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European Patent Office
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Your ref. 03753571.3/2119
Our ref. HK/P100557EP00

The Hague,
29 January 2013

Re: European patent application No. 03753571.3
Janssen R&D Ireland

This concerns the communication pursuant to Article 94(3) EPC issued September 20, 2012. Therein, the Examining Division refers to the Third Party Observations received in this application, and has indicated to take these into account under Article 114(1) EPC.

In response to the invitation to file observations, and in the light of the Third Party Observations, we care to proffer the following comments. Also, an Experimental Report is attached, including additional Examples 25 and 26, accompanied by additional Table 27 and additional Figures 27 to 33.

As to Article 83 EPC, reference is made in the communication to the statement in said Third Party Observations that "not a single concrete example" could be found in the application documents for the preparation of "the respective Form B or any hydrates/polymorphs." It is further mentioned that in Example 2 only a mixture of Forms D and B can be obtained.

Additionally, in the communication it is reiterated that for form I and J no data at all would be available. In respect hereof, we kindly remark that this objection does not relate to the current claims. Form I is the tetrahydrofuranate and Form J is the isopropanolate. We refer to page 3, line 32. These forms are not within the scope of the pending claims. The independent product claims relate solely to Form A (ethanolate, see claim 1) and form B (hydrate, claim 11). To the extent that independent claims are present in other categories, these claims (7, 9, 10, 16,17,18) are all limited by their reference to the definition of the pseudopolymorphs of their preceding claims.

Further, we respectfully disagree with the analysis that Example 2 would not support the invention. In this Example, Form B is expressly obtained.

Moreover, we kindly draw the Examining Division's attention to the fact that the application as filed contains another disclosure of a method to produce Form B.

Example 7 on page 27 of the present application discloses an adsorption-desorption method that is performed with Form A (ethanolate). Form A itself can be produced as indicated in the description, see Example 1. Example 7 shows a set of conditions (page 27, lines 27-31) that result in the ethanolate form changing into the hydrate form (same page, lines 34-35). This embodies a clear teaching to a person skilled in the art how to produce Form B, viz. by obtaining Form A (as disclosed) and subjecting it to the set of conditions (as disclosed).

On the basis of the foregoing, we advance that the application doubtlessly provides a sufficient disclosure for pseudopolymorphic Form B.

The communication further contains an invitation to the applicant to indicate how the skilled person could prepare all the ethanol solvates of claims 1-10 and all the hydrates of claims 11-18.

In response hereto, we emphasize that the skilled person will be well capable, on the basis of the description, of making the various solvates and hydrates.

The description explains that the term pseudopolymorph is applied to crystalline forms that have solvent molecules incorporated in their lattice structures. The skilled person will immediately infer from this statement that the solvates of the present invention are channel solvates. In such solvates, the solvent molecules are contained in lattice channels and lie next to other solvent molecules of adjoining unit cells along an axis of the lattice, forming channels through the crystal. We refer to Kenneth R. Morris, " Structural Aspects of Hydrates and Solvates", which is Chapter 4 in "Polymorphism in Pharmaceutical Solids," (1999) Harry G. Brittain, Ed., page 125, last paragraph. For completeness' sake, we add that, already merely from the title of the chapter, it will be clear that the author discusses the structural aspects of hydrates and solvates alike. Also
from page 6, line 10 of the description, it will be understood that above reference to incorporated solvent molecules equally applies to hydrates (viz. if the solvent is water).

The amount of solvent in the solvates according to the invention can be varied depending on the conditions applied (page 7, line 16-17).

This is further clarified, inter alia, in Example 4. See page 23, lines 27-30, where it is indicated that form A loses ethanol under specific temperature conditions, with an optimum of 120 °C. The amount of ethanol present in form A (1:1) is around 7.5%, see Table 12, page 26. Example 4 unequivocally guides the skilled person to obtaining ethanolates with different ranges of solvation, without undue burden. Viz., by applying a range of high temperature conditions, and subsequently determining the amount of residual ethanol.

With regard to water as a solvent, additional guidance is provided in Example 12 (page 31, lines 1-8) and the accompanying Figure 20. Example 12 employs different conditions of relative humidity so as to affect the adsorption and desorption of water of form B. First and foremost, it thus indicates that form B is capable of adsorbing and desorbing water. The manner in which this occurs, will be immediately apparent to the skilled person, when having regard to the curves shown in Figure 20. The shape of these curves indicates that the range of the number of water molecules associated with the compound of formula X, is a continuum, as opposed to a discrete variable. In the latter case, one would expect a curve showing discrete steps rather than the relatively straight lines of Figure 20.

Finally, as to sufficiency of disclosure, we kindly point out that the description actually enlightens the skilled reader about the fact that the compound of formula (X) can comprise up to 5 molecules of solvent (in casu: ethanol or water) per molecule of the compound. This is taught on page 7, lines 17-19.

The communication further raises an objection of lack of inventive step.

Thereby the Examining Division reverts to our letter of December 18, 2007, and considers that the comparative data should have been provided with reference to the closest prior art. To this end, the communication refers to “the racemate” as being the necessary comparison, and then criticizes the data provided as being in comparison with the amorphous form. We respectfully fail to understand this.

Present independent claim 1 recites an ethanolate pseudopolymorph of a compound of formula (X). Present independent claim 11 recites a hydrate pseudopolymorph of a compound of formula (X). These are both crystalline forms of said compound. It is unclear to the applicant what the examiner means with his referral to a racemate as

closest prior art. The applicant is of the opinion that a racemate has no apparent relation to a specific form of a compound, e.g. an amorphous or crystalline form.

D5 (WO 95/06030) discloses hydroxyethylamino sulfonamides as retroviral protease inhibitors. Table 16K on page 204 of D5 discloses the structure of the compound of formula (X). D5 further discloses at page 158 that the compounds of this table 16K can be prepared following the procedures of examples 1-21. When looking at procedures 1-21 of D5, the skilled person will note that, among the examples given, example 18B represents the closest structural analogue of the compound of formula (X). After detailing a synthetic method for the preparation of the disclosed compound, Example 18B further discloses at page 135, line 6-8 that silica gel chromatography of the crude product of this structural analogue resulted in a white foam. A white foam indicates that the product is not in a crystalline form, but in an amorphous state.

Therefore, we advance that the teaching of the closest prior art is an amorphous (non-crystalline) form of the compound of formula (X) obtainable by an analogous method according to example 18B of D5. We emphasize that the comparison as made, is thus fully appropriate. In fact, the prior art does not disclose any form of the compound of formula X closer to the present invention, than the very form with which the comparison was made, viz. the compound of formula X in an amorphous state.

The invention as claimed differs from the aforementioned prior art. The difference is that the compound of formula (X) is provided in a crystalline form, and specifically the ethanolate or the hydrate crystalline form.

First of all, we emphasize that it was not known from the prior art at all, nor even remotely suggested, that the present compound could be provided in a crystalline form, let alone in a specific ethanolate or hydrate form as provided by the invention.

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