

Charles M. Lizza  
William C. Baton  
SAUL EWING ARNSTEIN & LEHR LLP  
One Riverfront Plaza, Suite 1520  
Newark, NJ 07102-5426  
(973) 286-6700  
[clizza@saul.com](mailto:clizza@saul.com)

*Attorneys for Plaintiff  
Celgene Corporation*

**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

**CELGENE CORPORATION,**

**Plaintiff,**

**v.**

**SYNTHON PHARMACEUTICALS INC.,  
SYNTHON B.V., SYNTHON S.R.O., and  
ALVOGEN PINE BROOK, LLC,**

**Defendants.**

**Civil Action No. \_\_\_\_\_**

**COMPLAINT FOR  
PATENT INFRINGEMENT**

**(Filed Electronically)**

Plaintiff Celgene Corporation (“Celgene”), by its undersigned attorneys, for its Complaint against defendants Synthon Pharmaceuticals Inc. (“Synthon Pharmaceuticals”), Synthon B.V. (“Synthon B.V.”), Synthon s.r.o. (“Synthon s.r.o.”, together with Synthon Pharmaceuticals and Synthon B.V., “Synthon”) and Alvogen Pine Brook, LLC (“Alvogen”) (collectively, “Defendants”), alleges as follows:

**Nature of the Action**

1. This is an action for patent infringement under the patent laws of the United States, 35 U.S.C. §100, *et seq.*, arising from the filing of Abbreviated New Drug Application (“ANDA”) No. 210232 with the United States Food and Drug Administration (“FDA”) seeking approval to commercially market generic versions of Celgene’s 1 mg, 2 mg, 3 mg, and 4 mg

POMALYST® drug products (“Synthon’s ANDA Products”) prior to the expiration of United States Patent Nos. 10,093,647 (the “‘647 patent”), 10,093,648 (the “‘648 patent”), and 10,093,649 (the “‘649 patent”) (collectively, “the patents-in-suit”) owned by Celgene.

### **The Parties**

2. Plaintiff Celgene is a biopharmaceutical company committed to improving the lives of patients worldwide. Celgene focuses on, and invests heavily in, the discovery and development of products for the treatment of severe and life-threatening conditions. Celgene is a world leader in the treatment of many such diseases, including cancer. Celgene is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 86 Morris Avenue, Summit, New Jersey 07901.

3. On information and belief, Synthon Pharmaceuticals is a North Carolina corporation, having a principal place of business at 1007 Slater Road, Suite 150, Durham, North Carolina 27703.

4. On information and belief, Synthon B.V. is a corporation organized and existing under the laws of the Netherlands, having a principal place of business at Microweg 22, P.O. Box 7071, 6503 CM Nijmegen, the Netherlands.

5. On information and belief, Synthon s.r.o. is a Czech Republic entity having a principal place of business at Brnenska 32/cp. 597, 678 01 Blansko, Czech Republic.

6. On information and belief, Alvogen is a Delaware corporation, having a principal place of business at 10B Bloomfield Avenue, Pine Brook, New Jersey 07058.

### **The Patents-in-Suit**

7. On October 9, 2018, the United States Patent and Trademark Office (“USPTO”) duly and lawfully issued the ’647 patent, entitled, “Crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate, compositions and methods of use thereof,” to Celgene as

assignee of the inventor Jerry Lee Atwood. A copy of the '647 patent is attached hereto as Exhibit A.

8. On October 9, 2018, the USPTO duly and lawfully issued the '648 patent, entitled, "Crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate, compositions and methods of use thereof," to Celgene as assignee of the inventor Jerry Lee Atwood. A copy of the '648 patent is attached hereto as Exhibit B.

9. On October 9, 2018, the USPTO duly and lawfully issued the '649 patent, entitled, "Crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate, compositions and methods of use thereof," to Celgene as assignee of the inventor Jerry Lee Atwood. A copy of the '649 patent is attached hereto as Exhibit C.

#### **The Pomalyst® Drug Product**

10. Celgene holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for pomalidomide capsules (NDA No. 204026), which it sells under the trade name POMALYST®. POMALYST® is an FDA-approved medication used for the treatment of multiple myeloma.

11. The claims of the patents-in-suit cover, *inter alia*, solid forms of pomalidomide.

#### **Jurisdiction and Venue**

12. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

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

#### **A. Synthon**

14. This Court has personal jurisdiction over Synthon Pharmaceuticals by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey. On information

and belief, Synthon Pharmaceuticals is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business ID No. 0100946900. On information and belief, Synthon Pharmaceuticals has purposefully conducted and continues to conduct business in this Judicial District.

15. On information and belief, Synthon Pharmaceuticals is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District. On information and belief, this Judicial District will be a destination for the generic drug product described in ANDA No. 210232. On information and belief, Synthon Pharmaceuticals prepares and/or aids in the preparation and submission of ANDAs to the FDA.

16. On information and belief, Synthon B.V. is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District. On information and belief, this Judicial District will be a destination for the generic drug product described in ANDA No. 210232. On information and belief, Synthon B.V. prepares and/or aids in the preparation and submission of ANDAs to the FDA.

17. On information and belief, Synthon s.r.o is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District. On information and belief, this Judicial District will be a destination for the generic drug product described in ANDA No. 210232. On information and belief, Synthon s.r.o. prepares and/or aids in the preparation and submission of ANDAs to the FDA.

18. On information and belief, Synthon Pharmaceuticals maintains extensive and systematic contacts with pharmaceutical retailers, wholesalers, and/or distributors in New Jersey providing for the distribution of Synthon's products in the State of New Jersey.

19. On information and belief, Synthon regularly and continuously transacts business within New Jersey, including by making pharmaceutical products for sale in New Jersey and selling pharmaceutical products in New Jersey. On information and belief, Synthon derives substantial revenue from the sale of those products in New Jersey.

20. This Court has personal jurisdiction over Synthon B.V. and/or Synthon s.r.o. because, *inter alia*, they: (1) have purposefully availed themselves of the privilege of doing business in New Jersey, including directly or indirectly through their subsidiary, agent, and/or alter ego, Synthon Pharmaceuticals, a company registered with the State of New Jersey; and (2) maintain extensive and systematic contacts with the State of New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Synthon Pharmaceuticals.

21. On information and belief, Synthon Pharmaceuticals acts at the direction, and for the benefit, of Synthon B.V. and/or Synthon s.r.o.

22. On information and belief, Synthon Pharmaceuticals, Synthon B.V., and Synthon s.r.o. are members of the same corporate family.

23. On information and belief, Synthon Pharmaceuticals, Synthon B.V., and Synthon s.r.o. work in concert with respect to the regulatory approval, manufacturing, importation, marketing, sale, and distribution of generic pharmaceutical products throughout the United States, including in this Judicial District.

24. On information and belief, Synthon Pharmaceuticals Inc., Synthon B.V., and/or Synthon s.r.o. have partnered with Alvogen in the submission of ANDA No. 210232 and will continue to partner with Alvogen towards the regulatory approval, manufacturing, use, importation, marketing, offer for sale, sale, and distribution of generic pharmaceutical products, including the generic drug product described in ANDA No. 210232, throughout the United States, including in New Jersey, prior to the expiration of the patents-in-suit.

25. This Court has personal jurisdiction over Synthon because, *inter alia*, it has committed an act of patent infringement under 35 U.S.C. § 271(e)(2), and has sent notice of that infringement to Celgene in the State of New Jersey. On information and belief, Synthon intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will continue to lead to foreseeable harm and injury to Celgene in New Jersey and in this Judicial District.

26. On information and belief, Synthon Pharmaceuticals and Synthon B.V. have previously been sued in this Judicial District and have not challenged personal jurisdiction or venue. *See, e.g., Otsuka Pharmaceutical Co., Ltd. v. Sandoz, Inc., et al.*, Civil Action No. 07-1000 (MLC)(JJH) (D.N.J.), D.I. 77 at ¶¶ 8, 11.

27. On information and belief, Synthon Pharmaceuticals and Synthon B.V. have availed themselves of this Court by bringing counterclaims in this Judicial District. *See, e.g., Otsuka Pharmaceutical Co., Ltd. v. Sandoz, Inc., et al.*, Civil Action No. 07-1000 (MLC)(JJH) (D.N.J.), D.I. 77.

28. In the alternative, this Court has personal jurisdiction over Synthon B.V. because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Celgene's claims arise under federal law; (b) Synthon B.V. is a foreign defendant not subject to general

personal jurisdiction in the courts of any state; and (c) Synthon B.V. has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to the FDA and/or manufacturing, importing, offering to sell, and/or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Synthon B.V. satisfies due process.

29. In the alternative, this Court has personal jurisdiction over Synthon s.r.o. because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Celgene's claims arise under federal law; (b) Synthon s.r.o. is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Synthon s.r.o. has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to the FDA and/or manufacturing, importing, offering to sell, and/or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Synthon s.r.o. satisfies due process.

#### **B. Alvogen**

30. This Court has personal jurisdiction over Alvogen by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey. On information and belief, Alvogen is in the business of, among other things, manufacturing, marketing, offering for sale, selling, and importing pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District. On information and belief, Alvogen has conducted and continues to conduct business in this Judicial District, including the purposeful sale and distribution of drug products.

31. This Court has personal jurisdiction over Alvogen because, *inter alia*, it has purposefully availed itself of the privilege of doing business in New Jersey.

32. On information and belief, Alvogen derives substantial revenue from the sale of generic pharmaceutical products and/or active pharmaceutical ingredient(s) (“API”) used in various generic pharmaceutical products sold throughout the United States, including in this Judicial District.

33. On information and belief, Defendants work in concert with respect to the regulatory approval, manufacturing, marketing, sale, and distribution of generic pharmaceutical products and/or API throughout the United States, including in this Judicial District.

34. On information and belief, Alvogen partnered with Synthon and participated in the preparation and/or filing of ANDA No. 210232. On information and belief, Alvogen will continue to partner with Synthon towards the regulatory approval, manufacturing, use, importation, marketing, offer for sale, sale, and distribution of generic pharmaceutical products, including the generic drug product described in ANDA No. 210232, throughout the United States, including in New Jersey, prior to the expiration of the patents-in-suit.

35. On information and belief, Alvogen serves as a United States marketing partner with respect to ANDA No. 210232.

36. This Court has personal jurisdiction over Alvogen because, *inter alia*, it has committed an act of patent infringement under 35 U.S.C. § 271(e)(2). On information and belief, Alvogen intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will continue to lead to foreseeable harm and injury to Celgene in New Jersey and in this Judicial District. This Judicial District is a likely destination for the generic drug product described in ANDA No. 210232. On information and belief, Alvogen intends to benefit from ANDA No. 210232 if ANDA No. 210232 is approved.

37. On information and belief, Alvogen has previously not contested personal jurisdiction in this Judicial District. *See, e.g., Indivior Inc., et al., v. Alvogen Pine Brook LLC*, Civil Action No. 18-5285 (KM)(CLW) (D.N.J.); *Celgene Corp. v. Lotus Pharm. Co., Ltd., et al.*, Civil Action No. 17-6842 (SDW)(LDW) (D.N.J.).

38. On information and belief, Alvogen has availed itself of this Court by bringing counterclaims in this Judicial District. *See, e.g., Celgene Corp. v. Lotus Pharm. Co., Ltd., et al.*, Civil Action No. 17-6842 (SDW)(LDW) (D.N.J.).

39. Alvogen has previously been sued in this Judicial District and has not contested venue. *See, e.g., Indivior Inc., et al. v. Alvogen Pine Brook LLC*, Civil Action No. 18-5285 (KM)(CLW) (D.N.J.).

#### **Acts Giving Rise To This Suit**

40. Pursuant to Section 505 of the FFDCA, Defendants submitted ANDA No. 210232 seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of pomalidomide capsules 1 mg, 2 mg, 3 mg, and 4 mg (“Synthon’s ANDA Products”), before the patents-in-suit expire.

41. On information and belief, following FDA approval of ANDA No. 210232, Defendants Synthon and Alvogen will work in concert with one another to make, use, offer for sale, or sell Synthon’s ANDA Products throughout the United States, or import such generic products into the United States.

42. On information and belief, in connection with the filing of ANDA No. 210232 as described above, Defendants provided written certifications to the FDA pursuant to Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (“Synthon’s Paragraph IV Certifications”), alleging, *inter alia*, that the claims of United States Patent Nos. 8,198,262 (“262 patent”), 8,673,939 (“939 patent”), 8,735,428 (“428 patent”), 8,828,427 (“427 patent”), and 9,993,467

(“‘467 patent”) are invalid, unenforceable, and/or will not be infringed by the activities described in ANDA No. 210232.

43. No earlier than May 4, 2018, Defendants sent written notice of their Paragraph IV Certification to Celgene (“Synthon’s May 2018 Notice Letter”). Synthon’s May 2018 Notice Letter alleged that the claims of the ‘262 patent, the ‘939 patent, the ‘428 patent, and the ‘427 patent are invalid and/or will not be infringed by the activities described in ANDA No. 210232. Synthon’s May 2018 Notice Letter also informed Celgene that Synthon seeks approval to market Synthon’s Proposed Products before the patents named in Synthon’s May 2018 Notice Letter expire. Synthon specifically directed Synthon’s May 2018 Notice Letter to Celgene’s headquarters in Summit, New Jersey, in this Judicial District.

44. No earlier than October 5, 2018, Defendants sent written notice of their Paragraph IV Certification to Celgene (“Synthon’s October 2018 Notice Letter”). Synthon’s October 2018 Notice Letter alleged that the claims of the ‘467 patent are invalid and/or will not be infringed by the activities described in ANDA No. 210232. Synthon’s October 2018 Notice Letter also informed Celgene that Synthon seeks approval to market Synthon’s Proposed Products before the expiration of the ‘467 patent. Synthon specifically directed Synthon’s October 2018 Notice Letter to Celgene’s headquarters in Summit, New Jersey, in this Judicial District.

45. In light of Defendants’ filing of ANDA No. 210232 and the USPTO’s issuance of the patents-in-suit, Celgene sent a letter to counsel for Defendants dated November 20, 2018, in which Celgene informed counsel for Defendants that, on information and belief, the products proposed in ANDA No. 210232 will likely infringe one or more claims of the patents-in-suit. To the extent that Defendants disagreed, Celgene requested that Defendants provide samples of

Synthon's ANDA Products, the active pharmaceutical ingredient used to make those ANDA Products, and additional documentation concerning the representativeness of the requested samples, as well as all safety, storage, and handling information that Defendants deem appropriate for its samples, by December 20, 2018.

46. Defendants did not respond to Celgene's November 20, 2018 letter.

**Count I: Infringement of the '647 Patent**

47. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

48. On information and belief, Synthon's ANDA Products contain crystalline pomalidomide as set forth in the claims of the '647 patent.

49. Defendants, by the submission of their Paragraph IV Certifications as part of ANDA No. 210232 to the FDA, have indicated that they seek approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Synthon's ANDA Products, prior to the expiration of the '647 patent.

50. ANDA No. 210232 has been pending before the FDA since at least May 4, 2018, the date that Synthon sent Synthon's May 2018 Notice Letter to Celgene.

51. Defendants' submission of ANDA No. 210232 to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Synthon's ANDA Products, prior to the expiration of the '647 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

52. There is a justiciable controversy between Celgene and Defendants as to the infringement of the '647 patent.

53. Unless enjoined by this Court, upon FDA approval of ANDA No. 210232, Defendants will infringe one or more claims of the '647 patent under 35 U.S.C. § 271(a) by

making, using, offering to sell, selling, and/or importing Synthon's ANDA Products in the United States.

54. Unless enjoined by this Court, upon FDA approval of ANDA No. 210232, Defendants will induce infringement of one or more claims of the '647 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Synthon's ANDA Products in the United States. On information and belief, upon FDA approval of ANDA No. 210232, Defendants will intentionally encourage acts of direct infringement with knowledge of the '647 patent and knowledge that its acts are encouraging infringement.

55. Unless enjoined by this Court, upon FDA approval of ANDA No. 210232, Defendants will contributorily infringe one or more claims of the '647 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Synthon's ANDA Products in the United States. On information and belief, Defendants have had and continue to have knowledge that Synthon's ANDA Products are especially adapted for a use that infringes one or more claims of the '647 patent and that there is no substantial non-infringing use for Synthon's ANDA Products.

56. Celgene will be substantially and irreparably damaged and harmed if Defendants' infringement of the '647 patent is not enjoined.

57. Celgene does not have an adequate remedy at law.

58. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

#### **Count II: Infringement of the '648 Patent**

59. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

60. On information and belief, Synthon's ANDA Products contain crystalline pomalidomide as set forth in the claims of the '648 patent.

61. Defendants, by the submission of their Paragraph IV Certifications as part of ANDA No. 210232 to the FDA, have indicated that they seek approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Synthon's ANDA Products, prior to the expiration of the '648 patent.

62. ANDA No. 210232 has been pending before the FDA since at least May 4, 2018, the date that Defendants sent Synthon's May 2018 Notice Letter to Celgene.

63. Defendants' submission of ANDA No. 210232 to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Synthon's ANDA Products, prior to the expiration of the '648 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

64. There is a justiciable controversy between Celgene and Defendants as to the infringement of the '648 patent.

65. Unless enjoined by this Court, upon FDA approval of ANDA No. 210232, Defendants will infringe one or more claims of the '648 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Synthon's ANDA Products in the United States.

66. Unless enjoined by this Court, upon FDA approval of ANDA No. 210232, Defendants will induce infringement of one or more claims of the '648 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Synthon's ANDA Products in the United States. On information and belief, upon FDA approval of ANDA No. 210232,

Defendants will intentionally encourage acts of direct infringement with knowledge of the '648 patent and knowledge that its acts are encouraging infringement.

67. Unless enjoined by this Court, upon FDA approval of ANDA No. 210232, Defendants will contributorily infringe one or more claims of the '648 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Synthon's ANDA Products in the United States. On information and belief, Defendants have had and continue to have knowledge that Synthon's ANDA Products are especially adapted for a use that infringes one or more claims of the '648 patent and that there is no substantial non-infringing use for Synthon's ANDA Products.

68. Celgene will be substantially and irreparably damaged and harmed if Defendants' infringement of the '648 patent is not enjoined.

69. Celgene does not have an adequate remedy at law.

70. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

### **Count III: Infringement of the '649 Patent**

71. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

72. On information and belief, Synthon's ANDA Products contain crystalline pomalidomide as set forth in the claims of the '649 patent.

73. Defendants, by the submission of their Paragraph IV Certification as part of ANDA No. 210232 to the FDA, have indicated that they seek approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Synthon's ANDA Products, prior to the expiration of the '649 patent.

74. ANDA No. 210232 has been pending before the FDA since at least May 4, 2018, the date that Defendants sent Synthon's May 2018 Notice Letter to Celgene.

75. Defendants' submission of ANDA No. 210232 to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Synthon's ANDA Products, prior to the expiration of the '649 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

76. There is a justiciable controversy between Celgene and Defendants as to the infringement of the '649 patent.

77. Unless enjoined by this Court, upon FDA approval of ANDA No. 210232, Defendants will infringe one or more claims of the '649 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Synthon's ANDA Products in the United States.

78. Unless enjoined by this Court, upon FDA approval of ANDA No. 210232, Defendants will induce infringement of one or more claims of the '649 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Synthon's ANDA Products in the United States. On information and belief, upon FDA approval of ANDA No. 210232, Defendants will intentionally encourage acts of direct infringement with knowledge of the '649 patent and knowledge that its acts are encouraging infringement.

79. Unless enjoined by this Court, upon FDA approval of ANDA No. 210232, Defendants will contributorily infringe one or more claims of the '649 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Synthon's ANDA Products in the United States. On information and belief, Defendants have had and continue to have knowledge that Synthon's ANDA Products are especially adapted for a use that infringes one or

more claims of the '649 patent and that there is no substantial non-infringing use for Synthon's ANDA Products.

80. Celgene will be substantially and irreparably damaged and harmed if Defendants' infringement of the '649 patent is not enjoined.

81. Celgene does not have an adequate remedy at law.

82. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

#### **PRAYER FOR RELIEF**

WHEREFORE, Plaintiff Celgene respectfully requests the following relief:

- (A) A Judgment that Defendants have infringed the patents-in-suit by submitting ANDA No. 210232;
- (B) A Judgment that Defendants have infringed, and that Defendants' making, using, offering to sell, selling, or importing Synthon's ANDA Products will infringe one or more claims of the patents-in-suit;
- (C) An Order that the effective date of FDA approval of ANDA No. 210232 be a date which is not earlier than the later of the expiration of the patents-in-suit, or any later expiration of exclusivity to which Celgene is or becomes entitled;
- (D) Preliminary and permanent injunctions enjoining Defendants and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, offering to sell, selling, or importing Synthon's ANDA Products until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Celgene is or becomes entitled;
- (E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Defendants, their officers, agents, attorneys and employees, and those acting in privity

or concert with them, from practicing any solid forms of pomalidomide, as claimed in the patents-in-suit, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit, until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Celgene is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Synthon's ANDA Products will directly infringe, induce and/or contribute to infringement of the patents-in-suit;

(G) To the extent that Defendants have committed any acts with respect to the solid forms of pomalidomide claimed in the patents-in-suit, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Celgene damages for such acts;

(H) If Defendants engage in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Synthon's ANDA Products prior to the expiration of the patents-in-suit, a Judgment awarding damages to Celgene resulting from such infringement, together with interest;

(I) A Judgment declaring that the patents-in-suit remain valid and enforceable;

(J) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and awarding Celgene its attorneys' fees incurred in this action;

(K) A Judgment awarding Celgene its costs and expenses incurred in this action; and

(L) Such further and other relief as this Court may deem just and proper.

Dated: April 12, 2019

By: s/ Charles M. Lizza

Charles M. Lizza  
William C. Baton  
SAUL EWING ARNSTEIN & LEHR LLP  
One Riverfront Plaza, Suite 1520  
Newark, New Jersey 07102-5426  
(973) 286-6700  
clizza@saul.com

Of Counsel:

F. Dominic Cerrito  
Eric C. Stops  
Andrew S. Chalson  
QUINN EMANUEL URQUHART & SULLIVAN, LLP  
51 Madison Avenue, 22nd Floor  
New York, New York 10010  
(212) 849-7000

*Attorneys for Plaintiff  
Celgene Corporation*

Anthony M. Insogna  
Cary Miller, Ph.D.  
JONES DAY  
4655 Executive Drive  
San Diego, CA 92121  
(858) 314-1200

Matthew J. Hertko  
JONES DAY  
77 W. Wacker Drive, Suite 3500  
Chicago, IL 60601  
(312) 782-3939

**CERTIFICATION PURSUANT TO L. CIV. R. 11.2 & 40.1**

Pursuant to Local Civil Rules 11.2 and 40.1, I hereby certify that the matter captioned *Celgene Corporation v. Synthon Pharmaceuticals Inc., et al.*, Civil Action No. 18-10775 (ES)(MAH) (D.N.J.) is related to the matter in controversy because the matter in controversy involves the same plaintiff and the same defendants, and because defendants in the matters are seeking FDA approval to market generic versions of the same pharmaceutical products.

I further certify that the matters captioned *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 19-5797 (ES)(MAH) (D.N.J.), *Celgene Corporation v. Aurobindo Pharma Limited, et al.*, Civil Action No. 19-5799 (ES)(MAH) (D.N.J.), *Celgene Corporation v. Mylan Pharmaceuticals Inc., et al.*, Civil Action No. 19-5802 (ES)(MAH) (D.N.J.), *Celgene Corporation v. Breckenridge Pharmaceutical, Inc., et al.*, Civil Action No. 19-5804 (ES)(MAH) (D.N.J.), *Celgene Corporation v. Apotex Inc.*, Civil Action No. 19-5806 (ES)(MAH) (D.N.J.), and *Celgene Corporation v. Teva Pharmaceuticals USA, Inc., et al.*, Civil Action No. 19-8758 (ES)(MAH) (D.N.J.) are related to the matter in controversy because the matter in controversy involves the same plaintiff, the same patents, and because defendants in the matters are seeking FDA approval to market generic versions of the same pharmaceutical products.

I further certify that the matter captioned *Celgene Corporation v. Hetero Labs Ltd., et al.*, Civil Action No. 17-3387 (ES)(MAH) (D.N.J.) is related to the matter in controversy because the matter in controversy involves the same plaintiff and because defendants are seeking FDA approval to market generic versions of the same pharmaceutical products.

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: April 12, 2019

Of Counsel:

F. Dominic Cerrito  
Eric C. Stops  
Andrew S. Chalson  
QUINN EMANUEL URQUHART  
& SULLIVAN, LLP  
51 Madison Avenue, 22nd Floor  
New York, New York 10010  
(212) 849-7000

Anthony M. Insogna  
Cary Miller, Ph.D.  
JONES DAY  
4655 Executive Drive  
San Diego, CA 92121  
(858) 314-1200

Matthew J. Hertko  
JONES DAY  
77 W. Wacker Drive, Suite 3500  
Chicago, IL 60601  
(312) 782-3939

By: s/ Charles M. Lizza  
Charles M. Lizza  
William C. Baton  
SAUL EWING ARNSTEIN & LEHR LLP  
One Riverfront Plaza, Suite 1520  
Newark, New Jersey 07102-5426  
(973) 286-6700  
clizza@saul.com

*Attorneys for Plaintiff  
Celgene Corporation*

# **EXHIBIT A**



US010093647B1

(12) **United States Patent**  
**Atwood**

(10) **Patent No.:** US 10,093,647 B1  
(b4) **Date of Patent:** Oct. 9, 2018

(54) **CRYSTALLINE 4-AMINO-2-(2,6-DIOXOPIPERIDINE-3-YL)ISOINDOLINE-1,3-DIONE DIHYDRATE, COMPOSITIONS AND METHODS OF USE THEREOF**

(71) Applicant: **Celgene Corporation**, Summit, NJ (US)

(72) Inventor: **Jerry Lee Atwood**, Columbia, MO (US)

(73) Assignee: **Celgene Corporation**, Summit, NJ (US)

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

(21) Appl. No.: 15/849,285

(22) Filed: Dec. 20, 2017

**Related U.S. Application Data**

(60) Provisional application No. 62/511,878, filed on May 26, 2017.

(51) **Int. Cl.**

C07D 401/04 (2006.01)  
A61K 31/4035 (2006.01)  
A61K 31/45 (2006.01)

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

CPC ..... C07D 401/04 (2013.01); A61K 31/4035 (2013.01); A61K 31/45 (2013.01); C07B 2200/13 (2013.01)

(58) **Field of Classification Search**

CPC ..... C07D 401/04  
USPC ..... 546/200; 514/323  
See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

4,551,177 A	11/1985	Trubiano et al.
5,385,901 A	1/1995	Kaplan et al.
5,593,696 A	1/1997	McNally et al.
5,594,637 A	1/1997	Eisenberg et al.
5,619,991 A	4/1997	Sloane
5,635,517 A	6/1997	Muller et al.
5,712,291 A	1/1998	D'Amato
5,731,325 A	3/1998	Andrusis, Jr. et al.
5,798,368 A	8/1998	Muller et al.
5,832,449 A	11/1998	Cunningham
5,882,656 A	3/1999	Bechard et al.
5,974,203 A	10/1999	Tadokoro et al.
6,045,501 A	4/2000	Elsayed et al.
6,055,507 A	4/2000	Cunningham
6,063,026 A	5/2000	Schauss et al.
6,131,090 A	10/2000	Basso et al.
6,202,923 B1	3/2001	Boyer et al.
6,281,230 B1	8/2001	Muller et al.
6,315,720 B1	11/2001	Williams et al.
6,316,471 B1	11/2001	Muller et al.
6,335,349 B1	1/2002	Muller et al.
6,476,052 B1	11/2002	Muller et al.
6,555,554 B2	4/2003	Muller et al.
6,561,976 B2	5/2003	Elsayed et al.

6,561,977 B2	5/2003	Williams et al.
6,627,646 B2 *	9/2003	Bakale ..... C07D 401/12 514/303
6,755,784 B2	6/2004	Williams et al.
6,878,733 B1	4/2005	Shenoy et al.
6,896,399 B2	5/2005	Nomura et al.
6,908,432 B2	6/2005	Elsayed et al.
7,041,680 B2	5/2006	Muller et al.
7,119,106 B2	10/2006	Muller et al.
7,189,740 B2	3/2007	Zeldis
7,393,862 B2	7/2008	Zeldis
7,393,863 B2	7/2008	Zeldis
7,465,800 B2	12/2008	Jaworsky et al.
7,629,360 B2	12/2009	Muller et al.
7,709,031 B2	5/2010	Greenway et al.
7,709,502 B2	5/2010	Muller et al.
7,855,217 B2	12/2010	Jaworski et al.
7,863,297 B2	1/2011	Zeldis
7,959,566 B2	6/2011	Williams et al.
7,968,569 B2	6/2011	Zeldis
7,994,327 B2	8/2011	Ge et al.
8,158,653 B2	4/2012	Muller et al.
8,188,118 B2	5/2012	Zeldis
8,198,262 B2	6/2012	Zeldis
8,198,306 B2	6/2012	Zeldis
8,204,763 B2	6/2012	Elsayed et al.
8,207,200 B2	6/2012	Zeldis
8,315,886 B2	11/2012	Williams et al.
8,530,498 B1	9/2013	Zeldis
8,589,188 B2	11/2013	Elsayed et al.
8,626,531 B2	1/2014	Williams et al.
8,648,095 B2	2/2014	Zeldis
8,673,939 B2	3/2014	Zeldis

(Continued)

**FOREIGN PATENT DOCUMENTS**

WO	WO 96/13790 A1	5/1996
WO	WO 98/03502 A1	1/1998

(Continued)

**OTHER PUBLICATIONS**

Bernstein, "Polymorphism in . . ." p. 115-118, 272. (Year: 2002).\* Davidovich et al., "Detection of polymorphism . . ." Am. Pharm. Rev. 7(1) p. 10, 12, 14, 16, 100. (Year: 2004).\*

Dean "Analytical Chem . . ." p. 10.24-10.26. (Year: 1995).\*

Ivanisevic et al. "Use of X-ray . . ." Pharm. Sci. Encycl. p. 1-42. (Year: 2010).\*

Seddon "Pseudopolymorph . . ." Crystal Growth & design v.4(6) p. 1087 (2 pages from internet). (Year: 2004).\*

Rodriguez-Spong et al., "General principles, etc.," Adv. Drug Delivery Reviews 56 241-274. (Year: 2004).\*

(Continued)

*Primary Examiner* — Patricia L Morris

(74) *Attorney, Agent, or Firm* — Jones Day

(57) **ABSTRACT**

Provided herein is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate. Pharmaceutical compositions comprising the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate are also disclosed.

(56)

**References Cited****U.S. PATENT DOCUMENTS**

8,722,647 B2	5/2014	Zeldis	
8,735,428 B2	5/2014	Zeldis	
8,759,375 B2	6/2014	Zeldis	
8,828,427 B2 *	9/2014	Tutino .....	A61K 9/4858 424/452
9,101,621 B2	8/2015	Zeldis	
9,101,622 B2	8/2015	Zeldis	
9,695,146 B2 *	7/2017	Stahly .....	C07D 401/04
2002/0054899 A1	5/2002	Zeldis et al.	
2007/0155791 A1	7/2007	Zeldis et al.	
2008/0051431 A1	2/2008	Verhelle et al.	
2017/0258778 A1	9/2017	Stahly et al.	

**FOREIGN PATENT DOCUMENTS**

WO	WO 98/13783 A1	4/1998
WO	WO 99/10829 A1	3/1999
WO	WO 00/51053 A1	8/2000
WO	WO 02/43720 A2	6/2002
WO	WO 02/59106 A1	8/2002
WO	WO 02/064083 A2	8/2002
WO	WO 2011/050962 A1	5/2011
WO	WO 2013/012485 A2	1/2013
WO	WO 2013/126326 A1	8/2013
WO	WO 2014/160690 A1	10/2014
WO	WO 2018/013689 A1	1/2018

**OTHER PUBLICATIONS**

- Kirk-Othmer Encyclopedia of Chemical Technology, 8, pp. 95-147. (Year: 2002).\*
- Vippagunta et al., "Crystalline Solids", Advanced Drug Delivery Reviews 48 .3-26. (Year: 2001).\*
- Guillory (in Brittain ed.), "Polymorphism in Pharmaceutical Solids," NY: Marcel Dekker, Inc., 1-2, 183-226. (Year: 1999).\*
- Braga et al., "Making crystals from . . ." J. Royal Soc. Chem. Commun. p. 3635-3645. (Year: 2005).\*
- CMU Pharmaceutical polymorphism, internet p. 1-3 printout Apr. 3, 2008. (Year: 2002).\*
- Singhal et al., "Drug Polymorphism, etc.," Advanced Drug Delivery reviews 56, p. 335-347. (Year: 2004).\*
- Concise Encyclopedia Chemistry, NY: Walter de Gruyter, 872-873. (Year: 1993).\*
- Jain et al., "Polymorphism in Pharmacy", Indian Drugs, 23(6) 315-329. (Year: 1986).\*
- Muzaffar et al., "Polymorphism and Drug Availability, etc.," J of Pharm. (Lahore), 1(1), 59-66. (Year: 1979).\*
- U.S. Pharmacopia #23, National Formulary #18,1843-1844. (Year: 1995).\*
- Doelker, english translation of S.T.P. Pratiques, 9(5), 399-409, pp. 1-33. (Year: 1999).\*
- Doelker, english translation of Ann. Pharm. Fr.,60: 161-176, pp. 1-39. (Year: 2002).\*
- Taday et al., "Using Terahertz, etc.," J of Pharm. Sci., 92(4), 831-838. (Year: 2003).\*
- Otuska et al., "Effect of Polymorphic, etc.," Chem. Pharm. Bull., 47(6) 852-8569. (Year: 1999).\*
- Nie et al., "Source analysis, etc.," CA 1743748. (Year: 2015).\*
- Celgene Corporation, POMALYST® (pomalidomide) packaging label, Retrieved online on Dec. 14, 2017, retrieved online at <<http://www.pomalyst.com/?pi=yes&gclid=CMF4keDY-tMCFZOCfgods7oPsA>>, revised Jun. 2016.
- Dimartino et al., "Preparation and physical characterization of forms II and III of paracetamol," J. Thermal. Anal., 48(3):447-458 (1997).
- Gennaro, Remington: The Science and Practice of Pharmacy, 20th Ed., Lipincott Williams & Wilkins, pp. 172-182 (2000).
- Knapman, "Polymorphic Predictions: Understanding the nature of crystalline compounds can be critical in drug development and manufacture," Modern Drug Discoveries, 53-57 (2000).
- The United States Pharmacopeia, 37th Edition, United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 503-509 (2014).
- "CDC meeting: Mar. 26, 1997 minutes and agenda regarding thalidomide.".
- "Celgene's Revlimid an orphan drug, says FDA," Marketletter Oct. 15, 2001.
- "Center for drug evaluation and research approval package for: Application number: 18-662/S-038," (2000).
- "Center for drug evaluation and research approval package for: Application No. NDA 20-785 approval letter(s)," Sep. 19, 1997 and Jul. 16, 1998.
- "Celgene drug promises activity in solid tumors," Markletter Jun. 18, 2001.
- "Center for drug evaluation and research, Application number: 2040260rig1s000," Pharmacolgy Review(s), dated Dec. 13, 2012. [retrieved on Oct. 29, 2016]. Retrieved from the internet: <[http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2013/204026Orig1s000PharmR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204026Orig1s000PharmR.pdf)>.
- "Center for Drug Evaluation and Research, Approval Package for: Application number: 14-691/S-020," ALKERAN® (melphalan) Tablets, product information, GlaxoSmithKline (2001).
- "EntreMed moves towards commercialization with production of thalidomide analogs; Next generation drug candidates to be manufactured in preparation for clinical studies," PR Newswire (2001).
- Adams et al., "Proteasome inhibitors: A novel class of potent and effective antitumor agents," *Cancer Res.* 59:2615-2622 (1999).
- Adjei et al., "A phase I trial of the farnesyl transferase inhibitor SCH66336: evidence for biological and clinical activity," *Cancer Res.*, 60:1871-1877 (2000).
- Alder et al., "The return of thalidomide—A shunned compound makes a scientific comeback," *Science News* 146:424-425 (1994).
- Alexanian et al., "High-dose glucocorticoid treatment of resistant myeloma," *Ann. Intern. Med.* 105:8-11 (1986).
- Alexanian et al., "Consolidation therapy of multiple myeloma with thalidomide-dexamethasone after intensive chemotherapy," *Ann Oncol.* 13:1116-1119 (2002).
- Anderson et al., "Multiple myeloma: New insights and therapeutic approaches," *Hematology Am. Soc. Hematol. Educ. Program* 2000:147-165 (2000).
- Anderson et al., "Novel biologically based therapies for myeloma," VIII the International Myeloma Workshop, Banff, Alberta, Canada, May 4-8, 2001; Abstract #S27.
- Anderson, "The role of immunomodulatory drugs in multiple myeloma," *Semin. Hematol.*, 40(4 Suppl. 4):23-32 (2003).
- Banker ed., *Modern Pharmaceutics*, 3<sup>rd</sup> Edition, Marcel Dekker, Inc., New York, NY, pp. 451 and 596 (1996).
- Barlogie et al., "Effective Treatment of Advanced Multiple Myeloma Refractory to Alkylating Agents," *N. Engl. J. Med.*, 310(21):1353-1356 (1984).
- Barlogie et al., "Thalidomide and CC-5013 in multiple myeloma: the University of Arkansas experience," *Semin. Hematol.*, 40(4):33-38 (2003).
- Barlogie et al., "Thalidomide in the management of multiple myeloma," *Semin. Hematol.*, 38:250-259 (2001).
- Beaumont et al., "Design of ester prodrugs to enhance oral absorption of poorly permeable compounds: challenges to the discovery scientist," *Curr. Drug Metab.*, 4:461-485 (2003).
- Bjorkstrand et al., "Prognostic factors in autologous stem cell transplantation for multiple myeloma: an EBMT registry study," *Leuk. Lymphoma* 15:265-272 (1994).
- Bor, "Thalidomide shows that it can heal, too from deformers of babies to force for good," *Baltimore Sun* (1995).
- Broder et al., "Dideoxycytidine: Current clinical experience and future prospects. A summary," *Am. J. Med.* 88:31S-33S (1990).
- Burleson, "Review of computer applications in institutional pharmacy—1975-1981," *Am. J. Hosp. Pharm.* 39:53-70 (1982).
- Bwire et al., Managing the teratogenic risk of thalidomide and lenalidomide: An industry perspective, *Expert Opin. Drug Saf.* 10:3-8 (2011).
- Cairo, "Dose reductions and delays: Limitations of myelosuppressive chemotherapy," *Cancer Network* (2000).

(56)

**References Cited****OTHER PUBLICATIONS**

- Canal et al., "Benefits of pharmacological knowledge in the design and monitoring of cancer chemotherapy," *Pathology Oncol. Res.* 4:171-178 (1998).
- Celgene assigned patents/applications indexed with pomalidomide from USPATFULL accessed Oct. 27, 2016.
- Celgene Corporation Awarded Additional Patent Protection for Lead IMiD(TM), REVIMID(TM); Comprehensive Patent Protection for REVIMID Includes Coverage of the Active Ingredient, Pharmaceutical Compositions, and Therapeutic Uses PR Newswire Aug. 28, 2001.
- Celgene Corporation, "Initial Phase I solid tumor data on Celgene's lead IMiD™, Revimid™," Press Release, Jun. 2001.
- Celgene Corporation, Form 424B4 (2000).
- Celgene News Release, "Positive interim results presented at the VIIIth international myeloma workshop on Celgene Corporation's lead IMiD™ (REV/MID™)," May 8, 2001.
- Cheson, "New drug development in non-Hodgkin lymphomas," *Curr. Oncol. Rep.* 3:250-259 (2001).
- Choi et al., "Role of gallic acid in inflammatory allergic process," *Korean Journal Physiology & Pharmacology*, 10(2):101-108 (2006) (abstract only).
- Chu et al., "Principles of cancer management: Chemotherapy," in *Cancer: Principles and Practice of Oncology*, 6th edition, De Vita et al., (eds.), Lippincott Williams & Wilkins, Philadelphia, PA Chapter 17 (2001).
- Cimons, "How a body responds to drugs depends on the genes," *Los Angeles Times*, Jul. 24, 2000.
- Collins et al., "Potential roles for preclinical pharmacology in phase 1 clinical trials," *Cancer Treat. Rep.*, 70:73-80 (1986).
- Corral et al., "Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF- $\alpha$ ," *J. Immunol.* 163:380-386 (1999).
- Corral et al., "Immunomodulation by thalidomide and thalidomide analogues," *Ann. Rheum. Dis.*, 58(Suppl 1):I107-I113 (1999).
- Crane et al., "Immunomodulatory drugs," *Cancer Investigation* 23:625-634 (2005).
- D'Amato et al., "Mechanism of action of thalidomide and 3-aminothalidomide in multiple myeloma," *Semin. Oncol.*, 28:597-601 (2001).
- D'Amato et al., "Thalidomide is an Inhibitor of Angiogenesis," *Proc. Natl. Acad. Sci. USA*, 91(9):4082-4085 (1994).
- Damaj et al., "Thalidomide therapy induces response in relapsed mantle cell lymphoma," *Leukemia* 17:1914-1915 (2003).
- Dancey et al., "Neutrophil kinetics in man," *J. Clin. Invest.* 58:705-715 (1976).
- Davies et al., "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma," *Blood*, 98(1):210-216 (2001).
- Devita et al., eds., "Plasma cell neoplasm." In *Cancer Principles & Practice of Oncology*, 5th Ed.; Lippincott-Raven Publishers, pp. 2344-2379 (1997).
- Dimopoulos et al., "Thalidomide and dexamethasone combination for multiple myeloma refractory to dexamethasone-based regimens," *Blood* 96(Suppl):286b (2000).
- Dimopoulos et al., "Thalidomide and dexamethasone combination for refractory multiple myeloma," *Ann. Oncol.* 12:991-995 (2001).
- Dishman et al., "Pharmacists' transcript role in clozapine therapy at a veterans affairs medical center," *Am. J. Hosp. Pharm.* 51:899-901 (1994).
- Drach et al., "Treatment of mantle cell lymphoma: Targeting the microenvironment," *Expert Rev. Anticancer Ther.* 5:477-485 (2005).
- Dredge et al., "Immunological effects of thalidomide and its chemical and functional analogs," *Crit. Rev. Immunol.*, 22(5&6):425-437 (2002).
- Dredge et al., "Novel thalidomide analogues display anti-angiogenic activity independently of immunomodulatory effects," *Br. J. Cancer*, 87(10):1166-1172 (2002).
- Dredge et al., "Protective antitumor immunity induced by a costimulatory thalidomide analog in conjunction with whole tumor cell vaccination is mediated by increased Th1-type immunity," *J. Immunol.* 168:4914-4919 (2002).
- Dredge et al., "Thalidomide analogs as emerging anti-cancer drugs," *Anti-Cancer Drugs*, 14:331-335 (2003).
- Durie and Stepan, "Efficacy of low dose thalidomide in multiple myeloma," *Eur. J. Oncol.* 1:1-8 (2000).
- Dykes, "Genes, disease and medicine," *Br. J. Clin. Pharmacol.*, 42:683-695 (1996).
- Edwards, "Thalidomide: Is there a silver lining?" *Science News* 131:198 (1987).
- Elliot et al., "The proteasome: A new target for novel drug therapies," *Am. J. Clin. Pathol.* 116:637-646 (2001).
- EORTC Pharmacokinetics and Metabolism Group, "Pharmacokinetically guided dose escalation in phase I clinical trials. Commentary and proposed guidelines," *Eur. J. Cancer Clin. Oncol.*, 23(7):1083-1087 (1987).
- FDA Guideline for Industry, "International conference on harmonisation; dose-response information to support drug registration; guideline; availability," 59 FR 55972-01, 1994 WL 615579 (1994).
- Figg et al., "Pharmacokinetics of thalidomide in an elderly prostate cancer population," *J. Pharm. Sci.* 88:121-125 (1999).
- Filella et al., "Cytokines (IL-6, TNF-alpha, IL-1 alpha) and soluble interleukin-2 receptor as serum tumor markers in multiple myeloma," *Cancer Detect. Prev.* 20:52-56 (1996).
- Foerster et al., "Effects of thalidomide and EM12 on the synthesis of TNF- $\alpha$ in cocultures of human monocytes and lymphocytes," Abstract 517 (1995).
- Friedman et al., "Introduction to clinical trials" *Fundamentals of Clinical Trials*, 3<sup>rd</sup> edition, Springer, New York, NY, Chapter 1 (1998).
- Fujita et al., "Thalidomide and its analogues inhibit lipopolysaccharide-mediated induction of cyclooxygenase-2," *Clin. Cancer Res.*, 7:3349-3355 (2001).
- Fuse et al., "Prediction of the maximal tolerated dose (MTD) and therapeutic effect of anticancer drugs in humans: integration of pharmacokinetics with pharmacodynamics and toxicodynamics," *Cancer Treat. Rev.*, 21:133-157 (1995).
- Gahrton et al., "Progress in haematopoietic stem cell transplantation for multiple myeloma," *J. Intern. Med.* 248:185-201 (2000).
- Gardner et al., "Assessing the effectiveness of a computerized pharmacy system." In *Decision Support Systems in Critical Care*; Shabot et al., eds.; pp. 174-183 (1994).
- Glasmacher et al., "Oral idarubicin, dexamethasone and vincristine (VID) in the treatment of multiple myeloma," *Leukemia* 11:S22-S26 (1997).
- Grönroos et al., "A medication database—a tool for detecting drug interactions in hospital," *Eur. J. Clin. Pharmacol.* 53:13-17 (1997).
- Gupta et al., "Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications," *Leukemia*, 15(12):1950-1961 (2001).
- Hamera et al., "Alcohol, cannabis, nicotine, and caffeine use and symptom distress in Schizophrenia," *J. Nerv. Ment. Dis.* 183:559-565 (1995).
- He et al., "Synthesis of thalidomide analogs and their biological potential for treatment of graft versus host disease," 206th ACS National Meeting 0-8412-2620-2, American Chemical Society, Chicago, IL, Abstract 216 (1993).
- Heger et al., "Embryotoxic effects of thalidomide derivatives in the non-human primate callithrixjacchus. IV teratogenicity of  $\mu$ g/kg doses of the EMJ 2 enantiomers," *Teratog. Carcinog. Mutagen.* 14:115-122 (1994).
- Hideshima et al., "Novel therapies targeting the myeloma cell and its bone marrow microenvironment," *Semin. Oncol.* 28:607-612 (2001).
- Hideshima et al., "The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells," *Cancer Res.* 61:3071-3076 (2001).
- Hideshima et al., "Thalidomide (Thal) and its analogs overcome drug resistance of human multiple myeloma (MM) cells to conventional therapy," *Abstract 1313, American Society of Hematology*, Dec. 1-5, 2000.

(56)

**References Cited****OTHER PUBLICATIONS**

- Hidemitsu et al., "Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy," *Blood* 96(9):2943-2950 (2000).
- Hochster et al., "Activity and pharmacodynamics of 21-Day topotecan infusion in patients with ovarian cancer previously treated with platinum-based chemotherapy. New York Gynecologic Oncology Group," *J. Clin. Oncol.* 17:2553-2561 (1999).
- Hus et al., "Thalidomide treatment of resistant or relapsed multiple myeloma patients," *Haematologica* 86:404-408 (2001).
- Jagannath et al., "Pomalidomide (POM) with or without low-dose dexamethasone (LoDEX) in patients (Pts) with relapsed and refractory multiple myeloma (RRMM): MM-002 phase II age subgroup analysis," *J. Clin. Oncol.* 31, Abstrct # 8532, (2013).
- Jönsson, "Chemical structure and teratogenic properties. 3. A review of available data on structure-activity relationships and mechanism of action of thalidomide analogues," *Acta Pharm. Suec.* 9:521-542 (1972).
- Jourdan et al., "Tumor necrosis factor is a survival and proliferation factor for human myeloma cells," *Eur. Cytokine Netw.* 10:65-70 (1999).
- Keravich et al., "Challenges of thalidomide distribution in a hospital setting," *Am. J. Health Syst. Pharm.* 56:1721-1725 (1999).
- Kibbe ed., Handbook of Pharmaceutical Excipients, 3rd edition, pp. 160-162 (2000).
- Klausner et al., "Thalidomide as an anti-TNF-alpha inhibitor: implications for clinical use," *Clin. Immunol. Immunopathol.*, 81(3):219-223 (1996).
- Klausner et al., "The effect of thalidomide on the pathogenesis of human immunodeficiency virus type 1 and M. tuberculosis infection," *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.*, 11(3):247-257 (1996).
- Knight, "Cancer patients ahead of FDA on thalidomide use," *Washington Post* Jun. 25, 2001.
- Kosten et al., "Substance abuse and Schizophrenia: Editors' Introduction," *Schizophrenia Bulletin* 23:181-186 (1997).
- Kropff et al., "Hyperfractionated cyclophosphamide in combination with pulsed dexamethasone and thalidomide (hyper-CDT) in primary refractory or relapsed multiple myeloma," *Blood*, 96(11):168a (2000).
- Kumar et al., "Thalidomide and lenalidomide in the treatment of multiple myeloma," *Eur. J. Cancer*, 42:1612-1622 (2006).
- Kyle et al., "Therapeutic application of thalidomide in multiple myeloma," *Semin. Oncol.* 28:583-587 (2001).
- Lacy et al., "Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma," *J. Clin. Oncol.* 27:5008-5014 (2009).
- Lacy et al., "Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: Comparison of 2 dosing strategies in dual-refractory disease," *Blood* 118:2970-2975 (2011).
- Langbein, "Celgene releases first data on Actimid in cancer patients," *Reuters News*, Jul. 8, 2002.
- Lee et al., "A pilot trial of hyperfractionated thoracic radiation therapy with concurrent cisplatin and oral etoposide for locally advanced inoperable non-small-cell lung cancer: a 5-year follow-up report," *Int. J. Radiat. Oncol. Biol. Phys.* 42:479-486 (1998).
- Lentzsch et al., "3-amino-phthalimido-glutarimide (S-3APG) inhibits angiogenesis and growth in drug resistant multiple myeloma (MM) in vivo," *Abstract 1976, American Society of Hematology*, 43rd Annual Meeting Orlando, Florida, Dec. 7-11, 2001.
- Lentzsch et al., "Immunomodulatory analogs of thalidomide inhibit growth of Hs sultan cells and angiogenesis in vivo," *Leukemia*, 17:41-44 (2003).
- Lentzsch et al., "Immunomodulatory derivatives (IMiDs) of thalidomide (Thal) inhibit the proliferation of multiple myeloma (MM) cell lines and block VEGF-induced activation of the MAPK-pathway," *Blood* 96:579 (Abstract# 2486) (2000).
- Lentzsch et al., "S-3-amino-phthalimido-glutarimide inhibits angiogenesis and growth of B-cell neoplasias in mice," *Cancer Research* 62:2300-2305 (2002).
- Linder et al., "Pharmacogenetics: a laboratory tool for optimizing therapeutic efficiency," *Clin. Chem.*, 43(2):254-266 (1997).
- Linnarsson, "Decision support for drug prescription integrated with computer-based patient records in primary care," *Med. Inform.* 18:131-142 (1993).
- Lipkin, "Deriving new drugs from thalidomide," *Science News* 148:171 (1995).
- Mann et al., "Passage of chemicals into human and animal semen: mechanisms and significance," *Crit. Rev. Toxicol.* 11:1-14 (1982).
- Marriott et al., "Immunotherapeutic and antitumour potential of thalidomide analogues," *Expert Opin. Biol. Ther.* 1:1-8 (2001).
- Marriott et al., "Immunotherapeutic and antitumour potential of thalidomide analogues," *Expert Opin. Biol. Ther.*, 1(4):675-682 (2001).
- Marriott et al., "Thalidomide and its analogues have distinct and opposing effects on TNF-alpha and TNFR2 during co-stimulation of both CD4+ and CD8+ T cells," *Clin. Exp. Immunol.*, 130:75-84 (2002).
- Marwick, "Thalidomide back—under strict control," *JAMA* 278:1135-1137 (1997).
- Menill, "Substance Abuse and Women on Welfare," in *National Center on Addiction and Substance Abuse at Columbia University*, Jun. 1994.
- Milner et al., "Attitudes of young adults to prenatal screening and genetic correction for human attributes and psychiatric conditions," *Am. J. Med. Genet.*, 76:111-119 (1998).
- Mitchell et al., "A pregnancy-prevention program in women of childbearing age receiving isotretinoin," *N. Engl. J. Med.* 333:101-106 (1995).
- Mitsiades et al., "Concepts in the use of TRAIL/Apo2L: An emerging biotherapy for myeloma and other neoplasias," *Expert Opin. Investig. Drugs* 10:1521-1530 (2001).
- Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications," *Blood*, 2002, 99:4525-4530, *American Society of Hematology*.
- Montero et al., "Economic study of neutropenia induced by myelotoxic chemotherapy," *Pharm. World Sci.* 16:187-192 (1994).
- Moreira et al., "Thalidomide exerts its inhibitory action on tumor necrosis factor  $\alpha$  by enhancing mRNA degradation," *J. Exp. Med.*, 177(6):1675-1680 (1993).
- Morgan et al., "Lenalidomide (Revlimid), in combination with cyclophosphamide and dexamethasone (RCD), is an effective and tolerated regimen for myeloma patients," *Br. J. Haematol.* 137:268-269 (2007).
- Muller et al., "Amino-substituted thalidomide analogs: potent inhibitors of TNF-alpha production," *Bioorg. Med. Chem. Lett.*, 9(11):1625-1630 (1999).
- Muller, Thalidomide: From tragedy to new drug discovery, *Chemtech* 27:21-25 (1997).
- Mundt, "Interactive voice response systems in clinical research and treatment," *Psychiatr. Serv.* 48:611-612, 623 (1997).
- National Cancer Institute, Common Toxicity Criteria Manual, Ver. 2.0, Jun. 1, 1999.
- NCT00480363: "QUIREDEX: Revlimid (lenalidomide) and dexamethasone (ReDex) treatment versus observation in patients with smoldering multiple myeloma with high risk of progression (QUIREDEX)," (2013).
- Noguera et al., "Effect of thalidomide and some derivatives on the adhesion of lymphocytes to endothelial cells," Abstract 518 (1995).
- Olson et al., "Thalidomide (N-phthaloylglutamimide) in the treatment of advanced cancer," *Clin. Pharm. Ther.*, 6(3):292-297 (1965).
- Palumbo et al., "Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma," *Haematologica* 86:399-403 (2001).
- Pastuszak et al., "Use of the retinoid pregnancy prevention program in Canada: Patterns of contraception use in women treated with isotretinoin and etretinate," *Reprod. Toxicol.* 8:63-68 (1994).
- Pestotnik et al., "Therapeutic antibiotic monitoring: Surveillance using a computerized expert system," *Am. J. Med.* 88:43-48 (1990).

(56)

**References Cited****OTHER PUBLICATIONS**

- Peterson et al., "Expanding the scope of crystal form evaluation in pharmaceutical science," *J. Pharm. Pharmaceut. Sci.*, 9(3):317-326 (2006).
- Piper et al., "Anti-inflammatory immunosuppressive thalidomide analogs. Screening," *Int. J. Leprosy* 49:511-512 (1981).
- Powell et al., "Guideline for the clinical use and dispensing of thalidomide," *Postgrad. Med. J.* 70:901-904 (1994).
- Pro et al., "Phase II study of thalidomide in patients with recurrent Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL)," *Blood* 98:246b (Abstract#4712) (2001).
- Querfeld et al., "Preliminary results of a phase II study of CC-5013 (lenalidomide, revlimid®) in patients with cutaneous T-cell lymphoma," *Blood* 106:936a-937a (2005).
- Raje et al., "Thalidomide and immunomodulatory drugs as cancer therapy," *Curr. Opin. Oncol.*, 14:635-640 (2002).
- Raje et al., "Thalidomide—a revival story," *N. Engl. J. Med.* 341(21):1606-1609 (1999).
- Rajkumar et al., "Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial," *Lancet* 371:29-37 (2008).
- Rajkumar et al., "Phase III trial of lenalidomide plus highdose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): A trial coordinated by the Eastern Cooperative Oncology Group," *J. Clin. Oncol.* 25:18S (2007).
- Rajkumar et al., "Thalidomide plus dexamethasone (Thal/Dex) and thalidomide alone (Thal) as first line therapy for newly diagnosed myeloma (MM)," *Blood* 96(Supp.):168a (2000).
- Rajkumar et al., "Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma," *Blood*, 106(13):4050-4053 (2005).
- Rajkumar et al., "Thalidomide in the treatment of plasma cell malignancies," *J. Clin. Oncol.* 19:3593-3595 (2001).
- Rajkumar, "Thalidomide in multiple myeloma," *Oncology* 14:11-16 (2000).
- Ratain, "Pharmacology of Cancer Chemotherapy." In *Cancer: Principles & Practice of Oncology*, pp. 335-459 (2001).
- Rautio et al., "Prodrugs: design and clinical applications," *Nat. Rev. Drug Discov.*, 7:255-270 (2008).
- Reiman et al., "Meeting synopsis, VIII International Myeloma Workshop, Banff Springs Hotel, Banff, Alberta, Canada, May 4-8, 2001," *Eur. J. Haematol.* 67:199-202 (2001).
- Ribatti et al., "Angiogenesis spectrum in the stroma of B-cell non-Hodgkin's lymphomas. An immunohistochemical and ultrastructural study," *Eur. J. Haematol.* 56:45-53 (1996).
- Richardson et al., "A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma," *Blood* 108:3458-3464 (2006).
- Richardson et al., "Thalidomide in multiple Myeloma," *Biomed. Pharmacother.* 56:115-128 (2002).
- Richardson et al., "Thalidomide: Emerging role in cancer medicine," *Ann. Rev. Med.* 53:629-657 (2002).
- Richardson et al., "A multi-center, randomized, phase II study to evaluate the efficacy and safety of two CDC-5013 dose regimens when used alone or in combination with dexamethasone (Dex) for the treatment of relapsed or refractory multiple myeloma (MM)," *Abstract 386, Blood*, 100(11 Part 1):104a (2002).
- Richardson et al., "A phase I study of oral CC5013, an immunomodulatory thalidomide (Thal) derivative, in patients with relapsed and refractory multiple myeloma (MM)," *Blood* 98:775a (2001).
- Richardson et al., "A phase 1/2 multi-center, randomized, open label dose escalation study to determine the maximum tolerated dose (MTD), safety, and efficacy of pomalidomide (POM) alone or in combination with low-dose dexamethasone (DEX) in patients (PTS) with relapsed and refractory multiple myeloma (RRMM) who have received prior treatment (TX) that includes lenalidomide (LEN) and bortezomib (BORT)," *Haematologica*, 96:S31 (2011).
- Richardson et al., "A phase I study of the safety and efficacy of CC5013 treatment for patients with relapsed multiple myeloma: Preliminary results," VIII the International Myeloma Workshop, Banff, Alberta, Canada, May 4-8, 2001; Abstract #P230.
- Richardson et al., "Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma," *Blood* 100:3063-3067 (2002).
- Robert et al., "Phase I and pharmacologic study of 7- and 21-day continuous etoposide infusion in patients with advanced cancer," *Cancer Chemother. Pharmacol.* 38:459-465 (1996).
- Rubinstein et al., "Phase I clinical trial design," Biometric Research Branch, National Cancer Institute (2003).
- Samlowski et al., "Evaluation of gemcitabine in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: A southwest oncology group phase II study," *Invest. New Drugs* 19:311-315 (2001).
- Sampaio et al., "Prolonged treatment with recombinant interferon gamma induces erythema nodosum leprosum in lepromatous leprosy patients," *J. Exp. Med.* 175:1729-1737 (1992).
- Sampaio et al., "Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes," *J. Exp. Med.* 173:699-703 (1991).
- Schey et al., "Phase I Study of an Immunomodulatory Thalidomide Analog, CC-4047, in Relapsed or Refractory Multiple Myeloma," *J. Clin. Oncol.* 22(16):3269-3276 (2004).
- Schey et al., "Pomalidomide therapy for myeloma," *Expert Opin. Invest. Drugs* 20:691-700 (2011).
- Schey et al., "A phase I study of an immunomodulatory thalidomide analogue (CC4047) in relapse/refractory multiple myeloma," *International Society for Experimental Hematology*, Abstract #248, (2002).
- Schey, "Thalidomide in the management of multiple myeloma," *Hematology* 7:291-299 (2002).
- Schlossman et al., "Bone marrow transplantation in multiple myeloma," *Curr. Opin. Oncol.* 11:102-108 (1999).
- Seppa, "Thalidomide combats myeloma blood cancer," *Science News* 156:326 (1999).
- Shaughnessy et al., "Global gene expression analysis shows loss of c-myc and IL-6 receptor gene mRNA after exposure of myeloma to thalidomide and IMiD," *Abstract 2485, American Society of Hematology*, 42<sup>nd</sup> Annual Meeting San Francisco, CA, Dec. 1-5, 2000.
- Shinn et al., "Development of a computerized drug interaction database (MEDICOM) for use in a patient specific environment," *Drug Inf. J.* 17:205-210 (1983).
- Siegel et al., "Long-term safety and efficacy of pomalidomide (POM) with or without low-dose dexamethasone (LoDEX) in relapsed and refractory multiple myeloma (RRMM) patients enrolled in the MM-002 phase II trial," *J. Clin. Oncol.* 31, 2013 (Abstract No. 8588).
- Singhal et al., "Antitumor activity of thalidomide in refractory multiple myeloma," *N. Engl. J. Med.*, 341(21):1565-1571 (1999).
- Smith et al., "Design and results of phase I cancer clinical trials: three-year experience at M.D. Anderson Cancer Center," *J. Clin. Oncol.*, 14:287-295 (1996).
- Smith, R. et al., "Studies on the Relationship Between the Chemical Structure and Embryotoxic Activity of Thalidomide and Related Compounds," in *A Symposium on Embryopathic Activity of Drugs*, J. & A. Churchill Ltd., Session 6, pp. 194-209 (1965).
- Sorbera et al., "CC-5013. Treatment of multiple myeloma. Treatment of Melanoma. Treatment of myelodysplastic syndrome. Angiogenesis inhibitor. TNF-α production inhibitor," *Drugs of the Future*, 28(5):425-431 (2003).
- Soyka et al., "Prevalence of alcohol and drug abuse in schizophrenic inpatients," *Eur. Arch. Psychiatry Clin. Neurosci.* 242:362-372 (1993).
- Srkaloovic et al. "Use of melphalan, thalidomide, and dexamethasone in treatment of refractory and relapsed multiple myeloma," *Med. Oncol.* 19:219-226 (2002).
- Steed, "The role of co-crystals in pharmaceutical design," *Trends in Pharmacol. Sci.*, 34(3):185-193 (2013).
- Steiner et al., "The assessment of refill compliance using pharmacy records: methods, validity, and applications," *J. Clin. Epidemiol.* 50:105-116 (1997).

(56)

**References Cited****OTHER PUBLICATIONS**

- Stirling et al., "Thalidomide. A surprising recovery," *J. Am. Pharm. Assoc.* NS37:306-313 (1997).
- Stirling, "Thalidomide: A novel template for anticancer drugs," *Seminars Oncology* 28:602-606 (2001).
- Szelényi et al., "Cyclophosphamide, adriamycin and dexamethasone (CAD) is a highly effective therapy for patients with advanced multiple myeloma," *Ann. Oncol.* 12:105-108 (2001).
- Thalomid™ (thalidomide) Capsules Revised Package Insert (Jul. 15, 1998).
- The Comprehensive Guide to Banff, Understanding the VIIIth International Myeloma Workshop published by the International Myeloma Foundation (2001).
- Thomas et al., "Current role of thalidomide in cancer treatment," *Curr. Opin. Oncol.* 12:564-573 (2000).
- Transcript of the Forty-Seventh Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (Sep. 4, 1997).
- Transcript of the Forty-Seventh Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (Sep. 5, 1997).
- Tseng et al., "Rediscovering thalidomide: a review of its mechanism of action, side effects, and potential uses," *J. Am. Acad. Dermatol.* 35:969-979 (1996).
- Tsenova et al., "Use of IMiD3, a thalidomide analog, as an adjunct to therapy for experimental tuberculous meningitis," *Antimicrob Agents Chemother.*, 46(6):1887-1895 (2002).
- Vacca et al., "Angiogenesis in B cell lymphoproliferative diseases. Biological and clinical studies," *Leuk. Lymphoma* 20:27-38 (1995).
- Vanchieri, "Preparing for thalidomide's comeback," *Annals Internal Med.*, 127(10):951-952 (1997).
- Verma, "Gallic acid: molecular rival of cancer," *Environ. Toxicol. Pharmacol.*, 35(3):473-485 (2013).
- Vij et al., "Pomalidomide (POM) with Low-Dose Dexamethasone (LoDex) in Patients with Relapsed and Refractory Multiple Myeloma (RRMM): Outcomes Based on Prior Treatment Exposure," presented at 54th ASH Annual Meeting and Exposition, Atlanta, Georgia, Dec. 8-11, 2012, Abstract #4070.
- Vippagunta et al., "Crystalline solids," *Adv. Drug Deliv. Rev.*, 48(1):3-26 (2001).
- Vogelsang et al., "Thalidomide for the treatment of chronic graft-versus-host disease," *N. Engl. J. Med.* 326:1055-1058 (1992).
- Weber et al., "Thalidomide alone or with dexamethasone for multiple myeloma," *Blood* 94:604 (1999).
- Weber et al., "Thalidomide with dexamethasone of resistant multiple myeloma," *Blood* 96:167 (2000).
- Welte et al., "Influence of socially desirable responding in a study of stress and substance abuse," *Alcohol Clin. Exp. Res.* 17:758-761 (1993).
- Wilson et al., "Response to thalidomide in chemotherapy-resistant mantle cell lymphoma: a case report," *Br. J. Haematol.* 119:128-130 (2002).
- Wolf et al., "Science, medicine, and the future pharmacogenetics," *BMJ*, 320:987-990 (2000).
- Wolff ed., *Burger's Medicinal Chemistry and Drug Discovery*, 5<sup>th</sup> Edition, vol. 1, John Wiley & Sons, Inc., pp. 975-977 (1995).
- Yuen et al., "Phase I study of an antisense oligonucleotide to protein kinase C- $\alpha$ (ISIS 3521/CGP 64128A) in patients with cancer," *Clin. Cancer Res.* 5:3357-3363 (1999).
- Zangari et al., "Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide chemotherapy," *Blood* 98:1614 (2001).
- Zangari et al., Results of phase I study of CC-5013 for the treatment of multiple myeloma (MM) patients who relapse after high dose chemotherapy (HDT), *Blood* 98(11), Abstract# 3226 (2001).
- Zangari et al., "Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy," *Blood*, 100:1168-1171 (2002).
- Zeldis et al., "S.T.E.P.S.: A comprehensive program for controlling and monitoring access to thalidomide," *Clin. Ther.* 21:319-330 (1999).

\* cited by examiner

FIGURE 1

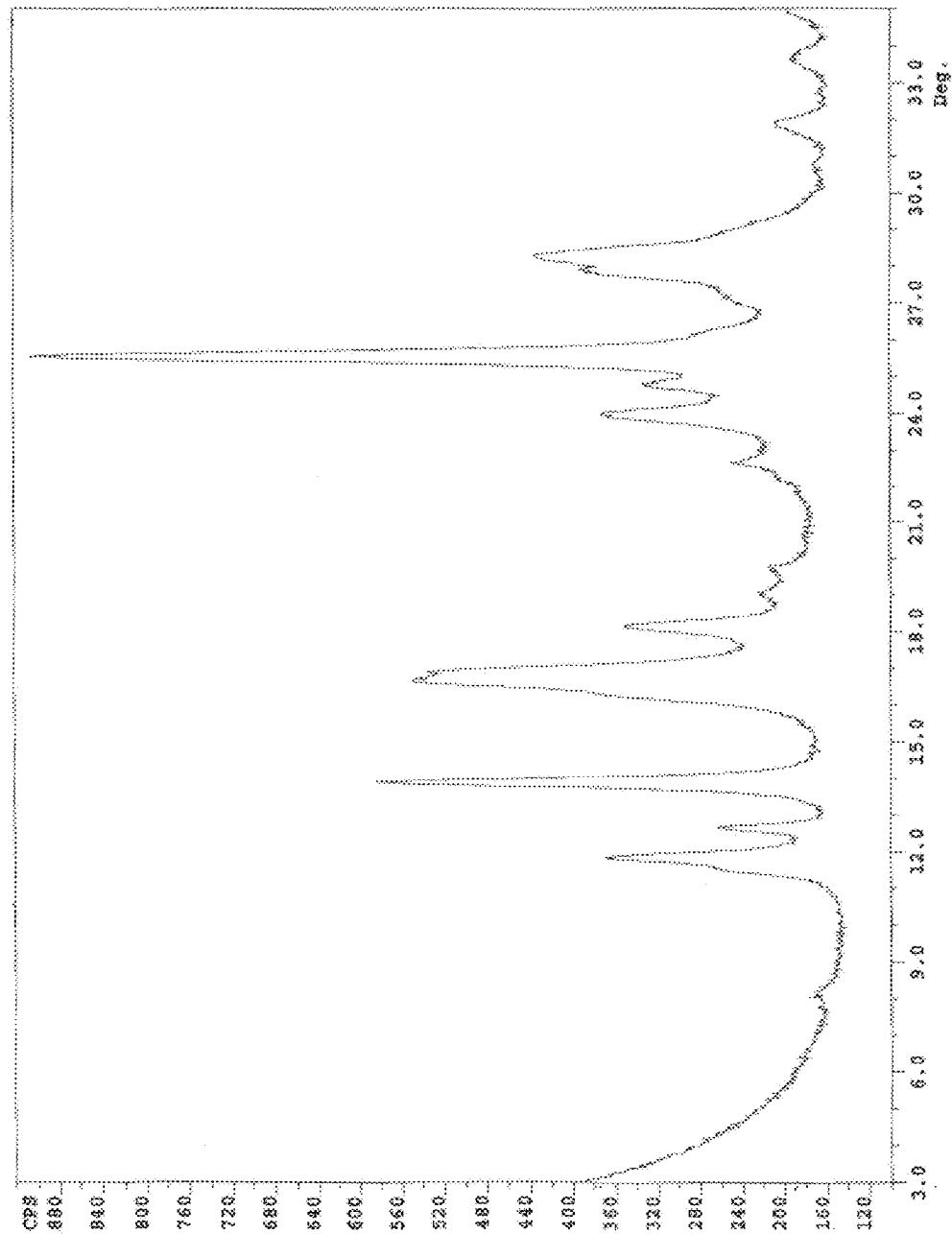


FIGURE 2

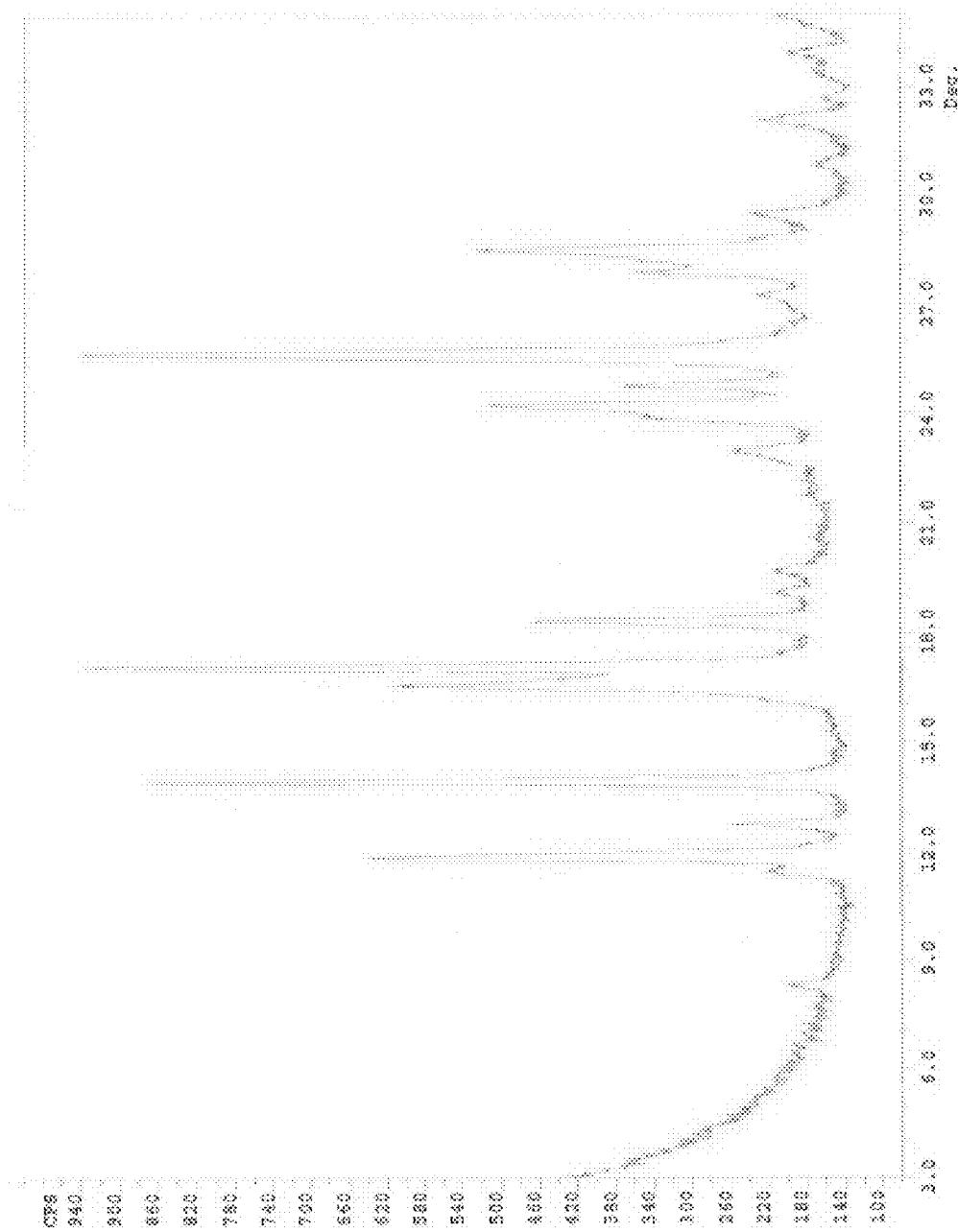


FIGURE 3

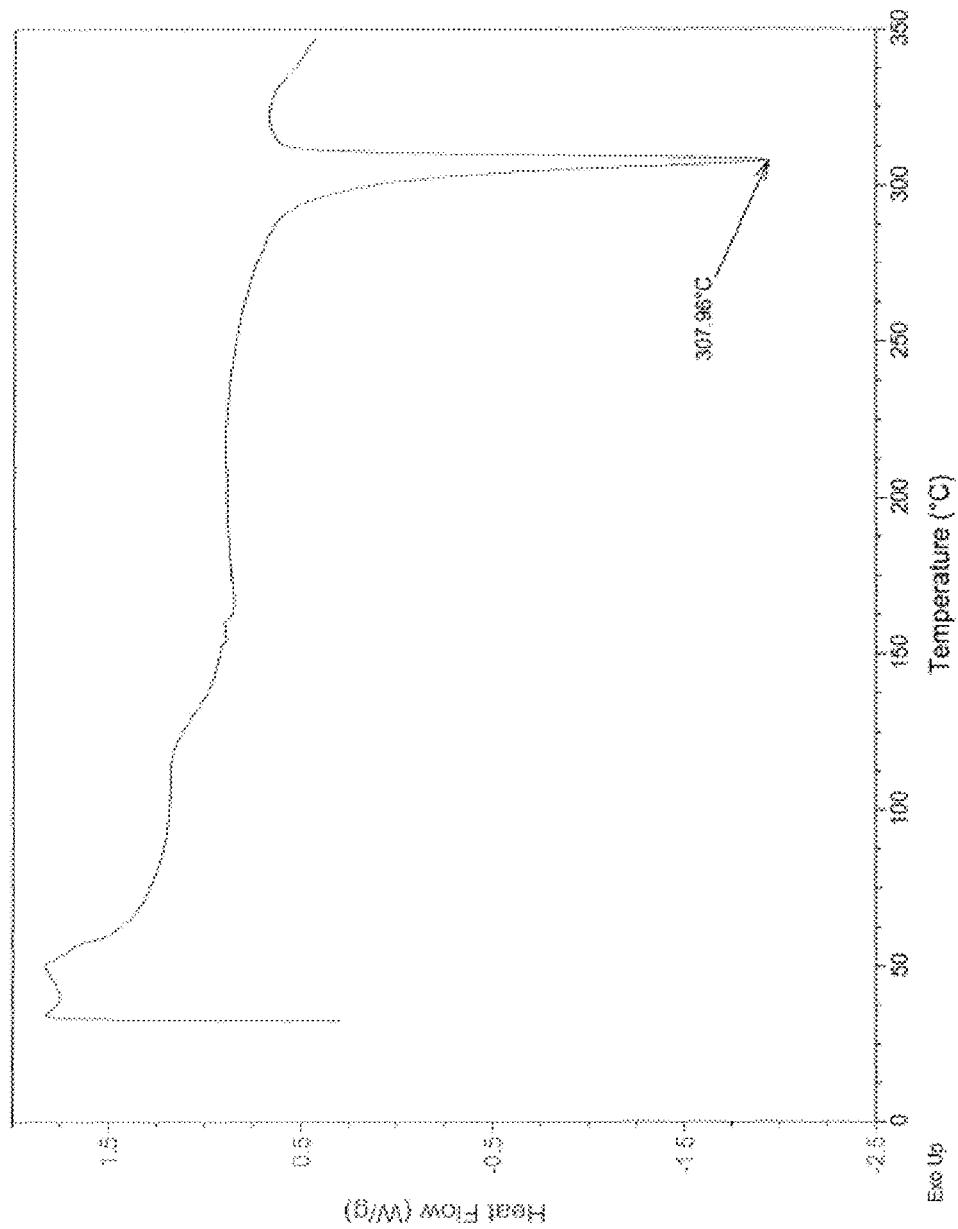


FIGURE 4

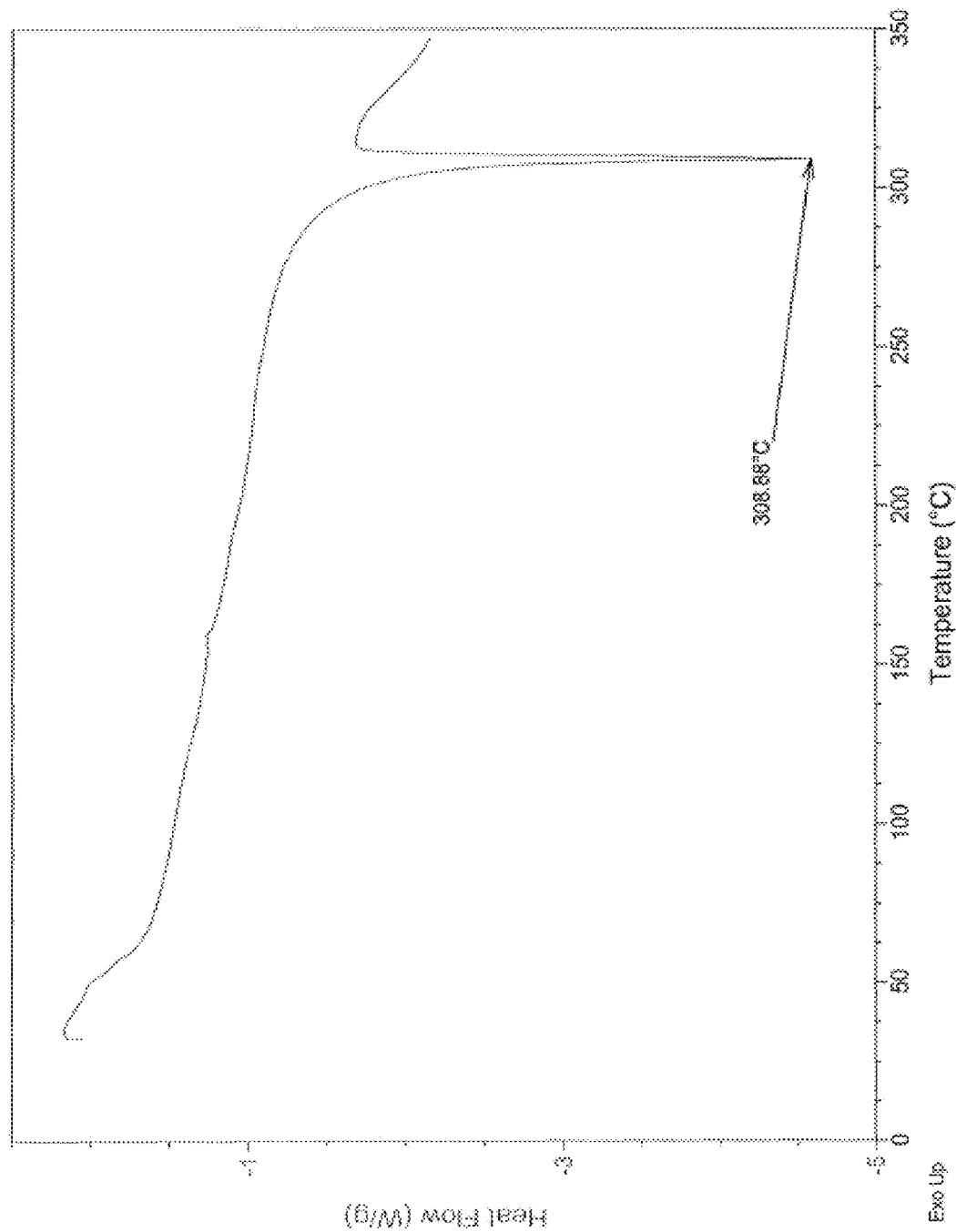


FIGURE 5

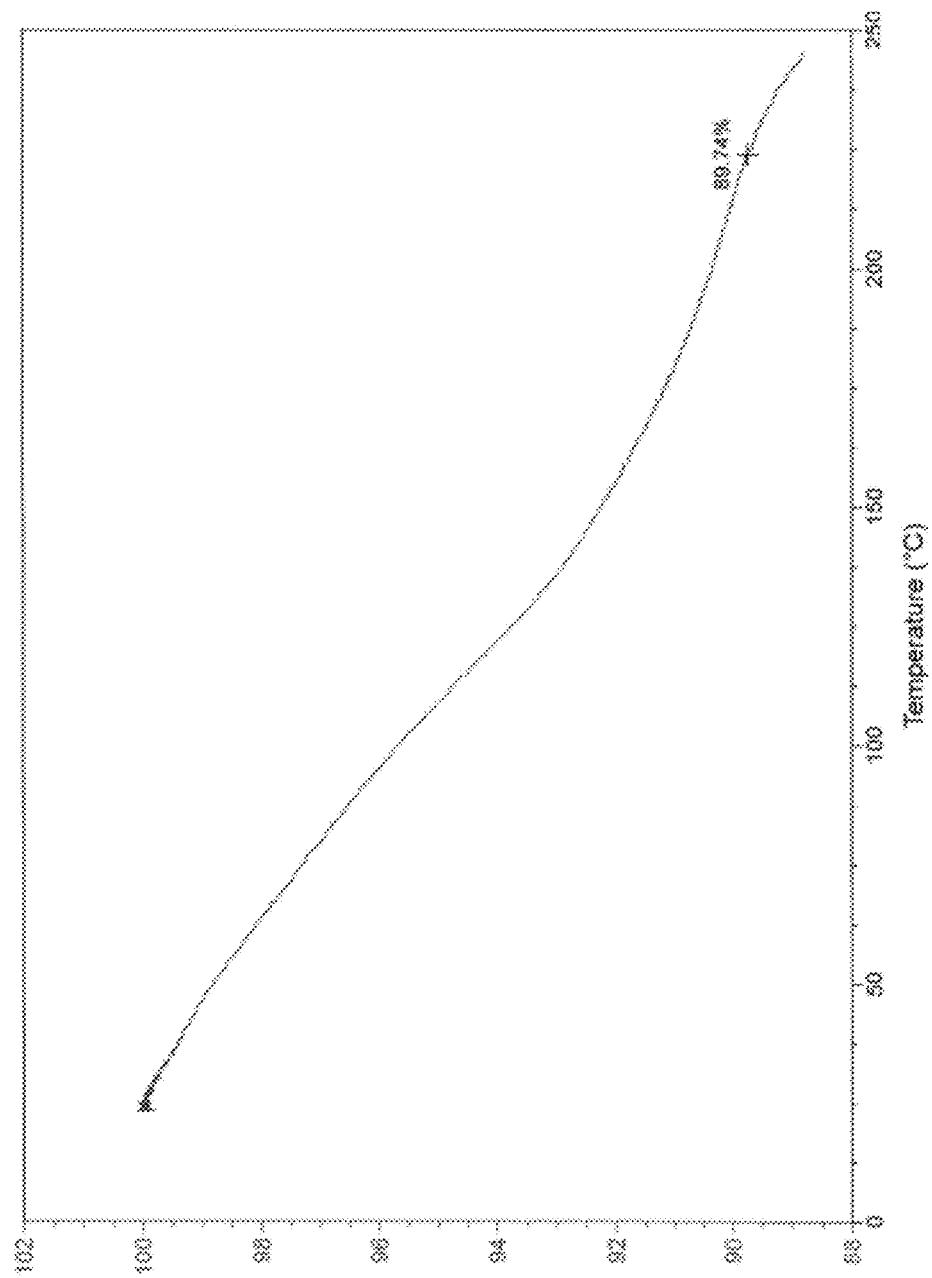
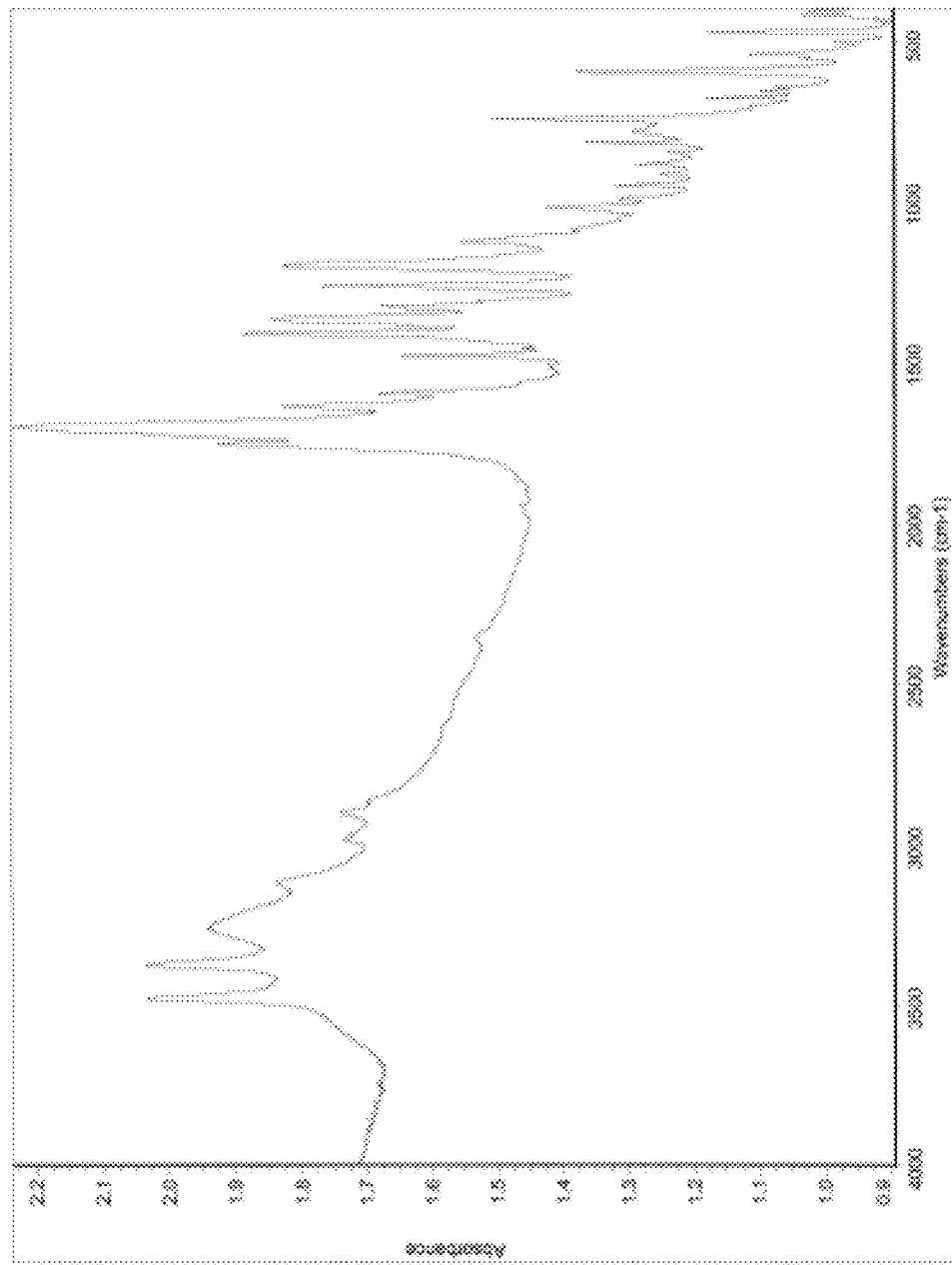


FIGURE 6



**1**

**CRYSTALLINE  
4-AMINO-2-(2,6-DIOXOPIPERIDINE-3-YL)  
ISOINDOLINE-1,3-DIONE DIHYDRATE,  
COMPOSITIONS AND METHODS OF USE  
THEREOF**

This application claims priority to U.S. Provisional application No. 62/511,878, filed May 26, 2017, the entirety of which is incorporated herein by reference.

**FIELD**

Provided herein is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate. Pharmaceutical compositions comprising such solid and methods of use for treating, preventing, and managing various disorders are also provided herein.

**BACKGROUND**

Many compounds can exist in different crystal forms, or polymorphs, which exhibit different physical, chemical, and spectroscopic properties. For example, certain polymorphs of a compound may be more readily soluble in particular solvents, may flow more readily, or may compress more easily than others. See, e.g., P. DiMartino, et al., *J. Thermal Anal.*, 48:447-458 (1997). In the case of drugs, certain solid forms may be more bioavailable than others, while others may be more stable under certain manufacturing, storage, and biological conditions.

Polymorphic forms of a compound are known in the pharmaceutical arts to affect, for example, the solubility, stability, flowability, fractability, and compressibility of the compound, as well as the safety and efficacy of drug products comprising it. See, e.g., Knapman, K. *Modern Drug Discoveries*, 2000, 53. Therefore, the discovery of new polymorphs of a drug can provide a variety of advantages.

The identification and selection of a solid form of a pharmaceutical compound are complex, given that a change in solid form may affect a variety of physical and chemical properties, which may provide benefits or drawbacks in processing, formulation, stability, bioavailability, storage, handling (e.g., shipping), among other important pharmaceutical characteristics. Useful pharmaceutical solids include crystalline solids and amorphous solids, depending on the product and its mode of administration. Amorphous solids are characterized by a lack of long-range structural order, whereas crystalline solids are characterized by structural periodicity. The desired class of pharmaceutical solid depends upon the specific application; amorphous solids are sometimes selected on the basis of, e.g., an enhanced dissolution profile, while crystalline solids may be desirable for properties such as, e.g., physical or chemical stability.

Pomalidomide has a chemical name of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione. Pomalidomide is a compound that inhibits, for example, LPS induced monocyte TNF $\alpha$ , IL-1 $\beta$ , IL-12, IL-6, MIP-1, MCP-1, GM-CSF, G-CSF, and COX-2 production, and may be used in treating various disorders. See, e.g., U.S. Pat. Nos. 5,635,517, 6,316,471, 6,476,052, 7,393,863, 7,629,360, 7,863,297, 8,198,262, 8,673,939, 8,735,428, 8,759,375, 8,722,647, and 9,282,215. Pomalidomide has direct anti-myeloma tumoricidal and immunomodulatory activities, and inhibits stromal cell support for multiple myeloma tumor cell growth. Pomalidomide inhibits proliferation and induces apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibits the proliferation of lenalidomide-resistant multiple

**2**

myeloma cell lines and synergizes with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhances T cell- and natural killer (NK) cell-mediated immunity, and inhibits production of pro-inflammatory cytokines (e.g., TNF- $\alpha$  and IL-6) by monocytes. Pomalidomide also inhibits angiogenesis by blocking the migration and adhesion of endothelial cells. A molecular target of pomalidomide is cereblon, a protein that forms a ubiquitin E3 ligase complex with DNA damage-binding protein (DDB1), culin 4 (CUL4) and protein Roc1. Pomalidomide binding to cereblon induces the polyubiquitination of two substrate proteins Ikaros (IKF1) and Aiolos (IKZF3). Pomalidomide is known to have CNS penetration. Due to its diversified pharmacological properties, pomalidomide is useful in treating, preventing, and/or managing various diseases or disorders.

Pomalidomide and methods of synthesizing pomalidomide are described, e.g., in U.S. Pat. Nos. 5,635,517, 6,335,349, 6,316,471, 6,476,052, 7,041,680, 7,709,502, and 7,994,327. The chemical structure of pomalidomide has been known since at least the 1960s, but little is known regarding solid forms. An amorphous solid and one crystalline form (anhydrous) have been described in WO 2013/126326. A novel crystalline form of pomalidomide is described herein.

Pomalidomide is the active ingredient in POMALYST®, which in combination with dexamethasone was approved by the FDA in 2013 for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated a disease progression on or within 60 days of completion of the last therapy. The label for POMALYST® can be found at <http://www.pomalyst.com/?pi=yes&gclid=CMF4keDY-tMCFZOCfgods7oPsA>.

New polymorphic forms of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione can further the development of formulations for the treatment of chronic illnesses, and may yield numerous formulation, manufacturing and therapeutic benefits.

**SUMMARY**

Provided herein is a crystalline form of pomalidomide. Also provided herein are pharmaceutical compositions comprising a crystalline form of pomalidomide. Further provided herein are methods of treating or preventing a variety of disease and disorders, which comprise administering to a patient a therapeutically effective amount of a crystalline form of pomalidomide. Also provided herein are methods of treating multiple myeloma, optionally in combination with dexamethasone.

Also provided herein are methods of preparing, isolating, and characterizing crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate provided herein.

**BRIEF DESCRIPTION OF THE DRAWINGS**

FIG. 1 provides a representative X-ray powder diffraction (XRPD) pattern of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate.

FIG. 2 provides a representative X-ray powder diffraction (XRPD) pattern of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate.

FIG. 3 provides a representative differential scanning calorimetry (DSC) thermogram of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate.

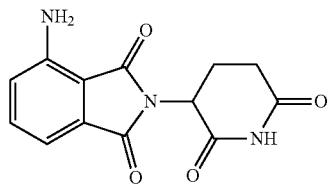
FIG. 4 provides a representative differential scanning calorimetry (DSC) thermogram of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate.

FIG. 5 provides a representative thermogravimetric analysis (TGA) thermogram of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate.

FIG. 6 provides a representative infrared (IR) spectrum of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate.

## DEFINITIONS

As used herein, and unless otherwise specified, the compound referred to herein by the name pomalidomide or 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione, corresponds to a compound of Formula (I), depicted below.



Pomalidomide can be obtained via standard, synthetic methods (see e.g., U.S. Pat. No. 5,635,517).

Unless otherwise specified, the term "crystalline" and related terms used herein, when used to describe a substance, component, product, or form, mean that the substance, component, product, or form is substantially crystalline, for example, as determined by X-ray diffraction. (see, e.g., *Remington's Pharmaceutical Sciences*, 20<sup>th</sup> ed., Lippincott Williams & Wilkins, Philadelphia Pa., 173 (2000); *The United States Pharmacopeia*, 37<sup>th</sup> ed., 503-509 (2014)).

As used herein, and unless otherwise specified, the terms "about" and "approximately," when used in connection with doses, amounts, or weight percents of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by one of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. In certain embodiments, the terms "about" and "approximately," when used in this context, contemplate a dose, amount, or weight percent within 30%, within 20%, within 15%, within 10%, or within 5%, of the specified dose, amount, or weight percent.

As used herein, and unless otherwise specified, the terms "about" and "approximately," when used in connection with a numeric value or range of values which is provided to characterize a particular solid form, e.g., a specific temperature or temperature range, such as, for example, that describes a melting, dehydration, desolvation, or glass transition temperature; a mass change, such as, for example, a mass change as a function of temperature or humidity; a solvent or water content, in terms of, for example, mass or a percentage; or a peak position, such as, for example, in analysis by, for example, IR or Raman spectroscopy or XRPD; indicate that the value or range of values may deviate to an extent deemed reasonable to one of ordinary skill in the art while still describing the solid form. Techniques for characterizing crystal forms and amorphous forms include, but are not limited to, thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC),

X-ray powder diffractometry (XRPD), single-crystal X-ray diffractometry, vibrational spectroscopy, e.g., infrared (IR) and Raman spectroscopy, solid-state and solution nuclear magnetic resonance (NMR) spectroscopy, optical microscopy, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography and quantitative analysis, particle size analysis (PSA), surface area analysis, solubility studies, and dissolution studies. In certain embodiments, the terms "about" and "approximately,"

- 10 when used in this context, indicate that the numeric value or range of values may vary within 30%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1.5%, 1%, 0.5%, or 0.25% of the recited value or range of values. In the context of molar ratios, "about" and "approximately" indicate that the numeric value or range of values may vary within 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1.5%, 1%, 0.5%, or 0.25% of the recited value or range of values. It should be understood that the numerical values of the peaks of an X-ray powder diffraction pattern may vary from one machine to another, or from one sample to another, and so the values quoted are not to be construed as absolute, but with an allowable variability, such as  $\pm 0.2$  degrees two theta ( $^{\circ}2\theta$ ), or more. For example, in some embodiments, the value of an XRPD peak position may vary by up to  $\pm 0.2$  degrees 20 while still describing the particular XRPD peak.

As used herein, and unless otherwise specified, a solid form that is "substantially physically pure" is substantially free from other solid forms. In certain embodiments, a crystal form that is substantially physically pure contains less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.05%, or 0.01% of one or more other solid forms on a weight basis. The detection of other solid forms can be accomplished by any method apparent to a person of ordinary skill in the art, including, but not limited to, diffraction analysis, thermal analysis, elemental combustion analysis and/or spectroscopic analysis.

As used herein, and unless otherwise specified, a solid form that is "substantially chemically pure" is substantially free from other chemical compounds (i.e., chemical impurities). In certain embodiments, a solid form that is substantially chemically pure contains less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.05%, or 0.01% of one or more other chemical compounds on a weight basis. The detection of other chemical compounds can be accomplished by any method apparent to a person of ordinary skill in the art, including, but not limited to, methods of chemical analysis, such as, e.g., mass spectrometry analysis, spectroscopic analysis, thermal analysis, elemental combustion analysis and/or chromatographic analysis.

As used herein, and unless otherwise indicated, a chemical compound, solid form, or composition that is "substantially free" of another chemical compound, solid form, or composition means that the compound, solid form, or composition contains, in certain embodiments, less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2% 0.1%, 0.05%, or 0.01% by weight of the other compound, solid form, or composition.

Unless otherwise specified, the terms "solvate" and "solvated," as used herein, refer to a solid form of a substance which contains solvent. The terms "hydrate" and "hydrated" refer to a solvate wherein the solvent is water. The term "dihydrate" refers to a hydrate containing approximately two moles of water per mole of compound.

As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" refer to the eradication or amelioration of a disease or disorder, or of one or more symptoms associated with the disease or disorder. In certain embodiments, the terms refer to minimizing the spread or worsening of the disease or disorder resulting from the administration of one or more prophylactic or therapeutic agents to a subject with such a disease or disorder. In some embodiments, the terms refer to the administration of a compound provided herein, with or without other additional active agent, after the onset of symptoms of a particular disease.

Unless otherwise specified, the term "composition" as used herein is intended to encompass a product comprising the specified ingredient(s) (and in the specified amount(s), if indicated), as well as any product which results, directly or indirectly, from combination of the specified ingredient(s) in the specified amount(s). By "pharmaceutically acceptable," it is meant a diluent, excipient, or carrier in a formulation must be compatible with the other ingredient(s) of the formulation and not deleterious to the recipient thereof.

Unless otherwise specified, the term "subject" is defined herein to include animals, such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, and the like. In specific embodiments, the subject is a human.

Unless otherwise specified, to the extent that there is a discrepancy between a depicted chemical structure of a compound provided herein and a chemical name of a compound provided herein, the chemical structure shall control.

#### DETAILED DESCRIPTION

Crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate can be prepared by the methods described herein, including the methods described in the Example below, or by techniques known in the art, including heating, cooling, freeze drying, lyophilization, quench cooling the melt, rapid solvent evaporation, slow solvent evaporation, solvent recrystallization, antisolvent addition, slurry recrystallization, crystallization from the melt, desolvation, recrystallization in confined spaces such as, e.g., in nanopores or capillaries, recrystallization on surfaces or templates such as, e.g., on polymers, recrystallization in the presence of additives, such as, e.g., co-crystal counter-molecules, desolvation, dehydration, rapid cooling, slow cooling, exposure to solvent and/or water, drying, including, e.g., vacuum drying, vapor diffusion, sublimation, grinding (including, e.g., cryo-grinding, solvent-drop grinding or liquid assisted grinding), microwave-induced precipitation, sonication-induced precipitation, laser-induced precipitation and precipitation from a supercritical fluid. The particle size of the resulting solid forms, which can vary, e.g., from nanometer dimensions to millimeter dimensions, can be controlled, e.g., by varying crystallization conditions, such as, e.g., the rate of crystallization and/or the crystallization solvent system, or by particle-size reduction techniques, e.g., grinding, milling, micronizing or sonication.

While not intending to be bound by any particular theory, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate is characterized by physical properties, e.g., stability, solubility and dissolution rate, appropriate for pharmaceutical and therapeutic dosage forms. Moreover, while not wishing to be bound by any particular theory, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate is characterized by physical

properties (e.g., density, compressibility, hardness, morphology, cleavage, stickiness, solubility, water uptake, electrical properties, thermal behavior, solid-state reactivity, physical stability, and chemical stability) affecting particular processes (e.g., yield, filtration, washing, drying, milling, mixing, tabletting, flowability, dissolution, formulation, and lyophilization) which make certain solid forms suitable for the manufacture of a solid dosage form. Such properties can be determined using particular analytical chemical techniques, including solid-state analytical techniques (e.g., X-ray diffraction, microscopy, spectroscopy and thermal analysis), as described herein and known in the art.

Certain embodiments herein provide compositions comprising crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate. Certain embodiments provide compositions of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate in combination with other active ingredients. Certain embodiments provide methods of using these compositions in the treatment, prevention or management of diseases and disorders including, but not limited to, the diseases and disorders provided herein.

Certain embodiments herein provide crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate can be obtained from a 4:1 1,4-dioxane/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate can be obtained from a 4:1 THF/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate can be obtained from an 1:1:1 acetone/water/isopropyl alcohol mixture.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate.

In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate may be characterized by X-ray powder diffraction analysis.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate having an X-ray powder diffraction pattern comprising peaks at 13.9, 16.6, and 25.5 degrees  $2\theta \pm 0.2$  degrees  $2\theta$ .

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate wherein the X-ray powder diffraction pattern further comprises peaks at 11.9, 16.9, and 28.2 degrees  $2\theta \pm 0.2$  degrees  $2\theta$ .

In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate is characterized by XRPD peaks located at one, two, three, four, five, six, seven, eight, nine, ten, eleven or twelve of the following approximate positions: 11.9, 12.7, 13.9, 16.6, 16.9, 18.1, 22.6, 23.9, 24.8, 25.5, 27.8, 28.2, and 31.8 degrees  $2\theta$ . In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate is characterized by an XRPD pattern which matches the pattern exhibited in FIG. 1. In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate is characterized by an XRPD pattern which matches the pattern exhibited in FIG. 2. In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate is characterized by an XRPD pattern having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 peaks matching peaks in a representative XRPD pattern provided herein.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate having an X-ray powder diffraction pattern corresponding to the representative X-ray powder diffraction pattern depicted in FIG. 1.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate having an X-ray powder diffraction pattern corresponding to the representative X-ray powder diffraction pattern depicted in FIG. 2.

In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate may be characterized by thermal analysis.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate having a differential scanning calorimetry thermogram comprising an endotherm with a maximum at about 308° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate, having a differential scanning calorimetry thermogram comprising an endotherm with a maximum at about 309° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate having a differential scanning calorimetry thermogram corresponding to the representative differential scanning calorimetry thermograms depicted in FIG. 3.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate having a differential scanning calorimetry thermogram corresponding to the representative differential scanning calorimetry thermograms depicted in FIG. 4.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate having approximately 11.6% of water by mass.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 10.3% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 10.1% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 10.4% when heated from about 30° C. to about 225° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate having a thermogravimetric analysis thermogram comprising a weight loss of between about 10.1% and about 10.4% when heated from about 30° C. to about 225° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate having a thermogravimetric analysis thermogram corresponding to the representative thermogravimetric analysis thermogram depicted in FIG. 5.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate having an infrared spectrum corresponding to the representative infrared spectrum depicted in FIG. 6.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate which is substantially physically pure.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate which is substantially chemically pure.

In one embodiment, provided is a pharmaceutical composition comprising a crystal form of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate.

#### Pharmaceutical Compositions

10 Pharmaceutical compositions and single unit dosage forms comprising crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate are provided herein. Also provided herein are methods for preparing pharmaceutical compositions and single unit dosage forms comprising crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate. For example, in certain embodiments, individual dosage forms comprising crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate provided herein or prepared using crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate provided herein may be suitable for oral, mucosal (including rectal, nasal, or vaginal), parenteral (including subcutaneous, intramuscular, bolus injection, intraarterial, or intravenous), sublingual, transdermal, buccal, or topical administration.

In certain embodiments, pharmaceutical compositions and dosage forms provided herein comprise crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate. Certain embodiments herein provide pharmaceutical compositions and dosage forms comprising a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate, wherein the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate is substantially pure. Certain embodiments herein provide pharmaceutical compositions and dosage forms comprising a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate as provided herein, which is substantially free of other crystalline solid forms of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione and/or amorphous solid forms of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione. Pharmaceutical compositions and dosage forms provided herein typically also comprise one or more pharmaceutically acceptable excipients, diluents or carriers.

45 Single unit dosage forms provided herein are suitable for oral or parenteral (e.g., subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial) administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules powders and sterile solids that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

Capsules may contain a shell.

The composition, shape, and type of dosage forms provided herein will typically vary depending on their use. A parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease or disorder. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. See, e.g., *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton Pa. (1990).

Typical pharmaceutical compositions and dosage forms 65 comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided

herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form.

In one embodiment, suitable excipients include mannitol, pregelatinized starch, and sodium stearyl fumarate.

Capsule shells may contain gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, white ink, and black ink.

Capsule shells may contain gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, FD&C red 3, and white ink.

Capsule shells may contain gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, and white ink.

Capsule shells may contain gelatin, titanium dioxide, FD&C blue 1, FD&C blue 2, and white ink.

Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms provided herein lie within the range of from about 0.1 mg to about 1,000 mg per day, given as a single once-a-day dose in the morning or as divided doses throughout the day. More specifically, the daily dose may be administered twice, three times, or four times daily in equally divided doses. Specifically, a daily dose range may be from about 0.1 mg to about 500 mg per day, more specifically, between about 0.1 mg and about 200 mg per day. A daily dose range may be 1 mg, 2 mg, 3 mg, 4 mg, or 5 mg. In managing the patient, the therapy may be initiated at a lower dose, perhaps about 1 mg to about 25 mg, and increased if necessary up to about 200 mg to about 1,000 mg per day as either a single dose or divided doses, depending on the patient's global response.

#### Oral Dosage Forms

Pharmaceutical compositions provided herein that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton Pa. (1990).

Typical oral dosage forms provided herein are prepared by combining the active ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceu-

tical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101™, AVICEL-PH-103™, AVICEL RC-581™, AVICEL-PH-105™ (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, Pa.), and mixtures thereof. A specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-58™. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM™.

Disintegrants are used in the compositions provided herein to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, specifically from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms provided herein include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other alginic acids, other celluloses, gums, and mixtures thereof.

## 11

Lubricants that can be used in pharmaceutical compositions and dosage forms provided herein include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200<sup>TM</sup>, manufactured by W.R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, Tex.), CAB-O-SIL<sup>TM</sup> (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass.), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about one weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

## Parenteral Dosage Forms

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial injection. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms provided herein are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms provided herein.

## EXAMPLES

Preparation of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate: 20 mg of pomalidomide Form A (anhydride) was slurried in a mixture of 20 mL 1,4-dioxane and 5 mL water in a 50 mL round bottom flask. The pomalidomide was completely dissolved at 70° C. with the use of a rotary evaporator. The temperature was raised to 90° C., and an aspirator vacuum was then applied. Within 10 minutes, the solvent was evaporated and a pale yellow liquid remained in the flask. The flask was cooled to room temperature (ca. 22° C.), and the pale yellow liquid was triturated with 20 mL water. After centrifugation, a pale yellow solid was isolated. The pale yellow solid was dried under a vacuum of 50 torr for three hours. The resulting pale yellow, free flowing powder was taken for analysis.

## 12

Karl-Fischer titration revealed the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate contained 10.5% water.

XRPD data for the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate is shown below in Table 1.

Scan Type: Normal  
Start Angle: 3 deg  
Stop Angle: 35 deg.  
10 Num Points: 1601  
Step Size: 0.02 deg.  
Datafile Res: 1600  
Scan Rate: 0.000667  
Scan Mode: Step  
15 Wavelength: 1.540562 Å  
Tube divergent 2.00 mm  
Tube scatter 4.00 mm  
Detector scatter 0.50 mm  
20 Detector reflection 0.30 mm

TABLE 1

XRPD data for crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate.			
Peaks: (Deg.)	Position (Dsp.)	Intensity (cps)	Rel. Int. %
11.9	7.4363	244.44	39.80
12.7	6.9710	181.48	29.55
13.9	6.3741	385.77	62.80
16.6	5.3250	367.50	59.83
16.9	5.2498	356.33	58.01
18.1	4.8975	235.19	38.29
22.6	3.9263	174.07	28.34
23.9	3.7223	251.85	41.00
24.8	3.5859	231.48	37.69
25.5	3.4876	614.25	100.00
27.8	3.2080	261.11	42.51
28.2	3.1628	290.35	47.27
31.8	2.8142	144.44	23.52

40 Additional experiments to prepare crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate are listed below.

Preparation of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate: 20 mg of 45 pomalidomide Form A (anhydride) was slurried in a mixture of 7 mL acetone, 7 mL isopropanol, and 7 mL water in a 50 mL round bottom flask. The pomalidomide was completely dissolved at 70° C. with the use of a rotary evaporator. The temperature was raised to 90° C., and an aspirator vacuum was applied. Within 10 minutes, the solvent was evaporated and a pale yellow solid remained in the flask. The pale yellow solid was dried under a vacuum of 50 torr for 0.5 hours followed by further drying at room temperature without vacuum for 12 hours. The resulting pale yellow, free flowing powder was taken for analysis. TGA analysis 50 revealed the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate contained 10.1% water.

Preparation of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate: 20 mg of 60 pomalidomide Form A (anhydride) was slurried in a mixture of 20 mL THF and 5 mL water in a 50 mL round bottom flask. The pomalidomide was completely dissolved at 70° C. with the use of a rotary evaporator. The temperature was raised to 80° C., and an aspirator vacuum was applied. Within 10 minutes, the solvent was evaporated and a pale yellow solid remained in the flask. The flask was cooled to room temperature (ca. 22° C.), and the pale yellow solid was

dried under a vacuum of 50 torr for 1.5 hours. The resulting pale yellow, free flowing powder was taken for analysis. TGA analysis revealed the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate contained 10.4% water.

**Additional Experiments that Did not Result in Crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate**

The following unsuccessful experiments were performed by mixing in a flask Form A of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione with solvents until dissolution, then the flask was placed on a rotoevaporator (fast rotation; vacuum by water aspirator) at various bath temperatures until dryness or until apparent dryness.

Certain experiments produced an oil, which were then triturated as follows: pure HPLC grade water was added to flask containing the oil, and the flask was stirred. If a solid was formed, it was further dried.

TABLE 2

Conditions that did not result in a crystalline dihydrate of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione.				
Solvent	Co-solvent	Ratio of solvent/ co-solvent	Temper- ature (° C.)	Notes
1,4-dioxane	N/A		60	
THF	Water	10:1	60	Triturated vacuum dried
THF	Water	1:1	80	
Ethanol	Water	1:1	80	100° C. for 12 hours after initial drying
Ethanol	Water	1:1	80	Dried further for 20 min at 100° C., then 30 min at 150° C.
THF	Water	1:1	80	
1,4-dioxane	Water	1:1	80	Triturated, dried at 150° C. for 1 h
THF	Water	95:5	65	
Ethanol	Water	95:5	90	
Ethanol	Water	98:2	90	
THF	Water	9:1	85	
Ethanol	THF/Water	2:1:2	60	
Ethanol	THF/Water	2:1:2	95	
Ethanol	THF/Water	1:6:1	95	
Ethanol	THF/Water	6:4:1	95	
Ethanol	THF/Water	1:2:1	95	
1,4-dioxane	Water	1:1	95	Triturated
1,4-dioxane	Water	1:1	95	Triturated, air tried, 45m in vacuo
Ethanol	THF/Water	3:5:3	80	Air dried 3 h
Ethanol	THF/Water	3:5:3	80	
Acetone	i-PrOH/ Water	1:1:1	90	
Acetone	i-PrOH/ Water	1:1:1	95	Material was moist
Acetone	i-PrOH/ Water	1:1:1	95	Air dried 18 h
Acetone	i-PrOH/ Water	1:1:1	95	Air current dried 3 h
Acetone	i-PrOH/ Water	1:1:1	95	Air current dried 1 h
Acetone	i-PrOH/ Water	1:1:1	85	
1,4-dioxane	Water	1:1	85	Material was moist
THF	Water	1:1	80	Air dried
THF	Water	1:1	80	Dried in vacuo for 2 h at 200° C.

TABLE 2-continued

Conditions that did not result in a crystalline dihydrate of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione.					
5	Solvent	Co-solvent	Ratio of solvent/ co-solvent	Temper- ature (° C.)	Notes
10	1,4-dioxane	Water	1:1	90	Triturated, dried in vacuo 16 h
10	THF	Water	4:1	95	
	THF	Water	4:1	80	
	THF	Water	4:1	65	
	1,4-dioxane	Water	1:1	95	
	1,4-dioxane	Water	4:1	80	Oil, triturated, air dried 4 h
15	1,4-dioxane	Water	3:1	85	Air dried 3 h
	1,4-dioxane	Water	3:1	85	Dried overnight at room temperature
	1,4-dioxane	Water	3:1	85	Triturated, dried
	THF	Water	4:1	80	Air dried 1 h
	THF	Water	12:1	70	Air dried
	THF	Water	6:1	80	Air dried
20	MeCN	Water	2:1	80	Material was moist
	MeCN	Water	2:1	80	Dried overnight
	MeCN	Water	2:1	90	Air dried
	1,4-dioxane	Ethanol/ THF/Water	1:1:1:2	85	Air dried
25	1,4-dioxane	THF/Water	6:6:1	50	Material was moist
	1,4-dioxane	THF/Water	6:6:1	50	Dried at 90° C. in vacuo
	1,4-dioxane	THF/Water	6:6:1	50	Air dried
	Acetone	THF/Water	10:3:3	90	Air dried
	THF	Water	25:1	60	Air dried
	THF	Water	25:1	60	
30	THF	Water	20:1	70	
	THF	Water	4:1	80	Air dry
	THF	Water	10:1	65	Air dry
	THF	Water	10:1	75	
	Acetone	THF/Water	10:1:1	60	Air dry
	1,4-dioxane	Water	3:1	85	Triturated
35	1,4-dioxane	Water	12:1	60	Triturated

## Characterization Methodology

- 40 Samples generated as described in the solid form screen were typically analyzed by X-Ray Powder Diffraction (XRPD). XRPD was conducted on a Scintag X2 X-ray powder diffractometer using Cu K $\alpha$  radiation at 1.54 Å. In general, positions of XRPD peaks are expected to individually vary on a measurement-by-measurement basis by about  $\pm 0.2^\circ 2\theta$ . In general, as understood in the art, two XRPD patterns match one another if the characteristic peaks of the first pattern are located at approximately the same positions as the characteristic peaks of the second pattern. As understood in the art, determining whether two XRPD patterns match or whether individual peaks in two XRPD patterns match may require consideration of individual variables and parameters such as, but not limited to, preferred orientation, phase impurities, degree of crystallinity, particle size, variation in diffractometer instrument setup, variation in XRPD data collection parameters, and/or variation in XRPD data processing, among others. The determination of whether two patterns match may be performed by eye and/or by computer analysis. An example of an XRPD pattern collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. 1.
- An example of an XRPD pattern collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. 2.
- 45 50 55 60 65 70 75 80 85 90 95 100
- 55 Differential Scanning Calorimetry (DSC) analyses were performed on a TA Instruments Q100™. About 5 mg of sample was placed into a tared DSC closed aluminum pan
- 60 65 70 75 80 85 90 95 100

**15**

and the weight of the sample was accurately recorded. An example of a DSC thermogram collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. 3.

An example of a DSC thermogram collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. 4.

Thermal Gravimetric Analyses (TGA) were performed on a TA Instruments Q50™ About 10 mg of sample was placed on an open aluminium pan, accurately weighed and loaded into the TGA furnace. An example of a TGA thermogram collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. 5.

Water determination by the Karl Fischer method was performed using a Metrohm 831 KF Coulometer. The sample was dissolved in anhydrous acetone and injected into the titrator.

Infrared spectroscopy was performed using a ThermoNi-colet Nexus 670 spectrometer. A sample of ca. 1 mg of the dihydrate in ca. 100 mg KBr. The mixture was then pressed into a pellet, which was used for the IR study. An example of an IR spectrum collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. 6.

The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the disclosure and are encompassed by the appended claims.

Citation or identification of any reference in this application is not an admission that such reference is available as prior art. The full scope of the disclosure is better understood with reference to the appended claims.

The invention claimed is:

**1.** Crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione dihydrate, having an X-ray powder diffraction pattern comprising peaks at 13.9, 16.6, and 25.5 degrees  $2\theta \pm 0.2$  degrees  $2\theta$ .

**16**

**2.** The dihydrate of claim **1** wherein the X-ray powder diffraction pattern further comprises peaks at 11.9, 16.9, and 28.2 degrees  $2\theta \pm 0.2$  degrees  $2\theta$ .

**3.** The dihydrate of claim **1**, having an X-ray powder diffraction pattern corresponding to the representative X-ray powder diffraction pattern depicted in FIG. 1.

**4.** The dihydrate of claim **1**, having an X-ray powder diffraction pattern corresponding to the representative X-ray powder diffraction pattern depicted in FIG. 2.

**5.** The dihydrate of claim **1**, having a differential scanning calorimetry thermogram comprising an endotherm with a maximum at about 308° C.

**6.** The dihydrate of claim **1**, having a differential scanning calorimetry thermogram comprising an endotherm with a maximum at about 309° C.

**7.** The dihydrate of claim **1** having a differential scanning calorimetry thermogram corresponding to the representative differential scanning calorimetry thermogram depicted in FIG. 3.

**8.** The dihydrate of claim **1** having a differential scanning calorimetry thermogram corresponding to the representative differential scanning calorimetry thermogram depicted in FIG. 4.

**9.** The dihydrate of claim **1** having about 11.6% of water by mass.

**10.** The dihydrate of claim **1** having a thermogravimetric analysis thermogram comprising a weight loss of between about 10.1% and about 10.4% when heated from about 30° C. to about 225° C.

**11.** The dihydrate of claim **1** having a thermogravimetric analysis thermogram corresponding to the representative thermogravimetric analysis thermogram depicted in FIG. 5.

**12.** The dihydrate of claim **1** having an infrared spectrum corresponding to the representative infrared spectrum depicted in FIG. 6.

\* \* \* \* \*

# **EXHIBIT B**



US010093648B1

(12) **United States Patent**  
**Atwood**

(10) **Patent No.:** US 10,093,648 B1  
(b4) **Date of Patent:** Oct. 9, 2018

(54)	<b>CRYSTALLINE 4-AMINO-2-(2,6-DIOXOPIPERIDINE-3-YL)ISOINDOLINE-1,3-DIONE HEMIHYDRATE, COMPOSITIONS AND METHODS OF USE THEREOF</b>	6,755,784 B2	6/2004	Williams et al.
		6,878,733 B1	4/2005	Shenoy et al.
		6,896,399 B2	5/2005	Nomura et al.
		6,908,432 B2	6/2005	Elsayed et al.
		7,041,680 B2	5/2006	Muller et al.
		7,119,106 B2	10/2006	Muller et al.
		7,189,740 B2	3/2007	Zeldis
		7,393,862 B2	7/2008	Zeldis
		7,393,863 B2	7/2008	Zeldis
		7,465,800 B2	12/2008	Jaworsky et al.
		7,629,360 B2	12/2009	Muller et al.
(71)	Applicant: <b>Celgene Corporation</b> , Summit, NJ (US)	7,709,031 B2	5/2010	Greenway et al.
(72)	Inventor: <b>Jerry Lee Atwood</b> , Columbia, MO (US)	7,709,502 B2	5/2010	Muller et al.
(73)	Assignee: <b>Celgene Corporation</b> , Summit, NJ (US)	7,855,217 B2	12/2010	Jaworski et al.
(* )	Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.	7,863,297 B2	1/2011	Zeldis
(21)	Appl. No.: <b>15/849,324</b>	7,959,566 B2	6/2011	Williams et al.
(22)	Filed: <b>Dec. 20, 2017</b>	7,968,569 B2	6/2011	Zeldis
		7,994,327 B2	8/2011	Ge et al.
		8,158,653 B2	4/2012	Muller et al.
		8,188,118 B2	5/2012	Zeldis
		8,198,262 B2	6/2012	Zeldis
		8,198,306 B2	6/2012	Zeldis
		8,204,763 B2	6/2012	Elsayed et al.
		8,207,200 B2	6/2012	Zeldis
		8,315,886 B2	11/2012	Williams et al.
		8,530,498 B1	9/2013	Zeldis
		8,589,188 B2	11/2013	Elsayed et al.
		8,626,531 B2	1/2014	Williams et al.
		8,648,095 B2	2/2014	Zeldis
		8,673,939 B2	3/2014	Zeldis
		8,722,647 B2	5/2014	Zeldis
		8,735,428 B2	5/2014	Zeldis
		8,759,375 B2	6/2014	Zeldis
		8,828,427 B2 *	9/2014	Tutino ..... A61K 9/4858 424/452
(51)	<b>Int. Cl.</b> <b>C07D 401/04</b> (2006.01)	9,101,621 B2	8/2015	Zeldis
(52)	<b>U.S. Cl.</b> CPC ..... <b>C07D 401/04</b> (2013.01); <b>C07B 2200/13</b> (2013.01)	9,101,622 B2	8/2015	Zeldis
(58)	<b>Field of Classification Search</b> CPC ..... C07D 401/04 USPC ..... 546/200; 514/323 See application file for complete search history.	9,695,146 B2 *	7/2017	Stahyl et al. ..... C07D 401/12
		2002/0054899 A1	5/2002	Zeldis et al.
		2007/0155791 A1	7/2007	Zeldis et al.
		2008/0051431 A1	2/2008	Verhelle et al.
		2017/0258778 A1	9/2017	Stahly et al.

## FOREIGN PATENT DOCUMENTS

WO	WO 96/13790 A1	5/1996
WO	WO 98/03502 A1	1/1998
WO	WO 98/13783 A1	4/1998
WO	WO 99/10829 A1	3/1999
WO	WO 00/51053 A1	8/2000
WO	WO 02/43720 A2	6/2002
WO	WO 02/59106 A1	8/2002
WO	WO 02/064083 A2	8/2002
WO	WO 2011/050962 A1	5/2011
WO	WO 2013/012485 A2	1/2013
WO	WO 2013/126326 A1	8/2013
WO	WO 2014/160690 A1	10/2014
WO	WO 2018/013689 A1	1/2018

## OTHER PUBLICATIONS

Bernstein, "Polymorphism in . . ." p. 115-118, 272. (Year: 2002).\*

(Continued)

*Primary Examiner* — Patricia L Morris  
*(74) Attorney, Agent, or Firm* — Jones Day

(57) **ABSTRACT**

Provided herein is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate. Pharmaceutical compositions comprising the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate are also disclosed.

(56)

**References Cited****OTHER PUBLICATIONS**

- Davidovich et al., "Detection of polymorphism . . ." Am. Pharm. Rev. 7(1) p. 10, 12, 14, 16, 100.. (Year: 2004).\*
- Dean "Analytical Chem . . ." p. 10.24-10.26. (Year: 1995).\*
- Ivanisevic et al. "Use of X-ray . . ." Pharm. Sci. Encycl. p. 1-42.. (Year: 2010).\*
- Seddon "Pseudopolymorph . . ." Crystal Growth & design v.4(6) p. 1087 (2 pages from internet). (Year: 2004).\*
- Rodriguez-Spong et al., "General principles, etc.," Adv. Drug Delivery Reviews 56 241-274. (Year: 2004).\*
- Kirk-Othmer Encyclopedia of Chemical Technology, 8, pp. 95-147. (Year: 2002).\*
- Vippagunta et al., "Crystalline Solids", Advanced Drug Delivery Reviews 48 .3-26. (Year: 2001).\*
- Guillory (in Brittain ed.), "Polymorphism in Pharmaceutical Solids., NY: Marcel Dekker, Inc., 1-2, 183-226. (Year: 1999).\*
- Braga et al., "Making crystals from . . ." J. Royal Soc. Chem. Commun. p. 3635-3645. (Year: 2005).\*
- CMU Pharmaceutical polymorphism, internet p. 1-3 printout Apr. 3, 2008. (Year: 2002).\*
- Singhal et al., "Drug Polymorphism, etc.," Advanced Drug Delivery reviews 56, p. 335-347. (Year: 2004).\*
- Concise Encyclopedia Chemistry, NY: Walter de Gruyter, 872-873. (Year: 1993).\*
- Jain et al., "Polymorphism in Pharmacy", Indian Drugs, 23(6) 315-329. (Year: 1986).\*
- Muzaffar et al., "Polymorphism and Drug Availability, etc.," J of Pharm. (Lahore), 1(1), 59-66. (Year: 1979).\*
- U.S. Pharmacopia #23, National Formulary #18,1843-1844. (Year: 1995).\*
- Doelker, english translation of S.T.P, Pratiques, 9(5), 399-409, pp. 1-33. (Year: 1999).\*
- Doelker, english translation of Ann. Pharm. Fr., 60: 161-176, pp. 1-39. (Year: 2002).\*
- Taday et al., "Using Terahertz, etc.," J of Pharm. Sci., 92(4), 831-838. (Year: 2003).\*
- Otuska et al., "Effect of Polymorphic, etc.," Chem. Pharm. Bull., 47(6) 852-8569. (Year: 1999).\*
- Nie et al., "Source analysis, etc.," CA 1743748. (Year: 2015).\*
- Celgene Corporation, POMALYST® (pomalidomide) packaging label, Retrieved online on Dec. 14, 2017, retrieved online at <<http://www.pomalyst.com/?pi=yes&gclid=CMF4keDY-tMCFZOCfgods7oPsA>>, revised Jun. 2016.
- Dimartino et al., "Preparation and physical characterization of forms II and III of paracetamol," J. Thermal. Anal., 48(3):447-458 (1997).
- Gennaro, Remington: The Science and Practice of Pharmacy, 20th Ed., Lipincott Williams & Wilkins, pp. 172-182 (2000).
- Knapman, "Polymorphic Predictions: Understanding the nature of crystalline compounds can be critical in drug development and manufacture," Modern Drug Discoveries, 53-57 (2000).
- The United States Pharmacopeia, 37th Edition, United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 503-509 (2014).
- "CDC meeting: Mar. 26, 1997 minutes and agenda regarding thalidomide."
- "Celgene's Revlimid an orphan drug, says FDA," Marketletter Oct. 15, 2001.
- "Center for drug evaluation and research approval package for Application number: 18-662/S-038," (2000).
- "Center for drug evaluation and research approval package for Application No. NDA 20-785 approval letter(s)," Sep. 19, 1997 and Jul. 16, 1998.
- "Celgene drug promises activity in solid tumors," Marketletter Jun. 18, 2001.
- "Center for drug evaluation and research, Application No. 204026Orig1s000," Pharmacology Review(s), dated Dec. 13, 2012. [retrieved on Oct. 29, 2016]. Retrieved from the internet: <[http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2013/204026Orig1s000PharmR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204026Orig1s000PharmR.pdf)>.
- "Center for Drug Evaluation and Research, Approval Package for: Application number: 14-691/S-020," ALKERAN® (melphalan) Tablets, product information, GlaxoSmithKline (2001).
- "EntreMed moves towards commercialization with production of thalidomide analogs; Next generation drug candidates to be manufactured in preparation for clinical studies," PR Newswire (2001).
- Adams et al., "Proteasome inhibitors: A novel class of potent and effective antitumor agents," Cancer Res. 59:2615-2622 (1999).
- Adjei et al., "A phase I trial of the farnesyl transferase inhibitor SCH66336: evidence for biological and clinical activity," Cancer Res., 60:1871-1877 (2000).
- Alder et al., "The return of thalidomide—A shunned compound makes a scientific comeback," Science News 146:424-425 (1994).
- Alexanian et al., "High-dose glucocorticoid treatment of resistant myeloma," Ann. Intern. Med. 105:8-11 (1986).
- Alexanian et al., "Consolidation therapy of multiple myeloma with thalidomide-dexamethasone after intensive chemotherapy," Ann Oncol. 13:1116-1119 (2002).
- Anderson et al., "Multiple myeloma: New insights and therapeutic approaches," Hematology Am. Soc. Hematol. Educ. Program 2000:147-165 (2000).
- Anderson et al., "Novel biologically based therapies for myeloma," VIII the International Myeloma Workshop, Banff, Alberta, Canada, May 4-8, 2001; Abstract #S27.
- Anderson, "The role of immunomodulatory drugs in multiple myeloma," Semin. Hematol., 40(4 Suppl. 4):23-32 (2003).
- Banker ed., Modern Pharmaceutics, 3<sup>rd</sup> Edition, Marcel Dekker, Inc., New York, NY, pp. 451 and 596 (1996).
- Barlogie et al., "Effective Treatment of Advanced Multiple Myeloma Refractory to Alkylating Agents," N. Engl. J. Med., 310(21):1353-1356 (1984).
- Barlogie et al., "Thalidomide and CC-5013 in multiple myeloma: the University of Arkansas experience," Semin. Hematol., 40(4):33-38 (2003).
- Barlogie et al., "Thalidomide in the management of multiple myeloma," Semin. Hematol., 38:250-259 (2001).
- Beaumont et al., "Design of ester prodrugs to enhance oral absorption of poorly permeable compounds: challenges to the discovery scientist," Curr. Drug Metab., 4:461-485 (2003).
- Bjorkstrand et al., "Prognostic factors in autologous stem cell transplantation for multiple myeloma: an EBMT registry study," Leuk. Lymphoma 15:265-272 (1994).
- Bor, "Thalidomide shows that it can heal, too from deformities of babies to force for good," Baltimore Sun (1995).
- Broder et al., "Dideoxycytidine: Current clinical experience and future prospects. A summary," Am. J. Med. 88:31S-33S (1990).
- Burleson, "Review of computer applications in institutional pharmacy—1975-1981," Am. J. Hosp. Pharm. 39:53-70 (1982).
- Bwire et al., Managing the teratogenic risk of thalidomide and lenalidomide: An industry perspective, Expert Opin. Drug Saf. 10:3-8 (2011).
- Cairo, "Dose reductions and delays: Limitations of myelosuppressive chemotherapy," Cancer Network (2000).
- Canal et al., "Benefits of pharmacological knowledge in the design and monitoring of cancer chemotherapy," Pathology Oncol. Res. 4:171-178 (1998).
- Celgene assigned patents/applications indexed with pomalidomide from USPATFULL accessed Oct. 27, 2016.
- Celgene Corporation Awarded Additional Patent Protection for Lead IMiD(TM), REVIMID(TM); Comprehensive Patent Protection for REVIMID Includes Coverage of the Active Ingredient, Pharmaceutical Compositions, and Therapeutic Uses PR Newswire Aug. 28, 2001.
- Celgene Corporation, "Initial Phase I solid tumor data on Celgene's lead IMiD™, Revimid™," Press Release, Jun. 2001.
- Celgene Corporation, Form 424B4 (2000).
- Celgene News Release, "Positive interim results presented at the VIIIth international myeloma workshop on Celgene Corporation's lead IMiD™ (REV/MID™)," May 8, 2001.
- Cheson, "New drug development in non-Hodgkin lymphomas," Curr. Oncol. Rep. 3:250-259 (2001).

(56)

**References Cited****OTHER PUBLICATIONS**

- Choi et al., "Role of gallic acid in inflammatory allergic process," *Korean Journal Physiology & Pharmacology*, 10(2):101-108 (2006) (abstract only).
- Chu et al., "Principles of cancer management: Chemotherapy," in *Cancer: Principles and Practice of Oncology*, 6th edition, De Vita et al., (eds.), Lippincott Williams & Wilkins, Philadelphia, PA Chapter 17 (2001).
- Cimons, "How a body responds to drugs depends on the genes," *Los Angeles Times*, Jul. 24, 2000.
- Collins et al., "Potential roles for preclinical pharmacology in phase 1 clinical trials," *Cancer Treat. Rep.*, 70:73-80 (1986).
- Corral et al., "Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF- $\alpha$ ," *J. Immunol.* 163:380-386 (1999).
- Corral et al., "Immunomodulation by thalidomide and thalidomide analogues," *Ann. Rheum. Dis.*, 58(Suppl 1):I107-I113 (1999).
- Crane et al., "Immunomodulatory drugs," *Cancer Investigation* 23:625-634 (2005).
- D'Amato et al., "Mechanism of action of thalidomide and 3-aminothalidomide in multiple myeloma," *Semin. Oncol.*, 28:597-601 (2001).
- D'Amato et al., "Thalidomide is an Inhibitor of Angiogenesis," *Proc. Natl. Acad. Sci. USA*, 91(9):4082-4085 (1994).
- Damaj et al., "Thalidomide therapy induces response in relapsed mantle cell lymphoma," *Leukemia* 17:1914-1915 (2003).
- Dancey et al., "Neutrophil kinetics in man," *J. Clin. Invest.* 58:705-715 (1976).
- Davies et al., "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma," *Blood*, 98(1):210-216 (2001).
- Devita et al., eds., "Plasma cell neoplasm." In *Cancer Principles & Practice of Oncology*, 5th Ed.; Lippincott-Raven Publishers, pp. 2344-2379 (1997).
- Dimopoulos et al., "Thalidomide and dexamethasone combination for multiple myeloma refractory to dexamethasone-based regimens," *Blood* 96(Supp):286b (2000).
- Dimopoulos et al., "Thalidomide and dexamethasone combination for refractory multiple myeloma," *Ann. Oncol.* 12:991-995 (2001).
- Dishman et al., "Pharmacists' transcript role in clozapine therapy at a veterans affairs medical center," *Am. J. Hosp. Pharm.* 51:899-901 (1994).
- Drach et al., "Treatment of mantle cell lymphoma: Targeting the microenvironment," *Expert Rev. Anticancer Ther.* 5:477-485 (2005).
- Dredge et al., "Immunological effects of thalidomide and its chemical and functional analogs," *Crit. Rev. Immunol.*, 22(5&6):425-437 (2002).
- Dredge et al., "Novel thalidomide analogues display anti-angiogenic activity independently of immunomodulatory effects," *Br. J. Cancer*, 87(10):1166-1172 (2002).
- Dredge et al., "Protective antitumor immunity induced by a costimulatory thalidomide analog in conjunction with whole tumor cell vaccination is mediated by increased Th1-type immunity<sup>1</sup>," *J. Immunol.* 168:4914-4919 (2002).
- Dredge et al., "Thalidomide analogs as emerging anti-cancer drugs," *Anti-Cancer Drugs*, 14:331-335 (2003).
- Durie and Stepan, "Efficacy of low dose thalidomide in multiple myeloma," *Eur. J. Oncol.* 1:1-8 (2000).
- Dykes, "Genes, disease and medicine," *Br. J. Clin. Pharmacol.*, 42:683-695 (1996).
- Edwards, "Thalidomide: Is there a silver lining?" *Science News* 131:198 (1987).
- Elliot et al., "The proteasome: A new target for novel drug therapies," *Am. J. Clin. Pathol.* 116:637-646 (2001).
- EORTC Pharmacokinetics and Metabolism Group, "Pharmacokinetically guided dose escalation in phase I clinical trials. Commentary and proposed guidelines," *Eur. J. Cancer Clin. Oncol.*, 23(7):1083-1087 (1987).
- FDA Guideline for Industry, "International conference on harmonisation; dose-response information to support drug registration; guideline; availability," 59 FR 55972-01, 1994 WL 615579 (1994).
- Figg et al., "Pharmacokinetics of thalidomide in an elderly prostate cancer population," *J. Pharm. Sci.* 88:121-125 (1999).
- Filella et al., "Cytokines (IL-6, TNF-alpha, IL-1 alpha) and soluble interleukin-2 receptor as serum tumor markers in multiple myeloma," *Cancer Detect. Prev.* 20:52-56 (1996).
- Foerster et al., "Effects of thalidomide and EM12 on the synthesis of TNF- $\alpha$  in coaggregates of human monocytes and lymphocytes," *Abstract* 517 (1995).
- Friedman et al., "Introduction to clinical trials" *Fundamentals of Clinical Trials*, 3rd edition, Springer, New York, NY, Chapter 1 (1998).
- Fujita et al., "Thalidomide and its analogues inhibit lipopolysaccharide-mediated induction of cyclooxygenase-2," *Clin. Cancer Res.*, 7:3349-3355 (2001).
- Fuse et al., "Prediction of the maximal tolerated dose (MTD) and therapeutic effect of anticancer drugs in human: integration of pharmacokinetics with pharmacodynamics and toxicodynamics," *Cancer Treat. Rev.*, 21:133-157 (1995).
- Gahrton et al., "Progress in haematopoietic stem cell transplantation for multiple myeloma," *J. Intern. Med.* 248:185-201 (2000).
- Gardner et al., "Assessing the effectiveness of a computerized pharmacy system." In *Decision Support Systems in Critical Care*; Shabot et al., eds.; pp. 174-183 (1994).
- Glasmacher et al., "Oral idarubicin, dexamethasone and vincristine (VID) in the treatment of multiple myeloma," *Leukemia* 11:S22-S26 (1997).
- Grönroos et al., "A medication database—a tool for detecting drug interactions in hospital," *Eur. J. Clin. Pharmacol.* 53:13-17 (1997).
- Gupta et al., "Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications," *Leukemia*, 15(12):1950-1961 (2001).
- Hamera et al., "Alcohol, cannabis, nicotine, and caffeine use and symptom distress in Schizophrenia," *J. Nerv. Ment. Dis.* 183:559-565 (1995).
- He et al., "Synthesis of thalidomide analogs and their biological potential for treatment of graft versus host disease," 206th ACS National Meeting 0-8412-2620-2, American Chemical Society, Chicago, IL, Abstract 216 (1993).
- Heger et al., "Embryotoxic effects of thalidomide derivatives in the non-human primate callithrixjacchus. IV teratogenicity of  $\mu\text{g}/\text{kg}$  doses of the EMJ 2 enantiomers," *Teratog. Carcinog. Mutagen.* 14:115-122 (1994).
- Hideshima et al., "Novel therapies targeting the myeloma cell and its bone marrow microenvironment," *Semin. Oncol.* 28:607-612 (2001).
- Hideshima et al., "The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells," *Cancer Res.* 61:3071-3076 (2001).
- Hideshima et al., "Thalidomide (Thal) and its analogs overcome drug resistance of human multiple myeloma (MM) cells to conventional therapy," *Abstract 1313, American Society of Hematology*, Dec. 1-5, 2000.
- Hideshima et al., "Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy," *Blood* 96(9):2943-2950 (2000).
- Hochster et al., "Activity and pharmacodynamics of 21-Day topotecan infusion in patients with ovarian cancer previously treated with platinum-based chemotherapy. New York Gynecologic Oncology Group," *J. Clin. Oncol.* 17:2553-2561 (1999).
- Hus et al., "Thalidomide treatment of resistant or relapsed multiple myeloma patients," *Haematologica* 86:404-408 (2001).
- Jagannath et al., "Pomalidomide (POM) with or without low-dose dexamethasone (LoDEX) in patients (Pts) with relapsed and refractory multiple myeloma (RRMM): MM-002 phase II age subgroup analysis," *J. Clin. Oncol.* 31, Abstrct # 8532, (2013).
- Jönsson, "Chemical structure and teratogenic properties. 3. A review of available data on structure-activity relationships and mechanism of action of thalidomide analogues," *Acta Pharm. Suec.* 9:521-542 (1972).

(56)

**References Cited****OTHER PUBLICATIONS**

- Jourdan et al., "Tumor necrosis factor is a survival and proliferation factor for human myeloma cells," *Eur. Cytokine Netw.* 10:65-70 (1999).
- Keravich et al., "Challenges of thalidomide distribution in a hospital setting," *Am. J. Health Syst. Pharm.* 56:1721-1725 (1999).
- Kibbe ed., *Handbook of Pharmaceutical Excipients*, 3rd edition, pp. 160-162 (2000).
- Klausner et al., "Thalidomide as an anti-TNF-alpha inhibitor: implications for clinical use," *Clin. Immunol. Immunopathol.*, 81(3):219-223 (1996).
- Klausner et al., "The effect of thalidomide on the pathogenesis of human immunodeficiency virus type 1 and M. tuberculosis infection," *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.*, 11(3):247-257 (1996).
- Knight, "Cancer patients ahead of FDA on thalidomide use," *Washington Post* Jun. 25, 2001.
- Kosten et al., "Substance abuse and Schizophrenia: Editors' Introduction," *Schizophrenia Bulletin* 23:181-186 (1997).
- Kropff et al., "Hyperfractionated cyclophosphamide in combination with pulsed dexamethasone and thalidomide (hyper-CDT) in primary refractory or relapsed multiple myeloma," *Blood*, 96(11):168a (2000).
- Kumar et al., "Thalidomide and lenalidomide in the treatment of multiple myeloma," *Eur. J. Cancer*, 42:1612-1622 (2006).
- Kyle et al., "Therapeutic application of thalidomide in multiple myeloma," *Semin. Oncol.* 28:583-587 (2001).
- Lacy et al., "Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma," *J. Clin. Oncol.* 27:5008-5014 (2009).
- Lacy et al., "Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: Comparison of 2 dosing strategies in dual-refractory disease," *Blood* 118:2970-2975 (2011).
- Langbein, "Celgene releases first data on Actimid in cancer patients," *Reuters News*, Jul. 8, 2002.
- Lee et al., "A pilot trial of hyperfractionated thoracic radiation therapy with concurrent cisplatin and oral etoposide for locally advanced inoperable non-small-cell lung cancer: a 5-year follow-up report," *Int. J. Radiat. Oncol. Biol. Phys.* 42:479-486 (1998).
- Lentzsch et al., "3-amino-phthalimido-glutarimide (S-3APG) inhibits angiogenesis and growth in drug resistant multiple myeloma (MM) in vivo," *Abstract 1976, American Society of Hematology*, 43rd Annual Meeting Orlando, Florida, Dec. 7-11, 2001.
- Lentzsch et al., "Immunomodulatory analogs of thalidomide inhibit growth of Hs sultan cells and angiogenesis in vivo," *Leukemia*, 17:41-44 (2003).
- Lentzsch et al., "Immunomodulatory derivatives (IMiDs) of thalidomide (Thal) inhibit the proliferation of multiple myeloma (MM) cell lines and block VEGF-induced activation of the MAPK-pathway," *Blood* 96:579 (Abstract# 2486) (2000).
- Lentzsch et al., "S-3-amino-phthalimido-glutarimide inhibits angiogenesis and growth of B-cell neoplasias in mice," *Cancer Research* 62:2300-2305 (2002).
- Linder et al., "Pharmacogenetics: a laboratory tool for optimizing therapeutic efficiency," *Clin. Chem.*, 43(2):254-266 (1997).
- Linnarsson, "Decision support for drug prescription integrated with computer-based patient records in primary care," *Med. Inform.* 18:131-142 (1993).
- Lipkin, "Deriving new drugs from thalidomide," *Science News* 148:171 (1995).
- Mann et al., "Passage of chemicals into human and animal semen: mechanisms and significance," *Crit. Rev. Toxicol.* 11:1-14 (1982).
- Marriott et al., "Immunotherapeutic and antitumour potential of thalidomide analogues," *Expert Opin. Biol. Ther.* 1:1-8 (2001).
- Marriott et al., "Immunotherapeutic and antitumour potential of thalidomide analogues," *Expert Opin. Biol. Ther.*, 1(4):675-682 (2001).
- Marriott et al., "Thalidomide and its analogues have distinct and opposing effects on TNF-alpha and TNFR2 during co-stimulation of both CD4+ and CD8+ T cells," *Clin. Exp. Immunol.*, 130:75-84 (2002).
- Marwick, "Thalidomide back—under strict control," *JAMA* 278:1135-1137 (1997).
- Menill, "Substance Abuse and Women on Welfare," in *National Center on Addiction and Substance Abuse at Columbia University*, Jun. 1994.
- Milner et al., "Attitudes of young adults to prenatal screening and genetic correction for human attributes and psychiatric conditions," *Am. J. Med. Genet.*, 76:111-119 (1998).
- Mitchell et al., "A pregnancy-prevention program in women of childbearing age receiving isotretinoin," *N. Engl. J. Med.* 333:101-106 (1995).
- Mitsiades et al., "Concepts in the use of TRAIL/Apo2L: An emerging biotherapy for myeloma and other neoplasias," *Expert Opin. Investig. Drugs* 10:1521-1530 (2001).
- Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications," *Blood*, 2002, 99:4525-4530, *American Society of Hematology*.
- Montero et al., "Economic study of neutropenia induced by myelotoxic chemotherapy," *Pharm. World Sci.* 16:187-192 (1994).
- Moreira et al., "Thalidomide exerts its inhibitory action on tumor necrosis factor  $\alpha$  by enhancing mRNA degradation," *J. Exp. Med.*, 177(6):1675-1680 (1993).
- Morgan et al., "Lenalidomide (Revlimid), in combination with cyclophosphamide and dexamethasone (RCD), is an effective and tolerated regimen for myeloma patients," *Br. J. Haematol.* 137:268-269 (2007).
- Muller et al., "Amino-substituted thalidomide analogs: potent inhibitors of TNF-alpha production," *Bioorg. Med. Chem. Lett.*, 9(11):1625-1630 (1999).
- Muller, Thalidomide: From tragedy to new drug discovery, *Chemtech* 27:21-25 (1997).
- Mundt, "Interactive voice response systems in clinical research and treatment," *Psychiatr. Serv.* 48:611-612, 623 (1997).
- National Cancer Institute, *Common Toxicity Criteria Manual*, Ver. 2.0, Jun. 1, 1999.
- NCT00480363: "QUIREDEX: Revlimid (lenalidomide) and dexamethasone (ReDex) treatment versus observation in patients with smoldering multiple myeloma with high risk of progression (QUIREDEX)," (2013).
- Noguera et al., "Effect of thalidomide and some derivatives on the adhesion of lymphocytes to endothelial cells," *Abstract 518* (1995).
- Olson et al., "Thalidomide (N-phthaloylglutamimide) in the treatment of advanced cancer," *Clin. Pharm. Ther.*, 6(3):292-297 (1965).
- Palumbo et al., "Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma," *Haematologica* 86:399-403 (2001).
- Pastuszak et al., "Use of the retinoid pregnancy prevention program in Canada: Patterns of contraception use in women treated with isotretinoin and etretinate," *Reprod. Toxicol.* 8:63-68 (1994).
- Pestotnik et al., "Therapeutic antibiotic monitoring: Surveillance using a computerized expert system," *Am. J. Med.* 88:43-48 (1990).
- Peterson et al., "Expanding the scope of crystal form evaluation in pharmaceutical science," *J. Pharm. Pharmaceut. Sci.*, 9(3):317-326 (2006).
- Piper et al., "Anti-inflammatory immunosuppressive thalidomide analogs. Screening," *Int. J. Leprosy* 49:511-512 (1981).
- Powell et al., "Guideline for the clinical use and dispensing of thalidomide," *Postgrad. Med. J.* 70:901-904 (1994).
- Pro et al., "Phase II study of thalidomide in patients with recurrent Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL)," *Blood* 98:246b (Abstract# 4712) (2001).
- Querfeld et al., "Preliminary results of a phase II study of CC-5013 (lenalidomide, revlimid®) in patients with cutaneous T-cell lymphoma," *Blood* 106:936a-937a (2005).
- Raje et al., "Thalidomide and immunomodulatory drugs as cancer therapy," *Curr. Opin. Oncol.*, 14:635-640 (2002).
- Raje et al., "Thalidomide—a revival story," *N. Engl. J. Med.* 341(21):1606-1609 (1999).

(56)

**References Cited****OTHER PUBLICATIONS**

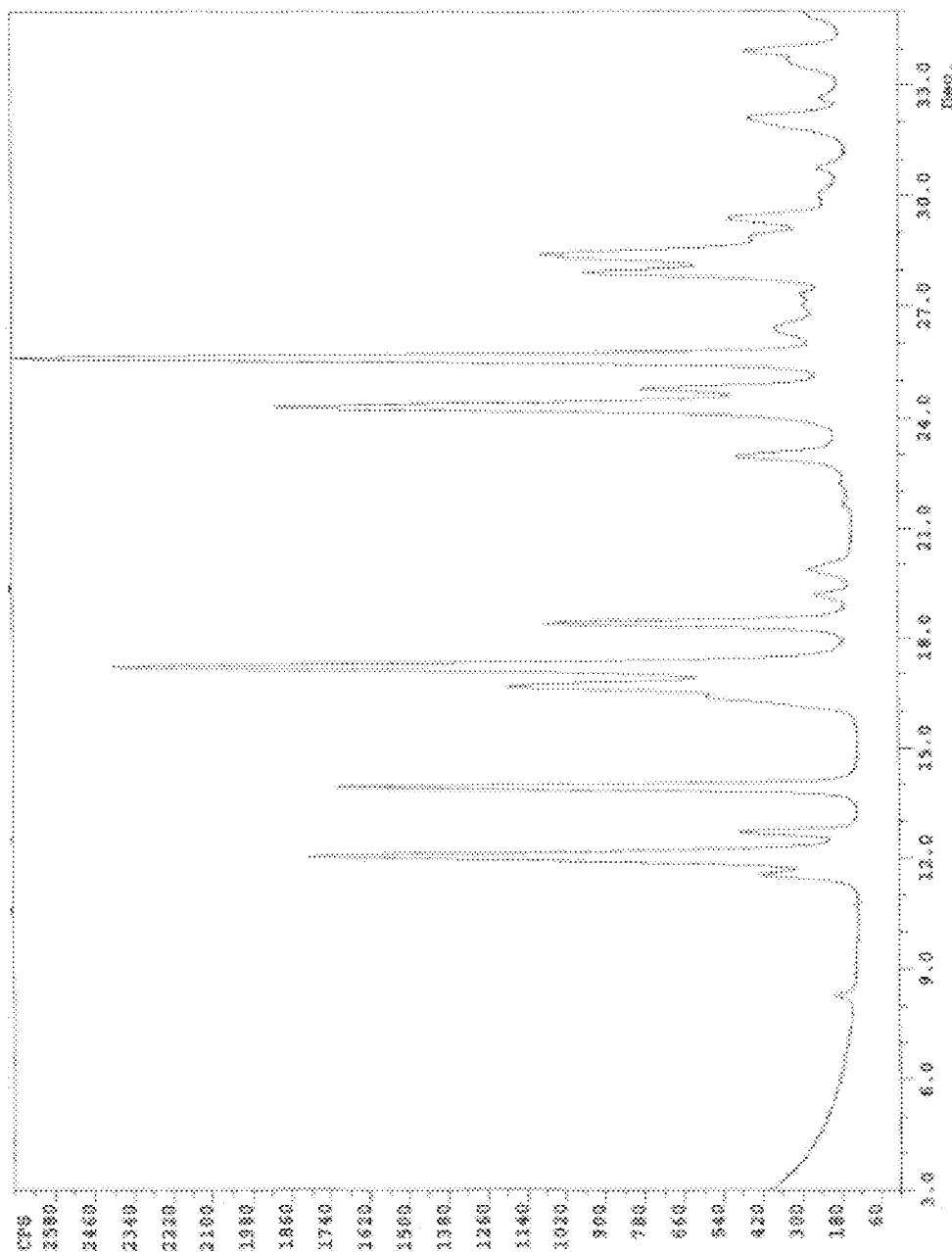
- Rajkumar et al., "Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial," *Lancet* 11:29-37 (2010).
- Rajkumar et al., "Phase III trial of lenalidomide plus highdose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): A trial coordinated by the Eastern Cooperative Oncology Group," *J. Clin. Oncol.* 25:18S (2007).
- Rajkumar et al., "Thalidomide plus dexamethasone (Thal/Dex) and thalidomide alone (Thal) as first line therapy for newly diagnosed myeloma (MM)," *Blood* 96(Suppl.):168a (2000).
- Rajkumar et al., "Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma," *Blood*, 106(13):4050-4053 (2005).
- Rajkumar et al., "Thalidomide in the treatment of plasma cell malignancies," *J. Clin. Oncol.* 19:3593-3595 (2001).
- Rajkumar, "Thalidomide in multiple myeloma," *Oncology* 14:11-16 (2000).
- Ratain, "Pharmacology of Cancer Chemotherapy." In *Cancer: Principles & Practice of Oncology*, pp. 335-459 (2001).
- Rautio et al., "Prodrugs: design and clinical applications," *Nat. Rev. Drug Discov.*, 7:255-270 (2008).
- Reiman et al., "Meeting synopsis, VIII International Myeloma Workshop, Banff Springs Hotel, Banff, Alberta, Canada, May 4-8, 2001," *Eur. J. Haematol.* 67:199-202 (2001).
- Ribatti et al., "Angiogenesis spectrum in the stroma of B-cell non-Hodgkin's lymphomas. An immunohistochemical and ultrastructural study," *Eur. J. Haematol.* 56:45-53 (1996).
- Richardson et al., "A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma," *Blood* 108:3458-3464 (2006).
- Richardson et al., "Thalidomide in multiple Myeloma," *Biomed. Pharmacother.* 56:115-128 (2002).
- Richardson et al., "Thalidomide: Emerging role in cancer medicine," *Ann. Rev. Med.* 53:629-657 (2002).
- Richardson et al., "A multi-center, randomized, phase II study to evaluate the efficacy and safety of two CDC-5013 dose regimens when used alone or in combination with dexamethasone (Dex) for the treatment of relapsed or refractory multiple myeloma (MM)," *Abstract 386, Blood*, 100(11 Part 1):104a (2002).
- Richardson et al., "A phase I study of oral CC5013, an immunomodulatory thalidomide (Thal) derivative, in patients with relapsed and refractory multiple myeloma (MM)," *Blood* 98:775a (2001).
- Richardson et al., "A phase 1/2 multi-center, randomized, open label dose escalation study to determine the maximum tolerated dose (MTD), safety, and efficacy of pomalidomide (POM) alone or in combination with low-dose dexamethasone (DEX) in patients (PTS) with relapsed and refractory multiple myeloma (RRMM) who have received prior treatment (TX) that includes lenalidomide (LEN) and bortezomib (BORT)," *Haematologica*, 96:S31 (2011).
- Richardson et al., "A phase I study of the safety and efficacy of CC5013 treatment for patients with relapsed multiple myeloma: Preliminary results," VIII the International Myeloma Workshop, Banff, Alberta, Canada, May 4-8, 2001; Abstract #P230.
- Richardson et al., "Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma," *Blood* 100:3063-3067 (2002).
- Robert et al., "Phase I and pharmacologic study of 7- and 21-day continuous etoposide infusion in patients with advanced cancer," *Cancer Chemother. Pharmacol.* 38:459-465 (1996).
- Rubinstein et al., "Phase I clinical trial design," Biometric Research Branch, National Cancer Institute (2003).
- Samlowski et al., "Evaluation of gemcitabine in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: A southwest oncology group phase II study," *Invest. New Drugs* 19:311-315 (2001).
- Sampaio et al., "Prolonged treatment with recombinant interferon gamma induces erythema nodosum leprosum in lepromatous leprosy patients," *J. Exp. Med.* 175:1729-1737 (1992).
- Sampaio et al., "Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes," *J. Exp. Med.* 173:699-703 (1991).
- Schey et al., "Phase I Study of an Immunomodulatory Thalidomide Analog, CC-4047, in Relapsed or Refractory Multiple Myeloma," *J. Clin. Oncol.* 22(16):3269-3276 (2004).
- Schey et al., "Pomalidomide therapy for myeloma," *Expert Opin. Invest. Drugs* 20:691-700 (2011).
- Schey et al., "A phase I study of an immunomodulatory thalidomide analogue (CC4047) in relapse/refractory multiple myeloma," *International Society for Experimental Hematology, Abstract #248*, (2002).
- Schey, "Thalidomide in the management of multiple myeloma," *Hematology* 7:291-299 (2002).
- Schlossman et al., "Bone marrow transplatation in multiple myeloma," *Curr. Opin. Oncol.* 11:102-108 (1999).
- Seppa, "Thalidomide combats myeloma blood cancer," *Science News* 156:326 (1999).
- Shaughnessy et al., "Global gene expression analysis shows loss of c-myc and IL-6 receptor gene mRNA after exposure of myeloma to thalidomide and IMiD," *Abstract 2485, American Society of Hematology, 42<sup>nd</sup> Annual Meeting San Francisco, CA, Dec. 1-5, 2000.*
- Shinn et al., "Development of a computerized drug interaction database (MEDICOM) for use in a patient specific environment," *Drug Inf. J.* 17:205-210 (1983).
- Siegel et al., "Long-term safety and efficacy of pomalidomide (POM) with or without low-dose dexamethasone (LoDEX) in relapsed and refractory multiple myeloma (RRMM) patients enrolled in the MM-002 phase II trial," *J. Clin. Oncol.* 31, 2013 (Abstract No. 8588).
- Singhal et al., "Antitumor activity of thalidomide in refractory multiple myeloma," *N. Engl. J. Med.*, 341(21):1565-1571 (1999).
- Smith et al., "Design and results of phase I cancer clinical trials: three-year experience at M.D. Anderson Cancer Center," *J. Clin. Oncol.*, 14:287-295 (1996).
- Smith, R. et al., "Studies on the Relationship Between the Chemical Structure and Embryotoxic Activity of Thalidomide and Related Compounds," in *A Symposium on Embryopathic Activity of Drugs*, J. & A. Churchill Ltd., Session 6, pp. 194-209 (1965).
- Sorbera et al., "CC-5013. Treatment of multiple myeloma. Treatment of Melanoma. Treatment of myelodysplastic syndrome. Angiogenesis inhibitor. TNF- $\alpha$  production inhibitor," *Drugs of the Future*, 28(5):425-431 (2003).
- Soyka et al., "Prevalence of alcohol and drug abuse in schizophrenic inpatients," *Eur. Arch. Psychiatry Clin. Neurosci.* 242:362-372 (1993).
- Srkalovic et al. "Use of melphalan, thalidomide, and dexamethasone in treatment of refractory and relapsed multiple myeloma," *Med. Oncol.* 19:219-226 (2002).
- Steed, "The role of co-crystals in pharmaceutical design," *Trends in Pharmacol. Sci.*, 34(3):185-193 (2013).
- Steiner et al., "The assessment of refill compliance using pharmacy records: methods, validity, and applications," *J. Clin. Epidemiol.* 50:105-116 (1997).
- Stirling et al., "Thalidomide. A surprising recovery," *J. Am. Pharm. Assoc.* NS37:306-313 (1997).
- Stirling, "Thalidomide: A novel template for anticancer drugs," *Seminars Oncology* 28:602-606 (2001).
- Szelényi et al., "Cyclophosphamide, adriamycin and dexamethasone (CAD) is a highly effective therapy for patients with advanced multiple myeloma," *Ann. Oncol.* 12:105-108 (2001).
- Thalomid™ (thalidomide) Capsules Revised Package Insert (Jul. 15, 1998).
- The Comprehensive Guide to Banff, Understanding the VIIth International Myeloma Workshop published by the International Myeloma Foundation (2001).
- Thomas et al., "Current role of thalidomide in cancer treatment," *Curr. Opin. Oncol.* 12:564-573 (2000).
- Transcript of the Forty-Seventh Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (Sep. 4, 1997).

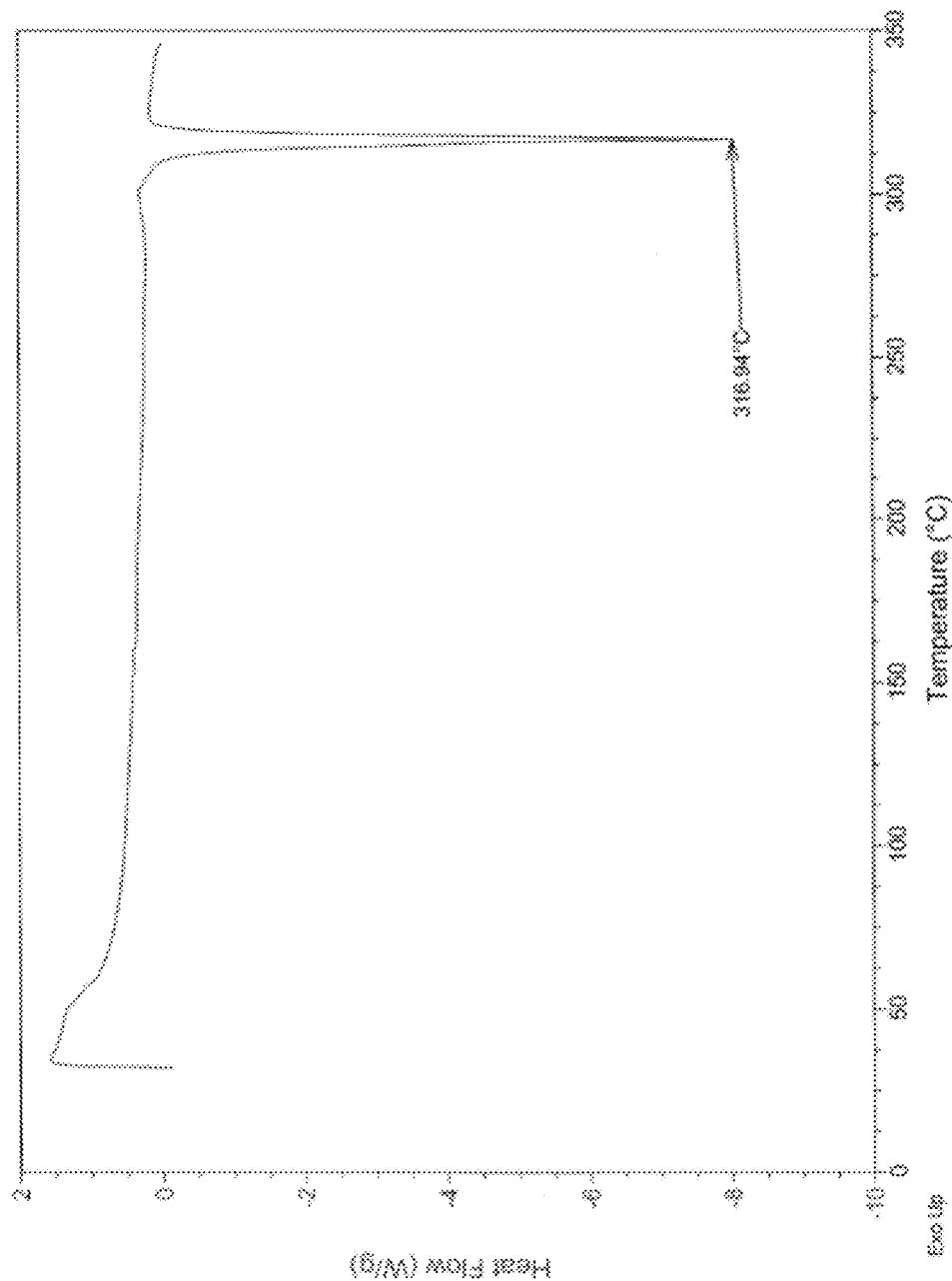
(56)

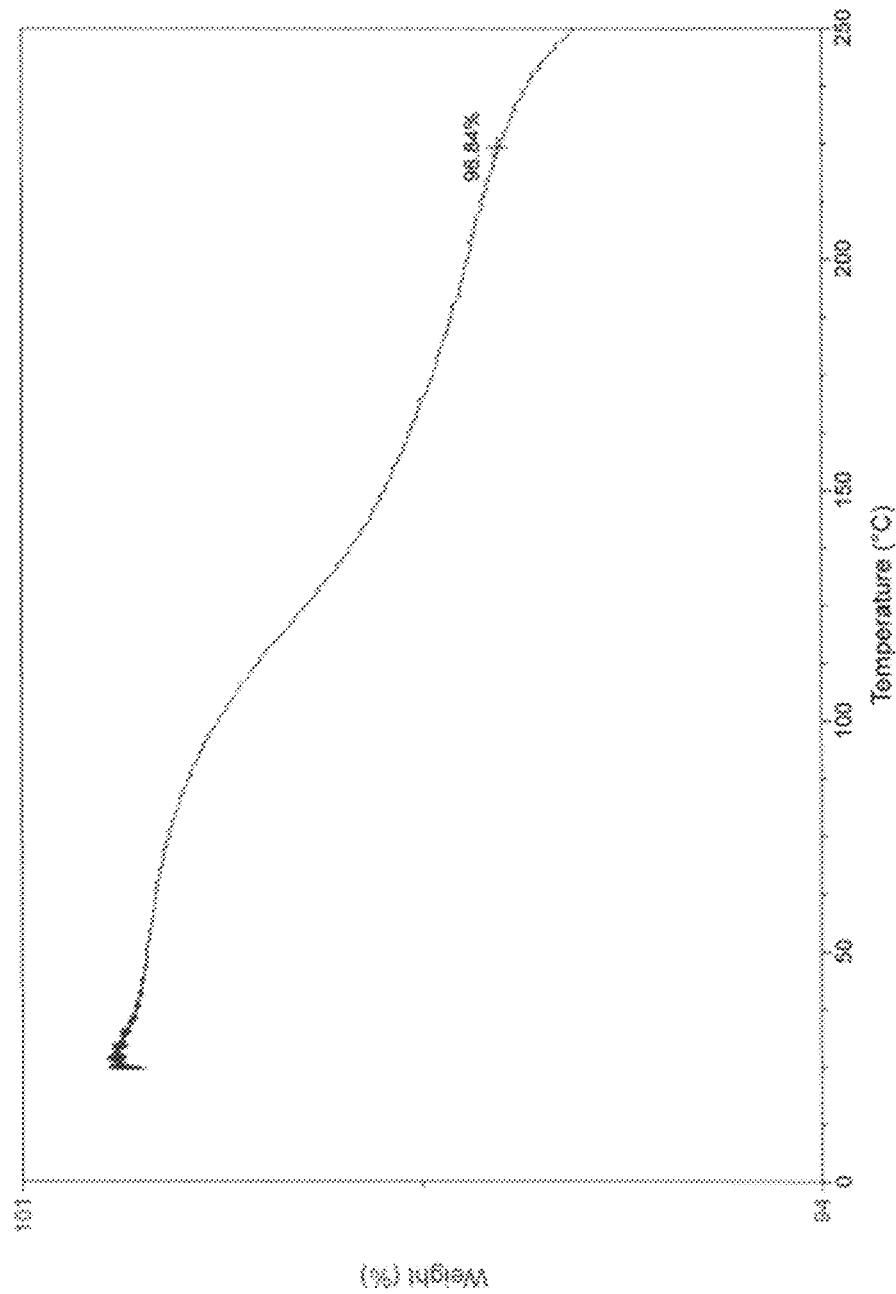
**References Cited****OTHER PUBLICATIONS**

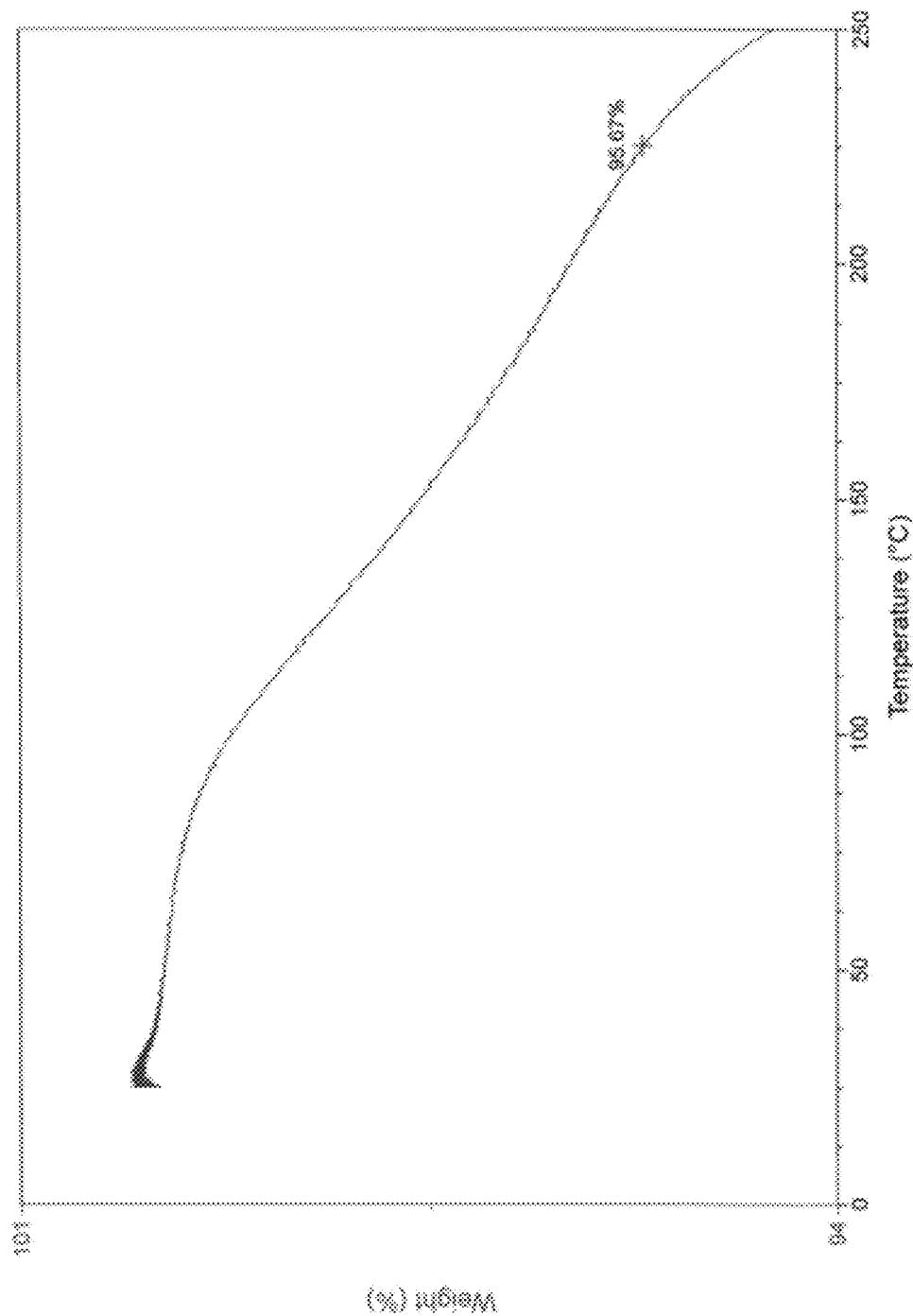
- Transcript of the Forty-Seventh Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (Sep. 5, 1997).
- Tseng et al., "Rediscovering thalidomide: a review of its mechanism of action, side effects, and potential uses," *J. Am. Acad. Dermatol.* 35:969-979 (1996).
- Tsenova et al., "Use of IMiD3, a thalidomide analog, as an adjunct to therapy for experimental tuberculous meningitis," *Antimicrob Agents Chemother.*, 46(6):1887-1895 (2002).
- Vacca et al., "Angiogenesis in B cell lymphoproliferative diseases. Biological and clinical studies," *Leuk. Lymphoma* 20:27-38 (1995).
- Vanchieri, "Preparing for thalidomide's comeback," *Annals Internal Med.*, 127(10):951-952 (1997).
- Verma, "Gallic acid: molecular rival of cancer," *Environ. Toxicol. Pharmacol.*, 35(3):473-485 (2013).
- Vij et al., "Pomalidomide (POM) with Low-Dose Dexamethasone (LoDex) in Patients with Relapsed and Refractory Multiple Myeloma (RRMM): Outcomes Based on Prior Treatment Exposure," presented at 54th ASH Annual Meeting and Exposition, Atlanta, Georgia, Dec. 8-11, 2012, Abstract #4070.
- Vippagunta et al., "Crystalline solids," *Adv. Drug Deliv. Rev.*, 48(1):3-26 (2001).
- Vogelsang et al., "Thalidomide for the treatment of chronic graft-versus-host disease," *N. Engl. J. Med.* 326:1055-1058 (1992).
- Weber et al., "Thalidomide alone or with dexamethasone for multiple myeloma," *Blood* 94:604 (1999).
- Weber et al., "Thalidomide with dexamethasone of resistant multiple myeloma," *Blood* 96:167 (2000).
- Welte et al., "Influence of socially desirable responding in a study of stress and substance abuse," *Alcohol Clin. Exp. Res.* 17:758-761 (1993).
- Wilson et al., "Response to thalidomide in chemotherapy-resistant mantle cell lymphoma: a case report," *Br. J. Haematol.* 119:128-130 (2002).
- Wolf et al., "Science, medicine, and the future pharmacogenetics," *BMJ*, 320:987-990 (2000).
- Wolff ed., *Burger's Medicinal Chemistry and Drug Discovery*, 5<sup>th</sup> Edition, vol. 1, John Wiley & Sons, Inc., pp. 975-977 (1995).
- Yuen et al., "Phase I study of an antisense oligonucleotide to protein kinase C- $\alpha$  (ISIS 3521/CGP 64128A) in patients with cancer," *Clin. Cancer Res.* 5:3357-3363 (1999).
- Zangari et al., "Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide chemotherapy," *Blood* 98:1614 (2001).
- Zangari et al., Results of phase I study of CC-5013 for the treatment of multiple myeloma (MM) patients who relapse after high dose chemotherapy (HDT), *Blood* 98(11), Abstract# 3226 (2001).
- Zangari et al., "Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy," *Blood*, 100:1168-1171 (2002).
- Zeldis et al., "S.T.E.P.S.: A comprehensive program for controlling and monitoring access to thalidomide," *Clin. Ther.* 21:319-330 (1999).

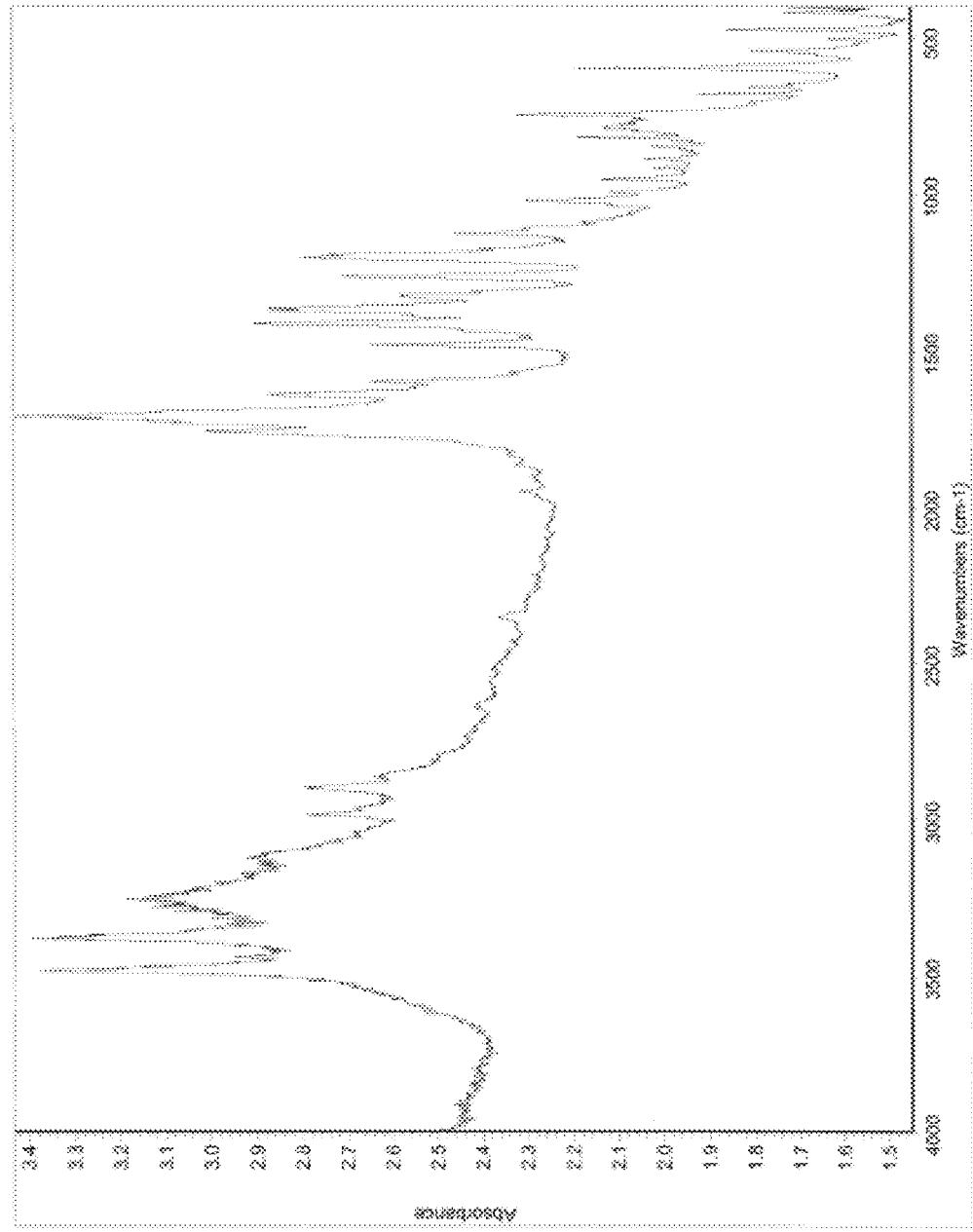
\* cited by examiner

**FIGURE 1**

**FIGURE 2**

**FIGURE 3**

**FIGURE 4**

**FIGURE 5**

## 1

**CRYSTALLINE  
4-AMINO-2-(2,6-DIOXOPIPERIDINE-  
3-YL)ISOINDOLINE-1,3-DIONE  
HEMIHYDRATE, COMPOSITIONS AND  
METHODS OF USE THEREOF**

This application claims priority to U.S. Provisional application No. 62/562,302, filed Sep. 22, 2017, the entirety of which is incorporated herein by reference.

## FIELD

Provided herein is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate. Pharmaceutical compositions comprising such solid and methods of use for treating, preventing, and managing various disorders are also provided herein.

## BACKGROUND

Many compounds can exist in different crystal forms, or polymorphs, which exhibit different physical, chemical, and spectroscopic properties. For example, certain polymorphs of a compound may be more readily soluble in particular solvents, may flow more readily, or may compress more easily than others. See, e.g., P. DiMartino, et al., *J. Thermal Anal.*, 48:447-458 (1997). In the case of drugs, certain solid forms may be more bioavailable than others, while others may be more stable under certain manufacturing, storage, and biological conditions.

Polymorphic forms of a compound are known in the pharmaceutical arts to affect, for example, the solubility, stability, flowability, fractability, and compressibility of the compound, as well as the safety and efficacy of drug products comprising it. See, e.g., Knapman, K. *Modern Drug Discoveries*, 2000, 53. Therefore, the discovery of new polymorphs of a drug can provide a variety of advantages.

The identification and selection of a solid form of a pharmaceutical compound are complex, given that a change in solid form may affect a variety of physical and chemical properties, which may provide benefits or drawbacks in processing, formulation, stability, bioavailability, storage, handling (e.g., shipping), among other important pharmaceutical characteristics. Useful pharmaceutical solids include crystalline solids and amorphous solids, depending on the product and its mode of administration. Amorphous solids are characterized by a lack of long-range structural order, whereas crystalline solids are characterized by structural periodicity. The desired class of pharmaceutical solid depends upon the specific application; amorphous solids are sometimes selected on the basis of, e.g., an enhanced dissolution profile, while crystalline solids may be desirable for properties such as, e.g., physical or chemical stability.

Pomalidomide has a chemical name of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione. Pomalidomide is a compound that inhibits, for example, LPS induced monocyte TNF $\alpha$ , IL-1 $\beta$ , IL-12, IL-6, MIP-1, MCP-1, GM-CSF, G-CSF, and COX-2 production, and may be used in treating various disorders. See, e.g., U.S. Pat. Nos. 5,635,517, 6,316,471, 6,476,052, 7,393,863, 7,629,360, 7,863,297, 8,198,262, 8,673,939, 8,735,428, 8,759,375, 8,722,647, and 9,282,215. Pomalidomide has direct anti-myeloma tumoricidal and immunomodulatory activities, and inhibits stromal cell support for multiple myeloma tumor cell growth. Pomalidomide inhibits proliferation and induces apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibits the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergizes with dexamethasone in

## 2

both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhances T cell- and natural killer (NK) cell-mediated immunity, and inhibits production of pro-inflammatory cytokines (e.g., TNF- $\alpha$  and IL-6) by monocytes. Pomalidomide also inhibits angiogenesis by blocking the migration and adhesion of endothelial cells. A molecular target of pomalidomide is cereblon, a protein that forms a ubiquitin E3 ligase complex with DNA damage-binding protein (DDBA), culin 4 (CUL4) and protein Roc1. Pomalidomide binding to cereblon induces the polyubiquitination of two substrate proteins Ikaros (IKZF1) and Aiolos (IKZF3). Pomalidomide is known to have CNS penetration. Due to its diversified pharmacological properties, pomalidomide is useful in treating, preventing, and/or managing various diseases or disorders.

Pomalidomide and methods of synthesizing pomalidomide are described, e.g., in U.S. Pat. Nos. 5,635,517, 6,335,349, 6,316,471, 6,476,052, 7,041,680, 7,709,502, and 7,994,327. The chemical structure of pomalidomide has been known since at least the 1960s, but little is known regarding solid forms. An amorphous solid and one crystalline form (anhydrous) have been described in WO 2013/126326. A novel crystalline form of pomalidomide is described herein.

Pomalidomide is the active ingredient in POMALYST®, which in combination with dexamethasone was approved by the FDA in 2013 for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated a disease progression on or within 60 days of completion of the last therapy. The label for POMALYST® can be found at <http://www.pomalyst.com/?pi=yes&gclid=CMF4keDY-tMCFZOCfgods7oPsA>.

New polymorphic forms of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione can further the development of formulations for the treatment of chronic illnesses, and may yield numerous formulation, manufacturing and therapeutic benefits.

## SUMMARY

Provided herein is a crystalline form of pomalidomide. Also provided herein are pharmaceutical compositions comprising a crystalline form of pomalidomide. Further provided herein are methods of treating or preventing a variety of disease and disorders, which comprise administering to a patient a therapeutically effective amount of a crystalline form of pomalidomide. Also provided herein are methods of treating multiple myeloma, optionally in combination with dexamethasone.

Also provided herein are methods of preparing, isolating, and characterizing crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate provided herein.

Also provided herein are pharmaceutical compositions containing crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate provided herein.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 provides a representative X-ray powder diffraction (XRPD) pattern of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate.

FIG. 2 provides a representative differential scanning calorimetry (DSC) thermogram of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate.

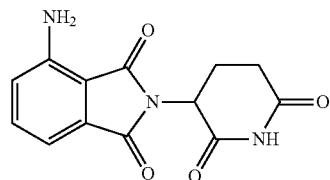
FIG. 3 provides a representative thermogravimetric analysis (TGA) thermogram of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate.

FIG. 4 provides a representative thermogravimetric analysis (TGA) thermogram of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate.

FIG. 5 provides a representative infrared (IR) spectrum of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate.

## DEFINITIONS

As used herein, and unless otherwise specified, the compound referred to herein by the name pomalidomide or 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione, corresponds to a compound of Formula (I), depicted below.



(I)

Pomalidomide can be obtained via standard, synthetic methods (see e.g., U.S. Pat. No. 5,635,517).

Unless otherwise specified, the term "crystalline" and related terms used herein, when used to describe a substance, component, product, or form, mean that the substance, component, product, or form is substantially crystalline, for example, as determined by X-ray diffraction. (see, e.g., *Remington's Pharmaceutical Sciences*, 20<sup>th</sup> ed., Lippincott Williams & Wilkins, Philadelphia Pa., 173 (2000); *The United States Pharmacopeia*, 37<sup>th</sup> ed., 503-509 (2014)).

As used herein, and unless otherwise specified, the terms "about" and "approximately," when used in connection with doses, amounts, or weight percents of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by one of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. In certain embodiments, the terms "about" and "approximately," when used in this context, contemplate a dose, amount, or weight percent within 30%, within 20%, within 15%, within 10%, or within 5%, of the specified dose, amount, or weight percent.

As used herein, and unless otherwise specified, the terms "about" and "approximately," when used in connection with a numeric value or range of values which is provided to characterize a particular solid form, e.g., a specific temperature or temperature range, such as, for example, that describes a melting, dehydration, desolvation, or glass transition temperature; a mass change, such as, for example, a mass change as a function of temperature or humidity; a solvent or water content, in terms of, for example, mass or a percentage; or a peak position, such as, for example, in analysis by, for example, IR or Raman spectroscopy or XRPD; indicate that the value or range of values may deviate to an extent deemed reasonable to one of ordinary skill in the art while still describing the solid form. Techniques for characterizing crystal forms and amorphous forms include, but are not limited to, thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC),

X-ray powder diffractometry (XRPD), single-crystal X-ray diffractometry, vibrational spectroscopy, e.g., infrared (IR) and Raman spectroscopy, solid-state and solution nuclear magnetic resonance (NMR) spectroscopy, optical microscopy, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography and quantitative analysis, particle size analysis (PSA), surface area analysis, solubility studies, and dissolution studies. In certain embodiments, the terms "about" and "approximately,"

- 10 when used in this context, indicate that the numeric value or range of values may vary within 30%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1.5%, 1%, 0.5%, or 0.25% of the recited value or range of values. In the context of molar ratios, "about" and "approximately" indicate that the numeric value or range of values may vary within 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1.5%, 1%, 0.5%, or 0.25% of the recited value or range of values. It should be understood that the numerical values of the peaks of an X-ray powder diffraction pattern may vary from one
- 15 machine to another, or from one sample to another, and so the values quoted are not to be construed as absolute, but with an allowable variability, such as  $\pm 0.2$  degrees two theta ( $^{\circ}2\theta$ ), or more. For example, in some embodiments, the value of an XRPD peak position may vary by up to  $\pm 0.2$  degrees 20 while still describing the particular XRPD peak.

As used herein, and unless otherwise specified, a solid form that is "substantially physically pure" is substantially free from other solid forms. In certain embodiments, a crystal form that is substantially physically pure contains less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.05%, or 0.01% of one or more other solid forms on a weight basis. The detection of other solid forms can be accomplished by any method apparent to a person of ordinary skill in the art, including, but not limited to, diffraction analysis, thermal analysis, elemental combustion analysis and/or spectroscopic analysis.

As used herein, and unless otherwise specified, a solid form that is "substantially chemically pure" is substantially free from other chemical compounds (i.e., chemical impurities). In certain embodiments, a solid form that is substantially chemically pure contains less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.05%, or 0.01% of one or more other chemical compounds on a weight basis. The detection of other chemical compounds can be accomplished by any method apparent to a person of ordinary skill in the art, including, but not limited to, methods of chemical analysis, such as, e.g., mass spectrometry analysis, spectroscopic analysis, thermal analysis, elemental combustion analysis and/or chromatographic analysis.

As used herein, and unless otherwise indicated, a chemical compound, solid form, or composition that is "substantially free" of another chemical compound, solid form, or composition means that the compound, solid form, or composition contains, in certain embodiments, less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2% 0.1%, 0.05%, or 0.01% by weight of the other compound, solid form, or composition.

Unless otherwise specified, the terms "solvate" and "solvated," as used herein, refer to a solid form of a substance which contains solvent. The terms "hydrate" and "hydrated" refer to a solvate wherein the solvent is water. The term "hemihydrate" refers to a hydrate containing approximately one mole of water per two moles of compound.

As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" refer to the eradication or amelioration of a disease or disorder, or of one or more symptoms associated with the disease or disorder. In certain embodiments, the terms refer to minimizing the spread or worsening of the disease or disorder resulting from the administration of one or more prophylactic or therapeutic agents to a subject with such a disease or disorder. In some embodiments, the terms refer to the administration of a compound provided herein, with or without other additional active agent, after the onset of symptoms of a particular disease.

Unless otherwise specified, the term "composition" as used herein is intended to encompass a product comprising the specified ingredient(s) (and in the specified amount(s), if indicated), as well as any product which results, directly or indirectly, from combination of the specified ingredient(s) in the specified amount(s). By "pharmaceutically acceptable," it is meant a diluent, excipient, or carrier in a formulation must be compatible with the other ingredient(s) of the formulation and not deleterious to the recipient thereof.

Unless otherwise specified, the term "subject" is defined herein to include animals, such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, and the like. In specific embodiments, the subject is a human.

Unless otherwise specified, to the extent that there is a discrepancy between a depicted chemical structure of a compound provided herein and a chemical name of a compound provided herein, the chemical structure shall control.

#### DETAILED DESCRIPTION

Crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate can be prepared by the methods described herein, including the methods described in the Example below, or by techniques known in the art, including heating, cooling, freeze drying, lyophilization, quench cooling the melt, rapid solvent evaporation, slow solvent evaporation, solvent recrystallization, antisolvent addition, slurry recrystallization, crystallization from the melt, desolvation, recrystallization in confined spaces such as, e.g., in nanopores or capillaries, recrystallization on surfaces or templates such as, e.g., on polymers, recrystallization in the presence of additives, such as, e.g., co-crystal counter-molecules, desolvation, dehydration, rapid cooling, slow cooling, exposure to solvent and/or water, drying, including, e.g., vacuum drying, vapor diffusion, sublimation, grinding (including, e.g., cryo-grinding, solvent-drop grinding or liquid assisted grinding), microwave-induced precipitation, sonication-induced precipitation, laser-induced precipitation and precipitation from a supercritical fluid. The particle size of the resulting solid forms, which can vary, e.g., from nanometer dimensions to millimeter dimensions, can be controlled, e.g., by varying crystallization conditions, such as, e.g., the rate of crystallization and/or the crystallization solvent system, or by particle-size reduction techniques, e.g., grinding, milling, micronizing or sonication.

While not intending to be bound by any particular theory, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate is characterized by physical properties, e.g., stability, solubility and dissolution rate, appropriate for pharmaceutical and therapeutic dosage forms. Moreover, while not wishing to be bound by any particular theory, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate is character-

ized by physical properties (e.g., density, compressibility, hardness, morphology, cleavage, stickiness, solubility, water uptake, electrical properties, thermal behavior, solid-state reactivity, physical stability, and chemical stability) affecting particular processes (e.g., yield, filtration, washing, drying, milling, mixing, tableting, flowability, dissolution, formulation, and lyophilization) which make certain solid forms suitable for the manufacture of a solid dosage form. Such properties can be determined using particular analytical chemical techniques, including solid-state analytical techniques (e.g., X-ray diffraction, microscopy, spectroscopy and thermal analysis), as described herein and known in the art.

Certain embodiments herein provide compositions comprising crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate. Certain embodiments provide compositions of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate in combination with other active ingredients. Certain embodiments provide methods of using these compositions in the treatment, prevention or management of diseases and disorders including, but not limited to, the diseases and disorders provided herein.

Certain embodiments herein provide crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate can be obtained from a 12:1 THF/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate can be obtained from a 1:1 ethanol/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate can be obtained from a 2:4:2 ethanol/THF/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate can be obtained from a 5:1 ethanol/THF mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate can be obtained from a 1:1 1,4-dioxane/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate can be obtained from a 4:5 1,4-dioxane/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate can be obtained from a 3:1 1,4-dioxane/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate can be obtained from a 6:1 THF/water mixture.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate.

In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate may be characterized by X-ray powder diffraction analysis.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having an X-ray powder diffraction pattern comprising peaks at 12.0, 17.2, and 25.6 degrees  $2\theta \pm 0.2$  degrees  $2\theta$ .

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate wherein the X-ray powder diffraction pattern further comprises peaks at 13.9, 16.7, and 24.3 degrees  $2\theta \pm 0.2$  degrees  $2\theta$ .

In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate is characterized by XRPD peaks located at one, two, three, four,

five, six, seven, eight, nine, ten, eleven or twelve of the following approximate positions: 8.3, 11.6, 12.0, 12.7, 13.9, 16.4, 16.7, 17.2, 18.4, 19.2, 19.9, 22.9, 24.3, 24.8, 25.6, 26.4, 27.9, 28.4, 28.9, 29.4, 30.8, 32.6, and 33.9 degrees 20. In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate is characterized by an XRPD pattern which matches the pattern exhibited in FIG. 1. In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate is characterized by an XRPD pattern having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 peaks matching peaks in the representative XRPD pattern provided herein.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having an X-ray powder diffraction pattern corresponding to the representative X-ray powder diffraction patterns depicted in FIG. 1.

In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate may be characterized by thermal analysis.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having a differential scanning calorimetry thermogram comprising an endotherm with a maximum at about 317° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having a differential scanning calorimetry thermogram corresponding to the representative differential scanning calorimetry thermograms depicted in FIG. 2.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having approximately 3.2% of water by mass. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having approximately 2.8% of water by mass. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having approximately 2.9% of water by mass. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having approximately 3.0% of water by mass. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having approximately 3.3% of water by mass. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having approximately 3.6% of water by mass. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having approximately 3.7% of water by mass. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having approximately 3.8% of water by mass.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having a thermogravimetric analysis thermogram comprising a weight loss of between about 3.2% and about 4.3% when heated from about 30° C. to about 225° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having a thermogravimetric analysis thermogram comprising a weight loss of between about 2.8% and about 4.3% when heated from about 30° C. to about 225° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihy-

drate having a thermogravimetric analysis thermogram comprising a weight loss of about 3.2% when heated from about 30° C. to about 225° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 4.3% when heated from about 30° C. to about 225° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having a thermogravimetric analysis thermogram corresponding to the representative thermogravimetric analysis thermogram depicted in FIG. 3.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having a thermogravimetric analysis thermogram corresponding to the representative thermogravimetric analysis thermogram depicted in FIG. 4.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate having an infrared spectrum corresponding to the representative infrared spectrum depicted in FIG. 5.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate which is substantially physically pure.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate which is substantially chemically pure.

In one embodiment, provided is a pharmaceutical composition comprising a crystal form of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate.

#### Pharmaceutical Compositions

Pharmaceutical compositions and single unit dosage forms comprising crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate are provided herein. Also provided herein are methods for preparing pharmaceutical compositions and single unit dosage forms comprising crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate. For example, in certain embodiments, individual dosage forms comprising crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate provided herein or prepared using crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate provided herein may be suitable for oral, mucosal (including rectal, nasal, or vaginal), parenteral (including subcutaneous, intramuscular, bolus injection, intraarterial, or intravenous), sublingual, transdermal, buccal, or topical administration.

In certain embodiments, pharmaceutical compositions and dosage forms provided herein comprise crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate. Certain embodiments herein provide pharmaceutical compositions and dosage forms comprising a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate, wherein the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate is substantially pure. Certain embodiments herein provide pharmaceutical compositions and dosage forms comprising a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate as provided herein, which is substantially free of other crystalline solid forms of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione and/or amorphous solid forms of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione. Pharmaceutical compo-

sitions and dosage forms provided herein typically also comprise one or more pharmaceutically acceptable excipients, diluents or carriers.

Single unit dosage forms provided herein are suitable for oral or parenteral (e.g., subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial) administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; powders and sterile solids that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

Capsules may contain a shell.

The composition, shape, and type of dosage forms provided herein will typically vary depending on their use. A parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease or disorder. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. See, e.g., *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton Pa. (1990).

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form.

In one embodiment, suitable excipients include mannitol, pregelatinized starch, and sodium stearly fumarate.

Capsule shells may contain gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, white ink, and black ink.

Capsule shells may contain gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, FD&C red 3, and white ink.

Capsule shells may contain gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, and white ink.

Capsule shells may contain gelatin, titanium dioxide, FD&C blue 1, FD&C blue 2, and white ink.

Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms provided herein lie within the range of from about 0.1 mg to about 1,000 mg per day, given as a single once-a-day dose in the morning or as divided doses throughout the day. More specifically, the daily dose may be administered twice, three times, or four times daily in equally divided doses. Specifically, a daily dose range may be from about 0.1 mg to about 500 mg per day, more specifically, between about 0.1 mg and about 200 mg per day. A daily dose range may be 1 mg, 2 mg, 3 mg, 4 mg, or 5 mg. In managing the patient, the therapy may be initiated at a lower dose, perhaps about 1 mg to about 25 mg, and increased if necessary up to about 200 mg to about 1,000 mg per day as either a single dose or divided doses, depending on the patient's global response.

#### Oral Dosage Forms

Pharmaceutical compositions provided herein that are suitable for oral administration can be presented as discrete

dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton Pa. (1990).

Typical oral dosage forms provided herein are prepared by combining the active ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrose, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101™, AVICEL-PH-103™, AVICEL RC-581™, AVICEL-PH-105™ (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, Pa.), and mixtures thereof. A specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVI-

**11**

CEL RC-58<sup>TM</sup>. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103<sup>TM</sup> and Starch 1500 LM<sup>TM</sup>.

Disintegrants are used in the compositions provided herein to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, specifically from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms provided herein include, but are not limited to, agar-agar, alginic acid, calcium carbonate, micro-crystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage forms provided herein include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200<sup>TM</sup>, manufactured by W.R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, Tex.), CAB-O-SIL<sup>TM</sup> (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass.), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about one weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

## Parenteral Dosage Forms

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial injection. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms provided herein are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous

**12**

vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms provided herein.

## Examples

<sup>10</sup> Preparation of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate: 10 mg of pomalidomide Form A (anhydrate) was placed in a 50 mL round bottom flask with 24 mL THF and 2 mL water. The flask was then placed on a rotary evaporator with the bath temperature at 80° C. All of the pomalidomide dissolved. An aspirator vacuum was then applied and the yellow crystalline solid was obtained within about two minutes. The solid was further air dried by exposure for 2 hours.

<sup>20</sup> Karl-Fischer titration revealed the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate contained 3.0% water.

<sup>25</sup> XRPD data for the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate is shown below in Table 1.

Scan Type: Normal

Start Angle: 3 deg

Stop Angle: 35 deg.

Num Points: 1601

<sup>30</sup> Step Size: 0.02 deg.

Datafile Res: 1600

Scan Rate: 0.001000

Scan Mode: Step

Wavelength: 1.540562 Å

<sup>35</sup> Tube divergent 2.00 mm

Tube scatter 4.00 mm

Detector scatter 0.50 mm

Detector reflection 0.30 mm

TABLE 1

XRPD data for crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate.				
45	Position		Intensity	Rel. Int.
	(Deg)	(Dsp.)	(cps)	(%)
	8.3	10.6104	132.10	6.84
	11.6	7.6238	292.59	15.14
	12.0	7.3394	1210.88	62.66
	12.7	6.9703	332.80	17.22
	13.9	6.3490	1175.57	60.83
	16.4	5.4082	399.07	20.65
	16.7	5.3167	810.58	41.95
	17.2	5.1523	1661.93	86.00
	18.4	4.8287	741.18	38.35
	19.2	4.6215	171.60	8.88
	19.9	4.4576	185.19	9.58
	22.9	3.8721	333.43	17.25
	24.3	3.6631	1353.18	70.02
	24.8	3.5919	555.83	28.76
	25.6	3.4773	1932.47	100.00
	26.4	3.3782	256.79	13.29
	27.9	3.1938	672.83	34.82
	28.4	3.1403	729.08	37.73
	28.9	3.0893	316.05	16.35
	29.4	3.0378	353.07	18.27
	30.8	2.9039	167.90	8.69
	32.6	2.7471	171.60	8.88
	33.9	2.6411	327.40	16.94

## 13

Additional experiments to prepare crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate are listed below.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 ethanol:water solution at 80° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator and dried at 100° C. for 2 hours. The resulting solid was found to have 3.0% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 2:4:2 ethanol:THF:water solution at 95° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator and further air dried. The resulting solid was found to have 3.0% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 5:1 95% ethanol:THF solution at 90° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator and vacuum dried at rt for 1 hour. The resulting solid was found to have 3.1% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 1,4-dioxane:water solution at 75° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator, triturated with water and air dried. The resulting solid was found to have 3.7% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 4:5 1,4-dioxane:water solution at 85° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator, triturated with water and air dried. The resulting solid was found to have 2.8% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 4:1 1,4-dioxane:water solution at 85° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator, triturated with water and air dried, then left open to air for 10 d. The resulting solid was found to have 3.8% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 12:1 THF:water solution at 80° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator and air dried for 3 h. The resulting solid was found to have 3.3% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 3:1 1,4-dioxane:water solution at 75° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator, triturated with water and vacuum dried. The resulting solid was found to have 3.8% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 1,4-dioxane:water solution at 80° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator, triturated with water and air dried, then vacuum dried, then heated at 100 C for 14 h. The resulting solid was found to have 3.6% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 6:1 THF:water solution at 50° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator and air dried. The resulting solid was found to have 2.9% water by TGA analysis.

## 14

Additional Experiments that did not Result in Crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate

The following unsuccessful experiments were performed by mixing in a flask Form A of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione with solvents until dissolution, then the flask was placed on a rotoevaporator (fast rotation; vacuum by water aspirator) at various bath temperatures until dryness or until apparent dryness.

Certain experiments produced an oil, which were then triturated as follows: pure HPLC grade water was added to flask containing the oil, and the flask was stirred. If a solid was formed, it was further dried.

15

TABLE 2

Conditions that did not result in a crystalline hemihydrate of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione.					
	Solvent	Co-solvent	Ratio of solvent/co-solvent	Temperature (° C.)	Notes
20	1,4-dioxane	N/A		60	
	THF	Water	10:1	60	Triturated vacuum dried
25	THF	Water	1:1	80	
	Ethanol	Water	1:1	80	100° C. for 12 hours after initial drying
	Ethanol	Water	1:1	80	Dried further for 20 min at 100° C., then 30 min at 150° C.
30	THF	Water	1:1	80	
	1,4-dioxane	Water	1:1	80	
	THF	Water	24:5	80	
	THF	Water	23:5	80	
	1,4-dioxane	Water	1:1	80	Triturated, dried at 150° C. for 1 h
35	THF	Water	95:5	65	
	Ethanol	Water	95:5	90	
	Ethanol	Water	98:2	90	
	THF	Water	9:1	85	
	Ethanol	THF/Water	2:1:2	60	
	Ethanol	THF/Water	2:1:2	95	
	Ethanol	THF/Water	1:6:1	95	
	Ethanol	THF/Water	6:4:1	95	
	Ethanol	THF/Water	1:2:1	95	
	1,4-dioxane	Water	1:1	95	Triturated
	1,4-dioxane	Water	1:1	95	Triturated, air tried, 45m in vacuo
	Ethanol	THF/Water	3:5:3	80	Air dried 3 h
	Ethanol	THF/Water	3:5:3	80	
40	Acetone	i-PrOH/Water	1:1:1	90	
	Acetone	i-PrOH/Water	1:1:1	95	Material was moist
	Acetone	i-PrOH/Water	1:1:1	95	Air dried 18 h
	Acetone	i-PrOH/Water	1:1:1	95	Air current dried 3 h
	Acetone	i-PrOH/Water	1:1:1	95	Air current dried 1 h
	Acetone	i-PrOH/Water	1:1:1	85	
	1,4-dioxane	Water	1:1	85	Material was moist
	THF	Water	1:1	80	Air dried
	THF	Water	1:1	80	Dried in vacuo for 2 h at 200° C.
	1,4-dioxane	Water	1:1	90	Triturated, dried in vacuo 16 h
45	THF	Water	4:1	95	
	THF	Water	4:1	80	
	THF	Water	4:1	65	
	1,4-dioxane	Water	1:1	95	
	1,4-dioxane	Water	4:1	80	Oil, triturated, air dried 4 h
50	THF	Water	3:1	85	Air dried 3 h
	1,4-dioxane	Water	3:1	85	Dried overnight at room temperature
	1,4-dioxane	Water	3:1	85	Triturated, dried
	THF	Water	4:1	80	Air dried 1 h
	THF	Water	12:1	70	Air dried
	THF	Water	6:1	80	Air dried
55	MeCN	Water	2:1	80	Material was moist

15

TABLE 2-continued

Conditions that did not result in a crystalline hemihydrate of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione.				
Solvent	Co-solvent	Ratio of solvent/ co-solvent	Temper- ature (° C.)	Notes
MeCN	Water	2:1	80	Dried overnight
MeCN	Water	2:1	90	Air dried
1,4-dioxane	Ethanol/THF/ Water	1:1:1:2	85	Air dried
1,4-dioxane	THF/Water	6:6:1	50	Material was moist
1,4-dioxane	THF/Water	6:6:1	50	Dried at 90° C. in vacuo
1,4-dioxane	THF/Water	6:6:1	50	Air dried
Acetone	THF/Water	10:3:3	90	Air dried
THF	Water	25:1	60	Air dried
THF	Water	25:1	60	
THF	Water	20:1	70	
THF	Water	4:1	80	Air dry
THF	Water	10:1	65	Air dry
THF	Water	10:1	75	
Acetone	THF/Water	10:1:1	60	Air dry
1,4-dioxane	Water	3:1	85	Triturated
1,4-dioxane	Water	12:1	60	Triturated

## Characterization Methodology

Samples generated as described in the solid form screen were typically analyzed by X-Ray Powder Diffraction (XRPD). XRPD was conducted on a Scintag X2 X-ray powder diffractometer using Cu K $\alpha$  radiation at 1.54 Å. In general, positions of XRPD peaks are expected to individually vary on a measurement-by-measurement basis by about  $\pm 0.2^\circ$ . In general, as understood in the art, two XRPD patterns match one another if the characteristic peaks of the first pattern are located at approximately the same positions as the characteristic peaks of the second pattern. As understood in the art, determining whether two XRPD patterns match or whether individual peaks in two XRPD patterns match may require consideration of individual variables and parameters such as, but not limited to, preferred orientation, phase impurities, degree of crystallinity, particle size, variation in diffractometer instrument setup, variation in XRPD data collection parameters, and/or variation in XRPD data processing, among others. The determination of whether two patterns match may be performed by eye and/or by computer analysis. An example of an XRPD pattern collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. 1.

Differential Scanning Calorimetry (DSC) analyses were performed on a TA Instruments Q100™. About 5 mg of sample was placed into a tared DSC closed aluminum pan and the weight of the sample was accurately recorded. An example of a DSC thermogram collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. 2.

Thermal Gravimetric Analyses (TGA) were performed on a TA Instruments Q50™. About 10 mg of sample was placed on an open aluminum pan, accurately weighed and loaded into the TGA furnace. An example of a TGA thermogram

16

collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. 3.

An example of a TGA thermogram collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. 4.

Water determination by the Karl Fischer method was performed using a Metrohm 831 KF Coulometer. The sample was dissolved in anhydrous acetone and injected into the titrator.

Infrared spectroscopy was performed using a Thermo Nicolet Nexus 670 spectrometer. A sample of ca. 1 mg of the hemihydrate in ca. 100 mg KBr. The mixture was then pressed into a pellet, which was used for the IR study. An example of an IR spectrum collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. 5.

The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the disclosure and are encompassed by the appended claims.

Citation or identification of any reference in this application is not an admission that such reference is available as prior art. The full scope of the disclosure is better understood with reference to the appended claims.

The invention claimed is:

1. Crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione hemihydrate, having an X-ray powder diffraction pattern comprising peaks at 12.0, 17.2, and 25.6 degrees  $2\theta \pm 0.2$  degrees 2θ.
2. The hemihydrate of claim 1, wherein the X-ray powder diffraction pattern further comprises peaks at 13.9, 16.7, and 24.3 degrees  $2\theta \pm 0.2$  degrees 2θ.
3. The hemihydrate of claim 1, having an X-ray powder diffraction pattern corresponding to the representative X-ray powder diffraction pattern depicted in FIG. 1.
4. The hemihydrate of claim 1, having a differential scanning calorimetry thermogram comprising an endotherm with a maximum at about 317° C.
5. The hemihydrate of claim 1, having a differential scanning calorimetry thermogram corresponding to the representative differential scanning calorimetry thermograms depicted in FIG. 2.
6. The hemihydrate of claim 1, having about 3.2% of water by mass.
7. The hemihydrate of claim 1, having a thermogravimetric analysis thermogram comprising a weight loss of between about 2.8% and about 4.3% when heated from about 30° C. to about 225° C.
8. The hemihydrate of claim 1, having a thermogravimetric analysis thermogram corresponding to the representative thermogravimetric analysis thermogram depicted in FIG. 3.
9. The hemihydrate of claim 1, having a thermogravimetric analysis thermogram corresponding to the representative thermogravimetric analysis thermogram depicted in FIG. 4.
10. The hemihydrate of claim 1, having an infrared spectrum corresponding to the representative infrared spectrum depicted in FIG. 5.

\* \* \* \* \*

# **EXHIBIT C**



US010093649B1

(12) **United States Patent**  
**Atwood**

(10) **Patent No.:** US 10,093,649 B1  
(b4) **Date of Patent:** Oct. 9, 2018

- (54) **CRYSTALLINE 4-AMINO-2-(2,6-DIOXOPIPERIDINE-3-YL)ISOINDOLINE-1,3-DIONE MONOHYDRATE, COMPOSITIONS AND METHODS OF USE THEREOF**
- (71) Applicant: **Celgene Corporation**, Summit, NJ (US)
- (72) Inventor: **Jerry Lee Atwood**, Columbia, MO (US)
- (73) Assignee: **Celgene Corporation**, Summit, NJ (US)
- (\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 15/849,442

(22) Filed: Dec. 20, 2017

**Related U.S. Application Data**

(60) Provisional application No. 62/562,280, filed on Sep. 22, 2017.

(51) **Int. Cl.**  
C07D 401/04 (2006.01)  
A61K 31/4035 (2006.01)  
A61K 31/45 (2006.01)

(52) **U.S. Cl.**  
CPC ..... C07D 401/04 (2013.01); A61K 31/4035 (2013.01); A61K 31/45 (2013.01); C07B 2200/13 (2013.01)

(58) **Field of Classification Search**  
CPC ..... C07D 401/04  
USPC ..... 546/200; 514/323  
See application file for complete search history.

(56) **References Cited****U.S. PATENT DOCUMENTS**

4,551,177 A	11/1985	Trubiano et al.
5,385,901 A	1/1995	Kaplan et al.
5,593,696 A	1/1997	McNally et al.
5,594,637 A	1/1997	Eisenberg et al.
5,619,991 A	4/1997	Sloane
5,635,517 A	6/1997	Muller et al.
5,712,291 A	1/1998	D'Amato
5,731,325 A	3/1998	Andrusis, Jr. et al.
5,798,368 A	8/1998	Muller et al.
5,832,449 A	11/1998	Cunningham
5,882,656 A	3/1999	Becharde et al.
5,974,203 A	10/1999	Tadokoro et al.
6,045,501 A	4/2000	Elsayed et al.
6,055,507 A	4/2000	Cunningham
6,063,026 A	5/2000	Schauss et al.
6,131,090 A	10/2000	Basso et al.
6,202,923 B1	3/2001	Boyer et al.
6,281,230 B1	8/2001	Muller et al.
6,315,720 B1	11/2001	Williams et al.
6,316,471 B1	11/2001	Muller et al.
6,335,349 B1	1/2002	Muller et al.
6,476,052 B1	11/2002	Muller et al.
6,555,554 B2	4/2003	Muller et al.
6,561,976 B2	5/2003	Elsayed et al.

6,561,977 B2	5/2003	Williams et al.
6,627,646 B2 *	9/2003	Bakale ..... C07D 401/12 514/303
6,755,784 B2	6/2004	Williams et al.
6,878,733 B1	4/2005	Shenoy et al.
6,896,399 B2	5/2005	Nomura et al.
6,908,432 B2	6/2005	Elsayed et al.
7,041,680 B2	5/2006	Muller et al.
7,119,106 B2	10/2006	Muller et al.
7,189,740 B2	3/2007	Zeldis
7,393,862 B2	7/2008	Zeldis
7,393,863 B2	7/2008	Zeldis
7,465,800 B2	12/2008	Jaworsky et al.
7,629,360 B2	12/2009	Muller et al.
7,709,031 B2	5/2010	Greenway et al.
7,709,502 B2	5/2010	Muller et al.
7,855,217 B2	12/2010	Jaworski et al.
7,863,297 B2	1/2011	Zeldis
7,959,566 B2	6/2011	Williams et al.
7,968,569 B2	6/2011	Zeldis
7,994,327 B2	8/2011	Ge et al.
8,158,653 B2	4/2012	Muller et al.
8,188,118 B2	5/2012	Zeldis
8,198,262 B2	6/2012	Zeldis
8,198,306 B2	6/2012	Zeldis
8,204,763 B2	6/2012	Elsayed et al.
8,207,200 B2	6/2012	Zeldis
8,315,886 B2	11/2012	Williams et al.
8,530,498 B1	9/2013	Zeldis
8,589,188 B2	11/2013	Elsayed et al.
8,626,531 B2	1/2014	Williams et al.
8,648,095 B2	2/2014	Zeldis
8,673,939 B2	3/2014	Zeldis

(Continued)

**FOREIGN PATENT DOCUMENTS**

WO	WO 96/13790 A1	5/1996
WO	WO 98/03502 A1	1/1998

(Continued)

**OTHER PUBLICATIONS**

Bernstein, "Polymorphism in . . ." p. 115-118, 272. (Year: 2002).\*  
Davidovich et al., "Detection of polymorphism . . ." Am. Pharm. Rev. 7(1) p. 10, 12, 14, 16, 100.. (Year: 2004).\*  
Dean "Analytical Chem . . ." p. 10.24-10.26. (Year: 1995).\*  
Ivanisevic et al. "Use of X-ray . . ." Pharm. Sci. Encycl. p. 1-42.. (Year: 2010).\*  
Seddon "Pseudopolymorph . . ." Crystal Growth & design v.4(6) p. 1087 (2 pages from internet). (Year: 2004).\*  
Rodriguez-Spong et al., "General principles, etc.," Adv. Drug Delivery Reviews 56 241-274. (Year: 2004).\*  
Kirk-Othmer Encyclopedia of Chemical Technology, 8, pp. 95-147. (Year: 2002).\*  
Vippagunta et al., "Crystalline Solids", Advanced Drug Delivery Reviews 48 3-26. (Year: 2001).\*

(Continued)

Primary Examiner — Patricia L Morris  
(74) Attorney, Agent, or Firm — Jones Day

(57) **ABSTRACT**

Provided herein is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate. Pharmaceutical compositions comprising the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate are also disclosed.

(56)	References Cited		
U.S. PATENT DOCUMENTS			
8,722,647 B2	5/2014	Zeldis	
8,735,428 B2	5/2014	Zeldis	
8,759,375 B2	6/2014	Zeldis	
8,828,427 B2 *	9/2014	Tutino .....	A61K 9/4858 424/452
9,101,621 B2	8/2015	Zeldis	
9,101,622 B2	8/2015	Zeldis	
9,695,146 B2 *	7/2017	Stahly .....	C07D 401/04
2002/0054899 A1	5/2002	Zeldis et al.	
2007/0155791 A1	7/2007	Zeldis et al.	
2008/0051431 A1	2/2008	Verhelle et al.	
2017/0258778 A1	9/2017	Stahly et al.	
FOREIGN PATENT DOCUMENTS			
WO	WO 98/13783 A1	4/1998	
WO	WO 99/10829 A1	3/1999	
WO	WO 00/51053 A1	8/2000	
WO	WO 02/43720 A2	6/2002	
WO	WO 02/59106 A1	8/2002	
WO	WO 02/064083 A2	8/2002	
WO	WO 2011/050962 A1	5/2011	
WO	WO 2013/012485 A2	1/2013	
WO	WO 2013/126326 A1	8/2013	
WO	WO 2014/160690 A1	10/2014	
WO	WO 2018/013689 A1	1/2018	
OTHER PUBLICATIONS			
Guillory (in Brittain ed.), "Polymorphism in Pharmaceutical Solids.," NY: Marcel Dekker, Inc., 1-2, 183-226. (Year: 1999).*			
Braga et al., "Making crystals from . . ." J. Royal Soc. Chem. Commun. p. 3635-3645. (Year: 2005).*			
CMU Pharmaceutical polymorphism, internet p. 1-3 printout Apr. 3, 2008. (Year: 2002).*			
Singhal et al., "Drug Polymorphism, etc.,," Advanced Drug Delivery reviews 56, p. 335-347. (Year: 2004).*			
Concise Encyclopedia Chemistry, NY: Walter de Gruyter, 872-873. (Year: 1993).*			
Jain et al., "Polymorphism in Pharmacy", Indian Drugs, 23(6) 315-329. (Year: 1986).*			
Muzaffar et al., "Polymorphism and Drug Availability, etc.,," J of Pharm. (Lahore), 1(1), 59-66. (Year: 1979).*			
U.S. Pharmacopedia #23, National Formulary #18,1843-1844. (Year: 1995).*			
Doelker, english translation of S.T.P, Pratiques, 9(5), 399-409, pp. 1-33. (Year: 1999).*			
Doelker, english translation of Ann. Pharm. Fr.,60: 161-176, pp. 1-39. (Year: 2002).*			
Taday et al., "Using Terahertz, etc.,," J of Pharm. Sci., 92(4), 831-838. (Year: 2003).*			
Otuska et al., "Effect of Polymorphic, etc.,," Chem. Pharm. Bull., 47(6) 852-8569. (Year: 1999).*			
Nie et al., "Source analysis, etc.,," CA 1743748. (Year: 2015).*			
Celgene Corporation, Pomalyst® (pomalidomide) packaging label, Retrieved online on Dec. 14, 2017, retrieved online at <http://www.pomalyst.com/?pi=yes&gclid=CMF4keDY-tMCFZ0Cfgodz7oPsA>, revised Jun. 2016.			
Dimartino et al., "Preparation and physical characterization of forms II and III of paracetamol," J. Thermal. Anal., 48(3):447-458 (1997).			
Gennaro, Remington: <i>The Science and Practice of Pharmacy</i> , 20th Ed., Lipincott Williams & Wilkins, pp. 172-182 (2000).			
Knapman, "Polymorphic Predictions: Understanding the nature of crystalline compounds can be critical in drug development and manufacture," Modern Drug Discoveries, 53-57 (2000).			
<i>The United States Pharmacopeia</i> , 37th Edition, United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 503-509 (2014).			
"CDC meeting: Mar. 26, 1997 minutes and agenda regarding thalidomide."			
"Celgene's Revlimid an orphan drug, says FDA," Marketletter Oct. 15, 2001.			
"Center for drug evaluation and research approval package for: Application No. 18-662/S-038," (2000).			
"Center for drug evaluation and research approval package for: Application No. NDA 20-785 approval letter(s)," Sep. 19, 1997 and Jul. 16, 1998.			
"Celgene drug promises activity in solid tumors," Marketletter Jun. 18, 2001.			
"Center for drug evaluation and research, Application No. 204026Orig1s000," Pharmacolgy Review(s), dated Dec. 13, 2012. [retrieved on Oct. 29, 2016]. Retrieved from the internet: <http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204026Orig1s000PharmR.pdf>.			
"Center for Drug Evaluation and Research, Approval Package for: Application No. 14-691/S-020," Alkeran® (melphalan) Tablets, product information, GlaxoSmithKline (2001).			
"EnteMed moves towards commercialization with production of thalidomide analogs; Next generation drug candidates to be manufactured in preparation for clinical studies," PR Newswire (2001).			
Adams et al., "Proteasome inhibitors: A novel class of potent and effective antitumor agents," <i>Cancer Res.</i> 59:2615-2622 (1999).			
Adjei et al., "A phase I trial of the farnesyl transferase inhibitor SCH66336: evidence for biological and clinical activity," <i>Cancer Res.</i> , 60:1871-1877 (2000).			
Alder et al., "The return of thalidomide—A shunned compound makes a scientific comeback," <i>Science News</i> 146:424-425 (1994).			
Alexanian et al., "High-dose glucocorticoid treatment of resistant myeloma," <i>Ann. Intern. Med.</i> 105:811 (1986).			
Alexanian et al., "Consolidation therapy of multiple myeloma with thalidomide-dexamethasone after intensive chemotherapy," <i>Ann Oncol.</i> 13:1116-1119 (2002).			
Anderson et al., "Multiple myeloma: New insights and therapeutic approaches," <i>Hematology Am. Soc. Hematol. Educ. Program</i> 2000:147-165 (2000).			
Anderson et al., "Novel biologically based therapies for myeloma," VIII the International Myeloma Workshop, Banff, Alberta, Canada, May 4-8, 2001; Abstract #S27.			
Anderson, "The role of immunomodulatory drugs in multiple myeloma," <i>Semin. Hematol.</i> , 40(4 Suppl. 4):23-32 (2003).			
Banker ed., <i>Modern Pharmaceutics</i> , 3rd Edition, Marcel Dekker, Inc., New York, NY, pp. 451 and 596 (1996).			
Barlogie et al., "Effective Treatment of Advanced Multiple Myeloma Refractory to Alkylating Agents," <i>N. Engl. J. Med.</i> , 310(21):1353-1356 (1984).			
Barlogie et al., "Thalidomide and CC-5013 in multiple myeloma: the University of Arkansas experience," <i>Semin. Hematol.</i> , 40(4):33-38 (2003).			
Barlogie et al., "Thalidomide in the management of multiple myeloma," <i>Semin. Hematol.</i> , 38:250-259 (2001).			
Beaumont et al., "Design of ester prodrugs to enhance oral absorption of poorly permeable compounds: challenges to the discovery scientist," <i>Curr. Drug Metab.</i> , 4:461-485 (2003).			
Bjorkstrand et al., "Prognostic factors in autologous stem cell transplantation for multiple myeloma: an EBMT registry study," <i>Leuk. Lymphoma</i> 15:265-272 (1994).			
Bor, "Thalidomide shows that it can heal, too from deformers of babies to force for good," <i>Baltimore Sun</i> (1995).			
Broder et al., "Dideoxycytidine: Current clinical experience and future prospects. A summary," <i>Am. J. Med.</i> 88:31S-33S (1990).			
Burleson, "Review of computer applications in institutional pharmacy—1975-1981," <i>Am. J. Hosp. Pharm.</i> 39:53-70 (1982).			
Bwire et al., Managing the teratogenic risk of thalidomide and lenalidomide: An industry perspective, <i>Expert Opin. Drug Saf.</i> 10:3-8 (2011).			
Cairo, "Dose reductions and delays: Limitations of myelosuppressive chemotherapy," <i>Cancer Network</i> (2000).			
Canal et al., "Benefits of pharmacological knowledge in the design and monitoring of cancer chemotherapy," <i>Pathology Oncol. Res.</i> 4:171-178 (1998).			
Celgene assigned patents/applications indexed with pomalidomide from USPATFULL accessed Oct. 27, 2016.			

(56)

**References Cited****OTHER PUBLICATIONS**

- Celgene Corporation Awarded Additional Patent Protection for Lead IMiD(TM), Revimid(TM); Comprehensive Patent Protection for Revimid Includes Coverage of the Active Ingredient, Pharmaceutical Compositions, and Therapeutic Uses PR Newswire Aug. 28, 2001.
- Celgene Corporation, "Initial Phase I solid tumor data on Celgene's lead IMiD™, Revimid™," Press Release, Jun. 2001.
- Celgene Corporation, Form 424B4 (2000).
- Celgene News Release, "Positive interim results presented at the VIIIth international myeloma workshop on Celgene Corporation's lead IMiD™ (REV/MID™)," May 8, 2001.
- Cheson, "New drug development in non-Hodgkin lymphomas," *Curr. Oncol. Rep.* 3:250-259 (2001).
- Choi et al., "Role of gallic acid in inflammatory allergic process," *Korean Journal Physiology & Pharmacology*, 10(2):101-108 (2006) (abstract only).
- Chu et al., "Principles of cancer management: Chemotherapy," in *Cancer: Principles and Practice of Oncology*, 6th edition, De Vita et al., (eds.), Lippincott Williams & Wilkins, Philadelphia, PA Chapter 17 (2001).
- Cimons, "How a body responds to drugs depends on the genes," *Los Angeles Times*, Jul. 24, 2000.
- Collins et al., "Potential roles for preclinical pharmacology in phase 1 clinical trials," *Cancer Treat. Rep.*, 70:73-80 (1986).
- Corral et al., "Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF- $\alpha$ ," *J. Immunol.* 163:380-386 (1999).
- Corral et al., "Immunomodulation by thalidomide and thalidomide analogues," *Ann. Rheum. Dis.*, 58(Suppl 1):I107-I113 (1999).
- Crane et al., "Immunomodulatory drugs," *Cancer Investigation* 23:625-634 (2005).
- D'Amato et al., "Mechanism of action of thalidomide and 3-aminothalidomide in multiple myeloma," *Semin. Oncol.*, 28:597-601 (2001).
- D'Amato et al., "Thalidomide is an Inhibitor of Angiogenesis," *Proc. Natl. Acad. Sci. USA*, 91(9):4082-4085 (1994).
- Damaj et al., "Thalidomide therapy induces response in relapsed mantle cell lymphoma," *Leukemia* 17:1914-1915 (2003).
- Dancey et al., "Neutrophil kinetics in man," *J. Clin. Invest.* 58:705-715 (1976).
- Davies et al., "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma," *Blood*, 98(1):210-216 (2001).
- Devita et al., eds., "Plasma cell neoplasm." In *Cancer Principles & Practice of Oncology*, 5th Ed.; Lippincott-Raven Publishers, pp. 2344-2379 (1997).
- Dimopoulos et al., "Thalidomide and dexamethasone combination for multiple myeloma refractory to dexamethasone-based regimens," *Blood* 96(Supp):286b (2000).
- Dimopoulos et al., "Thalidomide and dexamethasone combination for refractory multiple myeloma," *Ann. Oncol.* 12:991-995 (2001).
- Dishman et al., "Pharmacists' transcript role in clozapine therapy at a veterans affairs medical center," *Am. J. Hosp. Pharm.* 51:899-901 (1994).
- Drach et al., "Treatment of mantle cell lymphoma: Targeting the microenvironment," *Expert Rev. Anticancer Ther.* 5:477-485 (2005).
- Dredge et al., "Immunological effects of thalidomide and its chemical and functional analogs," *Crit. Rev. Immunol.*, 22(5&6):425-437 (2002).
- Dredge et al., "Novel thalidomide analogues display anti-angiogenic activity independently of immunomodulatory effects," *Br. J Cancer*, 87(10):1166-1172 (2002).
- Dredge et al., "Protective antitumor immunity induced by a costimulatory thalidomide analog in conjunction with whole tumor cell vaccination is mediated by increased Th1-type immunity," *J. Immunol.* 168:4914-4919 (2002).
- Dredge et al., "Thalidomide analogs as emerging anti-cancer drugs," *Anti-Cancer Drugs*, 14:331-335 (2003).
- Durie and Stepan, "Efficacy of low dose thalidomide in multiple myeloma," *Eur. J. Oncol.* 1:1-8 (2000).
- Dykes, "Genes, disease and medicine," *Br. J. Clin. Pharmacol.*, 42:683-695 (1996).
- Edwards, "Thalidomide: Is there a silver lining?" *Science News* 131:198 (1987).
- Elliot et al., "The proteasome: A new target for novel drug therapies," *Am. J. Clin. Pathol.* 116:637-646 (2001).
- EORTC Pharmacokinetics and Metabolism Group, "Pharmacokinetically guided dose escalation in phase I clinical trials. Commentary and proposed guidelines," *Eur. J. Cancer Clin. Oncol.*, 23(7):1083-1087 (1987).
- FDA Guideline for Industry, "International conference on harmonisation; dose-response information to support drug registration; guideline; availability," 59 FR 55972-01, 1994 WL 615579 (1994).
- Figg et al., "Pharmacokinetics of thalidomide in an elderly prostate cancer population," *J. Pharm. Sci.* 88:121-125 (1999).
- Filella et al., "Cytokines (IL-6, TNF-alpha, IL-1 alpha) and soluble interleukin-2 receptor as serum tumor markers in multiple myeloma," *Cancer Detect. Prev.* 20:52-56 (1996).
- Foerster et al., "Effects of thalidomide and EM12 on the synthesis of TNF- $\alpha$  in cocultures of human monocytes and lymphocytes," Abstract 517 (1995).
- Friedman et al., "Introduction to clinical trials" *Fundamentals of Clinical Trials*, 3rd edition, Springer, New York, NY, Chapter 1 (1998).
- Fujita et al., "Thalidomide and its analogues inhibit lipopolysaccharide-mediated induction of cyclooxygenase-2," *Clin. Cancer Res.*, 7:3349-3355 (2001).
- Fuse et al., "Prediction of the maximal tolerated dose (MTD) and therapeutic effect of anticancer drugs in humans: integration of pharmacokinetics with pharmacodynamics and toxicodynamics," *Cancer Treat. Rev.*, 21:133-157 (1995).
- Gahrton et al., "Progress in haematopoietic stem cell transplantation for multiple myeloma," *J. Intern. Med.* 248:185-201 (2000).
- Gardner et al., "Assessing the effectiveness of a computerized pharmacy system." In *Decision Support Systems in Critical Care*; Shabot et al., eds.; pp. 174-183 (1994).
- Glasmacher et al., "Oral idarubicin, dexamethasone and vincristine (VID) in the treatment of multiple myeloma," *Leukemia* 11:S22-S26 (1997).
- Grönroos et al., "A medication database—a tool for detecting drug interactions in hospital," *Eur. J. Clin. Pharmacol.* 53:13-17 (1997).
- Gupta et al., "Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications," *Leukemia*, 15(12):1950-1961 (2001).
- Hamera et al., "Alcohol, cannabis, nicotine, and caffeine use and symptom distress in Schizophrenia," *J. Nerv. Ment. Dis.* 183:559-565 (1995).
- He et al., "Synthesis of thalidomide analogs and their biological potential for treatment of graft versus host disease," 206th ACS National Meeting 0-8412-2620-2, American Chemical Society, Chicago, IL, Abstract 216 (1993).
- Heger et al., "Embryotoxic effects of thalidomide derivatives in the non-human primate callithrixjaccchus. IV teratogenicity of  $\mu$ g/kg doses of the EMJ 2 enantiomers," *Teratog. Carcinog. Mutagen.* 14:115-122.
- Hideshima et al., "Novel therapies targeting the myeloma cell and its bone marrow microenvironment," *Semin. Oncol.* 28:607-612 (2001).
- Hideshima et al., "The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells," *Cancer Res.* 61:3071-3076 (2001).
- Hideshima et al., "Thalidomide (Thal) and its analogs overcome drug resistance of human multiple myeloma (MM) cells to conventional therapy," *Abstract 1313, American Society of Hematology*, Dec. 1-5, 2000.
- Hideshima et al., "Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy," *Blood* 96(9):2943-2950 (2000).
- Hochster et al., "Activity and pharmacodynamics of 21-Day topotecan infusion in patients with ovarian cancer previously treated with

(56)

**References Cited****OTHER PUBLICATIONS**

- platinum-based chemotherapy. New York Gynecologic Oncology Group," *J. Clin. Oncol.* 17:2553-2561 (1999).
- Hus et al., "Thalidomide treatment of resistant or relapsed multiple myeloma patients," *Haematologica* 86:404-408 (2001).
- Jagannath et al., "Pomalidomide (POM) with or without low-dose dexamethasone (LoDEX) in patients (Pts) with relapsed and refractory multiple myeloma (RRMM): MM-002 phase II age subgroup analysis," *J. Clin. Oncol.* 31, Abstrct # 8532, (2013).
- Jönsson, "Chemical structure and teratogenic properties. 3. A review of available data on structure-activity relationships and mechanism of action of thalidomide analogues," *Acta Pharm. Suec.* 9:521-542 (1972).
- Jourdan et al., "Tumor necrosis factor is a survival and proliferation factor for human myeloma cells," *Eur. Cytokine Netw.* 10:65-70 (1999).
- Keravich et al., "Challenges of thalidomide distribution in a hospital setting," *Am. J. Health Syst. Pharm.* 56:1721-1725 (1999).
- Kibbe ed., *Handbook of Pharmaceutical Excipients*, 3rd edition, pp. 160-162 (2000).
- Klausner et al., "Thalidomide as an anti-TNF-alpha inhibitor: implications for clinical use," *Clin. Immunol. Immunopathol.*, 81(3):219-223 (1996).
- Klausner et al., "The effect of thalidomide on the pathogenesis of human immunodeficiency virus type 1 and M. tuberculosis infection," *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.*, 11(3):247-257 (1996).
- Knight, "Cancer patients ahead of FDA on thalidomide use," *Washington Post* Jun. 25, 2001.
- Kosten et al., "Substance abuse and Schizophrenia: Editors' Introduction," *Schizophrenia Bulletin* 23:181-186 (1997).
- Kropff et al., "Hyperfractionated cyclophosphamide in combination with pulsed dexamethasone and thalidomide (hyper-CDT) in primary refractory or relapsed multiple myeloma," *Blood*, 96(11):168a (2000).
- Kumar et al., "Thalidomide and lenalidomide in the treatment of multiple myeloma," *Eur. J. Cancer*, 42:1612-1622 (2006).
- Kyle et al., "Therapeutic application of thalidomide in multiple myeloma," *Semin. Oncol.* 28:583-587 (2001).
- Lacy et al., "Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma," *J. Clin. Oncol.* 27:5008-5014 (2009).
- Lacy et al., "Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: Comparison of 2 dosing strategies in dual-refractory disease," *Blood* 118:2970-2975 (2011).
- Langbein, "Celgene releases first data on Actimid in cancer patients," *Reuters News*, Jul. 8, 2002.
- Lee et al., "A pilot trial of hyperfractionated thoracic radiation therapy with concurrent cisplatin and oral etoposide for locally advanced inoperable non-small-cell lung cancer: a 5-year follow-up report," *Int. J. Radiat. Oncol. Biol. Phys.* 42:479-486 (1998).
- Lentzsch et al., "3-amino-phthalimido-glutarimide (S-3APG) inhibits angiogenesis and growth in drug resistant multiple myeloma (MM) in vivo," Abstract 1976, *American Society of Hematology*, 43rd Annual Meeting Orlando, Florida, Dec. 7-11, 2001.
- Lentzsch et al., "Immunomodulatory analogs of thalidomide inhibit growth of Hs sultan cells and angiogenesis in vivo," *Leukemia*, 17:41-44 (2003).
- Lentzsch et al., "Immunomodulatory derivatives (IMiDs) of thalidomide (Thal) inhibit the proliferation of multiple myeloma (MM) cell lines and block VEGF-induced activation of the MAPK-pathway," *Blood* 96:579 (Abstract# 2486) (2000).
- Lentzsch et al., "S-3-amino-phthalimido-glutarimide inhibits angiogenesis and growth of B-cell neoplasias in mice", *Cancer Research* 62:2300-2305 (2002).
- Linder et al., "Pharmacogenetics: a laboratory tool for optimizing therapeutic efficiency," *Clin. Chem.*, 43(2):254-266 (1997).
- Linnarsson, "Decision support for drug prescription integrated with computer-based patient records in primary care," *Med. Inform.* 18:131-142 (1993).
- Lipkin, "Deriving new drugs from thalidomide," *Science News* 148:171 (1995).
- Mann et al., "Passage of chemicals into human and animal semen: mechanisms and significance," *Crit. Rev. Toxicol.* 11:1-14 (1982).
- Marriott et al., "Immunotherapeutic and antitumour potential of thalidomide analogues," *Expert Opin. Biol. Ther.* 1:1-8 (2001).
- Marriott et al., "Immunotherapeutic and antitumour potential of thalidomide analogues," *Expert Opin. Biol. Ther.*, 1(4):675-682 (2001).
- Marriott et al., "Thalidomide and its analogues have distinct and opposing effects on TNF-alpha and TNFR2 during co-stimulation of both CD4+ and CD8+ T cells," *Clin. Exp. Immunol.*, 130:75-84 (2002).
- Marwick, "Thalidomide back—under strict control," *JAMA* 278:1135-1137 (1997).
- Menill, "Substance Abuse and Women on Welfare," in *National Center on Addiction and Substance Abuse at Columbia University*, Jun. 1994.
- Milner et al., "Attitudes of young adults to prenatal screening and genetic correction for human attributes and psychiatric conditions," *Am. J. Med. Genet.*, 76:111-119 (1998).
- Mitchell et al., "A pregnancy-prevention program in women of childbearing age receiving isotretinoin," *N. Engl. J. Med.* 333:101-106 (1995).
- Mitsiades et al., "Concepts in the use of TRAIL/Apo2L: An emerging biotherapy for myeloma and other neoplasias," *Expert Opin. Investig. Drugs* 10:1521-1530 (2001).
- Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications," *Blood*, 2002, 99:4525-4530, *American Society of Hematology*.
- Montero et al., "Economic study of neutropenia induced by myelotoxic chemotherapy," *Pharm. World Sci.* 16:187-192 (1994).
- Moreira et al., "Thalidomide exerts its inhibitory action on tumor necrosis factor  $\alpha$  by enhancing mRNA degradation," *J. Exp. Med.*, 177(6):1675-1680 (1993).
- Morgan et al., "Lenalidomide (Revlimid), in combination with cyclophosphamide and dexamethasone (RCD), is an effective and tolerated regimen for myeloma patients," *Br. J. Haematol.* 137:268-269 (2007).
- Muller et al., "Amino-substituted thalidomide analogs: potent inhibitors of TNF-alpha production," *Bioorg. Med. Chem. Lett.*, 9(11):1625-1630 (1999).
- Muller, Thalidomide: From tragedy to new drug discovery, *Chemtech* 27:21-25 (1997).
- Mundt, "Interactive voice response systems in clinical research and treatment," *Psychiatr. Serv.* 48:611-612, 623 (1997).
- National Cancer Institute, *Common Toxicity Criteria Manual*, Ver. 2.0, Jun. 1, 1999.
- NCT00480363: "Quiredex: Revlimid (lenalidomide) and dexamethasone (ReDex) treatment versus observation in patients with smoldering multiple myeloma with high risk of progression (Quiredex)," (2013).
- Noguerla et al., "Effect of thalidomide and some derivatives on the adhesion of lymphocytes to endothelial cells," Abstract 518 (1995).
- Olson et al., "Thalidomide (N-phthaloylglutamimide) in the treatment of advanced cancer," *Clin. Pharm. Ther.*, 6(3):292-297 (1965).
- Palumbo et al., "Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma," *Haematologica* 86:399-403 (2001).
- Pastuszak et al., "Use of the retinoid pregnancy prevention program in Canada: Patterns of contraception use in women treated with isotretinoin and etretinate," *Reprod. Toxicol.* 8:63-68 (1994).
- Pestotnik et al., "Therapeutic antibiotic monitoring: Surveillance using a computerized expert system," *Am. J. Med.* 88:43-48 (1990).
- Peterson et al., "Expanding the scope of crystal form evaluation in pharmaceutical science," *J. Pharm. Pharmaceut. Sci.*, 9(3):317-326 (2006).
- Piper et al., "Anti-inflammatory immunosuppressive thalidomide analogs. Screening," *Int. J. Leprosy* 49:511-512 (1981).

(56)

**References Cited****OTHER PUBLICATIONS**

- Powell et al., "Guideline for the clinical use and dispensing of thalidomide," *Postgrad. Med. J.* 70:901-904 (1994).
- Pro et al., "Phase II study of thalidomide in patients with recurrent Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL)," *Blood* 98:246b (Abstract# 4712) (2001).
- Querfeld et al., "Preliminary results of a phase II study of CC-5013 (lenalidomide, revlimid®) in patients with cutaneous T-cell lymphoma," *Blood* 106:936a-937a (2005).
- Raje et al., "Thalidomide and immunomodulatory drugs as cancer therapy," *Curr. Opin. Oncol.*, 14:635-640 (2002).
- Raje et al., "Thalidomide—a revival story," *N. Engl. J. Med.* 341(21):1606-1609 (1999).
- Rajkumar et al., "Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial," *Lancet* 11:29-37 (2010).
- Rajkumar et al., "Phase III trial of lenalidomide plus highdose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): A trial coordinated by the Eastern Cooperative Oncology Group," *J. Clin. Oncol.* 25:18S (2007).
- Rajkumar et al., "Thalidomide plus dexamethasone (Thal/Dex) and thalidomide alone (Thal) as first line therapy for newly diagnosed myeloma (MM)," *Blood* 96(Supp.):168a (2000).
- Rajkumar et al., "Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma," *Blood*, 106(13):4050-4053 (2005).
- Rajkumar et al., "Thalidomide in the treatment of plasma cell malignancies," *J. Clin. Oncol.* 19:3593-3595 (2001).
- Rajkumar, "Thalidomide in multiple myeloma," *Oncology* 14:11-16 (2000).
- Ratain, "Pharmacology of Cancer Chemotherapy." In *Cancer: Principles & Practice of Oncology*, pp. 335-459 (2001).
- Rautio et al., "Prodrugs: design and clinical applications," *Nat. Rev. Drug Discov.*, 7:255-270 (2008).
- Reiman et al., "Meeting synopsis, VIII International Myeloma Workshop, Banff Springs Hotel, Banff, Alberta, Canada, May 4-8, 2001," *Eur. J. Haematol.* 67:199-202 (2001).
- Ribatti et al., "Angiogenesis spectrum in the stroma of B-cell non-Hodgkin's lymphomas. An immunohistochemical and ultrastructural study," *Eur. J. Haematol.* 56:45-53 (1996).
- Richardson et al., "A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma," *Blood* 108:3458-3464 (2006).
- Richardson et al., "Thalidomide in multiple Myeloma," *Biomed. Pharmacother.* 56:115-128 (2002).
- Richardson et al., "Thalidomide: Emerging role in cancer medicine," *Ann. Rev. Med.* 53:629-657 (2002).
- Richardson et al., "A multi-center, randomized, phase II study to evaluate the efficacy and safety of two CDC-5013 dose regimens when used alone or in combination with dexamethasone (Dex) for the treatment of relapsed or refractory multiple myeloma (MM)," Abstract 386, *Blood*, 100(11 Part 1):104a (2002).
- Richardson et al., "A phase I study of oral CC5013, an immunomodulatory thalidomide (Thal) derivative, in patients with relapsed and refractory multiple myeloma (MM)," *Blood* 98:775a (2001).
- Richardson et al., "A phase 1/2 multi-center, randomized, open label dose escalation study to determine the maximum tolerated dose (MTD), safety, and efficacy of pomalidomide (POM) alone or in combination with low-dose dexamethasone (DEX) in patients (PTS) with relapsed and refractory multiple myeloma (RRMM) who have received prior treatment (TX) that includes lenalidomide (LEN) and bortezomib (BORT)," *Haematologica*, 96:S31 (2011).
- Richardson et al., "A phase I study of the safety and efficacy of CC5013 treatment for patients with relapsed multiple myeloma: Preliminary results," VIII the International Myeloma Workshop, Banff, Alberta, Canada, May 4-8, 2001; Abstract #P230.
- Richardson et al., "Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma," *Blood* 100:3063-3067 (2002).
- Robert et al., "Phase I and pharmacologic study of 7- and 21-day continuous etoposide infusion in patients with advanced cancer," *Cancer Chemother. Pharmacol.* 38:459-465 (1996).
- Rubinstein et al., "Phase I clinical trial design," Biometric Research Branch, National Cancer Institute (2003).
- Samlowski et al., "Evaluation of gemcitabine in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: A southwest oncology group phase II study," *Invest. New Drugs* 19:311-315 (2001).
- Sampaio et al., "Prolonged treatment with recombinant interferon gamma induces erythema nodosum leprosum in lepromatous leprosy patients," *J. Exp. Med.* 175:1729-1737 (1992).
- Sampaio et al., "Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes," *J. Exp. Med.* 173:699-703 (1991).
- Schey et al., "Phase I Study of an Immunomodulatory Thalidomide Analog, CC-4047, in Relapsed or Refractory Multiple Myeloma," *J. Clin. Oncol.* 22(16):3269-3276 (2004).
- Schey et al., "Pomalidomide therapy for myeloma," *Expert Opin. Invest. Drugs* 20:691-700 (2011).
- Schey et al., "A phase I study of an immunomodulatory thalidomide analogue (CC4047) in relapse/refractory multiple myeloma," *International Society for Experimental Hematology*, Abstract #248, (2002).
- Schey, "Thalidomide in the management of multiple myeloma," *Hematology* 7:291-299 (2002).
- Schlossman et al., "Bone marrow transplantation in multiple myeloma," *Curr. Opin. Oncol.* 11:102-108 (1999).
- Seppa, "Thalidomide combats myeloma blood cancer," *Science News* 156:326 (1999).
- Shaughnessy et al., "Global gene expression analysis shows loss of c-myc and IL-6 receptor gene mRNA after exposure of myeloma to thalidomide and IMiD," Abstract 2485, *American Society of Hematology*, 42<sup>nd</sup> Annual Meeting San Francisco, CA, Dec. 1-5, 2000.
- Shinn et al., "Development of a computerized drug interaction database (MEDICOM) for use in a patient specific environment," *Drug Inf. J.* 17:205-210 (1983).
- Siegel et al., "Long-term safety and efficacy of pomalidomide (POM) with or without low-dose dexamethasone (LoDEX) in relapsed and refractory multiple myeloma (RRMM) patients enrolled in the MM-002 phase II trial," *J. Clin. Oncol.* 31, 2013 (Abstract No. 8588).
- Singhal et al., "Antitumor activity of thalidomide in refractory multiple myeloma," *N. Engl. J. Med.*, 341(21):1565-1571 (1999).
- Smith et al., "Design and results of phase I cancer clinical trials: three-year experience at M.D. Anderson Cancer Center," *J. Clin. Oncol.*, 14:287-295 (1996).
- Smith, R. et al., "Studies on the Relationship Between the Chemical Structure and Embryotoxic Activity of Thalidomide and Related Compounds," in *A Symposium on Embryopathic Activity of Drugs*, J. & A. Churchill Ltd., Session 6, pp. 194-209 (1965).
- Sorbera et al., "CC-5013. Treatment of multiple myeloma. Treatment of Melanoma. Treatment of myelodysplastic syndrome. Angiogenesis inhibitor. TNF-α production inhibitor," *Drugs of the Future*, 28(5):425-431 (2003).
- Soyka et al., "Prevalence of alcohol and drug abuse in schizophrenic inpatients," *Eur. Arch. Psychiatry Clin. Neurosci.* 242:362-372 (1993).
- Srkalovic et al. "Use of melphalan, thalidomide, and dexamethasone in treatment of refractory and relapsed multiple myeloma," *Med. Oncol.* 19:219-226 (2002).
- Steed, "The role of co-crystals in pharmaceutical design," *Trends in Pharmacol. Sci.*, 34(3):185-193 (2013).
- Steiner et al., "The assessment of refill compliance using pharmacy records: methods, validity, and applications," *J. Clin. Epidemiol.* 50:105-116 (1997).
- Stirling et al., "Thalidomide. A surprising recovery," *J. Am. Pharm. Assoc.* NS37:306-313 (1997).
- Stirling, "Thalidomide: A novel template for anticancer drugs," *Seminars Oncology* 28:602-606 (2001).

(56)

**References Cited****OTHER PUBLICATIONS**

- Szelényi et al., "Cyclophosphamide, adriamycin and dexamethasone (CAD) is a highly effective therapy for patients with advanced multiple myeloma," *Ann. Oncol.* 12:105-108 (2001).
- Thalomid™ (thalidomide) Capsules Revised Package Insert (Jul. 15, 1998).
- The Comprehensive Guide to Banff, Understanding the VIIIth International Myeloma Workshop published by the International Myeloma Foundation (2001).
- Thomas et al., "Current role of thalidomide in cancer treatment," *Curr. Opin. Oncol.* 12:564-573 (2000).
- Transcript of the Forty-Seventh Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (Sep. 4, 1997).
- Transcript of the Forty-Seventh Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (Sep. 5, 1997).
- Tseng et al., "Rediscovering thalidomide: a review of its mechanism of action, side effects, and potential uses," *J. Am. Acad. Dermatol.* 35:969-979 (1996).
- Tsenova et al., "Use of IMiD3, a thalidomide analog, as an adjunct to therapy for experimental tuberculous meningitis," *Antimicrob Agents Chemother.*, 46(6):1887-1895 (2002).
- Vacca et al., "Angiogenesis in B cell lymphoproliferative diseases. Biological and clinical studies," *Leuk. Lymphoma* 20:27-38 (1995).
- Vanchieri, "Preparing for thalidomide's comeback," *Annals Internal Med.*, 127(10):951-952 (1997).
- Verma, "Gallic acid: molecular rival of cancer," *Environ. Toxicol. Pharmacol.*, 35(3):473-485 (2013).
- Vij et al., "Pomalidomie (POM) with Low-Dose Dexamethasone (LoDex) in Patients with Relapsed and Refractory Multiple Myeloma (RRMM): Outcomes Based on Prior Treatment Exposure," presented at 54th ASH Annual Meeting and Exposition, Atlanta, Georgia, Dec. 8-11, 2012, Abstract #4070.
- Vippagunta et al., "Crystalline solids," *Adv. Drug Deliv. Rev.*, 48(1):3-26 (2001).
- Vogelsang et al., "Thalidomide for the treatment of chronic graft-versus-host disease," *N. Engl. J. Med.* 326:1055-1058 (1992).
- Weber et al., "Thalidomide alone or with dexamethasone for multiple myeloma," *Blood* 94:604 (1999).
- Weber et al., "Thalidomide with dexamethasone of resistant multiple myeloma," *Blood* 96:167 (2000).
- Welte et al., "Influence of socially desirable responding in a study of stress and substance abuse," *Alcohol Clin. Exp. Res.* 17:758-761 (1993).
- Wilson et al., "Response to thalidomide in chemotherapy-resistant mantle cell lymphoma: a case report," *Br. J. Haematol.* 119:128-130 (2002).
- Wolf et al., "Science, medicine, and the future pharmacogenetics," *BMJ*, 320:987-990 (2000).
- Wolff ed., *Burger's Medicinal Chemistry and Drug Discovery*, 5<sup>th</sup> Edition, vol. 1, John Wiley & Sons, Inc., pp. 975-977 (1995).
- Yuen et al., "Phase I study of an antisense oligonucleotide to protein kinase C- $\alpha$  (ISIS 3521/CGP 64128A) in patients with cancer," *Clin. Cancer Res.* 5:3357-3363 (1999).
- Zangari et al., "Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide chemotherapy," *Blood* 98:1614 (2001).
- Zangari et al., Results of phase I study of CC-5013 for the treatment of multiple myeloma (MM) patients who relapse after high dose chemotherapy (HDT), *Blood* 98(11), Abstract# 3226 (2001).
- Zangari et al., "Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy," *Blood*, 100:1168-1171 (2002).
- Zeldis et al., "S.T.E.P.S.: A comprehensive program for controlling and monitoring access to thalidomide," *Clin. Ther.* 21:319-330 (1999).

\* cited by examiner

FIGURE 1

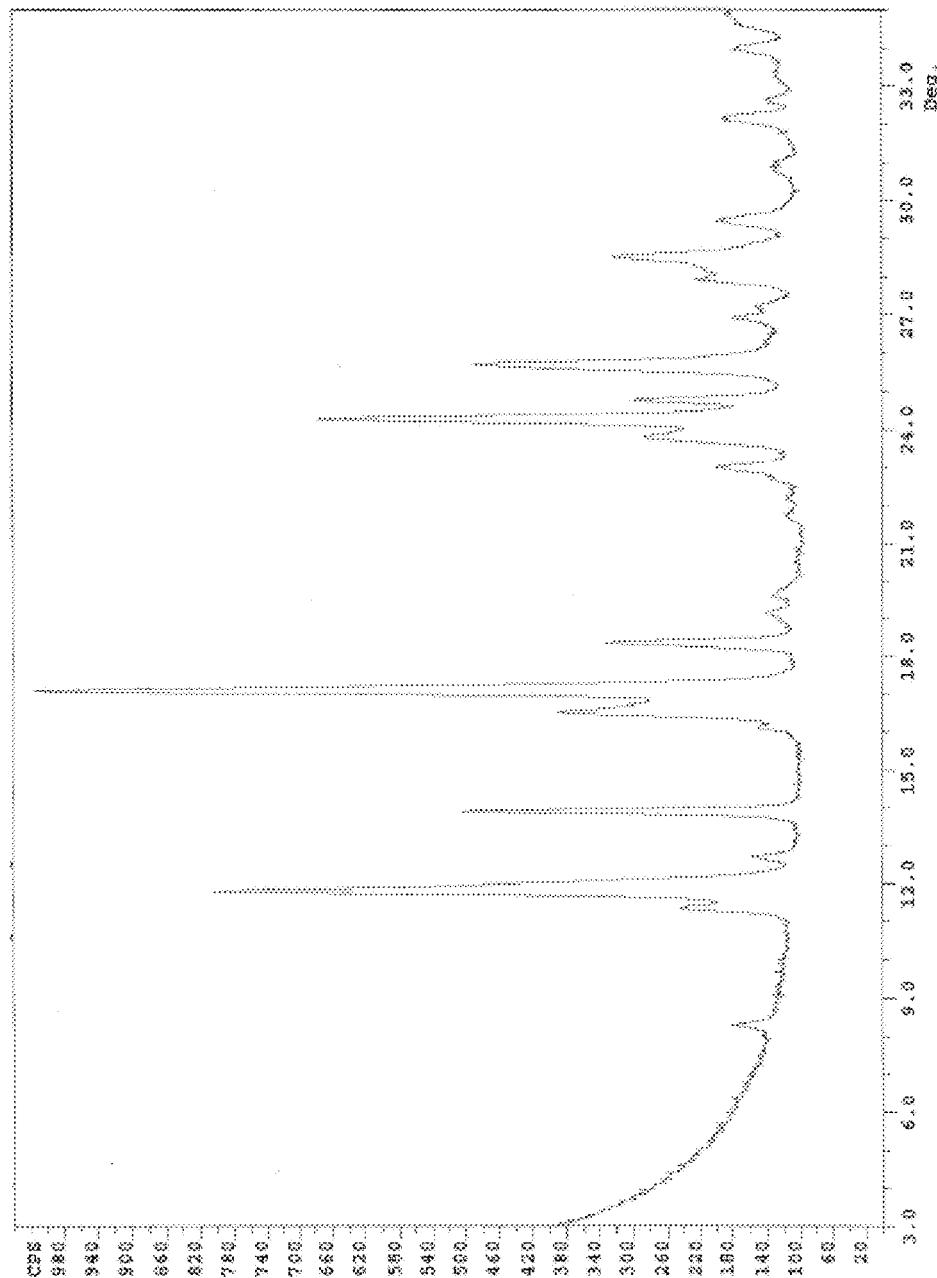


FIGURE 2

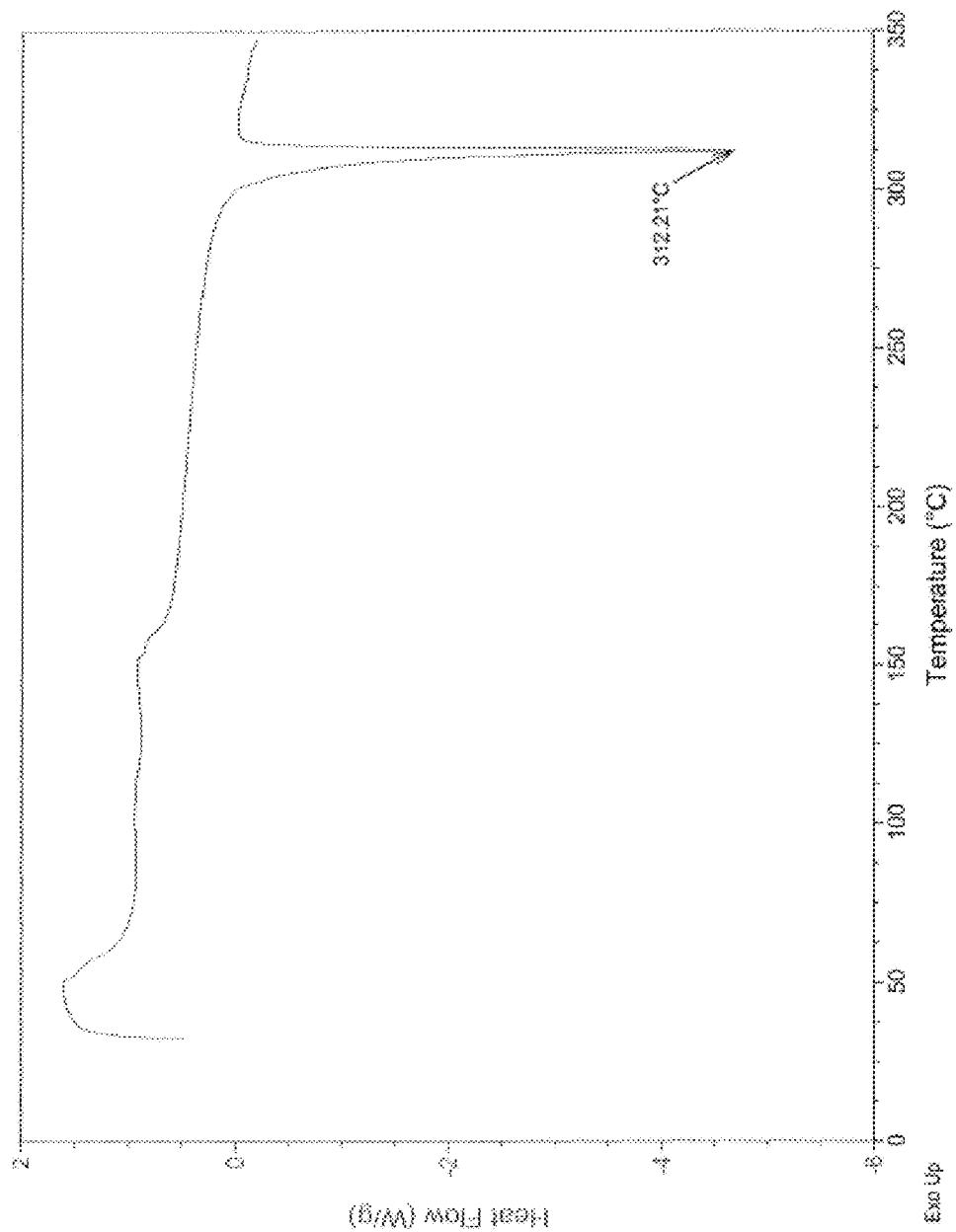


FIGURE 3

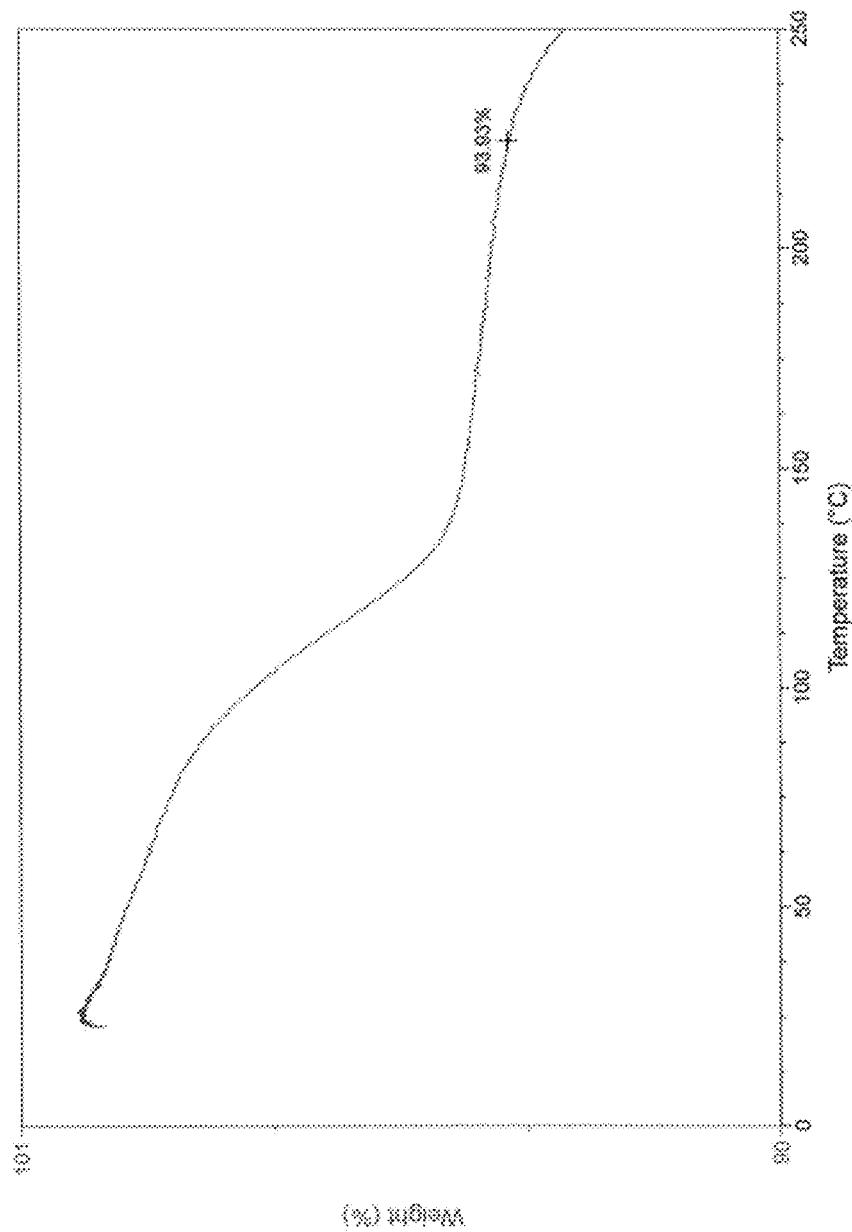
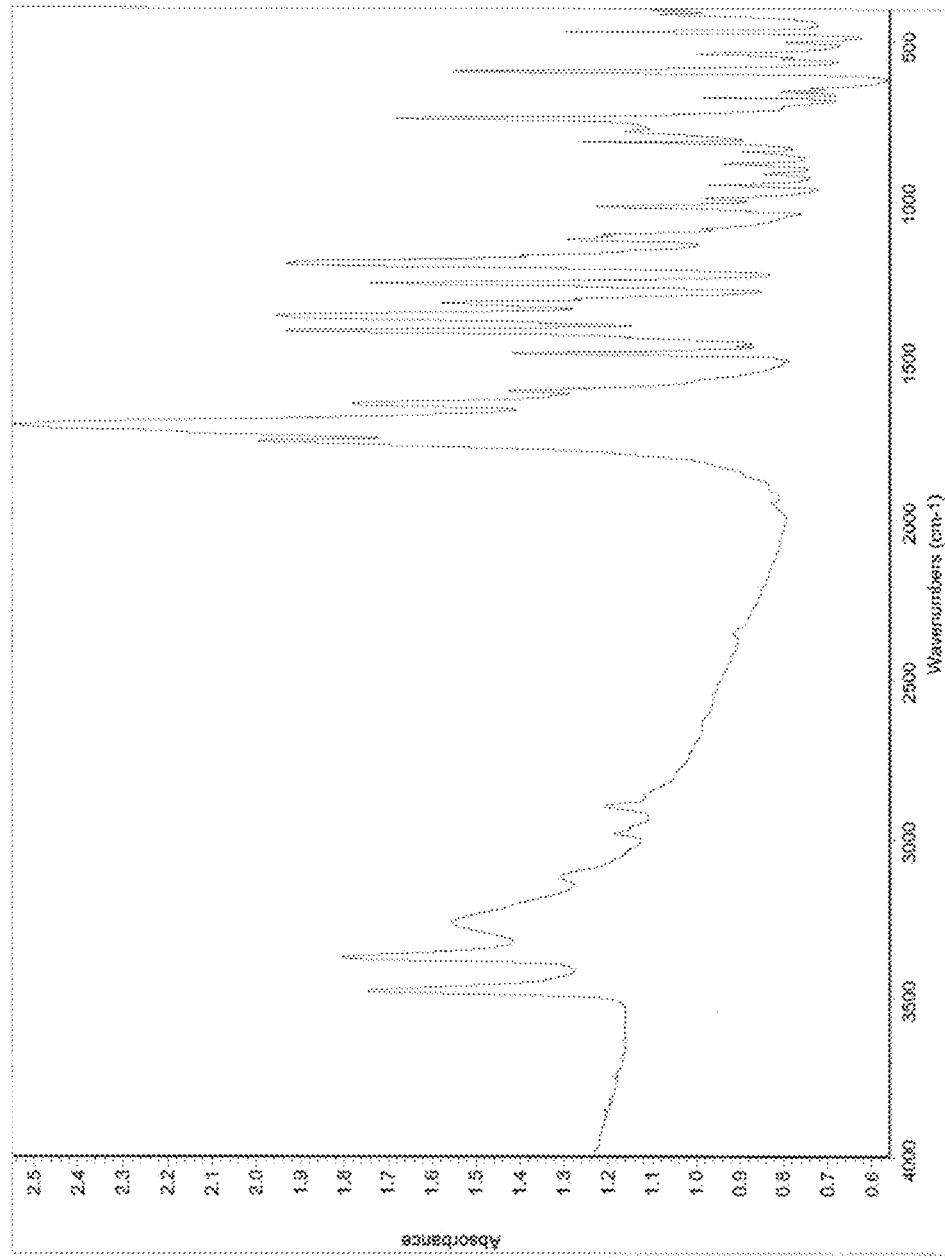


FIGURE 4



## 1

**CRYSTALLINE  
4-AMINO-2-(2,6-DIOXOPIPERIDINE-3-YL)ISOINDOLINE-1,3-DIONE  
MONOHYDRATE, COMPOSITIONS AND  
METHODS OF USE THEREOF**

This application claims priority to U.S. Provisional application No. 62/562,280, filed Sep. 22, 2017, the entirety of which is incorporated herein by reference.

## FIELD

Provided herein is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate. Pharmaceutical compositions comprising such solid and methods of use for treating, preventing, and managing various disorders are also provided herein.

## BACKGROUND

Many compounds can exist in different crystal forms, or polymorphs, which exhibit different physical, chemical, and spectroscopic properties. For example, certain polymorphs of a compound may be more readily soluble in particular solvents, may flow more readily, or may compress more easily than others. See, e.g., P. DiMartino, et al., *J. Thermal Anal.*, 48:447-458 (1997). In the case of drugs, certain solid forms may be more bioavailable than others, while others may be more stable under certain manufacturing, storage, and biological conditions.

Polymorphic forms of a compound are known in the pharmaceutical arts to affect, for example, the solubility, stability, flowability, fractability, and compressibility of the compound, as well as the safety and efficacy of drug products comprising it. See, e.g., Knapman, K. *Modern Drug Discoveries*, 2000, 53. Therefore, the discovery of new polymorphs of a drug can provide a variety of advantages.

The identification and selection of a solid form of a pharmaceutical compound are complex, given that a change in solid form may affect a variety of physical and chemical properties, which may provide benefits or drawbacks in processing, formulation, stability, bioavailability, storage, handling (e.g., shipping), among other important pharmaceutical characteristics. Useful pharmaceutical solids include crystalline solids and amorphous solids, depending on the product and its mode of administration. Amorphous solids are characterized by a lack of long-range structural order, whereas crystalline solids are characterized by structural periodicity. The desired class of pharmaceutical solid depends upon the specific application; amorphous solids are sometimes selected on the basis of, e.g., an enhanced dissolution profile, while crystalline solids may be desirable for properties such as, e.g., physical or chemical stability.

Pomalidomide has a chemical name of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione. Pomalidomide is a compound that inhibits, for example, LPS induced monocyte TNF $\alpha$ , IL-1 $\beta$ , IL-12, IL-6, MIP-1, MCP-1, GM-CSF, G-CSF, and COX-2 production, and may be used in treating various disorders. See, e.g., U.S. Pat. Nos. 5,635,517, 6,316,471, 6,476,052, 7,393,863, 7,629,360, 7,863,297, 8,198,262, 8,673,939, 8,735,428, 8,759,375, 8,722,647, and 9,282,215. Pomalidomide has direct anti-myeloma tumoricidal and immunomodulatory activities, and inhibits stromal cell support for multiple myeloma tumor cell growth. Pomalidomide inhibits proliferation and induces apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibits the proliferation of lenalidomide-resistant multiple

## 2

myeloma cell lines and synergizes with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhances T cell- and natural killer (NK) cell-mediated immunity, and inhibits production of pro-inflammatory cytokines (e.g., TNF- $\alpha$  and IL-6) by monocytes. Pomalidomide also inhibits angiogenesis by blocking the migration and adhesion of endothelial cells. A molecular target of pomalidomide is cereblon, a protein that forms a ubiquitin E3 ligase complex with DNA damage-binding protein (DDBA), culin 4 (CUL4) and protein Roc 1. Pomalidomide binding to cereblon induces the polyubiquitination of two substrate proteins Ikaros (IKF1) and Aiolos (IKZF3). Pomalidomide is known to have CNS penetration. Due to its diversified pharmacological properties, pomalidomide is useful in treating, preventing, and/or managing various diseases or disorders.

Pomalidomide and methods of synthesizing pomalidomide are described, e.g., in U.S. Pat. Nos. 5,635,517, 6,335,349, 6,316,471, 6,476,052, 7,041,680, 7,709,502, and 7,994,327. The chemical structure of pomalidomide has been known since at least the 1960s, but little is known regarding solid forms. An amorphous solid and one crystalline form (anhydrous) have been described in WO 2013/126326. A novel crystalline form of pomalidomide is described herein.

Pomalidomide is the active ingredient in POMALYST®, which in combination with dexamethasone was approved by the FDA in 2013 for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated a disease progression on or within 60 days of completion of the last therapy. The label for POMALYST® can be found at <http://www.pomalyst.com/?pi=yes&gclid=CMF4keDY-tMCFZOCfgods7oPsA>.

New polymorphic forms of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione can further the development of formulations for the treatment of chronic illnesses, and may yield numerous formulation, manufacturing and therapeutic benefits.

## SUMMARY

Provided herein is a crystalline form of pomalidomide. Also provided herein are pharmaceutical compositions comprising a crystalline form of pomalidomide. Further provided herein are methods of treating or preventing a variety of disease and disorders, which comprise administering to a patient a therapeutically effective amount of a crystalline form of pomalidomide. Also provided herein are methods of treating multiple myeloma, optionally in combination with dexamethasone.

Also provided herein are methods of preparing, isolating, and characterizing crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate provided herein.

Also provided herein are pharmaceutical compositions containing crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate provided herein.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 provides a representative X-ray powder diffraction (XRPD) pattern of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate.

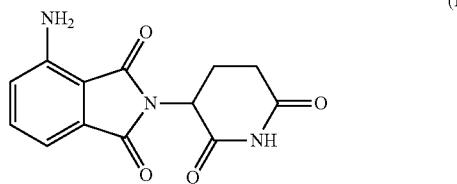
FIG. 2 provides a representative differential scanning calorimetry (DSC) thermogram of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate.

FIG. 3 provides a representative thermogravimetric analysis thermogram (TGA) of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate.

FIG. 4 provides a representative infrared (IR) spectrum of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate.

### DEFINITIONS

As used herein, and unless otherwise specified, the compound referred to herein by the name pomalidomide or 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione, corresponds to a compound of Formula (I), depicted below.



Pomalidomide can be obtained via standard, synthetic methods (see, e.g., U.S. Pat. No. 5,635,517).

Unless otherwise specified, the term "crystalline" and related terms used herein, when used to describe a substance, component, product, or form, mean that the substance, component, product, or form is substantially crystalline, for example, as determined by X-ray diffraction. (see, e.g., *Remington's Pharmaceutical Sciences*, 20<sup>th</sup> ed., Lippincott Williams & Wilkins, Philadelphia Pa., 173 (2000); *The United States Pharmacopeia*, 37<sup>th</sup> ed., 503-509 (2014)).

As used herein, and unless otherwise specified, the terms "about" and "approximately," when used in connection with doses, amounts, or weight percents of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by one of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. In certain embodiments, the terms "about" and "approximately," when used in this context, contemplate a dose, amount, or weight percent within 30%, within 20%, within 15%, within 10%, or within 5%, of the specified dose, amount, or weight percent.

As used herein, and unless otherwise specified, the terms "about" and "approximately," when used in connection with a numeric value or range of values which is provided to characterize a particular solid form, e.g., a specific temperature or temperature range, such as, for example, that describes a melting, dehydration, desolvation, or glass transition temperature; a mass change, such as, for example, a mass change as a function of temperature or humidity; a solvent or water content, in terms of, for example, mass or a percentage; or a peak position, such as, for example, in analysis by, for example, IR or Raman spectroscopy or XRPD; indicate that the value or range of values may deviate to an extent deemed reasonable to one of ordinary skill in the art while still describing the solid form. Techniques for characterizing crystal forms and amorphous forms include, but are not limited to, thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), single-crystal X-ray diffractometry, vibrational spectroscopy, e.g., infrared (IR) and Raman spectroscopy, solid-state and solution nuclear

magnetic resonance (NMR) spectroscopy, optical microscopy, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography and quantitative analysis, particle size analysis (PSA), surface area analysis, solubility studies, and dissolution studies. In certain embodiments, the terms "about" and "approximately," when used in this context, indicate that the numeric value or range of values may vary within 30%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1.5%, 1%, 0.5%, or 0.25% of the recited value or range of values. In the context of molar ratios, "about" and "approximately" indicate that the numeric value or range of values may vary within 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1.5%, 1%, 0.5%, or 0.25% of the recited value or range of values. It should be understood that the numerical values of the peaks of an X-ray powder diffraction pattern may vary from one machine to another, or from one sample to another, and so the values quoted are not to be construed as absolute, but with an allowable variability, such as  $\pm 0.2$  degrees two theta ( $^{\circ} 2\theta$ ), or more. For example, in some embodiments, the value of an XRPD peak position may vary by up to  $\pm 0.2$  degrees  $2\theta$  while still describing the particular XRPD peak.

As used herein, and unless otherwise specified, a solid form that is "substantially physically pure" is substantially free from other solid forms. In certain embodiments, a crystal form that is substantially physically pure contains less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.05%, or 0.01% of one or more other solid forms on a weight basis. The detection of other solid forms can be accomplished by any method apparent to a person of ordinary skill in the art, including, but not limited to, diffraction analysis, thermal analysis, elemental combustion analysis and/or spectroscopic analysis.

As used herein, and unless otherwise specified, a solid form that is "substantially chemically pure" is substantially free from other chemical compounds (i.e., chemical impurities). In certain embodiments, a solid form that is substantially chemically pure contains less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.05%, or 0.01% of one or more other chemical compounds on a weight basis. The detection of other chemical compounds can be accomplished by any method apparent to a person of ordinary skill in the art, including, but not limited to, methods of chemical analysis, such as, e.g., mass spectrometry analysis, spectroscopic analysis, thermal analysis, elemental combustion analysis and/or chromatographic analysis.

As used herein, and unless otherwise indicated, a chemical compound, solid form, or composition that is "substantially free" of another chemical compound, solid form, or composition means that the compound, solid form, or composition contains, in certain embodiments, less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.05%, or 0.01% by weight of the other compound, solid form, or composition.

Unless otherwise specified, the terms "solvate" and "solvated," as used herein, refer to a solid form of a substance which contains solvent. The terms "hydrate" and "hydrated" refer to a solvate wherein the solvent is water. The term "monohydrate" refers to a hydrate containing approximately one mole of water per mole of compound.

As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" refer to the eradication or amelioration of a disease or disorder, or of one or more

5

symptoms associated with the disease or disorder. In certain embodiments, the terms refer to minimizing the spread or worsening of the disease or disorder resulting from the administration of one or more prophylactic or therapeutic agents to a subject with such a disease or disorder. In some embodiments, the terms refer to the administration of a compound provided herein, with or without other additional active agent, after the onset of symptoms of a particular disease.

Unless otherwise specified, the term "composition" as used herein is intended to encompass a product comprising the specified ingredient(s) (and in the specified amount(s), if indicated), as well as any product which results, directly or indirectly, from combination of the specified ingredient(s) in the specified amount(s). By "pharmaceutically acceptable," it is meant a diluent, excipient, or carrier in a formulation must be compatible with the other ingredient(s) of the formulation and not deleterious to the recipient thereof.

Unless otherwise specified, the term "subject" is defined herein to include animals, such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, and the like. In specific embodiments, the subject is a human.

Unless otherwise specified, to the extent that there is a discrepancy between a depicted chemical structure of a compound provided herein and a chemical name of a compound provided herein, the chemical structure shall control.

## DETAILED DESCRIPTION

Crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate can be prepared by the methods described herein, including the methods described in the Example below, or by techniques known in the art, including heating, cooling, freeze drying, lyophilization, quench cooling the melt, rapid solvent evaporation, slow solvent evaporation, solvent recrystallization, antisolvent addition, slurry recrystallization, crystallization from the melt, desolvation, recrystallization in confined spaces such as, e.g., in nanopores or capillaries, recrystallization on surfaces or templates such as, e.g., on polymers, recrystallization in the presence of additives, such as, e.g., co-crystal counter-molecules, desolvation, dehydration, rapid cooling, slow cooling, exposure to solvent and/or water, drying, including, e.g., vacuum drying, vapor diffusion, sublimation, grinding (including, e.g., cryo-grinding, solvent-drop grinding or liquid assisted grinding), microwave-induced precipitation, sonication-induced precipitation, laser-induced precipitation and precipitation from a supercritical fluid. The particle size of the resulting solid forms, which can vary, e.g., from nanometer dimensions to millimeter dimensions, can be controlled, e.g., by varying crystallization conditions, such as, e.g., the rate of crystallization and/or the crystallization solvent system, or by particle-size reduction techniques, e.g., grinding, milling, micronizing or sonication.

While not intending to be bound by any particular theory, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate is characterized by physical properties, e.g., stability, solubility and dissolution rate, appropriate for pharmaceutical and therapeutic dosage forms. Moreover, while not wishing to be bound by any particular theory, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate is characterized by physical properties (e.g., density, compressibility, hardness, morphology, cleavage, stickiness, solubility, water uptake, electrical properties, thermal behavior, solid-state

6

reactivity, physical stability, and chemical stability) affecting particular processes (e.g., yield, filtration, washing, drying, milling, mixing, tabletting, flowability, dissolution, formulation, and lyophilization) which make certain solid forms 5 suitable for the manufacture of a solid dosage form. Such properties can be determined using particular analytical chemical techniques, including solid-state analytical techniques (e.g., X-ray diffraction, microscopy, spectroscopy and thermal analysis), as described herein and known in the art.  
10

Certain embodiments herein provide compositions comprising crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate. Certain embodiments provide compositions of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate in combination with other active ingredients. Certain embodiments provide methods of using these compositions in the treatment, prevention or management of diseases and disorders including, but not limited to, the diseases and disorders provided herein.

Certain embodiments herein provide crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrates can be obtained from a 2:1 THF/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrates can be obtained from a 1:12 1,2-dioxane/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrates can be obtained from a 1:1 1,4-dioxane/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrates can be obtained from a 1:1:1 acetone/isopropanol alcohol/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrates can be obtained from a 2:1:1 ethanol/THF/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrates can be obtained from a 1:1 1,4-dioxane/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrates can be obtained from a 1:1 ethanol/water mixture.

45 In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate.

In certain embodiments, crystalline 4-amino-2-(2,6-dioxo-3-yl)isoindoline-1,3-dione monohydrate may be characterized by X-ray powder diffraction analysis.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having an X-ray powder diffraction pattern comprising peaks at 11.8, 17.1, and 24.2 degrees  $2\theta \pm 0.2$  degrees  $2\theta$ .

55 In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate wherein the X-ray powder diffraction pattern further comprises peaks at 13.9, 16.5, and 25.7 degrees  $2\theta \pm 0.2$  degrees  $2\theta$ .

In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate is characterized by XRPD peaks located at one, two, three, four, five, six, seven, eight, nine, ten, eleven or twelve of the following approximate positions: 8.3, 11.3, 11.8, 12.7, 13.9, 16.1, 16.5, 17.1, 18.3, 19.1, 19.6, 23.8, 24.2, 24.7, 25.7, 26.9, 27.2, 27.9, 28.5, 29.5, 32.1, 32.6, and 33.9 degrees 2θ. In certain embodiments, crystalline 4-amino-2-(2,6-dioxopip-

eridine-3-yl)isoindoline-1,3-dione monohydrate is characterized by an XRPD pattern which matches the pattern exhibited in FIG. 1. In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate is characterized by an XRPD pattern having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 peaks matching peaks in the representative XRPD pattern provided herein.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having an X-ray powder diffraction pattern corresponding to the representative X-ray powder diffraction patterns depicted in FIG. 1.

In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate may be characterized by thermal analysis.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a differential scanning calorimetry thermogram comprising an endotherm with a maximum at about 312° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a differential scanning calorimetry thermogram corresponding to the representative differential scanning calorimetry thermograms depicted in FIG. 2.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having approximately 6.2% of water by mass.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 6.1% when heated from about 30° C. to about 225° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 4.9% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 5.6% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 5.7% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 5.8% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 6.1% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 6.5% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 6.7% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 6.7% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 6.7% when heated from about 30° C. to about 225° C.

weight loss of about 6.8% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 6.9% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 7.4% when heated from about 30° C. to about 225° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of between about 4.9% and about 7.4% when heated from about 30° C. to about 225° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram corresponding to the representative thermogravimetric analysis thermogram depicted in FIG. 3.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having an infrared spectrum corresponding to the representative infrared spectrum depicted in FIG. 4.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate which is substantially physically pure.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate which is substantially chemically pure.

In one embodiment, provided is a pharmaceutical composition comprising a crystal form of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate.

#### Pharmaceutical Compositions

Pharmaceutical compositions and single unit dosage forms comprising crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate are provided herein. Also provided herein are methods for preparing pharmaceutical compositions and single unit dosage forms comprising crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate. For example, in certain embodiments, individual dosage forms comprising crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate provided herein or prepared using crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate provided herein may be suitable for oral, mucosal (including rectal, nasal, or vaginal), parenteral (including subcutaneous, intramuscular, bolus injection, intraarterial, or intravenous), sublingual, transdermal, buccal, or topical administration.

In certain embodiments, pharmaceutical compositions and dosage forms provided herein comprise crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate. Certain embodiments herein provide pharmaceutical compositions and dosage forms comprising a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate, wherein the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate is substantially pure. Certain embodiments herein provide pharmaceutical compositions and dosage forms comprising a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate as provided herein, which is substantially free of other crystalline solid forms of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione and/or amorphous solid forms of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione.

eridine-3-yl)isoindoline-1,3-dione. Pharmaceutical compositions and dosage forms provided herein typically also comprise one or more pharmaceutically acceptable excipients, diluents or carriers.

Single unit dosage forms provided herein are suitable for oral or parenteral (e.g., subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial) administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules powders and sterile solids that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

Capsules may contain a shell.

The composition, shape, and type of dosage forms provided herein will typically vary depending on their use. A parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease or disorder. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. See, e.g., *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton Pa. (1990).

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form.

In one embodiment, suitable excipients include mannitol, pregelatinized starch, and sodium stearyl fumarate.

Capsule shells may contain gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, white ink, and black ink.

Capsule shells may contain gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, FD&C red 3, and white ink.

Capsule shells may contain gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, and white ink.

Capsule shells may contain gelatin, titanium dioxide, FD&C blue 1, FD&C blue 2, and white ink.

Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms provided herein lie within the range of from about 0.1 mg to about 1,000 mg per day, given as a single once-a-day dose in the morning or as divided doses throughout the day. More specifically, the daily dose may be administered twice, three times, or four times daily in equally divided doses. Specifically, a daily dose range may be from about 0.1 mg to about 500 mg per day, more specifically, between about 0.1 mg and about 200 mg per day. A daily dose range may be 1 mg, 2 mg, 3 mg, 4 mg, or 5 mg. In managing the patient, the therapy may be initiated at a lower dose, perhaps about 1 mg to about 25 mg, and increased if necessary up to about 200 mg to about 1,000 mg per day as either a single dose or divided doses, depending on the patient's global response.

#### Oral Dosage Forms

Pharmaceutical compositions provided herein that are suitable for oral administration can be presented as discrete

dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton Pa. (1990).

Typical oral dosage forms provided herein are prepared by combining the active ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrose, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101™, AVICEL-PH-103™, AVICEL RC-581™, AVICEL-PH-105™ (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, Pa.), and mixtures thereof. A specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVI-

**11**

CEL RC-58<sup>TM</sup>. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103<sup>TM</sup> and Starch 1500 LM<sup>TM</sup>.

Disintegrants are used in the compositions provided herein to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, specifically from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms provided herein include, but are not limited to, agar-agar, alginic acid, calcium carbonate, micro-crystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage forms provided herein include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200<sup>TM</sup>, manufactured by W.R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, Tex.), CAB-O-SIL<sup>TM</sup> (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass.), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about one weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

## Parenteral Dosage Forms

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial injection. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms provided herein are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous

**12**

vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms provided herein.

## EXAMPLES

<sup>10</sup> Preparation of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate: 10 mg of pomalidomide Form A (anhydrate) was placed in a 50 mL round bottom flask with 20 mL THF and 10 mL water. The flask was then placed on a rotary evaporator with the bath temperature at 80° C. All of the pomalidomide dissolved. An aspirator vacuum was then applied and the yellow crystalline solid was obtained within about two minutes. The solid was further air dried by exposure to the laboratory atmosphere for 25 days.

<sup>20</sup> Karl-Fischer titration revealed the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate contained 6.3% water.

<sup>25</sup> XRPD data for the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate is shown below in Table 1.

<sup>30</sup> Scan Type: Normal

Start Angle: 3 deg

Stop Angle: 35 deg.

<sup>35</sup> Num Points: 1601

Step Size: 0.02 deg.

Datafile Res: 1600

Scan Rate: 0.001000

Scan Mode: Step

<sup>40</sup> Wavelength: 1.540562 Å

Tube divergent 2.00 mm

Tube scatter 4.00 mm

Detector scatter 0.50 mm

Detector reflection 0.30 mm

TABLE 1

XRPD data for crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate.			
Peaks: (Deg.)	Position (Dsp.)	Intensity (cps)	Rel. Int. %
8.3	10.6504	123.31	17.67
11.3	7.7913	163.28	23.39
11.8	7.4995	559.60	80.17
12.7	6.9455	105.26	15.08
13.9	6.3726	340.48	48.78
16.1	5.5041	103.76	14.87
16.5	5.3709	259.85	37.23
17.1	5.1943	697.98	100.00
18.3	4.8425	226.92	32.51
19.1	4.6392	92.73	13.29
19.6	4.5161	87.72	12.57
23.8	3.7408	192.38	27.56
24.2	3.6695	483.43	69.26
24.7	3.5969	207.62	29.75
25.7	3.4685	338.07	48.43
26.9	3.3145	126.32	18.10
27.2	3.2752	100.75	14.43
27.9	3.1956	152.38	21.83
28.5	3.1315	220.72	31.62
29.5	3.0280	134.34	19.25
32.1	2.7884	130.83	18.74
32.6	2.7472	95.74	13.72
33.9	2.6410	123.31	17.67

## 13

Additional experiments to prepare crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate are listed below.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:12 1,4-dioxane:water solution at 60° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator, triturated with water, and vacuum dried at rt for 2 hours. The resulting solid was found to have 6.1% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 2:1 THF:water solution at 80° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator and air dried. The resulting solid was found to have 5.8% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 1,4-dioxane:water solution at 85° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator and air dried overnight. The resulting solid was found to have 6.7% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 1,4-dioxane:water solution at 80° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator, triturated with water. The resulting solid was found to have 6.5% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 1,4-dioxane:water solution at 90° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator, triturated with water, vacuum dried, 100 C for 1 h. The resulting solid was found to have 5.8% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1:1, acetone:IPA:water solution at 90° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator, dried overnight at rt, vacuum for 0.5 h. The resulting solid was found to have 4.9% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 2:1:1 ethanol:THF:water solution at 95° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator. The resulting solid was found to have 5.7% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 1,4-dioxane:water solution at 80° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator, triturated with water, and dried under vacuum. The resulting solid was found to have 5.6% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 ethanol:water solution at 80° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator. The resulting solid was found to have 7.4% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 ethanol:water solution at 80° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator. The resulting solid was found to have 6.9% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 ethanol:water solution at 80° C. The pomalidomide dissolved completely in the solution. The

## 14

solution was taken to dryness on a rotary evaporator, and further dried at 50° C. for 2 h. The resulting solid was found to have 6.8% water by TGA analysis.

5 Additional Experiments that Did not Result in Crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate

10 The following unsuccessful experiments were performed by mixing in a flask Form A of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione with solvents until dissolution, then the flask was placed on a rotoevaporator (fast rotation; vacuum by water aspirator) at various bath temperatures until dryness or until apparent dryness.

Certain experiments produced an oil, which were then triturated as follows: pure HPLC grade water was added to flask containing the oil, and the flask was stirred. If a solid was formed, it was further dried.

TABLE 2

Conditions that did not result in a crystalline monohydrate of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione.				
		Ratio of solvent/ co-solvent	Temperature (° C.)	Notes
30	Solvent	Co-solvent		
	1,4-dioxane	N/A	60	
	THF	Water	10:1	60 Triturated vacuum dried
	THF	Water	1:1	80
	Ethanol	Water	1:1	80 100° C. for 12 hours after initial drying
	Ethanol	Water	1:1	Dried further for 20 min at 100° C., then 30 min at 150° C.
35	THF	Water	1:1	80
	1,4-dioxane	Water	1:1	80
	THF	Water	24:5	80
	THF	Water	23:5	80
40	1,4-dioxane	Water	1:1	80 Triturated, dried at 150° C. for 1 h
	THF	Water	95:5	65
	Ethanol	Water	95:5	90
	Ethanol	Water	98:2	90
	THF	Water	9:1	85
	Ethanol	THF/Water	2:1:2	60
	Ethanol	THF/Water	2:1:2	95
	Ethanol	THF/Water	1:6:1	95
	Ethanol	THF/Water	6:4:1	95
	Ethanol	THF/Water	1:2:1	95
	1,4-dioxane	Water	1:1	95 Triturated
	1,4-dioxane	Water	1:1	95 Triturated, air dried, 45 m in vacuo
45	Ethanol	THF/Water	3:5:3	80 Air dried 3 h
	Ethanol	THF/Water	3:5:3	80
	Acetone	i-PrOH/Water	1:1:1	90
	Acetone	i-PrOH/Water	1:1:1	95 Material was moist
	Acetone	i-PrOH/Water	1:1:1	Air dried 18 h
	Acetone	i-PrOH/Water	1:1:1	Air current dried 3 h
	Acetone	i-PrOH/Water	1:1:1	Air current dried 1 h
50	Acetone	i-PrOH/Water	1:1:1	85
	1,4-dioxane	Water	1:1	85 Material was moist
	THF	Water	1:1	Air dried
	THF	Water	1:1	Dried in vacuo for 2 h at 200° C.
55	1,4-dioxane	Water	1:1	Triturated, dried in vacuo 16 h
	THF	Water	4:1	95
	THF	Water	4:1	80
	THF	Water	4:1	65
60	1,4-dioxane	Water	1:1	95
	1,4-dioxane	Water	4:1	80 Oil, triturated, air dried 4 h
65	1,4-dioxane	Water	4:1	80

## 15

TABLE 2-continued

Conditions that did not result in a crystalline monohydrate of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione.

Solvent	Co-solvent	Ratio of solvent/ co-solvent	Tem- pera- ture (° C.)	Notes
1,4-dioxane	Water	3:1	85	Air dried 3 h
1,4-dioxane	Water	3:1	85	Dried overnight at room temperature
1,4-dioxane	Water	3:1	85	Triturated, dried
THF	Water	4:1	80	Air dried 1 h
THF	Water	12:1	70	Air dried
THF	Water	6:1	80	Air dried
MeCN	Water	2:1	80	Material was moist
MeCN	Water	2:1	80	Dried overnight
MeCN	Water	2:1	90	Air dried
1,4-dioxane	Ethanol/ THF/Water	1:1:1:2	85	Air dried
1,4-dioxane	THF/Water	6:6:1	50	Material was moist
1,4-dioxane	THF/Water	6:6:1	50	Dried at 90° C. in vacuo
1,4-dioxane	THF/Water	6:6:1	50	Air dried
Acetone	THF/Water	10:3:3	90	Air dried
THF	Water	25:1	60	Air dried
THF	Water	25:1	60	
THF	Water	20:1	70	
THF	Water	4:1	80	Air dry
THF	Water	10:1	65	Air dry
THF	Water	10:1	75	
Acetone	THF/Water	10:1:1	60	Air dry
1,4-dioxane	Water	3:1	85	Triturated
1,4-dioxane	Water	12:1	60	Triturated

## Characterization Methodology

Samples generated as described in the solid form screen were typically analyzed by X-Ray Powder Diffraction (XRPD). XRPD was conducted on a Scintag X2 X-ray powder diffractometer using Cu K $\alpha$  radiation at 1.54 Å. In general, positions of XRPD peaks are expected to individually vary on a measurement-by-measurement basis by about  $\pm 0.2^\circ$ . In general, as understood in the art, two XRPD patterns match one another if the characteristic peaks of the first pattern are located at approximately the same positions as the characteristic peaks of the second pattern. As understood in the art, determining whether two XRPD patterns match or whether individual peaks in two XRPD patterns match may require consideration of individual variables and parameters such as, but not limited to, preferred orientation, phase impurities, degree of crystallinity, particle size, variation in diffractometer instrument setup, variation in XRPD data collection parameters, and/or variation in XRPD data processing, among others. The determination of whether two patterns match may be performed by eye and/or by computer analysis. An example of an XRPD pattern collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. 1.

Differential Scanning calorimetry (DSC) analyses were performed on a TA Instruments Q100™. About 5 mg of sample was placed into a tared DSC closed aluminum pan and the weight of the sample was accurately recorded. An example of a DSC thermogram collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. 2.

## 16

Thermal Gravimetric Analyses (TGA) were performed on a TA Instruments Q50™. About 10 mg of sample was placed on an open aluminium pan, accurately weighed and loaded into the TGA furnace.

An example of a TGA thermogram collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. 3.

Water determination by the Karl Fischer method was performed using a Metrohm 831 KF Coulometer. The sample was dissolved in anhydrous acetone and injected into the titrator.

Infrared spectroscopy was performed using a ThermoNi-colet Nexus 670 spectrometer. A sample of ca. 1 mg of the monohydrate in ca. 100 mg KBr. The mixture was then pressed into a pellet, which was used for the IR study. An example of an IR spectrum collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. 4.

The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the disclosure and are encompassed by the appended claims.

Citation or identification of any reference in this application is not an admission that such reference is available as prior art. The full scope of the disclosure is better understood with reference to the appended claims.

The invention claimed is:

1. Crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate, having an X-ray powder diffraction pattern comprising peaks at 11.8, 17.1, and 24.2 degrees  $2\theta \pm 0.2$  degrees  $2\theta$ .

2. The monohydrate of claim 1, wherein the X-ray powder diffraction pattern further comprises peaks at 13.9, 16.5, and 25.7 degrees  $2\theta \pm 0.2$  degrees  $2\theta$ .

3. The monohydrate of claim 1, having an X-ray powder diffraction pattern corresponding to the representative X-ray powder diffraction pattern depicted in FIG. 1.

4. The monohydrate of claim 1, having a differential scanning calorimetry thermogram comprising an endotherm with a maximum at about 312° C.

5. The monohydrate of claim 1, having a differential scanning calorimetry thermogram corresponding to the representative differential scanning calorimetry thermogram depicted in FIG. 2.

6. The monohydrate of claim 1, having about 6.2% of water by mass.

7. The monohydrate of claim 1, having a thermogravimetric analysis thermogram comprising a weight loss of between about 4.9% and about 7.4% when heated from about 30° C. to about 225° C.

8. The monohydrate of claim 1, having a thermogravimetric analysis thermogram corresponding to the representative thermogravimetric analysis thermogram depicted in FIG. 3.

9. The monohydrate of claim 1, having an infrared spectrum corresponding to the representative infrared spectrum depicted in FIG. 4.

\* \* \* \* \*