Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 6 October 2023

Case Number: T 1165/20 - 3.3.02

Application Number: 10830880.0

Publication Number: 2498610

IPC: A01N43/78, A61K31/425

Language of the proceedings: EN

Title of invention:
SELECTIVE SPHINGOSINE 1 PHOSPHATE RECEPTOR MODULATORS AND METHODS OF CHIRAL SYNTHESIS

Patent Proprietor:
RECEPTOS LLC

Opponent:
Generics [UK] Ltd

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1165/20 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 6 October 2023

Appellant: (Opponent)	Generics [UK] Ltd Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Patent Proprietor)	RECEPTOS LLC 430 East 29th Street, 14 Floor New York, NY 10016 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 6 March 2020 concerning maintenance of the European Patent No. 2498610 in amended form.**

Composition of the Board:

Chairman	M. O. Müller
Members:	A. Lenzen
	R. Romandini

Summary of Facts and Submissions

I. The present decision concerns the appeal, filed by the opponent (appellant) against the opposition division's decision (decision under appeal), according to which European patent No. 2 498 610 (patent) in amended form meets the requirements of the EPC.

II. The decision under appeal is based on the main request, of which the set of claims was filed with the letter dated 13 May 2019.

In particular, the opposition division held that the claimed subject-matter of the main request involved an inventive step starting from D1 as the closest prior art in combination with D4 and/or D5 because the skilled person would not have had a reasonable expectation of solving the objective technical problem. This was partly because D1 only disclosed *in vitro* data for the compound at issue and the skilled person could not have reasonably foreseen how this compound would perform in the *in vivo* test described in D4/D5.

III. Reference is made in the present decision to the following documents filed before the opposition division:

D1 WO 2009/151529 A1
D2 WO 2004/058149 A2
D4 Rivera, J. et al., Nature Reviews Immunology 2008, Vol. 8, pages 753 to 763
D5 Song, J. et al., The Journal of Pharmacology and Experimental Therapeutics 2008, Vol. 324, No. 1, pages 276 to 283

IV. In preparation for the oral proceedings, which had been arranged at the parties' request, the board issued a communication pursuant to Article 15(1) RPBA 2020.

V. The oral proceedings before the board were held by videoconference on 6 October 2023. Both parties participated. At the end of the hearing, the chair announced the order of the present decision.

VI. For the parties' submissions relevant to the present decision, reference is made to the reasons for the decision provided below.

VII. The parties' final requests at the end of the oral proceedings were as follows.

The appellant requested that the decision under appeal be set aside and the patent be revoked in its entirety.

The respondent requested that the appeal be dismissed, thus effectively requesting that the decision under appeal be confirmed and the patent be maintained in the form considered allowable by the opposition division.

Reasons for the Decision

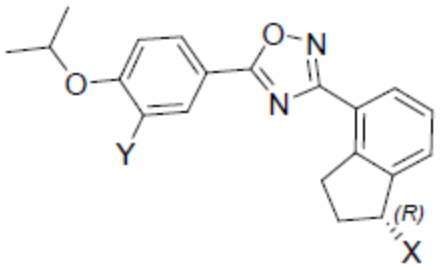
Main request (patent in amended form considered allowable by the opposition division) - Inventive step (Article 56 EPC)

1. According to the description of the patent, the invention relates to compounds which are agonists of the sphingosine 1-phosphate receptor subtype 1 (S1P1 agonists) and their use in the treatment of a malcondition mediated by S1P1 activation, or when

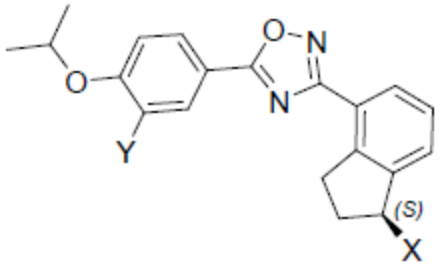
activation of S1P1 is medically indicated (patent, paragraphs [0001] and [0006]).

Claim 1 of the main request is more specific, with respect to both the S1P1 agonists and the malconditions to be treated. It reads as follows:

> "*A compound of Formula I-R or Formula I-S, or a pharmaceutically acceptable salt thereof for use in a method for treating an inflammatory bowel disease (IBD) at a frequency and for a duration of time sufficient to provide a beneficial effect to the patient,*



I-R



I-S

> *wherein X is $-NHCH_2CH_2OH$ and Y is $-CN$.*"

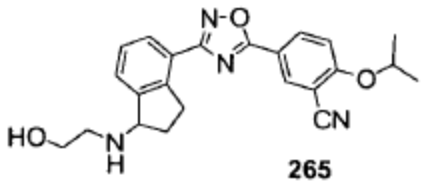
Hence, claim 1 concerns a second medical use and is essentially directed to the S1P1 agonists of formula I-R or I-S for use in a method for treating IBD, i.e.

an autoimmune disease. Claims 2 to 12 of the main request are dependent on claim 1.

The parties agreed that a 1:1 mixture of compounds I-R and I-S, i.e. their racemate, is a compound according to claim 1. Below, this racemate will be referred to simply as "compound I". The parties also agreed that ulcerative colitis and Crohn's disease are two forms of IBD. The board shares both views. Thus, the subject-matter of claim 1 relates to, *inter alia*, compound I for use in a method for treating ulcerative colitis or Crohn's disease.

2. The appellant's sole objection related to an alleged lack of inventive step starting from D1 as the closest prior art.

Similarly to the patent, D1 (page 2, lines 5 to 8) also relates to S1P1 agonists and their use in the treatment of a malcondition mediated by S1P1 activation, or when activation of S1P1 is medically indicated. According to D1 (page 1, lines 24 to 26), S1P1 agonists could be of value in the treatment of malconditions such as multiple sclerosis, transplant rejection and adult respiratory distress syndrome. Table 1 on pages 172 to 176 reports on the activity of 271 specific compounds on the S1P1 receptor. Compound 265 of Table 1, i.e.



265

,

is a potent S1P1 agonist. The only *in vivo* data reported in D1 relate to compounds 32 and 236 of Table 1. Both are potent S1P1 agonists, but only

compound 236 was found to induce lymphopenia. Compound 32, on the other hand, did not induce lymphopenia (D1, page 132, lines 21 to 24).

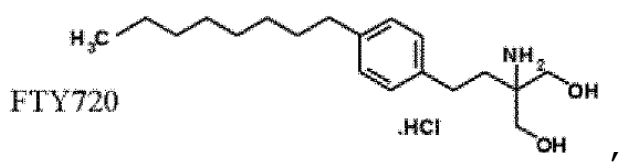
3. Starting from D1, the appellant essentially argued as follows.

As regards a second medical use, the selection of the closest prior art was not limited to prior art directed to the same medical use. Instead, a document disclosing the same compound as claimed but for a different medical use could also constitute the closest prior art. Although D1 did not even mention IBD, ulcerative colitis or Crohn's disease, it nevertheless disclosed compound 265 as a potent S1P1 agonist. This was compound I of claim 1 of the main request. Thus, compound 265 of D1 represented a feasible starting point for the assessment of inventive step. The subject-matter of claim 1 of the main request differed from D1 in that it was directed to the treatment of IBD. Hence, the objective technical problem was to provide a further medical use of compound 265 of D1.

It is assumed below - in favour of the appellant - that this is correct.

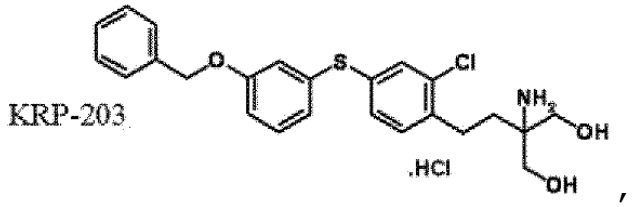
4. As regards obviousness, the appellant pointed to D5 and D4.

4.1 D5 is a research paper. Its authors start out by describing their previous findings, according to which S1P1 agonist FTY720,



FTY720 ,

ameliorated established colitis in the IL-$10^{-/-}$ mouse model, a model for Crohn's disease. The mechanism responsible for this effect involves an accelerated homing and sequestration of circulating lymphocytes, resulting in a reduction of peripheral blood lymphocytes and of lymphocyte migration to the inflammatory site. The authors then go on to describe their discovery of the structurally similar S1P1 agonist KRP-203,



,

to report on another group's findings concerning the use of this compound in a rat allograft model, and to hypothesise - in view of these findings - that KRP-203 might be more potent and more advantageous than FTY720 for long-term use for the treatment of chronic colitis in IL-$10^{-/-}$ mice. The actual scientific contribution of D5 is related to the application of KRP-203 to IL-$10^{-/-}$ mice. According to the authors of D5, KRP-203 is effective in the treatment of established colitis in IL-$10^{-/-}$ mice. The reasons for this include, *inter alia*, the fact that this compound accelerates sequestration of circulating lymphocytes, resulting in a reduction of peripheral blood lymphocytes and of lymphocyte migration to the inflammatory site (page 282, last paragraph, and Figure 4).

4.2 D4 is a review article concerning the alliance of sphingosine-1-phosphate and its receptors, i.e. S1P1 to S1P5, in immunity. The article states that S1P1 is expressed by most immune cells, which suggests that

this receptor might have broad functions in the immune system (page 755, right column). It reports, *inter alia*, on the results of D5 (D4, page 761, left column, last paragraph).

5. The board acknowledges that it can be derived from the above disclosure of D1 that compound 265, which is compound I as covered by claim 1 of the main request, is an S1P1 agonist. The board further acknowledges that, on the basis of D5 and D4, it can be concluded that the two specific S1P1 agonists, namely FTY720 and KRP-203, are effective in treating colitis in mice, a condition falling under the broader term IBD in claim 1 of the main request. However, as correctly pointed out in the decision under appeal and by the respondent, for the claimed use of compound 265 not to involve an inventive step, the skilled person would have had to have a reasonable expectation that compound 265 of D1 would be suitable for treating colitis in mice.

6. In particular, the opposition division repudiated a reasonable expectation of success because the *in vitro* data disclosed in D1 for compound 265 did not allow the conclusion that this compound would also be effective in the *in vivo* models described in D4/D5.

The board agrees with the appellant that this reason alone would not be sufficient at least if - as also submitted by the appellant - D4/D5 taught that the S1P1 agonistic effect of a substance alone was sufficient for its suitability for the treatment of colitis in mice. In such a case, the skilled person might very well have had a reasonable expectation of the suitability of compound 265 for the treatment of colitis in mice, i.e. irrespective of the fact that D1 only discloses *in vitro* data for compound 265. However,

the teaching of D4/D5 cannot be stretched as far as it has been stretched by the appellant.

6.1 The board agrees with the respondent that the teaching of D5 is clearly directed to two specific compounds, FTY720 and KRP-203. Although D5 emphasises the S1P1 agonistic effect of these compounds with regard to their use for the treatment of colitis in mice, it cannot be concluded from this alone - contrary to the appellant's argument - that any S1P1 agonists would be suitable *per se* for the treatment of colitis in mice. Indeed, D5 does not contain a statement to this effect. Insofar as D5 (last sentence) suggests treatment of IBD, this suggestion is referring only to KRP-203, but no generalisation is made to the effect that any S1P1 agonists *per se* may be suitable for the treatment of IBD. The review article D4 - which deals in great breadth with the importance of S1P1 for immunity and which summarises, *inter alia*, the results of D5 - does not contain a corresponding statement either.

6.2 From the teachings of D5 and D4, the skilled person would therefore only have concluded that the authors consider the agonistic effect of FYT720 and KRP-203 on S1P1 to be relevant to the treatment of colitis in mice or to the treatment of IBD, but not that the agonistic activity of a compound on S1P1 alone renders that compound suitable for the treatment of colitis in mice or for the treatment of IBD.

6.3 The skilled person would not reach a different conclusion in light of D2 (page 1, lines 6 to 18), on which the appellant relied only in the written proceedings. D2 discloses that S1P1 agonists are immunosuppressive. It also discloses that immunosuppressive agents have been shown to be useful

in the treatment of, *inter alia*, IBD, Crohn's disease and ulcerative colitis, but it does not mention specific immunosuppressive agents. It cannot be concluded from this that S1P1 agonists are suitable *per se* for the treatment of IBD, Crohn's disease or ulcerative colitis.

6.4 In its argumentation regarding D5 and D4, the appellant focused solely on the S1P1 agonistic effect of the compounds FYT720 and KRP-203 mentioned therein. However, it did not take into account the fact that in these documents - as submitted by the respondent and not disputed by the appellant - the reduction of the number of lymphocytes in the peripheral blood, i.e. the induction of lymphopenia, is emphasised as essential for a successful treatment. If one were to follow the appellant's reasoning, for the sake of argument, and read the sense of a generality into D5/D4, the skilled person would have considered necessary not only the S1P1 agonistic effect of a compound, but also its ability to induce lymphopenia. However, it is clear from D1 that not all S1P1 agonists disclosed therein induce lymphopenia. Of the compounds which were tested *in vivo*, i.e. compounds 32 and 235, only the latter induced lymphopenia, whereas the former did not. Even knowing that compound 265 of D1 is an S1P1 agonist, the skilled person would have had doubts as to whether it also induces lymphopenia. Therefore, the skilled person would not have had a reasonable expectation that compound 265 of D1 would be suitable for the treatment of colitis in mice or for the treatment of IBD.

6.5 The appellant also argued that the skilled person, bearing in mind their common general knowledge, would understand that the diseases mentioned in D1 were autoimmune diseases. D1 thus taught the general

suitability of S1P1 agonists for the treatment of autoimmune diseases. This general suitability was also confirmed in paragraph [0104] of the application forming the basis of the patent. Thus, the skilled person would have had a reasonable expectation that the S1P1 agonists mentioned in D1 could also be used to treat other autoimmune diseases, such as IBD.

Even if the skilled person recognises the diseases mentioned in D1 as autoimmune diseases, it cannot be concluded from the wording of D1 ("*Thus, agonists of receptors, such as agonists of S1P1, could be of value in the treatment of malconditions such as multiple sclerosis, transplant rejection, and adult respiratory distress syndrome.*") that S1P1 agonists are *per se* suitable for the treatment of the diseases mentioned in D1, let alone all autoimmune diseases. Similarly to D5 and D4 (see above), there is no corresponding statement whatsoever in D1. Lastly, the application as filed, e.g. paragraph [0104] thereof, cannot be used against inventive step.

7. In the present case, the board concludes that the skilled person would not have had a reasonable expectation of compound 265 of D1 being suitable for treating colitis in mice, as set out for compounds FTY720 and KRP-203 in D4 and referred to in D5.

8. Hence, the subject-matter of claim 1 of the main request involves an inventive step. The same must apply *a fortiori* also to the subject-matter of dependent claims 2 to 12 of the main request. The main request is allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow M. O. Müller

Decision electronically authenticated