**IN THE UNITED STATES DISTRICT COURT**
**FOR THE NORTHERN DISTRICT OF WEST VIRGINIA**

**NOVARTIS PHARMACEUTICALS CORPORATION,**

**Plaintiff/Counter-Defendant,**

**v.** **CIVIL NO. 1:19-CV-201 (KLEEH)**

**MYLAN PHARMACEUTICALS INC.,**

**Defendant/Counter-Claimant.**

**AMENDED[1] MEMORANDUM OPINION AND ORDER MAKING FINDINGS OF FACT AND GRANTING JUDGMENT IN FAVOR OF PLAINTIFF NOVARTIS PHARMACEUTICALS CORPORATION**

In this patent infringement action, the Plaintiff, Novartis Pharmaceuticals Corporation ("Novartis"), and the Defendant, Mylan Pharmaceuticals, Inc. ("Mylan"), dispute whether claims 1 and 11 of United States Patent No. 8,877,938 (the "'938 Patent") and claim 5 of Patent No. 9,388,134 (the "'134 Patent") are valid and enforceable. The parties stipulate that if Mylan infringes claim 1 of the '938 Patent, it also infringes claim 11 of the '938 patent and claim 5 of the '134 Patent. The asserted claims are associated with Novartis's product "Entresto" and Mylan's filing of Abbreviated New Drug Applications ("ANDAs") with the Food and Drug Administration ("FDA") seeking to commercially manufacture, use, offer to sell, and/or sell generic sacubitril/valsartan tablets

[1] Upon review and consideration, the Court has amended Paragraph 20 on page 68.

for the treatment of heart failure.

## I. FINDINGS OF FACT

### A. Background

#### i. Patents-in-Suit and Asserted Claims

1. Novartis owns the '938 and '134 patents. Joint Statement of Uncontested Facts to the Joint Pretrial Order (C.A. No. 19-cv-201-TSK, D.I. 104) ("UF"), Ex. 1 at 11, ¶¶ 59-60.

2. Novartis asserts that Mylan infringes claims 1 and 11 of the '938 patent and claim 5 of the '134 patent. UF, Ex. 1F at 2, ¶ 11; Tr. 43:1-4 (Matzger).

3. Mylan has stipulated that if the Court finds that Mylan's ANDA Products will infringe the '938 patent claim 1, then Mylan will also infringe the '938 patent claim 11 and the '134 patent claim 5. D.I. 100. Thus, the Court will only address the '938 patent claim 1.

4. The '938 patent claim 1 recites trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)priopionate-(S)-3'-methyl-2'-(pentanoyl{2"-tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate ("trisodium [sacubitril-valsartan] hemipentahydrate" or "TSVH") in crystalline form. JTX 5 at claim 1; UF, Ex. 1 at 13-15, ¶¶ 77, 80; Tr. 43:18-44:18 (Matzger).

5. TSVH comprises sacubitril, valsartan, sodium, and water molecules in a ratio of 1:1:3:2.5, respectively. Tr. 43:23-44:12 (Matzger); Tr. 447:16-20, 453:16-454:2 (Rogers); UF, Ex. 1 at 21, ¶¶ 35-36; JTX 5 at 16:14-45. The theoretical weight percent of the 2.5 water molecules in TSVH is 4.70% w/w. Tr. 67:2-68:1 (Matzger); PTX 1068.

6. A chemical compound and its crystalline form are distinct concepts. Tr. 61:17-62:4 (Matzger); *see* JTX 8A at NPC-VS-0003150-53, 3769. The term "crystalline form" refers to a chemical compound that is arranged in a regular repeating array in three dimensions to form a crystal lattice. Tr. 45:12-46:11 (Matzger); Tr. 448:9-20 (Rogers); Tr. 269:15-25 (Friscic). Different three-dimensional arrangements of the same chemical compound in crystalline form are referred to as "polymorphs." Tr.53:7-23 (Matzger); Tr. 270:19-271:14 (Friscic).

7. A crystalline form that is a "hydrate" contains water bound within the crystal lattice. Tr. 46:16-24 (Matzger); Tr. 403:10-13 (Friscic). Water bound within the crystal lattice is referred to as "bound water" or "water of hydration." Tr. 46:16-24 (Matzger); Tr. 254:25-255:8 (Motto); JTX 5 at 30:55-58; JTX 355 at 15. "Surface water" or "adsorbed water" is water that is not part of the crystal lattice but is on the outside of the crystal

lattice or particles. Tr. 46:25-47:6, 105:2-19, 128:7-17, 134:11-17 (Matzger); Tr. 403:14-16 (Friscic).

8. The term "hemipentahydrate" in TSVH refers to 2.5 *bound* water molecules per molecule of trisodium [sacubitril-valsartan]. Tr. 43:23-44:12, 46:16-24 (Matzger). When determining whether a trisodium [sacubitril-valsartan] compound is a "hemipentahydrate," only bound water is included and not surface water. Tr. 46:16-47:6, 48:16-20, 70:12-17, 125:9-126:6 (Matzger); Tr. 403:18-23 (Friscic).

**ii. Trial Witnesses**

9. Dr. Robin Rogers is a Professor Emeritus at the University of Alabama, and an endowed chair or named chair at the Queen's University of Belfast, McGill University, and the University of Alabama. Tr. 443:17-444:15 (Rogers); PTX 834A. He is a fellow of the American Association for the Advancement of Science, a fellow of the Royal Society of Chemistry, a fellow of the American Chemical Society, and a member of the American Crystallographic Association. *Id.* He is the founder of the American Chemical Society journal *Crystal Growth & Design*, one of the premier journals concerning crystalline states-of-matter. *Id.* He has analyzed thousands of single crystal structures. Tr. 445:4-7 (Rogers).

10. Dr. Rogers was qualified by the Court as an expert in the field of solid-state chemistry, including the analysis of single crystal data, crystallization, hydration, and polymorphism, and their applications in pharmaceutical products. Tr. 445:20-446:3. The Court finds Dr. Rogers to be credible and the testimony within his areas of expertise persuasive.

11. Dr. Matzger has been a Professor of Chemistry and Macromolecular Science and Engineering at the University of Michigan since 2000 and owns a company, ChemXLerate, that provides testing services for solid pharmaceutical forms. Tr. 40:4-12 (Matzger); PTX 952A. Dr. Matzger has extensive experience as a solid-state chemist, particularly in the characterization of the water content of crystalline compounds. Tr. 40:18-41:3 (Matzger).

12. Dr. Matzger was qualified by the Court as an expert in solid state chemistry, including analytical testing techniques for characterizing compounds in crystalline form, including water content testing and analysis. Tr. 41:16-23. The Court finds Dr. Matzger's testimony credible and likewise finds his testimony within his areas of expertise persuasive.

13. Mr. John D. Kirsch testified by deposition. Mr. Kirsch was Mylan's Rule 30(b)(6) designee on Mylan's ANDA, ANDA Products, and API. Tr. 185:18-20.

14. Mr. Jianming Wang testified by deposition. Mr. Wang was one of Crystal's Rule 30(b)(6) designees on Crystal's development and characterization of Form II. Tr. 211:7-12.

**iii. Person of Ordinary Skill in the Art**

15. As of the August 11, 2006 priority date, a POSA in the context of the '938 and '134 patents would have had a Ph.D. or a Master's degree in a chemistry-related field with two or more years of pharmaceutical chemistry experience. Tr. 56:20-57:13 (Matzger); UF, Ex. 1 at 14, ¶¶ 79, 85. The POSA alternatively could have a Bachelor's degree in chemistry or a related field with correspondingly longer experience. Tr. 56:20-57:13 (Matzger).

16. While Dr. Friscic relied on a different POSA definition that includes experience with crystallization and characterization of solid forms of pharmaceutical compounds, those differences in POSA definitions would not impact Dr. Matzger's conclusions. Tr. 56:20-57:16 (Matzger). Dr. Matzger would have been a POSA under both Novartis's and Dr. Friscic's definitions as of 2006. Tr. 57:14-16 (Matzger).

**iv. Mylan's ANDA Products**

17. Mylan filed ANDA No. 213646 ("Mylan's ANDA") with FDA seeking approval for generic sacubitril/valsartan tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg ("Mylan ANDA Products").

UF, Ex. 1 at 7, ¶ 52; UF, Ex. 1F at 1, ¶¶ 1-2.

18. Mylan has three ANDA Products, each comprising a different dosage strength of the same API. UF, Ex. 1F at 1, ¶ 1; Tr. 63:9-18 (Matzger); JTX 561 at 3-4.

19. The API used in Mylan's ANDA Products is referred to as Form II. Tr. 64:21-25 (Matzger); Tr. 396:18-20 (Friscic); Tr. 446:11-17 (Rogers); JTX 673 at 4-6. Crystal developed Form II, and Crystal and Mylan both obtain Form II from the same supplier, Harman Finochem, manufactured according to the same DMF. Tr. 49:5-23, 94:12-23 (Matzger); Tr. 281:1-6, 397:2-7 (Friscic); Tr. 224:21-23 (Wang).

20. Mylan imports Form II into the United States and formulates Form II into its ANDA Products in Puerto Rico. Tr. 436:7-14, 437:4-10 (Friscic); JTX 561 at 31; JTX 673 at 8.

21. Form II is a trisodium [sacubitril-valsartan] hydrate compound in crystalline form. Tr. 64:3-65:3 (Matzger); Tr. 398:4-6 (Friscic); PTX 614 at 12; JTX 673 at 4-6.

22. Mylan's ANDA describes Form II as a trihydrate, meaning that each trisodium [sacubitril-valsartan] complex allegedly contains 3 molecules of bound water per each sacubitril and valsartan. Tr. 64:3-14 (Matzger); Tr. 272:9-18 (Friscic); PTX 614 at 12; JTX 673 at 4-6.

23. The water content specification for Form II in Mylan's ANDA is "[n]ot more than 7.0%," which means there is no lower limit and allows Mylan's API to have 4.70% w/w bound water corresponding to a hemipentahydrate. Tr. 69:18-25 (Matzger); JTX 591 at 1; JTX 593 at 1.

24. Mylan has not studied the amount of bound water in Form II or the single crystal structure of Form II; instead, Mylan in its ANDA relies on Harman Finochem's characterization of Form II as a trihydrate and the 2019 Single Crystal Report from Crystal (JTX 647). Tr. 199:6-22 (Kirsch); Tr. 133:16-23, 144:11-145:2 (Matzger); Tr. 423:1-6 (Friscic).

25. The DMF for Form II and Crystal's '087 patent disclosing Form II likewise rely on the 2019 Single Crystal Report from Crystal to characterize From II as a trihydrate. Tr. 142:25-143:15, 144:11-145:2 (Matzger); Tr. 423:1-10 (Friscic).

26. Dr. Rogers's analysis of the single crystal structure of Form II and Dr. Matzger's testing of Form II demonstrate that Form II is a hemipentahydrate with 2.5 bound waters. Tr. 447:16-20, 462:9-17, 490:21-491:11 (Rogers); Tr. 66:20-24, 106:5-21, 145:3-6 (Matzger).

**B. Infringement**

**i. Claim Construction**

27. This matter was part of multi-district litigation before the United States District Court for the District of Delaware. Before this case was remanded back to this Court for trial the Delaware District Court construed the term "trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)priopionate-(S)-3'-methyl-2'-(pentanoyl{2"-tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate in crystalline form" in the '938 patent claim 1 as "substantially pure trisodium [sacubitril-valsartan] hemipentahydrate in crystalline form." UF, Ex. 1 at 16-17, ¶¶ 7, 10; C.A. No. 20-md-2930-RGA, D.I. 295 at 2; Tr. 52:3-18 (Matzger); Tr. 269:3-6 (Friscic).

28. The term "substantially pure" in the Court's claim construction and '938 patent means "at least 90% chemical purity." Tr. 145:14-149:12 (Matzger); JTX 5 at 6:4-22 ("[A]s used herein, 'substantially pure' refers to at least 90% . . . purity."); *see also* JTX 5 at 9:7-10; JTX 6A at NPC-VS-0002604-2606, 2611.

29. "Trisodium [sacubitril-valsartan] hemipentahydrate in crystalline form" recited in the '938 patent claim 1 is not limited to one specific crystalline form (or polymorph) of TSVH based on

the strong presumption of claim differentiation. Tr. 57:20-62:3 (Matzger).

30. Neither Mylan nor its expert Dr. Friscic offered any evidence on the meaning of "substantially pure" or "[TSVH] in crystalline form." Tr. 540:9-541:9.

**ii. The Two Disputed Infringement Issues: Whether Mylan's API Is "Substantially Pure" and Whether Mylan's API Is a "Hemipentahydrate"**

31. The '938 patent claim 1 can be separated into three elements: (1) substantially pure (2) TSVH (3) in crystalline form. JTX 5, at claim 1; UF, Ex. 1 at 14, ¶ 80; Tr. 43:18-22, 65:21-66:5 (Matzger).

32. Mylan has stipulated that its API Form II is in crystalline form as required by the '938 patent claim 1. UF, Ex. 1F ¶ 14; Tr. 65:21-66:5 (Matzger).

33. Form II is a trisodium [sacubitril-valsartan] hydrate complex as recited in the '938 patent claim 1. Tr. 64:3-65:3 (Matzger); Tr. 398:4-6 (Friscic); PTX 614 at 12; JTX 673 at 4-6.

34. The only disputed infringement issues for the '938 patent claim 1 are (1) whether Mylan's API is substantially pure, and (2) whether Mylan's API is a hemipentahydrate. Tr. 66:14-19 (Matzger); Tr. 398:7-399:3 (Friscic).

**iii. Mylan Infringes the '938 Patent Claim 1**

**a. Mylan's Form II API is Substantially Pure**

35. Crystal Pharmaceutical (Suzhou) Co., Ltd. ("Crystal"), the company that developed Form II, admitted that its ANDA Products contain substantially pure Form II and stipulated to that fact. UF, Ex. 1B ¶ 7. As discussed below, Mylan's API Form II, both alone and in its ANDA Products, is substantially pure.

36. Form II alone: Mylan's ANDA specification requires Form II to be substantially pure, *i.e.*, at least 90% chemically pure, because Form II must have not more than ("NMT") a total of 2.95% w/w impurities and residual solvents related to Form II. Tr. 149:13-24 (Matzger); Tr. 188:11-190:22, 192:14-17 (Kirsch); PTX 1108; JTX 591; JTX 593; JTX 672.

37. As summarized in the table below, Mylan reported that Batch Nos. 903901 and 903502 of Form II, which Dr. Matzger tested and on which Mylan has relied to seek FDA approval, have less than about 0.50% w/w total impurities and residual solvents. JTX 591; JTX 593; Tr. 70:22-71:6 (Matzger); PTX 1096.

| **Impurities for Mylan's API** | **Specification (JTX 591; JTX 593; JTX 672)** | **Measured Results for Batch No. 903901** | **Measured Results for Batch No. 903502 (JTX 591)** |
|---|---|---|---|

| **(Form II)**[2] | | **(JTX 593)** | |
|---|---|---|---|
| Isomeric impurities | NMT 0.80% | LT 0.37% | LT 0.21% |
| Related compounds | NMT 0.5% | LT 0.05% | LT 0.05% |
| Residual solvents | NMT 1.649% | LT 0.0826% | LT 0.0944% |
| Nitrosamine impurities | NMT 0.00008% | LT 0.000008% | LT 0.00000413% |
| TOTAL | NMT 2.94908% | LT 0.502608% | LT 0.35440413% |

38. Harman Finochem also employs purification steps as needed when manufacturing Form II to ensure Form II complies with the above specification. PTX 717A at 29564 ("material take[n] for *purification* if result not complies [*sic*]"), 29565 (further "purification" step).

39. While Dr. Matzger testified that Form II contains amorphous material, he explained that there was not "any substantial amount of amorphous material in the API," *i.e.*, less

[2] Certain impurities or residual solvents for Form II are reported in parts per million ("ppm"), where 1 ppm = 0.0001%. Certain measured impurities or residual solvents in Mylan's certificates of analysis are also reported as being "LT" or less than the reported value.

than about 0.5% w/w. Tr. 181:16-25 (Matzger). The insubstantial amount of amorphous material in Form II does not impact its substantial purity. Tr. 181:19-182:7, 183:1-4 (Matzger).

40. Form II in Mylan's ANDA Products: Mylan's ANDA specification requires Mylan's ANDA Products to contain substantially pure Form II with less than 10% w/w chemical impurities because Mylan's ANDA Products must contain NMT about 1.0% w/w total impurities related to Form II. Tr. 149:13-24 (Matzger); Tr. 192:14-195:17 (Kirsch); PTX 1108; JTX 549; JTX 550; JTX 551; JTX 561 at 9.

41. That Mylan's API Form II, both alone and in Mylan's ANDA Products, is substantially pure is further supported by the fact that Form II is in crystalline form. UF, Ex. 1F ¶ 14; Tr. 118:11-119:16 (Matzger); Tr. 438:6-12 (Friscic); PTX 1097; PTX 1103. The process of crystallization "produces very pure material." Tr. 151:22-153:2 (Matzger); JTX 679 at 481 ("Organic compounds . . . are usually *purified by crystallization* . . . ." (emphases added)).

42. During claim construction, Mylan admitted that crystalline material "was also, by definition, substantially pure." D.I. 66-2 at 66; Tr. 151:22-153:2 (Matzger).

43. Contrary to Mylan's and Dr. Friscic's suggestion that

Mylan's API may contain separate sacubitril and valsartan (Tr. 34:15-23 (Mylan opening); Tr. 346:4-25 (Friscic)), Mylan's ANDA and the DMF describe Form II as a complex of sacubitril and valsartan, not as separate components. Tr. 64:3-20 (Matzger); PTX 614 at 12; PTX 717A at 29536; JTX 673 at 4-6. Neither Mylan's ANDA nor the DMF mentions the presence of valsartan or sacubitril alone.

44. Mylan conducted IR on its batches of Form II "to identify the drug substance as Sacubitril/Valsartan," *i.e.*, the complex Form II. JTX 673 at 4, 21; JTX 591 at 1 (Batch No. 903901 of Form II confirmed to be "Sacubitril/Valsartan" by IR); JTX 593 (Batch No. 903502 confirmed to be "Sacubitril/Valsartan" by IR); *see also* PTX 717A at 29580 (DMF reporting: "We have confirmed the *Sacubitril/Valsartan structure* by spectral studies like IR, Mass spectrum, NMR (Carbon & Proton), CHN & X-RD." (emphasis added)); Tr. 436:3-9 (Friscic) (agreeing Mylan's ANDA refers to the complex Form II as "Sacubitril/Valsartan").

45. Mylan uses a dry granulation process to incorporate Form II into Mylan's ANDA Products, which means no solvent is used and the Form II complex remains intact during ANDA product manufacture. Tr. 151:17-21 (Matzger); Tr. 436:21-437:3 (Friscic); JTX 561 at 9.

46. Form II does not dissociate into separate sacubitril and valsartan in Mylan's ANDA Products. Mylan in its prescribing label

represents that its ANDA Products contain a trisodium [sacubitril-valsartan] hydrate complex, which does not dissociate into separate sacubitril and valsartan components until after the product is administered to a patient. Tr. 150:13-151:6 (Matzger); Tr. 187:23-188:6 (Kirsch); PTX 614 at 12.

47. Mylan's own studies demonstrate Mylan's Form II does not dissociate into separate sacubitril and valsartan either before or after it is incorporated into Mylan's ANDA Products. Mylan represented to FDA that "Mylan has performed studies on both the drug substance and drug product to ascertain that Sacubitril/Valsartan Form II is stable during drug product manufacture and stability (long term and accelerated) with no conversion to other polymorphic forms . . . . [T]he form II polymorphic form remains unchanged during drug product manufacture and under routine storage/stability." Tr. 150:13-151:6 (Matzger); JTX 670 at 6, 13-14; *see also* Tr. 197:6-198:9, 198:17-24 (Kirsch) (admitting that Mylan incorporates Form II into its drug product and "[t]hat's what it continues to be in our drug product").

48. Dr. Matzger confirmed by XRPD both that Mylan's API is the complex Form II and that Form II is present as a complex in

Mylan's ANDA Products.[3] Tr. 118:11-119:16 (Matzger); PTX 1097. The additional XRPD peaks not corresponding to Form II in Dr. Matzger's XRPD testing of Mylan's ANDA Products are from inactive ingredients referred to as "excipients" used to make the formulation, not from separate sacubitril or valsartan or impurities in Form II. Tr. 118:11-119:16 (Matzger); PTX 1097; *see also* Tr. 49:24-50:11, 63:9-18 (Matzger) (explaining Mylan's ANDA Products contain Form II and excipients); JTX 561 at 3-4.

49. It is undisputed that Mylan is not trying to sell an ANDA product with impurities. Tr. 151:22-152:9, 152:24-153:2 (Matzger); Tr. 347:11-23 (Friscic).

50. Dr. Friscic incorrectly relied on Mylan's HPLC method, in which Form II is dissolved in a liquid to test for chemical impurities, to assert that Dr. Matzger had only demonstrated the substantial purity of sacubitril and valsartan as individual components. Tr. 150:13-151:6 (Matzger); Tr. 346:4-25, 436:15-20 (Friscic).

51. Mylan's HPLC method is not part of Mylan's manufacturing

[3] XRPD is a common technique used for identifying crystal forms. Tr. 116:2-15 (Matzger); Tr. 277:20-278:11 (Friscic). In XRPD, X-rays are reflected off a powdered sample at certain angles. Tr. 116:2-15 (Matzger). The reflections create a pattern with characteristic peaks which can be used as a fingerprint to identify a compound in a particular crystalline form. *Id.*

process for its ANDA Products. Tr. 436:15-437:3 (Friscic).

52. Dr. Friscic admitted on cross-examination that Mylan's API Form II is a complex and remains unchanged during tableting (or formulation) for Mylan's ANDA Products. Tr. 398:4-6, 436:7-9, 438:8-12, 439:4-11 (Friscic); JTX 673 at 4.

**b. Dr. Rogers's Analysis of the Single Crystal Structure Demonstrates that Mylan's API Is a Hemipentahydrate**

53. As explained below, Dr. Rogers analyzed the chemistry of the single crystal structure for Form II and determined that it is a hemipentahydrate. Tr. 447:16-20 (Rogers).

**i) Single Crystal Analysis Tutorial**

54. The term "unit cell" refers to the smallest repeating unit of a crystal. Tr. 448:21-449:1 (Rogers); Tr. 270:2-16 (Friscic).

55. The term "asymmetric unit" refers to the smallest group of atoms that are unique to a crystal structure, and that a crystallographer must find to generate a model of the entire structure. Tr. 449:2-24 (Rogers); Tr. 271:7-15 (Friscic).

56. The term "disorder" refers to the fact that, because crystals are not perfectly uniform, certain atoms may not be present at the same location in every asymmetric unit that make up

a crystal, or may be present in some asymmetric units but completely absent from others. Tr. 450:1-5, 450:12-451:3 (Rogers).

57. The term "occupancy" describes the frequency with which an atom is present at a certain position in a crystal. Tr. 450:6-11, 451:23-452:15 (Rogers). If an atom is not always present at a particular location in a crystal, *i.e.*, is disordered, then it will have an occupancy of less than 100%, or 1.0. Tr. 451:23-452:15 (Rogers); JTX 701 at 16.

58. The number of water molecules in a crystal structure (*i.e.*, "bound" water) can be determined using single crystal analysis. Tr. 277:16-19 (Friscic); Tr. 447:16-20 (Rogers).

59. The determination of the number of bound water molecules using single crystal analysis is unaffected by the presence of surface water, or anything else (*e.g.*, impurities), outside the structure of the single crystal being analyzed. Tr. 295:18-296:5 (Friscic).

60. Synchrotron radiation produces very bright X-rays that generate good data for single crystal analysis. Tr. 278:12-20 (Friscic). Synchrotron radiation was used to generate the single crystal data for Form II. Tr. 370:13-14 (Friscic). The single crystal data for Form II were generated by Crystal — not Mylan. Tr. 446:18-447:11 (Rogers); Tr. 281:5-10 (Friscic).

61. To determine the structure of a crystal using single crystal data, a crystallographer must analyze the chemistry of the crystal, including the local chemical environment of the atoms and water molecules in the crystal. Tr. 454:4-455:20, 463:23-25, 467:16-24 (Rogers); Tr. 426:5-16 (Friscic) (admitting that bond lengths and angles should checked for sensibility).

62. If a crystallographer observes disorder in the asymmetric unit of a crystal structure, the crystallographer must resolve the disorder and determine the correct occupancy of the atoms and molecules involved with that disorder. Tr. 452:16-24, 458:13-16 (Rogers).

63. If a crystal structure suggested by software disagrees with what is known about the chemistry of the crystal structure (*e.g.*, the types of atoms that make up the structure, how close they can be, and how they are associated), the structure is likely wrong and the chemistry will dictate what the correct structure should be. Tr. 457:4-458:16 (Rogers); JTX 736 at 52.

**ii) Single Crystal Analysis Shows that Form II is a Hemipentahydrate**

64. It is undisputed that the formula unit of Form II is trisodium [sacubitril-valsartan] • x $H_2O$. Tr. 296:6-16 (Friscic); 453:21-454:2 (Rogers).

65. It is also undisputed that the asymmetric unit of Form

II consists of three formula units of trisodium [sacubitril-valsartan] • x $H_2O$, such that the asymmetric unit of Form II contains a total of 3x water molecules. Tr. 460:13-461:6 (Rogers).

66. There are ten positions for the water molecules in the asymmetric unit of Form II, labeled OW1, OW2, OW3, OW4, OW5, OW6, OW7A, OW7B, OW8 and OW9. Tr. 461:8-15 (Rogers).

67. Although the positions of the water molecules in the asymmetric unit of Form II are described in terms of their oxygen atoms (the "O" in "OW"), each water molecule consists not just of a single oxygen atom, but also two hydrogen atoms. Tr. 454:4-455:7 (Rogers).

68. For the single crystal structure of Form II to be chemically correct, the structure must provide sufficient room around each "OW" water oxygen atom to accommodate two hydrogen atoms in their proper geometry in Form II, as well as the hydrogen bonds that an "OW" water molecule forms with other nearby atoms. Tr. 455:8-20 (Rogers).

69. Crystal correctly models the water molecule OW7 in Form II as disordered over two positions in the asymmetric unit of Form II, such that it is present at position OW7A at 50% occupancy and at position OW7B at 50% occupancy. Tr. 461:11-21 (Rogers).

70. Crystal models the other eight water molecules — OW1,

OW2, OW3, OW4, OW5, OW6, OW8 and OW9 — in the asymmetric unit of Form II as present at 100%, or 1.0, occupancy in the asymmetric unit of Form II; however, Crystal incorrectly models OW1, OW3, and OW8 at 100% occupancy. Tr. 461:16-21, 462:9-17 (Rogers).

71. The occupancies of the water molecules in Crystal's incorrect model total 9 water molecules per asymmetric unit of Form II. Tr. 461:16-21 (Rogers). Nine water molecules per asymmetric unit, divided by 3 formula units per asymmetric unit, equals 3 water molecules per formula unit (*i.e.*, x = 3). *Id.* Crystal thus incorrectly concludes that Form II is a trihydrate. *Id.*

72. Dr. Rogers analyzed the chemistry of all the water molecules in Form II. Tr. 534:20-535:2 (Rogers). Based upon that analysis, Dr. Rogers determined that OW1, OW3 and OW8 cannot be present at 100% occupancy in the asymmetric unit of Form II, but instead can only be present at 50% occupancy. Tr. 462:9-15 (Rogers).

73. The occupancies of the water molecules in Dr. Rogers's correct model total 7.5 water molecules per asymmetric unit of Form II. Tr. 462:9-17 (Rogers). 7.5 water molecules per asymmetric unit, divided by 3 formula units per asymmetric unit, equals 2.5 water molecules per formula unit of Form II (*i.e.*, x = 2.5). *Id.*

Thus, Form II is a hemipentahydrate. *Id.*; PTX 1050.

74. There are multiple reasons why OW1, OW3 and OW8 are present at only 50% occupancy in Form II. Tr. 463:12-25 (Rogers).

75. First, among the water molecules present in Form II, OW1, OW3 and OW8 have the largest $U_{eq}$ thermal parameters. Tr. 464:2-14 (Rogers). For OW1, $U_{eq}$ = 0.260(8); for OW3, $U_{eq}$ = 0.413(17); for OW8, $U_{eq}$ = 0.273(9). *Id.*; JTX 652; PTX 1067.

76. Although the large thermal parameters of OW1, OW3 and OW8 are not dispositive of disorder, they provide a clue to a crystallographer that OW1, OW3 and OW8 may be disordered. Tr. 465:5-11 (Rogers).

77. Second, OW1, OW3 and OW8 are each near sodium atoms which Crystal itself acknowledges are disordered in Form II. Tr. 465:15-466:6 (Rogers).

78. Although the proximity of OW1, OW3 and OW8 to disordered sodium atoms is not dispositive of disorder, that proximity provides a clue to a crystallographer that OW1, OW3 and OW8 may also be disordered. Tr. 465:15-466:6, 467:10-14 (Rogers).

79. Third, analysis of the local chemical environments for OW1, OW3 and OW8 demonstrates that OW1, OW3 and OW8 are in fact disordered, such that OW1, OW3 and OW8 must be present at 50% occupancy in Form II. Tr. 463:23-25, 467:16-24 (Rogers).

80. Crystal's trihydrate model of Form II, in which OW1, OW3 and OW8 are present at 100% occupancy, is chemically impossible. Tr. 458:25-459:2 (Rogers). By contrast, Dr. Rogers's hemipentahydrate model of Form II, in which OW1, OW3 and OW8 are present at 50% occupancy, is chemically correct. Tr. 535:3-6 (Rogers).

**(a) OW1 Is at 50% Occupancy in Form II**

81. OW1 is closest to the disordered sodium atom, Na8. Tr. 465:21-23 (Rogers).

82. It is undisputed that Na8 is disordered over two positions such that Na8 is present at position Na8A in 50% of the asymmetric units that make up any given crystal of Form II and is present at position Na8B in the other 50% of the asymmetric units. Tr. 466:9-19 (Rogers).

83. When Na8 is at position Na8A, OW1 does not fit within the structure of Form II. Tr. 469:19-20 (Rogers); PTX 1032. When Na8 is at position Na8A, there are only 2.080 angstroms ("Å") between Na8A and OW1. Tr. 469:19-20 (Rogers); PTX 1032. 2.080 Å is insufficient to accommodate the OW1 water molecule, including its hydrogen atoms, in the geometry in which OW1 is fixed within Form II by its bond to another sodium atom, Na6. Tr. 469:19-24 (Rogers).

84. The majority of sodium-to-oxygen ("Na-O") distances in

the Inorganic Crystal Structure Database are between about 2.3-2.6 Å. Tr. 428:19-23 (Friscic). To the extent the structures in the Inorganic Crystal Structure Database contain Na-O distances less than 2.2 Å, Dr. Friscic did not consider whether those distances corresponded to sodium hydroxide molecules (*i.e.*, non-water molecules) nor did Dr. Friscic examine any such structures to determine if they were chemically reasonable. Tr. 427:16-428:15, 428:24-429:20 (Friscic).

85. The majority of Na-O distances in Dr. Friscic's Cambridge Structural Database search are between about 2.3-2.4 Å. Tr. 375:12-21 (Friscic). Only about 1 percent of structures in Dr. Friscic's search of the Cambridge Structural Database have Na-O distances less than 2.2 Å. Tr. 430:20-24 (Friscic).

86. Fanwick 2019 indicates that high and low values obtained from a search of carbon-to-oxygen bond distances in the Cambridge Structural Database are not reasonable. Tr. 432:3-20 (Friscic); JTX 736 (Fanwick 2019) at 40.

87. Dr. Friscic cited three outlier structures from the Cambridge Structural Database with Na-O distances of about 2.1 Å: Nandi 2014 (JTX 718), Tancrez 2005 (JTX 726), and Zhong 2004 (JTX 727). Tr. 375:22-377:5 (Friscic). Form II would not be expected to have similar Na-O distances to those structures because they are

chemically distinct from Form II. Tr. 512:19-513:15 (Rogers). Specifically, Dr. Rogers explained that, whereas the Nandi 2014 and Tancrez 2005 structures are highly charged lanthanide structures and the Zhong 2004 structure is a zirconium IV complex, Form II is neither. *Id.*

88. Leaving aside Na-O distances reported in the scientific literature, the 2.080 Å distance between Na8A and OW1 is an outlier in the context of Form II. Tr. 470:5-12, 513:16-22 (Rogers). It is the shortest sodium atom-to-water molecule distance in Form II. *Id.*

89. Dr. Friscic admitted that, to determine whether an Na-O distance for a particular crystal structure is reasonable, one would have to examine the chemistry of that structure, as opposed to just relying on the distance. Tr. 428:24-429:4, 430:25-431:11 (Friscic). But Dr. Friscic, unlike Dr. Rogers, did not examine the chemistry of Na8A and OW1 in Form II to determine whether a distance of 2.080 Å between them was chemically reasonable.

90. When Na8 is at position Na8B, OW1 fits within the structure of Form II. Tr. 471:14-19 (Rogers). When Na8 is at position Na8B, there are 2.939 Å between Na8B and OW1, which is sufficient to accommodate OW1. *Id.*; PTX 1033.

91. Because OW1 fits within the structure of Form II only

when Na8 is present at position Na8B, which is in 50% of the asymmetric units of Form II, OW1 must be present at 50% occupancy in Form II. Tr. 471:25-472:5 (Rogers).

92. Thus, in Form II, OW1 is present in half the asymmetric units that make up the crystal, wherein Na8 is present at position Na8B. Tr. 478:17-479:20 (Rogers). In the other half of the asymmetric units, wherein Na8 is present at position Na8A, OW1 is not there. *Id.*

93. There is a second reason why the OW1 water molecule is present at 50% occupancy in Form II based on the disorder of OW7 as it relates to OW1. Tr. 472:15-17 (Rogers). As Crystal itself acknowledges, OW7 is disordered over two positions, OW7A and OW7B, each at 50% occupancy, in Form II. Tr. 461:12-15, 472:17-23 (Rogers). When OW7 is present at position OW7A in 50% of the asymmetric units of Form II, OW7 hydrogen-bonds with OW1 and two oxygen anions, O281 and O181. Tr. 474:1-5 (Rogers); PTX 1066. When OW7 is at position OW7B in the other 50% of the asymmetric units of Form II, OW7 hydrogen-bonds with a different water molecule, OW5 (OW1 being absent from those asymmetric units) and with the O281 and O181 anions. Tr. 473:14-25 (Rogers); PTX 1066. There is no reason for OW7 to be disordered, and to be at position OW7B, unless OW1 is present at only 50% occupancy in Form II. Tr. 474:6-

13 (Rogers); PTX 1066.

94. The typical range of distances between two oxygen atoms in a hydrogen-bond donor-to-acceptor relationship is about 2.7-3.3 Å. Tr. 474:14-475:2 (Rogers); JTX 704 (McRee 1999) at 266. The distances between OW7A and OW1, O281 and O181, and between OW7B and OW5, O281 and O181, are consistent with that range, and indicate to the crystallographer that the above-mentioned hydrogen bonds formed by OW7 are present in Form II. *Id.*

95. This second reason why OW1 is at 50% occupancy in Form II depends on the hydrogen bonding of OW7; it does not depend on Na-O distances. Tr. 475:6-11 (Rogers).

96. Dr. Friscic did not dispute this second reason why OW1 is at 50% occupancy in Form II. Tr. 475:3-5 (Rogers).

97. Because OW7 is held in place by three hydrogen bonds at both positions OW7A and OW7B, OW7 is not "weakly" or "loosely" bound within the crystal structure of Form II. Tr. 518:20-519:13 (Rogers); *contra* Tr. 320:9-18, 342:13-17 (Friscic). Instead, OW7 is strongly bound, whether at position OW7A or OW7B. Tr. 518:20-519:13 (Rogers).

**(b) OW3 Is at 50% Occupancy in Form II**

98. OW3 is closest to the disordered sodium atom Na8. Tr. 465:24-25 (Rogers).

99. When Na8 is at position Na8A, Na8 is 3.740 Å away from OW3 — too far to bind OW3 — and there is no other nearby sodium atom that can bind OW3. Tr. 475:13-476:6 (Rogers); PTX 1032.

100. By contrast, when Na8 is at position Na8B, Na8 binds OW3. When Na8 is at position Na8B, Na8 is 2.358 Å away from OW3, within the range of typical Na-O bond distances. Tr. 476:19-25 (Rogers); PTX 1033; JTX 700 at 608.

101. Dr. Friscic did not identify what atom(s) in Form II bind OW3, other than Na8 when Na8 is present at position Na8B. Tr. 380:6-381:1 (Friscic); Tr. 477:18-23 (Rogers).

102. Because OW3 is bound within the structure of Form II only when Na8 is present at position Na8B in 50% of the asymmetric units of Form II, OW3 must be present at 50% occupancy in Form II. Tr. 476:19-477:7 (Rogers).

103. Thus, in Form II, OW3 is present in only half of the asymmetric units that make up the crystal, wherein Na8 is present at position Na8B. Tr. 478:17-479:20 (Rogers); PTX 1035. In the other half of the asymmetric units, wherein Na8 is present at position Na8A, OW3 is not there. *Id.*

**(c) OW8 Is at 50% Occupancy in Form II**

104. OW8 is closest to the disordered sodium atom Na10. Tr. 466:1-2 (Rogers).

105. Crystal itself recognizes that Na10 cannot be present at 100% occupancy in Form II. Tr. 480:20-481:1 (Rogers). If it were, there would be only 2.078 Å between adjacent Na10 sodium atoms. *Id.* 2.078 Å is insufficient to accommodate two adjacent Na10 sodium atoms. *Id.* Crystal thus models Na10 as disordered, such that Na10 is present only in 50% of the asymmetric units of Form II. *Id.*

106. Like Na10, OW8 cannot be present at 100% occupancy in Form II. Tr. 481:15-482:10 (Rogers); PTX 1065. If it were, there would only be 3.002 Å between adjacent OW8 water molecules. *Id.* 3.002 Å is insufficient to accommodate two adjacent OW8 water molecules, including their hydrogen atoms, in the geometry in which they are fixed in Form II, *i.e.*, with their hydrogen atoms pointed at each other. *Id.* In that geometry, the adjacent OW8 water molecules cannot hydrogen-bond with one another. Tr. 484:5-10 (Rogers).

107. Thus, like Na10, OW8 is present only in 50% of the asymmetric units of Form II. Tr. 487:25-488:5 (Rogers).

108. A second problem occurs when OW8 is modeled at 100% occupancy: modeling OW8 at 100% occupancy gives rise to a chemically impossible configuration in which Na10 is too close to the hydrogen atom of OW8 and blocks the hydrogen bond that must be present between OW8 and a nearby oxygen atom, O329. Tr. 484:12-

485:11 (Rogers); PTX 1043; JTX 704 (McRee 1999) at 266. This chemically impossible configuration disappears once OW8 is modeled at 50% occupancy. Tr. 487:10-24 (Rogers); PTX 1044. For this additional reason, OW8 must be present at 50% occupancy in Form II. Tr. 487:25-488:5 (Rogers).

109. There is no evidence to support that the OW8-O329 hydrogen bond can "bend" around Na10 in Form II as Dr. Friscic alleged. Tr. 485:21-486:4 (Rogers). Steiner 1992 does not provide such evidence because it discusses hydrogen bonds in "strictly *non*ionic surroundings." Tr. 486:9-22 (Rogers); JTX 729 (Steiner 1992) at 819 (emphasis added). In contrast to the hydrogen bonds in Steiner 1992, the OW8-O329 hydrogen bond in Form II not only exists in ionic surroundings (due to the presence of the Na10 sodium cation), but itself is ionic (because O329 is an oxygen anion). Tr. 486:24-487:4 (Rogers). Steiner 1992 thus does not support that the OW8-O329 hydrogen bond can "bend" around Na10 in Form II. Tr. 487:5-8 (Rogers).

110. Dr. Friscic admitted that, in considering the hydrogen bonding of OW8 to other neighboring atoms, a crystallographer needs to consider the bonding geometries, distances and angles between OW8 and its neighboring atoms. Tr. 433:14-434:1 (Friscic).

**iii) The Relevant Statistics for Dr. Rogers's Refinement Are the Same as Those for Crystal's and Dr. Friscic's Refinements**

111. In the field of crystallography, chemistry, not statistics, determines whether the model of a crystal structure is correct. Tr. 495:13-496:6; JTX 736 at 52; JTX 708 at 234.

112. Nevertheless, modeling OW1, OW3 and OW8 at 50% occupancy, as Dr. Rogers did, does not significantly change the relevant statistics for Dr. Rogers's January 2022 refinement of his model ("Dr. Rogers's refinement"), compared to the statistics for Crystal's 2019 refinement ("Crystal's refinement") and the statistics for Dr. Friscic's June 2022 refinement ("Dr. Friscic's refinement"), which adjusts the occupancies of OW1, OW3 and OW8 in Dr. Rogers's refinement back to 100%, or 1.0. Tr. 494:4-495:11 (Rogers).

**(a) R-Factor and Goodness of Fit Statistics**

113. The R-factor is an agreement index essentially indicating how good a refinement is. Tr. 496:20-24 (Rogers). The R-factors for Crystal's refinement, Dr. Rogers's refinement, and Dr. Friscic's refinement, rounded to two decimal places, are all the same: 0.12. Tr. 496:20-497:4, 527:9-24 (Rogers); PTX 1061.

114. Dr. Friscic admits that an R-factor of 0.12 is "extremely reasonable" for a structure of the size and complexity as Form II.

Tr. 497:13-498:1 (Rogers).

115. The goodness of fit ("GoF") is a statistic indicating how close the data is to what it should be. Tr. 498:7-14 (Rogers). The GoF statistics for Crystal's refinement, Dr. Rogers's refinement, and Dr. Friscic's refinement, rounded to one decimal place, are all the same: 2.1. Tr. 498:7-14 (Rogers); PTX 1061.

116. The International Union of Crystallography does not consider differences in GoF statistics beyond one decimal place to be significant. Tr. 498:17-499:4 (Rogers); JTX 713.

**(b) Maximum and Mean Shift/ESD Values**

117. The maximum shift/esd statistic for Dr. Rogers's refinement is 0.194. Tr. 504:20-505:4 (Rogers); JTX 657. Fanwick 2019 instructs crystallographers that, if a maximum shift/esd statistic is "considerably less than one," then further changes in the statistic amount to "noise," and the refinement can be stopped. Tr. 506:10-22 (Rogers); DTX 1428 at 175. Because Dr. Rogers's maximum shift/esd statistic is 0.194 — considerably less than one — his refinement was complete and could be stopped. Tr. 506:23-507:18 (Rogers); 358:24-25 (Friscic); JTX 657.

118. In view of Fanwick 2019's guidance, it makes no chemical sense for a crystallographer to refine for 64 cycles, as Dr. Friscic did. Tr. 507:15-18 (Rogers); DTX 1428 at 175. Dr. Friscic

himself characterized refining for 64 cycles as "overkill." Tr. 361:6-9 (Friscic).

119. That the maximum shift/esd statistic for Dr. Rogers's refinement generated a checkCIF alert does not mean that Dr. Rogers's refinement is wrong; instead, it tells the crystallographer to investigate. Tr. 499:14-500:21 (Rogers); JTX 736 (Fanwick 2019) at 43-44.

120. The maximum shift/esd statistic for Dr. Rogers's refinement is not a measure of the resolution of the structure of Form II as a whole; instead, it is attributable to just one thermal parameter ($U_{12}$) for just one carbon atom in Form II (C374), which was not well refined in Crystal's model of Form II. Tr. 504:22-505:10 (Rogers); PTX 1051.

121. The maximum shift/esd statistic for Dr. Rogers's refinement, and the one thermal parameter for the one carbon atom causing it, do not have anything to do with the occupancies of the OW1, OW3 and OW8 water molecules in Form II. Tr. 505:5-13 (Rogers).

122. The mean shift/esd statistic for Dr. Rogers's refinement is 0.016. Tr. 508:8-15 (Rogers); JTX 657. This statistic, which averages all shift/esd values for all 400-plus atoms and 1100-plus parameters that make up Form II, shows that the structure that Dr. Rogers modeled — in which OW1, OW3 and OW8 are at 50%

occupancy — is stable and is fully refined. *Id.*

**(c) Thermal Parameters and U1/U3 Ratios**

123. Although the thermal ellipsoids of OW1 and OW8 became more "cigar-shaped" in Dr. Rogers's refinement of Form II, the 50% occupancies of OW1 and OW8 are chemically correct in Dr. Rogers's refinement. Tr. 501:14-502:2 (Rogers). By contrast, the 100% occupancies of OW1 and OW8 are chemically incorrect in Crystal's refinement and in Dr. Friscic's refinement. *Id.*

124. The $U_{eq}$ thermal parameters for OW1 and OW8 decreased in Dr. Rogers's refinement as compared to Crystal's refinement. Tr. 501:8-13 (Rogers); PTX 1056. That is because OW1 and OW8 were incorrectly modeled at 100% occupancy by Crystal and correctly modeled at 50% occupancy by Dr. Rogers. Tr. 501:8-18, 528:8-12 (Rogers).

125. There is no scientific reference of record indicating that the ratio of U1/U3 thermal parameters for an atom in a crystal structure must be equal to or less than 3. Tr. 503:3-10 (Rogers).

126. Crystal's and Dr. Friscic's refinements of Form II include, respectively, 19 and 43 atoms having a U1/U3 ratio greater than 3. Tr. 503:12-22 (Rogers); PTX 1056; PTX 1064. Dr. Friscic did not explain why, in view of those numbers, Crystal's and Dr. Friscic's refinements allegedly are acceptable, whereas Dr.

Rogers's refinement allegedly is not.

#### iv) The Different Unit Cell Parameters for Form II and LCZ696[4] Do Not Mean that Form II Is Not a Hemipentahydrate

127. The fact that Form II has different unit cell parameters than LCZ696 does not mean that Form II is not a hemipentahydrate. Tr. 515:15-516:18 (Rogers). Different polymorphs of the same hydrate can have the same amount of bound water, yet have different unit cell parameters. Tr. 515:15-516:18 (Rogers); JTX 731 at 958.

### c. Dr. Matzger's Testing Also Demonstrates that Mylan's API Is a Hemipentahydrate

128. As explained below, Dr. Matzger conducted multiples tests on samples of Mylan's API (Form II) and determined that it is a hemipentahydrate. Tr. 70:18-21 (Matzger).

#### i) Mylan's API Contains Surface Water that Must Be Accounted for to Determine the Amount of Bound Water

129. A sample of TSVH in crystalline form may contain both bound water and surface water. Tr. 46:16-47:6, 123:19-23 (Matzger); *see also* Tr. 417:21-24 (Friscic) (agreeing that "as long as there's . . . some water in the air, there will be some surface water").

130. Dr. Friscic admitted that when determining the amount of

[4] LCZ696 is the moniker ascribed to the crystalline complex serving as the active ingredients in Entresto®.

bound water constituting the hydrate, one must also account for whether surface water is present. Tr. 403:18-23 (Friscic); Tr. 73:4-17; 128:7-17 (Matzger). Crystal also recognized that surface water must be distinguished from bound water to determine the amount of bound water in Form II. Tr. 218:15-18, 218:24-25 (Wang); Tr. 410:23-411:11 (Friscic).

131. Bound water is more tightly held, whereas surface water can be removed fairly readily. Tr. 47:7-14, 85:14-86:1 (Matzger). Due to these differences in bound water and surface water, analytical testing techniques, such as DVS and TGA, may be used to differentiate between bound water and surface water. Tr. 48:4-15, 73:4-75:7, 84:13-85:4, 85:14-86:1, 86:11-18 (Matzger); JTX 600 at 1; JTX 749 at 1049, 1054; JTX 751 at 239-40; *see also* Tr. 218:24-25 (Wang) (testifying that Crystal used "DVS to distinguish bound and adsorbed water").

132. Relative humidity ("RH") refers to the amount of humidity, or water, in the air: 0% RH means the air contains no water, whereas 100% RH means the air contains as much water as it can potentially hold. Tr. 83:25-84:12 (Matzger).

133. Form II is hygroscopic, meaning it takes up surface water, as demonstrated by the fact that it takes up over 1% w/w surface water from 10% to 60% RH. Tr. 94:12-23 (Matzger); Tr.

404:14-19; 405:18-24 (Friscic); JTX 646 at 8-9. The more hygroscopic a material is, the more surface water it takes up with increasing RH. Tr. 94:24-95:3 (Matzger); JTX 646 at 8-9.

134. It is undisputed that Form II contains surface water at conditions above 2% RH. Tr. 105:2-19 (Matzger); Tr. 417:21-24, 419:20-420:1 (Friscic); JTX 646 at 3. Dr. Matzger demonstrated by DVS that Form II takes up about 1.6-1.7% w/w surface water between 2% and 50% RH. Tr. 89:19-90:2, 93:22-94:8, 94:12-23 (Matzger); PTX 1104. Dr. Friscic admitted that between 10% and 60% RH, Form II takes up over 1% w/w surface water and that over the range of 20% to 40% RH, which are normal laboratory conditions, Form II takes up surface water. Tr. 405:18-406:8, 406:17-20, 419:12-420:1 (Friscic); JTX 646 at 8-9.

135. Form II may have more total water than the 4.70% w/w for a hemipentahydrate due to presence of surface water plus 2.5 bound waters. Tr. 70:12-17 (Matzger).

**ii) Dr. Matzger's Controlled Humidity TGA Testing Demonstrates that Mylan's API Is a Hemipentahydrate**

136. TGA is an analytical technique that measures the change in the weight of a sample as a function of increasing temperature and/or time. Tr. 72:13-73:3 (Matzger).

137. It is undisputed that TGA can be used to determine the

amount of bound water in a hydrate. Tr. 73:4-17 (Matzger); Tr. 408:7-13 (Friscic).

138. In TGA of a hydrate, water loss is indicated by the weight decreasing. Tr. 73:18-75:17 (Matzger); JTX 745 at 1. Water that is more loosely held (*e.g.*, surface water) is removed from the sample at lower temperatures while water that is more tightly held (*e.g.*, bound water) is removed from the sample at higher temperatures. Tr. 73:18-75:17 (Matzger); JTX 349 at 507.

139. Controlled humidity TGA is an analytical technique that allows for control of both temperature and RH — by mixing dry nitrogen gas with a humid stream of nitrogen in the same way DVS is conducted — within a TGA device. Tr. 97:22-98:11 (Matzger); JTX 748 at 165.

140. Dr. Matzger conducted his controlled humidity TGA experiments with a TGA instrument equipped with a gas line that allowed him to adjust the RH in the instrument. Tr. 98:21-99:19 (Matzger). About 10 mg of Form II was placed into an open pan and equilibrated in the TGA device at 2% RH for one hour. *Id.* After equilibrating at 2% RH, the sample was then equilibrated at 0% RH for eight hours. *Id.* After eight hours, the sample was heated at a constant rate of 10 °C/min. until decomposition at 200 °C. *Id.*

141. In Dr. Matzger's controlled humidity TGA experiments,

Form II samples were first equilibrated at 2% RH to remove the surface water because Dr. Matzger demonstrated by DVS that 2% RH was the point where all surface water had been lost but before bound water was lost. Tr. 98:21-100:1 (Matzger); *infra* ¶¶ 149-151; *see also* Tr. 105:2-19 (Matzger); Tr. 419:12-420:1 (Friscic) (admitting that Crystal identified 2% RH as the slope change point by DVS used to "obtain a good estimate of the amounts of bound and surface water"); JTX 646 at 3.

142. Form II samples were then equilibrated at 0% RH to mimic the critical step observed in Dr. Matzger's DVS experiment where two bound waters were lost from the sample. Tr. 100:2-8 (Matzger); *infra* ¶¶ 149-151; *see also* Tr. 418:11-24 (Friscic) (admitting that Form II loses two bound waters at 0% RH).

143. As summarized in the table below, Dr. Matzger's controlled humidity TGA experiments showed two bound water loss events corresponding closely to the theoretical 4.70% w/w bound water for a hemipentahydrate. Tr. 100:14-101:19 (Matzger); PTX 1106. In each of the two controlled humidity TGA experiments, there was a slow water loss event from 2% to 0% RH corresponding to two bound waters. Tr. 100:14-101:19, 102:5-16 (Matzger); PTX 1106. There was then a second water loss event upon heating the sample at 0% RH corresponding to a half bound water. Tr. 100:14-101:19,

102:5-16 (Matzger); PTX 1106.

| **Matzger Experiment No.** | **Weight Loss from 2% to 0% RH** | **Weight Loss Upon Heating to About 200 °C** | **Total Weight Loss** |
|---|---|---|---|
| AJM-III-8.1 | 3.63% | 1.01% | 4.64% |
| AJM-III-8.2 | 3.67% | 1.01% | 4.68% |
| Theoretical Loss of Bound Waters | 2 bound waters: 3.76% | 0.5 bound water: 0.94% | 2.5 bound waters: 4.70% |

144. Mylan's and Dr. Friscic's criticisms of Dr. Matzger's controlled humidity TGA results are addressed in ¶¶ 173-175, 178-184, and 200 below.

**iii) Dr. Matzger's DVS Results Combined with His Hi-Res TGA Results Demonstrate that Mylan's API Is a Hemipentahydrate**

145. DVS is an analytical technique that measures the change in weight as a function of RH. Tr. 83:12-24 (Matzger).

146. In a DVS experiment, increasing RH may result in an increase in weight, referred to as sorption, due to the sample taking up water. Tr. 83:12-24 (Matzger). Decreasing RH may result in a decrease in weight, referred to as desorption, due to the sample losing water. *Id.*

147. DVS can be used to differentiate between surface and bound water. Tr. 84:13-85:4 (Matzger); Tr. 419:12-19 (Friscic); JTX 646 at 3. In DVS, the gain or loss of bound water typically occurs over a narrow range of RH but relatively slowly. Tr. 84:13-

85:4, 85:14-86:1, 86:11-18 (Matzger); JTX 749 at 1049; JTX 751 at 239-40. Conversely, the gain or loss of surface water occurs over a broad range of RH but relatively quickly at each RH step. Tr. 84:13-85:4, 85:14-23-86:1, 86:11-18 (Matzger); JTX 749 at 1054; JTX 751 at 239-40.

148. Dr. Matzger conducted his DVS experiments by placing about 10 mg of Form II in a pan into a DVS instrument. Tr. 86:19-88:11 (Matzger). The experiment was conducted at 25 °C. *Id.* The sample was equilibrated at 10% RH prior to running the experiment. *Id.* The RH was then changed in 2% steps, equilibrating the sample at each step, whereby the RH was decreased to 0%, then increased to 50%, then decreased to 10% RH to observe the weight change in Form II over those ranges. *Id.* The equilibrium criteria at each step required a weight change of less than 0.001% over 5 minutes, with a minimum hold time of 5 minutes and a maximum hold time of 800 minutes. *Id.* Dr. Matzger performed XRPD experiments on one sample before and after the DVS experiment to ensure the crystal form did not change due to the experiment. *Id.*

149. Dr. Matzger's DVS demonstrated that Form II lost or gained water relatively slowly (*i.e.*, after several hours) over the narrow range of 0% to 2% RH corresponding to *bound* water. Tr. 88:22-92:16 (Matzger); PTX 1104 at 1-5. In contrast, Form II lost

or gained water relatively quickly in relatively constant or equal amounts at each step over the broad range of 2% to 50% RH corresponding to surface water. Tr. 88:22-92:16 (Matzger); PTX 1104 at 1-6.

150. Consistent with Dr. Matzger's DVS results, Crystal reported that the slope change point without surface and only bound water in its DVS analysis for Form II is at about 2% RH. Tr. 105:2-19 (Matzger); Tr. 419:20-420:1 (Friscic); JTX 617 at 1, 3; JTX 646 at 3.

151. As summarized below, the results of Dr. Matzger's two DVS experiments demonstrate that between 0% and 2% RH, Form II lost or gained two bound waters (*i.e.*, 3.70% to 3.80% w/w), and from 2% to 50% RH, Form II gained about 1.6% to 1.7% w/w surface water. Tr. 88:22-90:7, 93:22-94:8 (Matzger); Tr. 418:11-24 (Friscic); PTX 1068; PTX 1104.

| **Matzger Exp. No.** | **Bound Water Loss from 2% to 0% RH** | **Bound Water Gain from 0% to 2% RH** | **Theoretical Gain/Loss of Two Bound Waters** | **Surface Water Gain from 2% to 50% RH** |
|---|---|---|---|---|
| AJM-III-7.1 | 3.80% | 3.71% | 3.76% | 1.639% |
| AJM-III-7.4 | 3.80% | 3.70% | 3.76% | 1.656% |

152. In Dr. Matzger's DVS testing, Form II lost only two bound waters at 0% RH, and not 2.5 bound waters, because the last half bound water is tightly held and could not be removed without

heating at high temperatures. Tr. 90:8-15, 97:15-98:8 (Matzger).

153. As summarized in the table below, by combining the two bound waters (average of 3.75% to 3.76% w/w) measured by DVS with the undisputed last half tightly bound water (0.952% w/w) measured by Hi-res TGA, Form II contains an estimated 4.70% to 4.71% w/w bound water, which is within 0.01% of the theoretical 4.70% w/w for 2.5 bound waters. Tr. 81:8-82:10, 90:8-15, 95:17-96:6 (Matzger); PTX 1068; PTX 1101; PTX 1104; *infra* ¶¶ 161, 164.

| **Number of Bound Water Molecules** | **Theoretical Bound Water** | **Matzger DVS Exp. AJM-III-7.1 Results** | **Matzger DVS Exp. AJM-III-7.4 Results** |
|---|---|---|---|
| 2 $H_2O$ | 3.76% | 3.76% (avg. by DVS) | 3.75% (avg. by DVS) |
| 0.5 $H_2O$ | 0.94% | 0.952% (by Hi-res TGA) | 0.952% (by Hi-Res TGA) |
| Total 2.5 $H_2O$ | 4.70% | Estimated 4.71% | Estimated 4.70% |

154. Mylan's and Dr. Friscic's criticisms of Dr. Matzger's DVS results are addressed in ¶¶ 173-175, 178-184, and 200 below.

**iv) Dr. Matzger's Hi-Res TGA Testing Also Demonstrates that Mylan's API is a Hemipentahydrate**

155. High resolution or Hi-res TGA is a recognized method for differentiating between water loss events. Tr. 76:6-24 (Matzger); JTX 349 at 507. In Hi-res TGA, increased resolution or separation of overlapping weight loss events is achieved by slowing the heating rate during weight loss transitions. Tr. 76:6-24 (Matzger); JTX 349 at 507; JTX 745 at 1.

156. Dr. Matzger conducted Hi-res TGA using a TA Instruments TGA 5500. 77:8-78:4 (Matzger). About 15 mg of Form II was placed into a pan and sealed with a lid containing a small hole made using a 30-gauge needle (*i.e.*, a pinhole pan). *Id.* The sample was held at room temperature for two hours (isothermal period) in the TGA device during which dry nitrogen gas (*i.e.*, 0% RH) was blown over the pinhole pan. *Id.* After the two-hour isothermal period, the sample was subjected to heating by Hi-res TGA up to 150 °C. *Id.*

157. Conducting TGA with a pinhole pan helps separate water loss events. Tr. 78:5-79:4, 79:14-80:16 (Matzger); JTX 755A at 409.

158. A pinhole pan alters the environment to which a sample is exposed as compared to an open pan. Tr.78:5-79:4, 111:11-112:2 (Matzger); JTX 752 at 449-50. In TGA with an open pan, dry nitrogen gas flows directly over the solid sample, quickly carrying away any water that is lost from the sample. Tr. 78:5-79:4 (Matzger); JTX 752 at 449-50. In contrast, in TGA with a pinhole pan, the sample is not directly exposed to the dry nitrogen gas; instead, a microenvironment is created inside the pan where the humidity is higher than the dry nitrogen environment outside the pan. Tr. 78:5-79:4 (Matzger); JTX 752 at 450.

159. In TGA with a pinhole pan, the water losses will be

slower and occur at higher temperatures than with an open pan. Tr. 78:5-79:4, 79:14-80:16 (Matzger); JTX 755A at 409.

160. Dr. Matzger used an isothermal period, where the sample was held at room temperature for two hours, to remove surface water from the Form II sample before beginning his Hi-res TGA experiment. Tr. 77:8-78:4, 81:2-7 (Matzger).

161. Dr. Matzger's Hi-res TGA experiment on Form II showed three water loss events. Tr. 81:8-82:10 (Matzger). The first water loss event during the isothermal period corresponded to surface water. *Id.* As summarized below, the second water loss event occurred upon heating Form II up to about 80 °C corresponding to two bound waters, and the third water loss event occurred upon further heating Form II to about 120 °C corresponding to half a tightly bound water. Tr. 81:8-82:10, 108:25-109:14 (Matzger); PTX 1068; PTX 1101.

| **Number of Bound Water Molecules** | **Theoretical Water Loss** | **Matzger Hi-res TGA Experiment Results** |
|---|---|---|
| 2 $H_2O$ | 3.76% | 3.942% |
| 0.5 $H_2O$ | 0.94% | 0.952% |
| Total 2.5 $H_2O$ | 4.70% | 4.89% |

162. The total measured bound water of 4.89% w/w in Form II by Hi-res TGA is close to the theoretical 4.70% w/w bound water for a hemipentahydrate, and far from the theoretical 5.58% w/w for a trihydrate. Tr. 81:8-82:10 (Matzger). In a TGA experiment, a

measured water loss within 0.1% to 0.3% w/w correlates well to the theoretical weight percent for a given hydrate. Tr. 109:22-110:20 (Matzger); Tr. 280:4-7 (Friscic); JTX 735 at 907; JTX 743 at 145.

163. The slightly increased water content above 4.70% w/w for a theoretical hemipentahydrate in Dr. Matzger's Hi-res TGA was due primarily to an overlap of surface and bound water in the second water loss event. *See* Tr. 82:21-83:9, 107:2-12 (Matzger).

164. It is undisputed that the last water loss event in Dr. Matzger's Hi-res TGA corresponds to half a tightly bound water in Form II. Tr. 82:21-83:2 (Matzger); Tr. 412:15-413:3 (Friscic); PTX 1101.

165. Dr. Matzger conducted controlled humidity TGA and DVS, discussed in ¶¶ 140-143 and 148-153 above, to resolve the possible overlap of surface and bound water in the Hi-res TGA. Tr. 82:21-83:9 (Matzger).

166. Mylan's and Dr. Friscic's criticisms of Dr. Matzger's Hi-res TGA results are addressed in ¶¶ 173-175, 185-192, 194-197, and 201 below.

**v) Dr. Matzger's Constant Heating Rate TGA**

167. Dr. Matzger initially conducted constant heating rate TGA testing to examine Form II. Tr. 112:5-24 (Matzger); PTX 1100.

168. Dr. Matzger's constant heating rate TGA results show

three different water loss events with the first water loss corresponding primarily to surface water, the second corresponding primarily to bound water, and the third corresponding to half a strongly bound water. Tr. 112:25-113:20 (Matzger); PTX 1100. However, the three water loss events overlapped, making it not possible to fully resolve or differentiate the surface water from the bound water. Tr. 112:25-114:20, 115:5-10 (Matzger); PTX 1100.

169. While the constant heating rate TGA results were not definitive due to overlapping of water loss events, they were consistent with Form II being a hemipentahydrate. Tr.115:5-16 (Matzger); PTX 1100.

170. Dr. Matzger addressed the overlapping water loss events observed in his constant heating rate TGA by conducting controlled humidity TGA, DVS and Hi-res TGA. Tr. 115:17-23 (Matzger); *supra* ¶¶ 140-143, 148-153, 156-163.

**iv. Mylan's Criticisms of Dr. Matzger's Controlled Humidity TGA, DVS, and Hi-Res TGA Testing Are Unfounded**

**a. The Trace Amounts of Impurities or Amorphous Material in Mylan's API Did Not Impact Dr. Matzger's Test Results**

171. Mylan's expert Dr. Friscic did not testify that trace amounts of impurities or amorphous material would impact Dr. Matzger's test results; instead, Mylan only raised this assertion during Dr. Matzger's cross examination. Tr. 169:12-171:25

(Matzger).

172. Contrary to Mylan's suggestion, Mylan's API does not contain 10% or 5% w/w chemical impurities or amorphous material. Tr. 170:2-18 (Matzger).

173. Mylan's API Batch No. 903901, which Dr. Matzger tested by controlled humidity TGA, DVS, and Hi-res TGA, contained less than about 0.5% w/w total chemical impurities related to TSVH and residual solvents. *Supra* ¶¶ 36-37; Tr. 70:22-71:9, 77:8-78:4, 86:19-88:1, 98:21-99:19 (Matzger); PTX 1096; JTX 593. Mylan's API also does not contain any substantial amount of amorphous material, *i.e.*, it has less than about 0.5% w/w. Tr. 181:19-25 (Matzger). Thus, Mylan's API that Dr. Matzger tested is at least about 99% pure crystalline TSVH (with less than about 0.5% w/w chemical impurities and about 0.5% w/w amorphous material).

174. It is also incorrect to assume the trace amount of chemical impurities or amorphous material in Mylan's API has no water associated with it. Tr. 170:12-171:3 (Matzger). An impurity with the same water content as TSVH would lead to no change in Dr. Matzger's calculations of bound water in Mylan's API. Tr. 170:21-171:3 (Matzger).

175. Even if the trace amount of chemical impurities or amorphous material in Mylan's API had no associated water (*i.e.*,

all water that Dr. Matzger measured by TGA or DVS corresponded to Mylan's crystalline API), Dr. Matzger's testing still demonstrates that the bound water measured in Mylan's API, with about 99% purity, corresponds to a theoretical 4.70% w/w bound water for a hemipentahydrate as summarized below ((measured bound water loss ÷ sample purity) x 100% = % bound water excluding impurities).[5] *Supra* ¶¶ 143, 153 (controlled humidity TGA and DVS results).

| **Matzger's Tests** | **Measured Bound Water Loss** | **Sample Purity** | **Percent Bound Water Excluding Impurities** |
|---|---|---|---|
| Controlled Humidity TGA Exp. 1 | 4.64% | 99% | 4.69% |
| Controlled Humidity TGA Exp. 2 | 4.68% | 99% | 4.73% |
| DVS Exp. 1 + Hi-res TGA | 4.71% | 99% | 4.76% |
| DVS Exp. 2 + Hi-res TGA | 4.70% | 99% | 4.75% |

**b. Dr. Friscic's Conclusions Regarding DVS and Hi-Res TGA are Entitled to Little Weight**

176. Dr. Friscic has only conducted a DVS experiment three or four times. Tr. 400:3-5 (Friscic). Dr. Friscic is not an expert in Hi-res TGA, and he has never conducted Hi-res TGA before. Tr.

[5] Dr. Matzger measured 4.89% w/w water by Hi-res TGA (*supra* ¶ 161), which excluding impurities and amorphous material equals 4.94% w/w water. But as explained in ¶ 163 above, Form II tested by Hi-res TGA contained slightly more water than the theoretical 4.70% w/w for a hemipentahydrate due to some overlap between surface and bound water in Form II. But Dr. Matzger's controlled humidity TGA and DVS confirmed Form II is a hemipentahydrate with results within less than 0.1% of the theoretical 4.70% w/w. *Supra* ¶¶ 143, 153.

399:11-400:2 (Friscic).

177. Dr. Friscic had access to DVS and TGA instruments and could have conducted his own testing on Form II. Tr. 400:6-403:3 (Friscic). Yet, Dr. Friscic did not conduct any DVS or TGA testing on Form II. Tr. 402:16-18, 403:1-3 (Friscic).

**c. No Significant Amount of Bound Water Was Lost Above 2% RH During Dr. Matzger's Controlled Humidity TGA or DVS**

178. Mylan's and Dr. Friscic's criticisms of Dr. Matzger's controlled humidity TGA and DVS results, which results are discussed in ¶¶ 140-143 and 148-153 above, are unsupported.

179. Dr. Friscic admitted that "by observing the change in the slope of the DVS curve and calculating the intersection between the two trend lines of the sorption and desorption cycles, Crystal was able to determine the relative humidity conditions at which the loss of bound water becomes significant . . . and in that way obtain a good estimate of the amounts of bound and surface water." Tr. 419:12-19 (Friscic); *see also* JTX 600 at 2; JTX 617 at 1, 3.

180. It is undisputed that the slope change point in the DVS curve for Form II is at about 2% RH, which is the point where all bound water is present without surface water. Tr. 105:2-19 (Matzger); Tr. 419:20-420:1 (Friscic); JTX 617 at 1, 3; JTX 646 at 3.

181. Dr. Friscic's assertions (i) that bound and surface

water are lost by DVS under the same equilibration conditions, (ii) that the amount of surface water lost at each RH step should decrease at lower RH, and (iii) that bound water would become surface water at lower RH, are not supported by any literature. Tr. 288:3-289:13, 336:6-337:5, 416:13-417:20 (Friscic); Tr. 132:18-133:6 (Matzger).

182. Dr. Friscic admitted that Form II is stable and does not convert to a different hydrate over a range of 25 to 40 °C and from 5% to 50% RH, *i.e.*, bound water is not being lost between 5% and 50% RH. Tr. 406:21-408:6 (Friscic); JTX 646 at 11.

183. To the extent bound water was lost from Form II above 2% RH in Dr. Matzger's DVS experiments, that amount was not significant — only 0.022% w/w based on the difference in step size from 4% to 2% RH compared to 6% to 4% RH. Tr. 103:7-104:22 (Matzger).

184. If one were to add an additional 0.022% w/w water to Dr. Matzger's controlled humidity TGA results, the measured amount of bound water in Form II would be 4.66% and 4.70% w/w, which are "just a little bit closer" to the theoretical 4.70% w/w bound water amount for a hemipentahydrate. Tr. 103:7-104:22 (Matzger).

**d. No Significant Amount of Bound Water Was Lost During the Isothermal Period of Dr. Matzger's Hi-Res TGA**

185. Mylan's and Dr. Friscic's criticisms of Dr. Matzger's

Hi-res TGA results, which results are discussed in ¶¶ 156-162 above, are unsupported.

186. There was no significant bound water lost from Form II during the isothermal period of Dr. Matzger's Hi-res TGA experimentation. Tr. 108:12-109:17 (Matzger); PTX 1101.

187. Dr. Matzger's Hi-res TGA data demonstrate that during the isothermal period, there was a single water loss event corresponding to surface water; however, not all the surface water in the Form II sample was lost during the isothermal period as evidenced by the weight loss curve still decreasing at the end of the isothermal period. Tr. 108:12-109:17, 128:23-129:24 (Matzger); PTX 1101.

188. No substantial amount of bound water was lost in Dr. Matzger's Hi-res TGA experiment until Form II was heated to 40 °C with most bound water in the second water loss event removed around 80 °C. Tr. 108:12-109:17 (Matzger); PTX 1101.

189. Dr. Matzger cited literature demonstrating that a pinhole pan causes bound water to be lost more slowly and at higher temperatures compared to an open pan. Tr. 79:14-80:16 (Matzger); JTX 755A at 409.

190. The pinhole pan caused Form II to lose water more slowly during the isothermal period compared to the DVS conducted with an

open pan because the environment inside the pinhole pan was humidified, *i.e.*, not at 0% RH, by the water being removed from Form II. Tr. 78:5-79:4, 79:14-80:16, 81:2-7, 111:11-112:2 (Matzger); JTX 752 at 449-50.

191. Dr. Friscic cited no literature to support his theory that nitrogen gas flowing over a pinhole pan creates "suction" that can "aggravate particles" in the pan. Tr. 337:14-21 (Friscic).

192. To confirm that no significant bound water was lost during the isothermal period of his Hi-res TGA, Dr. Matzger conducted controlled humidity TGA and DVS demonstrating that Form II contains 2.5 bound waters. Tr. 82:21-83:9, 106:5-107:12, 108:12-109:17 (Matzger).

**e. Dr. Friscic's Cited Hydrate References are Inapposite**

193. Dr. Friscic did not cite any literature to rebut Dr. Matzger's controlled humidity TGA or DVS results discussed in ¶¶ 140-143 and 148-153 above. Tr. 132:18-133:6 (Matzger).

194. The seven literature references that Dr. Friscic cited against Dr. Matzger's Hi-res TGA results, which results are discussed in ¶¶ 156-162 above, do not demonstrate that bound water was lost during Dr. Matzger's isothermal period because Dr. Friscic's examples are not chemically relevant to Form II — those examples were non-metal-coordinated hydrates, channel hydrates,

and/or formed under extreme conditions, whereas Form II is a metal-coordinated hydrate, is not a channel hydrate, and is stable under normal laboratory conditions. Tr. 129:25-132:2 (Matzger); Tr. 312:14-316:21 (Friscic); JTX 681A at 45-46; JTX 682 at C; JTX 683 at 13; JTX 684 at 5342-44; JTX 687 at 100-102; JTX 690 at 761-64; JTX 692 at 2333-35.

195. Dr. Friscic's non-Form II hydrate examples do not suggest Form II would lose bound water during the isothermal period of Dr. Matzger's Hi-res TGA. Tr. 129:25-132:2 (Matzger). Dr. Friscic admitted that just because one hydrate loses bound water under one set of conditions does not mean all hydrates will lose bound water under those conditions. Tr. 413:22-414:1 (Friscic). He also admitted that how a particular hydrate will lose bound water is unpredictable. Tr. 413:14-414:1 (Friscic).

196. In addition, the seven literature references, Dr. Matzger's and Crystal's DVS for Form II, and Novartis's DVS for LCZ696 that Dr. Friscic cited against Dr. Matzger's Hi-res TGA results do not demonstrate that bound water was lost during Dr. Matzger's isothermal period because Dr. Friscic's examples were tested under different conditions than Dr. Matzger used for his Hi-res TGA — those examples, including the DVS, were tested in open pans, whereas Dr. Matzger conducted his Hi-res TGA in a

pinhole pan. Tr. 111:11-112:2, 131:16-132:2 (Matzger); Tr. 414:16-18, 415:9-16 (Friscic); JTX 681A at 45-46; JTX 682 at C; JTX 683 at 13; JTX 684 at 5342-44; JTX 687 at 100-102; JTX 690 at 761-64; JTX 692 at 2333-35.

197. Dr. Friscic's examples in an open pan do not inform whether Form II would lose bound water during the isothermal period in Dr. Matzger's Hi-res TGA in a pinhole pan. Tr. 131:16-132:2 (Matzger). Dr. Friscic admitted that hydrates will lose water under myriad diverse conditions depending on the material. Tr. 413:14-414:1 (Friscic). He also admitted that whether and how quickly a material would dehydrate depends on the environment it is placed in, what kind of experiment one is performing, and the properties of the material. Tr. 415:17-21 (Friscic). A pinhole pan creates a different environment than an open pan. *Supra* ¶¶ 158-159.

**f. Neither Dr. Matzger's Sample Storage nor Preparation for His Water Content Testing Resulted in the Removal of Bound Water**

198. Dr. Matzger received samples of Mylan's API and ANDA Products identified in Mylan's ANDA and stored those samples in closed containers provided by Mylan in his laboratory according to the storage conditions outlined in Mylan's ANDA. Tr. 70:22-71:6 (Matzger); PTX 1096. It is undisputed that the samples Dr. Matzger received from Mylan are representative of Mylan's API and ANDA

Products, which he confirmed complied with Mylan's ANDA specifications. Tr. 70:22-71:9 (Matzger); PTX 1097; PTX 1099.

199. Dr. Friscic admitted that from 5% to 50% RH, encompassing the normal laboratory conditions of 20% to 40% RH, Form II is stable and does not convert to a different hydrate, *i.e.*, it is not gaining or losing bound water. Tr. 406:21-408:6 (Friscic); JTX 646 at 11.

200. No significant bound water was lost from Form II before Dr. Matzger conducted his controlled humidity TGA and DVS experiments because he first equilibrated Form II at 2% and 10% RH, respectively, which are above the point at which any significant bound water would be lost. Tr. 86:19-88:1, 98:21-100:1 (Matzger); *supra* ¶¶ 140-143 (controlled humidity TGA results), ¶¶ 148-153 (DVS results).

201. No bound water was lost from Form II before Dr. Matzger conducted his Hi-res TGA experiment because he took the sample of Form II directly from the container, sealed the sample into the pinhole pan, and placed the pinhole pan into the TGA device, thereby reducing exposure of Form II to laboratory conditions. Tr. 77:8-78:4, 156:20-157:8 (Matzger); *supra* ¶¶ 156-162 (Hi-res TGA results).

**v. Mylan's API Is Not a 2.6 or 2.67 Hydrate**

202. Dr. Rogers analyzed all of the water molecules in the Form II single crystal structure and demonstrated that the only chemically reasonable model is one where Form II is a hemipentahydrate. *Supra* Section B.iii.b.ii).

203. OW7 is not loosely held within the structure of Form II and is not easily lost to form a 2.67 hydrate. Tr. 473:12-474:13, 517:2-519:10 (Rogers); *supra* ¶ 97.

204. Dr. Matzger's controlled humidity TGA measured 4.64% and 4.68% w/w bound water, within about 0.06% of the theoretical value of 4.70% w/w for a hemipentahydrate. Tr. 100:14-101:19, 102:5-21, 106:5-107:1 (Matzger); PTX 1106.

205. Dr. Matzger's DVS in combination with the Hi-res TGA measured 4.71% and 4.70% w/w bound water, which are within about 0.01% of the theoretical value of 4.70% w/w for a hemipentahydrate. Tr. 95:17-96:6, 106:5-107:1 (Matzger); PTX 1104.

206. Dr. Matzger's Hi-res TGA testing measured 4.89% w/w bound water, which is within 0.2% of the theoretical 4.70% w/w for a hemipentahydrate. Tr. 81:8-82:10, 106:5-107:1 (Matzger); PTX 1101. Scientific literature indicates that measured values by TGA within 0.1% to 0.3% w/w correspond well with theoretical values for a given hydrate. Tr. 109:22-110:20 (Matzger); JTX 735 at 907;

JTX 743 at 1145.

207. Dr. Friscic admitted that for Crystal's internal testing, a calculated value within 0.2% to 0.3% w/w of the theoretical value corresponds to the theoretical hydrate. Tr. 409:14-410:22 (Friscic).

208. A POSA would further understand that water molecules must exist in whole numbers (*e.g.*, 2.5 bound waters correspond to 5 waters or some multiple thereof); thus, a 2.6 hydrate is not sensible from a whole number perspective for Form II, and an experimental measurement of 2.6 waters would correspond to a chemically reasonable 2.5 hydrate. Tr. 45:2-11, 172:3-7, 172:22-173:13 (Matzger).

**vi. Crystal's DVS and TGA Testing Fail to Demonstrate that Form II Is Not a Hemipentahydrate**

209. Crystal attempted to determine the amount of bound water in Form II using a combination of DVS and TGA by subtracting surface water measured by DVS from total water (*i.e.*, surface plus bound water) measured by TGA. Tr. 139:12-140:8 (Matzger); Tr. 217:16-218:25 (Wang); JTX 600 at 1, 2; JTX 617 at 3.

210. Crystal incorrectly quantified the amount of bound water because the Form II samples tested by DVS and TGA were not properly equilibrated. Tr. 134:21-135:10, 139:12-140:8 (Matzger).

211. Equilibration refers to holding a sample under a

particular condition (*e.g.*, a specific RH) until the weight no longer changes significantly. Tr. 86:19-88:1 (Matzger). If a sample is not properly equilibrated, including if the equilibration criteria are not appropriately stringent, the amount of measured water will be affected and can result in an incorrect quantification of bound water. Tr. 135:11-24 (Matzger); JTX 749 at 1052-53.

212. Crystal did not properly equilibrate its Form II samples by DVS as shown by Dr. Matzger's DVS results where ten times more water was lost from 2% to 0% RH compared to the same step in Crystal's DVS. Tr. 136:4-136:18 (Matzger); JTX 617 at 3; PTX 1104.

213. The differences in protocols for Dr. Matzger's and Crystal's DVS experiments further demonstrate that Crystal did not properly equilibrate its Form II samples by DVS. Crystal used ten times the amount of sample resulting in slower kinetics for equilibration compared to Dr. Matzger, and Crystal used a significantly less stringent equilibration criterion (weight change less than 0.002% over 1 minute) than Dr. Matzger (weight change less than 0.001% over 5 minutes). Tr. 86:19-88:11, 136:24-138:16 (Matzger); Tr. 416:2-9 (Friscic); JTX 600 at 10.

214. Graphs of Crystal's DVS data show that Form II was not properly equilibrated by Crystal as there is a lack of a plateau,

meaning the samples were still losing weight at the end of each RH step. Tr. 138:21-139:2 (Matzger); *compare* PTX 1080 *with* PTX 1104.

215. Before testing Form II by TGA, Crystal exposed the Form II samples to the laboratory conditions, which are typically about 20% to 40% RH, thereby gaining surface water. Tr. 140:13-141:24 (Matzger); *supra* ¶¶ 133-134.

216. Crystal's Form II samples when tested by TGA were not equilibrated at 5% RH as demonstrated by the wide range of 5.51% to 5.97% w/w total water content. Tr. 140:13-141:24 (Matzger); JTX 617 at 1, 3. If the Form II samples had been equilibrated at 5% RH before the TGA, the samples would have had the same total water content. Tr. 140:13-141:24 (Matzger).

217. Dr. Matzger's DVS and controlled humidity TGA results demonstrate that the total water content in Crystal's Form II samples of 5.51% to 5.97% w/w that Crystal measured by TGA are consistent with samples held at about 30% to 40% RH, not 5% RH. Tr. 140:13-141:24 (Matzger); JTX 617 at 1, 3; PTX 1107 (indicating that between about 30% to 40% RH, Form II contains about 5.57% to 5.95% w/w total water).

218. By failing to properly equilibrate its Form II samples used in the DVS and TGA experiments, Crystal overestimated the amount of bound water in its API. Tr. 139:12-140:8 (Matzger); JTX

617 at 3.

**vii. Novartis's Testing on LCZ696 Does Not Change the Fact that Form II Is a Hemipentahydrate**

219. There is no dispute that LCZ696 is a hemipentahydrate. Tr. 124:9-11 (Matzger); Tr. 421:7-11 (Friscic).

220. Novartis initially described LCZ696 as a trihydrate based on an assumption that there would be an integer (or whole number) for the water of crystallization (*i.e.*, bound water). Tr. 124:12-25 (Matzger); Tr. 420:2-9, 420:18-421:6 (Friscic); JTX 355 at 15.

221. Novartis later concluded that water measurements by TGA from 4.67% to 5.19% w/w supported a finding of a hemipentahydrate. Tr. 123:6-23 (Matzger); JTX 355 at 15; Tr. 237:21-238:15 (Karpinski); Tr. 254:19-255:8 (Motto). LCZ696 inventor Dr. Karpinski explained that the consistent TGA results for LCZ696 (*e.g.*, 4.81, 4.7, 4.67% w/w) close to the theoretical value expected for a hemipentahydrate prompted the inventors to conclude that LCZ696 was a hemipentahydrate and did not have an integer number of bound water as initially assumed. Tr. 237:21-238:15 (Karpinski); *see also* Tr. 254:19-255:8 (Motto).

222. Insofar as some of the individual TGA water measurements obtained by Novartis exceeded the theoretical 4.70% w/w weight loss for a hemipentahydrate, inventor Dr. Karpinski explained that

was because the samples giving rise to those measurements may not have been dried sufficiently, leaving surface water in them. Tr. 236:14-21 (Karpinski).

223. DVS testing by Novartis demonstrates that LCZ696 takes up 0.6% w/w surface water when going from 20% to 60% RH. Tr. 125:9-25 (Matzger); JTX 355 at 16, 26. When 0.6% w/w surface water is added to the 4.7% w/w bound water for a hemipentahydrate, LCZ696 may have a total measured water content of 5.3% w/w. Tr. 125:9-25 (Matzger); *see* JTX 355 at 15, 22 (reporting a total water content above 4.7% w/w). However, LCZ696 with 5.3% w/w total water content is still a hemipentahydrate because the hemipentahydrate refers only to bound water and does not include surface water. Tr. 126:1-6 (Matzger).

224. Novartis's TGA experiments for LCZ696 show two bound water loss events, with some TGA experiments also including an initial surface water loss event at low temperatures. Tr. 126:11-127:12 (Matzger); JTX 677 at 46015; JTX 355 at 25. The presence of surface water resulted in a total water content above 4.7% w/w, but LCZ696 is still a hemipentahydrate. Tr. 126:11-127:12 (Matzger); Tr. 236:14-21 (Karpinski); *see* JTX 677 at 46015 (reporting 5.088% w/w total water content); JTX 355 at 25 (reporting 4.808% w/w total water content).

225. Novartis's TGA testing does not change the conclusion that TGA can be used to determine Form II is a hemipentahydrate. Tr. 127:24-128:4 (Matzger).

## II. CONCLUSIONS OF LAW

### A. Introduction

1. Mylan has stipulated that if the Court finds that Mylan's ANDA Products will infringe the '938 patent claim 1, then Mylan will also infringe the '938 patent claim 11 and the '134 patent claim 5. D.I. 100; FOF ¶ 3. Thus, the Court will only address the '938 patent claim 1.

2. The '938 patent claim 1 can be separated into three elements: (1) substantially pure (2) trisodium [sacubitril-valsartan] hemipentahydrate ("TSVH") (3) in crystalline form. *Infra* ¶¶ 21, 37. Novartis demonstrated at trial by a preponderance of the evidence that Mylan's API, Form II, alone and Mylan's ANDA Products containing Form II will meet each of these elements and thus infringe the '938 patent claim 1. *Infra* Section C.v.

3. It is undisputed that "substantially pure" refers to at least 90% chemical purity and that TSVH in crystalline form is not limited to one specific crystalline form. *Infra* ¶ 36.

4. The only disputed issues are whether Mylan's API Form II is substantially pure and whether Form II is a hemipentahydrate,

as required by the '938 patent claim 1. *Infra* ¶¶ 37-39.

5. Mylan's own ANDA specifications and impurity testing confirm that its API, both alone and in Mylan's ANDA Products, is a substantially pure, *i.e.*, at least 90% chemically pure, trisodium [sacubitril-valsartan] complex. *Infra* Section C.iv. It was not necessary for Novartis to conduct additional testing on the purity of Mylan's API because Mylan is only permitted to use API and sell ANDA Products complying with its ANDA specifications. *Infra* Section C.iv.

6. Mylan relied on a single crystal analysis by Crystal, the company that developed Form II, to allege Form II is a trihydrate, not a hemipentahydrate. But a single crystal structure determined using single crystal analysis must be consistent with known chemistry; otherwise, the structure is not correct. *Infra* ¶ 90.

7. Novartis's expert Dr. Rogers analyzed the Form II single crystal structure and found that the occupancies for certain water molecules as analyzed by Crystal were chemically impossible. When the occupancies for those water molecules were corrected based on known chemistry, Dr. Rogers found that the single crystal structure for Form II demonstrates Form II is a hemipentahydrate. *Infra* Section C.v.a.

8. In an attempt to rebut Dr. Rogers's analysis of the chemistry of the structure for Form II, Mylan's expert Dr. Friscic argued certain statistics for Dr. Rogers's structure for Form II as a hemipentahydrate were allegedly worse than Crystal's structure for Form II as a trihydrate. But chemistry, not statistics, controls whether a single crystal structure is correct. And the statistics on which Dr. Friscic relied are not meaningfully different between Dr. Rogers's and Crystal's structures, and/or are not relevant to the occupancies of the relevant water molecules. *Infra* Section C.v.a.ii). Dr. Friscic thus failed to rebut Dr. Rogers's analysis of the single crystal structure based on known chemistry demonstrating that Form II is a hemipentahydrate.

9. Consistent with Dr. Rogers's analysis of the single crystal structure, Novartis's expert Dr. Matzger conducted multiple tests demonstrating that Form II is a hemipentahydrate. *Infra* Section C.v.b. Mylan's expert Dr. Friscic failed to rebut Dr. Matzger's results demonstrating Form II is a hemipentahydrate because (1) Dr. Friscic is not an expert in certain techniques that Dr. Matzger used, (2) Dr. Friscic incorrectly treated surface water as bound water, and (3) Dr. Friscic admitted on cross-examination that Dr. Matzger had correctly measured the bound water

in Form II. *Infra* Section C.vii.

10. In all, the trial evidence shows that Mylan's API is substantially pure and is a hemipentahydrate, such that Mylan's API and Mylan's ANDA Products will infringe the '938 patent claim 1.

**B. Background**

11. This is a patent lawsuit brought under the Hatch-Waxman Act, 21 U.S.C. § 355. Joint Statement of Uncontested Facts to the Joint Pretrial Order (C.A. No. 19-cv-201-TSK, D.I. 104) ("UF"), Ex. 1 at 2, ¶ 2. The Hatch-Waxman Act allows a patentee innovator drug maker to sue a generic drug maker for the infringement of certain patents — *i.e.*, patents listed in FDA's "Orange Book" that cover the innovator's drug product — in advance of the actual commercial launch of an allegedly infringing generic drug product. 35 U.S.C. § 271(e)(2)(A); *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 557 F.3d 1346, 1348 (Fed. Cir. 2009).

12. The jurisdictional trigger for a Hatch-Waxman suit is the submission to FDA by the generic drug maker of an abbreviated new drug application ("ANDA") containing one or more "Paragraph IV certifications," which certifications allege that the generic drug product described in the ANDA will not infringe an innovator's Orange Book-listed patent(s) and/or that those patent(s) are

invalid. 21 U.S.C. § 355(j)(2)(A)(vii)(IV); 35 U.S.C. § 271(e)(2).

13. Novartis holds New Drug Application ("NDA") No. 207620 for Entresto® (sacubitril/valsartan) approved for heart failure patients. UF Ex. 1 at 5-6, 11, ¶¶ 27, 33-34, 59.

14. Novartis owns the '938 and '134 patents and listed both in FDA's Orange Book for Entresto®. UF Ex. 1 at 5-6, 11, ¶¶ 27, 33-34, 59. *Eli Lilly*, 557 F3d. at 1348.

15. Mylan filed ANDA No. 213646 ("Mylan's ANDA") with FDA seeking approval of generic sacubitril/valsartan tablets ("Mylan's ANDA Products") under 21 U.S.C. § 355(j). UF Ex. 1 at 10, ¶¶ 52-53; UF Ex. 1F at 1, ¶¶ 1-2. Mylan included in its ANDA Paragraph IV certifications indicating that Mylan seeks FDA approval for its ANDA Products before the expiration of the '938 and '134 patents. UF Ex. 1 at 10, ¶ 53.

16. Mylan's submission of its ANDA to FDA including Paragraph IV certifications for the '938 and '134 patents was an act of infringement and triggered this lawsuit. 35 U.S.C. § 271(e)(2).

17. In response to Mylan's September 16, 2019 letter to Novartis indicating that Mylan had submitted its ANDA including Paragraph IV certifications for the '938 and '134 patents, Novartis sued Mylan for infringement of, *inter alia*, the '938 and '134

patents. UF Ex. 1 at 10, ¶ 53.

18. Novartis's suit against Mylan was transferred to the District of Delaware for pre-trial purposes in the multi-district litigation *In re Entresto (Sacubitril/ Valsartan) Patent Litigation*, C.A. No. 20-md-2930 (D. Del.). Novartis's suit against Mylan was remanded to the Northern District of West Virginia for trial on February 27, 2023 to March 1, 2023.

19. Novartis has standing to bring this action. UF, Ex. 1 at 2, ¶ 3.

20. Novartis and Mylan have agreed to stay the issue of invalidity at this time, leaving infringement as the sole issue with respect to this memorandum opinion and order. D.I. 83 ¶¶ 10-11.

**i. The '938 Patent Claim 1 Recites TSVH in Crystalline Form**

21. The '938 patent claim 1 recites TSVH in crystalline form. FOF ¶ 4. TSVH is a compound or complex of sacubitril, valsartan, sodium, and water molecules in a 1:1:3:2.5 molar ratio. FOF ¶ 5.

22. A POSA would understand that the compound TSVH and its crystalline forms are distinct concepts. FOF ¶ 6. TSVH in "crystalline form" means that the chemical compound TSVH is arranged in a regular repeating array in three dimensions forming a crystal lattice. *Id.* TSVH may exist in different crystalline

forms referred to as "polymorphs." *Id.*

23. The term "hemipentahydrate" in crystalline TSVH refers to 2.5 bound water molecules (*i.e.*, water that is part of the crystal lattice), which equal a theoretical 4.70% w/w of the total TSVH compound. FOF ¶¶ 5, 7-8.

24. A sample of TSVH in crystalline form may also contain surface water — *i.e.*, water that adheres to the surface of the crystal particles but is not part of the crystal lattice. FOF ¶¶ 7-8, 129. However, surface water is not considered when determining whether a trisodium [sacubitril-valsartan] compound in crystalline form is a hemipentahydrate. FOF ¶ 8.

**ii. Mylan's ANDA Products and API**

25. Mylan has three proposed ANDA Products, each comprising a different dosage strength of the same API referred to as Form II. FOF ¶¶ 17-19; UF, Ex. 1F at 1, ¶ 1. Form II is a trisodium [sacubitril-valsartan] hydrate compound in crystalline form. FOF ¶ 21. It is undisputed that Mylan's ANDA Products contain Form II in the same crystalline form as found in the samples of Mylan's API that Dr. Matzger tested. FOF ¶¶ 46-48.

26. Novartis asserts that by (1) using in or importing into the United States Mylan's API, Mylan will infringe the '938 patent claim 1 and (2) manufacturing, using, selling or offering for sale

in the United States Mylan's ANDA Products, Mylan will infringe the '938 patent claim 1. D.I. 1 at ¶¶ 53, 55.

27. Mylan's ANDA describes Form II as an alleged trihydrate, *i.e.*, having three bound water molecules, based on a 2019 Single Crystal Report (JTX 647). FOF ¶¶ 22, 24. But it is undisputed that the water content specification for Mylan's API in its ANDA of not more than 7.0% w/w allows Mylan's API to have 4.70% w/w bound water, corresponding to a hemipentahydrate. FOF ¶ 23. To the extent Mylan's API contains more than 4.70% w/w *total* water content, that is due to the presence of surface water. FOF ¶¶ 133-135.

28. Mylan did not develop Form II; instead, Crystal developed Form II. FOF ¶ 19. And Crystal and Mylan both obtain Form II manufactured under the same DMF from the same supplier, Harman Finochem. *Id.*

29. At trial, Mylan relied on Crystal's development documents and fact witness Mr. Jianming Wang for the characterization of Form II. Tr. 397:12-25 (Friscic); Tr. 211:7-12.

30. A trial between Novartis and Crystal was held in the District of Delaware in October 2022, where the parties addressed whether the same Form II that Mylan uses is a hemipentahydrate based on testimony from the same experts testifying from the same

expert reports and many of the same documents, including the same single crystal structure for Form II, as raised before this Court. *See* D.I. 87-1 at ¶¶ 5, 194-195; D.I. 104-19 at 2; D.I. 104-21 at 4; Tr. 396:18-397:25 (Friscic).

31. As discussed in Sections C.iv. and C.v. below, Mylan's API is substantially pure and Dr. Rogers's analysis of the single crystal structure for Form II and Dr. Matzger's testing of Form II demonstrated that Form II is a hemipentahydrate with 2.5 bound waters.

**C. Argument**

**i. Legal Standards**

32. Novartis must show by a preponderance of the evidence, *i.e.*, that it is more likely than not, that Mylan's API and/or Mylan's ANDA Products will meet the elements of the asserted claims. *Creative Compounds, LLC v. Starmark Labs.*, 651 F.3d 1303, 1314 (Fed. Cir. 2011).

33. An infringement determination is a two-step process where (1) the meaning of the claims are construed, and (2) the construed claims are compared to the accused product. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1581-82 (Fed. Cir. 1996). In the second step of the infringement determination, "the only proper comparison [of Form II and Mylan's ANDA Products] is

with the claims of the patent," not Novartis's commercial embodiment. *Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1423 (Fed. Cir. 1994).

34. Infringement can be found where testing or other evidence demonstrates that an API or ANDA product infringes, despite contrary representations about that API or product by the ANDA applicant to FDA. *See, e.g.*, *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1335-36, 1338 (Fed. Cir. 2005) (affirming, based on expert testimony, that defendant's product would contain a "hemihydrate" despite defendant's representations that its product contained an anhydrate); *In re Omeprazole Patent Litig.*, 84 F. App'x 76, 82-83 (Fed. Cir. 2003) (finding infringement where testing revealed the claimed "subcoating" despite defendant's assertion it did not have one); *Novartis Pharm. Corp. v. Par Pharm., Inc.*, 48 F. Supp. 3d 733, 739-41 (D. Del. 2014) (finding infringement where testing showed the presence of the claimed "antioxidant" despite it not being listed in the ANDA specification).

**ii. Claim Construction**

35. The Delaware Court previously construed "[TSVH] in crystalline form" recited in the '938 patent claim 1 as "substantially pure [TSVH] in crystalline form." FOF ¶ 27; UF, Ex.

1 at 16-17, ¶ 7; C.A. No. 20-md-2930-RGA, D.I. 295 at 2.

36. It is undisputed that "substantially pure" refers to at least 90% chemically pure. FOF ¶¶ 28, 30. It is further undisputed that "[TSVH] in crystalline form" is not limited to one specific crystalline form (or polymorph) of TSVH. FOF ¶¶ 29-30; Tr. 540:23-541:9 (Mylan).

**iii. The Only Disputed Infringement Issues Are Whether Mylan's API Is Substantially Pure and Whether Mylan's API Is a Hemipentahydrate**

37. The '938 patent claim 1 can be separated into three elements: (1) substantially pure (2) TSVH (3) in crystalline form. FOF ¶ 31.

38. Mylan has stipulated that its API is in crystalline form. FOF ¶ 32. Mylan's ANDA further describes Mylan's API as a trisodium [sacubitril-valsartan] (*i.e.*, TSV) hydrate. FOF ¶ 33.

39. Thus, the only disputed infringement issues for the '938 patent claim 1 are whether Mylan's API Form II is (1) substantially pure and (2) a hemipentahydrate. FOF ¶ 34.

40. Mylan has committed, or will commit, three separate categories of infringing acts. D.I. 1 at ¶¶ 52, 53, 55.

41. *First*, Mylan has infringed the '938 patent claim 1 by filing an ANDA for a drug that is covered by that patent claim. 35 U.S.C. § 271(e)(2)(A) ("It shall be an act of infringement to

submit an [ANDA] for a drug claimed in a patent ….”); D.I. 1 at ¶ 52; *see also* D.I. 100 at ¶¶ 1-2 (stipulating that if Mylan infringes the ’938 patent claim 1, Mylan’s filing of its ANDA also infringes the ’938 patent claim 11 and the ’134 patent claim 5).

42. *Second*, upon FDA approval of Mylan’s ANDA Products, Mylan’s importation into Puerto Rico of Form II, and Mylan’s use of Form II to manufacture commercially its ANDA Products there, will infringe the ’938 patent claim 1. D.I. 1 at ¶¶ 53, 55. “[W]hoever without authority . . . uses . . . within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent.” 35 U.S.C. § 271(a); 35 U.S.C. § 100(c) (“The terms ‘United States’ and ‘this country’ mean the United States of America, its territories and possessions.”); 48 U.S.C. § 734 (“The statutory laws of the United States . . . shall have the same force and effect in Puerto Rico as in the United States . . . .”); *Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc.*, 477 F. Supp. 3d 306, 342 (D. Del. 2020), *aff’d*, 858 Fed. App’x 359 (Fed. Cir. 2021) (finding court could exercise declaratory judgment jurisdiction over infringing act of using infringing API in the United States to manufacture ANDA product).

43. *Third*, upon FDA approval of Mylan’s ANDA Products,

Mylan's commercial manufacture, use, offer to sell or sale in the United States of its ANDA Products each will constitute separate acts of infringement. 35 U.S.C. § 271(a), (b); D.I. 1 at ¶¶ 53, 55; *see also* D.I. 100 ¶¶ 1-2 (stipulating that if Mylan's ANDA Products infringe the '938 patent claim 1, Mylan's ANDA Products will also infringe the '938 patent claim 11 and the use of Mylan's ANDA Products will infringe the '134 patent claim 5 and Mylan will induce that infringement).

**iv. Mylan's API Form II Is Substantially Pure**

44. Based on Mylan's ANDA specification and its own testing for impurities, Mylan's API is substantially pure, *i.e.*, it is at least 90% chemically pure.

45. "[I]f a product that an ANDA applicant is asking the FDA to approve for sale falls within the scope of an issued patent, a judgment of infringement must necessarily ensue." *Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271, 1278 (Fed. Cir. 2013). An ANDA specification that overlaps with the claim limitation is sufficient to find infringement. *Id.* (finding a specification of "0.0-0.6% is within the scope of the 'less than 0.25%' limitation").

46. Mylan's ANDA specification requires that Form II alone has not more than ("NMT") a combined total of 2.95% w/w impurities

and residual solvents related to Form II. FOF ¶ 36. *Sunovion*, 731 F.3d at 1279 ("[D]rug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug ….") (internal quotation and citation omitted). In batches of its API that Mylan's ANDA identifies to FDA as representative ("exhibit batches") of the API Mylan will use to manufacture its ANDA Products, Mylan measured less than about 0.5% w/w impurities and residual solvents. FOF ¶ 37. Mylan's API further contains only an insubstantial amount of amorphous material, less than about 0.5% w/w.[6] FOF ¶ 39.

47. Mylan's ANDA specifications also require that Mylan's ANDA Products contain NMT than about 1.0% w/w impurities related to Form II. FOF ¶ 40. Mylan's ANDA Products thus contain substantially pure Form II, *i.e.*, there are less than 10% w/w chemical impurities related to Form II, and will infringe the '938

[6] Contrary to Mylan's suggestion (Tr. 182:16-24), Novartis's assertion in another case that Mylan's ANDA Products also infringe the '918 patent, which recites an amorphous trisodium [sacubitril-valsartan] compound, is not inconsistent with Mylan's API being substantially pure crystalline TSVH as required by the '938 patent claim 1. "[S]ubstantially pure" in the '938 patent claim 1 requires at least 90% chemical purity, whereas even trace amounts of amorphous compound will infringe the '918 patent. *See SmithKline*, 403 F.3d at 1341 (holding defendant's product with "trace amounts" of the claimed compound would infringe). Thus, Mylan's API can be substantially pure TSVH in crystalline form according to the '938 patent claim 1, yet also contain trace amounts of amorphous material that infringe the '918 patent.

patent claim 1. *Sunovion*, 731 F.3d at 1278 (affirming infringement based on ANDA specification alone).

48. That Form II, both alone and in Mylan's ANDA Products, is substantially pure is further supported by the fact that Form II is in crystalline form, which Mylan has admitted is by definition, substantially pure. FOF ¶¶ 41-42; D.I. 66-2 at 66. Consistent with this admission, Crystal — the developer of Form II — admitted that its ANDA Products contain substantially pure Form II and stipulated to that fact in the pretrial order. FOF ¶ 35.

49. Mylan asserted at trial that its ANDA and purity testing by HPLC establish only the purity of individual sacubitril and valsartan, as opposed to being linked together or in a complex as required by the term "substantially pure." Tr. 28:25-30:17 (Mylan opening); Tr. 346:4-25 (Friscic). But Mylan's own documents and testing repeatedly identify Form II, both alone and in Mylan's ANDA Products, as a complex of sacubitril and valsartan, not separate components. FOF ¶¶ 43-47. Nowhere does Mylan's ANDA or the DMF indicate separate sacubitril or valsartan is present in Form II or Mylan's ANDA Products. Mylan's own ANDA and DMF thus prove that Form II is a complex, and not separate sacubitril and valsartan. *Liquid Dynamics Corp. v. Vaughan Co.*, 449 F.3d 1209,

1219-20 (Fed. Cir. 2006) (affirming reliance on circumstantial infringement evidence from defendant's own documents to prove infringement); *Martek BioSciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009) (holding that circumstantial evidence, in lieu of direct testing, was sufficient to prove infringement).

50. Dr. Matzger further confirmed by XRPD that Mylan's API is the complex Form II and that Form II is present in Mylan's ANDA Products. FOF ¶ 48. The presence of excipients used to formulate Form II into Mylan's ANDA Products does not impact the substantial purity of Form II. *Id. Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1347 (Fed. Cir. 2004) (holding that excipients are not considered impurities of the API).

51. The only circumstance in which Dr. Friscic alleged that Form II disassociates into separate sacubitril and valsartan is during "HPLC" *analytical testing*. FOF ¶ 50. But Dr. Friscic admitted that such HPLC analytical testing is not part of the *manufacturing process* for Mylan's ANDA Products. FOF ¶ 51. And Mylan manufactures its ANDA Products using dry granulation, *i.e.*, without liquids, keeping Form II intact as a complex. FOF ¶¶ 45, 52. Mylan further represented that Form II does not dissociate into separate sacubitril and valsartan in its ANDA Product. FOF ¶¶

46-47.

52. Mylan has also represented to FDA that Form II is stable and unchanged during the manufacture of Mylan's ANDA Products. FOF ¶ 47. Dr. Matzger confirmed the presence of Form II in Mylan's ANDA Products by XRPD. FOF ¶ 48. And Dr. Friscic admitted on cross examination that Form II is a complex and remains unchanged during manufacture of Mylan's ANDA Products. FOF ¶ 52.

53. Thus, Form II is a complex of sacubitril and valsartan, both before and after it is incorporated into Mylan's ANDA Products. And Novartis has shown by a preponderance of the evidence that Mylan's API, both alone and in Mylan's ANDA Products, is "substantially pure."

54. Mylan's suggestion on cross examination of Dr. Matzger that the trace amount of impurities in Form II could impact the determination of bound water (Tr. 166:21-171:25) is unsupported and should be rejected. FOF ¶ 171.

55. *First*, by Dr. Friscic's own admission, the single crystal structure for Form II is unaffected by impurities. FOF ¶ 59; Tr. 295:18-296:5 (Friscic). Thus, any impurities in samples of Form II are irrelevant to Dr. Rogers's analysis of the single crystal structure demonstrating that Form II is a hemipentahydrate, as discussed in Section C.v.a. below.

56. *Second*, the Form II samples that Dr. Matzger tested contained less than about 0.5% w/w impurities, not the 10% or 5% w/w Mylan suggested may be present, and only an insubstantial amount of amorphous material. FOF ¶¶ 37, 39. The trace amounts of impurities and amorphous material in the Form II samples that Dr. Matzger tested have no significant impact on the determination of bound water demonstrating that Form II is a hemipentahydrate, as discussed in Section C.vi.a. below.

**v. Mylan's API Form II Is a Hemipentahydrate**

**a. Dr. Rogers's Single Crystal Analysis Alone Proves that Mylan's API Form II Is a Hemipentahydrate**

57. Novartis's expert Dr. Rogers — Professor Emeritus at the University of Alabama, endowed chair or named chair at the Queen's University of Belfast, McGill University, and the University of Alabama, and founder of the premier American Chemical Society journal *Crystal Growth & Design* (FOF ¶¶ 9-10) — analyzed the chemistry of the single crystal structure for Form II, which by itself proves by a preponderance of the evidence that Form II is a hemipentahydrate. Mylan's assertion that Form II is a trihydrate therefore is incorrect.

58. For purposes of single crystal analysis, the smallest number of atoms that a crystallographer must find to model the structure of the entire crystal is called an "asymmetric unit."

FOF ¶ 55.

59. Because crystals are not perfectly uniform, crystals exhibit "disorder," meaning that certain atoms or water molecules may not be present at the same location in every asymmetric unit within the crystal, or may be present in some asymmetric units but completely absent from others. FOF ¶ 56.

60. When an atom or water molecule in a crystal is disordered, its "occupancy" at a particular position in the crystal will be less than 100% or 1.0. FOF ¶ 57.

61. It is undisputed that the formula unit of Form II is trisodium [sacubitril-valsartan] • x $H_2O$, where x is the number of water molecules. FOF ¶ 64.

62. It also is undisputed that the asymmetric unit of Form II consists of three formula units, such that each asymmetric unit consists of 3x water molecules. FOF ¶ 65.

63. The dispute between the parties is over what the number "x" is. Tr. 398:7-12 (Friscic); 460:13-461:1 (Rogers).

64. In the asymmetric unit of Form II, there are ten positions for water molecules, labeled OW1, OW2, OW3, OW4, OW5, OW6, OW7A, OW7B, OW8 and OW9. FOF ¶ 66.

65. Crystal correctly modeled the water molecule OW7 as disordered over two positions, OW7A and OW7B, in the asymmetric

unit of Form II, such that it is present at position OW7A at 50% occupancy and at position OW7B at 50% occupancy. FOF ¶ 69.

66. Crystal incorrectly modeled three of the remaining water molecules in the asymmetric unit of Form II — OW1, OW3 and OW8 — as present at 100% occupancy. FOF ¶ 70.

67. There are 9 total water molecules per asymmetric unit in Crystal's incorrect model of Form II, which, when divided by 3 formula units per asymmetric unit, equals 3 water molecules per formula unit (*i.e.*, x = 3). FOF ¶ 71. From this, Crystal wrongly concluded that Form II is a trihydrate. *Id.*

68. Crystal's trihydrate model of Form II is chemically impossible. FOF ¶ 80.

69. Dr. Rogers analyzed the chemistry of all the water molecules in Form II. FOF ¶ 72. Based upon that analysis, Dr. Rogers determined that the OW1, OW3, and OW8 water molecules cannot be present at 100% occupancy in the asymmetric unit of Form II, but instead can only be present at 50% occupancy. *Id.*

70. There are 7.5 total water molecules per asymmetric unit in Dr. Rogers's chemically correct model of Form II, which, when divided by 3 formula units per asymmetric unit, equals 2.5 water molecules per formula unit (*i.e.*, x = 2.5). FOF ¶ 73. Thus, Form II is a hemipentahydrate. *Id.*

**i) OW1, OW3, and OW8 Are Present at 50% Occupancy in the Single Crystal Structure of Form II**

71. There are multiple reasons why OW1, OW3, and OW8 are present at only 50% occupancy in Form II. FOF ¶ 74.

72. First, among the water molecules present in Form II, OW1, OW3, and OW8 have the largest thermal parameters, suggesting that OW1, OW3, and OW8 are disordered. FOF ¶¶ 75-76.

73. Second, OW1, OW3, and OW8 each are near sodium atoms that Crystal itself acknowledged are disordered, further suggesting that OW1, OW3, and OW8 are disordered.[7] FOF ¶¶ 77-78.

74. Third, the local chemical environments for OW1, OW3, and OW8 demonstrate that OW1, OW3, and OW8 must in fact be present at only 50% occupancy in Form II. FOF ¶ 79.

75. As to the local chemical environment of OW1, OW1 is closest to the disordered sodium atom Na8. FOF ¶ 81.

76. It is undisputed that Na8 is disordered over two positions, Na8A and Na8B, in Form II, such that Na8 is present at position Na8A at 50% occupancy and at position Na8B at 50% occupancy. FOF ¶ 82.

[7] Although large thermal parameters and proximity to disordered sodium atoms are not dispositive of disorder, they provide clues to the crystallographer that OW1, OW3, and OW8 are also disordered. FOF ¶¶ 25, 27.

77. When Na8 is at position Na8A, OW1 does not fit the structure of Form II, but when Na8 is at position Na8B, OW1 fits. FOF ¶¶ 83, 90-91. When Na8 is at position Na8A, there are only 2.080 angstroms ("Å") between Na8A and OW1, a distance insufficient to accommodate the OW1 water molecule, including its hydrogen atoms, in the geometry in which it is fixed in Form II.[8] FOF ¶ 83. But when Na8 is at position Na8B, there are 2.939 Å between Na8B and OW1, a distance sufficient to accommodate OW1. FOF ¶ 90.

78. Thus, in Form II, OW1 is present in only half the asymmetric units that make up the crystal, wherein Na8 is at position Na8B. FOF ¶ 92. In the other half of the asymmetric units, wherein Na8 is present at position Na8A, OW1 is not there. *Id.*

79. There is a second reason why OW1 is at 50% occupancy in Form II based on the disorder of OW7 as it relates to OW1. It is undisputed that OW7 is disordered over two positions: OW7A and OW7B. FOF ¶¶ 69, 93. When OW7 is present at position OW7A in 50%

[8] Dr. Friscic's own survey of structures in the Inorganic Crystal Structure Database and Cambridge Structural Database show that the majority of sodium-to-oxygen ("Na-O") distances are between about 2.3–2.6 Å and 2.3–2.4 Å, respectively. FOF ¶¶ 84-85. The three outlier examples from the Cambridge Structural Database that Dr. Friscic provided of unusually short Na-O distances of about 2.1 Å are not relevant to the chemistry of Form II. FOF ¶ 87. And unlike Dr. Rogers, Dr. Friscic did not examine the chemistry of Na8A and OW1 in Form II, including the geometry in which OW1 is fixed in Form II, to determine whether a distance of 2.080 Å between them was chemically reasonable. FOF ¶ 89.

of the asymmetric units of Form II, OW7 hydrogen-bonds with the OW1 and with two oxygen anions, O281 and O181. FOF ¶ 93. When OW7 is at position OW7B in the other 50% of the asymmetric units of Form II, OW7 hydrogen-bonds with a different water molecule, OW5 (OW1 being absent from those asymmetric units) and with O281 and O181. *Id.* As Dr. Rogers explained, there is no reason for OW7 to be disordered, and to be present at position OW7B, unless OW1 is present at only 50% occupancy in Form II. *Id.*

80. This second reason why OW1 is at 50% occupancy in Form II does not depend on Na-O distances. FOF ¶ 95. And Dr. Friscic did not dispute it. FOF ¶ 96.

81. As to the local chemical environment of OW3, OW3 is closest to disordered sodium atom Na8. FOF ¶ 98.

82. It is undisputed that when Na8 is at position Na8A, Na8 is 3.740 Å away from OW3 — too far to bind OW3 — and there is no other nearby sodium atom that can bind OW3. FOF ¶ 99. Nor did Dr. Friscic identify any atom(s) in Form II that could bind OW3 when Na8 is at position Na8A. FOF ¶ 101. But when Na8 is at position Na8B, Na8 is 2.358 Å away from OW3, within the range of typical Na-O bond distances. FOF ¶ 100. Thus, when Na8 is at position Na8B, Na8 binds OW3. *Id.*

83. Because OW3 is bound within the structure of Form II

only when Na8 is present at position Na8B in 50% of the asymmetric units of Form II, OW3 must be present at 50% occupancy in Form II. FOF ¶ 102.

84. Thus, in Form II, OW3 is present in only half of the asymmetric units that make up the crystal, where Na8 is present at position Na8B. FOF ¶ 103. In the other half of the asymmetric units, where Na8 is present at position Na8A, OW3 is not there. *Id.*

85. As to the local chemical environment of OW8, OW8 is closest to the disordered sodium atom Na10. FOF ¶ 104.

86. It is undisputed that Na10 cannot be present at 100% occupancy in Form II. FOF ¶ 105. If it were, there would be only 2.078 Å between adjacent Na10 sodium atoms, which is too short a distance to accommodate two sodium atoms. *Id.* Crystal thus models Na10 as disordered, such that Na10 is present only in 50% of the asymmetric units of Form II. *Id.*

87. Like Na10, OW8 cannot be present at 100% occupancy in Form II. FOF ¶ 106. If it were, there would only be 3.002 Å between adjacent OW8 water molecules. *Id.* 3.002 Å is too short a distance to accommodate two adjacent OW8 water molecules, including their hydrogen atoms, in the geometry in which they are fixed in Form II, *i.e.*, with their hydrogen atoms pointed at each other. *Id.*

Thus, like Na10, OW8 is present only in 50% of the asymmetric units of Form II. FOF ¶ 107.

88. A second problem occurs when OW8 is modeled at 100% occupancy: modeling OW8 at 100% occupancy gives rise to a chemically impossible configuration in which Na10 is too close to a hydrogen atom of OW8 and blocks the hydrogen bond that must be present between OW8 and a nearby oxygen atom, O329. FOF ¶ 108. This chemically impossible configuration, however, disappears once OW8 is modeled at 50% occupancy. *Id.* For this additional reason, OW8 must be present at 50% occupancy in Form II. *Id.*

89. In sum, Crystal's trihydrate model of Form II, in which OW1, OW3, and OW8 are present at 100% occupancy, is chemically impossible. FOF ¶ 80. By contrast, Dr. Rogers's hemipentahydrate model of Form II, in which OW1, OW3, and OW8 are present at 50% occupancy, is chemically correct. *Id.*

**ii) Dr. Friscic's Statistics-Based Arguments Fail To Rebut Dr. Rogers's Single Crystal Analysis**

90. In the field of crystallography, chemistry, not statistics, determines whether the model of a crystal structure is correct. FOF ¶ 111.

91. Nevertheless, correctly modeling OW1, OW3, and OW8 at 50% occupancy, as Dr. Rogers did, does not significantly change the relevant statistics for Dr. Rogers's January 2022 refinement

of his model ("Dr. Rogers's refinement"), compared to the statistics for Crystal's 2019 refinement ("Crystal's refinement"), and the statistics for Dr. Friscic's June 2022 refinement ("Dr. Friscic's refinement"). FOF ¶ 112.

92. The R-factors for Crystal's refinement, Dr. Rogers's refinement, and Dr. Friscic's refinement, when rounded to two decimal places, are all the same: 0.12. FOF ¶ 113. Dr. Friscic admitted that an R-factor of 0.12 is "extremely reasonable" for a structure of the size and complexity as Form II. FOF ¶ 114.

93. The goodness-of-fit statistics for Crystal's refinement, Dr. Rogers's refinement, and Dr. Friscic's refinement, when rounded to one decimal place, are all the same: 2.1. FOF ¶ 115. The International Union of Crystallography does not consider differences in goodness-of-fit statistics beyond one decimal place to be significant. FOF ¶ 116.

94. The maximum shift/esd statistic of 0.194 in Dr. Rogers's refinement is considerably less than one. FOF ¶ 117. According to Fanwick 2019, a maximum shift/esd statistic of "considerably less than one" indicates that a refinement is complete and can be stopped. *Id.* Because Dr. Rogers's maximum shift/esd statistic is considerably less than one, his refinement was complete and could be stopped. *Id.*

95. Dr. Rogers determined that the maximum shift/esd statistic for his refinement is attributable to just one thermal parameter, $U_{12}$, for just one carbon atom in Form II, C374, which is not well refined in Crystal's model of Form II. FOF ¶ 120. That thermal parameter for C374 is unrelated to the occupancies of OW1, OW3, and OW8 in Form II. FOF ¶ 121.

96. The mean shift/esd statistic for Dr. Rogers's refinement is 0.016. FOF ¶ 122. This statistic, which averages all shift/esd values for all 400-plus atoms and 1100 — plus parameters that make up Form II, shows that the structure that Dr. Rogers modeled — in which OW1, OW3, and OW8 are at 50% occupancy — is stable and is fully refined. *Id.*

97. Dr. Friscic did not address the mean shift/esd statistic for Dr. Rogers's refinement.

98. Dr. Friscic observed that the U1/U3 ratios for the OW1 and OW8 water molecules increased, and the thermal ellipsoids for OW1 and OW8 became more "cigar-shaped," in Dr. Rogers's refinement. Tr. 364:14-367:9 (Friscic). But Dr. Rogers explained that those statistical measures are irrelevant to whether the occupancies of OW1 and OW8 are chemically correct, and that, among Crystal's, Dr. Rogers's and Dr. Friscic's refinements, only Dr. Rogers's refinement has the chemically correct occupancies for OW1 and OW8

(*i.e.*, 50%). FOF ¶¶ 123-126.

99. Dr. Rogers further explained that there is no scientific reference of record which indicates that the ratio of U1/U3 thermal parameters for an atom in a crystal structure must be equal to or less than 3, and that, Crystal's and Dr. Friscic's refinements of Form II include, respectively, 19 and 43 atoms having a U1/U3 ratio greater than 3. FOF ¶¶ 125-126. Dr. Friscic did not explain why, in view of those numbers, Crystal's and Dr. Friscic's refinements allegedly are acceptable, whereas Dr. Rogers's refinement allegedly is not.

**b. Dr. Matzger's Testing Alone Also Proves that Mylan's API Is a Hemipentahydrate**

100. Consistent with Dr. Rogers's analysis of the single crystal structure, Novartis's expert Dr. Matzger — a Professor at the University of Michigan since 2000 and owner of the pharmaceutical analytical testing company ChemXLerate with over 20 years' experience characterizing the water content of crystalline materials (FOF ¶¶ 11-12) — conducted multiple TGA and DVS experiments demonstrating by a preponderance of the evidence that Form II is a hemipentahydrate. For this additional and independent reason, Mylan's Form II is a hemipentahydrate.

**i) Mylan's API Contains Surface Water that Must Be Removed to Determine the Amount of Bound Water**

101. Mylan's expert Dr. Friscic admitted that when determining the amount of bound water that constitutes a hydrate, one must also account for whether surface water is present. Tr. 403:18-23 (Friscic); FOF ¶¶ 129-130; *see also* Tr. 218:24-25 (Wang) (testifying that Crystal tested Form II to "distinguish bound and adsorbed [i.e., surface] water").

102. Form II is hygroscopic, meaning it tends to take up water including surface water, and contains both bound water and surface water at conditions above 2% RH and at normal laboratory conditions (*i.e.*, between about 20% and 40% RH). FOF ¶¶ 133-135, 141, 180.

103. Dr. Matzger demonstrated by DVS that Form II takes up about 1.6-1.7% w/w surface water between 2% and 50% RH. FOF ¶ 134. Consistent with Dr. Matzger's testing, Dr. Friscic admitted that Crystal's DVS testing demonstrated that Form II takes up over 1% w/w surface water from 10% to 60% RH. Tr. 405:18-406:8, 406:17-20 (Friscic); FOF ¶ 134.

104. The hygroscopic nature of Form II and the fact that Form II takes up significant surface water above 2% RH (including under normal laboratory conditions) explain why the total water content in Form II may exceed 4.70% w/w, notwithstanding that Form II is

a hemipentahydrate containing 4.70% w/w bound water. FOF ¶¶ 133-135. As explained below, Dr. Matzger designed his testing to distinguish between bound and surface water in Form II.

**ii) Dr. Matzger's Controlled Humidity TGA Results Prove that Form II Is a Hemipentahydrate**

105. Dr. Matzger's controlled humidity TGA experiments allowed him to differentiate between surface water and the total bound water in Form II by first equilibrating Form II at 2% RH, which based on his and Crystal's DVS testing would remove surface water but no significant bound water, then equilibrating Form II at 0% RH to remove two bound waters, and last heating Form II to determine how much bound water was left in Form II after equilibration at 0% RH. Tr. 88:12-21 (Matzger); FOF ¶¶ 140-142.

106. From 2% to 0% RH, Form II lost 3.63% or 3.67% w/w bound water, which corresponds closely to the theoretical 3.76% w/w for two bound waters. FOF ¶ 143.

107. Upon heating at 0% RH, Mylan's API lost an additional 1.01% w/w bound water closely corresponding to the theoretical 0.94% w/w for half a bound water. *Id.*

108. The total bound water of 4.64% and 4.68% w/w in Dr. Matzger's controlled humidity TGA corresponds very closely to the theoretical 4.70% w/w for a hemipentahydrate and alone

demonstrates that Form II is a hemipentahydrate. *Id.*

**iii) Dr. Matzger's DVS Results Combined with His Hi-Res TGA Results Also Prove that Form II Is a Hemipentahydrate**

109. Dr. Matzger's DVS experiments on Form II, which measured the change in weight as a function of RH, when combined with the undisputed half a tightly bound water measured by Hi-res TGA, also independently demonstrate that Form II is a hemipentahydrate. FOF ¶¶ 149-153.

110. Dr. Friscic admitted on cross-examination that "by observing the change in the slope of the DVS curve and calculating the intersection between the two trend lines . . . , [it is possible to] obtain a good estimate of the amounts of bound and surface water" in Form II. Tr. 419:12-19 (Friscic); FOF ¶ 147.

111. Because bound water is more tightly held within the crystal lattice whereas surface water is more loosely held outside the crystal lattice, DVS can distinguish between bound and surface water in two ways: bound water is typically gained or lost over a narrow range of RH but relatively slowly, whereas surface water is gained or lost over a broad range of RH but relatively fast at each RH step. FOF ¶¶ 7, 131, 147.

112. Dr. Matzger determined the amounts of surface and bound water in Form II by decreasing and increasing the RH in 2% steps

and observing the ranges of RH over which the weight changed and the rate at which those weight changes occurred. FOF ¶ 148.

113. Over the narrow range of 0% to 2% RH, Form II lost or gained 3.70% to 3.80% w/w water over the course of several hours (*i.e.*, relatively slowly), which weight changes correspond closely to the theoretical 3.76% w/w for two bound waters. FOF ¶¶ 149-151. It is undisputed that below 2% RH, Form II loses two bound waters. Tr. 418:11-24 (Friscic).

114. In contrast, over the broad range of 2% to 50% RH, Form II rapidly gained or lost water at each RH step for a total of about 1.6-1.7% w/w, which corresponds to surface water. FOF ¶¶ 149-151.

115. Consistent with Dr. Matzger's conclusions from his DVS testing, Dr. Friscic admitted on cross-examination that the slope change point without surface and only bound water in Crystal's DVS on Form II is at about 2% RH. Tr. 419:20-420:1 (Friscic); FOF ¶ 150.

116. Because the last half-bound water in Form II is tightly held and only removed at high temperatures, as demonstrated in Dr. Matzger's Hi-res TGA, Dr. Matzger's DVS experiments conducted at room temperature did not remove that half bound water. FOF ¶¶ 152, 161. However, when the two bound waters for Form II measured by

DVS are combined with the undisputed half bound water measured in Dr. Matzger's Hi-res TGA experiment, the result is that Form II has 2.5 bound waters and is a hemipentahydrate. FOF ¶ 153.

**iv) Dr. Matzger's Hi-Res TGA Results Also Prove that Form II Is a Hemipentahydrate**

117. Dr. Matzger's Hi-res TGA further demonstrates that Form II is a hemipentahydrate, not a trihydrate. FOF ¶¶ 161-162.

118. TGA is a recognized technique for determining the amount of bound water in a hydrate, by measuring the change in weight of a sample as a function of increasing temperature and/or time. FOF ¶¶ 136-138. Because surface water is more loosely held than bound water, surface water is typically lost at lower temperatures before bound water. FOF ¶¶ 131, 138. However, loss of surface water by TGA may overlap with bound water and/or two bound water loss events may overlap. Tr. 73:18-75:17, 112:25-113:20 (Matzger); JTX 349 at 507; JTX 745 at 1.

119. With Hi-res TGA, better separation of overlapping water loss events may be achieved by slowing the heating rate during weight loss transitions. FOF ¶ 155. A pinhole pan with a small pinhole in the lid may also be used to better separate overlapping water loss events. FOF ¶¶ 157-159.

120. With Hi-res TGA conducted with a pinhole pan, Dr. Matzger observed three water loss events for Form II. FOF ¶ 161. The first

water loss event, corresponding to surface water, occurred during an isothermal period, where the Form II sample was held in a pinhole pan for two hours without increasing the temperature. FOF ¶¶ 160-161.

121. Upon heating Form II to about 80 °C, Dr. Matzger observed the second water loss event equaling 3.942% w/w corresponding to the theoretical 3.76% w/w for two bound waters. FOF ¶ 161.

122. Upon further heating Form II to about 120 °C, Dr. Matzger observed the third water loss event equaling 0.952% corresponding to the theoretical 0.94% for half a tightly bound water. FOF ¶ 161.

123. The combined 4.89% w/w water loss for the second and third water loss events corresponds well with the theoretical 4.70% w/w bound water for a hemipentahydrate and is far from the theoretical 5.58% w/w for a trihydrate. FOF ¶¶ 161-162; *see also* FOF ¶¶ 206-207; Tr. 409:14-410:22 (Friscic) (admitting that calculated amounts of water within 0.2% to 0.3% w/w of the theoretical value corresponded to the theoretical hydrate).

124. It is undisputed that the third water loss event of 0.952% w/w in Dr. Matzger's Hi-res TGA for Form II corresponds well with the theoretical 0.94% w/w for a theoretical half a tightly bound water. FOF ¶¶ 161, 164.

125. To the extent the combined 4.89% w/w water loss for the second and third water loss events in Dr. Matzger's Hi-res TGA for Form II was greater than the theoretical 4.70% w/w bound water for a hemipentahydrate, that was due primarily to the overlap of surface and bound water in the second water loss event. FOF ¶¶ 161, 163.

126. As discussed in paragraphs 105-116 above, any disputes about the possible overlap of surface and bound water in Dr. Matzger's Hi-res TGA results were resolved by Dr. Matzger's controlled humidity TGA and DVS results. Tr. 82:21-83:9 (Matzger).

#### vi. Mylan's Criticisms of Dr. Matzger's Testing Fail to Rebut that Form II Is a Hemipentahydrate

127. Mylan and Dr. Friscic criticized Dr. Matzger's testing on various bases. But as explained in Sections C.vi.a–e below, none of those criticisms rebuts Dr. Matzger's conclusion that Form II is a hemipentahydrate.

##### a. Trace Impurities or Amorphous Material in Mylan's API Do Not Change the Fact that Mylan's API Is a Hemipentahydrate

128. During Dr. Matzger's cross-examination, Mylan used an incorrect hypothetical to suggest that Dr. Matzger's calculations of bound water in his Hi-res TGA would be wrong based on an alleged presence of 10% or 5% w/w impurities in Form II. Tr. 166:21-171:25 (Matzger). Mylan's attorney argument was not supported by its

expert Dr. Friscic or the facts.

129. Contrary to Mylan's hypothetical, Mylan's ANDA specification requires that Mylan's API contain NMT 2.95% w/w impurities, far less than Mylan's hypothetical 10% or 5% w/w impurities. FOF ¶¶ 36, 172-173. Mylan's own testing demonstrates that its exhibit batches of Form II that Dr. Matzger tested, which are representative of the Form II Mylan will use in its ANDA Products, in fact contain less than about 0.5% w/w impurities. FOF ¶¶ 37, 173. Mylan's API also contains only an insubstantial amount of amorphous material, *i.e.*, it has less than about 0.5%. FOF ¶¶ 39, 173.

130. It is further incorrect to assume, as Mylan did, that the trace amount of impurities or amorphous material in Mylan's API has no water associated with it. FOF ¶ 174. Even excluding the trace amount of impurities and amorphous material in Mylan's API from Dr. Matzger's calculations, the amount of bound water in Dr. Matzger's controlled humidity TGA and DVS in combination with Hi-res TGA would be between 4.69% and 4.76%, corresponding very closely to the theoretical 4.70% for a hemipentahydrate. FOF ¶ 175.

**b. Dr. Friscic's Criticisms of Dr. Matzger's DVS and Hi-Res TGA Are Entitled to Little Weight**

131. Dr. Friscic's opinions on Dr. Matzger's DVS and Hi-res

TGA are entitled to little weight. Dr. Friscic has only conducted a DVS experiment three or four times. Tr. 400:3-5 (Friscic); FOF ¶ 176. Dr. Friscic also admitted that he is not an expert in Hi-res TGA, nor has he ever conducted Hi-res TGA. Tr. 399:11-400:2 (Friscic); FOF ¶ 176.

132. In addition, to the extent Mylan or Dr. Friscic believed Dr. Matzger used improper DVS testing and/or TGA protocols, Dr. Friscic had access to DVS and TGA instruments and could have conducted his own testing on Form II. FOF ¶ 177.

133. Indeed, when "there was testing [Dr. Friscic] thought would be helpful to [his] opinions, either [he] or Dr. Titi conducted that testing." Tr. 401:14-21 (Friscic). Yet, Dr. Friscic did not conduct any DVS or TGA testing on Form II. Tr. 402:12-403:3 (Friscic).

**c. Dr. Friscic's Criticisms of Dr. Matzger's Controlled Humidity TGA and DVS Are Contradicted by Dr. Friscic's Own Admissions**

134. Dr. Friscic's only criticism of Dr. Matzger's controlled humidity TGA and DVS is that an increase in weight loss as Dr. Matzger decreased the RH to 2% by DVS suggests that a "reservoir of . . . bound water" is being lost above 2% RH. Tr. 336:5-337:5, 339:19-340:13 (Friscic).

135. But by Dr. Friscic's own admissions on cross-

examination, the slope change point between surface and bound water in the DVS curve for Form II is at about *2% RH*, such that no significant bound water is lost above 2% RH. Tr. 419:20-420:1 (Friscic); FOF ¶¶ 179-180, 182; *see also* Tr. 406:21-408:6 (Friscic) (admitting that from 5% to 50% RH, Form II does not convert to a different hydrate — *i.e.*, it is not losing bound water).

136. Dr. Friscic also did not quantify the alleged "reservoir of . . . bound water" that he asserted was lost above 2% RH. *See* Tr. 336:5-337:5 (Friscic).

137. Dr. Matzger explained, however, to the extent that bound water was lost from Form II above 2% RH in his DVS or controlled humidity TGA experiments, the amount was only an average of 0.022% w/w as indicated by the small difference in water lost from 4% to 2% RH compared to 6% to 4% RH. FOF ¶ 183. This 0.022% w/w amount of alleged bound water has no significant effect upon Dr. Matzger's DVS results and does not alter his finding that Form II lost two bound waters below 2% RH. FOF ¶ 184.

138. Because Form II does not lose any significant amount of bound water (*i.e.*, 0.022% w/w) when decreasing RH to 2% RH, it was appropriate for Dr. Matzger to equilibrate Form II at 2% RH in his controlled humidity TGA experiment to remove surface water without removing bound water. FOF ¶ 183.

139. After equilibrating Form II at 2% RH by controlled humidity TGA, Dr. Matzger measured 4.64% and 4.68% w/w bound water corresponding closely to the theoretical 4.70% w/w for a hemipentahydrate. FOF ¶ 143.

140. Even if one were to add the about 0.022% w/w water lost above 2% RH to Dr. Matzger's controlled humidity TGA or DVS results, Form II would still be a hemipentahydrate with 4.70% w/w bound water. FOF ¶ 184; Tr. 103:7-104:22 (Matzger) ("I've just added . . . .022 percent [to the controlled humidity TGA results] . . . . And what it does is it gets these numbers just a little bit closer to the 4.70 percent.").

**d. Dr. Friscic's Criticisms of Dr. Matzger's Hi-res TGA Are Not Supported by Any Data or Scientific Literature**

141. Dr. Friscic asserted that Dr. Matzger underestimated the amount of bound water in Mylan's API because during the isothermal period of Dr. Matzger's Hi-res TGA, Form II allegedly lost bound water because "[i]f surface water is being lost and bound water is being lost, then both are going to have equal chances to go through a pinhole." Tr. 337:6-12 (Friscic). This argument ignores the conditions inside the pinhole pan, which affect what type of water is lost.

142. During the isothermal period, the environment inside the

pinhole pan was humidified, *i.e.*, not at 0% RH, and thus Form II was not losing bound water. FOF ¶¶ 158, 190; *see* FOF ¶ 149 (demonstrating by DVS that Form II only lost bound water when RH was reduced to 0%). By examining the weight change over time in his Hi-res TGA, Dr. Matzger found a single water loss event corresponding to surface water that continued until, but was not complete at, the end of the isothermal period. FOF ¶ 187. Only upon heating to about 40 °C did Form II begin to lose bound water. FOF ¶ 188.

143. While Dr. Friscic cited various examples of hydrates that lose bound water "at relatively low temperatures and relative humidities" (Tr. 312:14-317:13 (Friscic)), those hydrates are not chemically relevant to Form II and were tested under conditions different than Dr. Matzger's Hi-res TGA experiment. FOF ¶¶ 194, 196.

144. Unlike Form II, which is a non-channel, metal-coordinated hydrate that is stable under normal laboratory conditions, Dr. Friscic's examples are channel hydrates, they are not metal-coordinated hydrates, and/or they form only under extreme conditions, and as a result, their water loss behavior would be expected to be different from Form II. FOF ¶ 194.

145. Dr. Friscic's non-Form II examples are not relevant to

how Form II would lose bound water. FOF ¶ 195. Dr. Friscic admitted on cross-examination that just because one hydrate loses bound water under one set of conditions does not mean all hydrates will lose bound water under those conditions; rather, how a particular hydrate will lose bound water is unpredictable. Tr. 413:14-414:1 (Friscic); FOF ¶ 195.

146. Dr. Friscic's hydrate examples, as well as Dr. Matzger's and Crystal's DVS on Form II and Novartis's DVS on LCZ696, also are not relevant to whether Form II lost bound water during the isothermal period of Dr. Matzger's Hi-res TGA, because those examples were tested in open pans, whereas Dr. Matzger used a pinhole pan for his Hi-res TGA. FOF ¶ 196.

147. Dr. Friscic's examples tested in *open* pans fail to inform whether Form II would lose bound water during Dr. Matzger's isothermal period with a *pinhole* pan. FOF ¶ 197. Dr. Friscic admitted on cross-examination that whether and how quickly a material would dehydrate really depends on the environment it is placed in, on what kind of experiment one is performing, and on the properties of the material. Tr. 415:17-21 (Friscic); FOF ¶ 197.

148. While Dr. Friscic further asserted that the flow of nitrogen gas over Dr. Matzger's pinhole pan created a "suction,"

Dr. Friscic cited no literature to support that theory. Tr. 337:14-21 (Friscic); FOF ¶ 191. By contrast, Dr. Matzger cited literature favorably demonstrating that the use of a pinhole pan causes a hydrate to lose water more slowly and at higher temperatures compared to an open pan. FOF ¶ 189.

**e. The Total Water Content in Form II Is Not Relevant to Whether Form II Contains 2.5 Bound Waters**

149. Dr. Friscic admitted that for his assertion that there allegedly is too much water for Form II to be a hemipentahydrate, he relied on the total water content measured in Dr. Matzger's constant heating rate TGA and Hi-res TGA. Tr. 307:2-308:7, 310:22-312:12, 411:12-412:7 (Friscic).

150. Dr. Friscic's reliance on total water content is improper because he admitted that Form II contains surface water in addition to bound water, surface water is not bound water, one must account for surface water when determining the amount of bound water, and not even Crystal treated all water in Form II measured by TGA as bound water. Tr. 405:18-406:8, 406:17-20, 411:2-11, 412:8-14 (Friscic); JTX 600 at 6 (Table 3-1); FOF ¶¶ 129-135.

151. Dr. Friscic's reliance on Dr. Matzger's constant heating rate TGA is further misplaced because Dr. Matzger observed that the three water loss events in his constant heating rate TGA for

Form II overlapped making it not possible to fully resolve or differentiate the surface water from the bound water. FOF ¶ 168. Dr. Matzger thus conducted controlled humidity TGA, DVS, and Hi-res TGA to address those overlapping water loss events. FOF ¶ 170.

152. Dr. Friscic also incorrectly concluded that the amount of bound water for Form II in Dr. Matzger's Hi-res TGA was greater than the total water in Dr. Matzger's controlled humidity TGA. Tr. 341:11-342:7 (Friscic). Dr. Matzger explained that the 4.89% w/w water he measured in his Hi-res TGA was greater than the theoretical 4.70% w/w for a hemipentahydrate because some surface water was still present at the conclusion of the isothermal period. FOF ¶¶ 163, 187.

153. The total water content measured in Dr. Matzger's controlled humidity TGA also is irrelevant to the amount of bound water in Form II. *Supra* ¶ 149. In his controlled humidity TGA, Dr. Matzger equilibrated Form II at 2% RH in his controlled humidity TGA experiment, which is the point where surface water is removed but no significant bound water has been lost. FOF ¶¶ 141, 149-150. Thus, any water lost before Form II was equilibrated at 2% RH (thereby resulting in less total water content) would have been surface water and is irrelevant to the amount of bound water in Form II measured by controlled humidity TGA. FOF ¶ 200.

154. During Dr. Matzger's cross-examination, Mylan also incorrectly suggested that Dr. Matzger had stored and handled Form II in a way that removed bound water. *See, e.g.*, Tr. 155:24-156:19 (Matzger) (criticizing Dr. Matzger on cross-examination for not measuring the humidity in his laboratory). Dr. Matzger, however, stored Form II according to the storage conditions in Mylan's ANDA. FOF ¶ 201.

155. Dr. Friscic also admitted on cross-examination that from 5% to 50% RH, including under normal laboratory conditions of about 20% to 40% RH, Form II is stable and does not convert to a different hydrate, *i.e.*, it is not gaining or losing bound water. Tr. 406:21-408:6 (Friscic); FOF ¶ 199. Thus, Mylan's speculation that *bound* water was lost from Form II during Dr. Matzger's storage or handling under normal laboratory conditions is contradicted by Mylan's own expert.

**vii. Mylan's API Does Not Have a Loosely Held Water that Could Result in a 2.67 or 2.6 Hydrate**

156. In a further attempt to argue that Dr. Matzger removed bound water from Form II above 2% RH by DVS and controlled humidity TGA or during the isothermal period of his Hi-res TGA, Dr. Friscic asserted that one water molecule, OW7, in the structure of Form II is "more loosely bound," which if lost would result in a 2.67 hydrate. Tr. 342:8-24 (Friscic).

157. Contrary to Dr. Friscic's assertion, OW7 is not loosely bound or easily lost from Form II. Dr. Rogers analyzed the chemistry of OW7 and found that it is held in place by strong hydrogen bonds. FOF ¶ 97. Thus, there is no bound water molecule in the crystal structure of Form II that could easily be lost to form a 2.67 hydrate.

158. Mylan and Dr. Friscic further asserted that Form II could be a 2.6 or 2.67 hydrate based on Dr. Matzger's Hi-res TGA result for Form II of 4.89% w/w. Tr. 171:23-173:8 (Matzger); Tr. 342:25-343:16 (Friscic).

159. This assertion, however, ignores that the 4.89% w/w water measured by Hi-res TGA for Form II likely contained a small amount of overlapping surface water, and also ignores Dr. Matzger's controlled humidity TGA and DVS results of 4.64% to 4.71% w/w bound water in Form II, in addition to Dr. Rogers' analysis of the single crystal structure. *See* FOF ¶¶ 143, 151, 163.

160. Contrary to Mylan's and Dr. Friscic's assertion that 4.89% w/w would correspond to a 2.6 hydrate, the scientific literature indicates that measured TGA values within 0.1% to 0.3% w/w correspond well with theoretical values for a given hydrate. FOF ¶ 206. And Dr. Friscic admitted on cross-examination that when reviewing Crystal's internal testing, he considered a calculated

value within 0.2% to 0.3% w/w of the theoretical value to correspond to the theoretical hydrate. Tr. 409:14-410:22 (Friscic); FOF ¶ 207.

161. A POSA further would understand that a 2.6 hydrate is not chemically reasonable because it would not correspond to a whole number of water molecules in the structure of Form II; thus, a POSA would understand an experimental measurement of 2.6 waters to indicate that Form II is a hemipentahydrate with 2.5 bound waters. FOF ¶ 208.

162. Thus, neither an analysis of the Form II single crystal structure nor Dr. Matzger's test results supports that Form II could lose a loosely held water to form a 2.67 or 2.6 hydrate. Instead, Dr. Rogers's analysis of the single crystal structure for Form II and Dr. Matzger's testing for Form II are consistent in demonstrating Form II is a hemipentahydrate.

**viii. Crystal's DVS and TGA Testing Fail to Rebut that Mylan's API Is a Hemipentahydrate**

163. Crystal's internal TGA and DVS testing on Form II were not properly conducted and thus fail to rebut Novartis's evidence of infringement or to demonstrate that Form II is not a hemipentahydrate. FOF ¶¶ 209-210.

164. Crystal attempted to estimate the amount of bound water

in Form II by measuring total water content (*i.e.*, surface and bound water) by TGA and subtracting the amount of surface water determined by DVS. FOF ¶ 209; Tr. 139:12-140:8 (Matzger); JTX 617 at 3.

165. To obtain an accurate estimate of bound water, the samples Crystal tested by DVS and TGA must be equilibrated at the same RH (5%) to have the same starting total and surface water contents. Tr. 139:12-140:8 (Matzger). If the TGA samples had more surface water than the DVS samples, that would lead to an overestimate of bound water. *Id.* As explained below, Crystal failed to properly equilibrate the Form II samples, leading to different amounts of total and surface water in the DVS and TGA samples and an incorrect estimate of bound water.

166. A comparison of Crystal's DVS protocol and results to Dr. Matzger's DVS protocol and results, where Dr. Matzger lost 10 times more water below 2% RH, demonstrate that Crystal failed to properly equilibrate its Form II samples by DVS. FOF ¶¶ 212-214.

167. A comparison of Crystal's TGA protocol and results, where Form II was exposed to laboratory conditions (*e.g.*, about 20% to 40% RH) before starting the experiment thereby negating any equilibration by DVS, to Dr. Matzger's results demonstrate that Crystal's Form II samples tested by TGA had total water content

corresponding to samples equilibrated at about 30% to 40% RH, which is far greater than the amount of total water content, including surface water, that would be expected at 5% RH. FOF ¶¶ 215-217.

168. By failing to properly equilibrate the Form II samples used in the DVS and TGA experiments, Crystal overestimated the amount of bound water in Form II. FOF ¶ 218.

**ix. The Descriptions of Form II as a Trihydrate in Mylan's ANDA, the DMF for Form II, and Crystal's '087 Patent Are Irrelevant**

169. To the extent Mylan relies on the descriptions of Form II as a trihydrate in its ANDA, the DMF for Form II, and/or Crystal's '087 patent, those descriptions do not support that Form II is a trihydrate for the following reasons.

170. *First*, Mylan's ANDA, the DMF for Form II, and the '087 patent describe Form II as a trihydrate based on the 2019 Single Crystal Report. FOF ¶¶ 24-25. But as explained in Section C.v.a. above, Dr. Rogers analyzed the 2019 Single Crystal Report and the underlying single crystal data for Form II and concluded that the model of Form II as a trihydrate is chemically impossible. Instead, the only chemically reasonably model is one in which Form II is a hemipentahydrate. FOF ¶ 80. *See, e.g.*, *SmithKline*, 403 F.3d at 1335-36, 1338 (affirming conclusion based on expert testimony that defendant's product would contain a "hemihydrate" despite

defendant's representations that its product contained an anhydrate).

171. *Second*, as explained in Section C.v.b. above, Novartis also demonstrated through Dr. Matzger's testing that Form II is a hemipentahydrate, not a trihydrate. *See, e.g.*, *In re Omeprazole*, 84 F. App'x at 82-83 (finding infringement where testing revealed the claimed "subcoating" despite defendant's assertion it did not have one); *Novartis*, 48 F. Supp. 3d at 739-41 (finding infringement where testing showed the presence of the claimed "antioxidant" despite it not being listed in the ANDA specification).

172. *Third*, the descriptions of Form II as a trihydrate in Mylan's ANDA, the Form II DMF, and Crystal's '087 patent further are irrelevant because Dr. Friscic admitted on cross examination that neither FDA nor the Patent Office has analyzed the amount of bound water in Form II, let alone had access to the single crystal data for Form II, Dr. Rogers's analysis of that data, or Dr. Matzger's testing on Form II all demonstrating that Form II is a hemipentahydrate. Tr. 421:12-424:1 (Friscic).

173. *Fourth*, that Crystal obtained a patent on Form II by representing to the Patent Office that Form II is a trihydrate does not preclude infringement of the '938 patent claim 1. *See Hoechst Celanese Corp. v. BP Chems. Ltd.*, 78 F.3d 1575, 1582 (Fed.

Cir. 1996) ("The fact of separate patentability presents no legal or evidentiary presumption of noninfringement ….").

**x. Novartis's Internal Documents for LCZ696 Are Irrelevant to Whether Form II Is a Hemipentahydrate**

174. Mylan's reliance on Novartis's internal documents for LCZ696 is both legally and factually irrelevant to whether Crystal infringes. *Contra* Tr. 322:7-327:1 (Friscic); *see also* Tr. 162:1-163:22 (cross-examining Dr. Matzger about alleged properties of LCZ696).

175. Infringement is based on a comparison of Mylan's API and/or ANDA Products to the asserted claims. *Zenith*, 19 F.3d at 1423. Thus, whether Form II is characterized by the same data or possesses the same properties as Novartis's LCZ696 is irrelevant because the '938 patent claim 1 requires only TSVH in crystalline form. *Supra* Section C.ii.

176. Novartis also may prove infringement by any method probative of infringement, including by circumstantial evidence. *Martek*, 579 F.3d at 1372. That Dr. Matzger used different testing parameters or techniques for Form II than Novartis used for LCZ696 (Tr. 322:17-20 (Friscic)) thus is irrelevant.

177. Dr. Friscic further incorrectly suggested that Novartis mischaracterized LCZ696 as a trihydrate based on TGA testing alone. Tr. 324:6-18 (Friscic); JTX 355 at 15. Dr. Friscic admitted on

cross-examination that "Novartis' initial description of LCZ696 as a trihydrate was based on [the] incorrect assumption that the number of water molecules in the crystal lattice would be a whole number." Tr. 420:18-421:6 (Friscic); FOF ¶ 220.

178. Contrary to Dr. Friscic's assertion that "the Novartis scientists were not convinced that TGA has the [*sic*] sufficient precision to indicate the state of hydration" (Tr. 325:2-7 (Friscic)), one of the inventors, Dr. Karpinski, testified that "the consistency of TGA results prompted us to get convinced that this is not an integer number as assumed initially but this [is instead] 2.5 water content stoichiometry" where the TGA results were close to 4.70% w/w corresponding to a hemipentahydrate. Tr. 235:9-236:8 (Karpinski); FOF ¶ 221.

179. Dr. Karpinski further testified that the single crystal structure for LCZ696 is consistent with the TGA data demonstrating that LCZ696 is a hemipentahydrate. Tr. 235:23-236:8 (Karpinski); FOF ¶ 221; *see also* JTX 355 at 15 (reporting TGA results of 4.81%, 4.70%, and 4.67% w/w water content in the last three LCZ696 batches tested).

180. Even if TGA alone was not precise enough to determine the amount of bound water in LCZ696 (or Form II), Dr. Matzger did not conduct only TGA, let alone the same TGA technique (constant

heating rate TGA) that Novartis used. Tr. 122:3-122:11 (Matzger).

181. Last, to the extent LCZ696 samples contained more than 4.70% w/w total water content, that was simply due to the presence of surface water. FOF ¶ 222.

182. As Dr. Matzger explained, between 20% and 60% RH, LCZ696 may gain up to 0.6% w/w surface water, which would result in about 5.3% w/w total water content. FOF ¶ 223. However, an LCZ696 sample with 5.3% w/w total water content is still a hemipentahydrate, which is based only on the amount of bound water (*i.e.*, 4.70% w/w) that does not change with an increase in surface water. FOF ¶¶ 223-224.

**D. Conclusion**

For the foregoing reasons, Novartis has shown by a preponderance of the evidence that Mylan's API is a substantially pure hemipentahydrate and Mylan's API and ANDA Products will infringe the '938 patent claim 1. Because Mylan's ANDA Products will infringe the '938 patent claim 1, Mylan will also infringe the '938 patent claim 11 and the '134 patent claim 5. D.I. 100.

It is so **ORDERED.**

The Clerk is directed to transmit copies of this Amended Memorandum Opinion and Order to counsel of record.

**AMENDED MEMORANDUM OPINION AND ORDER**
**MAKING FINDINGS OF FACT AND GRANTING JUDGMENT**
**IN FAVOR OF PLAINTIFF NOVARTIS PHARMACEUTICALS CORPORATION**

DATED: January 31, 2024

Tom S Kleeh

THOMAS S. KLEEH, CHIEF JUDGE
NORTHERN DISTRICT OF WEST VIRGINIA