly benefit from sales of RK's Generic Product.

MSN Defendants

166. The MSN Defendants previously submitted the MSN ANDA to the FDA, seeking approval to manufacture, use, and/or sell "Lurbinectedin for injection (4 mg/vial) product" ("MSN's Generic Product") at or prior to the expiration of the '615 Patent. *See Jazz Pharmaceuticals Ireland Limited, et al., v. Sandoz, Inc., et al.*, CA No. 24-cv-09110 (D.N.J. *filed* Sept. 11, 2024), D.I. 1. The '806 Patent will expire after the '615 Patent.

167. On information and belief, the MSN Defendants submitted the MSN ANDA to the FDA under § 505(j) of the FDCA, seeking approval to engage in the commercial manufacture, use, and/or sale of MSN's Generic Product as a generic version of Zepzelca®.

168. On information and belief, the MSN ANDA seeks FDA approval of MSN's Generic Product for the indication of treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy.

169. There is an actual, real, immediate, and justiciable controversy between Plaintiffs and the MSN Defendants regarding the infringement, validity, and enforceability of the '806 Patent.

170. On information and belief, following FDA approval of the MSN ANDA, the MSN Defendants will act in concert to make, use, offer to sell, or sell MSN's Generic Product throughout the United States, and/or import such a generic product into the United States.

171. On information and belief, following FDA approval of the MSN ANDA, the MSN Defendants intend to directly benefit from sales of MSN's Generic Product.

Count I

(Infringement of the '806 Patent by the InvaGen Defendants)

172. Plaintiffs incorporate each of the preceding paragraphs 1 to 171 as if fully set forth herein.

173. InvaGen's '806 Notice Letter indicates the InvaGen Defendants' intent to engage in the commercial manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of InvaGen's Generic Product prior to expiration of the '806 Patent.

174. The InvaGen Defendants are aware of the '806 Patent, including as demonstrated by InvaGen's '806 Notice Letter. Also, on information and belief, the InvaGen Defendants are aware of the '806 Patent by virtue of its listing in the Orange Book since July 2025.

175. The submission of InvaGen's ANDA seeking approval to engage in the commercial manufacture, use, offer for sale, or sale of InvaGen's Generic Product, prior to the expiration of

the ’806 Patent, constitutes infringement of one or more claims of the ’806 Patent under 35 U.S.C. § 271(e)(2)(A).

176. On information and belief, the InvaGen Defendants intend to engage in the commercial manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of InvaGen’s Generic Product with the proposed labeling immediately and imminently upon final approval of the InvaGen ANDA.

177. The ’806 Patent claims, *inter alia*, methods of treating metastatic SCLC using lurbinectedin in patients who have experienced ≥ Grade 3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin. Claim 1 recites:

> A method of treating metastatic small cell lung cancer (SCLC) in a patient with disease progression after platinum-based chemotherapy, said method comprising administering, within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin by intravenous infusion as a monotherapy, a dose of 2.6 mg/m^2 lurbinectedin by intravenous infusion as a monotherapy to a patient having at the time of the administration of the dose of 2.6 mg/m^2 of lurbinectedin:
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> a) metastatic SCLC with disease progression after platinum-based chemotherapy,
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> b) a platelet count of at least 100,000/mm^3,
>
> c) an absolute neutrophil count of at least 1500 cells/mm^3, and
>
> d) ≤ Grade 1 hepatotoxicity;
>
> wherein the patient previously experienced ≥ Grade 3 hepatotoxicity subsequent to receiving the dose of 3.2 mg/m^2 of lurbinectedin.

178. On information and belief, the InvaGen Defendants’ manufacture, use, sale, offer for sale, and/or importation into the United States of InvaGen’s Generic Product prior to the expiration of the ’806 Patent, including any applicable exclusivities or extensions, will actively induce infringement of at least Claim 1 of the ’806 Patent under 35 U.S.C. § 271(b). The InvaGen Defendants will aid another in the infringement of one or more claims of the ’806 Patent.

179. On information and belief, InvaGen's Generic Product will have instructions for use that substantially copy the instructions for Zepzelca®, which disclose and encourage the practice of all the elements of one or more claims of the '806 Patent, including at least Claim 1. Upon information and belief, the proposed labeling for InvaGen's Generic Product will direct the use of InvaGen's Generic Product for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. On information and belief, the proposed labeling for InvaGen's Generic Product will direct administering InvaGen's Generic Product by intravenous infusion as a monotherapy. On information and belief, the proposed labeling for InvaGen's Generic Product will identify Grade ≥3 hepatotoxicity as an adverse reaction to treatment with 3.2 mg/m^2 of lurbinectedin. On information and belief, the proposed labeling for InvaGen's Generic Product will direct administering a reduced dose of 2.6 mg/m^2 lurbinectedin following a patient experiencing Grade ≥3 hepatotoxicity at the 3.2 mg/m^2 dose, and within 35 days of receiving a 3.2 mg/m^2 dose of lurbinectedin. On information and belief, the proposed labeling for InvaGen's Generic Product will direct that the reduced dose of 2.6 mg/m^2 lurbinectedin be administered when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity.

180. On information and belief, InvaGen's Generic Product, if approved by the FDA, will be prescribed and administered by intravenous infusion as a monotherapy to patients with metastatic SCLC with disease progression after platinum-based chemotherapy, who experienced Grade ≥3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin and within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin, at a reduced dose of 2.6 mg/m^2 lurbinectedin when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil

count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity, which will constitute infringement of one or more claims of the ’806 Patent, including at least Claim 1.

181. On information and belief, this directly infringing use will occur with the InvaGen Defendants’ specific intent and encouragement and will be a use that the InvaGen Defendants know or should know will occur.

182. On information and belief, the InvaGen Defendants copied the claimed invention of the ’806 Patent.

183. On information and belief, the InvaGen Defendants will actively induce, encourage, aid, and abet this prescription and administration, with knowledge and specific intent that this use will be in contravention of Plaintiffs’ rights under the ’806 Patent.

184. On information and belief, the InvaGen Defendants’ acts will be performed with knowledge of the ’806 Patent and with intent to encourage infringement prior to patent expiry.

185. On information and belief, the InvaGen Defendants’ statement of the factual and legal bases for their opinions regarding non-infringement and invalidity of the ’806 Patent is devoid of an objective good faith basis in either the facts or the law. This case is exceptional.

186. Plaintiffs will be substantially and irreparably harmed by the infringing activities of the InvaGen Defendants as described above unless those activities are precluded by this Court. Plaintiffs have no adequate remedy at law.

Count II

(Declaratory Judgment of Infringement of the ’806 Patent Under 35 U.S.C. § 271(b) Against the InvaGen Defendants)

187. Plaintiffs incorporate each of the preceding paragraphs 1 to 171 as if fully set forth herein.

188. InvaGen's '806 Notice Letter indicates the InvaGen Defendants' intent to engage in the commercial manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of InvaGen's Generic Product with the proposed labeling immediately and imminently upon final approval of Invagen's ANDA and prior to expiration of the '806 Patent. Therefore, a case or controversy exists between the Invagen Defendants and Plaintiffs as to infringement of the '806 Patent.

189. The InvaGen Defendants are aware of the '806 Patent, including as demonstrated by InvaGen's '806 Notice Letter. Also, on information and belief, the InvaGen Defendants are aware of the '806 Patent by virtue of its listing in the Orange Book since July 2025.

190. The '806 Patent claims, *inter alia*, methods of treating metastatic SCLC using lurbinectedin in patients who have experienced ≥ Grade 3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin. Claim 1 recites:

> A method of treating metastatic small cell lung cancer (SCLC) in a patient with disease progression after platinum-based chemotherapy, said method comprising administering, within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin by intravenous infusion as a monotherapy, a dose of 2.6 mg/m^2 lurbinectedin by intravenous infusion as a monotherapy to a patient having at the time of the administration of the dose of 2.6 mg/m^2 of lurbinectedin:
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> a) metastatic SCLC with disease progression after platinum-based chemotherapy,
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> b) a platelet count of at least 100,000/mm^3,
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> c) an absolute neutrophil count of at least 1500 cells/mm^3, and
>
> d) ≤Grade 1 hepatotoxicity;
>
> wherein the patient previously experienced ≥ Grade 3 hepatotoxicity subsequent to receiving the dose of 3.2 mg/m^2 of lurbinectedin.

191. On information and belief, the InvaGen Defendants' manufacture, use, offer for sale, sale, marketing, distribution, and/or importation into the United States of InvaGen's Generic Product prior to the expiration of the '806 Patent, including any applicable exclusivities or

extensions, will actively induce infringement of at least Claim 1 of the ’806 Patent under 35 U.S.C. § 271(b). The InvaGen Defendants will aid another in the infringement of one or more claims of the ’806 Patent.

192. On information and belief, InvaGen’s Generic Product will have instructions for use that substantially copy the instructions for Zepzelca®, which disclose and encourage the practice of all the elements of one or more claims of the ’806 Patent, including at least Claim 1. Upon information and belief, the proposed labeling for InvaGen’s Generic Product will direct the use of InvaGen’s Generic Product for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. On information and belief, the proposed labeling for InvaGen’s Generic Product will direct administering InvaGen’s Generic Product by intravenous infusion as a monotherapy. On information and belief, the proposed labeling for InvaGen’s Generic Product will identify Grade ≥3 hepatotoxicity as an adverse reaction to treatment with 3.2 mg/m^2 of lurbinectedin. On information and belief, the proposed labeling for InvaGen’s Generic Product will direct administering a reduced dose of 2.6 mg/m^2 lurbinectedin following a patient experiencing Grade ≥3 hepatotoxicity at the 3.2 mg/m^2 dose, and within 35 days of receiving a 3.2 mg/m^2 dose of lurbinectedin. On information and belief, the proposed labeling for InvaGen’s Generic Product will direct that the reduced dose of 2.6 mg/m^2 lurbinectedin be administered when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity.

193. On information and belief, InvaGen’s Generic Product, if approved by the FDA, will be prescribed and administered by intravenous infusion as a monotherapy to patients with metastatic SCLC with disease progression after platinum-based chemotherapy, who experienced Grade ≥3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin and within

35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin, at a reduced dose of 2.6 mg/m^2 lurbinectedin when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity, which will constitute infringement of one or more claims of the ’806 Patent, including at least Claim 1.

194. On information and belief, this directly infringing use will occur with the InvaGen Defendants’ specific intent and encouragement and will be a use that the InvaGen Defendants knows or should know will occur.

195. On information and belief, the InvaGen Defendants copied the claimed invention of the ’806 Patent.

196. On information and belief, the InvaGen Defendants will actively induce, encourage, aid, and abet this prescription and administration, with knowledge and specific intent that this use will be in contravention of Plaintiffs’ rights under the ’806 Patent.

197. On information and belief, the InvaGen Defendants’ acts will be performed with knowledge of the ’806 Patent and with intent to encourage infringement prior to patent expiry.

198. Plaintiffs will be substantially and irreparably harmed by the infringing activities described above unless those activities are precluded by this Court. Plaintiffs have no adequate remedy at law.

Count III

(Infringement of the ’806 Patent by Sandoz)

199. Plaintiffs incorporate each of the preceding paragraphs 1 to 171 as if fully set forth herein.

200. On information and belief, Sandoz intends to engage in the commercial manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Sandoz’s Generic Product prior to expiration of the ’806 Patent.

201. On information and belief, Sandoz is aware of the ’806 Patent, including by virtue of its listing in the Orange Book since July 2025, and Sandoz will have actual knowledge of the ’806 Patent before Sandoz’s ANDA is approved.

202. The submission of Sandoz’s ANDA seeking approval to engage in the commercial manufacture, use, offer for sale, or sale of Sandoz’s Generic Product, prior to the expiration of the ’806 Patent, constitutes infringement of one or more of the claims of the ’806 Patent under 35 U.S.C. § 271(e)(2)(A).

203. On information and belief, Sandoz intends to engage in the commercial manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Sandoz’s Generic Product with the proposed labeling immediately and imminently upon final approval of the Sandoz ANDA.

204. The ’806 Patent claims, *inter alia*, methods of treating metastatic SCLC using lurbinectedin in patients who have experienced ≥ Grade 3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin. Claim 1 recites:

> A method of treating metastatic small cell lung cancer (SCLC) in a patient with disease progression after platinum-based chemotherapy, said method comprising administering, within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin by intravenous infusion as a monotherapy, a dose of 2.6 mg/m^2 lurbinectedin by intravenous infusion as a monotherapy to a patient having at the time of the administration of the dose of 2.6 mg/m^2 of lurbinectedin:
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> a) metastatic SCLC with disease progression after platinum-based chemotherapy,
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> b) a platelet count of at least 100,000/mm^3,
>
> c) an absolute neutrophil count of at least 1500 cells/mm^3, and
>
> d) ≤Grade 1 hepatotoxicity;
>
> wherein the patient previously experienced ≥ Grade 3 hepatotoxicity subsequent to receiving the dose of 3.2 mg/m^2 of lurbinectedin.

205. On information and belief, Sandoz's manufacture, use, sale, offer for sale, and/or importation into the United States of Sandoz's Generic Product prior to the expiration of the '806 Patent, including any applicable exclusivities or extensions, will actively induce infringement of at least Claim 1 of the '806 Patent under 35 U.S.C. § 271(b). Sandoz will aid another in the infringement of one or more of the claims of the '806 Patent.

206. On information and belief, Sandoz's Generic Product will have instructions for use that substantially copy the instructions for Zepzelca®, which disclose and encourage the practice of all the elements of one or more claims of the '806 Patent, including at least Claim 1. Upon information and belief, the proposed labeling for Sandoz's Generic Product will direct the use of Sandoz's Generic Product for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. On information and belief, the proposed labeling for Sandoz's Generic Product will direct administering Sandoz's Generic Product by intravenous infusion as a monotherapy. On information and belief, the proposed labeling for Sandoz's Generic Product will identify Grade ≥3 hepatotoxicity as an adverse reaction to treatment with 3.2 mg/m^2 of lurbinectedin. On information and belief, the proposed labeling for Sandoz's Generic Product will direct administering a reduced dose of 2.6 mg/m^2 lurbinectedin following a patient experiencing Grade ≥3 hepatotoxicity at the 3.2 mg/m^2 dose, and within 35 days of receiving a 3.2 mg/m^2 dose of lurbinectedin. On information and belief, the proposed labeling for Sandoz's Generic Product will direct that the reduced dose of 2.6 mg/m^2 lurbinectedin be administered when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity.

207. On information and belief, Sandoz's Generic Product, if approved by the FDA, will be prescribed and administered by intravenous infusion as a monotherapy to patients with

metastatic SCLC with disease progression after platinum-based chemotherapy, who experienced Grade ≥3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin and within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin, at a reduced dose of 2.6 mg/m^2 lurbinectedin when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity, which will constitute infringement of one or more claims of the '806 Patent, including at least Claim 1.

208. On information and belief, this directly infringing use will occur with Sandoz's specific intent and encouragement and will be a use that Sandoz knows or should know will occur.

209. On information and belief, Sandoz copied the claimed invention of the '806 Patent.

210. On information and belief, Sandoz will actively induce, encourage, aid, and abet this prescription and administration, with knowledge and specific intent that this use will be in contravention of Plaintiffs' rights under the '806 Patent.

211. On information and belief, Sandoz's acts will be performed with knowledge of the '806 Patent and with intent to encourage infringement prior to patent expiry.

212. Plaintiffs will be substantially and irreparably harmed by the infringing activities described above unless those activities are precluded by this Court. Plaintiffs have no adequate remedy at law.

Count IV

(Declaratory Judgment of Infringement of the '806 Patent Under 35 U.S.C. § 271(b) Against Sandoz)

213. Plaintiffs incorporate each of the preceding paragraphs 1 to 171 as if fully set forth herein.

214. On information and belief, Sandoz intends to engage in the commercial manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Sandoz's

Generic Product with the proposed labeling immediately and imminently upon final approval of Sandoz's ANDA and prior to the expiration of the '806 Patent. Therefore, a case or controversy exists between Sandoz and Plaintiffs as to infringement of the '806 Patent.

215. On information and belief, Sandoz is aware of the '806 Patent, including by virtue of its listing in the Orange Book since July 2025, and Sandoz will have actual knowledge of the '806 Patent before Sandoz's ANDA is approved.

216. The '806 Patent claims, *inter alia*, methods of treating metastatic SCLC using lurbinectedin in patients who have experienced ≥ Grade 3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin. Claim 1 recites:

> A method of treating metastatic small cell lung cancer (SCLC) in a patient with disease progression after platinum-based chemotherapy, said method comprising administering, within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin by intravenous infusion as a monotherapy, a dose of 2.6 mg/m^2 lurbinectedin by intravenous infusion as a monotherapy to a patient having at the time of the administration of the dose of 2.6 mg/m^2 of lurbinectedin:
>
> a) metastatic SCLC with disease progression after platinum-based chemotherapy,
>
> b) a platelet count of at least 100,000/mm^3,
>
> c) an absolute neutrophil count of at least 1500 cells/mm^3, and
>
> d) ≤Grade 1 hepatotoxicity;
>
> wherein the patient previously experienced ≥ Grade 3 hepatotoxicity subsequent to receiving the dose of 3.2 mg/m^2 of lurbinectedin.

217. On information and belief, Sandoz's manufacture, use, sale, offer for sale, and/or importation into the United States of Sandoz's Generic Product prior to the expiration of the '806 Patent, including any applicable exclusivities or extensions, will actively induce infringement of at least Claim 1 of the '806 Patent under 35 U.S.C. § 271(b). Sandoz will aid another in the infringement of one or more of the claims of the '806 Patent.

218. On information and belief, Sandoz's Generic Product will have instructions for use that substantially copy the instructions for Zepzelca®, which disclose and encourage the practice of all the elements of one or more claims of the '806 Patent, including at least Claim 1. Upon information and belief, the proposed labeling for Sandoz's Generic Product will direct the use of Sandoz's Generic Product for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. On information and belief, the proposed labeling for Sandoz's Generic Product will direct administering Sandoz's Generic Product by intravenous infusion as a monotherapy. On information and belief, the proposed labeling for Sandoz's Generic Product will identify Grade ≥3 hepatotoxicity as an adverse reaction to treatment with 3.2 mg/m^2 of lurbinectedin. On information and belief, the proposed labeling for Sandoz's Generic Product will direct administering a reduced dose of 2.6 mg/m^2 lurbinectedin following a patient experiencing Grade ≥3 hepatotoxicity at the 3.2 mg/m^2 dose, and within 35 days of receiving a 3.2 mg/m^2 dose of lurbinectedin. On information and belief, the proposed labeling for Sandoz's Generic Product will direct that the reduced dose of 2.6 mg/m^2 lurbinectedin be administered when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity.

219. On information and belief, Sandoz's Generic Product, if approved by the FDA, will be prescribed and administered by intravenous infusion as a monotherapy to patients with metastatic SCLC with disease progression after platinum-based chemotherapy, who experienced Grade ≥3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin and within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin, at a reduced dose of 2.6 mg/m^2 lurbinectedin when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil

count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity, which will constitute infringement of one or more claims of the ’806 Patent, including at least Claim 1.

220. On information and belief, this directly infringing use will occur with Sandoz’s specific intent and encouragement and will be a use that Sandoz knows or should know will occur.

221. On information and belief, Sandoz copied the claimed invention of the ’806 Patent.

222. On information and belief, Sandoz will actively induce, encourage, aid, and abet this prescription and administration, with knowledge and specific intent that this use will be in contravention of Plaintiffs’ rights under the ’806 Patent.

223. On information and belief, Sandoz’s acts will be performed with knowledge of the ’806 Patent and with intent to encourage infringement prior to patent expiry.

224. Plaintiffs will be substantially and irreparably harmed by the infringing activities described above unless those activities are precluded by this Court. Plaintiffs have no adequate remedy at law.

Count V

(Infringement of the ’806 Patent by the Zydus Defendants)

225. Plaintiffs incorporate each of the preceding paragraphs 1 to 171 as if fully set forth herein.

226. On information and belief, the Zydus Defendants intend to engage in the commercial manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Zydus’ Generic Product prior to expiration of the ’806 Patent.

227. On information and belief, the Zydus Defendants are aware of the ’806 Patent, including by virtue of its listing in the Orange Book since July 2025, and the Zydus Defendants will have actual knowledge of the ’806 Patent before Zydus’s ANDA is approved.

228. The submission of Zydus' ANDA seeking approval to engage in the commercial manufacture, use, offer for sale, or sale of Zydus' Generic Product, prior to the expiration of the '806 Patent, constitutes infringement of one or more of the claims of the '806 Patent under 35 U.S.C. § 271(e)(2)(A).

229. On information and belief, the Zydus Defendants intend to engage in the commercial manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Zydus' Generic Product with the proposed labeling immediately and imminently upon final approval of the Zydus ANDA.

230. The '806 Patent claims, *inter alia*, methods of treating metastatic SCLC using lurbinectedin in patients who have experienced ≥ Grade 3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin. Claim 1 recites:

> A method of treating metastatic small cell lung cancer (SCLC) in a patient with disease progression after platinum-based chemotherapy, said method comprising administering, within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin by intravenous infusion as a monotherapy, a dose of 2.6 mg/m^2 lurbinectedin by intravenous infusion as a monotherapy to a patient having at the time of the administration of the dose of 2.6 mg/m^2 of lurbinectedin:
>
> a) metastatic SCLC with disease progression after platinum-based chemotherapy,
>
> b) a platelet count of at least 100,000/mm^3,
>
> c) an absolute neutrophil count of at least 1500 cells/mm^3, and
>
> d) ≤Grade 1 hepatotoxicity;
>
> wherein the patient previously experienced ≥ Grade 3 hepatotoxicity subsequent to receiving the dose of 3.2 mg/m^2 of lurbinectedin.

231. On information and belief, the Zydus Defendants' manufacture, use, sale, offer for sale, marketing, distribution, and/or importation into the United States of Zydus' Generic Product prior to the expiration of the '806 Patent, including any applicable exclusivities or extensions, will

actively induce infringement of at least Claim 1 of the ’806 Patent under 35 U.S.C. § 271(b). The Zydus Defendants will aid another in the infringement of one or more claims of the ’806 Patent.

232. On information and belief, Zydus’ Generic Product will have instructions for use that substantially copy the instructions for Zepzelca®, which disclose and encourage the practice of all the elements of one or more claims of the ’806 Patent, including at least Claim 1. Upon information and belief, the proposed labeling for Zydus’ Generic Product will direct the use of Zydus’ Generic Product for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. On information and belief, the proposed labeling for Zydus’ Generic Product will direct administering Zydus’ Generic Product by intravenous infusion as a monotherapy. On information and belief, the proposed labeling for Zydus’ Generic Product will identify Grade ≥3 hepatotoxicity as an adverse reaction to treatment with 3.2 mg/m^2 of lurbinectedin. On information and belief, the proposed labeling for Zydus’ Generic Product will direct administering a reduced dose of 2.6 mg/m^2 lurbinectedin following a patient experiencing Grade ≥3 hepatotoxicity at the 3.2 mg/m^2 dose, and within 35 days of receiving a 3.2 mg/m^2 dose of lurbinectedin. On information and belief, the proposed labeling for Zydus’ Generic Product will direct that the reduced dose of 2.6 mg/m^2 lurbinectedin be administered when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity.

233. On information and belief, Zydus’ Generic Product, if approved by the FDA, will be prescribed and administered by intravenous infusion as a monotherapy to patients with metastatic SCLC with disease progression after platinum-based chemotherapy, who experienced Grade ≥3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin and within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin, at a reduced dose of 2.6 mg/m^2

lurbinectedin when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity, which will constitute infringement of one or more claims of the ’806 Patent, including at least Claim 1.

234. On information and belief, this directly infringing use will occur with the Zydus Defendants’ specific intent and encouragement and will be a use that the Zydus Defendants know or should know will occur.

235. On information and belief, the Zydus Defendants copied the claimed invention of the ’806 Patent.

236. On information and belief, the Zydus Defendants will actively induce, encourage, aid, and abet this prescription and administration, with knowledge and specific intent that this use will be in contravention of Plaintiffs’ rights under the ’806 Patent.

237. On information and belief, the Zydus Defendants’ acts will be performed with knowledge of the ’806 Patent and with intent to encourage infringement prior to patent expiry.

238. Plaintiffs will be substantially and irreparably harmed by the infringing activities described above unless those activities are precluded by this Court. Plaintiffs have no adequate remedy at law.

Count VI

(Declaratory Judgment of Infringement of the ’806 Patent Under 35 U.S.C. § 271(b) Against the Zydus Defendants)

239. Plaintiffs incorporate each of the preceding paragraphs 1 to 171 as if fully set forth herein.

240. On information and belief, the Zydus Defendants intend to engage in the commercial manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Zydus’ Generic Product with the proposed labeling immediately and imminently upon final

approval of Zydus' ANDA and prior to the expiration of the '806 Patent. Therefore, a case or controversy exists between the Zydus Defendants and Plaintiffs as to infringement of the '806 Patent.

241. On information and belief, the Zydus Defendants are aware of the '806 Patent, including by virtue of its listing in the Orange Book since July 2025, and the Zydus Defendants will have actual knowledge of the '806 Patent before Zydus's ANDA is approved.

242. The '806 Patent claims, *inter alia*, methods of treating metastatic SCLC using lurbinectedin in patients who have experienced ≥ Grade 3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin. Claim 1 recites:

> A method of treating metastatic small cell lung cancer (SCLC) in a patient with disease progression after platinum-based chemotherapy, said method comprising administering, within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin by intravenous infusion as a monotherapy, a dose of 2.6 mg/m^2 lurbinectedin by intravenous infusion as a monotherapy to a patient having at the time of the administration of the dose of 2.6 mg/m^2 of lurbinectedin:
>
> a) metastatic SCLC with disease progression after platinum-based chemotherapy,
>
> b) a platelet count of at least 100,000/mm^3,
>
> c) an absolute neutrophil count of at least 1500 cells/mm^3, and
>
> d) ≤Grade 1 hepatotoxicity;
>
> wherein the patient previously experienced ≥ Grade 3 hepatotoxicity subsequent to receiving the dose of 3.2 mg/m^2 of lurbinectedin.

243. On information and belief, the Zydus Defendants' manufacture, use, offer for sale, sale, marketing, distribution, and/or importation into the United States of Zydus' Generic Product prior to the expiration of the '806 Patent, including any applicable exclusivities or extensions, will actively induce infringement of at least Claim 1 of the '806 Patent under 35 U.S.C. § 271(b). The Zydus Defendants will aid another in the infringement of one or more claims of the '806 Patent.

244. On information and belief, Zydus' Generic Product will have instructions for use that substantially copy the instructions for Zepzelca®, which disclose and encourage the practice of all the elements of one or more claims of the '806 Patent, including at least Claim 1. Upon information and belief, the proposed labeling for Zydus' Generic Product will direct the use of Zydus' Generic Product for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. On information and belief, the proposed labeling for Zydus' Generic Product will direct administering Zydus' Generic Product by intravenous infusion as a monotherapy. On information and belief, the proposed labeling for Zydus' Generic Product will identify Grade ≥3 hepatotoxicity as an adverse reaction to treatment with 3.2 mg/m^2 of lurbinectedin. On information and belief, the proposed labeling for Zydus' Generic Product will direct administering a reduced dose of 2.6 mg/m^2 lurbinectedin following a patient experiencing Grade ≥3 hepatotoxicity at the 3.2 mg/m^2 dose, and within 35 days of receiving a 3.2 mg/m^2 dose of lurbinectedin. On information and belief, the proposed labeling for Zydus' Generic Product will direct that the reduced dose of 2.6 mg/m^2 lurbinectedin be administered when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity.

245. On information and belief, Zydus' Generic Product, if approved by the FDA, will be prescribed and administered by intravenous infusion as a monotherapy to patients with metastatic SCLC with disease progression after platinum-based chemotherapy, who experienced Grade ≥3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin and within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin, at a reduced dose of 2.6 mg/m^2 lurbinectedin when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil

count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity, which will constitute infringement of one or more claims of the ’806 Patent, including at least Claim 1.

246. On information and belief, this directly infringing use will occur with the Zydus Defendants’ specific intent and encouragement and will be a use that the Zydus Defendants know or should know will occur.

247. On information and belief, the Zydus Defendants copied the claimed invention of the ’806 Patent.

248. On information and belief, the Zydus Defendants will actively induce, encourage, aid, and abet this prescription and administration, with knowledge and specific intent that this use will be in contravention of Plaintiffs’ rights under the ’806 Patent.

249. On information and belief, the Zydus Defendants’ acts will be performed with knowledge of the ’806 Patent and with intent to encourage infringement prior to patent expiry.

250. Plaintiffs will be substantially and irreparably harmed by the infringing activities described above unless those activities are precluded by this Court. Plaintiffs have no adequate remedy at law.

Count VII

(Infringement of the ’806 Patent by the RK Defendants)

251. Plaintiffs incorporate each of the preceding paragraphs 1 to 171 as if fully set forth herein.

252. On information and belief, the RK Defendants intend to engage in the commercial manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of RK’s Generic Product prior to expiration of the ’806 Patent.

253. On information and belief, the RK Defendants are aware of the ’806 Patent, including by virtue of its listing in the Orange Book since July 2025, and the RK Defendants will have actual knowledge of the ’806 Patent before RK’s ANDA is approved.

254. The submission of RK’s ANDA seeking approval to engage in the commercial manufacture, use, offer for sale, or sale of RK’s Generic Product, prior to the expiration of the ’806 Patent, constitutes infringement of one or more of the claims of the ’806 Patent under 35 U.S.C. § 271(e)(2)(A).

255. On information and belief, the RK Defendants intend to engage in the commercial manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of RK’s Generic Product with the proposed labeling immediately and imminently upon final approval of the RK ANDA.

256. The ’806 Patent claims, *inter alia*, methods of treating metastatic SCLC using lurbinectedin in patients who have experienced ≥ Grade 3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin. Claim 1 recites:

> A method of treating metastatic small cell lung cancer (SCLC) in a patient with disease progression after platinum-based chemotherapy, said method comprising administering, within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin by intravenous infusion as a monotherapy, a dose of 2.6 mg/m^2 lurbinectedin by intravenous infusion as a monotherapy to a patient having at the time of the administration of the dose of 2.6 mg/m^2 of lurbinectedin:
>
> a) metastatic SCLC with disease progression after platinum-based chemotherapy,
>
> b) a platelet count of at least 100,000/mm^3,
>
> c) an absolute neutrophil count of at least 1500 cells/mm^3, and
>
> d) ≤Grade 1 hepatotoxicity;
>
> wherein the patient previously experienced ≥ Grade 3 hepatotoxicity subsequent to receiving the dose of 3.2 mg/m^2 of lurbinectedin.

257. On information and belief, the RK Defendants' manufacture, use, offer for sale, sale, marketing, distribution, and/or importation into the United States of RK's Generic Product prior to the expiration of the '806 Patent, including any applicable exclusivities or extensions, will actively induce infringement of at least Claim 1 of the '806 Patent under 35 U.S.C. § 271(b). The RK Defendants will aid another in the infringement of one or more claims of the '806 Patent.

258. On information and belief, RK's Generic Product will have instructions for use that substantially copy the instructions for Zepzelca®, which disclose and encourage the practice of all the elements of one or more claims of the '806 Patent, including at least Claim 1. Upon information and belief, the proposed labeling for RK's Generic Product will direct the use of RK's Generic Product for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. On information and belief, the proposed labeling for RK's Generic Product will direct administering RK's Generic Product by intravenous infusion as a monotherapy. On information and belief, the proposed labeling for RK's Generic Product will identify Grade ≥3 hepatotoxicity as an adverse reaction to treatment with 3.2 mg/m^2 of lurbinectedin. On information and belief, the proposed labeling for RK's Generic Product will direct administering a reduced dose of 2.6 mg/m^2 lurbinectedin following a patient experiencing Grade ≥3 hepatotoxicity at the 3.2 mg/m^2 dose, and within 35 days of receiving a 3.2 mg/m^2 dose of lurbinectedin. On information and belief, the proposed labeling for RK's Generic Product will direct that the reduced dose of 2.6 mg/m^2 lurbinectedin be administered when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity.

259. On information and belief, RK's Generic Product, if approved by the FDA, will be prescribed and administered by intravenous infusion as a monotherapy to patients with metastatic SCLC with disease progression after platinum-based chemotherapy, who experienced Grade ≥3

hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin and within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin, at a reduced dose of 2.6 mg/m^2 lurbinectedin when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity, which will constitute infringement of one or more claims of the ’806 Patent, including at least Claim 1.

260. On information and belief, this directly infringing use will occur with the RK Defendants’ specific intent and encouragement and will be a use that the RK Defendants knows or should know will occur.

261. On information and belief, the RK Defendants copied the claimed invention of the ’806 Patent.

262. On information and belief, the RK Defendants will actively induce, encourage, aid, and abet this prescription and administration, with knowledge and specific intent that this use will be in contravention of Plaintiffs’ rights under the ’806 Patent.

263. On information and belief, the RK Defendants’ acts will be performed with knowledge of the ’806 Patent and with intent to encourage infringement prior to patent expiry.

264. Plaintiffs will be substantially and irreparably harmed by the infringing activities described above unless those activities are precluded by this Court. Plaintiffs have no adequate remedy at law.

Count VIII

(Declaratory Judgment of Infringement of the ’806 Patent Under 35 U.S.C. § 271(b) Against the RK Defendants)

265. Plaintiffs incorporate each of the preceding paragraphs 1 to 171 as if fully set forth herein.

266. On information and belief, the RK Defendants intend to engage in the commercial manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of RK's Generic Product with the proposed labeling immediately and imminently upon final approval of RK's ANDA and prior to the expiration of the '806 Patent. Therefore, a case or controversy exists between the RK Defendants and Plaintiffs as to infringement of the '806 Patent.

267. On information and belief, the RK Defendants are aware of the '806 Patent, including by virtue of its listing in the Orange Book since July 2025, and the RK Defendants will have actual knowledge of the '806 Patent before RK's ANDA is approved.

268. The '806 Patent claims, *inter alia*, methods of treating metastatic SCLC using lurbinectedin in patients who have experienced ≥ Grade 3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin. Claim 1 recites:

> A method of treating metastatic small cell lung cancer (SCLC) in a patient with disease progression after platinum-based chemotherapy, said method comprising administering, within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin by intravenous infusion as a monotherapy, a dose of 2.6 mg/m^2 lurbinectedin by intravenous infusion as a monotherapy to a patient having at the time of the administration of the dose of 2.6 mg/m^2 of lurbinectedin:
>
> a) metastatic SCLC with disease progression after platinum-based chemotherapy,
>
> b) a platelet count of at least 100,000/mm^3,
>
> c) an absolute neutrophil count of at least 1500 cells/mm^3, and
>
> d) ≤Grade 1 hepatotoxicity;
>
> wherein the patient previously experienced ≥ Grade 3 hepatotoxicity subsequent to receiving the dose of 3.2 mg/m^2 of lurbinectedin.

269. On information and belief, the RK Defendants' manufacture, use, offer for sale, sale, marketing, distribution, and/or importation into the United States of RK's Generic Product prior to the expiration of the '806 Patent, including any applicable exclusivities or extensions, will

actively induce infringement of at least Claim 1 of the ’806 Patent under 35 U.S.C. § 271(b). The RK Defendants will aid another in the infringement of one or more claims of the ’806 Patent.

270. On information and belief, RK’s Generic Product will have instructions for use that substantially copy the instructions for Zepzelca®, which disclose and encourage the practice of all the elements of one or more claims of the ’806 Patent, including at least Claim 1. Upon information and belief, the proposed labeling for RK’s Generic Product will direct the use of RK’s Generic Product for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. On information and belief, the proposed labeling for RK’s Generic Product will direct administering RK’s Generic Product by intravenous infusion as a monotherapy. On information and belief, the proposed labeling for RK’s Generic Product will identify Grade ≥3 hepatotoxicity as an adverse reaction to treatment with 3.2 mg/m^2 of lurbinectedin. On information and belief, the proposed labeling for RK’s Generic Product will direct administering a reduced dose of 2.6 mg/m^2 lurbinectedin following a patient experiencing Grade ≥3 hepatotoxicity at the 3.2 mg/m^2 dose, and within 35 days of receiving a 3.2 mg/m^2 dose of lurbinectedin. On information and belief, the proposed labeling for RK’s Generic Product will direct that the reduced dose of 2.6 mg/m^2 lurbinectedin be administered when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity.

271. On information and belief, RK’s Generic Product, if approved by the FDA, will be prescribed and administered by intravenous infusion as a monotherapy to patients with metastatic SCLC with disease progression after platinum-based chemotherapy, who experienced Grade ≥3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin and within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin, at a reduced dose of 2.6 mg/m^2 lurbinectedin when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least

1500 cells/mm^3, and Grade ≤1 hepatotoxicity, which will constitute infringement of one or more claims of the ’806 Patent, including at least Claim 1.

272. On information and belief, this directly infringing use will occur with the RK Defendants’ specific intent and encouragement and will be a use that the RK Defendants know or should know will occur.

273. On information and belief, the RK Defendants copied the claimed invention of the ’806 Patent.

274. On information and belief, the RK Defendants will actively induce, encourage, aid, and abet this prescription and administration, with knowledge and specific intent that this use will be in contravention of Plaintiffs’ rights under the ’806 Patent.

275. On information and belief, the RK Defendants’ acts will be performed with knowledge of the ’806 Patent and with intent to encourage infringement prior to patent expiry.

276. Plaintiffs will be substantially and irreparably harmed by the infringing activities described above unless those activities are precluded by this Court. Plaintiffs have no adequate remedy at law.

Count IX

(Infringement of the ’806 Patent by the MSN Defendants)

277. Plaintiffs incorporate each of the preceding paragraphs 1 to 171 as if fully set forth herein.

278. On information and belief, the MSN Defendants intend to engage in the commercial manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of MSN’s Generic Product prior to expiration of the ’806 Patent.

279. On information and belief, the MSN Defendants are aware of the ’806 Patent, including by virtue of its listing in the Orange Book since July 2025, and the MSN Defendants will have actual knowledge of the ’806 Patent before MSN’s ANDA is approved.

280. The submission of MSN’s ANDA seeking approval to engage in the commercial manufacture, use, offer for sale, or sale of MSN’s Generic Product, prior to the expiration of the ’806 Patent, constitutes infringement of one or more of the claims of the ’806 Patent under 35 U.S.C. § 271(e)(2)(A).

281. On information and belief, the MSN Defendants intend to engage in the commercial manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of MSN’s Generic Product with the proposed labeling immediately and imminently upon final approval of the MSN ANDA.

282. The ’806 Patent claims, *inter alia*, methods of treating metastatic SCLC using lurbinectedin in patients who have experienced ≥ Grade 3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin. Claim 1 recites:

> A method of treating metastatic small cell lung cancer (SCLC) in a patient with disease progression after platinum-based chemotherapy, said method comprising administering, within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin by intravenous infusion as a monotherapy, a dose of 2.6 mg/m^2 lurbinectedin by intravenous infusion as a monotherapy to a patient having at the time of the administration of the dose of 2.6 mg/m^2 of lurbinectedin:
>
> a) metastatic SCLC with disease progression after platinum-based chemotherapy,
>
> b) a platelet count of at least 100,000/mm^3,
>
> c) an absolute neutrophil count of at least 1500 cells/mm^3, and
>
> d) ≤Grade 1 hepatotoxicity;
>
> wherein the patient previously experienced ≥ Grade 3 hepatotoxicity subsequent to receiving the dose of 3.2 mg/m^2 of lurbinectedin.

283. On information and belief, the MSN Defendants' manufacture, use, offer for sale, sale, marketing, distribution, and/or importation into the United States of MSN's Generic Product prior to the expiration of the '806 Patent, including any applicable exclusivities or extensions, will actively induce infringement of at least Claim 1 of the '806 Patent under 35 U.S.C. § 271(b). The MSN Defendants will aid another in the infringement of one or more claims of the '806 Patent.

284. On information and belief, MSN's Generic Product will have instructions for use that substantially copy the instructions for Zepzelca®, which disclose and encourage the practice of all the elements of one or more claims of the '806 Patent, including at least Claim 1. Upon information and belief, the proposed labeling for MSN's Generic Product will direct the use of MSN's Generic Product for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. On information and belief, the proposed labeling for MSN's Generic Product will direct administering MSN's Generic Product by intravenous infusion as a monotherapy. On information and belief, the proposed labeling for MSN's Generic Product will identify Grade ≥3 hepatotoxicity as an adverse reaction to treatment with 3.2 mg/m^2 of lurbinectedin. On information and belief, the proposed labeling for MSN's Generic Product will direct administering a reduced dose of 2.6 mg/m^2 lurbinectedin following a patient experiencing Grade ≥3 hepatotoxicity at the 3.2 mg/m^2 dose, and within 35 days of receiving a 3.2 mg/m^2 dose of lurbinectedin. On information and belief, the proposed labeling for MSN's Generic Product will direct that the reduced dose of 2.6 mg/m^2 lurbinectedin be administered when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity.

285. On information and belief, MSN's Generic Product, if approved by the FDA, will be prescribed and administered by intravenous infusion as a monotherapy to patients with

metastatic SCLC with disease progression after platinum-based chemotherapy, who experienced Grade ≥3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin and within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin, at a reduced dose of 2.6 mg/m^2 lurbinectedin when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity, which will constitute infringement of one or more claims of the '806 Patent, including at least Claim 1.

286. On information and belief, this directly infringing use will occur with the MSN Defendants' specific intent and encouragement and will be a use that the MSN Defendants know or should know will occur.

287. On information and belief, the MSN Defendants copied the claimed invention of the '806 Patent.

288. On information and belief, the MSN Defendants will actively induce, encourage, aid, and abet this prescription and administration, with knowledge and specific intent that this use will be in contravention of Plaintiffs' rights under the '806 Patent.

289. On information and belief, the MSN Defendants' acts will be performed with knowledge of the '806 Patent and with intent to encourage infringement prior to patent expiry.

290. Plaintiffs will be substantially and irreparably harmed by the infringing activities described above unless those activities are precluded by this Court. Plaintiffs have no adequate remedy at law.

Count X

(Declaratory Judgment of Infringement of the '806 Patent Under 35 U.S.C. § 271(b) Against the MSN Defendants)

291. Plaintiffs incorporate each of the preceding paragraphs 1 to 171 as if fully set forth herein.

292. On information and belief, the MSN Defendants intend to engage in the commercial manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of MSN's Generic Product with the proposed labeling immediately and imminently upon final approval of MSN's ANDA and prior to the expiration of the '806 Patent. Therefore, a case or controversy exists between the MSN Defendants and Plaintiffs as to infringement of the '806 Patent.

293. On information and belief, the MSN Defendants are aware of the '806 Patent, including by virtue of its listing in the Orange Book since July 2025, and the MSN Defendants will have actual knowledge of the '806 Patent before MSN's ANDA is approved.

294. The '806 Patent claims, *inter alia*, methods of treating metastatic SCLC using lurbinectedin in patients who have experienced ≥ Grade 3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin. Claim 1 recites:

> A method of treating metastatic small cell lung cancer (SCLC) in a patient with disease progression after platinum-based chemotherapy, said method comprising administering, within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin by intravenous infusion as a monotherapy, a dose of 2.6 mg/m^2 lurbinectedin by intravenous infusion as a monotherapy to a patient having at the time of the administration of the dose of 2.6 mg/m^2 of lurbinectedin:
>
> a) metastatic SCLC with disease progression after platinum-based chemotherapy,
>
> b) a platelet count of at least 100,000/mm^3,
>
> c) an absolute neutrophil count of at least 1500 cells/mm^3, and
>
> d) ≤Grade 1 hepatotoxicity;
>
> wherein the patient previously experienced ≥ Grade 3 hepatotoxicity subsequent to receiving the dose of 3.2 mg/m^2 of lurbinectedin.

295. On information and belief, the MSN Defendants' manufacture, use, offer for sale, sale, marketing, distribution, and/or importation into the United States of MSN's Generic Product prior to the expiration of the '806 Patent, including any applicable exclusivities or extensions, will

actively induce infringement of at least Claim 1 of the ’806 Patent under 35 U.S.C. § 271(b). The MSN Defendants will aid another in the infringement of one or more claims of the ’806 Patent.

296. On information and belief, MSN’s Generic Product will have instructions for use that substantially copy the instructions for Zepzelca®, which disclose and encourage the practice of all the elements of one or more claims of the ’806 Patent, including at least Claim 1. Upon information and belief, the proposed labeling for MSN’s Generic Product will direct the use of MSN’s Generic Product for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. On information and belief, the proposed labeling for MSN’s Generic Product will direct administering MSN’s Generic Product by intravenous infusion as a monotherapy. On information and belief, the proposed labeling for MSN’s Generic Product will identify Grade ≥3 hepatotoxicity as an adverse reaction to treatment with 3.2 mg/m^2 of lurbinectedin. On information and belief, the proposed labeling MSN’s Generic Product will direct administering a reduced dose of 2.6 mg/m^2 lurbinectedin following a patient experiencing Grade ≥3 hepatotoxicity at the 3.2 mg/m^2 dose, and within 35 days of receiving a 3.2 mg/m^2 dose of lurbinectedin. On information and belief, the proposed labeling for MSN’s Generic Product will direct that the reduced dose of 2.6 mg/m^2 lurbinectedin be administered when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity.

297. On information and belief, MSN’s Generic Product, if approved by the FDA, will be prescribed and administered by intravenous infusion as a monotherapy to patients with metastatic SCLC with disease progression after platinum-based chemotherapy, who experienced Grade ≥3 hepatotoxicity subsequent to receiving a dose of 3.2 mg/m^2 of lurbinectedin and within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin, at a reduced dose of 2.6 mg/m^2

lurbinectedin when the patient has a platelet count of at least 100,000/mm^3, an absolute neutrophil count of at least 1500 cells/mm^3, and Grade ≤1 hepatotoxicity, which will constitute infringement of one or more claims of the ’806 Patent, including at least Claim 1.

298. On information and belief, this directly infringing use will occur with the MSN Defendants’ specific intent and encouragement and will be a use that the MSN Defendants knows or should know will occur.

299. On information and belief, the MSN Defendants copied the claimed invention of the ’806 Patent.

300. On information and belief, the MSN Defendants will actively induce, encourage, aid, and abet this prescription and administration, with knowledge and specific intent that this use will be in contravention of Plaintiffs’ rights under the ’806 Patent.

301. On information and belief, the MSN Defendants’ acts will be performed with knowledge of the ’806 Patent and with intent to encourage infringement prior to patent expiry.

302. Plaintiffs will be substantially and irreparably harmed by the infringing activities described above unless those activities are precluded by this Court. Plaintiffs have no adequate remedy at law.

PRAYER FOR RELIEF

Against the InvaGen Defendants

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A Judgment that the InvaGen Defendants infringed one or more claims of United States Patent No. 12,324,806 by their submission of ANDA No. 219605 seeking FDA approval for the commercial manufacture, use, offer for sale, sale, and/or importation of InvaGen’s Generic Product before the expiration of the ’806 Patent under 35 U.S.C. § 271(e)(2)(A);

B. A Judgment (or Declaration) that the InvaGen Defendants’ commercial

manufacture, use, offer for sale, sale in, and/or importation into the United States of InvaGen's Generic Product will infringe one or more claims of United States Patent No. 12,324,806 under 35 U.S.C. § 271(b).

C. A permanent injunction under 35 U.S.C. §§ 271(e)(4)(B) and/or 283 restraining and enjoining the InvaGen Defendants, and their officers, agents, servants, and employees, and those persons in active concert or participation with any of them, from engaging in the commercial manufacture, use, offer for sale, sale in, and/or importation into the United States of InvaGen's Generic Product prior to the expiration date of United States Patent No. 12,324,806, inclusive of any extensions;

D. An Order under 35 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval of ANDA No. 219605 (the InvaGen ANDA) under Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of United States Patent No. 12,324,806, inclusive of any extensions;

E. A Judgment that the claims of United States Patent No. 12,324,806 are valid and enforceable;

F. If the InvaGen Defendants engage in the commercial manufacture, use, importation, offer for sale, and/or sale of InvaGen's Generic Product prior to expiration of the '806 Patent, a Judgment awarding damages to Plaintiffs resulting from such infringement, with all costs and interest;

G. A Declaration that this case is "exceptional" under 35 U.S.C. § 285 and an award of attorneys' fees;

H. An award of costs and expenses in this action; and

I. Such other and further relief as the Court may deem just and proper.

Against Sandoz

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A Judgment that Sandoz infringed one or more claims of United States Patent No. 12,324,806 by its submission of ANDA No. 219515 seeking FDA approval for the commercial manufacture, use, offer for sale, sale, and/or importation of Sandoz's Generic Product before the expiration of the '806 Patent under 35 U.S.C. § 271(e)(2)(A);

B. A Judgment (or Declaration) that Sandoz's commercial manufacture, use, offer for sale, sale in, and/or importation into the United States of Sandoz's Generic Product will infringe one or more claims of United States Patent No. 12,324,806 under 35 U.S.C. § 271(b).

C. A permanent injunction under 35 U.S.C. §§ 271(e)(4)(B) and/or 283 restraining and enjoining Sandoz, and its officers, agents, servants, and employees, and those persons in active concert or participation with any of them, from engaging in the commercial manufacture, use, offer for sale, sale in, and/or importation into the United States of Sandoz's Generic Product prior to the expiration date of United States Patent No. 12,324,806, inclusive of any extensions;

D. An Order under 35 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval of ANDA No. 219515 (the Sandoz ANDA) under Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of United States Patent No. 12,324,806, inclusive of any extensions;

E. A Declaration that the claims of United States Patent No. 12,324,806 are valid and enforceable;

F. If Sandoz engages in the commercial manufacture, use, importation, offer for sale, and/or sale of Sandoz's Generic Product prior to expiration of the '806 Patent, a Judgment awarding damages to Plaintiffs resulting from such infringement, with all costs and interest;

G. A Declaration that this case is "exceptional" under 35 U.S.C. § 285 and an award

of attorneys' fees;

H. An award of costs and expenses in this action; and

I. Such other and further relief as the Court may deem just and proper.

Against the Zydus Defendants

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A Judgment that the Zydus Defendants infringed one or more claims of United States Patent No. 12,324,806 by their submission of ANDA No. 219582 seeking FDA approval for the commercial manufacture, use, offer for sale, sale, and/or importation of Zydus' Generic Product before the expiration of the '806 Patent under 35 U.S.C. § 271(e)(2)(A);

B. A Judgment (or Declaration) that the Zydus Defendants' commercial manufacture, use, offer for sale, sale in, and/or importation into the United States of Zydus' Generic Product will infringe one or more claims of United States Patent No. 12,324,806 under 35 U.S.C. § 271(b).

C. A permanent injunction under 35 U.S.C. §§ 271(e)(4)(B) and/or 283 restraining and enjoining the Zydus Defendants, and their officers, agents, servants, and employees, and those persons in active concert or participation with any of them, from engaging in the commercial manufacture, use, offer for sale, sale in, and/or importation into the United States of Zydus' Generic Product prior to the expiration date of United States Patent No. 12,324,806, inclusive of any extensions;

D. An Order under 35 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval of ANDA No. 219582 (the Zydus ANDA) under Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of United States Patent No. 12,324,806, inclusive of any extensions;

E. A Declaration that the claims of United States Patent No. 12,324,806 are valid and enforceable;

F. If the Zydus Defendants engage in the commercial manufacture, use, importation, offer for sale, and/or sale of Zydus' Generic Product prior to expiration of the '806 Patent, a Judgment awarding damages to Plaintiffs resulting from such infringement, with all costs and interest;

G. A Declaration that this case is "exceptional" under 35 U.S.C. § 285 and an award of attorneys' fees;

H. An award of costs and expenses in this action; and

I. Such other and further relief as the Court may deem just and proper.

Against the RK Defendants

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A Judgment that the RK Defendants infringed one or more claims of United States Patent No. 12,324,806 by their submission of ANDA No. 219731 seeking FDA approval for the commercial manufacture, use, offer for sale, sale, and/or importation of RK's Generic Product before the expiration of the '806 Patent under 35 U.S.C. § 271(e)(2)(A);

B. A Judgment (or Declaration) that the RK Defendants' commercial manufacture, use, offer for sale, sale in, and/or importation into the United States of RK's Generic Product will infringe one or more claims of United States Patent No. 12,324,806 under 35 U.S.C. § 271(b).

C. A permanent injunction under 35 U.S.C. §§ 271(e)(4)(B) and/or 283 restraining and enjoining the RK Defendants, and their officers, agents, servants, and employees, and those persons in active concert or participation with any of them, from engaging in the commercial manufacture, use, offer for sale, sale in, and/or importation into the United States of RK's Generic Product prior to the expiration date of United States Patent No. 12,324,806, inclusive of any extensions;

D. An Order under 35 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval of ANDA No. 219731 (the RK ANDA) under Section 505(j) of the Federal Food, Drug,

and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of United States Patent No. 12,324,806, inclusive of any extensions;

E. A Declaration that the claims of United States Patent No. 12,324,806 are valid and enforceable;

F. If the RK Defendants engage in the commercial manufacture, use, importation, offer for sale, and/or sale of RK's Generic Product prior to expiration of the '806 Patent, a Judgment awarding damages to Plaintiffs resulting from such infringement, with all costs and interest;

G. A Declaration that this case is "exceptional" under 35 U.S.C. § 285 and an award of attorneys' fees;

H. An award of costs and expenses in this action; and

I. Such other and further relief as the Court may deem just and proper.

Against the MSN Defendants

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A Judgment that the MSN Defendants infringed one or more claims of United States Patent No. 12,324,806 by their submission of ANDA No. 219771 seeking FDA approval for the commercial manufacture, use, offer for sale, sale, and/or importation of MSN's Generic Product before the expiration of the '806 Patent under 35 U.S.C. § 271(e)(2)(A);

B. A Judgment (or Declaration) that the MSN Defendants' commercial manufacture, use, offer for sale, sale in, and/or importation into the United States of MSN's Generic Product will infringe one or more claims of United States Patent No. 12,324,806 under 35 U.S.C. § 271(b).

C. A permanent injunction under 35 U.S.C. §§ 271(e)(4)(B) and/or 283 restraining and enjoining the MSN Defendants, and their officers, agents, servants, and employees, and those persons in active concert or participation with any of them, from engaging in the commercial

manufacture, use, offer for sale, sale in, and/or importation into the United States of MSN's Generic Product prior to the expiration date of United States Patent No. 12,324,806, inclusive of any extensions;

D. An Order under 35 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval of ANDA No. 219771 (the MSN ANDA) under Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of United States Patent No. 12,324,806, inclusive of any extensions;

E. A Declaration that the claims of United States Patent No. 12,324,806 are valid and enforceable;

F. If the MSN Defendants engage in the commercial manufacture, use, importation, offer for sale, and/or sale of MSN's Generic Product prior to expiration of the '806 Patent, a Judgment awarding damages to Plaintiffs resulting from such infringement, with all costs and interest;

G. A Declaration that this case is "exceptional" under 35 U.S.C. § 285 and an award of attorneys' fees;

H. An award of costs and expenses in this action; and

I. Such other and further relief as the Court may deem just and proper.

Dated: September 4, 2025

s/ Charles M. Lizza

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LOCAL CIVIL RULES 11.2 AND 40.1 CERTIFICATION

Pursuant to Local Civil Rules 11.2 and 40.1, I hereby certify that this matter is related to *Jazz Pharmaceuticals Ireland Limited, et al v. Sandoz, Inc., et al*, No. 3:24-cv-09110 (RK)(RLS) (D.N.J.) because it involves the same plaintiffs, some of the same defendants, and because Defendants are seeking to make generic versions of the same branded pharmaceutical product.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: September 4, 2025

s/ Charles M. Lizza

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EXHIBIT A

US012324806B2

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

(10) **Patent No.: US 12,324,806 B2**
(45) **Date of Patent: *Jun. 10, 2025**

(54) **METHOD OF TREATING SCLC AND MANAGING HEPATOTOXICITY**

(71) Applicant: **PHARMA MAR, S.A.**, Madrid (ES)

(72) Inventors: **Carmen Kahatt**, Madrid (ES); **José María Fernandez**, Madrid (ES); **Salvador Fudio**, Madrid (ES); **Arturo Soto**, Madrid (ES); **Pilar Lardelli**, Madrid (ES); **Cristian Fernandez**, Madrid (ES)

(73) Assignee: **PHARMA MAR, S.A.**, Madrid (ES)

(*) 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.: **18/448,122**

(22) Filed: **Aug. 10, 2023**

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A61P 35/00	(2006.01)
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C07D 519/00	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/4995*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 31/4738*** (2013.01); ***A61K 31/4745*** (2013.01); ***A61K 31/573*** (2013.01); ***A61K 38/193*** (2013.01); ***A61P 11/00*** (2018.01); ***A61P 35/00*** (2018.01); ***C07D 519/00*** (2013.01); *C07B 2200/13* (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/4995; A61K 9/0019; A61K 31/4738; A61K 31/4745; A61K 31/573; A61K 38/193; A61K 9/19; A61K 45/06; A61K 47/12; A61K 47/26; A61K 2300/00; A61P 11/00; A61P 35/00; C07D 519/00; C07D 515/22; C07B 2200/13
See application file for complete search history.

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(Continued)

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(57) **ABSTRACT**

Provided are methods for the treatment of SCLC patients by administering therapeutic amounts of lurbinectedin by intravenous infusion. Also provided are methods of treating cancer by administering lurbinectedin in combination with other anticancer drugs, in particular topoisomerase inhibitors. The invention further relates to the administration of lurbinectedin in combination with anti-emetic agents for effective control of symptoms related to nausea and vomiting, reduced lurbinectedin dosages to achieve a safer administration and an increase in the number of treatment cycles. Stable lyophilized formulations of lurbinectedin are also provided.

30 Claims, 8 Drawing Sheets

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PharmaMar to host Conference Call and Webcast on Wednesday, Jan. 4, 2017 to discuss the License and Commercialization agreement with Chugai Pharmaceuticals for Lurbinectedin in Japan (Jan. 3, 2017).
PharmaMar continues to execute commercially in 2016, adds new partner for pipeline asset, and sees pipeline progress (Feb. 24, 2017).
The success of sarcoma treatment, seen by prestigious international oncologists (Mar. 29, 2017).
PharmaMar presents new data on the treatment of multiple myeloma andcancer at the AACR Congress (Apr. 4, 2017).
According to international oncologists, trabectedin is the therapeutic option of reference for the second line treatment of sarcoma (Apr. 7, 2017).
PharmaMar demonstrates its progress in R&D in New York (Apr. 27, 2017).
PharmaMar and Specialised Therapeutics Asia sign licensing and marketing agreement for lurbinectedin covering Australia, New Zealand and several Asian countries (May 17, 2017).
PharmaMar announces new data with its compounds Yondelis® and lurbinectedin during ASCO 2017 (May 18, 2017).
PharmaMar announces encouraging results in clinical trials of lurbinectedin in endometrial and breast cancers (Jun. 16, 2017).
PharmaMar will commercialize PM1183 with the trade name of Zepsyre ™ (Jun. 16, 2017).
FDA chooses Zepsyre™ (PM1183) from PharmaMar to explore potential development for pediatric cancers (Jun. 20, 2017).
PharmaMar will present new clinical data on PM1183 during ESMO 2017 (Aug. 31, 2017).
New positive data on PM1183 sees a response rate of 36% as single agent in patients with advanced and relapsed small-cell lung cancer (Sep. 12, 2017).
PharmaMar starts clinical studies with a new compound—PM14-in patients with solid tumors (Sep. 19, 2017).
PharmaMar will present final data on PM1183 during the 18th World Lung Conference in Japan (Oct. 10, 2017).
Final data on phase I/II in small-cell lung cancer with Zepsyre® presented at the IASCLC 18th World Conference on Lung Cancer in Japan (Oct. 18, 2017).
In real-life, Yondelis® improves the results obtained in previous clinical trials in soft tissue sarcoma (Oct. 24, 2017).
PharmaMar will present at ESGO new data on Yondelis® for gynecological cancers (Nov. 3, 2017).
PharmaMar and Boryung Pharm sign a licensing agreement for Zepsyre® (lurbinectedin) in Korea (Nov. 7, 2017).
Significant event: R&D: New licenses, patents and registered trademarks (Nov. 8, 2017).
PharmaMar presents positive results from a Phase II study of lurbinectedin in Ewing's sarcoma at the CTOS International Congress (Nov. 13, 2017).
PharmaMar to present at the Stifel 2017 Healthcare Conference (Nov. 14, 2017).
Phase III trial with Zepsyre® in small-cell lung cancer (Atlantis) to continue on the basis of positive recommendation by IDMC (Nov. 15, 2017).
Pharma Mar, S.A. announces the results of the Phase III clinical trial (Corail)Zepsyre® (lurbinectedin) in platinum-resistant ovarian cancer patients. (Jan. 2018).

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PharmaMar's Lurbinectedin Atlantis trial design and data in small-cell lung cancer will be an oral presentation at the IASCLC's annual meeting (Feb. 20, 2018).
PharmaMar announces data presentations for both its molecules Yondelis® and lurbinectedin at ASCO 2018 (May 17, 2018).
Positive recommendation of IDMC to Zepsyre® to continue the Phase III trial with in small-cell lung cancer (Atlantis) (May 29, 2018).
PharmaMar presents new results with lurbinectedin as a single agent in patients with recurrent small-cell lung cancer at ASCO 2018 (Jun. 4, 2018).
PharmaMar requests the modification from primary endpoint to OS for the Atlantis trial (Jun. 12, 2018).
PharmaMar and Chugai agree to terms for early termination of the license agreement for Zepsyre® in Japan (Jun. 26, 2018).
PharmaMar announces the signature of a Memorandum of Understanding with the Indonesian Oceanographic Research Center to address the fight against cancer (Jul. 9, 2018).
The Lancet Oncology journal chooses a PharmaMar poster as one of the most relevant of the ASCO 2018 congress (Jul. 13, 2018).
PharmaMar reaches an agreement with Impilo Pharma, a part of Immedica Group, for the promotion and distribution of Yondelis® in the Nordic countries and Eastern Europe (Jul. 27, 2018).
PharmaMar announces that the Atlantis study has reached the goal ofrecruitment (Jul. 30, 2018).
The U.S. Food and Drug Administration (FDA) has granted Orphan DrugPharmaMar's Lurbinectedin (Aug. 3, 2018).
PharmaMar will present in the ESMO congress results of lurbinectedin on Ovarian Cancer (Aug. 10, 2018).
PharmaMar will present in the IASLC congress results of lurbinectedin on Small-Cell Lung Cancer (Aug. 13, 2018).
PharmaMar will present the results of the Phase I/II Study with lurbinectedincombination with doxorubicin in relapsed small-cell lung cancer during the IASLC World Conference (Sep. 6, 2018).
PharmaMar presents the Overall Survival data from the Phase I/II Study of lurbinectedin in combination with doxorubicin for relapsed Small Cell Lung Cancer (Sep. 24, 2018).
PharmaMar will present at ESMO results of the phase III Corail study with lurbinectedin in platinum-resistant Ovarian Cancer (Oct. 18, 2018).
Zepsyre® receives positive recommendation of the IDMC to continue with the Phase III trial in small-cell lung cancer (Atlantis) (Oct. 26, 2018).
PharmaMar announces that Zepsyre® (lurbinectedin) shows noteworthy clinical activity in metastatic breast cancer with mutations in BRCA 1/2 (Nov. 8, 2018).
PharmaMar announces the meeting of its patient recruitment target in the phase II study with lurbinectedin as a single agent in small-cell lung cancer (Nov. 14, 2018).
Phase II trial of lurbinectedin in progressive mesothelioma finalizes its patient recruitment (Dec. 17, 2018).
PharmaMar receives positive opinion from EMA (Comp) for orphan drug designation of Zepsyre® (lurbinectedin) for small-cell lung cancer (Jan. 24, 2019).
PharmaMar's Zepsyre® Atlantis trial in small-cell lung cancer will be an oral presentation at the IASLC's Targeted Therapies annual meeting (Feb. 20, 2019).
Soft Tissue Sarcoma requires a multidisciplinary approach to reduce patient relapses and improve patient survival (Mar. 21, 2019).
PharmaMar announces positive results in its lurbinectedin monotherapy trial for small cell lung cancer (Mar. 25, 2019).
ASCO selects PharmaMar's lurbinectedin monotherapy trial for an oral presentation(Apr. 1, 2019).
PharmaMar is present with its Atlantis study at the IASLC Congress on small cell lung cancer in New York (Apr. 8, 2019).
PharmaMar and Specialized Therapeutics Asia meet in Madrid to define new agreements (Apr. 17, 2019).
PharmaMar and Luye Pharma sign License agreement for Development and Commercialization of lurbinectedin in China territories (Apr. 26, 2019).
ASCO selects lurbinectedin second line small cell lung cancer abstract for "Best of ASCO" program (May 15, 2019).
ASCO releases abstracts and publishes PharmaMar's lurbinectedin data insmall cell lung cancer (May 16, 2019).
Positive results of lurbinectedin Phase II trial (PharmaMar) for the treatment of relapsed small cell lung cancer are presented at ASCO (Jun. 1, 2019).
PharmaMar will host a conference call with investors after lurbinectedin results are presented at ASCO (Jun. 3, 2019).
IASLC publishes lurbinectedin (PharmaMar) abstracts titles for small cell lung cancer (Aug. 12, 2019).
PharmaMar will submit NDA for lurbinectedin under accelerated approval in SCLC in the USA (Aug. 19, 2019).
PharmaMar enters into a new licensing agreement with Janssen for Yondelis® (Aug. 26, 2019).
PharmaMar announces that its Phase I study on Japanese patients with lurbinectedin in monotherapy has achieved its objective (Aug. 27, 2019).
PharmaMar presents at MaNaPro & ECMNP its latest advances in the development of compounds of marine origin (Sep. 2, 2019).
PharmaMar presents new lurbinectedin data at the World Conference on Lung Cancer (Sep. 9, 2013).
Phase II study results of lurbinectedin in progressive mesothelioma will be presented in an oral session at ESMO 2019 (Sep. 23, 2019).
Phase Il Study results of trabectedin combined with low-dose radiation therapy for Soft Tissue Sarcoma are presented at ESMO (Sep. 30, 2019).
Lurbinectedin data in Progressive Malignant Pleural Mesothelioma presented at ESMO (Oct. 1, 2019).
PharmaMar has presented Yondelis® data in ovarian cancer at ESGO Nov. 4, 2019).
PharmaMar will participate in the Solebury Trout KOL Day in New York on Nov. 15, 2019 (Nov. 7, 2019).
PharmaMar has presented results of its antitumor compounds trabectedin and plocabulin at the CTOS Congress (Nov. 18, 2019).
PharmaMar receives Orphan Drug Designation for lurbinectedin from the Swiss Agency for Therapeutic Products for Small Cell Lung Cancer (Nov. 26, 2019).
PharmaMar has filed New Drug Application for lurbinectedin with the FDA for the treatment of relapsed small cell lung cancer (Dec. 17, 2019).
PharmaMar and Jazz Pharmaceuticals Sign Exclusive License Agreement for Lurbinectedin in the U.S. (Decmeber 19, 2019).
PharmaMar in San Francisco during the J.P. Morgan Annual Healthcare Conference in San Francisco (Jan. 9, 2020).
PharmaMar announces the initiation of a study of lurbinectedin in combination with immunotherapy (Jan. 14, 2020).
PharmaMar and Jazz Pharmaceuticals Announce the U.S. License Agreement for Lurbinectedin is Effective With the Expiration of the HSR Waiting Period (Jan. 22, 2020).
PharmaMar and Bionical Emas launch Expanded Access Program for lurbinectedin in relapsed Small Cell Lung Cancer in the U.S. (Jan. 27, 2020).
PharmaMar announces that it has received the upfront payment of $200 million from the license agreement with Jazz for lurbinectedin in the United States (Jan. 29, 2020).
PharmaMar and Jazz Pharmaceuticals Announce FDA Acceptance and Priority Review of New Drug Application for Lurbinectedin in Relapsed Small Cell Lung Cancer (Feb. 17, 2020).
Lurbinectedin receives Orphan Drug designation from the TGA for Small-Cell Lung Cancer in Australia (Feb. 19, 2020).
PharmaMar signs an agreement with Immedica Pharma to market lurbinectedin in Eastern Europe, the UK, Ireland, the Nordic countries and some Middle Eastern countries (Apr. 29, 2020).
PharmaMar and Megapharm sign a licensing agreement for lurbinectedin in Israel (May 11, 2020).
PharmaMar announces abstracts to be presented at ASCO 2020 (May 14, 2020).

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PharmaMar announces that TGA has granted the "Provisional Approval Pathway" for lurbinectedin in relapsed Small Cell Lung Cancer in Australia(Jun. 3, 2020).
PharmaMar to Host Virtual KOL Event on Lurbinectedin (Jun. 3, 2020).
PharmaMar announces the U.S. FDA approval of lurbinectedin (ZepzelcaTM) for the treatment of metastatic Small Cell Lung Cancer (Jun. 15, 2020).
PharmaMar announces that it has received payment of $100 million from Jazz Pharmaceuticals for the approval of ZepzelcaTM (lurbinectedin) in the U.S.(Jun. 29, 2020).
PharmaMar announces that lurbinectedin has received acceptance for its clinical trial application in China (Jun. 29, 2020).
PharmaMar announces that the NCCN® (National Comprehensive Cancer Network) has added Zepzelca™ (lurbinectedin) to Clinical Practice Guidelines in Oncology in the U.S.(Jul. 13, 2020).
PharmaMar has filed lurbinectedin for Temporary Marketing Authorisation with the Swiss Agency for Therapeutic Products (Jul. 20, 2020).
PharmaMar will present data for ZepzelcaTM (lurbinectedin) and Yondelis® (trabectedin) at ESMO 2020 (Sep. 14, 2020).
PharmaMar has presented new results for ZepzelcaTM (lurbinectedin) in sensitive patients with Small-Cell Lung Cancer, candidates for "re-challenge" (Sep. 17, 2020).
PharmaMar signs an agreement with Jazz Pharmaceuticals for lurbinectedin in Canada (Oct. 15, 2020).
PharmaMar will present new data for ZepzelcaTM (lurbinectedin) and Yondelis® (trabectedin) for advanced Soft-Tissue Sarcoma at CTOS 2020 ((Nov. 11, 2020).
PharmaMar and Luye Pharma have started a clinical trial with lurbinectedin in China (Dec. 1, 2020).
PharmaMar and Jazz Pharmaceuticals announce results of the Atlantis phase III study with lurbinectedin (Dec. 3, 2020).
PharmaMar will present new data for ZepzelcaTM (lurbinectedin) at rescheduled IASLC 2020 (Jan. 13, 2021).
PharmaMar presents new data on Zepzelca® (lurbinectedin) in combination with irinotecan at an oral session at (rescheduled) IASLC 2020 (Feb. 1, 2021).
PharmaMar signs a new agreement with Adium to commercialize Zepzelca® (lurbinectedin) in Latin America (Mar. 1, 20201).
ESMO includes lurbinectedin in its Clinical Practice Guidelines (Apr. 15, 2021).
PharmaMar announces abstracts to be presented at ASCO 2021 (May 20, 2021).
PharmaMar receives positive opinion from EMA (Comp) for Orphan Drug Designation of lurbinectedin for Mesothelioma (Jul. 28, 2021).
PharmaMar announces the approval of Zepzelca® (lurbinectedin) for the treatment of metastatic Small Cell Lung Cancer in the United Arab Emirates (Sep. 1, 2021).
PharmaMar announces abstracts to be presented during the IASLC 2021 World Conference on Lung Cancer (Sep. 2, 2021).
PharmaMar announces that Australia approves Zepzelca® (lurbinectedin) for the treatment of metastatic Small Cell Lung Cancer (Sep. 14, 2021).
PharmaMar announces Singapore Health Sciences Authority approval of Zepzelca® (lurbinectedin) for the treatment of metastatic Small Cell Lung Cancer (Sep. 22, 2021).
PharmaMar announces the approval of ZepzelcaTM (lurbinectedin) for the treatment of relapsed stage III or metastatic small cell lung cancer in Canada (Sep. 30, 2021).
PharmaMar signs a licensing and commercialization agreement with Lotus Pharmaceutical for lurbinectedin in Taiwan (Nov. 11, 2021).
PharmaMar and Jazz Pharmaceuticals announce initiation of confirmatory phase III clinical trial of Zepzelca® (lurbinectedin) for the treatment of patients with relapsed Small Cell Lung Cancer (Dec. 13, 2021).
PharmaMar signs a new licensing and commercialization agreement with Eczacibasi for lurbinectedin in Turkey (Dec. 22, 2021).
PharmaMar receives the first commercial milestone payment from Jazz Pharmaceuticals for US$25 million (Mar. 4, 2022).
Results of the phase II trial with lurbinectedin for the treatment of patients with relapsed Ewing Sarcoma (May 3, 2022).
PharmaMar has filed for approval of lurbinectedin for the treatment of metastatic Small Cell Lung Cancer in the UK (May 4, 2022).
PharmaMar announces abstracts to be presented at ASCO 2022 (Jun. 1, 2022).
Chinese health authorities approve lurbinectedin for "urgent clinical use" (Jul. 19, 2022).
Lurbinectedina recibe la designación de medicamento innovador de la MHRA del Reino Unido (Aug. 5, 2022).
PharmaMar announces the data to be presented at ESMO 2022 (Sep. 8, 2022).
PharmaMar announces the approval of Zepzelca® (lurbinectedin) for the treatment of metastatic Small Cell Lung Cancer in South Korea (Sep. 23, 2022).
PharmaMar receives Orphan Drug Designation for lurbinectedin from the Swiss Agency for Therapeutic Products for Malignant Mesothelioma (Dec. 27, 2022).
Lurbinectedin "Named Patient Program" for Small-Cell Lung Cancer launched in Hong Kong (Jan. 9, 2023).
PharmaMar announces the full approval of Zepzelca® (lurbinectedin) for the treatment of metastatic Small Cell Lung Cancer in Mexico (Jan. 24, 2023).
PharmaMar announces the approval of Zepzelca® (lurbinectedin) for the treatment of metastatic Small Cell Lung Cancer in Israel (Jan. 31, 2023).
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PharmaMar to present new data on its compounds at AACR 2023 Congress (Apr. 17, 2023).
European Commission grants orphan drug designation to PharmaMar's lurbinectedin for the treatment of Soft Tissue Sarcoma May 12, 2023).
PharmaMar announces abstracts to be presented at ASCO 2023 (May 26, 2023).
PharmaMar and Luye Pharma announce the acceptance of New Drug Application for lurbinectedin in China (Jun. 6, 2023).
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200
150
100
50
0
Counts / s
0
5
10
15
20
25
30
35
40
°2Theta (Cu K-alpha1 Radiation)

Fig. 1

700
600
500
400
300
200
100
0
Counts / s
0
5
10
15
20
25
30
35
40
°2Theta (Cu K-alpha1 Radiation)

Fig. 2a

Count / s
400
350
300
250
200
150
100
50
0
0
5
10
15
20
25
30
35
40
°2Theta (cu-K-alpha1 Radiation)

Fig. 2b

Mass Change: - 2.58%
H_2O
Mass Change: - 18.33%
decomposition
TG (%)
100
95
90
85
80
50
100
150
200
Temperature (°C)

Fig. 3

Heat Flow Exo Down (mW)
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-50
0
50
100
150
200
Temperature (°C)
164.0°C
132.5°C
Baseline substracted
Method Log:
1: Data storage: Off
2: Equilibrate at -50.00°C
3: Isothermal for 5.00 min
4: Data storage: On
5: Ramp 10.00°C/min to 180.00°C
6: Mark end of cycle 0
7: End of method

Fig. 4

Rel. Sample Weight [%]
107
103
99
95
Rel. Sample Weight [%]
0
20
40
60
80
100
Sample RH [%]

Fig. 5

counts/s
0
100
200
300
400
5
10
15
20
25
30
35
40
° 2 theta

Fig. 6

86.3
84
82
80
78
%T
76
74
72
70
68
66.4
4000.0
3000
2000
1500
1000
450.0
cm-1
3443.93
2930.66
1626.21
1753.43
1485.70
1455.76
1370.55
1262.76
1213.59
1151.79
952.13
915.61
801.29
587.78

Fig. 7a

86.4
84
82
80
%T
78
76
74
72
70.9
4000.0
3000
2000
1500
1000
450.0
cm-1
2928.29
1626.45
1754.91
1485.24
1456.15
1369.77
1197.18
1149.91
1088.02
1093.43
959.31
916.23
587.23

Fig. 7b

Fig. 8

Form A of lurbinectedin
Q/m= 43.1 ± 3.86 nC/g
Form B of lurbinectedin
Q/m= 4.96 ± 2.0 nC/g
Q: charge (nC)
m: mass (mg)
0,0
0,5
1,0
1,5
2,0
2,5
3,0
0
20
40
60
80
100
120
140
160
180
200
220
240

Fig. 9a

64.02 +/-7.98 nC/g
Form A of lurbinectedin
Form B of lurbinectedin
4.3 +/-0.4 nC/g
charge (nC)
mass (g)
0,0
0,5
1,0
1,5
2,0
2,5
3,0
3,5
0,02
0,04
0,06
0,08
0,10
0,12
0,14
0,16
0,18
0,20

Fig. 9b

Fig. 10a

Fig. 10b

METHOD OF TREATING SCLC AND MANAGING HEPATOTOXICITY

FIELD OF THE INVENTION

Provided are methods for the treatment of SCLC patients by administering therapeutic amounts of lurbinectedin by intravenous infusion. Also provided are methods of treating cancer by administering lurbinectedin in combination with other anticancer drugs, in particular topoisomerase inhibitors. The invention further relates to the administration of lurbinectedin in combination with anti-emetic agents for effective control of symptoms related to nausea and vomiting, reduced lurbinectedin dosages to achieve a safer administration and an increase in the number of treatment cycles. Stable lyophilized formulations of lurbinectedin are also provided.

BACKGROUND TO THE INVENTION

Lung cancer is the leading cause of cancer death in both men and women in the United States. In 1998, an estimated 171,500 new cases were diagnosed, and about 160,100 deaths resulted from this disease. More women die from lung cancer than breast, ovarian, and uterine cancer combined, and 4 times as many men die from lung cancer than from prostate cancer.

Lung cancer is a disease in which malignant (cancer) cells form in the tissues of the lung. The two major types of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC comprises only about 13-15% of all lung cancers at diagnosis; however, SCLC is the more aggressive form of lung cancer. With SCLC, the cancer cells tend to grow quickly and travel to other parts of the body, or metastasize, more easily. Its incidence is associated with smoking, almost two thirds of patients present with advanced disease, and although response rates to chemotherapy are high, the benefit is short-lived. The median survival of patients with untreated SCLC is two to four months (Clark, 1998; Glisson, 2003; Davies, 2004). The most common regimens include cisplatin or carboplatin and etoposide. Unfortunately, despite the 40-90% response rate to first-line chemotherapy, long-term survival is unusual because patients develop resistance to chemotherapy and relapse (Sundstrom, 2005; Jackman, 2005). The overall expected mean survival after disease relapse without treatment is two to four months (Huisman, 1999).

Treatment and survival have not changed substantially during the past two decades. Even limited-stage disease is rarely cured with radical local therapy (surgery or radiotherapy) and systemic chemotherapy (platinum plus etoposide) remains a cornerstone of first-line treatment in SCLC.

Topotecan is the only approved drug for second-line treatment of patients with a chemotherapy-free interval longer than 60 days. Topotecan monotherapy improves survival and quality of life, as well as cancer-related symptoms in the second-line setting. Alternatively, doxorubicin-based combination therapy can be administered with a similar outcome but a slightly lower rate of symptom control. In refractory patients no standard therapy exists. Amrubicin, a novel anthracyline, showed promising activity in refractory and relapsed patients. Phase III trials are ongoing. Other agents with activity include paclitaxel, docetaxel, gemcitabine, bendamustine and vinorelbine.

During the past few years, several clinical trials have evaluated the effect of addition of immunotherapy to conventional chemotherapy in patients with extensive SCLC.

Checkpoint inhibitors are currently under investigation, especially the CTLA-4 and PD-1/PD-L1 inhibitors. Nivolumab and Pembrolizumab were the first immunotherapeutic agents to be approved by the FDA for patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of chemotherapy.

Lurbinectedin (PM01183) is a synthetic tetrahydropyrrolo [4, 3, 2-de]quinolin-8(1H)-one alkaloid analogue with antineoplastic activity. Lurbinectedin is a selective inhibitor of oncogenic transcription, induces DNA double-strand break generating apoptosis, and modulates the tumor microenvironment. For example, by inhibiting active transcription in tumor-associated macrophages, lurbinectedin downregulates IL-6, IL-8, CCL2, and VEGF.

Lurbinectedin has demonstrated a highly potent in vitro activity against solid and non-solid tumor cell lines as well as a significant in vivo activity in several xenografted human tumor cell lines in mice, such as those for breast, kidney and ovarian cancer. Preliminary clinical results have shown that lurbinectedin has activity as a second line therapeutic as a single agent in SCLC. There is a need for treatment for SCLC and other solid tumors.

SUMMARY OF THE INVENTION

Phase 2 clinical trial results demonstrate an at least 30% (35.2%) overall response rate for SCLC patients with lurbinectedin as a second line agent administered as single agent. Results from a phase 1b-2 trial in solid tumor patients demonstrated activity of a combination of lurbinectedin and irinotecan, particularly in SCLC, endometrial carcinoma, soft tissue sarcoma and glioblastoma. Accordingly, provided herein are methods of treating SCLC, including metastatic SCLC, in patients in need thereof, especially those patients whose SCLC has progressed after prior therapy, such as platinum-containing therapy or immunotherapy, including among others patients who have failed to respond or to respond adequately to prior treatment, those who may have responded to prior treatment but then experienced progression of the disease, and those who may have had such response followed by progression more than once. Also provided are methods of treating solid tumors, particularly SCLC, endometrial carcinoma, soft tissue sarcoma, and glioblastoma, in patients in need thereof administering lurbinectedin in combination with a topoisomerase inhibitor, particularly irinotecan or SN-38. Stable lyophilized formulations are further provided.

The methods provided herein involve administering to a patient, including an adult patient, suffering from SCLC, including metastatic SCLC, particularly an SCLC patient who has progressed after prior platinum-based chemotherapy, an effective amount of lurbinectedin by intravenous infusion. In certain embodiments, provided are methods of administering to a patient suffering from SCLC, including metastatic SCLC, who has progressed after prior immunotherapy, particularly atezolizumab, including in combination with carboplatin and etoposide, or nivolumab, an effective amount of lurbinectedin by intravenous infusion. Lurbinectedin is preferably administered at a dose of 3.2 mg/m^2 every 21 days (or 3 weeks), typically over a period of multiple months, and in most cases until disease progression and death or the patient experiences unacceptable toxicity, depending upon the patient's response to the administration.

In certain embodiments, treatment effective amounts of lurbinectedin may be administered every 21 days or 3 weeks to the patient as a 1-hour IV infusion using dosing levels of

3.2 mg/m^2, to achieve mean total plasma Cmax of about 85.6 μg/L to 133.75 μg/L, preferably 107 μg/L, and mean AUC∞ of about 440.8 μg*h/L to 688.75 μg*h/L, preferably 551 μg*h/L. Treatment results in an overall response rate of greater than 30%, progression free survival for a median 3.5 months, (a range of 2.6 months to 4.3 months), including a median of 2.6 months in resistant patient population (CFTI less than 90 days for prior chemotherapy treatment) and a median of 4.6 months in sensitive patient populations (CFTI greater than or equal to 90 days for prior chemotherapy treatment). Overall survival for a median of 9.3 months (resistant patient population of 5.0 months and sensitive patient population of 11.9 months) may be achieved according to the methods disclosed herein.

In an embodiment, provided is a method of managing hematological adverse events associated with lurbinectedin treatment regimen by dose reduction and/or administration of G-CSF. The method provided relates to administering to an SCLC patient a lurbinectedin formulation by IV infusion at a dose of 3.2 mg/m^2; assessing, after administering the lurbinectedin, whether the patient experiences an adverse reaction associated with the lurbinectedin administration that is a Grade 3 (severe) non hematological toxicity, Grade 4 thrombocytopenia (platelet count less than 25,000 cells/mm3), Grade 3 thrombocytopenia (platelet count less than 50,000 cells/mm^3) with bleeding that requires transfusion, Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), or any grade neutropenia (Neutrophil count <LLN) that is associated with infection/sepsis or any other of the adverse reactions. At the next scheduled dose, preferably 3 weeks after the prior dose, and once the patient's neutrophil count is greater than 1500 cells/mm^3; platelet count is greater than about 100,000 mm^3; and hemoglobin levels are greater than about 9 g/d, (i) if the adverse reaction consists of an isolated Grade 4 neutropenia, then administering to the patient a dose of G-CSF and a dose of lurbinectedin that is the same as the previous dose, for example, 3.2 mg/m^2, or (ii) if the adverse reaction is a hematological abnormality that is not solely isolated Grade 4 neutropenia, then administering a dose that is reduced compared to the prior dose, for example is 80 to 85% of the prior dose, for example, 2.6 mg/m^2 if the prior dose is 3.2 mg/m^2. Optionally, if the adverse reaction is isolated Grade 4 neutropenia, then the dose may be reduced at the next scheduled dose, in particular, to 80 to 85% of the prior dose, for example, 2.6 mg/m^2 if the prior dose is 3.2 mg/m^2.

In the event that after receiving a reduced dosage of lurbinectedin, a patient experiences an adverse event that is a ≥Grade 3 (severe) non hematological toxicity, Grade 4 thrombocytopenia (Platelet count less than 25,000 cells/mm3), Grade 3 thrombocytopenia (Platelet count less than 50,000 cells/mm3) with bleeding that requires transfusion), or any grade neutropenia (Neutrophil count <LLN) that is associated with infection/sepsis or any other of the adverse reactions (but, in certain embodiments, not isolated Grade 4 neutropenia), then at the next scheduled dosage, preferably 3 weeks after the prior dose, and once the patient's neutrophil count is greater than 1500 cells/mm^3; platelet count is greater than about 100,000 mm^3; and hemoglobin levels are greater than about 9 g/d, administering a second reduced dosage to the patient which is 60 to 65% of the first, unreduced dose, particularly 2.0 mg/m^2 (60-65% of the 3.2 mg/m^2 dosage). Optionally, if the adverse reaction after the administration of a reduced dosage of lurbinectedin is isolated Grade 4 neutropenia, then the dose may be reduced at the next scheduled dose, in particular, to 60 to 65% of the first, unreduced dose, for example, 2.6 mg/m^2 if the initial dose is 3.2 mg/m^2.

In another embodiment, provided is a method of managing hematological toxicity, myleosupressive effects and/or hepatotoxicity that may be associated with lurbinectedin administration in the treatment of SCLC, including metastatic SCLC, in a patient, including an adult patient, by dose reduction and/or dose delay. Provided are methods of treating SCLC, including metastatic SCLC, by administering to a patient in need thereof with an absolute neutrophil count of at least 1500 cells/mm^3 and a platelet count of at least 100,000/mm^3, a dose of 3.2 mg/m^2 lurbinectedin, preferably by infusion over 60 minutes. In a further embodiment, 21 days after the previous dose, the patient has an absolute neutrophil count of at least 1500 cells/mm^3 and a platelet count of at least 100,000/mm^3 and is administered 3.2 mg/m^2 dose of lurbinectedin, preferably by infusion over 60 minutes. In embodiments, the patient is monitored for and has no hepatotoxicity prior to administration of lurbinectedin. Subsequent treatments are administered at 21 day (3 week) intervals to the patient having an absolute neutrophil count of at least 1500 cells/mm^3 and a platelet count of at least 100,000/mm^3, and preferably, does not have any Grade 2 or greater adverse reaction.

In certain embodiments, provided are methods of treating SCLC, including metastatic SCLC, in a patient in need thereof by administering lurbinectedin at a dose of 3.2 mg/m^2, including by infusion over 60 minutes, then monitoring the patient for adverse hematological or hepatic reactions or other adverse reaction that is Grade 2 or greater. In the event a patient having been administered a dose of 3.2 mg/m^2 lurbinectedin exhibits grade 4 neutropenia (neutrophil count less than 500 cells/mm^3) or any febrile neutropenia, then the subsequent dose of lurbinectedin is not administered until the later of 21 days after the prior dose or when the patient exhibits less than grade 1 neutropenia (at least 1500 cells/mm^3), which may be greater than 21 days past the previous dose, and then either administering lurbinectedin at a reduced dose of 2.6 mg/m^2 every three weeks or administering lurbinectedin at a dose of 3.2 mg/m^2 every three weeks with G-CSF prophylaxis. In the event, a patient having been administered a 3.2 mg/m^2 dose of lurbinectedin exhibits Grade 3 thrombocytopenia (25,000-50,000 platelets/mm^3) with bleeding or Grade 4 thrombocytopenia (less than 25,000 platelets/mm^3), then the subsequent dose of lurbinectedin is not administered until the later of 21 days after the previous dose or when the patient exhibits a platelet count of greater than or equal to 100,000/mm^3 and the subsequent dose is a reduced dose of 2.6 mg/m^2 every three weeks (21 days). In the event, a patient having been administered a 3.2 mg/m^2 dose of lurbinectedin exhibits hepatotoxicity or other adverse reaction that is either Grade 2 or Grade 3 or 4, then the subsequent dose of lurbinectedin is not administered until the later of 21 days after the previous dose or when the patient exhibits less than or equal to Grade 1 hepatotoxicity (or Grade 1 or less of the other adverse reaction), and the subsequent dose is a dose of 3.2 mg/m^2 every three weeks (21 days) if the patient had exhibited Grade 2 hepatotoxicity (or other adverse reaction) and the subsequent dose is a reduced dose of 2.6 mg/m^2 every three weeks (21 days) if the patient had exhibited Grade 3 or 4 hepatotoxicity or other adverse reaction. If after dose reduction, the patient exhibits one of Grade 4 neutropenia, or any grade febrile neutropenia, Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia, or hepatotoxicity or other adverse reaction at Grade 3 or 4, then the subsequent

dose is not administered until the later of 21 days or when the patient has recovered as detailed above and then administered a further reduced dose of 2 mg/m^2 lurbinectedin every three weeks or, in the case of Grade 4 neutropenia, is administered the same dose of lurbinectedin as the prior dose with G-CSF prophylaxis. If the patient ceases to tolerate (that is exhibits, after lurbinectedin administration, one of Grade 4 neutropenia, or any grade febrile neutropenia, Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia, or hepatotoxicity or other adverse reaction at Grade 3 or 4) at a dose of 2 mg/m^2 lurbinectedin or if delay in administration is greater than 2 weeks past the scheduled dose (at 21 days after the prior dose) for the patient to recover and meet the criteria for lurbinectedin administration, then treatment is discontinued.

Provided are methods of treating SCLC or solid tumor in a patient in need thereof by administration of a dose of 2 to 3.2 mg/m^2 lurbinectedin and avoiding co administration with a strong or a moderate CYP3A inhibitor or a strong or moderate CYP3A inducer. In certain embodiments, provided are methods of treating SCLC or solid tumor in a patient in need thereof where the patient is also administered a moderate CYP3A inhibitor, then administering a reduced dose of lurbinectedin, for example a dose of 2.6 mg/m^2 or a dose of 2 mg/m^2 to said patient every 3 weeks (21 days).

Also provided are embodiments in which an antiemetic is prophylactically administered prior to administration of lurbinectedin-associated (acute and delayed-phase) nausea and/or vomiting comprising administering an antiemetic prophylaxis on the day of and prior to administering a dose of 2 to 3.2 mg/m^2 lurbinectedin to the patient, particularly where the antiemetic agents comprise a corticosteroid and a serotonin antagonist. The treatment may be for SCLC, including metastatic SCLC, or any other solid tumor in a patient in need of such treatment. In certain embodiments, the corticosteroid is dexamethasone, preferably a dose of 8 mg administered intravenously, or a dose of a corticosteroid that is equivalent to 8 mg dexamethasone intravenously and where the serotonin antagonist is ondansetron, preferably a dose of 8 mg administered intravenously, or a dose of serotonin antagonist that is equivalent to 8 mg ondansetron administered intravenously. In certain embodiments, antiemetic therapy is administered post-infusion on the day of, or for 2, 3, or 4 days after administration of lurbinectedin, preferably comprising administering a corticosteroid, a serotonin antagonist and metoclopramide. In specific embodiments, the corticosteroid is dexamethasone administered orally at a dose of 4 mg, or a dose of corticosteroid equivalent to 4 mg oral dexamethasone; the serotonin antagonist is ondansetron administered orally at a dose of 8 mg, or a serotonin antagonist equivalent to 8 mg oral ondansetron; and metoclopramide is administered at a dose of 10 mg either intravenously or orally, or the dose equivalent to oral or intravenous 10 mg metoclopramide, wherein the metoclopramide is administered every 8 hours.

One aspect of the invention is a method of treating patients with solid tumors in need thereof by administering lurbinectedin in combination with a topoisomerase inhibitor, particularly irinotecan. In particular embodiments, the solid tumor patient is treated with a treatment regimen in which lurbinectedin is administered at a dose of 1 to 2.5 mg/m^2 on day 1 with a dose of 75 mg/m^2 irinotecan administered on day 1 and day 8 of the treatment cycle, and the irinotecan is administered with G-CSF. The treatment cycle is generally 21 days such that, in the second treatment cycle, a dose of 1 to 2.5 mg/m^2 lurbinectedin is administered with a dose of 75 mg/m^2 irinotecan is administered on day 22 and a dose of 75 mg/m^2 irinotecan is administered 7 days later on day 29 after the initial treatment. Subsequent treatments are administered generally every three weeks with the combination of 1 to 2.5 mg/m^2 lurbinectedin and 75 mg/m^2 irinotecan administered on day 1 of the cycle and 75 mg/m^2 irinotecan administered on day 8, with G-CSF. In certain embodiments, if the patient exhibits hematologic toxicity following the day 1 combination dosage, the dose of irinotecan is not administered at day 8. In some embodiments, the solid cancer is selected from endometrial cancer, SCLC, soft tissue sarcoma (including Ewing and synovial sarcoma), glioblastoma, pancreatic adenocarcinoma, mesothelioma, colorectal carcinoma, and epithelial ovarian cancer. In preferred embodiments, the solid tumor is endometrial cancer, SCLC, soft tissue sarcoma (including Ewing or synovial sarcoma), or glioblastoma.

In one aspect, provided is a stable, lyophilized formulation of lurbinectedin comprising lurbinectedin, a buffer derived from an organic acid (e.g., an organic carboxylic acid, such as lactate buffer) and a disaccharide, which formulation has a pH of 3.8 to 4.5 when reconstituted with 8 mL of water. Reference to reconstitution of 4 mg lurbinectedin in 8 mL having a concentration of 0.5 mg/mL may be based on a calculated concentration of 0.47 mg/mL in 8.55 mL.

In some embodiments, the lyophilized composition comprises or consists of 4 mg lurbinectedin, 22.1 mg lactic acid, 5.1 mg sodium hydroxide and 800 mg sucrose (or comprises or consists of these ingredients in this ratio). The composition is preferably packaged in a 30 ml vial and may be reconstituted in 8 mL water, to yield a solution containing 0.5 mg/ml lurbinectedin.

In some embodiments, the lyophilized formulation may be stored for 24 months or 36 months or more at 5° C.±3° C., during which time the lurbinectedin retains its therapeutic effectiveness and exhibits minimal chemical degradation. For example, after 24 months or 36 months of storage, the amount of Impurity D (lurbinectedin degradation product resulting from deacetylation of lurbinectedin) present in the composition is not more than 0.8% wt./wt. of the total lurbinectedin weight. In certain embodiments, the stored formulation does not contain more than 2.0%, 1.5%, or 1.3% (area or wt/wt) total degradation products.

Also provided are methods of storing the lurbinectedin lyophilized formulation and methods of treating SCLC and solid tumors by administration of a lurbinectedin infusion solution prepared from a stored, stable lyophilized lurbinectedin formulation.

The present invention identifies methods of treatment using lurbinectedin alone or in combination with further agents. Where reference is made to a method of treatment the present invention also encompasses lurbinectedin and/or said further agents in the manufacture of a medicament for the treatment of cancer and also lurbinectedin and/or said further agents for use in the treatment of cancers as disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**: X-ray powder diffractogram (XRPD) of Form A of lurbinectedin (Batch R05)

FIG. **2***a*: X-ray powder diffractograms (XRPD) of two batches of Form B of lurbinectedin (Batches 1924128-LT (overlaid) and 1924129-LT)

FIG. **2***b*: X-ray powder diffractograms (XRPD) of Form B of lurbinectedin made by mixing 15 mg Batch 1711182-2 (Form B partly crystalline) and 15 mg Batch P02 (amor-

phous) with 1 ml water. The suspension was stirred at r.t. for 24 hours. The resulting solid was filtered off).

FIG. **3**: TG-FTIR of Form B of lurbinectedin (Batch 1711182-2).

FIG. **4**: DSC of Form B of lurbinectedin (Batch 1711182-2).

FIG. **5**: DVS of Form B of lurbinectedin (Batch P05).

FIG. **6**: Superimposed XRPD patterns of Form B of lurbinectedin in an initial 1:1 mixture of Forms A and B of lurbinectedin, after 6 h of phase equilibration in water and after 24h of phase equilibration in water, from top to bottom. (Mixtures were prepared mixing Form A of lurbinectedin (batch P02) and Form B of lurbinectedin (batch 1711182-2)).

FIG. **7***a*: IR of Form A of lurbinectedin (Batch P04).

FIG. **7***b*: IR of Form B of lurbinectedin (Batch 1711182-2).

FIG. **8**: Scheme of the Faraday cage.

FIG. **9***a*: Electrostatic charge (nC) of different amounts of Form A of lurbinectedin (Batch P04) and Form B of lurbinectedin (Batch 1924129-LT).

FIG. **9***b*: Electrostatic charge (nC) of different amounts of Form A of lurbinectedin (Batch R05) and Form B of lurbinectedin (Batch 1924128-LT).

FIG. **10***a*: Charge density of Form A of lurbinectedin (Batch P04) and Form B of lurbinectedin (Batch 1924129-LT).

FIG. **10***b*: Charge density of Form A of lurbinectedin (Batch R05) and Form B or lurbinectedin (Batch 1924128-LT).

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are methods of for the efficacious treatment of small cell lung cancer (SCLC) based on the administration of lurbinectedin as monotherapy. Also provided are methods of treating solid tumors by administration of a combination of lurbinectedin and irinotecan. Such methods may be carried out by administration of lurbinectedin prepared from stable, lyophilized formulations disclosed herein.

Lurbinectedin

Lurbinectedin is a synthetic alkaloid and an ecteinascidin analog having the following chemical structure:

It is described for example, in U.S. Pat. No. 7,763,615, incorporated by reference herein in its entirety. Lurbinectedin may be prepared according to methods known in the art, for example, the process disclosed in International Application Publication PCT WO 2003/014127, which is incorporated herein by reference.

Any lurbinectedin compound referred to herein is intended to represent hydrates, solvates, amorphous and crystalline or partially crystalline forms, and mixtures thereof when such forms exist in the medium. In addition, lurbinectedin compounds referred to herein may exist in isotopically-labelled forms. All geometric hydrates, solvates, and isotopically labelled forms of the compounds referred to herein, and mixtures thereof, are considered within the scope of the formulations and methodologies of this invention.

In the present application, by "cancer" it is meant to include tumors, neoplasias, and any other malignant disease having as cause malignant tissue or cells.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, or inhibiting the progress of the disease or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above. In particular, the methods of "treatment" or "treating" herein may be used for alleviating one or more symptoms of solid tumors, delaying progression of solid tumors, shrinking tumor size in a solid tumor patient, inhibiting solid tumor growth, prolonging overall survival, prolonging progression free survival, preventing or delaying solid tumor metastasis, reducing (such as eradicating) preexisting solid tumor metastasis, reducing incidence or burden of preexisting solid tumor metastasis, or preventing recurrence of solid tumors.

The term "immunotherapy," as used herein, means therapy that modulates the immune response, including promoting an immune response or blocking inhibition of an immune response, to cancer cells, for example, but not limited to, antibodies, proteins or other agents that bind to a checkpoint inhibitor, such as, CTLA-4, PD-1, PD-L1 and others with like activity that promote immune response to cancer cells. Examples of immunotherapies include, but are not limited to, atezolizumab, nivolumab, pembrolizumab, ipilimumab, cemiplimab, durvalumab, avelumab and the like.

The grades of adverse events, such as neutropenia, thrombocytopenia, hepatotoxicity and other adverse reactions are according to the criteria set forth in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0 (May 28, 2009). Generally the Grades are as follows: Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living, such as food preparation, etc.; Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living, such as dressing, toileting, etc. but not bed ridden; Grade 4: Life-threatening consequences; urgent intervention indicated; Grade 5: Death related to adverse event.

Treatment of SCLC

Embodiments of this invention include methods of treating small cell lung cancer (SCLC), including metastatic SCLC, in a patient suffering therefrom by administering to the patient a therapeutically effective amount of lurbinectedin according to dosing regimen of one or more treatment

cycles using pharmaceutical formulations of lurbinectedin described herein. Lurbinectedin therapy, in certain embodiments, is second line therapy, such that patients have previously been administered, and disease has progressed in response to, therapies such as platinum-containing therapy or platinum-based chemotherapy and/or immune-oncology therapy. Such treatment regimens are preferably administering to the SCLC patient a dose of 2.0 to 3.2 mg/m^2 lurbinectedin, in preferred embodiments at least for an initial dose, 3.2 mg/m^2, by intravenous infusion, preferably over 1 hour, every three weeks (or 21 days), provided that dose may be reduced and/or delayed depending upon the occurrence of adverse events, particularly hematological abnormalities and hepatotoxicity as disclosed herein. In some embodiments, the SCLC patient is administered 3.2 mg/m^2 by intravenous infusion over 60 minutes repeated every 3 weeks until disease progression or unacceptable toxicity (for example, when a patient does not recover to meet criteria for dosing greater than 5 weeks after the prior dose or ceases to tolerate a second reduced dose of 2.0 mg/m^2). In aspects of the invention, treatment results in an overall response rate of greater than 30%, including greater than 35% or 35.2%; progression free survival for a median of 3.5 months, including 2.6 to 4.6 months, or 2.6 months (in resistant patient population (chemotherapy free interval (CTFI) less than 90 days)) to 4.6 months (in sensitive patient populations (CTFI greater than or equal to 90 days)); and overall survival for a median of 9.3 months (resistant patient population (CTFI less than 90 days) of 5.0 months and sensitive patient population (CTFI greater than or equal to 90 days) at 11.9 months).

In various embodiments, the invention provides methods for treating SCLC, including metastatic SCLC, in a patient in need thereof, especially those whose SCLC has progressed after prior therapy such as platinum-containing therapy or platinum-based chemotherapy, immunotherapy, or both, including among others patients who have failed to respond or to respond adequately to prior treatment, those who may have responded to prior treatment but then experienced progression of the disease, and those who may have had such response followed by progression more than once.

In some embodiments, the present disclosure provides methods for treating metastatic SCLC. In some embodiments, the present disclosure provides methods for treating adult patients with metastatic SCLC with disease progression after platinum-based chemotherapy.

SCLC Patients

Patients with SCLC, including metastatic SCLC, who fail to respond or progress through first-line platinum containing chemotherapy and/or immunotherapy are considered to be "refractory." Patients who initially respond to initial or "first-line" chemotherapy comprising platinum agents and then relapse/progress within 90 days (3 months) are considered to be "resistant." Patients who respond to initial treatment but then relapse or whose tumors progress within about 91 to 180 days (3-6 months) after the cessation of first-line therapy with platinum agents are considered sensitive and considered herein to have a "91 to 180 day progressive" SCLC. Patients who respond to initial relapse or whose tumors progress after 180 days are "sensitive"

The lurbinectedin therapy can be second-line therapy wherein the SCLC patient has been previously treated with one or more other chemotherapeutic agents such as carboplatin or cisplatin (platinum-based chemotherapy) and etoposide. In particular, the treatments are suited for SCLC patients who are relapsing or refractory to previous chemotherapy. In some embodiments, the SCLC patient ceased to respond or ceased to respond adequately to prior platinum-containing therapy or had no response to prior platinum-containing therapy. More specifically, lurbinectedin therapy can be used when a SCLC patient is refractory, resistant, or relapsed/progressive, including in certain embodiments, within 0 to 90 days, or within 91 to 180 days, after cessation of first-line platinum-containing chemotherapy, and, optionally, radiation treatment. SCLC patients that progress within 0 to 90 days or within the 91 to 180 day period after cessation of the first-line therapy, as well as patients whose SCLC is refractory to treatment and progress, including within 90 days, 180 days or at any time, or whose SCLC responds to initial treatment and then progresses within 90 days, 180 days or at any time of cessation of initial treatment, can advantageously be treated with lurbinectedin so as to increase one or more of their lengths of progression-free survival, overall survival, or duration of response. In some embodiments, the SCLC patient had a chemotherapy-free interval of at least 90 days, at least 120 days, at least 150 days, or at least 180 days after prior administration of the prior platinum containing therapy. In specific embodiments, the patient had not received platinum-containing therapy in at least 30 days or at least 60 days or at least 90 days prior to administration of lurbinectedin. In some embodiments, the present disclosure provides methods of treating patients with SCLC who have progressed after prior platinum-containing therapy. In some embodiments, the present disclosure provides methods of treating adult patients with metastatic SCLC with disease progression after platinum-based chemotherapy.

The lurbinectedin therapy can also be administered following first-line platinum-based chemotherapy, such as carboplatin or cisplatin and etoposide, in combination with checkpoint inhibitors, such as atezolizumab, pembrolizumab, ipilimumb, durvalumab, or a combination thereof, or following second-line therapy with nivolumab or other immunotherapy, such as atezolizumab, pembrolizumab, ipilimumab or durvalumab. In particular, the treatments are suited for SCLC patients who are relapsing or refractory to prior immunotherapy. For example, in some embodiments, lurbinectedin treatment is suited for SCLC patients who are relapsing or refractory to prior first-line carboplatin/etoposide/atezolizumab combination therapy or second-line immunotherapy with nivolumab. In some embodiments, the SCLC patient ceased to respond or ceased to respond adequately to prior immunotherapy or had no response to prior immunotherapy. More specifically, lurbinectedin therapy can be used when a SCLC patient is refractory, resistant, sensitive or relapsed/progressive within 91 to 180 days, after cessation of first-line platinum-containing chemotherapy in combination with immunotherapy or second-line nivolumab, and, in certain embodiments, the patient has received radiation treatment. SCLC patients that progress after cessation of the first-line immunotherapy (including in combination with platinum-containing therapy) or second-line immunotherapy at any time after therapy (including in certain embodiments within 90 days or within 180 days of treatment), as well as patients whose SCLC is refractory to treatment (has a chemotherapy free interval less than 90 days) and progresses within 180 days, or whose SCLC responds to initial treatment and then progresses within 180 days of cessation of initial treatment, can advantageously be treated with lurbinectedin so as to increase one or more of their progression-free survival, overall survival, or duration of response. In some embodiments, the SCLC patient had, with respect to prior treatment, a chemotherapy-free interval, including immunotherapy, of less than 90 days, and in

other embodiments, the SCLC had a chemotherapy-free interval of at least 90 days, at least 120 days, at least 150 days, or at least 180 days, but in certain embodiments, no more than 120 days, 150 days or 180 days. In specific embodiments, the patient had not received first-line immunotherapy (in combination with platinum-containing therapy) or second-line immunotherapy in at least 30 days or at least 60 days or at least 90 days prior to administration of lurbinectedin.

It is expected that when a treatment disclosed herein is administered to a SCLC patient, including a metastatic SCLC patient, in need of such treatment, said treatment will produce an effect as measured by the extent of the anticancer effect, the (overall) response rate, the time to disease progression, or the survival rate. In one embodiment, the overall response rate is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, or at least 60%. In some embodiments, the overall response rate is at least 11%, or at least 20%, or at least 25%, or at least 30%, or at least 35% for patients with a chemotherapy-free interval of less than 90 days or wherein the overall response rate is at least 30% or at least 40% or at least 45%, or at least 50% or at least 55% for patients with a chemotherapy-free interval of at least 90 days. In some embodiments, the duration of response is at least 5.3 months (from 4.1 months to 6.4 months) or at least 4.7 months (from 2.6 months to 5.6 months) for the resistant patient (chemotherapy-free interval of less than 90 days) or wherein the duration of response is at least 6.2 months (from 3.5 months to 7.3 months) for the sensitive patient with a chemotherapy-free interval of at least 90 days.

In certain embodiments, the SCLC patient treated with lurbinectedin as disclosed herein has a progression free survival of at least 3.5 months (from 2.6 months to 4.3 months), and, for resistant patients, a progression free survival of 2.6 months (from 1.3 months to 3.9 months), and for sensitive patients, a progression free survival of 4.6 months (from 2.8 months to 6.5 months). In other embodiments, the SCLC patient treated with lurbinectedin as disclosed herein as an overall survival of 9.3 months (from 6.3 to 11.8 months), and, for resistant patients, an overall survival of 5.0 months (from 4.1 months to 6.3 months), and for sensitive patients, an overall survival of 11.9 months (from 9.7 months to 16.2 months).

Alternatively, the treatment can be a second-line therapy for SCLC with extensive or limited disease that is refractory to initial chemotherapy or progressive within less than 90 days (3 months) of completing first line, platinum-containing therapy. SCLC patients that progress after cessation of the first-line therapy (including within 30 to 90 days of treatment, but may be at anytime), as well as patients whose SCLC is refractory to treatment and progress within 90 days, or whose SCLC responds to initial treatment and then progress within 90 days of cessation of initial treatment, can advantageously be treated with lurbinectedin so as to increase one or more of their progression-free survival, overall survival, or duration of response. In some embodiments, the SCLC patient had a chemotherapy-free interval for the prior treatment of less than 90 days, such as less than 30 days, less than 60 days, or less than 90 days.

In various embodiments, the SCLC patient is first treated with platinum-based chemotherapy therapy and immunotherapy, wherein the platinum-based chemotherapy and the immunotherapy were either given concurrently or consecutively, followed by administering to the patient an effective amount of lurbinectedin or cycles of lurbinectedin treatment as disclosed herein, including administering 3.2 mg/m^2 every three weeks (or as delayed or reduced in patients exhibiting hematologic toxicity). For example, in some embodiments, a SCLC patient had received prior immunotherapy comprising administering antibodies targeting PD-L1, CTLA-4, or PD-1, wherein the antibodies are selected from atezolizumab, nivolumab, pembrolizumab, ipilimumb, durvalumab, or a combination thereof. In some embodiments, the patient has previously been administered atezolizumab in combination with platinum-containing therapy and etoposide. In some embodiments, the patient has been administered nivolumab. Thus, provided are methods of treating a SCLC patient who has progressed on atezolizumab (including in combination with carboplatin and etoposide) or on nivolumab with lurbinectedin at 3.2 mg/m^2 every three weeks (or as delayed or reduced in patients exhibiting hematologic toxicity).

In some embodiments, the patient administered lurbinectedin is an adult.

Treatment Cycles

Administration of the pharmaceutical compositions comprising lurbinectedin is preferably by intravenous infusion. Infusion times of up to 72 hours can be used, but are preferably between 1 and 24 hours, and generally about 1 hour. Short infusion times which allow treatment to be carried out without an overnight stay in hospital are especially desirable. In a preferred embodiment, lurbinectedin is administered by infusion over 1 hour (60 minutes).

Preferably, the administration of lurbinectedin is performed in cycles. In a preferred administration schedule, an intravenous infusion of lurbinectedin is given to the patient the first day of each cycle and the patient is allowed to recover for the remainder of the cycle. The preferred duration of each cycle is 3 weeks or 21 days. The treatment cycle can, however, be increased or decreased, for example by 1 to 6 days, one week, or two weeks, or longer than 3 weeks, such as 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 or more days depending on patient response to the treatment. In certain embodiments, if the treatment cycle is delayed by more than 2 weeks because the patient has not recovered from an adverse event and does not meet hematological criteria for lurbinectedin treatment, then treatment with lurbinectedin may be discontinued. Administration of lurbinectedin by intravenous infusion during about 1 hour once every 3 weeks is the most preferred administration schedule, although other protocols can be devised as variations. Multiple cycles can be given as needed. Over the course of treatment of SCLC, 1 to 24 doses of lurbinectedin can be administered, with 4 to 8 doses being typically administered, at intervals of about 21 days (three weeks). Intervals of up to six weeks, e.g., 3 to 4 weeks, can be employed if, for example, it is necessary to modify the treatment schedule to reduce or manage side-effects (as discussed in detail below). Over the course of treatment of the cancer, 1 to 24 treatments of lurbinectedin can be administered, with 4 to 8 treatments being typically administered, at intervals of about 21 days (three weeks). In some embodiments, one dose of lurbinectedin is administered per treatment cycle and the patient undergoes at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 treatment cycles. In embodiments, lurbinectedin is administered in 3 week treatment cycles, or as delayed to permit the patient to recover from an adverse event, until disease progression or unacceptable toxicity.

Bioavailability of a drug is defined as the proportion of a drug or other substance that enters the circulation when introduced into the body and so is able to have an active effect. Measures of bioavailability well known in the art include the area under the plasma concentration-time curve

(AUC) and the concentration maximum (Cmax). Cmax is the maximum plasma concentration achieved after drug administration.

Provided herein are methods for lurbinectedin dosing by one or more pharmacokinetic parameters, wherein administration of said dosage is effective to treat resistant, refractory or progressive SCLC. In exemplary embodiments, the one or more pharmacokinetic parameters is peak concentration (Cmax) or area-under-the-curve (AUC). In one embodiment, 3.2 mg/m^2 of lurbinectedin is administered to a SCLC patient in need thereof as a 1-hour infusion, to achieve mean total plasma Cmax within 80% to 125% of about 107 μg/L and mean AUC∞ within 80% to 125% of about 551 μg*h/L. In some embodiments, lurbinectedin is administered to a SCLC patient on a 1 day on and 20 days off cycle (1/20 cycle). In one embodiment, the administration cycle is a 1/20 cycle and the target mean AUC∞ is about 551 μg*h/L. In one embodiment, the administration cycle is a 1120 cycle and the target mean AUC∞ is about 551 μg*h/L±5%, about 551 μg*h/L±10%, about 551 μg*h/L±20%, or about 551 μg*h/L±25%, In a preferred embodiments, the administration cycle is a 1/20 cycle and the target mean AUC∞ is within 80% to 125% of about 551 μg*h/L. In one embodiment, the administration cycle is a 1/20 cycle and the mean target Cmax is about 107 μg/L. In one embodiment, the administration cycle is a 1/20 cycle and the mean target Cmax is about 107 μg/L±5%, about 107 μg/L±10%, about 107 μg/L±20%, or about 107 μg/L±25%. In a preferred embodiments, the administration cycle is a 1/20 cycle and the mean target Cmax is within 80% to 125% of about 107 μg/L.

Renal, hepatic, and hematologic impairment need to be ruled out prior to administration lurbinectedin to a patient afflicted with SCLC. In one embodiment, a patient afflicted with SCLC, determined to have an absolute neutrophil count of at least 1500 cells/mm^3, a platelet count of at least 100,000/mm^3, and, optionally, hemoglobin levels of at least 9 g/dL (with transfusion if necessary), is administered a first dose of about 3.2 mg/m^2 lurbinectedin. In another embodiment, a patient afflicted with SCLC, determined to have a calculated hepatic clearance of greater than 30 mL/min and an AST or ALT less than 3×ULN or bilirubin less than 1.5×ULN, and a calculated creatinine clearance greater than 30 mL/min, is administered a first dose of about 3.2 mg/m^2 lurbinectedin. A second dose of 3.2 mg/m^2 lurbinectedin is administered to the patient about 21 days after the first dose, and further dosing at this level is continued if hematological, renal, and hepatic parameters remain stable. In a particular embodiment, the patient is administered a dose of lurbinectedin, particularly, an initial dose or scheduled dose 3 weeks after a prior dose, at 3.2 mg/m^2, or a reduced dose, if the patient has an absolute neutrophil count of at least 1500 cells/mm^3 and a platelet count of at least 100,000/mm^3. To achieve the preferred dosing, preferably about 3.2 mg/m^2 of lurbinectedin is administered per dose, e.g., per intravenous infusion. Dosing of lurbinectedin can include about 3.2 mg/m^2 lurbinectedin per dose, e.g., per intravenous infusion or a reduced dose thereof as discussed below.

Antiemetic Treatment

Best supportive care for SCLC, including metastatic SCLC, and in adult patients, and solid tumor treatment comprises a number of palliative treatments. For example, in one embodiment of the invention, best supportive care includes one or more, and preferably all, administration of analgesics to control pain, management of constipation, and treatment of dyspnea and treatment of anemia, e.g., by transfusions, so as to maintain hemoglobin levels (i.e., >9 g/dL).

In other embodiments, therapies are administered to specifically prevent and treat or manage nausea and/or vomiting associated with lurbinectedin administration, are set forth below.

Chemotherapeutics differ in their emetogenicity. In the absence of antiemetic prophylaxis, agents associated with >90% risk of emesis are classified as highly emetogenic chemotherapy and those associated with 30%-90% risk of emesis classified as moderately emetogenic chemotherapy.

Aspects include methods of prevention and treatment of lurbinectedin-induced (acute and delayed-phase) nausea and/or vomiting, wherein an effective antiemetic amount of a serotonin antagonist or corticosteroid, or a combination thereof, are administered to the patient prior to administration of lurbinectedin, particularly immediately prior to lurbinectedin administration, in order to reduce the side effects of nausea and vomiting that can accompany administration of lurbinectedin. A preferred embodiment is the treatment of SCLC, including metastatic SCLC in a patient in need thereof, or otherwise reducing the side effects of administering lurbinectedin to a patient, comprising: (1) administering one or more antiemetic agents effective to reduce nausea associated with administration of lurbinectedin to the patient on the day of and prior to administration of lurbinectedin to the patient; and (2) administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion. In certain embodiments, the lurbinectedin is administered as a single agent chemotherapeutic agent and/or is not administered in combination with doxorubicin. In other embodiments, the patient may be administered the anti-emetic therapy on the same day and prior to administration of of 2 mg/m^2 lurbinectedin in combination with 75 mg/m^2 irinotecan and, in certain embodiments, on day 8 of a treatment cycle with a dose of 75 mg/m^2 irinotecan.

In some embodiments, antiemetic agents are given intravenously or orally. If the one or more antiemetic agents are given intravenously, the one or more agents are administered between 30 and 90 minutes before administration of lurbinectedin, or at about 30 minutes, about 45 minutes, about 60 minutes, about 75 minutes, or about 90 minutes, before administration of lurbinectedin, preferably 30 or 60 minutes. If the one or more antiemetic agents are given orally, the one or more agents are administered between 30 to 60 minutes before administration of lurbinectedin, about 3 hours and 9 hours before administration of lurbinectedin, or about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, or about 9 hours before administration of lurbinectedin. In some embodiments, the antiemetic agents consist of a corticosteroid and a serotonin antagonists, wherein the corticosteroid is selected from the group consisting of dexamethasone, hydrocortisone, or methylprednisolone and the serotonin antagonist is selected from a group consisting of ondansetron, granisetron, and palonosetron. The dose of the corticosteroid is or is equivalent to about 4 mg to 20 mg of dexamethasone delivered intravenously, preferably 8 mg delivered intravenously. The dose of the serotonin antagonist is or is equivalent to about 8 mg to 16 mg of ondansetron delivered intravenously, preferably 8 mg delivered intravenously. If given orally, the dose can be increased to a dose equivalent of up to 24 mg of ondansetron. In preferred embodiments, the prophylactic antiemetic agents comprise dexamethasone intravenously administered at 8 mg, ondansetron intravenously administered at 8 mg, or a combination thereof.

In some embodiments, the method further comprises administering one or more antiemetic agents within 2, 3, or 4 days after administration of lurbinectedin to the patient, for example, administered on the same day after lurbinectedin administration, for example, within 2, 3, 4, 5, 6, 7 or 8 hours of lurbinectedin administration and/or on day 1, 2, 3, or 4 after lurbinectedin administration. The one or more antiemetic agents administered after lurbinectedin administration are selected from the group consisting of a corticosteroid, wherein the corticosteroid is selected from dexamethasone, hydrocortisone, and methylprednisolone, a serotonin antagonist, wherein the serotonin antagonist is selected from ondansetron, granisetron, and palonosetron, and metoclopramide. In preferred embodiments, the post-infusion antiemetic treatment is 4 mg dexamethasone (oral), 8 mg ondansetron (oral), or 10 mg metoclopramide (oral or as infusion), or a combination thereof. The metoclopramide may be administered at 8 hour intervals. In some embodiments, post-infusion antiemetic agents are administered intravenously. In some embodiments, the first dose of post-infusion antiemetic agents are given on the evening of, or 1, 2, 3, 4, 5, 6, 7 or 8 hours after lurbinectedin administration and continued for up to 1, 2, 3, or 4 days post infusion. In some embodiments, a corticosteroid, e.g. dexamethasone, is given at a dose equivalent to 4 mg of dexamethasone on the evening after, or 1, 2, 3, 4, 5, 6, 7 or 8 hours after chemotherapy and then twice per day for up to 1, 2, 3, or 4 days. In some embodiments, metoclopramide is administered at a dose of 10 to 20 mg, orally, every 8 hours post-chemotherapy for up to 1, 2, 3, or 4 days. In other embodiments, a serotonin antagonist, e.g. ondansetron, is given orally at a dose equivalent to 8 mg or 16 mg of ondansetron every 12 hours or 24 hours, respectively, for up to 1, 2 or 3 days after lurbinectedin administration.

In some embodiments, the antiemetic prophylaxis and optionally the post-infusion antiemetic treatment is administered to a SCLC patient who is given about 2.0 mg/m^2, about 2.6 mg/m^2, or about 3.2 mg/m^2 of lurbinectedin by intravenous infusion. The antiemetic prophylaxis and optionally the post-infusion antiemetic treatment is administered to a solid tumor patient who is administered 1.0 to 2.0 mg/m^2 lurbinectedin in combination with irinotecan.

Dosage and Dose Reduction

Additional embodiments of the invention include a dose modification in the event of identifying a ≥Grade 2 adverse event (AE) in a SCLC patient, particularly a metastatic SCLC adult patient, upon administration of a first dose of 3.2 mg/m^2 of lurbinectedin (for example, greater than 2 weeks) dose delays beyond the 21 day treatment cycle for lurbinectedin dosing on day 1.

In some embodiments, a lower amount of lurbinectedin is used as compared to the amount generally used for individual therapy. In some embodiments, the same or greater therapeutic benefit is achieved using a smaller amount (e.g., a lower dose or a less frequent dosing schedule) of lurbinectedin than the amount generally used for individual therapy. For example, the use of a smaller amount of lurbinectedin may result in a reduction in the number, severity, frequency, or duration of one or more side-effects associated with lurbinectedin infusion. For example, in preferred embodiments, the first dose modification is a dose reduction from about 3.2 mg/m^2 to about 2.6 mg/m^2 (or 80 to 85% of the initial dose) of lurbinectedin and the second dose modification is a dose reduction from about 2.6 mg/m^2 to about 2.0 mg/m^2 (or 60 to 65% of the initial dose) of lurbinectedin. If after the second dose reduction, the patient experiences an adverse event that would require further dose reduction, then treatment may be stopped. Adverse events which require frequent or prolonged (>2 weeks) dose delays include, but are not limited to, any hematologic toxicity that is Grade 3 or Grade 4, or any Grade 2, Grade 3 or Grade 4 non-hematologic toxicity or adverse reaction, such as hepatotoxicity. In the event of non-hematologic toxicities of Grade 2, Grade 3 or Grade 4, the following cycle is delayed until non-hematologic parameters have improved to Grade 1 or 0. Administration of two doses of lurbinectedin are always spaced apart by at least 21 days.

A treatment cycle is not initiated until hematologic parameters, such as neutrophil count, platelet count, and, optionally, hemoglobin level have improved such that absolute neutrophil count is greater than or equal to 1500 cells/mm^3, and platelet counts are greater than 100,000/mm^3, and, optionally, in certain embodiments hemoglobin levels are greater than or equal to 9 g/dL (with transfusion if necessary). For example, at first occurrence of greater than Grade 3 (severe) non-hematological toxicity, Grade 4 thrombocytopenia (platelet count less than 25,000 cells/mm^3), Grade 3 thrombocytopenia (platelet count less than 50,000 cells/mm^3) with bleeding that requires transfusion, Grade 4 neutropenia (neutrophil count less than 500 cells/mm^3), or of any grade neutropenia (neutrophil count <LLN) that is associated with infection/sepsis or any adverse reaction that requires frequent or prolonged (greater than 2 weeks) dose delay, the lurbinectedin dose is reduced from 3.2 mg/m^2 to 2.6 mg/m^2 (or 80 to 85% of the initial dose) and the next cycle is delayed until the patient's neutrophil count is greater than 1500 cells/mm^3; platelet count is greater than about 100,000/mm^3; and hemoglobin levels are greater than about 9 g/dL. In a certain embodiment, if the identified adverse event consists of isolated Grade 4 neutropenia, the method comprises administration to the patient a dose of G-CSF ("secondary G-CSF prophylaxis") as prophylaxis to manage the isolated Grade 4 neutropenia and then a dose of lurbinectedin that is equal to the previous dose rather than reducing the lurbinectedin dose. If after the first dose reduction, the patient suffers from one of the adverse events that requires a dose reduction (greater than Grade 3 (severe) non-hematological toxicity, Grade 4 thrombocytopenia (platelet count less than 25,000 cells/mm^3), Grade 3 thrombocytopenia (platelet count less than 50,000 cells/mm^3) with bleeding that requires transfusion, Grade 4 neutropenia (neutrophil count less than 500 cells/mm^3), or of any grade neutropenia (neutrophil count <LLN) that is associated with infection/sepsis or any adverse reaction that requires frequent or prolonged (greater than 2 weeks) dose delay), then the subsequent dose 3 weeks later is reduced to 2.0 mg/m^2 (60 to 65% of the initial dose), once the patient has recovered with neutrophils greater than or equal to 1500 cells/mm^3, platelet counts greater or equal to 100,000/mm^3 and hemoglobin levels greater than or equal to 9 g/dL (with transfusion if necessary). After the second dose reduction, the patient again has an adverse reaction which would require a dose reduction, the treatment is terminated. If a dose would be delayed by greater than 2 weeks because the patient has not recovered such that absolute neutrophil count is greater than or equal to 1500 cells/mm^3 and platelet count is greater than or equal to 100,000/mm^2, then treatment may be terminated.

If the identified adverse reaction is not solely isolated Grade 4 neutropenia, the method comprises administering to the patient a reduced dose of lurbinectedin. Administration of two doses of lurbinectedin must be spaced apart by at least 21 days regardless of the dose of lurbinectedin.

A preferred embodiment is the treatment of small cell lung cancer (SCLC), including metastatic SCLC, in a patient in need thereof, comprising: (1) administering a first dose of 3.2 mg/m^2 of lurbinectedin to the patient by intravenous infusion; (2) identifying an adverse reaction in the patient, wherein the adverse reaction is selected from the group consisting of: ≥Grade 3 (severe) non hematological toxicity, Grade 4 thrombocytopenia (Platelet count less than 25,000 cells/mm^3), Grade 3 thrombocytopenia (Platelet count less than 50,000 cells/mm^3) with bleeding that requires transfusion, Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), or any grade neutropenia (Neutrophil count <LLN) that is associated with infection/sepsis or any other of the adverse reactions; and (3) after the adverse reaction is identified and after the patient's neutrophil count is greater than 1500 cells/mm^3; platelet count is greater than about 100,000/mm^3; and hemoglobin levels are greater than about 9 g/dL: (i) if the identified adverse reaction consists of isolated Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), administering to the patient a dose of G-CSF and a dose of lurbinectedin that is equal to the previous dose; or (ii) if the identified adverse reaction is not solely isolated Grade 4 neutropenia, administering to the patient a reduced dose of lurbinectedin, wherein administration of two doses of lurbinectedin are spaced apart by 21 days or 20 to 23 days or at least 18, 19, 20, 21, 22, or 23 days.

In some embodiments, the first dose reduction is 80 to 85% of the first dose after first occurrence of the adverse reaction that it not solely isolated Grade 4 neutropenia or wherein a first reduced dose is 2.6 mg/m^2 after a first occurrence of the adverse reaction that is not solely isolated Grade 4 neutropenia. In some embodiments, a second reduced dose is 60-65% of the first dose after a second occurrence of the adverse reaction that is not solely isolated Grade 4 neutropenia or wherein a second reduced dose is to 2.0 mg/m^2 after a second occurrence of the adverse reaction that is not solely isolated Grade 4 neutropenia, wherein the second reduced is administered to the patient. Administration of lurbinectedin is discontinued after identification of the adverse reaction after administration of the second reduced dose.

Prior to administration of an initial or subsequent dose of lurbinectedin, the patient, including an adult patient, suffering from SCLC, particularly metastatic SCLC, has an absolute neutrophil count of at least 1,500 cells/mm^3 and a platelet count of at least 100,000/mm^3. Accordingly, provided is a method of treating a patient who has an absolute neutrophil count of at least 1,500 cells/mm^3 and a platelet count of at least 100,000 mm^3 for SCLC, including metastatic SCLC by administration of lurbinectedin at a dose of 3.2 mg/m^2 every 3 weeks, subject to dose delays or dose reductions if the patient experiences an adverse event.

Methods are provided for managing hematological toxicity, myleosupressive effects and/or hepatotoxicity that may be associated with lurbinectedin administration in the treatment of SCLC, including metastatic SCLC by dose reduction and/or dose delay. The adverse events that could trigger a dose delay or reduction include Grade 4 or any grade febrile neutropenia (Grade 4 neutropenia is neutrophil count less than 500 cells/mm^3), Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia (Grade 3 thrombocytopenia being 25,000-50,000 platelets/mm^3 and Grade 4 thrombocytopenia is less than 25,000 platelets/mm^3), Grade 2 or greater hepatotoxicity or other adverse reaction. In the case of all of these adverse reactions, the subsequent dose may be delayed until the patient has recovered such that the patient exhibits are less than or equal to Grade 1 neutropenia (greater than 1500 cells/mm^3), have a platelet count of 100,000/mm^3, or hepatotoxicity or the other adverse reaction that is Grade 1 or less. Patients exhibiting Grade 4 neutropenia or any grade febrile neutropenia, Grade 3 with bleeding or Grade 4 thrombocytopenia or Grade 3 or greater hepatotoxicity or other adverse reaction, after recovery, are administered a reduced dose for subsequent treatment cycles. If the prior dose was 3.2 mg/m^2, then the reduced dose is 2.6 mg/m2, and if the prior dose was 2.6 mg/m^2 then the reduced dose is 2.0 mg/m^2 every three weeks. If the patient experiences an adverse event that would indicate a dose reduction after a dose of 2.0 mg/m^2, then treatment may be terminated. For patients exhibiting Grade 4 neutropenia, the subsequent dose, once the patient has recovered, may not be reduced, that is may be the same as the prior dose every three weeks, if the patient is administered G-CSF prophylaxis. For patients exhibiting Grade 2 hepatotoxicity or other adverse reaction, the subsequent dose, after the patient has recovered to Grade 1 or less toxicity, is the same as the prior dose every three weeks.

Accordingly, provided are methods of treating SCLC, including metastatic SCLC, by administering to a patient in need thereof with an absolute neutrophil count of at least 1500 cells/mm^3 and a platelet count of at least 100,000/mm^3, a dose of 3.2 mg/m2 lurbinectedin, preferably by infusion over 60 minutes. In a further embodiment, 21 days after the previous dose, the patient has an absolute neutrophil count of at least 1500 cells/mm^3 and a platelet count of at least 100,000/mm^3 and is administered 3.2 mg/m2 dose of lurbinectedin, preferably by infusion over 60 minutes. In embodiments, the patient is monitored for and has no hepatotoxicity prior to administration of lurbinectedin. Subsequent treatments are administered at 21 day (3 week) intervals to the patient having an absolute neutrophil count of at least 1500 cells/mm^3 and a platelet count of at least 100,000/mm^3.

In certain embodiments, provided are methods of treating SCLC, including metastatic SCLC, in a patient in need thereof by administering lurbinectedin at a dose of 3.2 mg/m^2, including by infusion over 60 minutes, then monitoring the patient for adverse hematological or hepatic reactions. In the event a patient having been administered a dose of 3.2 mg/m^2 lurbinectedin exhibits grade 4 neutropenia (neutrophil count less than 500 cells/mm^3) or any febrile neutropenia, then the subsequent dose of lurbinectedin is not administered until the later of 21 days after the prior dose or when the patient exhibits less than grade 1 neutropenia (at least 1500 cells/mm^3), which may be greater than 21 days past the previous dose, and then either administering lurbinectedin at a reduced dose of 2.6 mg/m^2 every three weeks or administering lurbinectedin at a dose of 3.2 mg/m^2 every three weeks with G-CSF prophylaxis. In the event, a patient having been administered a 3.2 mg/m^2 dose of lurbinectedin exhibits Grade 3 thrombocytopenia (25,000-50,000 platelets/mm^3) with bleeding or Grade 4 thrombocytopenia (less than 25,000 platelets/mm^3), then the subsequent dose of lurbinectedin is not administered until the later of 21 days after the previous dose or when the patient exhibits a platelet count of greater than or equal to 100,000/mm^3 and the subsequent dose is a reduced dose of 2.6 mg/m^2 every three weeks (21 days). In the event, a patient having been administered a 3.2 mg/m^2 dose of lurbinectedin exhibits hepatotoxicity or other adverse reactions that is either Grade 2 or Grade 3 or 4, then the subsequent dose of lurbinectedin is not administered until the later of 21 days after the previous dose or when the patient exhibits less than or equal to Grade 1 hepatotoxicity (or other adverse reaction), and the subse-

quent dose is a dose of 3.2 mg/m^2 every three weeks if the patient had exhibited Grade 2 hepatotoxicity (or Grade 2 of other adverse reaction) and the subsequent dose is a reduced dose of a reduced dose of 2.6 mg/m^2 every three weeks (21 days) if the patient had exhibited Grade 3 or 4 hepatotoxicity or other adverse reaction. If, after dose reduction, the patient exhibits one of Grade 4 neutropenia, or any grade febrile neutropenia, Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia, or hepatotoxicity or other adverse reaction at Grade 3 or 4, then the subsequent dose is not administered until the later of 21 days or when the patient has recovered as detailed above and then administered a further reduced dose of 2 mg/m2 lurbinectedin every three weeks or, in the case of Grade 4 neutropenia, is administered the same dose or lurbinectedin as the prior dose with G-CSF prophylaxis. If the patient ceases to tolerate (that is exhibits, after lurbinectedin administration, one of Grade 4 neutropenia, or any grade febrile neutropenia, Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia, or hepatotoxicity or other adverse reaction at Grade 3 or 4) at a dose of 2 mg/m^2 lurbinectedin or if delay in administration is greater than 2 weeks past the scheduled dose (at 21 days after the prior dose), then treatment is discontinued.

Co-administration with a strong or a moderate CYP3A inhibitor increases lurbinectedin systemic exposure and thus, patients taking a CYP3A inhibitor are either taken off of the CYP3A inhibitor or advised to stop taking the CYP3A inhibitor, or, alternatively, the dose of lurbinectedin is reduced, for example, from a dose of 3.2 mg/m2 or a dose of 2.6 mg/m^2 or 2.0 mg/m^2. Examples of CYP3A inhibitors include clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal and grapefruit. Accordingly, provided are methods of treating patients for SCLC, particularly, metastatic SCLC, or solid tumors by administration of a dose of lurbinectedin, including 3.2 mg/m^2 lurbinectedin every 3 weeks where the patient is not taking a CYP3A inhibitor (and may have been taken off the CYP3A inhibitor in advance of lurbinectedin dosing to avoid drug interaction) or a dose less than 3.2 mg/m^2, including 2.6 mg/m^2 or 2.0 mg/m^2) if the patient is also taking a CYP3A inhibitor.

Coadministration with a strong CYP3A inducer decreases lurbinectedin systemic exposure which may reduce efficacy. Examples of CYP3A inducers include phenobarbital, phenytoin, rifampicin, St. John's Wort and glucocorticoids. Accordingly, provided are methods of treating patients for SCLC, particularly, metastatic SCLC, or solid tumors by administration of a dose of lurbinectedin, including 3.2 mg/m2 lurbinectedin every 3 weeks, where the patient is not taking a strong or moderate CYP3A inducer.

Combination Therapy for Solid Tumors

In other embodiments, the invention is directed to the combination of lurbinectedin with a topoisomerase I and/or II inhibitor in the treatment of cancer, and more particularly in the treatment of solid tumors, particularly endometrial cancer, SCLC, soft tissue sarcoma (including Ewing and synovial sarcoma), glioblastoma (including supratentorial or intratentorial tumors), pancreatic adenocarcinoma, mesothelioma, colorectal carcinoma, and epithelial ovarian cancer. In preferred embodiments, the solid tumor is endometrial cancer, SCLC, soft tissue sarcoma (including Ewing and synovial sarcoma) or glioblastoma. In some embodiments, the method of treating patients with solid tumors comprises administering lurbinectedin at a dose of 1 to 2.5 mg/m^2 in combination with other anticancer agents, such as a topoisomerase inhibitor selected from SN-38 or irinotecan, wherein the lurbinectedin is administered at a dose of 1 to 2.5 mg/m^2, particularly 2.0 mg/m^2, and wherein the topoisomerase inhibitor is administered at a dose equivalent to 50 to 75 mg of irinotecan/m^2. The chemotherapeutic group of topoisomerase I and/or II inhibitors includes, but is not limited to topotecan, SN-38, irinotecan, camptothecin, rubitecan, etoposide, amsacrine and teniposide. Particularly preferred is the combination of lurbinectedin with irinotecan in the treatment of cancer, particularly, solid tumors, and more particularly in the treatment of endometrial cancer, SCLC, soft tissue sarcoma (including, Ewing and synovial sarcoma), glioblastoma, pancreatic adenocarcinoma, mesothelioma, colorectal carcinoma, and epithelial ovarian cancer.

In some embodiments, lurbinectedin is administered at a dose of 1, 1.5, 2, or 2.4 mg/m^2 and the topoisomerase inhibitor is administered at a dose equivalent to 50 to 75 mg/m^2 of irinotecan. In preferred embodiments, lurbinectedin is administered at a dose of 2 mg/m^2 and irinotecan is administered at a dose of 75 mg/m^2. G-CSF is administered to the patient with the combination.

In some embodiments, lurbinectedin and the topoisomerase inhibitor are administered on day one of a treatment cycle. In some embodiments, the method further comprises administering G-CSF to the patient to manage the myelosuppressive effects of the therapy. In another embodiment, the topoisomerase inhibitor is further administered to the patient on day 7, 8, 9, or 10 of the treatment cycle. In some embodiments, the treatment cycle is a 18, 19, 20, 21, 22, 23, 24, or 25 day cycle.

In particular embodiments, provided are methods of treating solid tumors in a patient in need thereof by administration on day 1 of a treatment cycle a dose of lurbinectedin, particularly, a dose of 2.0 mg/m^2 and a dose of irinotecan at a dose of 75 mg/m2 and then on day 8 of the treatment cycle a dose of 75 mg/m^2 irinotecan, with G-CSF administration to manage myelosuppressive effects of the therapy. The treatment cycle may be a 3 week (21 day) cycle, such that a subsequent treatment cycle is initiated at day 22. In certain embodiments, patients who exhibit hematologic toxicity (including grade 3-4 adverse event) after the combination dose administered on day 1 of the treatment cycle may not be administered the irinotecan dose on day 8 (or any other time in that treatment cycle) or may be administered a reduced dose of irinotecan on day 8 of the treatment cycle or at any other time during the treatment cycle. The treatment may include multiple treatment cycles until disease progression or unacceptable toxicity. In particular, the patient may be administered 1, 2, 3, 4, 5 or more, including 8, 10, 12, 15, 20 or 30 or more cycles of the combination treatment.

In particular embodiments, the combination treatment method results in reduction in tumor size, a median progression free survival of at least 4.3 months (particularly for SCLC), of at least 7.1 months (particularly, for endometrial cancer), of at least 2.6 months (particularly, for soft tissue sarcoma), or of at least 1.4 months (particularly, for glioblastoma).

In one embodiment, the method further comprises administering one or more antiemetic agents on day one of a treatment cycle (as described in detail above for treatment of SCLC with lurbinectedin) and post-infusion anti-emetic treatment as described herein for treatment of SCLC.

Pharmaceutical Compositions and Methods of Preparation

Pharmaceutical compositions of lurbinectedin that can be used include solutions, lyophilized compositions, etc., with suitable excipients for intravenous administration.

In one aspect, lurbinectedin is supplied and stored as a stable and sterile lyophilized product comprising lurbinectedin, a buffer derived from an organic acid (e.g. an organic carboxylic acid buffer), a disaccharide, and a sufficient base to provide an appropriate pH for injection when the composition is reconstituted in an appropriate solvent.

In some embodiments, the organic carboxylic acid buffer is derived from an organic acid selected from the group consisting of lactic acid, butyric acid, propionic acid, acetic acid, succinic acid, citric acid, ascorbic acid, tartaric acid, malic acid, maleic acid, fumaric acid, glutamic acid, aspartic acid, gluconic acid, and α-ketoglutaric. In some embodiments, the organic carboxylic acid buffer is derived from an organic acid selected from lactic acid or succinic acid. In some embodiments, the organic carboxylic acid buffer is derived from lactic acid. In certain embodiments, the buffer is not a phosphate buffer.

In some embodiments, the disaccharide is selected from the group consisting of sucrose, trehalose or lactose, or a combination thereof. In some embodiments, the disaccharide is sucrose.

In some embodiments, the base is selected from the group consisting of carbonates, hydroxides, hydrogen carbonates and ammonium salts. Particularly preferred bases are sodium carbonate, potassium carbonate, calcium carbonate, NH_4OH, sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium hydrogen carbonate, potassium hydrogen carbonate and calcium hydrogen carbonate. In some embodiments, the base is sodium hydroxide.

In some embodiments, the pH of the reconstituted lyophilized composition is about 4. In some embodiments, the pH of the reconstituted lyophilized composition is about from about 3 to about 5. In some embodiments, the pH of the reconstituted lyophilized composition is about from about 3.5 to about 4.5. In some embodiments, the pH of the reconstituted lyophilized composition is 3.8 to 4.1.

In some embodiments, the stable lyophilized product comprises lurbinectedin; lactic acid; sodium hydroxide and sucrose and the pH of the reconstituted lyophilized composition is 3.8 to 4.1. In some embodiments, the stable lyophilized product comprises 4 mg lurbinectedin; 22.1 mg lactic acid; 5.1 mg sodium hydroxide (or, including, about 0.25 mmol lactate); and 800 mg sucrose. In some embodiments, the stable lyophilized product consists essentially of 4 mg lurbinectedin; 22.1 mg lactic acid; 5.1 mg sodium hydroxide (or, including, about 0.25 mmol lactate); and 800 mg sucrose.

The lurbinectedin-containing formulations of this invention can be made by freeze-drying a composition of this invention in the form of a buffered bulk solution including lurbinectedin, a buffer derived from an organic acid, such as a lactate buffer or a succinate buffer, and a disaccharide. The disaccharide is preferably sucrose. Usually the bulk solution will be buffered, for example to a pH of about 3 to 5, preferably about 3.5 to 4.5, more preferably pH 3.8 to 4.1. The preferred buffering agent is a sodium lactate buffer. In preferred embodiments, the lactate buffer comprises lactic acid and a base, preferably an inorganic, pharmaceutically accepted base such as sodium hydroxide.

As such, in embodiments of the present invention there is provided a buffered lyophilized composition including lurbinectedin, a buffer derived from an organic acid, such as a lactate buffer or a succinate buffer, and a disaccharide; wherein the buffer is configured such that upon reconstitution the pH of the reconstituted lyophilized composition is from about 3 to about 5, about 3.5 to about 4.5, or 3.8 to 4.1

The present invention has identified methodologies that allow for complete dissolution of lurbinectedin in desired buffers whilst minimizing impurity generation. In embodiments, the use of an organic acid buffer allows for direct dissolution of lurbinectedin in the organic acid buffer (preferably at pH about 1 to 5, about 2 to 4.5, about 3 to 4.5 or about 4) followed by addition of bulking agent such as disaccharide, preferably sucrose. Such a formulation strategy enables direct dissolution into the bulk formulation and avoids the need for a pre-dissolution step. In an embodiment, there is provided direct dissolution of lurbinectedin, comprising dissolving lurbinectedin in an organic acid buffer (preferably at pH about 1 to 5, about 2 to 4.5, about 3 to 4.5 or about 4), followed by addition of bulking agent such as disaccharide, preferably sucrose, to form a bulk solution. The bulk solution may undergo sterilizing filtration. The bulk solution may then be filled in vials according to the desired dose. The bulk solution in vials may then be lyophilized to form a lyophilized buffered lurbinectedin formulation. The lyophilized formulation may then be reconstituted to form a reconstituted solution. The reconstituted solution may be diluted to form an injection solution. Preferably, with direct dissolution the lurbinectedin is amorphous or substantially amorphous.

As explained herein, lurbinectedin has limited aqueous solubility. It was found that lurbinectedin solubility is improved in the bulk solution by first forming a concentrated pre-solution of the lurbinectedin in a buffer derived from an organic acid, for example lactic acid, succinic acid, citric acid, or acetic acid which is further diluted with water for injection. A disaccharide is then dissolved in an aqueous solution containing a basic ingredient, for example an aqueous sodium hydroxide solution, and upon adjusting the pH to a set value, the pre-solution of the lurbinectedin and the buffer solution containing a disaccharide are mixed to obtain the lurbinectedin bulk solution in an organic buffer, pH=4 containing a disaccharide (for example, sucrose). Following this process, the lurbinectedin concentration can be increased in the bulk solution enabling the vial fill volume to be reduced. In these embodiments of the present invention, the fill volume is usually reduced by about 80% with respect to that of the conventional fill volume. By way of illustration, but not as a limitation, embodiments of this invention provide a fill volume of 1 mg lurbinectedin in 2 ml solution within a 10 ml vial; or 4 mg lurbinectedin in 8 ml solution within a 30 ml vial. The fill volume can optionally be reduced further in other embodiments of this invention by increasing the lurbinectedin concentration.

Provided are processes useful for improving the solubility of lurbinectedin in the bulking solution that comprise dissolving lurbinectedin in lactic acid, for example 0.31M lactic acid (25 mg/mL), and subsequent dilution of the solution with water for injection to yield a lurbinectedin concentrated solution in 0.1M lactic acid, mixing the solution containing pre-dissolved lurbinectedin with a buffer salt solution comprising sodium lactate buffer and a disaccharide, and, optionally, adjusting the pH. In some illustrative, but not limiting, embodiments of this invention, pH adjustment is accomplished with a lactate buffer.

Illustrative embodiments of bulk solution for freeze drying according to the present invention are provided by a solution of lurbinectedin buffered at pH 4 with sodium hydroxide and lactic acid with sucrose as bulking agent.

An illustrative embodiment of the methodology according to this invention provides as follows: lurbinectedin is dissolved in 0.31M lactic acid, pH ~3 and subsequently diluted with water for injection to yield a lurbinectedin concentrated

solution of 8.3 mg/mL lurbinectedin in 0.1M lactic acid, pH ~3. Sodium lactate buffer salt solution is prepared by mixing 0.31M lactic acid solution with 0.01M sodium hydroxide solution to create a 0.05M lactate buffer salt solution. Sucrose is then added to the sodium lactate buffer salt solution. The 0.05M lactate buffer salt solution containing sucrose is diluted with water for injection to yield a 0.04M sodium lactate buffer, pH~4.2 containing 17% sucrose. Both solutions, 8.3 mg/mL lurbinectedin in 0.1M lactic acid, pH ~3 and 0.04M sodium lactate buffer, pH~4.2 containing 17% sucrose are then mixed. Dissolution is visually checked at all steps before continuing, and dissolution is considered complete when it is so appreciated visually The pH of the solution is checked and adjusted to a value in the range from about 1 to about 5, more preferably in the range from about 2 to about 4.5, even more preferably in the range from about 3 to about 4.5, and most preferably to a pH of about 4.0 by slow addition of a suitable acid or base. A preferred embodiment of such acid is lactic acid, in which case a preferred concentration is about 0.1M. A suitable base is optionally added for pH control. A preferred embodiment of such base is sodium hydroxide, preferably in solution, in which case a preferred concentration is about 0.1M. The volume is finally adjusted by addition of a suitable, biocompatible fluid, preferably water for injection. The resulting bulk solution preferably comprises 0.5 mg lurbinectedin in 0.03M sodium lactate buffer, pH=4, with 10% (w/v) sucrose. The bulk solution is then filled in vials according to the desired dose.

In embodiments, the lurbinectedin to be dissolved is at least partially crystalline. The lurbinectedin to be dissolved may be in the solid state form(s) described herein. Crystalline lurbinectedin (including partially crystalline) lurbinectedin has been found to be less soluble than amorphous lurbinectedin. By way of example, while the direct dissolution of amorphous lurbinectedin at 0.5 mg/mL in 0.03 M sodium lactate buffer pH 4 was completed in approximately 30 minutes, partly crystalline lurbinectedin reached only 60-70% of the target concentration in 2 hours, meaning that it had much slower dissolution kinetics.

It has been found that decreasing the pH accelerates the dissolution kinetics of partly crystalline lurbinectedin. As such, in embodiments, a concentrated lurbinectedin solution is prepared in organic acid before addition of other excipients. In preferred embodiments, the organic acid has a pH less than 4, preferably less than 3.5, more preferably less than 3, or around 3. The maximum solubility of lurbinectedin was investigated in different molarities of the organic acid lactic acid. Solubility was high and increased linearly ranging from 7.2 mg/ml for 0.05M lactic acid to 90.4 mg/ml for 0.5M lactic acid. In a preferred embodiment, lurbinectedin is dissolved in an organic acid with a molarity of around 0.1M to 0.5M, preferably around 0.2M to 0.4M, more preferably around 0.3M organic acid. An exemplary molarity is 0.31M organic acid.

Lurbinectedin may be pre-dissolved in high concentration organic acid. In a preferred embodiment, the pre-dissolution step is at least 30 minutes, at least 60 minutes or at least 90 minutes, between 30-90 minutes, between 60-90 minutes, between 60-70 minutes or around 60 minutes. Following dissolution, the pre-dissolution solution can be diluted to form the required concentration of, for example 8.3 mg/ml. Dilution may involve ×1, ×2, ×3 or more dilutions with WFI to obtain the target concentration. In embodiments, dilutions are carried out to achieve the desired concentration at appropriate molarity. By way of example, ×3 dilutions to add 2× the initial volume of organic acid may achieve 8.3 mg/mL in 0.1M organic acid (for example lactic acid).

During manufacture, there may be limited volume capacity for the dissolution step, and therefore lurbinectedin dissolution is advantageously achieved with limited organic acid. As such, using high molarity organic acid can achieve a high lurbinectedin concentration in a limited organic acid volume.

In embodiments, a multi-step compounding strategy is used to prepare lurbinectedin. Step 1 is the pre-dissolution step described above, for example: pre-dissolving partly crystalline lurbinectedin in lactic acid 0.31M at 25 mg/mL and diluting 3× with WFI to obtain the concentrated solution at 8.3 mg/mL in 0.1M lactic acid. To avoid precipitation of lurbinectedin, the remaining excipients should have acid pH when added to the compounding formulation. It has been found that the high concentration lurbinectedin solution can be mixed with a buffer solution at pH of 5.6 or less, for example between 4 to 5.6 or 4.2 to 5.6 without precipitation of lurbinectedin. As such, in Step 2, an organic buffer solution containing the bulking agent (eg disaccharide) may be prepared at suitable pH. By way of example, this may comprise the preparation of a 0.04 M sodium lactate buffer at pH of around 4.2 containing sucrose. In step 3, the solutions from step 1 and step 2 are combined to form the final bulk solution. The final bulk solution may be adjusted with WFI to achieve the final target weight. By way of example, in step 3, the 8.3 mg/mL lurbinectedin concentrated solution in 0.1M lactic acid with pH=3 is diluted with 0.04M sodium lactate buffer pH=4.2 containing sucrose. The final bulk solution composition after adjustment of WFI to final weight may be, by way of example, 0.5 mg/mL lurbinectedin in 0.03M sodium lactate buffer pH=4+10% (w/v) sucrose. The present invention therefore identifies a compounding strategy to formulate partially crystalline lurbinectedin.

In one embodiment, the lyophilized composition comprises or consists of 4 mg of lurbinectedin, 800 mg of sucrose, 22.1 mg of lactic acid and 5.1 mg of sodium hydroxide. In some embodiments, the weight ratio in the lyophilized composition is between 0.4% and 0.6% (w/w) of active compound, 96% to 98% (w/w) of sucrose, 2% to 3% (w/w) of lactic acid, and 0.5% to 0.7% (w/w) sodium hydroxide. In preferred embodiments, the weight ratio in the lyophilized composition is 0.5% (w/w) active compound, 96.2% (w/w) sucrose, 2.7% (w/w) lactic acid, and 0.6% (w/w) sodium hydroxide. The lyophilized formulation contains about 0.25 mmol of lactate ion for 4 mg of lurbinectedin. When reconstituted to 8 ml in the vial, the resulting solution is 0.5 mg/ml lurbinectedin, 0.03M sodium lactate buffer, 10% w/v sucrose at about pH 4.0 (range of pH 3.5 to 4.5, preferably 3.8 to 4.5).

The lyophilized material is usually present in a vial which contains a specified amount of lurbinectedin. Preferably the lyophilized composition of lurbinectedin is provided in a 30 mL vial. The specified amount of lurbinectedin in a lyophilized composition can be from between 0.2 to 5 mg, or about 1 mg, about 2 mg, about 3 mg, or about 4 mg. The specified amount of lurbinectedin in a lyophilized composition is preferably 4 mg. In lyophilized embodiments, the composition contains between 0.4% and 0.6% by weight of lurbinectedin, preferably it is 0.5%.

It is necessary to ensure the lurbinectedin is sterile and is aseptically filled into vials. This is critical for parenteral drugs. According to embodiments of the present invention, terminal sterilization by heat or gamma irradiation are not used to avoid degradation of lurbinectedin. Instead, according to embodiments of the present invention, a sterilization filtration of the bulk lurbinectedin solution is carried out

before aseptic vial filling. In embodiments, the filter may be filters such as PVDF or PES. In embodiments the filter may be a 0.2 μm filter.

Storage of Pharmaceutical Lurbinectedin Formulations

Embodiments of this invention also provide a method of storing a lyophilized lurbinectedin composition. It is necessary to ensure the lurbinectedin is stable during at least 24 months. The lurbinectedin lyophilized formulations are storage stable such that after prolonged storage at 5° C.±3° C., the lurbinectedin retains its therapeutic effectiveness and exhibits minimal chemical degradation (e.g., degradation is minimized and within acceptable tolerance; for example, the impurity and degradation products profile of the lurbinectedin, amount of each impurity and degradation product, lurbinectedin content, as determined by HPLC analysis, are substantially the same before and after prolonged storage).

In one aspect, the lyophilized lurbinectedin compositions of the present disclosure minimize the amount of a lurbinectedin degradation product resulting from deacetylation of lurbinectedin ("Impurity D") (having a relative retention time of 0.87 to 0.88 by commercial HPLC assay) when the composition is stored for prolonged times (e.g., at least 24 months). In some embodiments, the amount of impurity D present is less than 0.3%, 0.4%, 0.5%, 0.6%, 0.7% or 0.8% wt/wt of the total lurbinectedin weight in the formulation after prolonged storage at 5° C.±3° C. Impurity B, D and G have the following structures:

B

D

-continued

G

In a preferred embodiment the method of storing a lyophilized lurbinectedin composition comprises storing a lyophilized composition comprising 4 mg lurbinectedin; lactate buffer; and a disaccharide at a temperature of 5° C.±3° C. for at least 24 months, wherein the lyophilized composition is formulated such that reconstitution with 8 mL of water will yield a solution having a pH of 3.5 to 4.5 and a lurbinectedin concentration of 0.5 mg/ml and wherein after the at least 24 months storage, the amount of Impurity D present in the composition is not more than 0.8% wt./wt. of the total lurbinectedin weight. In some embodiments, the lyophilized lurbinectedin composition is stored at a temperature of 5° C.±3° C. for, or for at least, 24 months, 30 months, 36 months, 42 months, 48 months or 60 months, wherein after 24 months, 30 months, 36 months, 42 months, 48 months or 60 months of storage, the amount of a lurbinectedin degradation product Impurity D present in the composition is not more than 0.8% wt./wt. of the total lurbinectedin weight. In some embodiments, the amount of Impurity D present in the composition after storage at about 5° C.±3° C. for 60 months is not more than 0.8% wt./wt, or is less than 0.7% wt./wt., less than 0.6% wt./wt., less than 0.5% wt./wt., or less than 0.4% wt./wt. of the total lurbinectedin weight. In one embodiment, the amount of lurbinectedin degradation product Impurity D present in the composition is not more than 0.8% wt./wt. of the total lurbinectedin weight after at least 36 months of storage. In some embodiments, the total % impurities and degradation products (as % area) after storage at about 5° C.±3° C. for 24 months, 30 months or 36 months is not more than 0.6%, 0.7%, 0.8% 0.9% or 1.0% (% area). In some embodiments, the initial amount of Impurity D present in the composition (i.e., one day of lyophilization) is less than 0.4% wt./wt. of the total lurbinectedin weight. In some embodiments, the initial amount of Impurity D present in the composition is at least 0.05% wt./wt. or at least 0.1% wt./wt. of the total lurbinectedin weight. In some embodiments, the initial amount of Impurity D present in the composition is not more than 0.8% wt./wt., not more than 0.5% wt./wt. or not more than 0.1% wt./wt. of the total lurbinectedin weight. In some embodiments, after storage at about 5° C.±3° C. for 24 months, 30 months, 36 months, 48 months or 60 months the stable, lyophilized, lurbinectedin formulation shows negligible degradation of lurbinectedin assay content, for example, a decrease in the amount of lurbinectedin as compared to the amount of lurbinectedin within 1.0%, 0.5%,

or 0.2% of the total amount of lurbinectedin as compared to the bulk solution from which the formulation is made.

Accordingly, provided are stable, lyophilized lurbinectedin formulations comprising a buffer derived from an organic acid (e.g., an organic carboxylic acid buffer, such as, succinate, citrate, acetate or lactate buffer) at a molar ratio of buffer to lurbinectedin of about 48, including the molar ratio 52 to 46, 54 to 44, 50 to 48, 52 to 58, or the molar ratio 51 to 48, and sucrose as a bulking agent, which, when reconstituted in 8 mL of water has a pH of about 4.0, including pH 3.5-4.5 or pH 3.8-4.1, which comprises Impurity D at no more than 0.8% wt/wt, or is less than 0.7% wt./wt., less than 0.6% wt./wt., less than 0.5% wt./wt., or less than 0.4% wt./wt of the total weight of lurbinectedin and, preferably, the Impurity D does not increase to more than 0.8% wt/wt of the total weight of lurbinectedin after storage at 5° C.±3° C. for 12 months, 24 months, 30 months, 36 months, 48 months or 60 months; or storage at 25° C./60% RH for 3 months, 6 months, 9 months, 12 months or 18 months; or 40° C./60% RH for 1 month, 3 months, 6 months or 12 months. In these embodiments, the lurbinectedin is 95 to 105%, or 97 to 103% of 4 mg lurbinectedin or of the amount of lurbinectedin by assay at day 1.

Also provided are methods of reducing lurbinectedin degradation in a lyophilized formulation by incorporating a buffer derived from an organic acid, preferably a lactate or succinate buffer, in the lyophilized formulation with the lurbinectedin such that the Impurity D in the formulation does not exceed 0.5% wt/wt, 0.6% wt/wt, 0.7% wt/wt or 0.8% wt/wt of the total lurbinectedin weight after storage at 5° C.±3° C. for 12 months, 24 months, 30 months, 36 months, 48 months or 60 months; or storage at 25° C./60% RH for 3 months, 6 months, 9 months, 12 months or 18 months; or 40° C./60% RH for 1 month, 3 months, 6 months or 12 months, particularly when the amount of lurbinectedin is 95 to 105%, or 97 to 103% of 4 mg lurbinectedin or of the amount of lurbinectedin by assay at day 1.

Other impurities or degradation products that may be minimized in the storage of the stable, lyophilized lurbinectedin formulation may be the degradation products with the following relative retention time on the commercial HPLC method: rrt 0.68, rrt 0.80, rrt 1.11 (Impurity G), and rrt 1.12.

In further embodiments, the total residual water content for the lyophilized lurbinectedin formulation is not more than 3% (w/w), preferably not more than 1.5% (w/w), preferably not more than 1% (w/w), is preferably between 0.5-0.7% (w/w).

Embodiments of this invention further provide a pharmaceutical product comprising a vial containing a lyophilized lurbinectedin composition. In a preferred embodiment, the pharmaceutical product comprises a vial containing a lyophilized composition consisting of 4 mg lurbinectedin; 22.1 mg lactic acid; 5.1 mg sodium hydroxide (or, including, about 0.25 mmol lactate); and 800 mg sucrose; and a label affixed to the vial comprising an expiration date that is at least 48 months from the date of manufacture. In some embodiments, the label affixed to the vial comprises an expiration date that is at least 24 months, at least 30 months, at least 36 months, at least 42 months, or at least 48 months from the date of manufacture. In some embodiments, the vial has a size of 30 mL to 50 mL, such as 30 mL, 35 mL, 40 mL, 45 mL, or 50 mL. In a preferred embodiment, the vial is a 30 mL vial. A vial size of 30 mL is optimized to overcome limitations of larger vial sizes which lead to production capacity reduction due to reduced freeze dryer capacity and also adequate extractable volumes due to size. A vial size of 30 mL overcomes both of these limitations.

Lurbinectedin Solid State Forms and Uses Thereof

In embodiments according to the present invention, the pre-lyophilized lurbinectedin comprises at least some crystalline material. The pre-lyophilized lurbinectedin may be partially crystalline. Using partly crystalline pre-lyophilized lurbinectedin leads to advantages, including better control of impurities and/or degradation products.

The present invention has identified a novel solid state form of lurbinectedin that is easier to handle under typical pharmaceutical processing conditions than the known amorphous form, hereinafter Form A. The amorphous Form A can be obtained by the process described in WO 03/014127. Form A becomes electrostatically charged during its manipulation causing production problems. Therefore there is the need to obtain a form of lurbinectedin that is easier to handle under typical pharmaceutical processing conditions.

In embodiments according to the present invention there is provided a novel solid state form of lurbinectedin, in the following named Form B of lurbinectedin. Form B shows advantageous physical properties compared to the known Form A. For example, Form B shows improved triboelectric properties over existing known forms of lurbinectedin. Triboelectric charging is the process by which certain materials become electrically charged after contact with a different material through friction. In many pharmaceutical operations uncontrolled static electricity can cause serious production problems. These problems may include product contamination, product loss, cleaning and safety, and the problems can be exacerbated in a nanomolar cytotoxic drug such as lurbinectedin. Even in the most stringent cleanrooms, static charge attracts particulates from people, processes and equipment, so it is important to take appropriate measures to ensure it is kept to a minimum.

Form B shows a lower average charge density over the known form of lurbinectedin. Form B also shows a narrower dispersion of charge density over the known form of lurbinectedin. Form B of lurbinectedin has lower residual solvents over the known form of lurbinectedin. Form B also has a simplified impurity profile compared to the known form of lurbinectedin. These characteristics make it especially suitable for the preparation of a medicament. The pre-lyophilisation lurbinectedin may comprise Form B. The amount of Form B may vary and can be considered a crystalline mixture (partially crystalline). In other embodiments, the crystalline mixture may comprise other crystalline lurbinectedin (e.g. non form-B crystalline lurbinectedin).

In further embodiments, the present invention relates to a process for preparing Form B of lurbinectedin comprising: a) preparing an acidic aqueous solution comprising lurbinectedin or a protonated form thereof; and b) basifying the resulting acid aqueous solution with a base or a basic buffer to precipitate Form B of lurbinectedin. The Form B of lurbinectedin may be subsequently converted into a different physical form, preferably an amorphous form. The Form B may be used in the manufacturing process to prepare lyophilized bulk product.

In further embodiments, the present invention relates to pharmaceutical compositions comprising Form B of lurbinectedin and a pharmaceutically acceptable carrier. Such compositions may be pre-lyophilisation compositions.

In further embodiments, the present invention relates to a pharmaceutical composition comprising lurbinectedin manufactured using Form B of lurbinectedin and a pharmaceutically acceptable carrier. The pharmaceutical composition may no longer contain any Form B lurbinectedin, however the composition manufacturing process utilized at

least some Form B in one or more steps. In further embodiments, the present invention relates to Form B of lurbinectedin for use in the manufacture of a pharmaceutical composition comprising lurbinectedin. In yet further embodiments, the present invention relates to the use of Form B of lurbinectedin in the manufacture of a pharmaceutical composition comprising lurbinectedin. In yet further embodiments, the present invention relates to Form B of lurbinectedin for use as a medicament. Again, Form B may no longer be present in the final composition but may be utilized during manufacturing.

In further embodiments, the present invention relates to compositions comprising Form B of lurbinectedin and a pharmaceutically acceptable carrier for use as a medicament. In further embodiments, the present invention relates to Form B of lurbinectedin for use as a medicament for the treatment of cancer. In further embodiments, the present invention relates to compositions comprising Form B of lurbinectedin and a pharmaceutically acceptable carrier for use as a medicament for the treatment of cancer.

In further embodiments, the present invention relates to processes for the manufacture of pharmaceutical compositions comprising lurbinectedin that employ Form B of lurbinectedin, preferably as starting material.

In further embodiments, the present invention is also directed to the use of Form B of lurbinectedin, or the use of a pharmaceutical composition comprising Form B of lurbinectedin and a pharmaceutically acceptable carrier in the treatment of cancer. In further embodiments, the present invention is also directed to the use of Form B of lurbinectedin, or the use of a pharmaceutical composition comprising Form B of lurbinectedin and a pharmaceutically acceptable carrier in the preparation of a medicament for the treatment of cancer. Other embodiments of the invention are methods of treatment, and Form B of lurbinectedin for use in these methods. Therefore, the present invention further provides a method of treating any mammal, notably a human, affected by cancer which comprises administering to the affected individual a therapeutically effective amount of Form B of lurbinectedin or of a pharmaceutical composition comprising Form B of lurbinectedin and a pharmaceutically acceptable carrier; or a pharmaceutical composition made from a process utilizing Form B of lurbinectedin.

The present invention further provides a method of treating any mammal, notably a human, affected by cancer which comprises administering to the affected individual a therapeutically effective amount of lurbinectedin which has been manufactured via Form B of lurbinectedin. The present invention further provides a method of treating any mammal, notably a human, affected by cancer which comprises administering to the affected individual a therapeutically effective amount of a pharmaceutical composition comprising lurbinectedin which has been manufactured via Form B of lurbinectedin, and a pharmaceutically acceptable carrier.

In a further embodiment, the present invention relates to lurbinectedin having residual solvents of not more than 1%, 0.5%, 0.1% or substantially not detected. In a further embodiment, the present invention relates to lurbinectedin having a water content of above 1.6% w/w, or of 1.7-5% w/w. In a further embodiment, the present invention relates to lurbinectedin having a water content of not more than 5%, 4% or 3% w/w.

In the context of solid state forms of lurbinectedin, alkanes in the present invention may be branched or unbranched, and have from about 5 to about 10 carbon atoms. One more preferred class of alkanes has from 5 to 9 carbon atoms. Even more preferred are alkanes having 5, 6 or 7 carbon atoms. Particularly preferred alkanes of this invention are n-pentane, n-hexane, n-heptane, cyclohexane, and methylcyclohexane. As used herein, the term alkane, unless otherwise stated, refers to both cyclic and noncyclic alkanes.

Pharmaceutically acceptable solvents in the context of solid state forms of lurbinectedin are those classified under classes 2 and 3 of the guideline "Impurities: Guideline for residual solvents Q3C(R6)" of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

In an embodiment, the present invention relates to Form B of lurbinectedin.

Form B of lurbinectedin can be characterized by showing an X-ray powder diffractogram pattern comprising four or more characteristic peaks at 2-theta angles selected from 6.2±0.2°, 7.6±0.2°, 9.0±0.2°, 10.9±0.2°, 14.9±0.2° and 15.3±0.2°. Form B may alternatively be characterized by showing an X-ray powder diffractogram pattern comprising five or more of said characteristic peaks. Alternatively, Form B may be characterized by showing an X-ray powder diffractogram pattern comprising all six of said characteristic peaks.

Particularly, Form B of lurbinectedin can be characterized by an X-ray powder diffractogram pattern comprising peaks and intensities as shown in the following table:

Angle [2-theta]	Relative intensity [%]
6.2 ± 0.2°	79 ± 6
7.6 ± 0.2°	100 ± 3
9.0 ± 0.2°	63 ± 3
10.9 ± 0.2°	100 ± 3
14.9 ± 0.2°	76 ± 3
15.3 ± 0.2°	75 ± 3

In a preferred embodiment further peaks may be found at 2-theta angles of 12.4±0.2°, 19.2±0.2° and 26.5±0.2°. Particularly, Form B of lurbinectedin can be characterized by an X-ray powder diffractogram pattern comprising characteristic peaks and intensities as shown in the following table:

Angle [2-theta]	Relative intensity [%]
6.2 ± 0.2°	79 ± 6
7.6 ± 0.2°	100 ± 3
9.0 ± 0.2°	63 ± 3
10.9 ± 0.2°	100 ± 3
12.4 ± 0.2°	40 ± 3
14.9 ± 0.2°	76 ± 3
15.3 ± 0.2°	75 ± 3
19.2 ± 0.2°	34 ± 3
26.5 ± 0.2°	33 ± 3

In a more preferred embodiment, further peaks may be found at 2-theta angles of 18.4±0.2°, 20.7±0.2° and 24.9±0.2°. Particularly, Form B of lurbinectedin can be characterized by an X-ray powder diffractogram pattern comprising characteristic peaks and intensities as shown in the following table:

Angle [2-theta]	Relative intensity [%]	Angle [2-theta]	Relative intensity [%]
6.2 ± 0.2°	79 ± 6	15.3 ± 0.2°	75 ± 3
7.6 ± 0.2°	100 ± 3	18.4 ± 0.2°	29 ± 3
9.0 ± 0.2°	63 ± 3	19.2 ± 0.2°	34 ± 3
10.9 ± 0.2°	100 ± 3	20.7 ± 0.2°	32 ± 3
12.4 ± 0.2°	40 ± 3	24.9 ± 0.2°	26 ± 3
14.9 ± 0.2°	76 ± 3	26.5 ± 0.2°	33 ± 3

In a most preferred embodiment, the present invention relates to Form B of lurbinectedin that exhibits an X-ray powder diffraction pattern substantially the same as any one of the X-ray powder diffraction patterns shown in FIG. **2***a* or **2***b*.

In addition, Form B of lurbinectedin can be characterized by showing an IR spectrum comprising peaks at wavelengths of 2928, 1755, 1626, 1485, 1456, 1370, 1197, 1150, 1088, 1003, 959, 916, and 587. An illustrative IR spectrum is displayed in FIG. **7***b*.

In addition, Form B of lurbinectedin can be characterized by TG-FTIR degradation above 150° C. Alternatively, or in addition, Form B of lurbinectedin can be characterized by a TG-FTIR mass change to 150° C. being due to the loss of water. The loss due to water may be less than about 5%, less than about 4%, or less than about 3%. Alternatively, or in addition, Form B of lurbinectedin can be characterized by TG-FTIR indicating a loss of water, preferably around 2-3% water by weight, more preferably 2.6% water by weight. An illustrative TG-FTIR is displayed in FIG. **3**.

In addition, Form B of lurbinectedin can be characterized by DSC wherein degradation begins above 130° C. An illustrative DSC thermogram is displayed in FIG. **4**.

In an embodiment, Form B of lurbinectedin has an average charge density of not more than about 30 nC/g, not more than about 20 nC/g, not more than about 10 nC/g, not more than about 6 nC/g, not more than about 5 nC/g, about 5±2 nC/g, about 4±2 nC/g, about 4-5 nC/g, about 5 nC/g, or about 4 nC/g. In an embodiment, Form B of lurbinectedin has a dispersion of charge density of less than 4.8 nC/g, of between about 0.7 nC/g to less than 4.8 nC/g, or 2.4±2 nC/g. In an embodiment, Form B of lurbinectedin has a water content of above 1.6% w/w, or of 1.7-5% w/w. In an embodiment, Form B of lurbinectedin has residual solvents of not more than 1%, 0.5%, 0.1% or substantially not detected.

The present invention encompasses lurbinectedin comprising at least a detectible amount of Form B, up to 1% w/w Form B, up to 5% w/w Form B, up to 10% w/w Form B, up to 20% w/w Form B, up to 30% w/w Form B, up to 40% w/w Form B, up to 50% w/w Form B, up to 60% w/w Form B, up to 70% w/w Form B, up to 80% w/w Form B, up to 90% w/w Form B, up to 95% w/w Form B, up to 98% w/w Form B, or be substantially pure Form B. In an embodiment, partially crystalline lurbinectedin as described herein may comprise at least a detectible amount of Form B, up to 1% w/w Form B, up to 5% w/w Form B, up to 10% w/w Form B, up to 20% w/w Form B, up to 30% w/w Form B, up to 40% w/w Form B, up to 50% w/w Form B, up to 60% w/w Form B, up to 70% w/w Form B, up to 80% w/w Form B, up to 90% w/w Form B, up to 95% w/w Form B, up to 98% w/w Form B, or be substantially pure Form B. w/w is intended to mean the amount of lurbinectedin which is in the Form B state. As such, purely by way of example, 50% w/w means the lurbinectedin API comprises 50% by weight Form B and 50% by weight another form, for example amorphous Form A.

In an embodiment, the invention relates to a process for preparing Form B of lurbinectedin comprising:

a) preparing an acidic aqueous solution comprising lurbinectedin or a protonated form thereof; and

b) basifying the resulting acid aqueous solution with a base or a buffer to precipitate Form B of lurbinectedin.

In step a), a solution of lurbinectedin in acid water is provided. Examples of methods for preparing such solution include, but are not limited to: dissolving any solid form of lurbinectedin in acidic water; or extracting lurbinectedin from a solution comprising lurbinectedin in a water-immiscible organic phase to acidic water. In a preferred embodiment the acidic aqueous solution of lurbinectedin is obtained by dissolving lurbinectedin in acidic water.

Any form of lurbinectedin may be used e.g. amorphous lurbinectedin to form crystalline lurbinectedin. The concentration of lurbinectedin in acid water may range from about 10 to about 50 g/L. Particularly preferred are concentrations from about 15 to about 40 g/L, being more preferred concentrations from about 20 to about 30 g/L. Most preferred concentration of lurbinectedin in acid water is about 26 g/L.

The preferred pH of the acid water may range from about 1 to about 4, more preferably from about 1 to about 3, even more preferably from about 1 to about 2 and most preferably is about 1. The acid condition may be provided by an acid or by a buffer. Suitable pharmaceutically acceptable acids include hydrochloric acid, phosphoric acid, sulfuric acid, carboxylic acids such as aliphatic and aromatic carboxylic acids. More preferred acids include hydrochloric acid, phosphoric acid, sulfuric acid, trifluoroacetic acid, nitrobenzoic acid and citric acid. Suitable acid buffering agents provide a pH between about 1 to about 4. Examples of suitable acid buffering agents include but are not limited to phosphate buffer, citrate buffer, lactate buffer, ascorbate buffer, tartaric/citrate buffer, bicarbonate/hydrochloric acid buffer, acetate buffer, succinate buffer and glycine/hydrochloric acid buffer. More preferably the acid condition is provided by an acid and most preferably the acid is hydrochloric acid. The preferred pH of the solution of lurbinectedin in acidic water may range from about 1 to about 4, from about 1 to about 3, or about 2 to about 3.

In step b), the resulting acid aqueous solution is treated with an excess of base or buffer to basify it and precipitate Form B of lurbinectedin. The basification may be carried out with a base or with a buffer. The preferred pH of the resulting basic solution may range from about 8 to about 11, most preferably from about 9 to about 11. Suitable pharmaceutically acceptable bases include carbonates, hydroxides, hydrogen carbonates and ammonium salts. Particularly preferred bases are sodium carbonate, potassium carbonate, NH_4OH, lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium hydrogen carbonate and potassium hydrogen carbonate. Suitable basic buffers provide a pH between about 8 to about 11. Examples of suitable basic buffers include ammonium and phosphate buffers such as KH_2PO_4 buffer, Na_2HPO_4/citric acid, and NH_4Cl—NH_4OH. In a preferred embodiment the basification is carried out with a buffer and in a most preferred embodiment the basification is carried out with a NH_4Cl—NH_4OH buffer.

The obtained Form B of lurbinectedin can be separated by isolation operations such as filtration or centrifugation, preferably by filtration. Moreover, after separation, the separated solid may be subjected to a drying treatment by any

known method. The precipitate can be dried preferably under vacuum at a temperature preferably ranging from about 15 to 35° C., more preferably from about 20 to 30° C., and most preferably at about 25° C. for a time preferably ranging from about 10 to 24 hours, more preferably from about 16 to 20 hours and most preferably for about 18 hours.

In a preferred embodiment the acid aqueous solution obtained after step a) is washed one or more times with a pharmaceutically acceptable, water-immiscible, polar solvent and one or more times with a pharmaceutically acceptable, water-immiscible, non-polar solvent, before treating it with an excess of base or buffer in step b).

Examples of pharmaceutically acceptable, water immiscible, polar solvents suitable for this washing include chloroform, 1-butanol, 2-butanol, butyl acetate, ethyl acetate, methyl acetate, 1-pentanol, propyl acetate and dichloromethane. More preferred pharmaceutically acceptable, water-immiscible, polar solvents for this washing are chloroform, ethyl acetate and dichloromethane, with dichloromethane the most preferred.

Preferred pharmaceutically acceptable, water-immiscible, non-polar solvents suitable for this washing include C5-C7 alkanes such as n-heptane, n-hexane, n-pentane, cyclohexane and methylcyclohexane; being n-pentane the most preferred.

In an embodiment, the present invention relates to pharmaceutical compositions comprising Form B of lurbinectedin and a pharmaceutically acceptable carrier or manufactured from lurbinectedin comprising Form B. The lurbinectedin used in the compositions or used during the manufacture of the compositions may comprising lurbinectedin comprising at least a detectible amount of Form B, up to 1% w/w Form B, up to 5% w/w Form B, up to 10% w/w Form B, up to 20% w/w Form B, up to 30% w/w Form B, up to 40% w/w Form B, up to 50% w/w Form B, up to 60% w/w Form B, up to 70% w/w Form B, up to 80% w/w Form B, up to 90% w/w Form B, up to 95% w/w Form B, up to 98% w/w Form B, or be substantially pure Form B.

Partially crystalline lurbinectedin as disclosed herein may in embodiments comprise at least a detectible amount of Form B, up to 1% w/w Form B, up to 5% w/w Form B, up to 10% w/w Form B, up to 20% w/w Form B, up to 30% w/w Form B, up to 40% w/w Form B, up to 50% w/w Form B, up to 60% w/w Form B, up to 70% w/w Form B, up to 80% w/w Form B, up to 90% w/w Form B, up to 95% w/w Form B, up to 98% w/w Form B, or be substantially pure Form B. In alternative embodiments, other non-Form B crystalline lurbinectedin may form partially crystalline lurbinectedin at the same w/w amounts.

The partially crystalline lurbinectedin as disclosed herein may be used to form pharmaceutical compositions according to the present invention. Accordingly, in embodiments, partially crystalline lurbinectedin is used in the manufacture of a bulk lurbinectedin solution which is thereafter lyophilized to form the lyophilized lurbinectedin formulation. The partially crystalline lurbinectedin may comprise Form B as disclosed herein.

Although the partially crystalline lurbinectedin may not be present in the final dosage form (due to the dissolution and subsequent lyophilisation steps), it nevertheless may affect the properties of the final dosage form. By way of example, using partially crystalline lurbinectedin can reduce and/or simplify the total impurities including degradation products. Characteristic impurity profiles may demonstrate the use of partially crystalline lurbinectedin during manufacture. According to an embodiment, the total degradation products in the final lyophilized product may be not more than (NMT) 1.9%, 1.8%, 1.7%, 1.6%, 1.5%, 1.4%, or 1.3%. In a preferred embodiment, the total degradation products are NMT than 1.3%. According to a further embodiment, the final lyophilized product comprises NMT 0.8% of impurity D. According to a further embodiment, the final lyophilized product comprises NMT 0.3% of any unspecified impurity.

Using partially crystalline lurbinectedin may also advantageously control residual solvents. In an embodiment, the lurbinectedin comprises not more than 0.2% residual solvents, preferably not more than 0.1% residual solvents, preferably residual solvents are substantially not detected.

In an embodiment, the partially crystalline lurbinectedin used in the manufacture of the compositions disclosed herein may have an assay (%) in the range 94.0-102.0% and an impurities level lower than 1.0%. Specified impurities and their limits may be are impurity B (≤0.20%), impurity D (≤0.50%) and/or impurity G (≤0.50%). Any other individual non-specified impurity may have a limit of 50.20%.

Use of Pharmaceutical Lurbinectedin Formulations

The present invention identifies a number of methods of treatment using lurbinectedin alone or in combination with further agents. Where reference is made to a method of treatment, the present invention also encompasses lurbinectedin and/or said further agents in the manufacture of a medicament for the treatment of cancer and also lurbinectedin and/or said further agents for use in the treatment of cancer. The methods below may utilize compositions of the invention as defined herein.

In some embodiments the method of treating SCLC in a patient in need therefore comprises: (1) administering to the patient lurbinectedin at a dose of 3.2 mg/m^2 (or a reduced dose of 2.6 mg/m^2 or 2.0 mg/m^2) by intravenous infusion of a lurbinectedin infusion solution, wherein the lurbinectedin infusion solution administered to the patient is prepared from a lyophilized composition comprising 4 mg lurbinectedin, a lactate buffer, and a disaccharide reconstituted to form a reconstituted solution at a pH of 3.8 to 4.5. In preferred embodiments, the disaccharide is sucrose. In a preferred embodiment, the lyophilized composition comprises 4 mg lurbinectedin, a lactate buffer (preferably resulting from a solution comprising 22.1 mg lactic acid and 5.1 mg sodium hydroxide, including about 0.25 mmol of lactate), and a disaccharide (preferably sucrose, particularly 800 mg sucrose), wherein reconstitution of the lyophilized composition in about 8 mL of an aqueous solution provides a lurbinectedin solution at 0.5 mg/mL lurbinectedin having a pH of about 3.8 to about 4.5. In some embodiments, a lurbinectedin infusion solution is prepared by diluting the reconstituted solution with an isotonic solution, wherein the isotonic solution is a 0.9% sodium chloride solution or a 5% dextrose solution. In some embodiments, the reconstituted solution is diluted with at least 100 mL or at least 250 mL of the isotonic solution to prepare a lurbinectedin infusion solution. In some embodiments, after reconstitution or dilution, the solution can be stored for up to 24 hours following reconstitution, including infusion time, at either room temperature (i.e., about 23° C.)/light or under refrigerated (5° C.±3° C.) conditions. In particular embodiments, the % wt/wt of Impurity D relative to lurbinectedin does not increase by more than 0.1%, 0.2% or 0.3% wt/wt upon storage of the reconstituted or diluted solution for 24, 48 or 72 hours at either room temperature (i.e., about 23° C.)/light or under refrigerated (5° C.±3° C.) conditions.

Some embodiments provide a method of administering a pharmaceutical composition to a patient in need thereof, for example, a patient suffering from SCLC refractory to first line treatment, comprising (1) reconstituting a lyophilized

pharmaceutical composition in a vial after the composition has been stored for 30 to 36, or 48 months, wherein the lyophilized pharmaceutical composition was prepared by lyophilizing a stock solution comprising lurbinectedin, lactic acid, sodium hydroxide, and sucrose at a ratio of 4 mg lurbinectedin:22.1 mg lactic acid:5.1 mg sodium hydroxide: 800 mg sucrose: 8 mL water; and (2) administering the reconstituted solution to a patient, wherein the reconstituted solution may be diluted with an isotonic solution, such as a 0.9% sodium chloride solution or a 5% dextrose solution, from 100 ml to 250 ml volume for administration to the patient as an infusion solution.

In a further aspect, there is provided the use of lurbinectedin in the manufacture of a medicament for the treatment of small cell lung cancer (SCLC), wherein said treatment comprises:

(1) administering a prophylactic dose of a corticosteroid and a serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient on the day of and prior to administration of lurbinectedin to the patient; and

(2) administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion.

In a further aspect, there is provided the use of corticosteroid in the manufacture of a medicament for the treatment of small cell lung cancer (SCLC), wherein said treatment comprises:

(1) administering a prophylactic dose of said corticosteroid and a serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient on the day of and prior to administration of lurbinectedin to the patient; and

(2) administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion.

In a further aspect, there is provided the use of a serotonin antagonist in the manufacture of a medicament for the treatment of small cell lung cancer (SCLC), wherein said treatment comprises:

(1) administering a prophylactic dose of a corticosteroid and said serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient on the day of and prior to administration of lurbinectedin to the patient; and

(2) administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion.

In a further aspect, there is provided the use of lurbinectedin in the manufacture of a medicament for the treatment of small cell lung cancer (SCLC), wherein said method comprises:

(1) administering a first dose of 3.2 mg/m^2 of lurbinectedin to the patient by intravenous infusion; and

(2) identifying an adverse reaction in the patient, wherein the adverse reaction is selected from the group consisting of: ≥Grade 3 (severe) non hematological toxicity, Grade 4 thrombocytopenia (Platelet count less than 25,000 cells/mm^3), Grade 3 thrombocytopenia (Platelet count less than 50,000 cells/mm^3) with bleeding that requires transfusion, Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), or any grade neutropenia (Neutrophil count <LLN) that is associated with infection/sepsis or any other of the adverse reactions;

(3) after the adverse reaction is identified and after the patient's neutrophil count is greater than 1500 cells/mm^3; platelet count is greater than about 100,000 mm^3; and hemoglobin levels are greater than about 9 g/dL:

(i) if the identified adverse reaction consists of Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), administering to the patient a dose of G-CSF and a dose of lurbinectedin that is equal to the first dose; or

(ii) if the identified adverse reaction is not solely Grade 4 neutropenia, administering to the patient a reduced dose of lurbinectedin compared to the first dose, wherein administration of two doses of lurbinectedin are spaced apart by at least 21 days.

In a further aspect, there is provided the use of G-CSF in the manufacture of a medicament for the treatment of small cell lung cancer (SCLC), wherein said method comprises:

(1) administering a first dose of 3.2 mg/m^2 of lurbinectedin to the patient by intravenous infusion; and

(2) identifying an adverse reaction in the patient, wherein the adverse reaction is selected from the group consisting of: ≥Grade 3 (severe) non hematological toxicity, Grade 4 thrombocytopenia (Platelet count less than 25,000 cells/mm^3), Grade 3 thrombocytopenia (Platelet count less than 50,000 cells/mm^3) with bleeding that requires transfusion, Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), or any grade neutropenia (Neutrophil count <LLN) that is associated with infection/sepsis or any other of the adverse reactions;

(3) after the adverse reaction is identified and after the patient's neutrophil count is greater than 1500 cells/mm^3; platelet count is greater than about 100,000 mm^3; and hemoglobin levels are greater than about 9 g/dL:

(i) if the identified adverse reaction consists of Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), administering to the patient a dose of G-CSF and a dose of lurbinectedin that is equal to the first dose; or

(ii) if the identified adverse reaction is not solely Grade 4 neutropenia, administering to the patient a reduced dose of lurbinectedin compared to the first dose,

wherein administration of two doses of lurbinectedin are spaced apart by at least 21 days.

In a further aspect, there is provided the use of lurbinectedin in the manufacture of a medicament for the treatment of small cell lung cancer (SCLC), wherein said method comprises:

administering to the patient lurbinectedin at a dose of 3.2 mg/m^2 by intravenous infusion of a lurbinectedin infusion solution, wherein the lurbinectedin infusion solution administered to the patient is prepared from a lyophilized composition comprising 4 mg lurbinectedin, a buffer derived from an organic carboxylic acid, and a disaccharide reconstituted to form a reconstituted solution at a pH of 3.5 to 4.5.

In a further aspect, there is provided the use of lurbinectedin in the manufacture of a medicament for the treatment of endometrial cancer, SCLC, soft tissue sarcoma, glioblastoma, pancreatic adenocarcinoma, mesothelioma, colorectal carcinoma, or epithelial ovarian cancer, wherein said treatment comprises:

administering to the patient lurbinectedin and a topoisomerase inhibitor selected from SN-38 and irinotecan on day one of a treatment cycle;

wherein the lurbinectedin is administered at a dose of 1 to 2.5 mg/m^2 and

wherein the topoisomerase inhibitor is administered at a dose equivalent to 50 to 75 mg of irinotecan/m^2.

In a further aspect, there is provided the use of a topoisomerase inhibitor selected from SN-38 and irinotecan in the manufacture of a medicament for the treatment of endometrial cancer, SCLC, soft tissue sarcoma, glioblastoma, pancreatic adenocarcinoma, mesothelioma, colorectal carcinoma, or epithelial ovarian cancer, wherein said treatment comprises:

administering to the patient lurbinectedin and said topoisomerase inhibitor selected from SN-38 and irinotecan on day one of a treatment cycle;

wherein the lurbinectedin is administered at a dose of 1 to 2.5 mg/m^2 and

wherein the topoisomerase inhibitor is administered at a dose equivalent to 50 to 75 mg of irinotecan/m^2.

In a further aspect, there is provided the use of lurbinectedin in the manufacture of a medicament for the treatment of cancer, the treatment comprising

reconstituting a lyophilized pharmaceutical composition in a vial after the composition has been stored for 30 to 60 months,

wherein the lyophilized pharmaceutical composition was prepared by lyophilizing a stock solution comprising 4 mg of lurbinectedin, a buffer derived from an organic carboxylic acid, and sucrose,

wherein the composition comprises lurbinectedin and disaccharide at a ratio of 1 mol lurbinectedin:455 to 465 mol sucrose,

wherein the lyophilized composition is formulated such that reconstitution with 8 mL of water will yield a solution having a pH of 3.5 to 4.5; and

administering the reconstituted solution to a patient.

In a further aspect, there is provided the use of lurbinectedin in the manufacture of a medicament for the treatment of small cell lung cancer (SCLC), wherein said treatment comprises:

administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion;

wherein the patient was administered an immunotherapeutic antibody for treating SCLC prior to beginning the treatment cycle and

wherein the duration of response is at least 2 months, 3 months, 4 months, 5 months or 6 months or wherein the overall response rate is at least 40%.

In a further aspect, there is provided the use of lurbinectedin in the manufacture of a medicament for the treatment of small cell lung cancer (SCLC), wherein said treatment comprises:

administering lurbinectedin at a dose of 2 to 3.2 mg/m2 to a patient by intravenous infusion every 3 weeks, wherein the lurbinectedin is provided in a lyophilized formulation comprising lurbinectedin, a buffer derived from lactic acid, and sucrose, wherein the ratio of lurbinectedin:lactic acid:sucrose is between 1 mol:46 mol:455 mol and 1 mol:50 mol:465 mol, wherein the formulation is stable at 5 degree C.±3 degree C. for at least 24 months or at least 36 months or at least 48 months or at least 60 months such that the lurbinectedin degradation product from deacetylation does not exceed 0.8% wt./wt. of the total lurbinectedin weight.

In a further aspect, there is provided the use of lurbinectedin in the manufacture of a medicament for the treatment of small cell lung cancer (SCLC), wherein said treatment comprises:

1) dissolving a packaged, lyophilized composition comprising 4 mg lurbinectedin, a buffer derived from an organic acid and disaccharide in about 8 mL of water to provide a lurbinectedin solution having a pH of about 3.5 to about 4.1,

and

2) administering about 2 to 3.2 mg/m^2 of lurbinectedin to a patient whose SCLC has progressed after prior platinum-containing therapy by intravenous infusion every 3 weeks and

wherein the lyophilized composition comprises less than about 0.3% of Impurity D (w/w based on lurbinectedin) when the composition is packaged, and wherein upon storage at about 5 degrees C. for about 24, 36 or 48 months the composition comprises less than about 0.8% of Impurity D (w/w based on lurbinectedin).

In a further aspect, there is provided lurbinectedin for use in the treatment of small cell lung cancer (SCLC), wherein said treatment comprises:

(1) administering a prophylactic dose of a corticosteroid and a serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient on the day of and prior to administration of lurbinectedin to the patient; and

(2) administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion.

In a further aspect, there is provided a corticosteroid for use in the treatment of small cell lung cancer (SCLC), wherein said treatment comprises:

(1) administering a prophylactic dose of said corticosteroid and a serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient on the day of and prior to administration of lurbinectedin to the patient; and

(2) administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion.

In a further aspect, there is provided a serotonin antagonist for use in the treatment of small cell lung cancer (SCLC), wherein said treatment comprises:

(1) administering a prophylactic dose of a corticosteroid and said serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient on the day of and prior to administration of lurbinectedin to the patient; and

(2) administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion.

In a further aspect, there is provided lurbinectedin for use in the treatment of small cell lung cancer (SCLC), wherein said method comprises:

(1) administering a first dose of 3.2 mg/m^2 of lurbinectedin to the patient by intravenous infusion; and

(2) identifying an adverse reaction in the patient, wherein the adverse reaction is selected from the group consisting of: ≥Grade 3 (severe) non hematological toxicity, Grade 4 thrombocytopenia (Platelet count less than 25,000 cells/mm^3), Grade 3 thrombocytopenia (Platelet count less than 50,000 cells/mm^3) with bleeding that requires transfusion, Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), or any grade neutropenia (Neutrophil count <LLN) that is associated with infection/sepsis or any other of the adverse reactions;

(3) after the adverse reaction is identified and after the patient's neutrophil count is greater than 1500 cells/mm^3; platelet count is greater than about 100,000 mm^3; and hemoglobin levels are greater than about 9 g/dL:

(i) if the identified adverse reaction consists of Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), administering to the patient a dose of G-CSF and a dose of lurbinectedin that is equal to the first dose; or

(ii) if the identified adverse reaction is not solely Grade 4 neutropenia, administering to the patient a reduced dose of lurbinectedin compared to the first dose, wherein administration of two doses of lurbinectedin are spaced apart by at least 21 days.

In a further aspect, there is provided G-CSF for use in the treatment of small cell lung cancer (SCLC), wherein said method comprises:

(1) administering a first dose of 3.2 mg/m^2 of lurbinectedin to the patient by intravenous infusion; and

(2) identifying an adverse reaction in the patient, wherein the adverse reaction is selected from the group consisting of: ≥Grade 3 (severe) non hematological toxicity, Grade 4 thrombocytopenia (Platelet count less than 25,000 cells/mm^3), Grade 3 thrombocytopenia (Platelet count less than 50,000 cells/mm^3) with bleeding that requires transfusion, Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), or any grade neutropenia (Neutrophil count <LLN) that is associated with infection/sepsis or any other of the adverse reactions;

(3) after the adverse reaction is identified and after the patient's neutrophil count is greater than 1500 cells/mm^3; platelet count is greater than about 100,000 mm^3; and hemoglobin levels are greater than about 9 g/dL:

(i) if the identified adverse reaction consists of Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), administering to the patient a dose of G-CSF and a dose of lurbinectedin that is equal to the first dose; or

(ii) if the identified adverse reaction is not solely Grade 4 neutropenia, administering to the patient a reduced dose of lurbinectedin compared to the first dose,

wherein administration of two doses of lurbinectedin are spaced apart by at least 21 days.

In a further aspect, there is provided lurbinectedin for use in the treatment of small cell lung cancer (SCLC), wherein said method comprises:

administering to the patient lurbinectedin at a dose of 3.2 mg/m^2 by intravenous infusion of a lurbinectedin infusion solution, wherein the lurbinectedin infusion solution administered to the patient is prepared from a lyophilized composition comprising 4 mg lurbinectedin, a buffer derived from an organic carboxylic acid, and a disaccharide reconstituted to form a reconstituted solution at a pH of 3.5 to 4.5.

In a further aspect, there is provided lurbinectedin for use in the treatment of endometrial cancer, SCLC, soft tissue sarcoma, glioblastoma, pancreatic adenocarcinoma, mesothelioma, colorectal carcinoma, or epithelial ovarian cancer, wherein said treatment comprises:

administering to the patient lurbinectedin and a topoisomerase inhibitor selected from SN-38 and irinotecan on day one of a treatment cycle;

wherein the lurbinectedin is administered at a dose of 1 to 2.5 mg/m^2 and

wherein the topoisomerase inhibitor is administered at a dose equivalent to 50 to 75 mg of irinotecan/m^2.

In a further aspect, there is provided a topoisomerase inhibitor selected from SN-38 and irinotecan for use in the treatment of endometrial cancer, SCLC, soft tissue sarcoma, glioblastoma, pancreatic adenocarcinoma, mesothelioma, colorectal carcinoma, or epithelial ovarian cancer, wherein said treatment comprises: administering to the patient lurbinectedin and said topoisomerase inhibitor selected from SN-38 and irinotecan on day one of a treatment cycle;

wherein the lurbinectedin is administered at a dose of 1 to 2.5 mg/m^2 and

wherein the topoisomerase inhibitor is administered at a dose equivalent to 50 to 75 mg of irinotecan/m^2.

In a further aspect, there is provided lurbinectedin for use in the treatment of cancer, the treatment comprising

reconstituting a lyophilized pharmaceutical composition in a vial after the composition has been stored for 30 to 60 months,

wherein the lyophilized pharmaceutical composition was prepared by lyophilizing a stock solution comprising 4 mg of lurbinectedin, a buffer derived from an organic carboxylic acid, and sucrose,

wherein the composition comprises lurbinectedin and disaccharide at a ratio of 1 mol lurbinectedin:455 to 465 mol sucrose,

wherein the lyophilized composition is formulated such that reconstitution with 8 mL of water will yield a solution having a pH of 3.5 to 4.5; and

administering the reconstituted solution to a patient.

In a further aspect, there is provided lurbinectedin for use in the treatment of small cell lung cancer (SCLC), wherein said treatment comprises:

administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion;

wherein the patient was administered an immunotherapeutic antibody for treating SCLC prior to beginning the treatment cycle and

wherein the duration of response is at least 2 months, 3 months, 4 months, 5 months or 6 months or wherein the overall response rate is at least 40%.

In a further aspect, there is provided lurbinectedin for use in the treatment of small cell lung cancer (SCLC), wherein said treatment comprises:

administering lurbinectedin at a dose of 2 to 3.2 mg/m2 to a patient by intravenous infusion every 3 weeks, wherein the lurbinectedin is provided in a lyophilized formulation comprising lurbinectedin, lactic acid, and sucrose, wherein the ratio of lurbinectedin:lactic acid: sucrose is between 1 mol:46 mol:455 mol and 1 mol:50 mol:465 mol, wherein the formulation is stable at 5 degree C.±3 degree C. for at least 24 months or at least 36 months or at least 48 months or at least 60 months such that the lurbinectedin degradation product from deacetylation does not exceed 0.8% wt./wt. of the total lurbinectedin weight.

In a further aspect, there is provided lurbinectedin for use in the treatment of small cell lung cancer (SCLC), wherein said treatment comprises:

1) dissolving a packaged, lyophilized composition comprising 4 mg lurbinectedin, a buffer derived from an organic acid and disaccharide in about 8 mL of water to provide a lurbinectedin solution having a pH of about 3.5 to about 4.1, and

2) administering about 2 to 3.2 mg/m^2 of lurbinectedin to a patient whose SCLC has progressed after prior platinum-containing therapy by intravenous infusion every 3 weeks and

wherein the lyophilized composition comprises less than about 0.3% of Impurity D (w/w based on lurbinectedin) when the composition is packaged, and wherein upon storage at about 5 degrees C. for about 24, 36 or 48 months the composition comprises less than about 0.8% of Impurity D (w/w based on lurbinectedin).

In a further aspect, there is provided the use of lurbinectedin in the manufacture of a medicament for the treatment of solid tumors, including SCLC, endometrial carcinoma, soft tissue sarcoma or glioblastoma wherein said treatment comprises:

(1) administering a prophylactic dose of a corticosteroid and a serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient on the day of and prior to administration of lurbinectedin to the patient; and

(2) administering lurbinectedin at a dose of 2 mg/m^2 and 75 mg/m^2 of irinotecan to the patient by intravenous infusion.

In a further aspect, there is provided the use of corticosteroid in the manufacture of a medicament for the treatment of solid tumor, wherein said treatment comprises:

(1) administering a prophylactic dose of said corticosteroid and a serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient on the day of and prior to administration of lurbinectedin to the patient; and

(2) administering lurbinectedin at a dose of 2 mg/m^2 and irinotecan at a dose of 75 mg/m2 to the patient by intravenous infusion.

In a further aspect, there is provided the use of a serotonin antagonist in the manufacture of a medicament for the treatment of solid tumors, including SCLC, endometrial carcinoma, soft tissue sarcoma or glioblastoma, wherein said treatment comprises:

(1) administering a prophylactic dose of a corticosteroid and said serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient on the day of and prior to administration of lurbinectedin to the patient; and

(2) administering lurbinectedin at a dose of 2 mg/m^2 and irinotecan at a dose of 75 mg/m2 to the patient by intravenous infusion.

In a further aspect, there is provided the use of lurbinectedin in the manufacture of a medicament for the treatment of solid tumors, including SCLC, endometrial carcinoma, soft tissue sarcoma or glioblastoma, wherein said treatment comprises:

(1) administering lurbinectedin at a dose of 2 mg/m^2 and irinotecan at a dose of 75 mg/m2 to the patient by intravenous infusion;

(2) after 7 days administering ininotecan at a dose of 75 mg/m^2 irinotecan to the patient by intravenous infusion; and

(3) administering G-CSF to the patient to manage the myelosuppressive effect of the administration.

In a further aspect, there is provided the use of lurbinectedin in the manufacture of a medicament for the treatment of solid tumors, including SCLC, endometrial carcinoma, soft tissue sarcoma or glioblastoma wherein said method comprises:

(1) administering lurbinectedin at a dose of 2 mg/m^2 and ininotecan at a dose of 75 mg/m2 irinotecan to the patient by intravenous infusion; and

(2) identifying if the patient exhibits a hematological toxicity of Grade 3 or 4 after said administration;

(3) if there is no Grade 3 or 4 hematological toxicity in the patient, then administering 7 days after step 1 a dose of 75 mg/m^2 irinotecan to the patient by intravenous infusion.

In a further aspect, there is provided the use of lurbinectedin in the manufacture of a medicament for the treatment of solid tumor, wherein said method comprises: administering to the patient lurbinectedin at a dose of 2.0 mg/m^2 by intravenous infusion of a lurbinectedin infusion solution and a dose of 75 mg/m^2 irinotecan to the patient by intravenous infusion, wherein the lurbinectedin infusion solution administered to the patient is prepared from a lyophilized composition comprising 4 mg lurbinectedin, a buffer derived from an organic carboxylic acid, and a disaccharide reconstituted to form a reconstituted solution at a pH of 3.5 to 4.5.

EXAMPLES

Example 1: Preparation of Lurbinectedin in Different Buffers

A bulk lurbinectedin solution containing 0.5 mg/mL (the calculated reconstituted concentration is 0.47 mg/mL based on the final volume of 8.55 mL) was prepared in an acetate, citrate, lactate, and succinate buffered solution with the buffer concentrations of 0.02 to 0.05 M buffered to pH 3, 4, and 5 with sodium hydroxide. An example of a lurbinectedin formulation with lactate buffered to a pH=4 is provided in Table 1 below.

TABLE 1

Composition of lurbinectedin 4 mg reconstituted solution

Component	Concentration per vial (mg/mL)	Function
Lurbinectedin	0.5	Active ingredient
Sucrose	100	Bulking agent
Lactic acid	2.76	Buffering agent
Sodium hydroxide	0.64	Buffering agent

Example 2: Solubility of Lurbinectedin in Different Buffers

Bulk solutions of phosphate, acetate, citrate, lactate and succinate buffers were prepared to determine maximum solubility of lurbinectedin. Table 2 shows the maximum solubility of lurbinectedin in the 0.02M-0.05 M or 0.06-0.1 M buffers at pH=4. The results show that lurbinectedin was poorly solubilized in a phosphate buffer. The results also suggest that the molarity of the buffer does not have a significant impact on solubility.

TABLE 2

Lurbinectedin maximum solubility in various buffers pH = 4. Impact of buffer molarity

	Lurbinectedin maximun solubility (mg/mL)	
Buffer pH = 4	0.02-0.05M	0.06-01M
Monopotasium phosphate	0.21	0.32
Sodium acetate	0.94	0.86
Sodium citrate	0.93	0.93
Sodnm lactate	0.90	0.92
Sodium succinate	0.97	0.95

Example 3: Stability of Lurbinectedin Formulations with Different Organic Carboxylic Buffers at Different PH Values

Stability and solubility studies were conducted to determine a pH wherein lurbinectedin exhibits good stability. Table 3 shows the solubility and the impurities and degradation products profile of lurbinectedin in the alternative 0.02M-0.05 M buffers at pH 3, pH 4 and pH 5. The solubility was similar for pH 3 and pH 4 and drastically decreased at pH 5. This decrease in solubility is accompanied by an increase in degradation products as the buffer pH increases.

TABLE 3

Solubility and degradation products profile of lurbinectedin in different organic carboxylic buffers in the pH range 3 to 5

		Sodium acetate			Sodium citrate			Sodium lactate			Sodium succinate		
		pH 3	pH 4	pH 5	pH 3	pH 4	pH 5	pH 3	pH 4	pH 5	pH 3	pH 4	pH 5
Solubility (mg/mL)		0.95	0.94	0.03	0.94	0.93	0.50	0.94	0.90	0.03	0.96	0.97	0.04
Degradation products[1] (%)													
individual[2] (rrt)	0.26-0.27	—	—	0.52	—	—	—	—	—	0.22	—	—	—
	0.47	—	—	0.12	—	—	—	—	—	—	—	—	—
	0.69	—	—	0.71	—	—	—	—	—	0.56	—	—	0.74
	0.69-0.71	—	—	0.24	—	—	—	—	—	0.18	—	—	0.14
	0.71-0.75	0.10	—	0.18	0.12	—	0.10	0.12	0.12	0.16	0.11	0.10	0.18
	0.99	—	—	0.19	—	—	—	—	—	0.11	—	—	0.12
	1.03-1.10	0.35	0.40	0.60	0.14	0.12	0.13	0.15	0.15	0.58	0.35	0.39	0.40
	1.15-1.16	—	—	—	—	0.11	0.16	—	0.10	—	—	—	—
	1.22	—	—	—	—	—	—	—	—	—	—	—	0.18
	1.26-1.31	0.13	0.11	0.39	—	—	—	—	—	0.18	—	—	0.26
	1.29-1.34	—	—	0.84	—	—	—	—	—	0.79	—	—	0.84
	1.79-1.91	—	—	0.84	—	—	—	—	—	0.70	—	—	1.1
	Total[3]	0.8	0.8	4.6	0.6	0.6	0.7	0.7	0.7	3.5	0.7	0.8	4.1

rrt: Relative retention time.
[1]HPLC Developinent method: IANA-072 Ed02.
[2]Main degradation products. Area ≥ 0.10%
[3]Total % degradation products calculated as 100% -% area lurbinected in main peak

The stability of lurbinectedin in the different buffers was further evaluated at 14 days with 25° C./60% RH conditions. While lurbinectedin is relatively stable at pH 3 and 4, a significant decrease in assay and purity at pH=5 is observed (Table 4).

TABLE 4

Effect of pH on the solubility and stability (25° C./60% RH 14 days) of lurbinectedin in different 0.02M-0.05M organic carboxylic buffers in the pH range 3 to 5

		Concentration[1] (mg/mL)		Concentration	Purity[1] (%)		
Buffer	pH	t = 0 h	t = 14 d	decrease (%)	t = 0 h	t = 14 d	Degradation (%)
Sodium acetate	3	0.95	0.88	6.8	99.2	98.0	1.2
	4	0.94	0.89	5.7	99.2	98.0	1.2
	5	0.03	0.03	8.2	95.4	93.7	1.7
Sodium citrate	3	0.94	0.92	1.2	99.4	97.9	1.6
	4	0.93	0.88	6.0	99.4	96.2	3.2
	5	0.50	0.11	78.5	99.3	95.0	4.3
Sodium lactate	3	0.94	0.93	0.9	99.3	98.6	0.7
	4	0.90	0.87	3.0	99.3	97.8	1.5
	5	0.03	0.03	6.9	96.5	93.9	2.6
Sodium Succinate	3	0.96	0.93	3.2	99.3	97.7	1.5
	4	0.97	0.89	7.6	99.2	96.8	2.4
	5	0.04	0.03	8.1	95.9	94.2	1.8

[1]HPLC Development method: IANA-072 Ed02.

These results showed that an organic carboxylic buffer with pH not more than pH 4.5 is the most adequate to increase the concentration of lurbinectedin in solution and to maintain an adequate stability. Sodium lactate and sodium citrate buffers were considered the most appropriate.

Example 4: Stability of Lyophilized Vials Formulated in Sodium Lactate and Sodium Citrate Buffers with pH=4.0 under Stress Conditions (50° C.)

In order to determine which of the two buffers was the optimal for lurbinectedin, batches of lyophilized vials containing 1 mg lurbinectedin/vial were manufactured at a laboratory scale with lurbinectedin formulated at 0.5 mg/mL in 0.03M sodium lactate pH=4 and 0.05M sodium citrate pH=4. The pH 4 was chosen because of its greater physiological compatibility compared to pH 3. Sucrose was included as a bulking agent at 10% (w/v). The stability of the active principle in the lyophilized product under stress conditions of temperature (50° C.) was evaluated. Freeze-dried vials formulated in 0.05M monopotassium phosphate buffer pH=4 were also included in these studies for comparison. The stability results of lyophilized vials after 1 month at 50° C. are shown in Table 5. Due to the large number of degradation products that appear under these conditions, only those with an area 0.20% are reported.

The three formulations showed comparable characteristics at t=0. After storage at 50° C. for 1 month, quality attributes such as the appearance of the lyophilized solid, color and pH of the reconstituted solution and water content were not modified.

Lurbinectedin assay decreased significantly (between 11% and 17%) with respect to the initial content for the three compositions being the % degradation products the major

differences observed. The vials formulated in sodium lactate buffer or monopotassium phosphate buffer showed very similar behavior, however sodium citrate buffer promoted larger degradation after storage for 1 month at 50° C. In all cases, the main degradation product was an impurity eluting at rrt 0.49-0.50 (HPLC Development method), being significantly higher in the lyophilized vial formulated in the sodium citrate buffer. Other degradation products that also appeared in very significant percentages were impurity D (rrt 0.73-0.74) and impurities with rrt 0.25, rrt 0.28 and rrt 1.09-1.10.

Based on the solubility and stability results, it was concluded that the most suitable dissolution medium for an optimized lurbinectedin formulation was 0.03M sodium lactate buffer pH 4.

solutions was studied. The bulk solutions had a concentration of 0.5 mg lurbinectedin/mL at pH 3.6, pH 4.0 and pH 4.5, using 10% sucrose (w/v) as bulking agent (8 mL filling in 30 mL glass vials). The stability of these batches was evaluated under 25° C./60% RH to determine if small variations in pH could have a significant effect on the stability of the product.

The stability results of lyophilized vials after 6 months at 25° C. are shown in Table 6. All the batches showed similar behavior. Quality attributes such as the appearance of the lyophilized, appearance, color and pH of the reconstituted solution, water content (%) and assay were kept constant. Total degradation products did not undergo significant changes,

TABLE 5

Stability under stress conditions (1 month, 50° C.) of lurbinectedin freeze-dried vials formulated with 0.05M monopotassium buffer pH = 4 containing 10% (w/v) sucrose citrate buffer pH = 4 or 0.03M sodium lactate i phosphate buffer pH = 4, 0.05M sodium as bulking agent

	Monopotassium phosphate 0.05M pH = 4 Batch 1317-127		Sodium citrate 0.05M pH = 4 Batch 1317-136		Sodium lactate 0.03M pH = 4 Batch 1317-139	
Quality attribute	t = 0	1 month 50° C.	t = 0	1 month 50° C	t = 0	1 month 50° C.
Appearance	White lyophilized cake	Contracted cake of irregular shape. Sticky appearance and greenish-yellow color	White lyophilized cake	Contracted cake of irregular shape. Sticky appearance and greenish-yellow color	White lyophilized cake	Contracted cake of irregular shape Sticky appearance and yellowish color
Identification	Consistent with standard	Consistent with standard	Consistent with standard	Consistent with standard	Consistent with standard	Consistent with standard
Reconstitution time	≤1 min	≤3 min	≤1 min	≤1 min	≤1 min	≤1 min
Appearance of reconstitued solution	Clear solution, free of visible particles	Clear solution, free of visible particles	Clear solution, feee of visible particles	Clear solution, free of visible particles	Clear solution, free of visible particles	Clear solution, tree of visible particles
Color of reconstituted solution	Colorless solution	Yellowish solution	Colorless solution	Yellowish solution	Colorless solution	Slighty yellowish solution
pH of reconstituted solution	4.0	4.1	4.0	4.2	3.9	4.1
Water content (% w/w)	1.7	1.7	1.7	2.2	1.1	1.6
Impurities and degradation products[1] (%)						
Total[2]	0.7	9.0	0.7	15.0	0.7	8.5
Individual[3] (rrt)						
0.20-0.21	—	0.39	—	0.60	—	0.25
0.23	—	—	—	0.35	—	—
0.24	—	—	—	0.39	—	0.26
0.25	—	0.60	—	2.0	—	1.2
0.25-0.26	—	0.34	—	1.1	—	0.71
0.28	—	0.84	—	1.2	—	0.54
0.29-0.30	—	—	—	0.35	—	0.21
0.37-0.38	—	0.20	—	0.29	—	—
0.49-0.50	—	1.9	—	5.5	—	2.2
0.63	—	0.20	—	—	—	—
0.73-0.74 (Imp. D)	—	1.4	—	0.94	—	0.60
1.09-1.10	—	0.34	—	0.37	—	1.2
1.28-1.29	—	0.42	—		—	—
Assay (% nominal)	96.8	85.8	97.5	81.0	102.0	89.4
Assay (initial)	NA	88.6	NA	83.1	NA	87.6

[1]HPLC Development method: IANA-090 Ed05
[2]% total impurities and degradation products calculated as 100%-% area lurbinectedin main peak.
[3]Reported impurities and degradation products: Area ≥ 0.20%
NA; Not applicable

Example 5: Effect of Bulk Solution pH on Lyophilized Product Stability

The stability of 4 mg of lyophilized product produced from various 0.03M sodium lactate buffer lurbinectedin bulk

As conclusion and based on the solubility and stability data, the lurbinectedin solution and a freeze-dried presentation, 0.03M sodium lactate buffer pH 4.0 was selected as the most suitable dissolution medium for lurbinectedin presentations.

TABLE 6

Stability at 25° C./60% RH of lurbinectedin 4 mg vial 30 mL at different pH

	Batch 2021-79 (pH 3.6) Time at 25° C./60% RH			Batch 2021-52 (pH 4.0) limcat25° C./60% RH			Batch 2021-86 (pH 4.5) Time at 25° C./60% RH		
Quality attribute	0	3 months	6 months	0	3 months	6 months	0	3 months	6 months
Appearance	White lyophilized cake	White lyophilized cake	White lyophilized cake	White lyophilized cake	White lyophilized cake	White lyophilized cake	White lyophilized cake	White lyophilized cake	White lyophilized cake
Identification by HPLC (RT)	Consistent with standard	Consistent with standard	Consistent with standard	Consistent with standard	Consistent with standard	Consistent with standard	Consistent with standard	Consistent with standard	Consistent with standard
Reconstitution time in water	NMT 3 min	NMT 3 min	NMT 3 min	NMT 3 min	NMT 3 min	NMT 3 min	NMT 3 min	NMT 3 min	NMT 3 min
Appearance of reconstituted solution	Clear solution free of visible particles	Clear solution free of visible particles	Clear solution free of visible particles	Clear solution free of visible particles	Clear solution free of visible particles	Clear solution free of visible particles	Clear solution free of visible particles	Clear solution free of visible particles	Clear solution free of visible particles
Color of reconstituted solution	Colorless solution	Colorless solution	Colorless solution	Colorless solution	Colorless solution	Colorless solution	Colorless solution	Colorless solution	Colorless solution
pH of reconstituted solution	3.6	3.6	3.7	4.0	4.0	4.0	4.5	4.5	4.6
Water (% w/w)	1.4	1.6	1.4	1.2	1.4	1.2	1.3	1.4	1.4
Impurities and degradation products (% w/w)									
Total[2]	0.3	0.3	0.4	0.3	0.4	0.4	0.3	0.4	0.4
Individual[3] (rrt)									
0.87-0.88 (Imp D)	0.27	0.29	0.30	0.27	0.24	0.29	0.25	0.26	0.30
Assay (% nominal)	100.7	101.1	100.8	99.4	99.4	100.3	99.6	100.3	100.1

rrt: relative retention time.
[1]HPLC Commercial method: MPI-00769 6.0 [26]
[2]Total impurities and degradation products calculated as the sum of individual impurities ≥ 0.05 (% w/w)
[3]Impurities and degradation products: % w/w ≥ 0.20%

Example 6: Bulking Agent Concentration

The stability of 4 mg of lyophilized product produced from various 0.03M sodium lactate buffer lurbinectedin bulk solutions was studied. The bulk solutions had a concentration of 0.5 mg lurbinectedin/mL at pH 3.6, pH 4.0 and pH 4.5, using 10% sucrose (w/v) as bulking agent (8 mL filling in 30 mL glass vials). The stability of these batches was evaluated under 25° C./60% RH to determine if small variations in pH could have a significant effect on the stability of the product.

Once the dissolution medium was selected, different bulking agents were screened at different concentrations: sucrose (5%, 7.5% and 10%), mannitol (5%), and combination of sucrose and mannitol (5% sucrose+2.5% mannitol).

For that purpose, several freeze-dried batches of lurbinectedin were manufactured with a strength of 4 mg/vial incorporating the different bulking agents at various concentrations. Lurbinectedin was dissolved at 0.5 mg/mL in 0.03M sodium lactate buffer pH 4. The batches composition is detailed in Table 7. Batches were characterized and their stability under stress conditions evaluated (40° C./75% RH).

TABLE 7

Composition of batches of lurbinectedin 4 mg vial 30 mL manufactured with different contents of sucrose and mannitol

	Vial composition				
Component	10% Sucrose Batch 2021-52	7.5% Sucrose Batch 2021-51	5% Sucrose Batch 2021-50	5% Mannitol Batch 2021-53	5% Sucrose/ 2.5% Mannitol Batch 2021-54
Lurbinectedin	4 mg	4 mg	4 mg	4 mg	4 mg
Lactic acid	22.08 mg	22.08 mg	22.08 mg	22.08 mg	22.08 mg
Sodium hydroxide	5.12 mg	5.12 mg	5.12 mg	5.12 mg	5.12 mg
Mannitol	N.A.	N.A.	N.A.	400 mg	200 mg
Sucrose	800 mg	600 mg	400 mg	N.A.	400 mg
Water[1]	q.s. 8 mL	q.s. 8 mL	q.s. 8 mL	q.s. 8 mL	q.s. 8 mL

[1]Evaporates during lyophilization
N.A.: No applicable

Table 8 below shows the stability results of lyophilized batches with the different bulking agents after 3 months stored at 40° C./75% RH.

The batch formulated with 5% sucrose was stable, since it did not undergo changes in the appearance of the freeze-dried cake nor in the reconstituted solution, maintained the lurbinectedin assay, and only showed a slight increase in

degradation products, being impurity D the main degradation product observed (rrt 0.88 HPLC commercial method).

However, batches formulated with sucrose and mannitol mixtures or only mannitol degraded significantly during storage at 40° C. In both cases, the appearance of the freeze-dried cake differed from batches bearing only sucrose (5% or 10%). The formulation containing 5% mannitol suffered a very significant decrease in lurbinectedin assay (43% of the nominal target). In addition, the % degradation products increased in both formulations (up to 57% in the formulation containing 5% mannitol). The two major degradation products in formulations containing mannitol are those eluting at rrt 0.67-0.68 and rrt 1.06).

TABLE 8

Stress stability of lurbinectedin batches containing different bulking agents

	5% Sucrose Batch 2021-50		5% Sucrose + 2.5% Mannitol Batch 2021-54		5% Mannitol Batch 2021-53	
CQAs	t = 0	3 months at 40° C.	t = 0	3 months at 40° C.	t = 0	3 months at 40° C.
Appearance	White lyophilized cake	White lyophilized cake	White lyophilized cake	Very slightly yellow, shrinked and contracted cake	White lyophilized cake	Strickly yellow, cracked lyophilized cake
Identification	Consistent with standard	Consistent with standard	Consistent with standard	Consistent with standard	Consistent with standard	Consistent with standard
Reconstitution time in water	NMT 3 min	NMT 3 min	NMT 3 min	NMT 3 min	NMT 3 min	NMT 3 min
Appearance of reconstituted solution	Clear solution free of visible particles	Clear solution free of visible particles	Clear solution free of visible particles	Clear solution free of visible particles	Clear solution free of visible particles	Clear solution free of visible particles
Color of reconstituted solution	Colorless solution	Colorless solution	Colorless solution	Very slightly yellow solution	Colorless solution	Yellow solution
pH of reconstituted solution	4.0	4.0	4.0	4.1	4.0	4.0
Water content (% w/w)	0.8	1.0	1.6	1.8	0.6	0.7
Impurities and degradation products[1] (% w/w)						
Total[2]	0.3	0.8	0.3	14.5	0.3	57.3
Individual[3] (RRT)						
0.23-0.24	—	0.10	—	—	—	5.3
0.29	—	—	—	—	—	3.6
0.5	—	—	—	1.7	—	—
0.67-0.68	—	0.10	—	2.9	—	2.5
0.70-0.71	—	—	—	—	—	1.7
0.72	—	—	—	—	—	1.5
0.73	—	—	—	—	—	1.7
0.77	—	—	—	—	—	1.0
0.78	—	—	—	—	—	1.0
0.87-0.88 (D)	0.26	0.39	0.27	0.67	0.26	0.27
1.06	—	—	—	—	—	12.9
1.12	—	0.12	—	—	—	—
1.19-1.20	—	—	—	—	—	6.7
Assay (% nominal)	98.8	98.7	99.3	85.5	98.9	42.7

[1]HPLC Commercial Method: MPI-00769 6.0 [26]

[2]Total impurities and degradation products calculated as sum of all individual impurities with % w/w ≥ 0.05%.

[3]Reported individual impurities and degradation products: 5% Sucrose: (% w/w) ≥ 0.10%; 5% Sucrose + 2.5% Mannitol and 5% Mannitol: t = 0) (% w/w) ≥ 0.10% and t = 3 months (% w/w) ≥ 1.0%.

Table 9 shows the results of stability of lyophilized vials formulated in 0.03M sodium lactate buffer pH=4 with sucrose at different concentrations in the range 5%-10% under stress conditions (40° C./75% RH)

TABLE 9

Stress stability of lurbinectedin freeze-dried vials formulated in 0.03M lactate buffer pH 4 with sucrose as bulking agent at different concentrations

	5% Sucrose Batch 2021-50		7.5% Sucrose Batch 2021-51		10% Sucrose Batch 2021-52	
CQAS	t = 0	3 months at 40° C.	t = 0	3 months at 40° C.	t = 0	3 months at 40° C.
Appearance	White lyophilized cake	White lyophilized cake	White lyophilized cake	White lyophilized cake	White lyophilized cake	White lyophilized cake
Identification by HPLC (RT)	Consistent with standard	Consistent with standard	Consistent with standard	Consistent with Standard	Consistent with standard	Consistent with standard

TABLE 9-continued

Stress stability of lurbinectedin freeze-dried vials formulated in 0.03M lactate buffer pH 4 with sucrose as bulking agent at different concentrations

	5% Sucrose Batch 2021-50		7.5% Sucrose Batch 2021-51		10% Sucrose Batch 2021-52	
CQAS	t = 0	3 months at 40° C.	t = 0	3 months at 40° C.	t = 0	3 months at 40° C.
Reconstitution time in water	NMT 3 min	NMT 3 min	NMT 3 min	NMT 3 min	NMT 3 min	NMT 3 min
Appearance of reconstituted solution	Clear solution free of visible particles	Clear solution free of visible particles	Clear solution free of visible particles	Clear solution free of visible particles	Clear solution free of visible particles	Clear solution free of visible particles
Color of reconstituted solution	Colorless solution	Colorless solution	Colorless solution	Colorless solution	Colorless solution	Colorless solution
pH of reconstituted solution	4.0	4.0	4.0	4.1	4.0	4.0
Water content (% w/w)	0.8	1.0	1.1	1.2	1.2	1.5
Impurities and degradation products[1] (% w/w)						
Total[2]	0.3	0.8	0.3	0.8	0.3	0.7
Individual[3] (RRT)						
0.24	—	0.10	—	—	—	—
0.68	—	0.10	—	0.11	—	0.10
0.87-0.88 (D)	0.26	0.39	0.26	0.39	0.27	0.40
1.1.2	—	0.12	—	—	-—	-—
Assay (% nominal)	98.8	98.7	90.5	98.1	99.4	99.2

[1]HPLC Commercial Method: MPI-007696.0 [26]
[2]Total impurities and degradation products calculated as sum of all individual impurities with % w/w ≥ 0.05%
[3]Reported individual impurities and degradation products: % w/w ≥ 0.10%

The batches containing sucrose at 3 different concentrations showed similar behavior and remained stable. They did not undergo significant changes in the appearance of the freeze-dried cake and lurbinectedin assay (%). A slight increase in the % degradation products was observed. In particular, Impurity D (rrt 0.88, HPLC commercial method) was the main degradation product. The percentage of sucrose does not significantly affect the stability of the product, although 10% sucrose showed the lowest degradation.

As a conclusion, sucrose showed a protective effect to prevent lurbinectedin degradation during storage at high temperature. Based on these results, sucrose was selected as the most appropriate bulking agent being the concentration of 10% (w/v) an optimal quantity for a suitable and stable lurbinectedin presentation.

Example 7: Stability of Lurbinectedin at Long-Term Storage Conditions

The stability of lyophilized lurbinectedin composition (4 mg) at the conditions proposed for long-term storage (5° C.±3° C.) was evaluated during 36 months. A batch with high residual water content was chosen as it is considered as a worst case.

The product remained stable during the 36 months of the study (Table 10). None of the quality attribute underwent significant changes. The content of lurbinectedin suffered small variations attributed to the analytical variability during the first 24 months. The total degradation products did not change throughout the storage time. The related substance observed at reportable levels was Impurity D that remained constant and at the levels present in the active ingredient used to manufacture the batch.

TABLE 10

Stability Study of Lurbinectedin 4 mg at 5° C. ± 3° C.

	Acceptance	Time (months)									
Test[a]	Criteria	0	3	6	9	12	18	24	36	48	60
Appearance	White to off-white lypophilized	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Identification by HPLC (RT)	Consistent with standard	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Reconstitution time in water	NMT 3 min	<3 min	<3 min	<3 min	<3 min	<3 min	<3 min	<3 min	<3 min	<3 min	<3 min
Appearance of reconstituted solution	Clear solution essentially free of visible particles	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies

TABLE 10-continued

Stability Study of Lurbinectedin 4 mg at 5° C. ± 3° C.

Test[a]	Acceptance Criteria	Time (months) 0	3	6	9	12	18	24	36	48	60
Color of reconstituted solution	Colorless or slightly yellowish solution	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
pH of reconstituted solution	3.8 to 4.5	4.1	4.0	4.0	4.0	4.0	4.0	4.0	4.1	4.0	4.0
Subvisible particles (per vial)											
Larger than 10 μm	NMT 6000	16	NA	NA	NA	NA	NA	66	54	NA	52
Larger than 25 μm	NMT 600	1	NA	NA	NA	NA	NA	0	0	NA	1
Moisture (% w/w)	NMT 3.0	0.7	0.6	0.8	0.6	0.8	0.8	0.8	0.7	1.5	0.8
Degradation products (% w/w)											
Total	NMT 1.3	0.4	0.4	0.5	0.4	0.5	0.5	0.5	0.5	0.5	0.5
Specified											
Impurity D	NMT 0.8	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Unspecified, Individual	NMT 0.3	<0.1	<0.1	0.1	<0.1	0.1	<0.1	0.1	0.1	0.1	0.2
Assay (% of label claim)	90.0 to 100.0	99.1	98.8	100.0	100.3	99.9	98.5	100.7	98.8	98.2	99.4
Sterility	Sterile	Sterile	NA	NA	NA.	NA	NA	NA	Sterile	Sterile	Sterile

NA: Not applicable

Example 8: Clinical Study—Treatment of SCLC Patients with Lurbinectedin

A clinical study of lurbinectedin monotherapy for patients collectively afflicted with SCLC who have refractory or resistant disease, as defined herein, was carried out. In this clinical single-arm, multi-center, open-label, phase 2 trail, a cohort of 105 patients, who had measurable disease, including patients whose SCLC was unresponsive to first-line platinum-containing chemotherapy (cisplatin, carboplatin or oxaliplatin) (refractory) and patients whose SCLC recurred within or equal to 90 days after cessation of first-line therapy (resistant), were treated with lurbinectedin at a dosage of 3.2 mg/m^2 given intravenously over a period of 1 hour every 21 days. Lurbinectedin was provided as a sterile isotonic aqueous solution for IV infusion as described below.

Study Population

Adult patients aged at least 18 years with a pathologically proven diagnosis of SCLC were included if they had: pre-treatment with only one previous chemotherapy-containing treatment line (immunotherapy was allowed, combined with chemotherapy or alone); measurable response as per the Response Criteria in Solid Tumors (RECIST version 1.1), and documented progression before study entry; and an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or lower. Patients were required to have adequate bone marrow function (evaluated by laboratory tests for absolute neutrophil count, platelet count, and hemoglobin), kidneys (evaluated by serum creatinine and creatinine kinase), liver (evaluated by total bilirubin, albumin, and aminotransferases). The minimum interval between any previous treatment and study commencement had to be 3 weeks for chemotherapy, 4 weeks for immunotherapy or radiotherapy, and 2 weeks for any investigational or palliative therapy. Only patients with grade 1 or lower toxicities from any previous therapies were included, except for cases with alopecia and peripheral sensory neuropathy (both grade 2), which were also allowed. Women of child-bearing age had to receive adequate contraception during the study and for at least 3 months after study conclusion.

Patients were excluded if they have: previously received lurbinectedin or trabectedin; previous or concurrent malignant disease unless in complete remission for than 5 years; known CNS involvement (screening of CNS metastasis at baseline are mandatory); concomitant unstable or serious medical condition within the past year (history or presence of unstable angina, myocardial infarction, congestive heart failure, valvular heart disease, arrhythmia, severe dyspnoea, or active infection, such as hepatitis or HIV); impending need for radiotherapy; or inability or restricted ability to comply with the study protocol. More details on inclusion and exclusion criteria can be found in Table 11.

Inclusion	Exclusion
Age ≥18 years.	Prior treatment with lurbinectedin or trabectedin.
Voluntary signs informed consent of the patient before any study-specific procedure.	Prior or concurrent malignant disease unless in complete remission for more

-continued

Inclusion	Exclusion
Pathologically proven diagnosis of small cell lung cancer. Patients must have received one prior chemotherapy-containing line. Measurable disease as defined by the RECIST v.1.1, and documented progression before study entry. Eastern Cooperative Oncology group performance status ≤2. Adequate major organ function: Hemoglobin ≥9 g/dL, prior red blood cell transfusions is allowed if clinically indicated; absolute neutrophil counts ≥2.0 × 10^9/L; and platelet count ≥100 × 10^9/L. Alanineaminotransferaseandaspartate aminotransferase <3.0 × ULN. Total bilirubin <1.5 × ULN, or direct bilirubin <ULN. Albumin ≥3 g/dL. Serum creatinine ≤1.5 × ULN or creatinine clearance ≥30 mL/min. Creatine phosphokinase ≤2.5 × ULN. Washout periods prior to Day 1 of Cycle 1: At least three weeks since the last chemotherapy (six weeks if therapy contained nitrosureas or systemic mitomycin C). At least four weeks since the last monoclonal antibody-containing therapy, or radiotherapy >30 gray At least two weeks since the last biological/investigational therapy (excluding monoclonal antibodies) or palliative radiotherapy (≤10 fractions or ≤30 Gy total dose). Grade ≤1 toxicity due to any previous cancer therapy according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v.4. Grade 2 is allowed in case of alopecia and/or peripheral sensory neuropathy. Women of childbearing potential must have pregnancy excluded by appropriate testing before study entry. Fertile women have to agree to use a medically acceptable method of contraception throughout the treatment period and for at feast three months after treatment discontinuation. Fertile men had to agree to refrain from fathering a child or donating sperm during the trial and for four months after the last infusion.	than five years, except treated in situ carcinoma of the cervix, basal or squamous cell skin carcinoma, and in situ transitional cell bladder carcinoma. Known central nervous system involvement. Brain computed tomography-scan or magnetic resonance imaging results has to be provided at baseline. Relevant diseases or clinical situations which may increase the patient's risk: History within the last year or presence of unstable angina, myocardial infarction, congestive heart failure, or clinically relevant valvular heart disease or symptomatic arrhythmia or any asymptomatic ventricular arrhythmia requiring ongoing treatment. Grade ≥3 dyspnea or daily intermittent oxygen requirement within two weeks prior to the study treatment onset. Active infection. Unhealed wounds or presence of any external drainage. Known chronic active hepatitis or cirrhosis. Immunocompromised patients, including known infection by human immunodeficiency virus. Women who are pregnant or breast feeding and fertile patients (men and women) who are not using an effective method of contraception. * Impending need for radiotherapy (e.g., painful bone metastasis and/or risk of spinal cord compression). Limitation of the patient's ability to comply with the treatment or to follow-up the protocol. * Women of childbearing potential have to agree to use an effective contraception method to avoid pregnancy during the course of the trial (and for at least three months after the last infusion). Fertile men have to agree to refrain from fathering a child or donating sperm during the trial and for four months after the last infusion.

Study Drug Formulation—Preparation and Administration

Lurbinectedin was presented as lyophilized powder for concentration for solution for infusion in 4 mg vials. Before use, the 4 mg vials were reconstituted with 8 mL of water for injection to give a solution containing 0.5 mg/mL of lurbinectedin. For administration to patients as an i.v. infusion, reconstituted vials were diluted with glucose 50 mg/mL (5%) solution for infusion or sodium chloride 9 mg/mL (0.9%) solution for infusion. The full composition and the reconstituted solution per mL was as shown in Table 12.

TABLE 12

Composition of 4 mg lurbinectedin vials

Component	Concentration/ vial	Concentration/ vial after reconstitution
PM01183	4.0 mg	0.5 mg/ml
Sucrose	800 mg	100 mg/ml
Lactic acid	22.08 mg	2.76 mg/ml
Sodium hydroxide	5.12 mg	0.64 mg/ml

Dosage and Administration

Lurbinectedin was administered over a minimum total volume of 100 mL of solution for infusion (either on 5% glucose or 0.9% sodium chloride), through a central catheter, or over a minimum total volume of 250 mL if administered through a peripheral line, always over one hour at a fixed infusion rate.

Starting dose was 3.2 mg/m^2. Dose was capped at body surface area of 2.0 mg/m^2 (e.g. dose not allowed to exceed 6.4 mg). Patients received lurbinectedin i.v. as a one-hour infusion on Day 1 every three weeks until disease progression or unacceptable toxicity. Three weeks was defined as one treatment cycle.

Premedication

All patients received antiemetic prophylaxis before each treatment infusion. The i.v. formulations of these agents were used in this setting: Corticosteroid (dexamethasone 8 mg or equivalent), serotonin antagonists (ondansetron 8 mg or equivalent), extended treatment with oral serotonin antagonists, and oral dexamethasone for two consecutive days. If necessary, and in addition to the above, administration of 10 mg of oral or i.v. metoclopramide (or equivalent) every 8 hours. Aprepitant and equivalent agents were forbidden in patients treated with lurbinectedin.

Criteria for Treatment Continuation

Further treatment cycles were administered q3wk (±48 hours) if the patient fulfilled all the treatment criteria described in Table 13.

TABLE 13

Variable	Re-treatment (Day1)
ECOG PS	≤2
Hemoglobin*	≥8.0 g/dl
ANC	≥1.5 × 10^9/l
Platelets	≥100 × 10^9/l
AST/ALT	≤3.0 × ULN
Total bilirubin or	≤1.5 × ULN or
Albumin	≥3 g/dl
Serum creatinine	≤1.5 × ULN or creatinine clearance ≥ 30 ml/min
CPK	Grade ≤ 1
Other non-hematological drug-related AEs (except isolated increased GGT and/or AP; grade 2 asthenia, constipation, alopecia, peripheral	Grade ≤ 1
Active infection (including sepsis) and/ or bleeding (any	Absence

AE(s), adverse event(s);
ANC, absolute neutrophil count;
AP, alkaline phosphatase;
AST/ALT, aspartate aminotransferase/alanine aminotransferase;
CPK, creatinine phosphokinase;
ECOG, Eastern Cooperative Oncology Group;
GGT, gamma-glutamyltransferase;
PS, performance status;
ULN, upper limit of normal.

Patients received packed red blood cells transfusion and/or erythropoietin treatment, if clinically indicated, to increase/maintain adequate hemoglobin levels. If a patient did not meet the requirements for re-treatment on Day 1 of any following cycle, regardless of the reason, reassessments were performed at least every 48-72 hours. Treatment was then withheld, up to a maximum of three weeks beyond its due date, until appropriate recovery. Patients not meeting re-treatment criteria after a maximum 3-week delay had to withdraw from trial. For any delay due to treatment-related adverse events lasting for more than one week, a dose reduction was implemented upon recovery, following the rules explained in the next section.

Dose Modifications for Adverse Reactions

Patients continued the treatment if they presented with any of the following: (1) Grade ≥3 treatment-related non-hematological toxicity. Exceptions were: Grade ≥3 nausea and/or vomiting not optimally treated, grade 3 asthenia lasting ≤3 days, grade 3 diarrhea lasting ≤2 days or not optimally treated, grade 3 transient ALT/AST elevations which are rapidly reversible and not leading to subsequent delays, and non-clinically relevant biochemical abnormalities. (2) Grade 4 thrombocytopenia or Grade 3 thrombocytopenia concomitantly with grade ≥3 bleeding. (3) Grade 4 neutropenia, any grade febrile neutropenia or neutropenia associated with infection/sepsis. (4) Frequent of prolonged (>1 week) dose delays due to treatment-related adverse events. Patients who experienced Grade 3 or 4 hypersensitivity reactions were discontinued from study treatment.

Previous analysis with lurbinectedin administered following a dose based on body surface area showed that the incidence of febrile neutropenia with lurbinectedin use was lower than 10%. Therefore, according to guidelines from the American Society of Clinical Oncology and European Society for Medical Oncology, primary prophylaxis with granulocyte colony-stimulating factors (G-CSF) was not allowed (secondary prophylaxis with G-CSF for neutropenia was allowed).

Dose reduction levels are shown in Table 14 below:

TABLE 14

Dose Modification	
Dose Reduction	Lurbinectedin Dose (mg/m2)
1 (starting dose)	3.2**
−1	2.6
−2	2.0

**Dose will be capped at BSA of 2.0 m2 (i.e. dose will not exceed 6.4 mg) BSA, body surface area.

Up to 2 dose reductions were allowed per patient. Patients who continued to experience treatment-related toxicity and/or frequent dose delays after permitted dose reductions were withdrawn from the study. They could continue receiving the study medication if objective clinical benefit is adequately documented. Once a dose had been reduced for an individual patient, the dose was not re-escalated under any circumstances.

Efficacy Evaluations

The primary objective of this study was to assess the antitumor activity of lurbinectedin in terms of overall response rate (ORR) as primary endpoint and supported by duration of response (DOR) as secondary endpoint. ORR was assessed using RECIST v1.1. on a set of measurable lesions identified at baseline as target lesions or as non-target lesions (if any), and followed until disease progression (PD) by an appropriate method.

Radiological tumor assessment (CT scan or MRI) was performed at baseline, and every 6 weeks from the onset of the study treatment until cycle 6 or evidence of PD, and every 9 weeks thereafter. If an objective response was

observed, according to RECIST v1.1., it had to be confirmed by the same method at least four weeks after the date of the first documentation of response.

ORR was defined as the percentage of evaluable patients with a confirmed response, either complete (CR) or partial response (PR), from the start of treatment to the date of progression or the start of a subsequent therapy or end of patients follow-up according to RECIST v1.1. DOR was calculated from the date of first documented PD, recurrence, or death due to any cause in the responder patients. The date of response, the date of radiological or clinical PD, according to the investigator assessment and the independent assessment by an independent review committee (IRC), and the date of death was registered and documented, as appropriate. The IRC determined the patient's best response and assigned the date of first documentation of response and progression/censoring according to RECIST v1.1.

Counts and percentages, with their corresponding exact 95% confidence intervals were calculated for the binominal endpoints (i.e. ORR, clinical benefit). Time-to-event variables (OS, PFS, and DOR) and their set time estimates (i.e. PFS4/6 and OS6/12) were analyzed according to Kaplan-Meier method. The evaluation of the efficacy endpoints evaluated by IA and IRC were analyzed and compared.

Pharmacokinetic Evaluations

The plasma PK of lurbinectedin was evaluated during Cycles 1 and 2 in all treated patients. The sampling schedule is shown in Table 15 and Table 16, respectively.

PK analysis of plasma-concentration-time data of lurbinectedin was performed using non-linear mixed-effects modeling and/or non-compartment analysis.

TABLE 15

Blood samples from PK evaluations—Cycle 1

Sample No.	Day	Sampling time	Sampling window
#1	D1	Before infusion start	—
#2 *	D1	5 min before EOI	+/−4 min
#3	D1	30 min after EOI	+/−4 min
#4	D1	1 hour after EOI	+/−10 min
#5	D1	3 hours after EOI	+/−10 min
#6	D2	24 hours after EOI	+/−2 hours
#7	D4	72 hours after EOI	+/−24 hours
#8	D8	168 hours after EOI	+/−24 hours

* Sample #2 must be collected before EOI.
D, day;
EOI, end of infusion.

TABLE 16

Blood samples from PK evaluations—Cycle 2

Sample No.	Day	Sampling time	Sampling window
#9	D1	Before infusion start	—
#10 *	D1	5 min before EOI	+/−4 min
#11	D1	30 min after EOI	+/−4 min
#12	D1	1 hour after EOI	+/−10 min
#13	D1	3 hours after EOI	+/−10 min
#14	D8	168 hours after EOI	+/−24 hours

* Sample #10 must be collected before EOI
D, day;
EOI, end of infusion.

Safety Evaluation

Patients were evaluated for safety if they had received any partial or complete infusion of lurbinectedin. All adverse events were graded according to the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE, v4). The safety profile of patients was monitored throughout the treatment and up to 30 days after the last lurbinectedin infusion (end of treatment), or until the patient started a new anti-tumor therapy or until the date of death, whichever occurred first. Treatment delays, dose reduction requirements, transfusions, and reason for treatment discontinuation was monitored throughout the study. Any treatment-related adverse events were followed until recovery to at least grade 1 or stabilization of symptoms or until the start of a new anti-tumor therapy, whichever occurred first.

Study Endpoints

Primary Endpoint	
Overall Response Rate (ORR)	ORR is defined as the percentage of patients with a confirmed response, either complete (CR) or partial (PR), according to the RECIST (v. 1.1).
Secondary Endpoints	
Duration of Response (DR)	DR is defined as the time between the date when the response criteria (PR or CR, whichever one is first reached) are fulfilled to the first date when PD, recurrence or death is documented.
Clinical Benefit	Clinical Benefit is defined as ORR or stable disease lasting over four months (SD ≥ 4 months)
Progression-free Survival (PFS)	PSF is defined as the period of time from the date of first infusion to the date of PD, death (of any cause), or last tumor evaluation.
PFS4/PFS6	PFS4/PFS6 is defined as the Kaplan-Meier estimates of the probability of being free from progression and death after the first infusion at these time points (4 and 6 months).
Overall Survival (SO)	OS is defined as the period of time from the date of first infusion to the date of death or last contact in case of patients lost to follow-up or alive at the clinical cut-off established for the cohort.
OS6/OS12	OS6/OS12 is defined as the Kaplan-Meier estimates of the probability of being alive after the first infusion at these time points (6 and 12 months)
Plasma Pharmacokinetics (PK)	Non-compartmental (NCA) PK parameters: area under the curve (AUC), C_{max}, clearance (CL) and half-life ($t_{1/2}$). Population PK parameters of the compartment model to be developed (initially based on Volumes and Clearance), and PK/PD correlation parameters, if applicable.
Safety Profile	Clinical examinations. Clinical assessment of AEs and serious adverse events (SAEs). Changes in laboratory parameters (hematological and biochemical, including liver function tests). Reasons for treatment discontinuations. Reasons for dose reduction and treatment delays.

Statistical Methods

This phase II trial was designed to assess the antitumor activity of lurbinectedin in terms of ORR according to the RECIST v.1.1 assessed by IA and tumor evaluation was also done by IRC.

Up to 100 evaluable patients were recruited to test the null hypothesis that 15% or less patients get a response ($p<0.15$) versus the alternative hypothesis that 30% or more patients get a response ($p\geq0.30$). The variance of the standardized test was based on the null hypothesis. The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is 0.051 (normal approximation; ~0.05 if exact binomial distribution); hence, statistical power is 95% (normal approximation; ~95% if exact binomial distribution). With these assumptions, if the number of patients who achieved a confirmed response is 23, then this would allow the rejection of the null hypothesis. The judgement of

patient's evaluability and replacement of non-evaluable patients in each cohort for the interim analyses was guided by the investigator assessment.

Duration of Study Period

Patients were evaluated at scheduled visits within three study periods: (1) Pre-treatment: from signature of IC to the first infusion of the study treatment; (2) Treatment: from the first infusion of the study treatment to the end of treatment; and (3) Follow-up: after end of treatment; patients were followed-up every 4 weeks until resolution or stabilization of all drug-related adverse events, if any, or until start of new anti-tumor therapy. Patients were followed up for at least 1 year after their first lurbinectedin infusion. Patients who finished treatment without PD were followed every 2 months during the first six months and every 3 months thereafter until PD, start of a new anti-tumor therapy, death, or until end of study date.

Results

105 SCLC patients were enrolled into the study. All 105 patients were treated and included in the analysis for the primary endpoint. Of the 105 treated patients, 60% were male, 75% were white, 92% had ECOG PS 0 or 1, and the median age was 60 years (range, 40-83 years; 35.2% were ≥65 years old). Two of the 105 treated patients (1.9%) had previously undergone surgery (curative resection in one patient). Prior radiotherapy had been administered to 75 patients (71.4%). The patients had received a median of one prior line of chemotherapy for advanced disease (range, 1-2 lines). The chemotherapy-free interval was less than 30 days in 21 (21%) patients, less than 90 days in 45 (43%) patients, and 90 days or longer in 60 (57%) patients. One patient with CNS metastases at baseline was included, and another patient had rechallenge with carboplatin plus etoposide and atezolizumab as previous line of therapy; these two cases were considered protocol deviations, but they were minor and were included in the primary analysis.

618 treatment cycles in total were administered, with a median of four cycles per patient, and 46 (44%) patients received six cycles or more. The median relative dose intensity of the study drug was 97.4% of the planned maximum dose. Dose administration was delayed in 23 (22%) patients and reduced in 28 (26%) because of treatment-related adverse events (neutropenia was the most common cause of both dose delays in 13 (12%) and reductions in 17 (16%) of patients).

Efficacy of Lurbinectedin in SCLC Patients

At data cutoff, median follow-up was 17.1 months. According to the investigator assessment of all treated patients, 37 (35.2%) had an overall response as shown in Table 17.

Parameter	Assessment by	Overall (n = 105)	Resistant Disease (CTFI <90 days) (n = 45)	Sensitive Disease (CTFI ≥90 days) (n = 60)
Overall response rate (CR + PR) (95% CI)	Investigator	35.2% (26.2-45.2)	22.2% (11.2-37.1)	45.0% (32.1-58.4)
	IRC	30.5% (21.9-40.2)	13.3% (5.1-26.8)	43.3% (30.6-56.8)
Duration of response, median, months (95% CI)	Investigator	5.3 months (4.1-6.4)	4.7 months (2.6-5.6)	6.2 months (3.5-7.3)
	IRC	5.1 months (4.9-6.4)	4.8 months (2.4-5.3)	5.3 months (4.9-7.0)

In the pre-planned analysis of overall response by chemotherapy-free interval (≥90 days vs<90 days) of 60 patients who had a chemotherapy-free interval of 90 days or longer (i.e., those with chemotherapy-sensitive disease), 27 (45.0%) had an overall response, with a median duration of response of 6.2 months, whereas in 45 patients who had a chemotherapy-free interval of less than 90 days (i.e., chemotherapy-resistant disease), ten (22.2%) had an overall response, with a median duration of response of 4.7 months.

Progression-Free Survival

Investigator-assessed median progression-free survival was 3.5 months (95% CI 2.6-4.3) in the overall population: 4.6 months in patients with a chemotherapy-free interval of 90 days or longer and 2.6 months in patients with chemotherapy-free interval of less than 90 days. Eight (9%) of 94 patients who discontinued lurbinectedin treatment had disease progression with new lesions in the CNS. No increased incidence of CNS metastases was therefore observed.

Overall Survival

With a censoring of 37.1% (39 of 105 patients alive at data cutoff), median overall survival was 9.3 months (95% CI 6.3-11.8) in the overall population, 11.9 months (9.7-16.2) in patients with a chemotherapy-free interval of 90 days or longer, and 5.0 months (4.1-6.3) in patients with chemotherapy-free interval of less than 90 days. Notably, 29 (48%) of 60 patients with a chemotherapy-free interval of 90 days or longer and seven (16%) of 45 patients with a chemotherapy-free interval of less than 90 days were alive at 1 year after the first dose administration.

In a post-hoc analysis, of the 37 patients who had an initial objective response, median overall survival exceeded 1 year in the overall population (12.6 months, 95% CI 10.8-15.8) and in patients with sensitive disease (15.8 months, 10.2—not reached) and was 10.9 months in patients with resistant disease (10.9 months, 6.3-14.0).

Safety

All 105 treated patients were evaluable for safety (Table 18). The most common Grade 3-4 adverse events and laboratory abnormalities (in ≥2% of patients) were hematological disorders, including anemia (nine [9%] patients), leukopenia (30 [29%]), neutropenia (48 [46%]), thrombocytopenia (seven [7%]), and febrile neutropenia (five [5%]); of these, only febrile neutropenia was regarded as treatment related (Table 18). Notably, no cases of drug-induced liver injury were reported. 23 (22%) of 105 patients received G-CSF secondary prophylaxis or therapy for neutropenia. Serious treatment-related adverse events occurred in 11 (10%) of 105 patients; neutropenia and febrile neutropenia were the most common (five [5%] patients for each). Grade 3 pneumonia was reported in two (2%) patients; these episodes were associated with grade 3 febrile neutropenia and grade 4 neutropenia, lasted 3 days for one patient and 13 days for the other, and resolved with no clinical consequences. One patient had a grade 3 skin ulcer because of extravasation, with no clinical consequences. Only two (2%) patients discontinued lurbinectedin therapy because of treatment-related adverse events. No treatment-related deaths occurred, but 66 (63%) of 105 patients died from disease progression.

TABLE 18

	Grade 1-2	Grade 3	Grade 4
Haematological abnormalities (regardless of relation to study drug)*			
Anaemia	91 (87%)	9 (9%)	0
Leucopenia	53 (50%)	20 (19%)	10 (10%)
Neutropenia	27 (26%)	22 (21%)	26 (25%)
Thrombocytopenia	39 (37%)	3 (3%)	4 (4%)
Biochemical abnormalities (regardless of relation to study drug)*			
Creatinine†	86/104 (83%)	0	0
Alanine aminotransferase	69/103 (67%)	5/103 (5%)	0
γ-glutamyl transferase	52/103 (50%)	13/103 (13%)	2/103 (2%)
Aspartate aminotransferase	44/103 (43%)	2/103 (2%)	0
Alkaline phosphatase	31/103 (30%)	3/103 (3%)	0
Treatment-related adverse events			
Fatigue	54 (51%)	7 (7%)	0
Nausea	34 (32%)	0	0
Decreased appetite	22 (21%)	0	0
Vomiting	19 (18%)	0	0
Diarrhoea	13 (14%)	1 (1%)	0
Febrile neutropenia	0	2 (2%)	3 (3%)
Pneumonia	0	2 (2%)	0
Skin ulcer	0	1 (1%)	0

Data are n (%) of patients.
NCI-CTCAE = National Center Institute Common Terminology Criteria for Adverse Events version 4.0.
*Based on all patients with laboratory data available.
†Version 4.0 of NCI-CTCAE grades any creatinine increases from baseline as abnormalities, even if creatinine values remain within the normal range.

Prior Immunotherapy

Post-hoc exploratory analysis was done on the response in patients who had previously received immunotherapy (n=8). Data from this group of patients showed a trend for a better response to single-agent lurbinectedin following first-line platinum-containing chemotherapy in combination with checkpoint inhibitors or second-line with nivolumab (Table 19). This is an important finding in light of the recent approval of atezolizumab in first-line SCLC in combination with carboplatin/etoposide; hence, lurbinectedin could provide a viable option for patients who progress on immunotherapy.

TABLE 19

Disease (resistant or sensitive)[a]	Last prior therapy: No. of prior regimens	Agent or regimen	Best response	TTP (months)	Lurbinectedin treatment: Best response	PFS (months)	DoR (months)	OS (months)
Resistant	1	C/E/Atezolizuma	PR	3.9	PR	8.3	5.6	14.9
Resistant	2	Nivolumab	PD	2.5	PR	6.9	5.3	6.9+
Resistant	2	CE/Atezolizumab	PR	4.0	PR	6.3	5.1	12.6
Resistant	2	Nivolumab	SD	2.2	SD	6.0	—	12.0
Resistant	2	Nivolumab	SD	4.1	PD	1.3	—	4.9
Sensitive	1	CE/Atezolizumab	PR	7.6	PR	7.6	6.4	9.3
Sensitive	2	Nivolumab	PD	1.8	PR	4.7	2.8	10.8
Sensitive	2	Nivolumab	PD	1.4	PD	1.3	—	2.3

Summary and Conclusions

105 SCLC patients were enrolled and treated with lurbinectedin. Median follow-up was 17.1 months (IQR 6.5-25.3). Overall response by investigator assessment was seen in 37 patients (35.2%; 95% CI 26.2-45.2). The most common grade 3-4 adverse events (irrespective of causality) were hematological abnormalities-namely, anemia (in nine [9%] patients), leucopenia (30 [29%]), neutropenia (48 [46%]), and thrombocytopenia (seven [7%]). Serious treatment-related adverse events occurred in 11 (10%) patients, of which neutropenia and febrile neutropenia were the most common (five [5%] patients for each). No treatment-related deaths were reported.

Lurbinectedin was active as second-line therapy for SCLC in terms of overall response and had an acceptable and manageable safety profile. Lurbinectedin could represent a potential new treatment for patients with SCLC, who have few options especially in the event of a relapse.

Example 8: Clinical Study—Treatment of Solid Cancer Patients with Lurbinectedin and Irinotecan

A clinical study of lurbinectedin in combination with irinotecan for patients afflicted with solid tumors was carried out. A Phase 1 trial to evaluate escalating doses of lurbinectedin on Day (D) 1 plus a fixed dose of irinotecan 75 mg/m^2 on D1 and D8 every 3 weeks (q3w) in patients with advanced solid tumors. Patients were enrolled following a standard 3+3 dose escalation design. Phase Ib/II expansion part at the recommended dose (RD) was performed to explore efficacy in indications where antitumor activity signal was observed.

Study Population

Details on inclusion and exclusion criteria can be found in Table 20.

Inclusion	Exclusion
Voluntarily signed and dated written informed consent prior to any specific-study procedure.	Concomitant diseases/conditions: History or presence of unstable angina, myocardial infarction, congestive heart failure, or clinically significant valvular heart disease within the previous year.
Age ≥18 years.	Symptomatic arrhythmia or any uncontrolled arrhythmia requiring ongoing treatment.
Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1.	Myopathy or any clinical situation that causes significant and persistent elevation of CPK (>2.5 × ULN in two different determinations performed one week apart).
Life expectancy ≥3 months.	Ongoing chronic alcohol consumption or cirrhosis with Child-Pugh score B or C.
No more than two prior lines of cytotoxic-containing chemotherapy regimens for advanced disease. There is no limit for prior targeted therapy, hormonal therapy and immunotherapy (such as nivolumab).	Known Gilbert disease.
Histologically or cytologically confirmed diagnosis of advanced disease of any of the following tumor types: Glioblastoma; Soft-tissue sarcoma [excluding gastrointestinal stromal tumors (GIST)]; Endometrial carcinoma; Epithelial ovarian carcinoma (including primary peritoneal disease and/or fallopian tube carcinomas and/or endometrial adenocarcinomas) regardless of platinum sensitivity; Mesothelioma; Gastroenteropancreatic neuroendocrine tumors (GEP-NET); Small cell lung cancer (SCLC); Pancreatic adenocarcinoma; Gastric carcinoma; Colorectal carcinoma (CRC);	Active uncontrolled infection. Known human immunodeficiency virus (HIV) infection. Known human immunodeficiency virus (HIV) or known hepatitis C virus (HCV) infection or active hepatitis B. Any past or present chronic inflammatory colon and/or liver disease, past intestinal obstruction, pseudo or sub-occlusion or paralysis. Evident symptomatic pulmonary fibrosis or interstitial pneumonitis, pleural or cardiac effusion rapidly increasing and/or necessitating prompt local treatment within seven days. Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the patient's participation in this study. Prior treatment with PM01183, trabectedin (Yondelis ®) or topoisomerase I inhibitors (irinotecan, topotecan, etc.). Prior topoisomerase inhibitors (e.g., irinotecan) are only allowed in patients with colorectal carcinoma. Prior bone marrow or stem cell transplantation, or radiation therapy in more than 35% of bone marrow. Known brain metastases or leptomeningeal disease involvement. Glioblastoma lesions (primary or locally advanced) are eligible. In SCLC, patients with brain metastases or leptomeningeal disease involvement are eligible provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment (patients taking steroids in the process of already being tapered within two weeks prior to screening are allowed). Brain CT-scan or MRI results must be provided at baseline. Women who are pregnant or breast feeding and fertile patients (men and women) who are not using an effective method of contraception.(*) Limitation of the patient's ability to comply with the treatment or follow-up protocol.
Expansion phase: Tumor-specific cohort(s) at the RD:	
Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1.	
For patients with glioblastoma: Measurable disease according to RECIST v.1.1 and RANO criteria.	
Documented disease progression per RECIST v.1.1 during or immediately after last therapy according to any of the aforementioned criteria.	
For patients with glioblastoma: Documented disease progression per RECIST v.1.1 and RANO criteria.	
At least three weeks since the last anticancer therapy (excluding immunotherapy that must be at least two weeks, provided that is not combined with chemotherapy), including investigational drugs and radiotherapy, and at least six weeks since nitrosoureas and mitomycin C (systemic).	
For patients with glioblastoma: at least 12 weeks since the end of radiotherapy, except if: The patient has a new lesion outside of the radiotherapy field, or The patient has undergone brain surgery to remove the tumor before study entry, and progressive disease has been confirmed histologically.	
Adequate bone marrow, renal, hepatic, and metabolic function (assessed ≤7 days before inclusion in the study): Platelet count ≥100 × 10^9/L, hemoglobin ≥9.0 g/dL and absolute neutrophil count (ANC) ≥2.0 × 10^9/L. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 × the upper limit of normal (ULN), even in the presence of liver metastases. Alkaline phosphatase (ALP) ≤2.5 × ULN (≤5 × ULN if disease-related/in the case of liver metastases). Total bilirubin ≤1.5 × ULN or direct bilirubin ≤ULN. International Normalized Ratio (INR) < 1.5 (except if patient is on oral anticoagulation therapy).	

-continued

Inclusion	Exclusion
Calculated creatinine clearance (CrCL) ≥30 mL/minute (using Cockcroft-Gault formula).	
Creatine phosphokinase (CPK) ≤2.5 × ULN.	
Albumin ≥3.0 g/dL(*).	
Recovery to grade ≤1 or to baseline from any adverse event (AE) derived from previous treatment (excluding alopecia and/or cutaneous toxicity and/or peripheral neuropathy and/or fatigue grade ≤2).	

Study Drug Formulation—Preparation and Administration

Lurbinectedin was presented as lyophilized powder for concentration for solution for infusion in 4 mg vials. Before use, the 4 mg vials were reconstituted with 8 mL of water for injection to give a solution containing 0.5 mg/mL of lurbinectedin. For administration to patients as an i.v. infusion, reconstituted vials were diluted with glucose 50 mg/mL (5%) solution for infusion or sodium chloride 9 mg/mL (0.9%) solution for infusion. The full composition and the reconstituted solution per mL was as shown in Table 12 supra.

Irinotecan was presented as lyophilized powder for concentration for solution for infusion in 40 mg, 100 mg, or 300 mg vials.

Dosage and Administration

Lurbinectedin was administered over a minimum total volume of 100 mL of solution for infusion (either on 5% glucose or 0.9% sodium chloride), through a central catheter, or over a minimum total volume of 250 mL if administered through a peripheral line, always over one hour at a fixed infusion rate.

Dose levels in patients at the escalation phase (n=39) were as shown in Table 21. Patients received lurbinectedin i.v. as a one-hour infusion on Day 1 and irinotecan, i.v. as a 90-minute infusion at days 1 and 8 every three weeks. Three weeks was defined as one treatment cycle.

TABLE 21

Dose Level	Irinotecan (mg/m2), D1 & D8, q3w	Lurbinectedin (mg/m2), D1, q3w	Number of treated patients	DLTs/Evaluable patients	DLTs Description
1	75	1.0	6	1/6	Omission of D8 due to G3 neutropenia
2	75	1.5	4	1/4	Delay DLT (cycle 3); G3 FN
3 (MTD without G-CSF)	75	2.0	12	4/11	Omission of D8 due to G3 neutropenia, omission of D8 due to G4 neutropenia, 2 episodes of G3 FN
3* (RD with G-CSF)	75	2.0	13	3/12	Omission of D8 due to G2 thrombocytopenia, 2 episodes of omission D8 due to G3 neutropenia
4* (MTD with G-CSF)	75	2.4	4	2/3	Omission of D8 due to G2 thrombocytopenia, omission of D8 due to G4 neutropenia

Outcome Measures

Primary outcome measures were (1) maximum tolerated dose (MTD) and (2) recommended dose (RD). MTD was defined as lowest dose explored during dose escalation which one third or more of evaluable patients develop DLT in Cycle 1. RD was defined as highest dose level explored during dose escalation in which fewer than one third of evaluable patients develop DLT during Cycle 1.

Secondary outcome measures included safety evaluation, peak plasma concentration (Cmax), area-under-the plasma concentration versus time curve (AUC), volume of distribution based on the terminal half-life (Vz), volume of distribution at steady state (Vss), clearance (CL), half-life (t½), evaluation of antitumor response (RECIST v1.1, start of treatment until PD, other antitumor therapy, death or until 12 months after the inclusion of the last evaluable patient in the study (end of study), whichever occurs first), progression-free survival (from the date of first infusion of study treatment to the date of progression or death or until 12 months after end of study, whichever occurs first), and overall survival (from the date of first infusion to study treatment to the date or death or until 12 months after end of study, whichever occurs first).

Pharmacokinetic Evaluations

Patients underwent PK sampling for assessment of lurbinectedin, irinotecan, and SN38 (active metabolite of irinotecan), aimed at ruling out major drug-drug interactions.

Safety Evaluation

Patients were evaluated for safety if they had received any partial or complete infusion of lurbinectedin and irinotecan. All adverse events were graded according to the National

Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE, v4). The safety profile of patients was monitored throughout the treatment and up to 30 days after the last administration of study treatment (end of treatment), or until the patient started a new anti-tumor therapy or until the date of death, whichever occurred first. Treatment delays, dose reduction requirements, transfusions, and reason for treatment discontinuation was monitored throughout the study. Any treatment-related adverse events were followed until recovery to at least grade 1 or stabilization of symptoms or until the start of a new anti-tumor therapy, whichever occurred first.

Results

39 patients were initially treated at 5 dose levels (DL, see Table 21 supra); 13 at the recommended dose (RD). 56% were females, 69% had ECOG PS=1; median age was 58 years; median of 2 prior chemotherapy lines for advanced disease (range, 0-4) per pt. RD was defined as lurbinectedin 2.0 mg/m^2 on D1+irinotecan 75 mg/m^2 on D1 and D8 q3w+G-CSF. Dose limiting toxicities in Cycle 1 were observed in 2/3 evaluable patients at the maximum tolerated dose (MTD) and in 3/13 evaluable patients at the RD. At the MTD and the RD, DLTs were skipping irinotecan D8 doses due to grade (G) 3-4 neutropenia (n=3 patients) or G2-4 thrombocytopenia (n=2). At the RD common G1/2 toxicities were nausea, vomiting, fatigue, diarrhea, anorexia and neuropathy; G3/4 hematological abnormalities comprised neutropenia (33%), but no thrombocytopenia.

Pharmacokinetics Data

Concentration-time data of lurbinectedin, irinotecan, and SN-38 are available from 39 patients. Mean (±SD) of main PK parameters are provided in the Table below, along with those reported elsewhere for lurbinectedin single agent, and irinotecan and SN-38 (Camptosar Label).

Based on the comparability with reference PK data, these PK results of the three analytes evaluated do not suggest any type of major drug-drug interactions, thus indicating that the drug combination of lurbinectedin and irinotecan can be administered safely from a PK standpoint.

TABLE 22

Compound	Dose Level (mg/m2)	n	Cmax (ug/L)	CL (L/h)	HL (h)	Vz (L)
Lurbinectedin	1.0-2.4	39	—	9.9 (5.4)	44.2 (22.4)	580.9 (345.5)
	3.2 (ref)	329	127.5 (100.2)	12.4 (7.6)	42.6 (38.4)	664.7 (460.3)
Irinotecan	75	39	828.2 (174.7)	30.2 (10.3)	9.9 (4.3)	233.2 (83.3)
	125 (label)	64	1660 (797)	22.6 (10.2)	11.7 (9)	187 (82.5)
SN-38	—	39	18.1 (7.7)	810.3 (574)	18.6 (9.1)	18232.3 (8208.4)
	— (label)	64	26.3 (11.9)	NA	21.0 (20)	NA

Efficacy Data

Encouraging activity has been observed in patients with SCLC, including some cases as third line treatment. Signals of activity were also observed in endometrial carcinoma and soft tissue sarcoma (STS) and glioblastoma (GBM). Consequently, a Phase II expansion at the RD to further explore efficacy and safety in SCLC, GBM, STS, and endometrial carcinoma. A total of 59 patients were treated at the RD, including n=15 SCLC, n=11 endometrial cancer, n=10 STS, and n=20 GBM patients. Efficacy data per tumor type at all doses are shown in the table below.

TABLE 23

Tumor Type (No of evaluable patients)	SCLC (n = 13)	Endometrial (n = 10)	STS (n = 10)	GBM (n = 16)
Median no. of cycles (range)	8 (1-12)	7 (2-37)	4 (2-15)	2 (1-7)
ORR* (PR) [n(%)]	9 (69.2)	3 (30)	0	1 (6.3)
CBR (ORR + SD > 4 mo) (%)	76.9	60	40	18.8
DCR (ORR + SD) (%)	84.6	100	80	43.8
Median PFS (mo)	4.3	7.1	2.6	1.4
Median DoR (mo)	4.6	4.6	—	—
PFS rate at 6 mo (%)	36.3	50	33.8	7.1

Safety

Two patients (3.4%) discontinued treatment due to a treatment-related adverse event (Bilirubin G2, weakness G3). 17 patients (28.8%) had dose reductions (76% of reductions were due to day 8 irinotecan omissions related to adverse events). 19.8% of day 8 irinotecan infusions were omitted at the RD (mostly due to hematological toxicity). No treatment-related deaths occurred. A detailed description of adverse events and laboratory abnormalities observed in patients at RD is shown in Table 24.

TABLE 24

	Adverse Events & Laboratory Abnormalities	Patients at RD LUR + IRI (n = 59) G1-2 (%)	G3-4 (%)
Treatment-related adverse events	Fatigue	33 (55.9%)	5 (8.5%)
	Nausea	33 (55.9%)	1 (1.7%)
	Vomiting	15 (25.4%)	—
	Diarrhea	25 (42.4%)	5 (8.5%)
	Constipation	7 (11.9%)	—
	Abdominal Pain	6 (10.2%)	—
	Anorexia	18 (30.5%)	—
	Febrile Neutropenia	—	3 (5.1%)
Laboratory abnormalities	Anemia	46 (78%)	8 (13.6%)
	Neutropenia	21 (35.6%)	29 (49.1%)
	Thrombocytopenia	30 (50.8%)	6 (10.1%)
	ALT increase	23 (39%)	3 (5.1%)
	AST increases	23 (39%)	2 (3.4%)

Summary and Conclusions

The RD is lurbinectedin 2.0 mg/m^2 on day 1 and irinotecan 75 mg/m^2 on day 1 and day 8 q3wk, with GCS-F, in solid tumors. DLTs are mostly day 8 irinotecan omissions in cycle 1 due to hematological toxicity. Main toxicities observed were myelosuppression, gastrointestinal and fatigue. Gastrointestinal and myelosuppression were predictable and manageable. Promising activity has been observed in SCLC. Notable activity has been observed in endometrial carcinoma, and hints of activity have been found in STS (especially Ewing and synovial sarcoma). Modest activity has been observed in glioblastoma patients. Expansion cohorts in SCLC, endometrial carcinoma and STS patients are still ongoing, to enroll a total of 20 patients in each indication.

Lurbinectedin Solid State Form Examples

Abbreviations

DSC	Differential scanning calorimetry
DVS	Dynamic vapor sorption
XRPD	X-ray powder diffractograms
TG-FTIR	Thermogravimetry coupled with Fourier transformed infrared spectroscopy
r.h.	Relative humidity

The X-ray powder diffractograms (XRPD) were obtained with a Stadi P diffractometer (Stoe & Cie GmbH) in transmission geometry, equipped with a curved Ge-crystal monochromator, a Cu-Kα1 radiation source and a Mythen1K Detector in step scan detector mode. The pattern was recorded at a tube voltage of 40 kV, tube current of 40 mA, applying a stepsize of 0.02° 2-theta with 12 seconds per step in the angular range of 1.5° to 50.5° 2-theta. The detector step was 1° 2-theta. A typical precision of the 2-theta values is in the range of about ±0.2° 2-theta. Thus a diffraction peak that appears at 5.0° 2-theta can appear between 4.8 and 5.2 2-theta on most X-ray diffractometers under standard conditions.

TG-FTIR experiments were conducted with a Thermo-Microbalance TG-209 (Netzsch) equipped with a FT-IR Spectrometer Vector 22 (Bruker) using Al crucible (open or with microhole) under N2 atmosphere with a heating range between 25 and 250° C. and a heating rate of 10° C./min.

DSC experiments were carried out with a Perkin Elmer DSC 7 using closed Au crucibles with a heating range between −50 to 250° C. and a heating rate of 10 or 20° C./min.

DVS experiments were carried out with a Projekt Messtechnik SPS 11-100n multi-sample water vapor sorption analyzer. The sample was allowed to equilibrate at 50% r.h. before starting a pre-defined humidity program. The program was:

2h at 50% r.h.
50 to 0% r.h. (5%/h)
5h at 0% r.h.
0 to 95% r.h (5%/h)
5h at 95% r.h.
95 to 50% (5%/h)
2h at 50% r.h.

Example 9. Manufacture of Amorphous Form A of Lurbinectedin

Comp 1

-continued

(I)

Form A of lurbinectedin was obtained following the procedure described in WO 03/014127. The XRPD pattern of Form A of lurbinectedin confirmed that this form is amorphous. See FIG. **1**. Several batches of Form A of lurbinectedin were manufactured by this method. The analytical results of five of them are shown in Table

TABLE 25

		Batch				
		P01	P02	P03	P04	R05
Impurities (% Area)	Total	0.3	0.4	0.3	0.2	0.4
Residual Solvents (% w/w)	Total	1.4	1.9	1.9	2.1	2.5
	Acetonitrile	0.01	<LOQ	<LOQ	<LOQ	<LOQ
	Dichloro-methane	<LOQ	<LOQ	0.01	<LOQ	<LOQ
	Ethyl acetate	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Hexane	<LOQ	0.01	<LOQ	<LOQ	<LOQ
	Pentane	0.2	0.2	0.3	0.5	0.3
	Methanol	1.1	1.7	1.6	1.6	2.2
Water Content (% w/w)		0.9	1.2	1.6	1.6	1.1

ND: not detected

LOQ: limit of quantification

Table 26 shows the impurity profile of several batches of Form A lurbinectedin.

TABLE 26

Impurity RRT	Form A												
approx.	F02	G01	K02	K03	K04	M01	M02	M03	P01	P02	P03	P04	R05
0.66-0.69	0.19	0.06	—	—	—	—	—	—	—	—	—	—	—
0.72-0.76	0.06	0.11	0.09	0.07	0.10	0.10	0.08	0.12	0.10	0.09	0.09	0.09	0.10
0.90-0.92	—	—	—	—	—	—	—	—	—	—	—	—	—
1.10-1.11	0.17	0.50	0.13	0.17	0.20	0.08	0.10	0.11	0.15	0.09	0.08	—	0.09
1.12	—	—	—	—	—	—	—	—	—	—	0.07	—	—
1.27-1.34	0.12	—	—	—	—	—	—	—	—	—	—	—	—
1.29-1.30	—	—	0.07	0.37	0.11	0.10	0.17	0.10	0.09	0.06	0.09	0.10	0.05
1.30-1.32	0.09	0.13	0.19	0.08	0.08	0.18	0.08	0.11	—	0.13	—	—	—
1.28-1.37	—	—	—	—	—	—	0.08	—	—	—	—	—	—
2.37	—	—	—	—	—	—	—	—	—	—	—	—	0.13
2.41-2.52	0.07	—	—	—	—	—	—	—	—	—	—	—	—
2.85	0.07	—	—	—	—	—	—	—	—	—	—	—	—

RRT—Relative Retention Time

Example 10. Manufacture of Form B of Lurbinectedin

Crude lurbinectedin (10 g), which was obtained as described in Example 1, was dissolved in aqueous HCl (0.1 M, 390 mL). The aqueous solution was washed with CH_2Cl_2 (2×335 mL) and with n-pentane (1×335 mL) and treated with an aqueous solution of NH_4Cl/NH_4OH (prepared by dissolving 17.5 g of NH_4Cl and 20 mL of NH_4OH in 250 mL of water, 68 mL) to precipitate Form B of lurbinectedin, that was filtered, washed with water and dried under vacuum to give 7.5 g, 9.45 mmol, yield 81% of Form B of lurbinectedin.

Several batches of Form B of lurbinectedin were manufactured by this method. The analytical results of ten of them are shown in Table 27

TABLE 27

		Batch									
		1711182-2	1711189-2	1799069	1924129-LT	1924128-LT	R01	R02	R03	R04	P05
Total Impurities (% Area)		0.3	0.3	0.4	0.4	0.4	0.3	0.3	0.3	0.4	0.3
Residual Solvents (% w/w)	Total	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Acetonitrile	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	CH_2Cl_2	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	AcOEt	NA	NA	NA	NA	NA	<LOQ	NA	NA	NA	<LOQ
	Hexane	NA	NA	NA	NA	NA	<LOQ	NA	NA	NA	<LOQ
	Pentane	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Methanol	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	NA	<LOQ	<LOQ	<LOQ
Water Content (% w/w)		2.4	2.5	2.0	4.1	3.0	1.9	2.0	1.7	2.6	2.1

LOQ: limit of quantification
NA: not analysed

An additional advantage of Form B of lurbinectedin over Form A of lurbinectedin is the absence of residual solvents.

Table 28 shows the impurity profile (% area) of several batches of Form B of lurbinectedin

TABLE 28

Impurity RRT	Form B									
aprox	R01	R02	R03	R04	1711182-2	1711189-2	1799069	1924129-LT	1924128-LT	P05
0.66-0.69	—	—	0.05	0.05	—	0.05	—	0.07	0.06	—
0.72-0.76	0.22	0.28	0.22	0.26	0.34	0.30	0.31	0.24	0.25	0.24
0.90-0.92	—	—	—	—	—	—	—	0.08	0.07	—
1.10-1.11	0.09	—	—	0.07	—	—	0.06	—	—	0.07

TABLE 28-continued

Impurity RRT	Form B									
aprox	R01	R02	R03	R04	1711182-2	1711189-2	1799069	1924129-LT	1924128-LT	P05
1.12	—	—	—	—	—	—	—	—	—	—
1.27-1.34	—	—	—	—	—	—	—	—	—	—
1.29-1.30	—	—	—	—	—	—	—	—	—	—
1.30-1.32	—	—	—	—	—	—	—	—	—	—
1.28-1.37	—	—	—	—	—	—	—	—	—	—
2.41-2.52	—	—	—	—	—	—	—	—	—	—
2.85	—	—	—	—	—	—	—	—	—	—

RRT—Relative Retention Time

A comparison between the impurity profiles of forms A and B of lurbinectedin clearly shows that Form B of lurbinectedin consistently presents fewer impurities than Form A of lurbinectedin.

Solid State Characterization—Form B of lurbinectedin was characterized by XRPD, IR, TG-FTIR, DSC and DVS.

The XRPD pattern of several batches of Form B of lurbinectedin confirmed that this form is partly crystalline (broad peaks, amorphous background) and that the process for its manufacture is reproducible. See FIGS. **2***a* and **2***b*. XRPD angles 2-theta and their relative intensities of two batches of Form B of lurbinectedin are shown in Table 29

TABLE 29

XRPD angles 2-theta, relative intensities of two batches of Form B of lurbinectedin

Batch 1924128-LT		Batch 1924129-LT	
Angle [2-theta]	Relative intensity [%]	Angle [2-theta]	Relative intensity [%]
6.2	84	6.2	73
7.6	100	7.7	100
9.0	62	9.0	64
9.8	31	9.6	30
10.9	98	10.9	100
12.4	41	12.4	40
14.9	75	14.8	77
15.3	74	15.3	76
18.4	29	18.3	29
19.2	34	19.2	35
20.7	31	20.7	32
24.9	26	24.9	27
26.5	32	26.5	33

TG-FTIR indicates degradation above 150° C. for Form B of lurbinectedin. A release of 2.6% of water was detected. See FIG. **3**.

Estimation of the amorphous content by DSC was not possible. Degradation was observed to begin above 130° C., see FIG. **4**. A glass transition temperature or melting point was not detected.

DVS indicates a continuous water uptake and release with no steps and almost no hysteresis. This is due to the partly amorphous character of Form B. The sample is not deliquescent. A mass change of Δm (50 to 96% r.h.)≈4% was observed, indicating that Form B of lurbinectedin is hygroscopic. Upon lowering the relative humidity again, the water content decreased and nearly returned to the original mass, see FIG. **5**.

Relative Stability of Form B of lurbinectedin—three 1:1 mixtures of forms A and B of lurbinectedin (15 mg each) were prepared and suspended in water (1 mL). Samples were taken after 6 and 24 hours. The powder patterns after 6 and 24 hours agree with that of the Form B starting material. See FIG. **6**. Both patterns after phase equilibration show sharper peaks and higher peak resolution. These are indications of improved crystallinity. A quantification of the amorphous content was not possible with the available data.

IR spectra were obtained for Form A of lurbinectedin, shown in FIG. **7***a*, and for Form B of lurbinectedin, shown in FIG. **7***b*. The correlation factor between the IR of three batches of Form B of lurbinectedin and the IR of Form A of lurbinectedin varies from 0.81 to 0.86. On the other hand, the correlation factor of several IR spectra of Form A of lurbinectedin varies from 0.97 to 0.99.

Example 11. Electrostatic Charge Measurements in Air

The electrostatic charges of two batches of Form A of lurbinectedin (Batches P04 and R05) and of Form B of lurbinectedin (Batch 1924129-LT and 1924128-LT) have been measured using a Faraday cage (See FIG. **8**) constructed of stainless steel with concentric spheres with ratios 10, 15 and 20 cm. This technique consists in placing the sample to be measured (q) in the interior of the inner sphere (a) and measuring the difference of potential induced between sphere (a) and another conductor of reference, sphere (b). The external sphere (c) is grounded in order to shield the system. The measurements of the difference of potential were carried out with a precision electrometer (Keithley 617, resolution 10fC).

Measurements were carried out under controlled atmosphere of dry nitrogen in order to avoid the effect of ambient humidity on the electrostatic charge of the samples. Samples were introduced in glass capsules using non-conductor instrumental to avoid loses of electrostatic charge. The capsules loaded with the samples were introduced in the Faraday cage through a grounded conductor tube to avoid parasitic static charges in the glass capsule. The entry and removal of the capsules was done with a computer-controlled servo engine, in order to ensure a constant rate of introduction and removal of the capsules in each measurement to minimize the creation of static charges due to friction of the insulator elements.

Results: Several measurements with different amounts of material were carried out for each batch of each form of lurbinectedin. Before loading the capsules, they were washed and their remaining static charge was measured in order to correct the levels. Each sample was introduced and removed five times and, after each introduction, several consecutive measurements were taken in order to average any possible drift effect. FIGS. **9***a* and **9***b* summarized the results of such measurement for each pair of batches of forms A and B of lurbinectedin.

The measured charge Q increases with the amount of analyzed material. Both forms of lurbinectedin have a positive electrostatic charge. Form A of lurbinectedin has a total static charge considerably higher than Form B of lurbinectedin. The data was fitted by lineal regression (dashed lines in FIGS. **9***a* and **9***b*) to obtain the charge density (Q/m) as the slope of the line. The extrapolation of the lineal regression to a mass of 0 mg represents the remnant electrostatic charge of the glass capsules, and does not affect the value of Q/m. The results of this regression and the dispersion of charge density are summarized in Table 30. All ranges are given with a 95% confidence.

TABLE 30

Form	Batch	Average charge density (Q/m) (nC/g)	Dispersion of charge density (Q/m) (nC/g)
A	P04	43.1 ± 3.86	7.6 ± 2.8
	R05	64.02 ± 7.98	15.23 ± 5.64
B	1924129-LT	4.96 ± 2.0	3.4 ± 1.4
	1924128-LT	4.3 ± 0.4	1.01 ± 0.3

FIGS. **10***a* and **10***b* show the distribution of charge density for each pair of batches of forms A and B of lurbinectedin.

Form B of lurbinectedin is shown to have an average charge density one order of magnitude lower than Form A of lurbinectedin. This difference in triboelectrization has been demonstrated using two different batches of each form.

Example 12. Exemplary Process for the Manufacture of a Pharmaceutical Composition Using Form B as Starting Material

Form B of lurbinectedin was dissolved in a concentrated lactic acid solution (0.31 M) at a concentration of 25 mg/ml. Then, this solution was diluted with water of injection (WFI) to a lactic acid solution (0.1 M) containing PM01183 at a concentration of 8.33 mg/ml.

This solution was then added under stirring into a sucrose/buffer solution (pH=4.2) previously prepared, composed of lactic acid (3.7 mg/ml), sodium hydroxide (1.1 mg/ml) and the bulking agent, sucrose (167.7 mg/ml). If required, the mixed solution will be adjusted to pH=4.0 with lactic acid solution or sodium hydroxide solution.

Then, the bulk solution was brought to final volume or weight (considering a density value of 1.04 g/cc), generating the final bulk solution (0.5 mg/ml lurbinectedin, 2.76 mg/ml lactic acid, 0.64 mg/ml NaOH, 100 mg/ml sucrose).

The bulk solution was then filtered through sterilizing PVDF filters (0.22 m) and filled into 30 ml glass vials at 8 ml/vial.

The vials were lyophilised according to a cycle detailed in Table 31. After lyophilization, vials were sealed with flip-off seals and stored at +5° C.

TABLE 31

Step (conditions)	Time
Freezing, −5° C.	1.5 h
Freezing, −40° C.	5.5 h
Primary drying (−25° C., 0.1-0.2 mb)	60 h
Secondary drying (+25° C., maximum vacuum)	30 h
Stoppering	NA

NA: not applicable

Although the invention is described in detail with reference to specific embodiments thereof, it will be understood that variations which are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims (and clauses). Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims (and clauses).

All publications, patents and patent applications mentioned in this specification are herein incorporated by reference into the specification to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference in their entireties.

The invention will now be described with reference to the following clauses:

1. A method of treating small cell lung cancer (SCLC) in a patient in need thereof, comprising:
(1) administering a prophylactic dose of a corticosteroid and a serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient on the day of and prior to administration of lurbinectedin to the patient; and
(2) administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion.
2. The method of clause 1, wherein the corticosteroid is dexamethasone intravenously administered at a dose of 8 mg of dexamethasone or a dose of a corticosteroid equivalent to 8 mg of dexamethasone administered intravenously.
3. The method of clause 1 or 2, wherein the serotonin antagonist is ondansetron intravenously administered at a dose of 8 mg of ondansetron or a dose of a serotonin antagonist equivalent to 8 mg of ondansetron administered intravenously.
4. The method of any one of clauses 1 to 3, further comprising administering one or more antiemetic agents within 2, 3, or 4 days after administration of lurbinectedin to the patient.
5. The method of clause 4, wherein the one or more antiemetic agents administered after lurbinectedin administration are selected from a corticosteroid, a serotonin antagonist, and metoclopramide.
6. The method of clause 5, wherein the one or more antiemetic agents are administered at a dose of 4 mg dexamethasone, 8 mg ondansetron, or 10 mg metoclopramide, or a combination thereof.
7. The method of any of clauses 1-6, wherein the patient is not treated with doxorubicin in combination with the lurbinectedin.
8. The method of any of clauses 1-7, wherein the patient has progressed after prior platinum-containing therapy or prior immunotherapy.
9. A method of treating small cell lung cancer (SCLC), including metastatic SCLC, in a patient in need thereof, comprising:
(1) administering a first dose of 3.2 mg/m^2 of lurbinectedin to the patient by intravenous infusion if the patient has an absolute neutrophil count of at least 1500 $cells/mm^3$ and a platelet count of at least $100,000/mm^3$; and

(2) identifying an adverse reaction in the patient after said administering, wherein the adverse reaction is Grade 2 hepatotoxicity or other adverse reaction, ≥Grade 3 (severe) hepatotoxicity or other adverse reaction, Grade 4 thrombocytopenia (Platelet count less than 25,000 cells/mm^3), Grade 3 thrombocytopenia (Platelet count less than 50,000 cells/mm^3) with bleeding, Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), or any grade febrile neutropenia (Neutrophil count <LLN);

(3) after the adverse reaction is identified and at the later of 21 days of the first dose or after the patient's neutrophil count is greater than 1500 cells/mm^3; platelet count is greater than about 100,000 mm^3 and, optionally, hemoglobin levels are greater than about 9 g/dL and the hepatotoxicity or other adverse reaction is Grade 1 or less:

(i) if the identified adverse reaction consists of isolated Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), administering to the patient a dose of lurbinectedin that is equal to the first dose every three weeks with G-CSF prophylaxis;

(ii) if the identified adverse reaction consists of Grade 2 hepatoxocity or other adverse reaction, administering to the patient a dose of lurbinectedin that is equal to the first dose every three weeks; or

(ii) if the identified adverse reaction is Grade 3 (severe) hepatotoxicity or other adverse reaction, Grade 4 thrombocytopenia (Platelet count less than 25,000 cells/mm^3), Grade 3 thrombocytopenia (Platelet count less than 50,000 cells/mm^3) with bleeding, or any grade febrile neutropenia is, administering to the patient a reduced dose of lurbinectedin compared to the first dose every 3 weeks.

10. The method of clause 9, wherein the first reduced dose is 2.6 mg/m^2.

11. The method of clause 10, wherein if the patient experiences after being administered a reduced dose of 2.6 mg/m^2, an adverse reaction of ≥Grade 3 (severe) hepatotoxicity or other adverse reaction, Grade 4 thrombocytopenia (Platelet count less than 25,000 cells/mm^3), Grade 3 thrombocytopenia (Platelet count less than 50,000 cells/mm^3) with bleeding, or any grade febrile neutropenia, then at the later of 21 days of the administration of the prior dose or after the patient's neutrophil count is greater than 1500 cells/mm^3; platelet count is greater than about 100,000 mm^3 and, optionally, hemoglobin levels are greater than about 9 g/dL and the hepatotoxicity or other adverse reaction is Grade 1 or less, administering to the patient a second reduced dose of 2.0 mg/m^2 lurbinectedin every three weeks.

12. The method of clause 11, further comprising discontinuing administration of lurbinectedin after identification of the adverse reaction after administration of the second reduced dose or if the patient does not recover to an absolute neutrophil count of at least 1500 cells/mm^3 and platelet count of at least 100,000/mm^3 within 2 weeks of the scheduled dose.

13. The method of any of the preceding clauses in which the lurbinectedin is administered as an infusion formulation prepared by diluting a reconstituted lyophilized formulation comprising 4 mg lurbinectedin, a buffer derived from an organic carboxylic acid (e.g. lactic acid), and a disaccharide (e.g. sucrose), which, when reconstituted has a pH of 3.5 to 4.5.

14. A method of treating small cell lung cancer (SCLC) in a patient in need thereof, comprising:

administering to the patient lurbinectedin at a dose of 3.2 mg/m^2 by intravenous infusion of a lurbinectedin infusion solution, wherein the lurbinectedin infusion solution administered to the patient is prepared from a lyophilized composition comprising 4 mg lurbinectedin, a buffer derived from an organic carboxylic acid, and a disaccharide reconstituted to form a reconstituted solution at a pH of 3.5 to 4.5.

15. The method of clause 14, wherein the disaccharide is sucrose and optionally wherein the composition comprises lurbinectedin and sucrose at a ratio of 1 mol lurbinectedin:455 to 465 mol sucrose.

16. The method of clause 14 or 15 wherein the organic carboxylic acid is lactic acid and optionally wherein the composition comprises lurbinectedin and the lactic acid at a ratio of 1 mol lurbinectedin:44 to 54 mol lactic acid.

17. The method of any one of clauses 14 to 16 wherein the pH is 3.8 to 4.5

18. The method of any one of clauses 14 to 17, wherein the lyophilized composition is reconstituted in about 8 mL of an aqueous solution to obtain the reconstituted solution.

19. The method of clause 18, wherein the lurbinectedin infusion solution is prepared by diluting the reconstituted solution with an isotonic solution.

20. The method of any one of clauses 14 to 19, wherein the reconstituted solution is diluted with at least 100 mL or at least 250 mL of the isotonic solution to prepare the lurbinectedin infusion solution.

21. The method of clause 20, wherein the isotonic solution is a 0.9% sodium chloride solution or a 5% dextrose solution.

22. The method of any one of the preceding clauses, wherein the lyophilized composition comprises:

22.1 mg of lactic acid;

5.1 mg of sodium hydroxide; and

800 mg of sucrose

or wherein the lyophilized composition comprises 800 mg of sucrose, 0.245 mmol of lactate and 0.128 mmol of sodium.

23. The method of any one of the preceding clauses, wherein the lyophilized composition is provided in a 30 mL vial.

24. The method of any one of the preceding clauses, wherein the lyophilized composition comprises Impurity D at a value no greater than 0.8%, 0.7%, 0.6%, 0.5%, or 0.4% wt/wt based on the total weight of lurbinectedin.

25. The method of any one of the preceding clauses, wherein the lyophilized composition does not comprise a phosphate buffer.

26. The method of any one of the preceding clauses wherein the reconstituted solution or the lurbinectedin infusion solution comprises Impurity D at a value no greater than 0.8%, 0.7%, 0.6%, 0.5%, or 0.4% wt/wt based on the total weight of lurbinectedin.

27. The method of any one of clauses 14 to 26, further comprising administering a prophylactic dose of a corticosteroid and a serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient on the day of and prior to administration of lurbinectedin to the patient.

28. The method of clause 27, wherein the corticosteroid is dexamethasone intravenously administered at a dose of

8 mg of dexamethasone or a dose of a corticosteroid equivalent to 8 mg of dexamethasone administered intravenously.

29. The method of clause 27 or 28, wherein the serotonin antagonist is ondansetron intravenously administered at a dose of 8 mg of ondansetron or a dose of a serotonin antagonist equivalent to 8 mg of ondansetron administered intravenously.

30. The method of any one of clauses 27 to 29, further comprising administering one or more antiemetic agents within 2, 3, or 4 days after administration of lurbinectedin to the patient.

31. The method of clause 30, wherein the one or more antiemetic agents are selected from a corticosteroid, a serotonin antagonist, and metoclopramide.

32. The method of clause 31, wherein the one or more antiemetic agents are 4 mg dexamethasone, 8 mg ondansetron, or 10 mg metoclopramide, or a combination thereof.

33. The method of any preceding clause further comprising administering G-CSF to the patient identified as having a neutrophil countless than 500/mm^3 or any value below a normal range and associated with infection/sepsis.

34. The method of any preceding clause, wherein one dose of lurbinectedin is administered per treatment cycle and the patient undergoes at least 1, 2, 3, 4, 5, 6, 7, 8, 9 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 23, or 24 treatment cycles.

35. The method of any preceding clause, wherein the overall response rate is at least 11% or at least 20% for patients with a CTFI interval <90 days or wherein the overall response rate is at least 30% or at least 40% for patients with a CTFI interval >90 days.

36. The method of any preceding clause, wherein the duration of response is at least 2.5 months or at least 4.5 months for the patient with a CTFI interval <90 days or wherein the duration of response is at least 3.5 months, 5 months or 6 months for the patient with a CTFI interval >90 days.

37. The method of any preceding clause, wherein the patient had not received a platinum-containing therapy in at least 30 or at least 60 or at least 90 days prior to administration of lurbinectedin.

38. The method of any preceding clause, wherein the patient ceased responding to a platinum-containing therapy prior to administration of lurbinectedin.

39. The method of any preceding clause, wherein the patient has previously been administered an immunotherapy.

40. The method of clause 39, wherein the immunotherapy is an anti-CTLA-4 antibody, an anti-PD-1 antibody or an anti-PD-L1 antibody

41. The method of clause 40, wherein the immunotherapy is atezolizumab, optionally in combination with carboplatin and etoposide, or nivolumab.

42. The method of any of clauses 39 to 41, wherein the patient has progressed after being administered the immunotherapy.

43. The method of any preceding clause, wherein the patient has a calculated creatinine clearance greater than 30 mL/min and an AST or ALT less than 3×ULN or bilirubin less than 1.5×ULN.

44. The method of any preceding clause, wherein lurbinectedin is administered to a patient as a 1 hour intravenous infusion, to achieve total plasma C_{max} within 80% to 125% of about 107 μg/L and AUC∞ within 80% to 125% of about 551 μg*h/L.

45. A method of storing a lyophilized lurbinectedin composition comprising

storing a lyophilized composition comprising 4 mg lurbinectedin; a buffer derived from an organic carboxylic acid; and a disaccharide at a temperature of 5° C.±3° C. for at least 48 months,

wherein the lyophilized composition is formulated such that reconstitution with 8 mL of water will yield a solution having a pH of 3.5 to 4.5 and

wherein after the at least 24 months storage, the amount of Impurity D present in the composition is not more than 0.8% wt./wt. of the total lurbinectedin weight.

46. The method of clause 45, wherein after at least 48 months of storage, the amount of Impurity D present in the composition is not more than 0.8% wt./wt. of the total lurbinectedin weight.

47. The method of clause 45 or 46, wherein the lyophilized composition comprises 4 mg lurbinectedin; 22.1 mg lactic acid; 5.1 mg sodium hydroxide; and 800 mg sucrose or wherein the lyophilized composition comprises 800 mg of sucrose, 0.245 mmol of lactate and 0.128 mmol of sodium.

48. The method of any one of clauses 45 to 47, wherein the lyophilized composition is stored in a 30 mL vial.

49. A pharmaceutical product comprising

a vial containing a lyophilized composition consisting of 4 mg lurbinectedin; 22.1 mg lactic acid; 5.1 mg sodium hydroxide; and 800 mg sucrose or a lyophilized composition consisting of 800 mg of sucrose, 0.245 mmol of lactate and 0.128 mmol of sodium;

a label affixed to the vial comprising an expiration date that is at least 24 months from the date of manufacture.

50. The pharmaceutical product of clause 49, wherein the label affixed to the vial comprises an expiration date that is at least 48 months from the date of manufacture.

51. The pharmaceutical product of clause 49 or 50, wherein the vial is a 30 mL vial.

52. The pharmaceutical product of any one of clauses 49 to 51, wherein the lyophilized composition comprises Impurity D at a value no greater than 0.8%, 0.7%, 0.6%, 0.5%, or 0.4% wt/wt of the total lurbinectedin weight.

53. The pharmaceutical product of any one of clauses 49 to 52, wherein the lyophilized composition does not comprise a phosphate buffer.

54. A method of treating solid tumor, endometrial cancer, SCLC, soft tissue sarcoma, glioblastoma, pancreatic adenocarcinoma, mesothelioma, colorectal carcinoma, or epithelial ovarian cancer in a patient in need thereof, the method comprising:

administering to the patient lurbinectedin and a topoisomerase inhibitor selected from SN-38 and irinotecan on day one of a treatment cycle;

wherein the lurbinectedin is administered at a dose of 1 to 2.5 mg/m^2 and

wherein the topoisomerase inhibitor is administered at a dose equivalent to 50 to 75 mg of irinotecan/m^2.

55. The method of clause 54, wherein a dose of the topoisomerase inhibitor equivalent to 50 mg to 75 mg of irinotecan/m^2 is administered on day 8 of the treatment cycle.

56. The method of clause 54 or 55, wherein the treatment cycle is an 18, 19, 20, 21, 22, 23, 24, or 25 day cycle.

57. The method of any of clauses 54 to 56 wherein the lurbinectedin is administered at a dose of 2 mg/m^2.
58. The method of any of clauses 54 to 57 wherein the topoisomerase inhibitor is irinotecan and is administered at a dose of 75 mg/m^2.
59. The method of any of clauses 54 to 58 wherein the treatment cycle is 21 days.
60. The method of any of clauses 54 to 59 wherein the solid tumor is SCLC, endometrial carcinoma, soft tissue sarcoma or glioblastoma.
61. The method of any of clauses 54 to 60 wherein the patient is administered G-CSF to manage the myelosuppressive effects of said treatment.
62. The method of any of clauses 54 to 61 wherein if after the administration on day 1 the patient exhibits hematological toxicity, then omitting the administration of the dose of irinotecan on day 8 of the treatment cycle.
63. The method of any one of clauses 54 to 62, further comprising administering one or more antiemetics on day one of a treatment cycle.
64. The method of any of clauses 55 to 64 in which the lurbinectedin is administered as an infusion formulation prepared by diluting a reconstituted lyophilized formulation of 4 mg lurbinectedin, 22.1 mg lactic acid or 0.245 mmol lactate, 5.1 mg sodium hydroxide or 0.128 mmol sodium, and 800 mg sucrose, which, when reconstituted has a pH of 3.5 to 4.5.
65. The method of clause 64 wherein the pH is 3.8 to 4.5
66. The method of clause 64 or 65, wherein the lyophilized composition is reconstituted in about 8 mL of an aqueous solution to obtain the reconstituted solution.
67. The method of clause 66, wherein the lurbinectedin infusion solution is prepared by diluting the reconstituted solution with an isotonic solution.
68. The method of any one of clauses 64 to 67, wherein the reconstituted solution is diluted with at least 100 mL or at least 250 mL of the isotonic solution to prepare the lurbinectedin infusion solution.
69. The method of clause 68, wherein the isotonic solution is a 0.9% sodium chloride solution or a 5% dextrose solution.
70. The method of any one of clauses 64 to 69, wherein the lyophilized composition is provided in a 30 mL vial.
71. The method of any one of clauses 64 to 70, wherein the lyophilized composition comprises Impurity D at a value no greater than 0.8%, 0.7%, 0.6%, 0.5%, or 0.4% wt/wt.
72. The method of any one of clauses 64 to 71 wherein the reconstituted solution or the lurbinectedin infusion solution comprises Impurity D at a value no greater than 0.8%, 0.7%, 0.6%, 0.5%, or 0.4% wt/wt.
73. A pharmaceutical composition prepared by

lyophilizing an aqueous stock solution comprising lurbinectedin, an organic carboxylic acid, sodium hydroxide, and sucrose to produce a lyophilized powder,

wherein the concentration of lurbinectedin in the aqueous stock solution is 0.5 mg/mL, wherein the ratio lurbinectedin to sucrose is 1 mol of lurbinectedin to 455 to 465 mol sucrose and wherein the lyophilized powder is formulated such that reconstitution with 8 mL of water will yield a solution having a pH of 3.5 to 4.1; and

storing the lyophilized powder at 5° C.±3° C. for 30 months to 60 months to produce the pharmaceutical composition,

wherein after storage the amount of Impurity D present in the composition is not more than 0.8% wt./wt. of the total lurbinectedin weight.

74. A method of administering a pharmaceutical composition comprising

reconstituting a lyophilized pharmaceutical composition in a vial after the composition has been stored for 30 to 60 months,

wherein the lyophilized pharmaceutical composition was prepared by lyophilizing a stock solution comprising 4 mg of lurbinectedin, a buffer derived from an organic carboxylic acid, and sucrose,

wherein the composition comprises lurbinectedin and disaccharide at a ratio of 1 mol lurbinectedin:455 to 465 mol sucrose,

wherein the lyophilized composition is formulated such that reconstitution with 8 mL of water will yield a solution having a pH of 3.5 to 4.5; and

administering the reconstituted solution to a patient.

75. The method of clause 74, wherein the pharmaceutical composition comprises a lurbinectedin amount that is at least 95% of the amount of lurbinectedin on day one of storage.
76. The method of clause 74 or 75, wherein the vial is a 30 mL vial.
77. A method of treating SCLC in a patient in need thereof comprising

administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion;

wherein the patient was administered an immunotherapeutic antibody for treating SCLC prior to beginning the treatment cycle and

wherein the duration of response is at least 2 months, 3 months, 4 months, 5 months or 6 months or wherein the overall response rate is at least 40%.

78. The method of clause 77, wherein the immunotherapeutic antibody is an anti-CTLA-4 antibody, an anti-PD-1 antibody or an anti-PD-L1 antibody.
79. The method of clause 78, wherein the immunotherapeutic antibody is atezolizumab or nivolumab.
80. The method of clause 79, wherein the immunotherapeutic antibody was administered to the patient concurrently with a chemotherapeutic.
81. The method of clause 80, wherein the chemotherapeutic is carboplatin or etoposide.
82. The method of clause 81, wherein the immuno-oncogenic therapeutic antibody is atezolizumab and the chemotherapeutic is carboplatin or etoposide.
83. The method of any one of clause 69 to 74, wherein one dose of lurbinectedin is administered per treatment cycle and the treatment cycle is an 18, 19, 20, 21, 22, 23, 24, or 25 day cycle.
84. The method of any one of clause 77 to 83, wherein one dose of lurbinectedin is administered per treatment cycle and the patient undergoes at least 2, 3, 4, 5, 6, 7, 8, 9 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 23, or 24 treatment cycles.
85. The method of any one of clause 77 to 84, wherein the overall response rate is at least 40% or at least 50% or at least 60%.
86. The method of any one of clause 77 to 85, wherein the duration of response is at least 2 months, 3 months, 4 months, 5 months or 6 months.
87. The method of any one of clause 77 to 86, wherein the patient had not received the immuno-oncogenic therapeutic antibody in at least 30 or at least 60 or at least 90 days prior to administration of lurbinectedin.

88. The method of any one of clause 77 to 87, wherein the patient ceased responding to the immuno-oncogenic therapeutic antibody prior to administration of lurbinectedin.

89. The method of any one of clause 77 to 87, wherein an immune-oncogenic therapeutic antibody is not administered concurrently with lurbinectedin.

90. A pharmaceutical composition comprising

a lyophilized composition comprising 4 mg lurbinectedin, a buffer derived from an organic acid, and a disaccharide,

wherein the lurbinectedin and disaccharide are present at a ratio of 1 mol lurbinectedin to 455 to 465 mol disaccharide,

wherein the lyophilized composition is formulated such that reconstitution with 8 mL of water will yield a solution having a pH of 3.5 to 4.5, and

wherein the lyophilized composition further comprises a degradation product resulting from deacetylation of lurbinectedin at a value no greater than 0.8%, 0.7%, 0.6%, 0.5%, or 0.4%. wt./wt based upon the total weight of lurbinectedin.

91. The pharmaceutical composition of clause 90, wherein the lurbinectedin and the organic acid are present at a ratio of 1 mol lurbinectedin to 44 to 54 mol organic acid.

92. The pharmaceutical composition of clause 90 or 91, wherein the vial is a 30 mL vial.

93. The pharmaceutical composition of any one of clauses 90 to 92, wherein the lyophilized composition does not comprise a phosphate buffer.

94. The pharmaceutical composition of any one of clauses 90 to 93, wherein the buffer derived from an organic acid is selected from a lactic acid buffer, a butyric acid buffer, a propionic acid buffer, a acetic acid buffer, a succinic acid buffer, a citric acid buffer, a ascorbic acid buffer, a tartaric acid buffer, a malic acid buffer, a maleic acid buffer, a fumaric acid buffer, a glutamic acid buffer, an aspartic acid buffer, a gluconic acid buffer, and a α-ketoglutaric buffer.

95. The pharmaceutical composition of any one of clauses 90 to 94, wherein the buffer derived from an organic acid is lactic acid.

96. The pharmaceutical composition of any one of clauses 90 to 95, wherein the composition comprises 22.1 mg lactic acid; 5.1 mg sodium hydroxide; and 800 mg sucrose or wherein the composition comprises 800 mg of sucrose, 0.245 mmol of lactate and 0.128 mmol of sodium.

97. A method of reducing lurbinectedin degradation in a lyophilized formulation comprising lurbinectedin, the method comprising adding lactate buffer to a stock solution from which the lyophilized formulation is prepared, wherein the resulting ratio of lurbinectedin to lactate buffer is between 1 mol:44 mol and 1 mol:54 mol; wherein the lurbinectedin degradation product from deacetylation does not exceed 0.8% wt./wt. of the total lurbinectedin weight when stored at 5 degree C.±3 degree C. for at least 24 months or at least 36 months or at least 48 months or at least 60 months.

98. The method of clause 97, comprising adding sucrose to a stock solution from which the lyophilized formulation is prepared, wherein the resulting ratio of lurbinectedin to lactate buffer is between 1 mol:455 mol and 1 mol:465 mol;

99. The method of clause 97, wherein the lyophilized formulation does not contain a phosphate buffer.

100. A method of treating small cell lung cancer (SCLC) in a patient in need thereof, comprising administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to a patient by intravenous infusion every 3 weeks, wherein the lurbinectedin is provided in a lyophilized formulation comprising lurbinectedin, lactic acid, and sucrose, wherein the ratio of lurbinectedin:lactic acid:sucrose is between 1 mol:46 mol:455 mol and 1 mol:50 mol:465 mol, wherein the formulation is stable at 5 degree C.±3 degree C. for at least 24 months or at least 36 months or at least 48 months or at least 60 months such that the lurbinectedin degradation product from deacetylation does not exceed 0.8% wt./wt. of the total lurbinectedin weight.

101. The method of clause 100, wherein the topoisomerase inhibitor is administered at a dose equivalent to 75 mg of irinotecan/m^2 and lurbinectedin is administered at a dose of 2.0 mg/m^2.

102. A packaged, lyophilized composition, comprising

4 mg lurbinectedin, a buffer derived from an organic acid and a disaccharide packaged in a vial,

wherein the dissolution of the lyophilized composition in about 8 mL of water provides a lurbinectedin solution having a pH of about 3.5 to about 4.1, and

wherein the lyophilized composition comprises less than about 0.3% of Impurity D (w/w based on lurbinectedin) when the composition is packaged, and wherein upon storage at about 5 degrees C. for about 24 months or about 36 months or about 48 months the composition comprises not more than about 0.8% of Impurity D (w/w based on lurbinectedin).

103. The composition of clause 102, wherein the composition comprises substantially the same amount of Impurity D (w/w based on lurbinectedin) when the composition is packaged and after storage of the composition at about 5 degrees C. for about 24 months or about 36 months or about 48 months.

104. The composition of any one of clauses 102-103, wherein the buffer is a salt of an organic anion selected from the group consisting of acetate, succinate, citrate and lactate.

105. The composition of clause 104, wherein the salt is lactate.

106. The composition of any one of clauses 102-105, wherein the disaccharide is selected from the group consisting of sucrose, trehalose, lactose and a combination of two or all three disaccharides thereof.

107. The composition of clause 106, wherein the disaccharide is sucrose.

108. The composition of clause 107, wherein the w/w ratio of lurbinectedin to sucrose is about 1:200.

109. The composition of any one of clauses 102-108, wherein the composition comprises: 4 mg lurbinectedin, 22.1 mg lactic acid, 5.1 mg sodium hydroxide, and 800 mg sucrose or wherein the lyophilized composition comprises 800 mg of sucrose, 0.245 mmol of lactate and 0.128 mmol of sodium.

110. The composition of any one of clauses 102-109, wherein the dissolution in about 8 mL of water provides a lurbinectedin solution having a pH of about 4.0.

111. A packaged, lyophilized composition, comprising

4 mg lurbinectedin, a buffer derived from an organic acid and a disaccharide packaged in a vial,

wherein the dissolution of the lyophilized composition in about 8 mL of water provides a lurbinectedin solution having a pH of about 3.8 to about 4.1, and

wherein the lyophilized composition comprises less than about 0.3% of Impurity D (w/w based on lurbinectedin) when the composition is packaged, and wherein the composition comprises substantially the same amount Impurity D (w/w based on lurbinectedin) after the packaged composition has been stored at about 25 degrees C. and about 60% relative humidity for up to about 1, 2, 3, 6, 9, or 12 months.

112. The composition of clause 111 wherein the composition comprises: 4 mg lurbinectedin, 22.1 mg lactic acid, 5.1 mg sodium hydroxide, and 800 mg sucrose or wherein the lyophilized composition comprises 800 mg of sucrose, 0.245 mmol of lactate and 0.128 mmol of sodium.

113. The composition of clause 111 or clause 112, wherein dissolution in about 8 mL of water provides a lurbinectedin solution having a pH of about 4.0.

114. The composition of any one of clauses 102-113, wherein the composition is prepared by a process comprising:

(a) providing a solution of lurbinectedin and an organic acid;

(b) providing a solution of a base, an organic acid and a disaccharide;

(c) combining the solutions of Step (a) and Step (b);

(d) adjusting the pH of the solution of Step (c) to about 3.8 to about 4.1; and

(e) lyophilizing the solution of Step (d) to provide the lyophilized composition.

115. The composition of clause 114, wherein the organic acid is selected from the group consisting of citric acid, succinic acid, lactic acid and acetic acid.

116. The composition of clause 114, wherein the organic acid is lactic acid.

117. The composition of any one of clauses 114-116, wherein the base is sodium hydroxide.

118. The composition of any one of clauses 114-117, wherein the disaccharide is selected from the group consisting of sucrose, trehalose, lactose and a combination of two or all three disaccharides thereof.

119. The composition of any one of clauses 14-117, wherein the organic acid is lactic acid, the base is sodium hydroxide, and the disaccharide is sucrose.

120. A method of treating small cell lung cancer (SCLC) in a patient in need thereof, comprising:

1) dissolving a packaged, lyophilized composition comprising 4 mg lurbinectedin, a buffer derived from an organic acid and disaccharide in about 8 mL of water to provide a lurbinectedin solution having a pH of about 3.5 to about 4.1,

and

2) administering about 2 to 3.2 mg/m^2 of lurbinectedin to a patient whose SCLC has progressed after prior platinum-containing therapy by intravenous infusion every 3 weeks and

wherein the lyophilized composition comprises less than about 0.3% of Impurity D (w/w based on lurbinectedin) at packaging, and wherein upon storage at about 5 degrees C. for about 24 months the composition comprises less than about 0.8% of Impurity D (w/w based on lurbinectedin).

121. The method of clause 120, wherein the administration comprises:

1) dissolving a packaged, lyophilized composition comprising 4 mg lurbinectedin, a buffer derived from an organic acid and disaccharide in about 8 mL of water to provide a lurbinectedin solution having a pH of about 3.8 to about 4.1,

and

2) administering the lurbinectedin to the patient in need thereof,

wherein the lyophilized composition comprises less than about 0.3% of Impurity D (w/w based on lurbinectedin) when the composition is packaged, and wherein upon storage at about 5 degrees C. for about 24 months the composition comprises less than about 0.8% of Impurity D (w/w based on lurbinectedin).

122. The method of clause 120 or 121, wherein, prior to administration, the lyophilized composition is reconstituted in about 8 mL of an aqueous solution to obtain a reconstituted lurbinectedin solution.

123. The method of clause 122, wherein, prior to administration said reconstituted lurbinectedin solution is stored for up to 24 hours following reconstitution at room temperature or at 5° C.±3° C., wherein after storage the reconstituted lurbinectedin solution comprises Impurity D not more than 0.8%, 0.7%, 0.6%, 0.5%, or 0.4% wt/wt lurbinectedin.

124. The method of clause 122 or 123, wherein a lurbinectedin infusion solution is prepared by diluting the reconstituted solution with an isotonic solution.

125. The method of clause 124, wherein the reconstituted solution is diluted with at least 100 mL or at least 250 mL of the isotonic solution to prepare the lurbinectedin infusion solution.

126. The method of clause 124 or 125, wherein the isotonic solution is a 0.9% sodium chloride solution or a 5% dextrose solution.

127. The method of any of clauses 120 to 126 wherein the infusion lurbinectedin solution is stored for up to 24 hours following reconstitution of the lyophilized lurbinectedin formulation at room temperature or at 5° C.±3° C., wherein after storage the reconstituted lurbinectedin solution comprises Impurity D not more than 0.8%, 0.7%, 0.6%, 0.5%, or 0.4% wt/wt based on the total weight of lurbinectedin.

128. Use of lurbinectedin in the manufacture of a medicament for use in therapy for treating small cell lung cancer (SCLC) in a patient in need thereof wherein said medicament is to be administered at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion in combination with a prophylactic dose of a corticosteroid and a serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient, wherein the prophylactic dose is administered on the day of and prior to administration of lurbinectedin to the patient.

129. The use of clause 128, wherein the corticosteroid is dexamethasone formulated for intravenous administration at a dose of 8 mg of dexamethasone or a dose of a corticosteroid equivalent to 8 mg of dexamethasone administered intravenously.

130. The use of clause 128 or 129, wherein the serotonin antagonist is ondansetron formulated for intravenous administration at a dose of 8 mg of ondansetron or a dose of a serotonin antagonist equivalent to 8 mg of ondansetron administered intravenously.

131. The use of any one of clauses 128 to 130, wherein said medicament is administered in combination with one or more antiemetic agents, which are administered within 2, 3, or 4 days after administration of lurbinectedin to the patient.

132. The use of clause 131, wherein the one or more antiemetic agents administered after lurbinectedin

administration are selected from a corticosteroid, a serotonin antagonist, and metoclopramide.

133. The use of clause 132, wherein the one or more antiemetic agents are 4 mg dexamethasone, 8 mg ondansetron, or 10 mg metoclopramide, or a combination thereof.

134. The use of any of clauses 121-126, wherein the patient is not treated with doxorubicin in combination with the lurbinectedin.

135. The use of any of clauses 128-134, wherein the patient has progressed after prior platinum-containing therapy or prior immunotherapy.

136. Use of lurbinectedin in the manufacture of a medicament for use in therapy for treating small cell lung cancer (SCLC) in a patient in need thereof wherein said medicament is to be administered at a first dose of 3.2 mg/m^2 to the patient by intravenous infusion in a first treatment cycle and the same dose is administered in a subsequent treatment unless an adverse reaction is identified in the patient,

wherein the adverse reaction is selected from the group consisting of: ≥Grade 3 (severe) non hematological toxicity, Grade 4 thrombocytopenia (Platelet count less than 25,000 cells/mm^3), Grade 3 thrombocytopenia (Platelet count less than 50,000 cells/mm^3) with bleeding that requires transfusion, Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), or any grade neutropenia (Neutrophil count <LLN) that is associated with infection/sepsis or any other of the adverse reactions;

after the adverse reaction is identified and after the patient's neutrophil count is greater than 1500 cells/mm^3; platelet count is greater than about 100,000 mm^3; and hemoglobin levels are greater than about 9 g/dL: the

(i) if the identified adverse reaction consists of Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), a dose of G-CSF is administered in combination with a dose of lurbinectedin that is equal to the first dose in the subsequent treatment cycle; or

(ii) if the identified adverse reaction is not isolated Grade 4 neutropenia, a reduced dose of lurbinectedin compared to the first dose is administered to the patient,

wherein administration of two doses of lurbinectedin are spaced apart by at least 21 days.

137. The use of clause 136, wherein a first reduced dose is 80 to 85% of the first dose after a first occurrence of the adverse reaction that is not isolated Grade 4 neutropenia or wherein a first reduced dose is to 2.6 mg/m^2 after a first occurrence of the adverse reaction that is not isolated Grade 4 neutropenia.

138. The use of clause 137, wherein a second reduced dose is 60-65% of the first dose after a second occurrence of the adverse reaction that is not isolated Grade 4 neutropenia or wherein a second reduced dose is to 2.0 mg/m^2 after a second occurrence of the adverse reaction that is not isolated Grade 4 neutropenia, wherein the second reduced is administered to the patient.

139. The use of clause 138, wherein the administration of lurbinectedin is discontinued after identification of the adverse reaction after administration of the second reduced dose.

140. The use of any of the preceding clauses in which the medicament is administered as an infusion formulation prepared by diluting a reconstituted lyophilized formulation of 4 mg lurbinectedin, 22.1 mg lactic acid or 0.245 mmol lactate, 5.1 mg sodium hydroxide or 0.128 mmol sodium, and 800 mg sucrose, which, when reconstituted has a pH of 3.5 to 4.5.

141. Use of lurbinectedin in the manufacture of a medicament for use in therapy for treating small cell lung cancer (SCLC) in a patient in need thereof wherein said medicament is to be administered at a dose of 3.2 mg/m^2 to the patient by intravenous infusion of a lurbinectedin infusion solution, wherein the lurbinectedin infusion solution administered to the patient is prepared from a lyophilized composition comprising 4 mg lurbinectedin, a buffer derived from an organic carboxylic acid, and a disaccharide reconstituted to form a reconstituted solution at a pH of 3.5 to 4.5.

142. The use of clause 141, wherein the disaccharide is sucrose and optionally wherein the composition comprises lurbinectedin and sucrose at a ratio of 1 mol lurbinectedin:455 to 465 mol sucrose.

143. The use of clause 141 or 142 wherein the organic carboxylic acid is lactic acid and optionally wherein the composition comprises lurbinectedin and the lactic acid at a ratio of 1 mol lurbinectedin:44 to 54 mol lactic acid.

144. The use of any one of clauses 141 to 143 wherein the pH is 3.8 to 4.5

145. The use of any one of clauses 141 to 144, wherein the lyophilized composition is reconstituted in about 8 mL of an aqueous solution to obtain the reconstituted solution.

146. The use of clause 145, wherein the lurbinectedin infusion solution is prepared by diluting the reconstituted solution with an isotonic solution.

147. The use of any one of clauses 141 to 146, wherein the reconstituted solution is diluted with at least 100 mL or at least 250 mL of the isotonic solution to prepare the lurbinectedin infusion solution.

148. The use of clause 146, wherein the isotonic solution is a 0.9% sodium chloride solution or a 5% dextrose solution.

149. The use of any one of clauses 141 to 148, wherein the lyophilized composition comprises:

22.1 mg of lactic acid;

5.1 mg of sodium hydroxide; and

800 mg of sucrose

or wherein the lyophilized composition comprises 800 mg of sucrose, 0.245 mmol of lactate and 0.128 mmol of sodium.

150. The use of any one of clauses 141 to 149, wherein the lyophilized composition is provided in a 30 mL vial.

151. The use of any one of clauses 141 to 150, wherein the lyophilized composition comprises Impurity D at a value no greater than 0.8%, 0.7%, 0.6%, 0.5%, or 0.4% wt/wt based upon the total weight of lurbinectedin.

152. The use of any one of clauses 141 to 151, wherein the lyophilized composition does not comprise a phosphate buffer.

153. The use of any one of clauses 141 to 152 wherein the reconstituted solution or the lurbinectedin infusion solution comprises Impurity D at a value no greater than 0.8%, 0.7%, 0.6%, 0.5%, or 0.4% wt/wt based upon the total weight of lurbinectedin.

154. The use of any one of clauses 141 to 153, administered in combination with a prophylactic dose of a corticosteroid and a serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient, wherein the prophylactic dose

is administered on the day of and prior to administration of lurbinectedin to the patient.

155. The use of clause 154, wherein the corticosteroid is dexamethasone formulated for intravenous administration at a dose of 8 mg of dexamethasone or a dose of a corticosteroid equivalent to 8 mg of dexamethasone administered intravenously.

156. The use of clause 154 or 155, wherein the serotonin antagonist is ondansetron formulated for intravenous administration at a dose of 8 mg of ondansetron or a dose of a serotonin antagonist equivalent to 8 mg of ondansetron administered intravenously.

157. The use of any one of clauses 154 to 156, wherein said medicament is administered in combination with one or more antiemetic agents, which are administered within 2, 3, or 4 days after administration of lurbinectedin to the patient.

158. The use of clause 157, wherein the one or more antiemetic agents are selected from a corticosteroid, a serotonin antagonist, and metoclopramide.

159. The use of clause 158, wherein the one or more antiemetic agents are 4 mg dexamethasone, 8 mg ondansetron, or 10 mg metoclopramide, or a combination thereof.

160. The use of any preceding clause wherein said medicament is administered in combination with G-CSF to the patient identified as having a neutrophil countless than 500/mm^3 or any value below a normal range and associated with infection/sepsis.

161. The use of any preceding clause, wherein one dose of lurbinectedin is administered per treatment cycle and the patient undergoes at least 1, 2, 3, 4, 5, 6, 7, 8, 9 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 23, or 24 treatment cycles.

162. The use of any preceding clause, wherein the overall response rate is at least 11% or at least 20% for patients with a CTFI interval <90 days or wherein the overall response rate is at least 30% or at least 40% for patients with a CTFI interval >90 days.

163. The use of any preceding clause, wherein the duration of response is at least 2.5 months or at least 4.5 months for the patient with a CTFI interval <90 days or wherein the duration of response is at least 3.5 months, 5 months or 6 months for the patient with a CTFI interval >90 days.

164. The use of any preceding clause, wherein the patient had not received a platinum-containing therapy in at least 30 or at least 60 or at least 90 days prior to administration of lurbinectedin.

165. The use of any preceding clause, wherein the patient ceased responding to a platinum-containing therapy prior to administration of lurbinectedin.

166. The use of any preceding clause, wherein the patient has previously been administered an immunotherapy.

167. The use of clause 166, wherein the immunotherapy is an anti-CTLA-4 antibody, an anti-PD-1 antibody or an anti-PD-L1 antibody

168. The use of clause 167, wherein the immunotherapy is atezolizumab or nivolumab.

169. The use of any of clauses 166 to 168, wherein the patient has progressed after being administered the immunotherapy.

170. The use of any preceding clause, wherein the patient has a calculated creatinine clearance greater than 30 mL/min and an AST or ALT less than 3×ULN or bilirubin less than 1.5×ULN.

171. The use of any preceding clause, wherein lurbinectedin is administered to a patient as a 1 hour intravenous infusion, to achieve total plasma Cmax within 80% to 125% of about 107 μg/L and AUC∞ within 80% to 125% of about 551 μg*h/L.

172. Use of lurbinectedin in the manufacture of a medicament for use in therapy for treating endometrial cancer, SCLC, soft tissue sarcoma, glioblastoma, pancreatic adenocarcinoma, mesothelioma, colorectal carcinoma, or epithelial ovarian cancer in a patient in need thereof wherein said medicament is to be administered at a dose of 1 to 2.5 mg/m^2 to the patient by intravenous infusion in combination with a topoisomerase inhibitor selected from SN-38 and irinotecan on day one of a treatment cycle, wherein the topoisomerase inhibitor is administered at a dose equivalent to 50 to 75 mg of irinotecan/m^2.

173. The use of clause 172 wherein the lurbinectedin is administered at a dose of 2.0 mg/m^2 to and the irinotecan is administered at a dose of 75 mg/m^2 by intravenous administration on day 1 of the treatment cycle.

174. The use of clause 172 or 173, wherein a subsequent dose of irinotecan at 75 mg/m^2 is administered on day 8 of the treatment cycle.

175. The use of any of clauses 172 to 174 wherein said treatment cycle is 21 days.

176. The use of any of clauses 172 to 175, wherein the medicament is administered in combination with G-CSF during the treatment cycle.

177. The use of any of clauses 172 to 176, wherein if the patient exhibits hematologic toxicity after the dose on day 1, not administering a subsequent dose of irinotecan to said patient during the treatment cycle.

178. The use of any one of clauses 172 to 177, further comprising administering one or more antiemetics on day one of a treatment cycle.

179. The use of any one of clauses 172 to 178, wherein the patients is treated for endometrial cancer, SCLC, soft tissue sarcoma, or glioblastoma.

180. A use of a lyophilized pharmaceutical composition to administer a pharmaceutical composition to a patient in need thereof, wherein the lyophilized pharmaceutical composition is reconstituted in a vial after the composition has been stored for 30 to 60 months and administered to the patient,

wherein the lyophilized pharmaceutical composition was prepared by lyophilizing a stock solution comprising 4 mg of lurbinectedin, a buffer derived from an organic carboxylic acid, and sucrose,

wherein the composition comprises lurbinectedin and disaccharide at a ratio of 1 mol lurbinectedin:455 to 465 mol sucrose,

wherein the lyophilized composition is formulated such that reconstitution with 8 mL of water will yield a solution having a pH of 3.5 to 4.5.

181. The use of clause 180, wherein the pharmaceutical composition comprises a lurbinectedin amount that is at least 95% of the amount of lurbinectedin on day one of storage.

182. The use of clause 180 or 181, wherein the vial is a 30 mL vial.

183. A use of lurbinectedin in the manufacture of a medicament for treating SCLC in a patient in need thereof

wherein lurbinectedin is administered at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion;

wherein the patient was administered an immunotherapeutic antibody for treating SCLC prior to beginning the treatment cycle and

wherein the duration of response is at least 2 months, 3 months, 4 months, 5 months or 6 months or wherein the overall response rate is at least 40%.

184. The use of clause 183, wherein the immunotherapeutic antibody is an anti-CTLA-4 antibody, an anti-PD-1 antibody or an anti-PD-L1 antibody.

185. The use of clause 184, wherein the immunotherapeutic antibody is atezolizumab or nivolumab.

186. The use of clause 185, wherein the immunotherapeutic antibody was administered to the patient concurrently with a chemotherapeutic.

187. The use of clause 186, wherein the chemotherapeutic is carboplatin or etoposide.

188. The use of clause 187, wherein the immuno-oncogenic therapeutic antibody is atezolizumab and the chemotherapeutic is carboplatin or etoposide.

189. The use of any one of clause 183 to 188, wherein one dose of lurbinectedin is administered per treatment cycle and the treatment cycle is an 18, 19, 20, 21, 22, 23, 24, or 25 day cycle.

190. The use of any one of clause 183 to 189, wherein one dose of lurbinectedin is administered per treatment cycle and the patient undergoes at least 2, 3, 4, 5, 6, 7, 8, 9 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 23, or 24 treatment cycles.

191. The use of any one of clause 183 to 190, wherein the patent is administered 5 lurbinectedin doses over a 17-week period or at least 6 lurbinectedin doses over a 20-week period or at least 7 lurbinectedin doses over a 22 week period.

192. The use of any one of clause 183 to 191, wherein the overall response rate is at least 40% or at least 50% or at least 60%.

193. The use of any one of clause 183 to 192, wherein the duration of response is at least 2 months, 3 months, 4 months, 5 months or 6 months.

194. The use of any one of clause 183 to 193, wherein the patient had not received the immuno-oncogenic therapeutic antibody in at least 30 or at least 60 or at least 90 days prior to administration of lurbinectedin.

195. The use of any one of clause 183 to 194, wherein the patient ceased responding to the immuno-oncogenic therapeutic antibody prior to administration of lurbinectedin.

196. The use of any one of clause 183 to 195, wherein an immune-oncogenic therapeutic antibody is not administered concurrently with lurbinectedin.

197. A use of lurbinectedin in the manufacture of a medicament for use in treating small cell lung cancer (SCLC) in a patient in need thereof, wherein the lurbinectedin is administered at a dose of 2 to 3.2 mg/m2 to a patient by intravenous infusion every 3 weeks, wherein the medicament is provided in a lyophilized formulation comprising lurbinectedin, lactic acid, and sucrose, wherein the ratio of lurbinectedin: lactic acid:sucrose is between 1 mol:46 mol:455 mol and 1 mol:50 mol:465 mol, wherein the formulation is stable at 5 degree C.±3 degree C. for at least 24 months or at least 36 months or at least 48 months or at least 60 months such that the lurbinectedin degradation product from deacetylation does not exceed 0.8% wt./wt. of the total lurbinectedin weight.

198. The use of clause 197, wherein the medicament is used in combination with a topoisomerase inhibitor administered at a dose equivalent to 75 mg of irinotecan/m^2 and lurbinectedin administered at a dose of 2.0 mg/m^2.

199. A use of lurbinectedin for manufacture of a medicament for use in treating small cell lung cancer (SCLC) in a patient in need thereof, wherein the medicament is a packaged lyophilized composition that comprises 4 mg lurbinectedin, a buffer derived from an organic acid and disaccharide and is dissolved in about 8 mL of water to provide a lurbinectedin solution having a pH of about 3.5 to about 4.1,

for administration of about 2 to 3.2 mg/m^2 of lurbinectedin to a patient whose SCLC has progressed after prior platinum-containing therapy by intravenous infusion every 3 weeks and

wherein the lyophilized composition comprises less than about 0.3% of Impurity D (w/w based on lurbinectedin) when the composition is packaged, and wherein upon storage at about 5 degrees C. for about 24 months or about 36 months the composition comprises less than about 0.8% of Impurity D (w/w based on lurbinectedin).

200. The use of any one of clauses 128-199, wherein the medicament is a packaged, lyophilized composition comprising 4 mg lurbinectedin, a buffer derived from an organic acid and disaccharide and is dissolved in about 8 mL of water to provide a lurbinectedin solution having a pH of about 3.8 to about 4.1 for administration to the patient in need thereof,

wherein the lyophilized composition comprises less than about 0.3% of Impurity D (w/w based on lurbinectedin) when the composition is packaged, and wherein upon storage at about 5 degrees C. for about 24 months or about 36 months the composition comprises less than about 0.8% of Impurity D (w/w based on lurbinectedin).

201. The use of any of the proceeding clauses, wherein, prior to administration, the lyophilized composition is reconstituted in about 8 mL of an aqueous solution to obtain a reconstituted lurbinectedin solution.

202. The use of clause 201, wherein, prior to administration said reconstituted lurbinectedin solution is stored for up to 24 hours following reconstitution at room temperature or at 5° C.±3° C., wherein after storage the reconstituted lurbinectedin solution comprises Impurity D not more than 0.8%, 0.7%, 0.6%, 0.5%, or 0.4% wt/wt based upon the total weight of lurbinectedin.

203. The use of clause 201 or 202, wherein a lurbinectedin infusion solution is prepared by diluting the reconstituted solution with an isotonic solution.

204. The use of clause 203, wherein the reconstituted solution is diluted with at least 100 mL or at least 250 mL of the isotonic solution to prepare the lurbinectedin infusion solution.

205. The use of clause 203 or 204, wherein the isotonic solution is a 0.9% sodium chloride solution or a 5% dextrose solution.

206. The use of any of clauses 203 to 205 wherein the infusion lurbinectedin solution is stored for up to 24 hours following reconstitution of the lyophilized lurbinectedin formulation at room temperature or at 5° C.±3° C., wherein after storage the reconstituted lurbinectedin solution comprises Impurity D not more than 0.8%, 0.7%, 0.6%, 0.5%, or 0.4% wt/wt based upon the total weigh of lurbinectedin.

207. A composition for treatment of small cell lung cancer (SCLC) in a patient in need thereof, comprising:

(1) administering a prophylactic dose of a corticosteroid and a serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient on the day of and prior to administration of lurbinectedin to the patient; and

(2) administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion.

208. The composition of clause 207, wherein the corticosteroid is dexamethasone intravenously administered at a dose of 8 mg of dexamethasone or a dose of a corticosteroid equivalent to 8 mg of dexamethasone administered intravenously.

209. The composition of clause 207 or 208, wherein the serotonin antagonist is ondansetron intravenously administered at a dose of 8 mg of ondansetron or a dose of a serotonin antagonist equivalent to 8 mg of ondansetron administered intravenously.

210. The compostions of any one of clauses 207 to 209, further comprising administering one or more antiemetic agents within 2, 3, or 4 days after administration of lurbinectedin to the patient.

211. The composition of clause 210, wherein the one or more antiemetic agents administered after lurbinectedin administration are selected from a corticosteroid, a serotonin antagonist, and metoclopramide.

212. The composition of clause 211, wherein the one or more antiemetic agents are 4 mg dexamethasone, 8 mg ondansetron, or 10 mg metoclopramide, or a combination thereof.

213. The composition of any of clauses 207-212, wherein the patient has progressed after prior platinum-containing therapy or prior immunotherapy.

214. A composition for treatment of small cell lung cancer (SCLC) in a patient in need thereof, comprising:

(1) administering a first dose of 3.2 mg/m^2 of lurbinectedin to the patient by intravenous infusion; and

(2) identifying an adverse reaction in the patient, wherein the adverse reaction is selected from the group consisting of: ≥Grade 3 (severe) non hematological toxicity, Grade 4 thrombocytopenia (Platelet count less than 25,000 cells/mm^3), Grade 3 thrombocytopenia (Platelet count less than 50,000 cells/mm^3) with bleeding that requires transfusion, Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), or any grade neutropenia (Neutrophil count <LLN) that is associated with infection/sepsis or any other of the adverse reactions;

(3) after the adverse reaction is identified and after the patient's neutrophil count is greater than 1500 cells/mm^3; platelet count is greater than about 100,000 mm^3; and hemoglobin levels are greater than about 9 g/dL:

(i) if the identified adverse reaction consists of Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), administering to the patient a dose of G-CSF and a dose of lurbinectedin that is equal to the first dose; or

(ii) if the identified adverse reaction is not solely Grade 4 neutropenia, administering to the patient a reduced dose of lurbinectedin compared to the first dose,

wherein administration of two doses of lurbinectedin are spaced apart by at least 21 days.

215. The composition of clause 214, wherein a first reduced dose is 80 to 85% of the first dose after a first occurrence of the adverse reaction that is not solely Grade 4 neutropenia or wherein a first reduced dose is to 2.6 mg/m^2 after a first occurrence of the adverse reaction that is not solely Grade 4 neutropenia.

216. The composition of clause 215, wherein a second reduced dose is 60-65% of the first dose after a second occurrence of the adverse reaction that is not solely Grade 4 neutropenia or wherein a second reduced dose is to 2.0 mg/m^2 after a second occurrence of the adverse reaction that is not solely Grade 4 neutropenia, wherein the second reduced is administered to the patient.

217. The composition of clause 216, further comprising discontinuing administration of lurbinectedin after identification of the adverse reaction after administration of the second reduced dose.

218. The composition of any of the preceding clauses in which the lurbinectedin is administered as an infusion formulation prepared by diluting a reconstituted lyophilized formulation of 4 mg lurbinectedin, 22.1 mg lactic acid, 5.1 mg sodium hydroxide and 800 mg sucrose, which, when reconstituted has a pH of 3.5 to 4.5.

219. A composition for treatment of small cell lung cancer (SCLC) in a patient in need thereof, comprising:

administering to the patient lurbinectedin at a dose of 3.2 mg/m^2 by intravenous infusion of a lurbinectedin infusion solution, wherein the lurbinectedin infusion solution administered to the patient is prepared from a lyophilized composition comprising 4 mg lurbinectedin, a buffer derived from an organic carboxylic acid, and a disaccharide reconstituted to form a reconstituted solution at a pH of 3.5 to 4.5.

220. The composition of clause 219, wherein the disaccharide is sucrose and optionally wherein the composition comprises lurbinectedin and sucrose at a ratio of 1 mol lurbinectedin:455 to 465 mol sucrose.

221. The composition of clause 219 or 220 wherein the organic carboxylic acid is lactic acid and optionally wherein the composition comprises lurbinectedin and the lactic acid at a ratio of 1 mol lurbinectedin:44 to 54 mol lactic acid.

222. The composition of any one of clauses 219 to 221 wherein the pH is 3.8 to 4.5

223. The composition of any one of clauses 219 to 222, wherein the lyophilized composition is reconstituted in about 8 mL of an aqueous solution to obtain the reconstituted solution.

224. The composition of clause 223, wherein the lurbinectedin infusion solution is prepared by diluting the reconstituted solution with an isotonic solution.

225. The composition of any one of clauses 219 to 224, wherein the reconstituted solution is diluted with at least 100 mL or at least 250 mL of the isotonic solution to prepare the lurbinectedin infusion solution.

226. The composition of clause 225, wherein the isotonic solution is a 0.9% sodium chloride solution or a 5% dextrose solution.

227. The composition of any one of clauses 219 to 226, wherein the lyophilized composition comprises:

22.1 mg of lactic acid;

5.1 mg of sodium hydroxide; and

800 mg of sucrose.

228. The composition of any one of clauses 219 to 227, wherein the lyophilized composition is provided in a 30 mL vial.

229. The composition of any one of clauses 219 to 228, wherein the lyophilized composition comprises Impurity D at a value no greater than 0.8%, 0.7%, 0.6%, 0.5%, or 0.4% wt/wt based on the total weight of lurbinectedin.

230. The composition of any one of clauses 219 to 229, wherein the lyophilized composition does not comprise a phosphate buffer.

231. The composition of any one of clauses 219 to 231 wherein the reconstituted solution or the lurbinectedin infusion solution comprises Impurity D at a value no greater than 0.8%, 0.7%, 0.6%, 0.5%, or 0.4% wt/wt based on the total weight of lurbinectedin.

232. The composition of any one of clauses 219 to 231, further comprising administering a prophylactic dose of a corticosteroid and a serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient on the day of and prior to administration of lurbinectedin to the patient.

233. The composition of clause 232, wherein the corticosteroid is dexamethasone intravenously administered at a dose of 8 mg of dexamethasone or a dose of a corticosteroid equivalent to 8 mg of dexamethasone administered intravenously.

234. The composition of clause 232 or 233, wherein the serotonin antagonist is ondansetron intravenously administered at a dose of 8 mg of ondansetron or a dose of a serotonin antagonist equivalent to 8 mg of ondansetron administered intravenously.

235. The composition of any one of clauses 232 to 234, further comprising administering one or more antiemetic agents within 2, 3, or 4 days after administration of lurbinectedin to the patient.

236. The composition of clause 235, wherein the one or more antiemetic agents are selected from a corticosteroid, a serotonin antagonist, and metoclopramide.

237. The composition of clause 236, wherein the one or more antiemetic agents are 4 mg dexamethasone, 8 mg ondansetron, or 10 mg metoclopramide, or a combination thereof.

238. The composition of any preceding clause further comprising administering G-CSF to the patient identified as having a neutrophil countless than 500/mm^3 or any value below a normal range and associated with infection/sepsis.

239. The composition of any preceding clause, wherein one dose of lurbinectedin is administered per treatment cycle and the patient undergoes at least 1, 2, 3, 4, 5, 6, 7, 8, 9 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 23, or 24 treatment cycles.

240. The composition of any preceding clause, wherein the overall response rate is at least 11% or at least 20% for patients with a CTFI interval <90 days or wherein the overall response rate is at least 30% or at least 40% for patients with a CTFI interval >90 days.

241. The composition of any preceding clause, wherein the duration of response is at least 2.5 months or at least 4.5 months for the patient with a CTFI interval <90 days or wherein the duration of response is at least 3.5 months, 5 months or 6 months for the patient with a CTFI interval >90 days.

242. The composition of any preceding clause, wherein the patient had not received a platinum-containing therapy in at least 30 or at least 60 or at least 90 days prior to administration of lurbinectedin.

243. The composition of any preceding clause, wherein the patient ceased responding to a platinum-containing therapy prior to administration of lurbinectedin.

244. The composition of any preceding clause, wherein the patient has previously been administered an immunotherapy.

245. The composition of clause 244, wherein the immunotherapy is an anti-CTLA-4 antibody, an anti-PD-1 antibody or an anti-PD-L1 antibody

246. The composition of clause 245, wherein the immunotherapy is atezolizumab or nivolumab.

247. The composition of any of clauses 244 to 246, wherein the patient has progressed after being administered the immunotherapy.

248. The composition of any preceding clause, wherein the patient has a calculated creatinine clearance greater than 30 mL/min and an AST or ALT less than 3×ULN or bilirubin less than 1.5×ULN.

249. The composition of any preceding clause, wherein lurbinectedin is administered to a patient as a 1 hour intravenous infusion, to achieve total plasma Cmax within 80% to 125% of about 107 μg/L and AUC∞ within 80% to 125% of about 551 μg*h/L.

250. A composition for treatment of endometrial cancer, SCLC, soft tissue sarcoma, glioblastoma, pancreatic adenocarcinoma, mesothelioma, colorectal carcinoma, or epithelial ovarian cancer in a patient in need thereof, the treatment comprising

administering to the patient lurbinectedin and a topoisomerase inhibitor selected from SN-38 and irinotecan on day one of a treatment cycle;

wherein the lurbinectedin is administered at a dose of 1 to 2.5 mg/m^2 and

wherein the topoisomerase inhibitor is administered at a dose equivalent to 50 to 75 mg of irinotecan/m^2.

251. The composition of clause 250 wherein the lurbinectedin is administered at a dose of 2.0 mg/m^2 to and the irinotecan is administered at a dose of 75 mg/m^2 by intravenous administration on day 1 of the treatment cycle.

252. The composition of clause 250 or 251, wherein a subsequent dose of irinotecan at 75 mg/m^2 is administered on day 8 of the treatment cycle.

253. The composition of any of clauses 250 to 252 wherein said treatment cycle is 21 days.

254. The composition of any of clauses 250 to 254, wherein the medicament is administered in combination with G-CSF during the treatment cycle.

255. The composition of any of clauses 250 to 254, wherein if the patient exhibits hematologic toxicity after the dose on day 1, not administering a subsequent dose of irinotecan to said patient during the treatment cycle.

256. The composition of any one of clauses 250 to 255, further comprising administering one or more antiemetics on day one of a treatment cycle.

257. The composition of any one of clauses 250 to 256, wherein the patients is treated for endometrial cancer, SCLC, soft tissue sarcoma, or glioblastoma.

258. A composition for treatment of SCLC in a patient in need thereof comprising

administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion,

wherein the patient was administered an immunotherapeutic antibody for treating SCLC prior to beginning the treatment cycle and

wherein the duration of response is at least 2 months, 3 months, 4 months, 5 months or 6 months or wherein the overall response rate is at least 40%.

259. The composition of clause 258, wherein the immunotherapeutic antibody is an anti-CTLA-4 antibody, an anti-PD-1 antibody or an anti-PD-L1 antibody.

260. The composition of clause 259, wherein the immunotherapeutic antibody is atezolizumab or nivolumab.
261. The composition of clause 260, wherein the immunotherapeutic antibody was administered to the patient concurrently with a chemotherapeutic.
262. The composition of clause 261, wherein the chemotherapeutic is carboplatin or etoposide.
263. The composition of clause 262, wherein the immuno-oncogenic therapeutic antibody is atezolizumab and the chemotherapeutic is carboplatin or etoposide.
264. The composition of any one of clauses 258 to 263, wherein one dose of lurbinectedin is administered per treatment cycle and the treatment cycle is an 18, 19, 20, 21, 22, 23, 24, or 25 day cycle.
265. The composition of any one of clauses 258 to 264, wherein one dose of lurbinectedin is administered per treatment cycle and the patient undergoes at least 2, 3, 4, 5, 6, 7, 8, 9 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 23, or 24 treatment cycles.
266. The composition of any one of clauses 258 to 264, wherein the overall response rate is at least 40% or at least 50% or at least 60%.
267. The composition of any one of clauses 258 to 264, wherein the duration of response is at least 2 months, 3 months, 4 months, 5 months or 6 months.
268. The composition of any one of clauses 258 to 264, wherein the patient had not received the immuno-oncogenic therapeutic antibody in at least 30 or at least 60 or at least 90 days prior to administration of lurbinectedin.
269. The composition of any one of clauses 258 to 264, wherein the patient ceased responding to the immuno-oncogenic therapeutic antibody prior to administration of lurbinectedin.
270. The composition of any one of clauses 258 to 269, wherein an immune-oncogenic therapeutic antibody is not administered concurrently with lurbinectedin.
271. A composition for the treatment of small cell lung cancer (SCLC) in a patient in need thereof, comprising administering lurbinectedin at a dose of 2 to 3.2 mg/m2 to a patient by intravenous infusion every 3 weeks, wherein the lurbinectedin is provided in a lyophilized formulation comprising lurbinectedin, a buffer derived from lactic acid, and sucrose, wherein the ratio of lurbinectedin:lactic acid:sucrose is between 1 mol:46 mol:455 mol and 1 mol:50 mol:465 mol, wherein the formulation is stable at 5 degree C.±3 degree C. for at least 24 months or at least 36 months or at least 48 months or at least 60 months such that the lurbinectedin degradation product from deacetylation does not exceed 0.8% wt./wt. of the total lurbinectedin weight.
272. A composition for the treatment of small cell lung cancer (SCLC) in a patient in need thereof, comprising:
1) dissolving a packaged, lyophilized composition comprising 4 mg lurbinectedin, a buffer derived from an organic acid and disaccharide in about 8 mL of water to provide a lurbinectedin solution having a pH of about 3.5 to about 4.1,
and
2) administering about 2 to 3.2 mg/m^2 of lurbinectedin to a patient whose SCLC has progressed after prior platinum-containing therapy by intravenous infusion every 3 weeks and
wherein the lyophilized composition comprises less than about 0.3% of Impurity D (w/w based on lurbinectedin) when the composition is packaged, and wherein upon storage at about 5 degrees C. for about 24 months the composition comprises less than about 0.8% of Impurity D (w/w based on lurbinectedin).
273. The method, composition or use of any one of clauses 1-45, 54-72, 74-89, 100-101, and 120-272, 93-94 and 113-120, wherein the patient is an adult patient.
274. The method, composition or use of any one of clauses 1-45, 54-72, 74-89, 100-101, and 120-273, wherein the cancer is metastatic SCLC.
275. The method, composition or use of any one of clauses 1-45, 54-72, 74-89, 100-101, and 120-274, wherein the cancer is metastatic SCLC with disease progression after platinum based chemotherapy.
276. A method of reducing adverse events associated with the administration of lurbinectedin for the treatment of cancer in a patient in need thereof, the method comprising:
administering lurbinectedin at a dose of 3.2 mg/m2 to the patient by intravenous infusion;
determining if the patient experiences an adverse event selected from the group consisting of neutropenia, thrombocytopenia and hepatotoxicity; and
modifying the dose if the patient experiences neutropenia, thrombocytopenia or hepatotoxicity,
wherein the 3.2 mg/m2 dose of lurbinectedin is administered every 21 days when there is no dose modification (i.e., normal administration schedule).
277. The method of clause 276, wherein prior to the administration, the patient's absolute neutrophil count (ANC) is at least 1,500 cells/mm^3 and platelet count is at least 100,000/mm^3.
278. The method of any one of clauses 276-277, wherein the dose is modified by delaying the administration of lurbinectedin compared to the normal administration schedule.
279. The method of any one of clauses 276-278, wherein the dose is modified by reducing the amount of administered lurbinectedin compared to the normal administration schedule.
280. The method of clause 279, wherein the dose modification comprises administering lurbinectedin at a dose of 2.6 mg/m^2 every 21 days.
281. The method of clause 279, wherein the dose modification comprises administering lurbinectedin at a dose of 2.0 mg/m^2 every 21 days.
282. The method of any one of clauses 276-277, wherein when the patient experiences a Grade 4 neutropenia or any grade febrile neutropenia; the dose is modified by withholding lurbinectedin treatment until the patient's neutropenia is Grade ≤1 and when the patient's neutropenia is Grade ≤1 administering lurbinectedin at a dose of 2.6 mg/m^2 every 21 days.
283. The method of any one of clauses 276-277, wherein when the patient experiences an isolated Grade 4 neutropenia neutropenia (neutrophil count less than 500 cells/mm^3); the dose is modified by withholding lurbinectedin treatment until the patient's neutropenia is Grade ≤51 and when the patient's neutropenia is Grade ≤1 administering lurbinectedin at a dose of 3.2 mg/m^2 every 21 days in conjunction with G-CSF prophylaxis.
284. The method of any one of clauses 276-277, wherein when the patient experiences a Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia; the dose is modified by withholding lurbinectedin treatment until the patient's platelet count is at least 100,

000/mm^3 and when the patient's platelet count is at least 100,000/mm^3 administering lurbinectedin at a dose of 2.6 mg/m^2 every 21 days.

285. The method of any one of clauses 276-277, wherein when the patient experiences Grade 2 hepatotoxicity, the dose is modified by withholding lurbinectedin treatment until the patient's hepatotoxicity is Grade ≤1 and when the hepatotoxicity is Grade ≤1 administering lurbinectedin at a dose of 3.2 mg/m^2 every 21 days.

286. The method of any one of clauses 276-277, wherein when the patient experiences Grade 3 hepatotoxicity, the dose is modified by withholding lurbinectedin treatment until the patient's hepatotoxicity is Grade ≤1 and when the hepatotoxicity is Grade ≤1 administering lurbinectedin at a dose of 2.6 mg/m^2 every 21 days.

287. The method of any one of clauses 282-286, further comprising:

determining if the patient experiences an adverse event selected from the group consisting of neutropenia, thrombocytopenia and hepatotoxicity at the modified dose; and

further modifying the dose if the patient experiences neutropenia, thrombocytopenia or hepatotoxicity.

288. The method of clause 287, wherein when the patient experiences a Grade 4 neutropenia or any grade febrile neutropenia at the modified dose; the dose is further modified by withholding lurbinectedin treatment until the patient's neutropenia is Grade ≤1 and when the patient's neutropenia is Grade ≤1 administering lurbinectedin at a dose of 2.0 mg/m^2 every 21 days.

289. The method of clause 287, wherein when the patient experiences a Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia at the modified dose; the dose is further modified by withholding lurbinectedin treatment until the patient's platelet count is at least 100,000/mm^3 and when the patient's platelet count is at least 100,000/mm^3 administering lurbinectedin at a dose of 2.0 mg/m^2 every 21 days.

290. The method of clause 287, wherein when the patient experiences Grade 2 hepatotoxicity at the modified dose, the dose is further modified by withholding lurbinectedin treatment until the patient's hepatotoxicity is Grade ≤1 and when the hepatotoxicity is Grade ≤1 administering lurbinectedin at a dose of 3.2 mg/m^2 every 21 days.

291. The method of clause 287, wherein when the patient experiences Grade 3 hepatotoxicity at the modified dose, the dose is further modified by withholding lurbinectedin treatment until the patient's hepatotoxicity is Grade ≤1 and when the hepatotoxicity is Grade ≤1 administering lurbinectedin at a dose of 2.0 mg/m^2 every 21 days.

292. The method of any one of clauses 277-291, wherein the administration is permanently discontinued when the withholding of lurbinectedin treatment is greater than two weeks.

292a. The method of any one of clauses 282, 283 and 288, wherein when the withholding of lurbinectedin treatment to achieve Grade ≤1 neutropenia exceeds two weeks the administration is permanently discontinued.

292b. The method of any one of clauses 284 and 289, wherein when the withholding of lurbinectedin treatment to achieve a platelet count of at least 100,000/mm^3 exceeds two weeks the administration is permanently discontinued.

292c. The method of any one of clauses 285, 286, 290 and 291, wherein when the withholding of lurbinectedin treatment to achieve Grade ≤1 hepatotoxicity exceeds two weeks the administration is permanently discontinued.

293. The method of any one of clauses 277-291, wherein the administration is permanently discontinued if patient is unable to tolerate a dose of 2 mg/m^2.

294. The method of any one of clauses 277-293, wherein the cancer is metastatic SCLC with disease progression after platinum based chemotherapy.

295. A method of safely administering lurbinectedin for the treatment of cancer in a patient in need thereof, the method comprising:

determining if the patient is being administered a CYP3A inhibitor; and

when the patient is administered a moderate or strong CYP3A inhibitor warning of a potential drug/drug interaction due to the combination of the CYP3A inhibitor and lurbinectedin; and

when the coadministration of a moderate CYP3A inhibitor and lurbinectedin is cannot be avoided, administering lurbinectedin at a modified dose compared to the normal administration schedule.

296. The method of clause 295, wherein the warning is to avoid the coadministration of the strong or moderate CYP3A inhibitor and lurbinectedin.

297. The method of clause 295, wherein the patient is coadministered a moderate CYP3A inhibitor and lurbinectedin at lurbinectedin at a dose of 2.6 mg/m^2 every 21 days.

298. The method of clause 295, wherein the patient is coadministered a moderate CYP3A inhibitor and lurbinectedin at a dose of 2.0 mg/m^2 every 21 days.

299. A lyophilized composition, comprising

4 mg lurbinectedin, a buffer derived from an organic acid and a disaccharide, and

wherein the lyophilized composition comprises less than about 0.8% of Impurity D (w/w based on lurbinectedin) when the composition is stored at about 25 degrees C. and about 60% relative humidity for up to about 1, 2, 3, 6, 9, or 12 months.

300. The lyophilized composition of clause 299, wherein the lyophilized composition comprises less than about 0.5% of Impurity D (w/w based on lurbinectedin) when the composition is stored at about 25 degrees C. and about 60% relative humidity for up to about 1, 2, 3, 6, 9, or 12 months.

301. The lyophilized composition of clause 299, wherein the lyophilized composition comprises less than about 0.3% of Impurity D (w/w based on lurbinectedin) when the composition is stored at about 25 degrees C. and about 60% relative humidity for up to about 1, 2, 3, 6, 9, or 12 months.

302. The lyophilized composition of clause 299, wherein the lyophilized composition comprises less than about 0.1% of Impurity D (w/w based on lurbinectedin) when the composition is stored at about 25 degrees C. and about 60% relative humidity for up to about 1, 2, 3, 6, 9, or 12 months.

303. The lyophilized composition of any one of clauses 299-302, wherein the organic acid is selected from the group consisting of citric acid, succinic acid, lactic acid and acetic acid.

304. The lyophilized composition of clause 303, wherein the organic acid is lactic acid.

305. The lyophilized composition of any one of clauses 299-304, wherein the disaccharide is selected from the

group consisting of sucrose, trehalose, lactose and a combination of two or all three disaccharides thereof.

306. The lyophilized composition of any one of clauses 299-305, wherein the organic acid is lactic acid, and the disaccharide is sucrose.

307. The lyophilized composition of any one of clauses 299-306, wherein the composition comprises: 4 mg lurbinectedin, 22.1 mg lactic acid, 5.1 mg sodium hydroxide, and 800 mg sucrose or wherein the lyophilized composition comprises 800 mg of sucrose, 0.245 mmol of lactate and 0.128 mmol of sodium.

308. The lyophilized composition of any one of clauses 299-307, wherein the dissolution of the lyophilized composition in about 8 mL of water provides a lurbinectedin solution having a pH of about 3.8 to about 4.1

309. The lyophilized composition of any one of clauses 299-307, wherein dissolution in about 8 mL of water provides a lurbinectedin solution having a pH of about 4.0.

310. The lyophilized composition of any one of clauses 299-307, wherein dissolution in about 8 mL of water provides a lurbinectedin solution comprising 0.47-0.5 mg/mL of lurbinectedin and having a pH of about 3.5-4.5 and comprising.

311. The lyophilized composition of any one of clauses 299-310, wherein the lyophilized composition is packaged in a vial.

311a. The lyophilized composition of any one of clauses 299-311, wherein the lyophilized composition is packaged in a 30 mL vial.

312. Lurbinectedin Form B of the formula (I):

(I)

that exhibits a X-ray powder diffraction pattern comprising four or more peaks at 2-theta angles selected from the group consisting of 6.2±0.2°, 7.6±0.2°, 9.0±0.2°, 10.9±0.2°, 14.9±0.2° and 15.3±0.2°.

313. Lurbinectedin according to clause 312, wherein the X-ray powder diffraction pattern comprises five or more peaks at 2-theta angles selected from the group consisting of 6.2±0.2°, 7.6±0.2°, 9.0±0.2°, 10.9±0.2°, 14.9±0.2° and 15.3±0.2°.

314. Lurbinectedin according to clause 312, wherein the X-ray powder diffraction pattern comprises peaks at 2-theta angles of 6.2±0.2°, 7.6±0.2°, 9.0±0.2°, 10.9±0.2°, 14.9±0.2° and 15.3±0.2°.

315. Lurbinectedin according to any one of clauses 312 to 314, further comprising peaks at 2-theta angles of 12.4±0.2°, 19.2±0.2° and 26.5±0.2°.

316. Lurbinectedin according to any one of clauses 312 to 315, further comprising peaks at 2-theta angles of 18.4±0.2°, 20.7±0.2 and 24.9±0.2°.

317. Lurbinectedin according to clause 312 further comprising peaks and relative intensities of:

Angle [2-theta]	Relative intensity [%]
6.2 ± 0.2°	79 ± 6
7.6 ± 0.2°	100 ± 3
9.0 ± 0.2°	63 ± 3
10.9 ± 0.2°	100 ± 3
14.9 ± 0.2°	76 ± 3
15.3 ± 0.2°	75 ± 3

318. Lurbinectedin according to clause 312, further comprising peaks and relative intensities of:

Angle [2-theta]	Relative intensity [%]	Angle [2-theta]	Relative intensity [%]
6.2 ± 0.2°	79 ± 6	14.9 ± 0.2°	76 ± 3
7.6 ± 0.2°	100 ± 3	15.3 ± 0.2°	75 ± 3
9.0 ± 0.2°	63 ± 3	19.2 ± 0.2°	34 ± 3
10.9 ± 0.2°	100 ± 3	26.5 ± 0.2°	33 ± 3
12.4 ± 0.2°	40 ± 3		

319. Lurbinectedin according to clause 312, further comprising peaks and relative intensities of:

Angle [2-theta]	Relative intensity [%]	Angle [2-theta]	Relative intensity [%]
6.2 ± 0.2°	79 ± 6	15.3 ± 0.2°	75 ± 3
7.6 ± 0.2°	100 ± 3	18.4 ± 0.2°	29 ± 3
9.0 ± 0.2°	63 ± 3	19.2 ± 0.2°	34 ± 3
10.9 ± 0.2°	100 ± 3	20.7 ± 0.2°	32 ± 3
12.4 ± 0.2°	40 ± 3	24.9 ± 0.2°	26 ± 3
14.9 ± 0.2°	76 ± 3	26.5 ± 0.2°	33 ± 3

320. Lurbinectedin according to any one of clauses 312 to 319, that exhibits an X-ray powder diffraction patter substantially the same as any one of the X-ray powder diffraction patterns shown in FIG. **2***a* or **2***b*.

321. Lurbinectedin according to any one of clauses 312 to 320, further characterized by an IR spectrum comprising peaks at wavelengths (cm^{-1}) of 2928, 1755, 1626, 1485, 1456, 1370, 1197, 1150, 1088, 1003, 959, 916, and 587.

322. Lurbinectedin according to any one of clauses 312 to 321, further characterized by a TG-FTIR degradation above 150° C.; and/or characterized by a TG-FTIR mass change to 150° C. being due to loss of water; and/or characterized by a TG-FTIR mass change to 150° C. being due to loss of less than about 5%, less than about 4%, or less than about 3% water; and/or characterized by TG-FTIR indicating a loss of water, preferably around 2-3% water, more preferably 2.6% water.

323. Lurbinectedin according to any one of clauses 312 to 322, further characterized by DSC wherein degradation begins above 130° C.

324. Lurbinectedin according to any one of clauses 312 to 323, further characterized by an average charge density of not more than about 30 nC/g, not more than about 20 nC/g, not more than about 10 nC/g, not more than about

6 nC/g, not more than about 5 nC/g, about 5±2 nC/g, about 4±2 nC/g, about 4-5 nC/g, about 5 nC/g, or about 4 nC/g.

325. Lurbinectedin according to any one of clauses 312 to 324, further characterized by a dispersion of charge density of less than 4.8 nC/g, of between about 0.7 nC/g to less than 4.8 nC/g, or 2.4±2 nC/g.

326. Lurbinectedin according to any one of clauses 312 to 325, characterized by a water content of above 1.6% w/w, or of 1.7-5% w/w.

327. Lurbinectedin according to any one of clauses 312 to 326, further characterized by residual solvents of not more than 1%, 0.5%, 0.1% or substantially not detected.

328. Partially crystalline lurbinectedin.

329. Partially crystalline lurbinectedin according to clause 328, wherein the partially crystalline lurbinectedin comprises lurbinectedin Form B as defined in any one of clauses 312 to 327.

330. Partially crystalline lurbinectedin, according to clause 328 or 329, comprising at least a detectible amount of crystalline lurbinectedin, up to 1% crystalline lurbinectedin, up to 5% crystalline lurbinectedin, up to 10% crystalline lurbinectedin, up to 20% crystalline lurbinectedin, up to 30% crystalline lurbinectedin, up to 40% crystalline lurbinectedin, up to 50% crystalline lurbinectedin, up to 60% crystalline lurbinectedin, up to 70% crystalline lurbinectedin, up to 80% crystalline lurbinectedin, up to 90% crystalline lurbinectedin, up to 95% crystalline lurbinectedin, up to 98% crystalline lurbinectedin, or substantially pure crystalline lurbinectedin.

331. Partially crystalline lurbinectedin, according to any one of clauses 328 to 330, comprising at least a detectible amount of Form B, up to 1% w/w Form B, up to 5% w/w Form B, up to 10% w/w Form B, up to 20% w/w Form B, up to 30% w/w Form B, up to 40% w/w Form B, up to 50% w/w Form B, up to 60% w/w Form B, up to 70% w/w Form B, up to 80% w/w Form B, up to 90% w/w Form B, up to 95% w/w Form B, up to 98% w/w Form B, or substantially pure Form B.

332. Partially crystalline lurbinectedin, according to any one of clauses 328 to 331, comprising at least a detectible amount of amorphous lurbinectedin, up to 1% w/w amorphous lurbinectedin, up to 5% w/w amorphous lurbinectedin, up to 10% w/w amorphous lurbinectedin, up to 20% w/w amorphous lurbinectedin, up to 30% w/w amorphous lurbinectedin, up to 40% w/w amorphous lurbinectedin, up to 50% w/w amorphous lurbinectedin, up to 60% w/w amorphous lurbinectedin, up to 70% w/w amorphous lurbinectedin, up to 80% w/w amorphous lurbinectedin, up to 90% w/w amorphous lurbinectedin, up to 95% w/w amorphous lurbinectedin, or up to 98% w/w amorphous lurbinectedin.

333. A pharmaceutical composition or a pharmaceutical intermediate comprising partially crystalline lurbinectedin according to any one of clauses 328 to 332.

334. Pharmaceutical compositions made from a process including partially crystalline lurbinectedin according to any one of clauses 328 to 332.

335. The composition of clause 333 or clause 334, wherein the composition has a total water content of not more than 3%; and/or residual solvents of not more than 1%, 0.5%, 0.1% or substantially not detected; and/or total impurities of not more than 1.9%, 1.8%, 1.7%, 1.6%, 1.5%, 1.4%, or 1.3%; and/or not more than 0.8% of impurity D; and/or not more than 0.3% of any unspecified impurity; and/or total related substances of not more than 2.0% and any unspecified substances (highest) not more than 0.7%.

336. The pharmaceutical composition of any one of clauses 333 to 335, wherein the pharmaceutical composition is a lyophilized composition.

337. A process for the preparation of Form B of lurbinectedin as defined in any one of clauses 312 to 327, comprising the steps of:

a) preparing an acidic aqueous solution comprising lurbinectedin or a protonated form thereof; and

b) basifying the resulting acid aqueous solution with a base or a buffer to precipitate Form B of lurbinectedin.

338. The process according to clause 337 wherein the acidic aqueous solution comprising lurbinectedin is prepared by dissolving any form of lurbinectedin in acid water.

339. The process according to clause 337 wherein the acid water is an aqueous solution of HCl, preferably 0.1 M.

340. The process according to any one of clauses 337 to 339, wherein the resulting acid aqueous solution is basified with a buffer.

341. The process according to clause 340 wherein the buffer is NH_4Cl/NH_4OH.

342. The process according to any one of clauses 337 to 341, further comprising a washing step between steps a) and b), wherein the aqueous acid solution is washed one or more times with a pharmaceutically-acceptable, water immiscible, polar solvent and one or more times with a pharmaceutically-acceptable, water immiscible, non-polar solvent, preferably C5-C7 alkane.

343. The processes according to clause 342, wherein the aqueous acid solution is washed one or more times with dichloromethane and one or more times with n-pentane.

344. The process according to any one of clauses 337 to 343 wherein Form B of lurbinectedin is collected by filtration.

345. The process according to any one of clauses 337 to 344 wherein Form B of lurbinectedin is dried under vacuum.

346. The process according to any one of clauses 337 to 345 wherein Form B of lurbinectedin is converted into a different physical form.

347. The process according to clause 346 wherein the different physical form is amorphous.

348. A pharmaceutical composition comprising lurbinectedin as defined in any one of clauses 312 to 327, and a pharmaceutically acceptable carrier.

349. A pharmaceutical composition comprising lurbinectedin and a pharmaceutically acceptable carrier, wherein said pharmaceutical composition is manufactured via lurbinectedin as defined in any one of clauses 312 to 327.

350. The pharmaceutical composition to clause 348 or 349, wherein the pharmaceutical composition comprises lurbinectedin and a disaccharide.

351. A process for the manufacture of a lurbinectedin composition, said process employing lurbinectedin as defined in any one of clauses 312 to 327, or partially crystalline lurbinectedin as defined in any one of clauses 328 to 332; preferably as a starting material.

352. The process according to clause 351, wherein the process comprises pre-dissolving the lurbinectedin in an organic acid.

353. The process according to clause 352, wherein the organic acid has a pH less than 4, preferably less than 3.5, more preferably less than 3, or around 3.

354. The process according to clause 352 or 353, wherein the organic acid has a molarity of around 0.1M to 0.5M, preferably around 0.2M to 0.4M, more preferably around 0.3M, or 0.31M.

355. The process according to any one of clauses 352 to 354, wherein the organic acid has a molarity of around 0.1M to 0.5M, preferably around 0.2M to 0.4M, more preferably around 0.3M, or 0.31M.

356. The process according to any one of clauses 352 to 354, wherein the pre-dissolution step is at least 30 minutes, at least 60 minutes or at least 90 minutes, between 30-90 minutes, between 60-90 minutes, between 60-70 minutes or around 60 minutes.

357. The process according to any one of clauses 352 to clause 356, wherein the solution is diluted with water for injection (WFI) to form a target concentration; wherein the target concentration is optionally 8.3 mg/mL in 0.1M organic acid.

358. The process according to any one of clauses 352 to 357, wherein the organic acid is a carboxylic acid such as succinic acid, citric acid, acetic acid or lactic acid, preferably lactic acid.

359. The process according to any one of clauses 351 to 358, wherein a solution comprising an organic buffer and bulking agent (e.g. disaccharide) is prepared to form a buffer solution.

360. The process according to clause 359, wherein the buffer solution has a pH of about 5.6 or less, preferably about 4 to about 5.6, or about 4.2 to about 5.6.

361. The process according to clause 359 or 360, wherein the buffer is derived from an organic acid, preferably an organic carboxylic acid, such as organic carboxylic acid buffer, such as, a lactic acid buffer, a butyric acid buffer, a propionic acid buffer, a acetic acid buffer, a succinic acid buffer, a citric acid buffer, a ascorbic acid buffer, a tartaric acid buffer, a malic acid buffer, a maleic acid buffer, a fumaric acid buffer, a glutamic acid buffer, an aspartic acid buffer, a gluconic acid buffer, and a α-ketoglutaric buffer.

362. The process according to any one of clauses 359 to 361, wherein the bulking agent is a disaccharide, preferably sucrose.

363. The process according to any one of clauses 352 to 362, wherein the dissolved lurbinectedin solution as defined in any one of clauses 352 to 358 is mixed with the buffer solution according to any one of clauses 359 to 362 to form the final bulk solution.

364. The process according to clause 363, wherein the final bulk solution is adjusted with WFI to achieve the final target weight.

365. The process according to any one of clauses 352 to 364, wherein the final target composition comprises 0.5 mg/mL lurbinectedin in 0.03M sodium lactate buffer pH=4+10% (w/v) sucrose.

366. The process according to any one of clauses 352 to 365, wherein the bulk solution according to any one of clauses 363 to 365 undergoes sterilization filtration before filling into vials.

367. The process according to any one of clauses 351 to 366, wherein the composition undergoes freeze-drying to form a lyophilized formulation.

368. The process according to clause 367, wherein the lyophilized composition is labelled for use.

369. The process according to clause 367 or 368, wherein the lyophilized composition is reconstituted for use.

370. The process according to clause 369, wherein the composition is reconstitution with 8 mL of water to yield a solution having a pH of 3.5 to 4.5 and a lurbinectedin concentration of 0.5 mg/ml.

371. The process according to clause 369 or 370, wherein the reconstituted solution is diluted to form an infusion solution; optionally with 0.9% sodium chloride solution or a 5% dextrose solution; further optionally wherein the reconstituted solution is diluted with at least 100 mL or at least 250 mL to prepare a lurbinectedin infusion solution.

372. A lurbinectedin infusion solution made according to the process of any one of clauses 351 to 371.

373. A reconstituted solution made according to the process of any one of clauses 351 to 370.

374. A lyophilized composition made according to the process of any one of clauses 351 to 368.

375. A bulk composition made according to the process of any one of clauses 351 to 366.

376. Lurbinectedin as defined in any one of clauses 312 to 327, or partially crystalline lurbinectedin as defined in any one of clauses 328 to 332, for use as a medicament.

377. Lurbinectedin as defined in any one of clauses 312 to 327, or partially crystalline lurbinectedin as defined in any one of clauses 328 to 332, for use in the manufacture of a medicament.

378. Lurbinectedin as defined in any one of clauses 312 to 327, or partially crystalline lurbinectedin as defined in any one of clauses 328 to 332, for use in the manufacture of a medicament for the treatment of cancer.

379. A method of treating an individual affected by cancer comprising administering to said affected individual a therapeutically effective amount of lurbinectedin as defined in any one of clauses 312 to 327, or partially crystalline lurbinectedin as defined in any one of clauses 328 to 332.

380. A method of treating an individual affected by cancer comprising administering to said affected individual a therapeutically effective amount of a lurbinectedin composition manufactured using lurbinectedin as defined in any one of clauses 312 to 327, or partially crystalline lurbinectedin as defined in any one of clauses 328 to 332.

381. A composition, method, use or process as defined in any one of clauses 1 to 380, wherein reference to reconstitution of 4 mg lurbinectedin in 8 mL with a concentration of 0.5 mg/mL is reference to a calculated concentration of 0.47 mg/mL in 8.55 mL.

382. Lurbinectedin substantially as hereinbefore described with reference to the examples, excluding comparative examples.

383. Lurbinectedin compositions, substantially as hereinbefore described with reference to the examples, excluding comparative examples.

What is claimed:

1. A method of treating metastatic small cell lung cancer (SCLC) in a patient with disease progression after platinum-based chemotherapy, said method comprising administering, within 35 days of receiving a dose of 3.2 mg/m^2 of lurbinectedin by intravenous infusion as a monotherapy, a dose of 2.6 mg/m^2 lurbinectedin by intravenous infusion as a monotherapy to a patient having at the time of the administration of the dose of 2.6 mg/m^2 of lurbinectedin:

a) metastatic SCLC with disease progression after platinum-based chemotherapy,

b) a platelet count of at least 100,000/mm^3,

c) an absolute neutrophil count of at least 1500 cells/mm^3, and

d) ≤Grade 1 hepatotoxicity;

wherein the patient previously experienced ≥Grade 3 hepatotoxicity subsequent to receiving the dose of 3.2 mg/m^2 of lurbinectedin.

2. The method according to claim **1**, wherein one dose of lurbinectedin is administered per a treatment cycle, wherein a treatment cycle is 21 to 35 days, and wherein the patient is administered lurbinectedin for 2 to 24 treatment cycles.

3. The method according to claim **2**, wherein at least one treatment cycle of the 2 to 24 treatment cycles is 22 to 35 days.

4. The method according to claim **2**, wherein at least one of the 2 to 24 treatment cycles is 21 days.

5. The method according to claim **1** further comprising:

administering, within 35 days of receiving a dose of 2.6 mg/m^2 of lurbinectedin by intravenous infusion as a monotherapy, a dose of 2.0 mg/m^2 lurbinectedin by intravenous infusion as a monotherapy to the patient having at the time of the administration of the dose of 2.0 mg/m^2 of lurbinectedin:

(a) a platelet count of at least 100,000/mm^3,

(b) an absolute neutrophil count of at least 1500 cells/mm^3, and

(c) ≤Grade 1 hepatotoxicity;

wherein the patient previously experienced ≥Grade 3 hepatotoxicity subsequent to receiving the dose of 2.6 mg/m^2 of lurbinectedin.

6. The method according to claim **5**, wherein one dose of lurbinectedin is administered per a treatment cycle, wherein a treatment cycle is 21 to 35 days, and wherein the patient is administered lurbinectedin for 3 to 24 cycles.

7. The method according to claim **6**, wherein at least one treatment cycle of the 3 to 24 treatment cycles is 22 to 35 days.

8. The method according to claim **6**, wherein at least one of the 3 to 24 treatment cycles is 21 days.

9. The method according to claim **2**, in which an initial administration of a dose of 3.2 mg/m^2 had been administered to the patient after a chemotherapy-free interval of 90 days or longer following a platinum-based chemotherapy treatment, and the patient has a duration of response that is at least 6.2 months from the initial administration of the dose of 3.2 mg/m^2.

10. The method according to claim **3**, in which an initial administration of a dose of 3.2 mg/m^2 had been administered to the patient after a chemotherapy-free interval of 90 days or longer following a platinum-based chemotherapy treatment, and the patient has a duration of response that is at least 6.2 months from the initial administration of the dose of 3.2 mg/m^2.

11. The method according to claim **4**, in which an initial administration of a dose of 3.2 mg/m^2 had been administered to the patient after a chemotherapy-free interval of 90 days or longer following a platinum-based chemotherapy treatment, wherein the patient has a duration of response that is at least 6.2 months from the initial administration of the dose of 3.2 mg/m^2.

12. The method according to claim **6**, in which an initial administration of a dose of 3.2 mg/m^2 had been administered to the patient after a chemotherapy-free interval of 90 days or longer following a platinum-based chemotherapy treatment, and the patient has a duration of response that is at least 6.2 months from the initial administration of the dose of 3.2 mg/m^2.

13. The method according to claim **2**, in which an initial administration of a dose of 3.2 mg/m^2 had been administered to the patient after a chemotherapy-free interval of less than 90 days following a platinum-based chemotherapy, and the patient has a duration of response that is at least 4.7 months from the initial administration of the dose of 3.2 mg/m^2.

14. The method according to claim **3**, in which an initial administration of a dose of 3.2 mg/m^2 had been administered to the patient after a chemotherapy-free interval of less than 90 days following a platinum-based chemotherapy treatment, and the patient has a duration of response that is at least 4.7 months from the initial administration of the dose of 3.2 mg/m^2.

15. The method according to claim **4**, in which an initial administration of a dose of 3.2 mg/m^2 had been administered to the patient after a chemotherapy-free interval of less than 90 days following a platinum-based chemotherapy treatment, and the patient has a duration of response that is at least 4.7 months from the initial administration of the dose of 3.2 mg/m^2.

16. The method according to claim **6**, in which an initial administration of a dose of 3.2 mg/m^2 had been administered to the patient after a chemotherapy-free interval of less than 90 days following a platinum-based chemotherapy treatment, and the patient has a duration of response that is at least 4.7 months from the initial administration of the dose of 3.2 mg/m^2.

17. The method according to claim **2**, in which the patient is administered lurbinectedin for at least 4 treatment cycles.

18. The method according to claim **2**, in which the patient is administered lurbinectedin for at least 6 treatment cycles.

19. The method according to claim **2**, in which the patient is administered lurbinectedin for at least 10 treatment cycles.

20. The method according to claim **4**, in which the patient is administered lurbinectedin for at least 4 treatment cycles.

21. The method according to claim **4**, in which the patient is administered lurbinectedin for at least 6 treatment cycles.

22. The method according to claim **4**, in which the patient is administered lurbinectedin for at least 10 treatment cycles.

23. The method according to claim **6**, in which the patient is administered lurbinectedin for at least 4 treatment cycles.

24. The method according to claim **6**, in which the patient is administered lurbinectedin for at least 6 treatment cycles.

25. The method according to claim **6**, in which the patient is administered lurbinectedin for at least 10 treatment cycles.

26. A method of treating metastatic small cell lung cancer (SCLC) in a patient with disease progression after platinum-based chemotherapy, said method comprising:

(a) administering a dose of 3.2 mg/m^2 of lurbinectedin by intravenous infusion as a monotherapy to a patient having, at the time of the administration of the dose of 3.2 mg/m^2 of lurbinectedin:

(i) metastatic SCLC with disease progression after platinum-based chemotherapy,

(ii) an absolute neutrophil count of at least 1500 cells/mm^3,

(iii) a platelet count of at least 100,000/mm^3, and

(iv) ≤Grade 1 hepatotoxicity;

wherein the patient experienced ≥Grade 3 hepatotoxicity subsequent to the administration of the dose of 3.2 mg/m^2 of lurbinectedin and returns within 35 days of the administration of the dose of 3.2 mg/m^2 of lurbinectedin to ≤Grade 1 hepatotoxicity after experiencing the ≥Grade 3 hepatotoxicity; and

(b) administering by intravenous infusion as a monotherapy a dose of 2.6 mg/m^2 of lurbinectedin to the patient after the patient returns to ≤Grade 1 hepatotoxicity and has a platelet count of at least 100,000/mm^3 and an absolute neutrophil count of at least 1500 cells/mm^3.

27. The method according to claim **26**, wherein one dose of lurbinectedin is administered per a treatment cycle, wherein a treatment cycle is 21 to 35 days, and wherein the patient is administered lurbinectedin for 4 to 24 treatment cycles.

28. The method according to claim **26**, wherein at least one of the 4 to 24 treatment cycles is 21 days.

29. The method according to claim **26** further comprising:

administering, within 35 days of receiving a dose of 2.6 mg/m^2 of lurbinectedin by intravenous infusion as a monotherapy, a dose of 2.0 mg/m^2 lurbinectedin by intravenous infusion as a monotherapy to the patient having at the time of the administration of the dose of 2.0 mg/m^2 of lurbinectedin:

(a) a platelet count of at least 100,000/mm^3,

(b) an absolute neutrophil count of at least 1500 cells/mm^3, and

(c) ≤Grade 1 hepatotoxicity;

wherein the patient previously experienced ≥Grade 3 hepatotoxicity subsequent to receiving the dose of 2.6 mg/m^2 of lurbinectedin.

30. The method according to claim **29**, wherein one dose of lurbinectedin is administered per a treatment cycle, wherein a treatment cycle is 21 to 35 days, and wherein the patient is administered lurbinectedin for 4 to 24 treatment cycles.

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