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Datasheet for the decision of 6 July 2023

Case Number: T 0429/21 - 3.3.07

Application Number: 11823113.3

Publication Number: 2614860

IPC: A61P15/02, A61P27/02, A61K31/16, A61K31/513, A61K31/045, A61K31/4164, A61K31/435, A61K31/517, A61K31/55, A61K45/06, A61K31/00, A61K31/047, A61K31/075, A61K31/164, A61K31/167, A61K31/17, A61K31/196, A61K31/215, A61K31/22, A61K31/221, A61K31/245

Language of the proceedings: EN

Title of invention:

PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF DRY EYE

Applicant:

Universidad Miguel Hernández De Elche
Consejo Superior De Investigaciones Científicas (CSIC)

Headword:
PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF DRY EYE/
Universidad Miguel Hernández De Elche
Consejo Superior De Investigaciones Científicas
(CSIC)

Relevant legal provisions:
EPC Art. 56

Keyword:
All requests - Inventive step (No)
Improvement predictable

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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 0429/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 6 July 2023

Appellant: (Applicant 1)	Universidad Miguel Hernández De Elche Avda. Universidad s/n. 03202-Elche (Alicante) (ES)
Appellant: (Applicant 2)	Consejo Superior De Investigaciones Científicas (CSIC) Serrano 117 28006 Madrid (ES)
Representative:	K&L Gates LLP Markgrafenstraße 42 10117 Berlin (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 11 December 2020 refusing European patent application No. 11823113.3 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	D. Boulois
	Y. Podbielski

Summary of Facts and Submissions

I. The appeal lies from the decision of the Examining Division refusing European patent application No. 11 823 113.3. The decision was based on the sets of claims filed as the main request with letter of 28 May 2020, as auxiliary requests 1 and 2 filed with letter of 10 August 2020, and as auxiliary request 3 filed with letter of 23 October 2020.

Claim 1 of the main request read as follows:

"1. An ophthalmic composition for use in a method of treatment or prevention of xerophthalmia or dry eye syndrome, said composition comprising a therapeutically effective amount of a TRPM8 agonist, wherein said TRPM8 agonist is 2-isopropyl-5- methylcyclohexanecarboxylic acid (4-methoxyphenyl)-amide (WS-12)."

The subject-matter of claim 1 of all auxiliary requests 1-3 was identical to claim 1 of the main request.

II. The documents cited during the examination proceedings included *inter alia* the following:

D8: DAVID D MCKEMY: "Therapeutic potential of TRPM8 modulators", OPEN DRUG DISCOVERY JOURNAL, BENTHAM SCIENCE PUBLISHERS B.V,NL, vol. 2, no. Special Issue 2, 1 January 2010 (2010-01 -01), pages 81 -88,XP008166382

D9: SHERKHELI MUHAMMAD AZHAR ET AL: "Characterization of selective TRPM8 ligands and their structure activity response (S.A.R) relationship", JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES, CANADIAN SOCIETY FOR

PHARMACEUTICAL SCIENCES, EDMONTON, CA, vol. 13, no. 2, 22 July 2010 (2010-07-22), pages 242-253, XP002664433

D12: A Robbins ET AL: "Menthol stimulated lacrimation and induction of Fos in the trigeminal nucleus", Chicago, 21 October 2009 (2009-10-21), XP055750228, [retrieved on 2020-11-13] & DATABASE BIOSIS [Online]BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 21 October2009 (2009-10-21) A.Robbins et al: "Menthol stimulated lacrimation and induction of Fos in the trigeminal nucleus", Database accession no. PREV201100737122

D14: BÖDDING ET AL: "Characterisation of TRPM8 as a pharmacophore receptor", CELL CALCIUM, CHURCHILL LIVINGSTONE, GB,vol. 42, no. 6, 29 September 2007 (2007-09-29), pages 618-628, XP022271646

D15: BECK ET AL: "Prospects for prostate cancer imaging and therapy using high-affinity TRPM8 activators", CELL CALCIUM, CHURCHILL LIVINGSTONE, GB, vol.41, no. 3, 4 February 2007 (2007-02-04), pages 285-294, XP005744385

D16: SHERKHELI M A ET AL: "Menthol derivative WS-12 selectively activates transient receptor potential melastatin-8 (TRPM8) ion channels",PAKISTAN JOURNAL OF PHARMACEUTICAL SCIENCES, FACULTY OF PHARMACY, UNIVERSITY OF KARACHI, PK, vol. 21, no. 4, 1 October 2008(2008-10-01), pages 370-378, XP002664432

D17: Steven J Charlton: "Agonist efficacy and receptor desensitization: from partial truths to a fuller picture", BRITISH JOURNAL OF PHARMACOLOGY, vol. 158, no.1, 1 September 2009 (2009-09-01), pages 165-168, XP055695488

III. According to the decision under appeal, the main request and auxiliary requests 1 and 2 did not meet the requirements of Article 123(2) EPC, in particular in view of the feature claiming the EC_{50} value in claim 2 and in view of claims 9-11.

D12 was considered to be the closest prior art for the subject-matter of claims 1-7 of auxiliary request 3. The problem was the provision of a better TRPM8 agonist for use in dry eye syndrome. The solution was obvious in view of D8, as well as of D9 and D14-D17 which supported D8's teaching.

IV. The applicant (hereinafter the appellant), filed an appeal against the decision. With the statement of grounds of appeal dated 19 April 2021, the appellant submitted the following evidence:

D22: AERIE An Emerging Leader in Ophthalmology
D23: CAS Registry Number Extract

V. With the communication sent in preparation for oral proceedings, the Board expressed a preliminary view agreeing with the decision of the examining division.

VI. Oral proceedings before the Board took place on 6 July 2023.

VII. The appellant's arguments can be summarised as follows:

Inventive step

D12 was the closest prior art; the activity of menthol as TRPM8 agonist was a simple assumption in this document, since there was no absolute proof of its

action through the TRPM8 channels; the tear secretion in D12 could for instance have been triggered by a simple eye irritation.

The application showed that the compound WS-12 provided a better effect, as shown in Table 2, with the lowest EC_{50} value of all TRPM8 agonists. This was confirmed by D22, in slides 12 and 13. The problem was the provision of a better agent and medicament for the treatment of xerophthalmia. There was no clear pointer in the prior art for the selection of WS-12, and it was not a try and see approach that could be taken either.

VIII. Requests

The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed with letter dated 28 May 2020, or on the basis of one of auxiliary requests 1 or 2 filed with letter dated 10 August 2020, or of auxiliary request 3 filed with letter dated 23 October 2020.

Reasons for the Decision

1. Main request - Inventive step

1.1 The claimed invention relates to therapeutic compositions for the treatment of dry eye, more specifically to compositions comprising a TRPM8 receptor agonist ligand, namely the compound 2-isopropyl-5- methylcyclohexanecarboxylic acid (4-methoxyphenyl)-amide (WS-12).

1.2 D12 was considered to be the closest prior art for the assessment of inventive step; D12 is an abstract of a

presentation given on 21 October 2009 at the Neuroscience Meeting in Chicago.

D12 discloses the use of menthol in the treatment of dry eye syndrome through its action as agonist for the TRPM8 receptor. The effect of menthol was examined by application to the corneal surface on tear production in TRMP8 wild-type (WT) and TRPM8 knock-out mice (KO). A low concentration of menthol increased tearing in TRPM8 WT but not in TRPM8 KO, while a high concentration of menthol increased tearing in both TRPM8 WT and KO.

The authors of D12 conclude that menthol, through an action at the TRPM8 channels, evokes tears by selectively activating Vi/Vc neurons, and that this activation increases basal tear production without producing ocular irritation or pain (last sentence of the abstract).

D12 does not mention an alternative TRPM8 agonist which could be used for the treatment of dry eye syndrome.

1.3 The appellant questioned the technical value of D12 and argued that the conclusions of D12 were simple assumptions, not convincingly proven by the article, and that there was no evidence that the effects of the low or high concentrations of menthol were linked with an agonist action on the TRPM8 receptors.

The Board acknowledges that D12 is only the abstract of a presentation presented during a scientific meeting and might not be as technically complete as an usual scientific paper. The presentation of the study and its results is however very clear and scientifically founded. The technical conclusion shows also

unequivocally that menthol has an agonist action on TRPM8 and that the tear production is linked with the agonist action on the TRPM8 receptors. Hence, the Board does not see any reason to question the data and the results of the scientific presentation D12.

1.4 The problem as defined by the appellant is the provision of a better agent/medicament for use in the treatment of xerophthalmia. The examining division defined the problem in the same way, i.e the provision of a better TRPM8 agonist for use in dry eye syndrome treatment.

1.5 The appellant relies on Table 2 of the patent application and on D22 to support the existence of an improvement.

1.5.1 Table 2 of the application shows that the claimed compound WS-12 has a better EC_{50} on the TRPM8 receptors than all other TRPM8 agonists presented in the application, in particular menthol, as illustrated hereby:

Table 2. Summary of TRPM8 agonists

Compound	EC_{50} (μM)	Method
Icilin	0.2 ± 0.1^a	FL
	1.4^b	CI
	0.50^c	EP
	0.36 ± 0.03^d	EP
Menthol	10.4^b	CI
	83.6 ± 0.04^c	EP
	66.7 ± 3.3^d	EP
WS-12	0.193^b	CI
	0.680^b	EP
	0.039^c	EP
WS-3	3.7 ± 1.7^a	FL
WS-148	4.1^b	CI

WS-30	5.6[b]	CI
WS-11	6.25[c]	EP
WS-14	21.19[c]	EP
WS-23	44 ± 7.3[a]	FL
CPS-113	1.2[b]	CI
CPS-369	3.6[b]	CI
Frescolat ML	3.3 ± 1.5[a]	FL
Frescolat MGA	4.8 ± 1.1[a]	FL
Cooling Agent 10	6 ± 2.2[a]	FL
PMD-38	31 ± 1.1[a]	FL
Geraniol	5900 ± 1600[a]	FL
Linalool	6700 ± 2000[a]	FL
Eucalyptol	7700 ± 2000[a] 3400 ± 400[d]	FL EP
Hydroxyl-citronellal	19600 ± 2200[a]	FL

Even if the patent application does not directly show an effect of the specific TRPM8 agonist WS-12 in the treatment or prevention of xerophthalmia, the Board does not see any reason to question it, having regard to the example of the patent application which shows the stimulating action of menthol on the TRPM8 ion channels and the relationship of said TRPM8 channels or receptors on the tear production (see the example of the patent application, on pages 46-51 and the corresponding Figures). Moreover, in view of the informations present in the patent application, the Board does neither see a reason to question the higher efficacy of WS-12 in comparison to menthol, in view of the lower EC_{50}. In view of this teaching, the skilled

person would indeed expect an improved activity as a consequence of a lower EC_{50} (see Table 2 above). Accordingly, it is credible that WS-12 is a better agent/medicament for use in the treatment of xerophthalmia than menthol, even in the absence of any explicit comparison with the agonist activity of menthol on TRPM8 receptors.

1.5.2 The efficacy of WS-12 in the treatment of dry eye syndrome is confirmed by the teaching of slides 12 and 13 of D22. Said slides show the results of a study involving the compound AR-15512 (WS-12) and that said compound demonstrates a significant and dose dependent increase in tear production. Said document does not provide a comparison with the effect obtained over other compounds, such as in particular menthol.

1.6 Hence, the problem is as defined by the appellant, namely the provision of a better agent/medicament for use in the treatment of xerophthalmia.

The claimed solution is the use of the compound WS-12.

1.7 With regard to obviousness, the Board notes that TPM8 agonists were known at the effective date of the present application, and that WS-12 was identified as the TRPM8 agonist with the lowest EC_{50}.

1.7.1 D8 is a study on the therapeutic potential of TRPM8 modulators, which discloses that WS-12 is the most potent TRPM8 agonist (see D8, page 83, right-hand column, third paragraph). This result is illustrated by the EC_{50} given in Table 1 of D8 on pages 84 and 85. This Table gives for menthol and for WS-12 the same EC50 values reported in Table 2 of the patent

application, namely 66.7µM for menthol and 193nM for WS-12.

1.7.2 D9 is a study on the characterization of selective TRPM8 ligands and their structure activity response, teaching that some newly characterized ligands have a six-fold higher potency expressed by the EC_{50} value, and up to two-fold increase in efficacy compared to menthol, and cites WS-12 as one of these agonists (see Abstract). Figure 3 and Table 1 of D9 give the EC_{50} value of WS-12, i.e 12 µM, and the comparative potency and efficacy. Table 1 shows in particular that WS-12 provides the highest pharmacological response at pH 6.1 and pH 7.4 and its efficacy is 1.65 times the efficacy of menthol.

1.7.3 The results of D8 and D9 are confirmed by D15 and D16, as mentioned by the examining division in its decision (cf. the abstracts of D15 and D16).

1.7.4 In the Board's view, it was known from D12 that the TRPM8 receptors act on the tear production; this document clearly identified menthol as a TRPM8 agonist acting through this pathway on the tear production. When looking for a potentially better TRPM8 agonist, i.e a substance more effective than menthol, the skilled person would test the known TRPM8 agonists and would focus in particular on those agonist(s) providing the best activity. This would inevitably lead the skilled person to the selection of the compound WS-12 which is disclosed as the compound having the lowest EC_{50} value for TRPM8 receptors and represents therefore the most promising TRPM8 agonist.

Under these circumstances, the Board is convinced that the person skilled in the art looking for a solution to

the problem as defined above would have been led by the technical teaching of *inter alia* documents D8 and D9 to test the molecules described therein, starting with the most effective molecules, and this test would have resulted in the selection of the compound WS-12.

Hence, the decision of the examining division was justified, and the claimed subject-matter lacks an inventive step over D12.

1.8 Consequently, the main request does not meet the requirements of Article 56 EPC.

2. Auxiliary requests 1-3 - Inventive step

These requests have been modified with respect to the dependent claims whereas claim 1 is identical to claim 1 of the main request. Consequently, the conclusion reached with regard to inventive step of the main request applies to auxiliary requests 1-3, and none of these requests meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated