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Datasheet for the decision of 21 March 2024

Case Number: T 0209/22 - 3.3.04

Application Number: 10781527.6

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Language of the proceedings: EN

Title of invention:
Combinations of a muscarinic receptor antagonist and a beta-2 adrenoreceptor agonist

Patent Proprietor:
Glaxo Group Limited

Opponents:
Teva UK Limited
Breuer, Markus
Sima Patent ve Lisanslama Hizmetleri Ltd.Sti.

Relevant legal provisions:
EPC 1973 Art. 100(c), 100(b), 100(a), 54, 56

Keyword:
Inventive step - reasonable expectation of success

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Case Number: T 0209/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 21 March 2024

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 3 December 2021 rejecting the opposition filed against European patent No. 2506844 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairwoman M. Pregetter
Members: R. Hauss
A. Bacchin

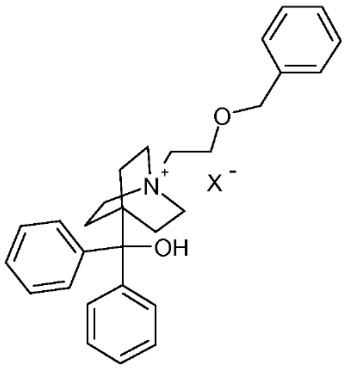
Summary of Facts and Submissions

I. European patent No. 2 506 844 (patent in suit) was granted with a set of 18 claims.

Claim 1 reads as follows:

"1. A pharmaceutical combination product for use in the treatment of chronic obstructive pulmonary disease (COPD) and/or asthma, wherein the product comprises

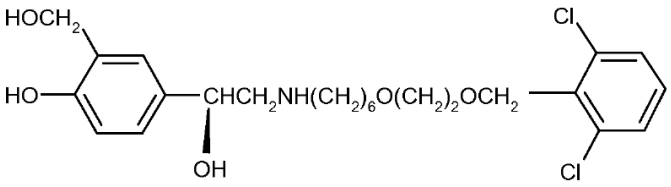
a) a compound of the formula:



Compound (I)

wherein X^- is a pharmaceutically acceptable anion; and

b) a compound of the formula:



or a pharmaceutically acceptable salt thereof (Compound (II));

and further wherein the product is administered once per day."

II. The compounds in claim 1 are also known as **umeclidinium** (this is the cation in the structure formula of compound (I)), and **vilanterol** (this is the compound according to the structure formula of compound (II)).

III. Three oppositions were filed against the patent in suit. The patent was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the application as filed.

IV. The patent proprietor requested as its main request that the oppositions be rejected and the patent maintained as granted.

V. The documents cited in the proceedings before the opposition division included the following:

D3: WO 03/024439 A1

D4: WO 2005/104745 A2

D5: J. Med. Chem. 52, 2493-2505 (2009)

D8: ANORO Summary of Product Characteristics (no date)

D21: ClinicalTrials.gov archive: History of changes for Study: NCT00976144 (2017)

D44: Respir. Med. 112, 65-74 (2016)

D55: Eur. Respir. J. 31, 416-468 (2008)

VI. The decision under appeal is the opposition division's decision rejecting the oppositions, announced on 1 July 2021 and posted on 3 December 2021.

VII. According to the decision under appeal:

(a) The subject-matter of the claims as granted did not extend beyond the content of the application as filed (Article 100(c) EPC). In the case of claim 1, the required basis in the application as filed could be found in claims 1, 50 and 57, and page 1, lines 5 to 7 of the application as filed.

(b) The data in the patent in suit was considered sufficient to show the suitability of the claimed drug combination for the claimed therapeutic indication and for once-daily administration. The skilled person was also enabled to identify suitable dosages. Thus, the claimed subject-matter met the requirement of sufficiency of disclosure (Article 100(b) EPC).

(c) The claimed subject-matter was novel over the disclosure of document D21. Contrary to the opponents' further objection based on a combination of D21 and supplementary documents, it had not been established either that a public prior use occurred (Articles 100(a), 52(1) and 54 EPC).

(d) Inventive step was assessed starting from the disclosure of document D3, which represented the closest prior art. D3 disclosed vilanterol for once-daily administration but did not disclose umeclidinium. The objective technical problem was to provide an improved pharmaceutical product for use in the treatment of COPD and/or asthma which allowed for once-daily administration and high patient compliance. Neither document D3 itself nor common general knowledge or document D5 (also relied on by the opponents) provided the skilled person with any indication or reasonable expectation of success that combining vilanterol

with umeclidinium would solve the objective technical problem of providing an efficacious combination permitting a dosage regime of once-daily administration. As a consequence, the subject-matter of the claims as granted involved an inventive step (Articles 100(a), 52(1) and 56 EPC).

VIII. Opponents 1 and 2 (appellants) both appealed this decision.

IX. In reply to the appeals, the patent proprietor (respondent) requested that the appeals be dismissed and filed two sets of claims as auxiliary requests 1 and 2. With the same letter, the respondent also submitted documents D73 and D74 in support of its reasoning in relation to inventive step.

D73: Respir. Med. 108, 1752-1760 (2014)
D74: Pulm. Ther. 4, 171-183 (2018)

X. The board issued a summons for oral proceedings.

XI. In response, opponent 3 advised the board that it would not be attending the oral proceedings.

XII. In a communication under Article 15(1) RPBA issued in preparation for oral proceedings and advising the parties of its preliminary opinion, the board mentioned the following points:

(a) The board was of the view that the grounds of opposition under Article 100(b) and (c) did not prejudice the maintenance of the patent as granted. Regarding the issue of added subject-matter, the board agreed with the opposition division's finding that the necessary basis for claim 1 as granted was provided by claims 1, 50 and 57, and page 1, lines 5 to 7 of the application as filed.

(b) As to novelty, neither the clinical study with healthy volunteers described in D21 nor the written disclosure of D21 could have anticipated the claimed subject matter, considering that the claim feature *"for use in the treatment of chronic obstructive pulmonary disease (COPD) and/or asthma"* required attaining the claimed therapeutic effect in the treatment of COPD and/or asthma (Articles 100(a), 52(1) and 54 EPC).

(c) Inventive step was to be assessed starting from the disclosure of document D3. The objective technical problem could be formulated as "providing a combination product comprising vilanterol and a specific anticholinergic for use in the treatment of COPD or asthma and which also facilitates patient compliance". The discussion in relation to obviousness was expected to focus in particular on the question whether, at the effective date, there was a direct route that would have led to the development of the claimed combination product with a reasonable expectation of success.

XIII. Oral proceedings before the board were held on 21 March 2024, in the absence of opponent 3.

XIV. The appellants' arguments may be summarised as follows:

Amendments

When combining claims 1, 50, 52 and 57 as filed, more than one selection would be required to arrive at the subject-matter in claim 1 as granted.

Novelty

The clinical study described in document D21, which took place before the priority date of the patent in suit, constituted public prior use that anticipated the

claimed combination therapy. Furthermore, D21 itself (a written disclosure of the study protocol) was prior art under Article 54(2) EPC and its content was novelty-destroying. While D21 did not reveal the identity of the study drugs, the person skilled in the art could have obtained this information by obtaining and analysing the study drugs - denoted by the same identifier codes as in the study of D21 - that had been handed out in trials for the respective monotherapies.

Sufficiency of disclosure

Reliance, in the patent in suit, on the FEV_1-parameter alone (FEV_1 = forced expiratory volume in one second) could not establish the suitability of the claimed combination of active agents for COPD treatment. The study report outlined in paragraphs [0103] and [0104] of the patent in suit (and the corresponding passages of the application as filed) related to a study in healthy subjects and did not provide sufficient information in support of the therapeutic efficacy of the claimed drug combination. The suitability of the combination for once-daily administration was not disclosed, either.

Inventive step

The objection regarding lack of inventive step was based on an approach starting from the disclosure in document D3 of the long-acting β_2-adrenoreceptor agonist ("LABA") vilanterol, to be combined with an anticholinergic agent, such as the long-acting muscarinic antagonist ("LAMA") tiotropium mentioned in D3.

Appellant-opponent 1 agreed with the formulation of the objective technical problem provided by the board (see point XII.(c) above) as the provision of a combination

product comprising vilanterol and a specific anticholinergic for use in the treatment of COPD or asthma and which also facilitated patient compliance.

Appellant-opponent 2 agreed in principle with this formulation of the objective technical problem, except that the aspect of facilitating patient compliance should not be included.

The skilled person seeking to solve the objective technical problem, in view of the teaching in D3 and the common general knowledge that it was advantageous to combine active agents of the LABA and LAMA classes, would have considered document D5 with the aim of identifying further suitable long-acting LAMAs to be combined with vilanterol.

Based on the teaching in D3 and D5 that both vilanterol and umeclidinium (the preferred compound in D5) were promising candidates for achieving a long duration of action there would have been a reasonable expectation of success that bronchodilation would be achieved with once-daily dosing of a combination of vilanterol and umeclidinium in human patients.

XV. The respondent's arguments may be summarised as follows:

Amendments

The basis for claim 1 as granted was provided by the application as filed from a combination of claim 1 with claim 50, when read with the description at page 5, lines 5 to 7, and claim 57.

Novelty

The written disclosure of D21 only provided a study protocol. The study protocol *per se* did not permit any conclusions to be drawn on the efficacy of the

treatment. It was furthermore contested that the study medications in the studies relating to the combination therapy or to the respective monotherapies became publicly available.

Sufficiency of disclosure

FEV_1 was the most widely used and reported parameter for assessing lung function in COPD and asthma patients. An improvement in FEV_1 was accepted in the technical field as indicative of improving the patient's well-being by providing for a bronchodilatory effect. A description of a clinical trial for the claimed drug combination was presented on pages 25 and 26 of the application as filed, indicating that the largest improvement in bronchodilation vs placebo was seen in the combination treatment group (i.e. larger than for the monotherapies). While this result was obtained with healthy volunteers, bronchodilation was needed in the treatment of both COPD and asthma. The monotherapy studies described on pages 23 and 24, employing once-daily treatment, had in each case resulted in significant bronchodilation over 24 hours, and these tests had been conducted in COPD patients. It was thus credible that once-daily treatment with the combination would provide efficacy in COPD and asthma in patients. The appellants' objections were not based on serious doubt substantiated by verifiable facts.

Inventive step

The respondent agreed with the objective technical problem as formulated in the board's communication under Article 15(1) RPBA, but submitted that it should furthermore include the requirement that the combination product result in improved efficacy relative to monotherapy. In this respect, reference was made to the post-published document D44, which

investigated the relationship between dual therapy with umeclidinium/vilanterol and the monotherapies with either agent. Since no comparative data was available, it was not known whether this additional technical effect made for an improved or an alternative therapy in comparison with combination products according to D3. It would be acceptable to the respondent to assume, in the appellants' favour, that improved efficacy relative to monotherapy was also attainable with embodiments of D3 ("alternative" therapy).

Starting from the disclosure of D3, there was no pointer in the prior art to combining vilanterol with umeclidinium. Even assuming that D5 and umeclidinium would have been considered by the person skilled in the art, a research programme involving several clinical trials would have had to be performed to develop the treatment with vilanterol once-daily, the treatment with umeclidinium once-daily and the combination treatment once-daily. As the research reported in the prior art had not moved to the clinical stage, it was not possible to make any reliable prediction as to the duration of action of the compounds, their efficacy and safety, nor as to the efficacy of the combination, so that there could have been no expectation of success but rather merely a hope to succeed.

XVI. Appellant-opponent 1 requested that the decision under appeal be set aside and that the patent be revoked. The appellant furthermore requested that documents D73 and D74 not be admitted.

XVII. Appellant-opponent 2 requested that the decision under appeal be set aside and that the patent be revoked.

XVIII. The respondent requested that the appeals be dismissed and the patent be maintained as granted;

or in the alternative, that the patent be maintained in amended form on the basis of the claims of one of auxiliary requests 1 or 2, both filed with the reply to the statement setting out the grounds of appeal.

XIX. The non-appealing opponent 3 (party as of right) did not present any argument or request.

Reasons for the Decision

1. Oral proceedings, absence of opponent 3

1.1 In conformity with Article 15(3) RPBA and Rule 115(2) EPC, the oral proceedings before the board took place in the absence of opponent 3.

1.2 Opponent 3 had been duly summoned and had not presented any requests or arguments in writing (see points X., XI. and XIII. above). Thus, opponent 3 chose not to avail itself of the opportunity to present its comments on the grounds and evidence in the appeal case (Article 113(1) EPC).

2. Claimed subject-matter

2.1 Claim 1 is the only independent claim of the patent as granted (main request). It relates to a pharmaceutical combination product comprising compound (I) (a salt of umeclidinium) and compound (II) (vilanterol or a salt thereof) for use in the treatment of COPD and/or asthma by once-daily administration.

2.2 According to the established case law of the Boards of Appeal, where a therapeutic application is claimed in the format provided in Article 54(5) EPC (as is the case for present claim 1), attaining the claimed therapeutic effect is regarded as a functional

technical feature of the claim that may establish novelty and inventive step.

3. Amendments (Article 100(c) EPC)

3.1 Claim 1 in the application as filed is directed to a pharmaceutical combination product comprising compound (I) and compound (II). The definition of compounds (I) and (II) is the same as in claim 1 as granted.

Claim 50 as filed relates to a method for the prophylaxis or treatment of inflammatory or respiratory tract diseases, comprising administering to a patient in need thereof a product as defined in any of claim 1 or its dependent claims.

According to page 1, lines 5 to 7, as filed, the invention relates to pharmaceutical products and compositions for use in the treatment of COPD, asthma and related diseases. The similar passage on page 5, lines 5 to 7 states that "[t]he invention also provides said pharmaceutical combination product for use in the treatment of inflammatory or respiratory tract diseases, such as chronic obstructive pulmonary disease (COPD) and/or asthma".

Claim 57, which is dependent on claim 50, specifies that the product is administered once per day.

3.2 The conversion of a claim to a therapeutic method, such as claim 57, to a claim in the format provided in Article 54(5) EPC does not add subject-matter, and this was not contested by the appellants.

3.3 Claims 50 and 57 as filed relate to prophylaxis or treatment. Deleting an alternative embodiment (in this

case, prophylaxis is no longer present in claim 1 as granted) does not give rise to added subject-matter.

3.4 The same logic applies to limiting the treatment to that of COPD and asthma without including further related diseases.

3.5 That the combination product according to the invention is for use in the treatment of COPD and asthma is provided as the first piece of information in the description as filed, in the "Field of the Invention" section on page 1, lines 5 to 7, and again in the passage on page 5, lines 5 to 7.

3.6 The combination of claim 57 with these passages in the description provides the required basis for the combination of technical features in claim 1 as granted. This combination does not present the person skilled in the art with information that could not have been derived directly from the application as filed.

3.7 In conclusion, the ground of opposition under Article 100(c) EPC does not prejudice the maintenance of the patent as granted.

4. Novelty (Articles 100(1), 52(1) and 54 EPC)

4.1 Appellant-opponent 2 contended that the clinical study described in document D21, which took place before the priority date of the patent in suit, constituted public prior use that anticipated the combination therapy according to claim 1 as granted. In a second approach, the appellant also argued that D21 itself (a written disclosure of the study protocol) anticipated the claimed subject-matter.

4.2 These objections must fail already because the study of D21 was a phase I study performed on healthy volunteers (i.e., not on patients suffering from COPD or asthma). The claim feature that requires attaining the claimed therapeutic effect in the treatment of COPD or asthma (see point 2.2 above) could not have been anticipated in such a context, simply because the study subjects did not suffer from COPD or asthma. Accordingly, neither D21 itself nor the alleged prior use based on D21 provide a basis for denying novelty. In this situation it is not necessary to analyse the further circumstances of the alleged prior public use or any further issues raised with regard to novelty in view of the written disclosure of D21.

4.3 For these reasons, the ground of opposition of lack of novelty under Articles 100(a), 52(1) and 54 EPC does not prejudice the maintenance of the patent as granted.

5. Sufficiency of disclosure (Article 100(b) EPC)

5.1 As already mentioned (see point 2.2 above), claim 1 as granted defines a therapeutic application and is drafted in the format provided in Article 54(5) EPC. The therapeutic efficacy of the claimed combination by once-daily administration is a technical effect which is, at the same time, a technical feature of the claim.

5.2 For the requirement of sufficiency to be met, the claimed efficacy has to be credible at the effective date of the patent, i.e. on the basis of the information provided in the patent application together with the common general knowledge then available to the skilled person.

5.3 The appellants objected that (1) reliance on the FEV_1-parameter alone (forced expiratory volume in one

second) could not establish the suitability of the claimed combination of active agents for COPD and asthma treatment and that (2) the suitability of the combination for once-daily administration was not disclosed in the application as filed.

5.4 The board arrived at different conclusions, for the following reasons:

5.4.1 Vilanterol and umeclidinium are disclosed in documents D3 and D4, respectively, as potential agents for the treatment of respiratory diseases such as, in particular, COPD and asthma.

Both documents are referenced in the application as filed (see page 2, lines 19 to 27 and page 3, lines 1 to 5). The agents according to D3, including vilanterol, are identified in D3 as β_2-adrenoreceptor agonists having an advantageous profile of action with long duration (see D3: page 1, third paragraph; page 13, line 23 to page 15, line 1; supported by *in vitro* data on page 99), while the agents according to D4, including umeclidinium, are identified in D4 as muscarinic acetylcholine receptor antagonists (see D4: title; page 2, lines 17 to 26; claims 6 to 10).

5.4.2 On pages 23 to 25, the application as filed summarises the results of clinical studies that were performed in relation to umeclidinium or vilanterol monotherapy. In particular, it is mentioned that both compounds had been found to provide 24h duration of bronchodilatory action in COPD patients (see page 24, second paragraph, and page 25, first paragraph).

5.4.3 A further study, in which a combination of umeclidinium bromide and vilanterol triacetate was administered to healthy volunteers, resulted in the finding that the combination was well tolerated and effective in

providing bronchodilation, and in particular that it showed the largest difference relative to placebo (see the application as filed, pages 25 to 26). While no quantitative data or assessment of statistical significance in relation to the observed improvement ("largest difference") is reported, it may be concluded from this comparative statement that the combination was at least as efficacious as the monotherapies in providing bronchodilation, in a four-way crossover study with sixteen subjects.

5.4.4 The studies described in the application as filed used the FEV_1 parameter as relevant outcome measure. While the FEV_1 parameter may not reflect improvements in all aspects of COPD (as argued by appellant-opponent 2), it was nevertheless accepted in the art and by regulatory authorities as indicative of relieving a patient's symptoms caused by bronchoconstriction (see D55: page 417, first paragraph and page 440, last paragraph stating that FEV_1 is *"[t]he universally used measure of lung function in clinical studies of COPD"*). The fact that there may be a justified general interest in considering additional symptoms and complementary parameters (as also discussed in D55) is not sufficient to raise serious substantiated doubt about the suitability of FEV_1 as an outcome measure for assessing the therapeutic efficacy of the claimed combination.

5.4.5 Based on the information provided in the application as filed, there is thus a strong presumption that dual therapy with umeclidinium/vilanterol would be effective in the treatment of asthma or COPD, and that a dosage regimen of once-daily administration would be feasible. Both aspects would have been regarded as credible at the effective date.

5.4.6 Further corroboration is provided by post-published document D8, which shows that a combination product conforming to claim 1 ("ANORO") was indeed authorised in May 2014 for the treatment of COPD by once-daily administration (see D8: page 2, points 2 to 4.2 and page 15, point 9). D8 (see pages 9 to 11) also reports the supporting results of phase III clinical studies, not only with regard to the FEV_1 parameter, but also including favourable symptomatic and other outcomes.

5.4.7 The functional effect of bronchodilation is required in the treatment of both COPD and asthma. The claimed efficacy against asthma is, therefore, credible. The appellants have not established serious doubt in relation to the dual therapy's efficacy in relieving asthma.

5.5 The experimental set-up of the combination study on healthy volunteers described in the application as filed corresponds to the study set-up described in D21 (see points 5.4.3, 4.1 and 4.2 above). The appellants submitted that, if D21 and the corresponding study, in the board's opinion, did not take away the novelty of the claimed subject-matter, then it followed that the combination study as described in the application as filed could not be regarded as enabling in support of the claimed therapeutic use.

5.6 The board does not agree with this conclusion since the description of the combination study in the application as filed is not the sole evidence on which the board's conclusion on sufficiency of disclosure is based. Furthermore, different standards indeed apply.

5.6.1 To be novelty-destroying, a prior-art disclosure must meet the standard of direct and unambiguous disclosure of the claimed subject-matter. This criterion was not

met by D21 and the corresponding clinical study with regard to attaining the claimed therapeutic effect, because the study was performed with healthy subjects (see section 4 above).

5.6.2 The study with healthy subjects as described on pages 25 to 26 of the application as filed likewise does not disclose attaining a therapeutic effect in the treatment of COPD or asthma patients.

5.6.3 However, it is the subject-matter of claim 1 that is to be assessed for sufficiency of disclosure. According to the terms of claim 1, the therapeutic effect is attained. The question to be considered under the issue of sufficiency is whether this was credible at the effective date. The required support is by no means restricted to the description of the combination study on pages 25 to 26 of the application as filed, but can be based on any pertinent content in the application as filed, in view of common general knowledge at the effective date.

5.6.4 For the requirement of sufficiency of disclosure to be met, it is not always necessary that attaining the technical effect in question should be disclosed directly and unambiguously in the application as filed (e.g., in the form of results of a clinical phase III trial demonstrating efficacy in the claimed therapeutic use). Rather, as stated in point 5.2 above, the applicable standard is that attaining the technical effect in question has to be credible. This has to be assessed according to the circumstances of each individual case.

5.6.5 In the case in hand, the information presented in the application as filed is regarded as adequate for establishing sufficiency of disclosure, for the reasons

given above. This conclusion is not exclusively based on the results observed in the study performed on healthy volunteers but on a combination of this with further data discussed in the application as filed (see points 5.4.1 to 5.4.5 and 5.4.7 above). It is furthermore corroborated by post-published data (see point 5.4.6 above).

5.6.6 Hence, the appellants' argument according to point 5.5 above cannot succeed.

5.7 For these reasons, the ground of opposition under Article 100(b) EPC does not prejudice the maintenance of the patent as granted.

6. Inventive step (Articles 100(1), 52(1) and 56 EPC)

Patent in suit

6.1 The patent in suit seeks to provide a pharmaceutical combination product for the treatment of COPD and/or asthma.

6.2 Claim 1 as granted relates to a combination product comprising umeclidinium and vilanterol (or a pharmaceutically acceptable salt thereof) that is administered once per day.

Starting point in the prior art

6.3 Since the appellants argued that the claimed subject-matter was not inventive over the disclosure of document D3 in combination with that of document D5, and this approach was considered in the decision under appeal, the board found it appropriate to assess inventive step starting from the disclosure of D3. During the oral proceedings before the board, the appellants stated that they did not wish to pursue any

alternative approach starting from a different document (see the Minutes of the oral proceedings on page 7).

6.4 Document D3 discloses β_2-adrenoreceptor agonists (LABAs) in the form of specified phenethanolamine derivatives, intended for the treatment of respiratory diseases including COPD and asthma (see D3: page 1, claim 1; page 14, line 14 to page 15, line 1). D3 states that the compounds of the invention have the potential to combine long duration of effect with rapid onset of action and may be suitable for once-daily administration (see page 13, lines 23 to 32).
D3 provides data from *in vitro* tests (see page 99) for onset time (typically less than 30 minutes) and duration of action (typically more than 3 hours). Vilanterol, including salts thereof, is a particularly preferred compound (see claim 5; example 78; page 11, lines 28 to 31). Combinations with other active agents, in particular a PDE4 inhibitor, a corticosteroid or an anticholinergic agent (such as tiotropium) are envisaged (see page 16, line 6 to page 17, line 13; page 21, line 16, to page 22, line 1; claim 8).

6.5 All parties agreed that it was reasonable to start the inventive-step assessment from the disclosure in D3 of the combination of vilanterol with an anticholinergic agent (claims 5, 7 and 8 or claim 5 in combination with page 16, lines 5 to 19), which may be selected on the basis of its similarity with the claimed subject-matter, in accordance with the problem-and-solution approach.

Distinguishing features

6.6 Like tiotropium (mentioned in D3), umeclidinium is an anticholinergic agent belonging to the class of long-acting muscarinic receptor antagonists (LAMAs). It was

not in dispute that document D3 does not disclose umeclidinium.

6.7 The therapeutic indications COPD and asthma are part of the general disclosure of D3 that applies to any embodiment (see point 6.4 above). However, D3 does not disclose putting into practice any combination's therapeutic use and its once-daily administration in a treatment according to claim 1 of the main request.

Objective technical problem and solution

6.8 Using the claim format according to Article 54(5) EPC, claim 1 implements a medical use of vilanterol, a particularly preferred and individualised compound of D3, for a combination treatment as envisaged in D3. Once-daily dosing provides an advantage in terms of convenience, which is generally known to be a compliance-enhancing factor.

6.9 Since the starting point in D3 is the combination of vilanterol and an anticholinergic agent, a technical effect that is an "improvement" could only be shown by a comparative test comparing the combination of vilanterol and umeclidinium to the combination of vilanterol and anticholinergic agents disclosed in D3, and especially tiotropium as the agent most similar to umeclidinium on account of its long duration of action. Such comparative data is not on file.

6.10 Starting from the disclosure of document D3, the objective technical problem may thus be formulated as providing a combination product comprising vilanterol and a specific anticholinergic agent for use in the treatment of COPD or asthma and which also facilitates patient compliance.

6.11 This problem is deemed to be solved by the claimed subject-matter.

6.12 Achieving a dosage regimen of once-daily administration is part of the solution, which is why once-daily administration should not be specified as a requirement in the objective technical problem. To take account of this, the board used the less specific requirement for facilitating patient compliance, which avoids providing a pointer to once-daily dosing.

6.13 The parties suggested different formulations of the objective technical problem, which the board did not adopt for the following reasons.

6.13.1 Appellant-opponent 2 objected to including the requirement "facilitates patient compliance" into the objective technical problem.

6.13.2 The board considers that the inclusion of this requirement is appropriate as it is based on the dosage regimen of once-daily administration, which is provided as a feature of claim 1 and which is indeed known to facilitate patient compliance. The requirement is not based on a presumption of improved patient compliance in comparison with existing once-daily regimens.

6.13.3 The respondent was of the view that the objective technical problem should also include the requirement that the combination product resulted in improved efficacy relative to monotherapy. According to the respondent, this effect was addressed, at least as a general trend, in the application as filed (stating on page 25, line 39, to page 26, line 2, that the FEV_1 values observed for the combination showed the largest difference relative to placebo), and it was confirmed by post-published evidence in D44. Thus, the technical

effect of improved efficacy of dual therapy in relation to monotherapy should also be taken into account in the assessment of obviousness.

6.13.4 The assessment of obviousness set out below is based on the objective technical problem as formulated by the board in point 6.10 above (i.e. without consideration of the additional alleged effect of improved efficacy in relation to monotherapy). This results in the finding, in the respondent's favour, that the claimed subject-matter involves an inventive step. As a consequence, it is not necessary to analyse the merit of the respondent's line of argument in relation to the additional alleged effect of improved efficacy in relation to monotherapy.

Obviousness of the solution

6.14 As set out above, the starting point in D3 for the assessment of inventive step is the envisaged combination of vilanterol with an anticholinergic agent, intended in particular for the treatment of COPD and/or asthma.

6.15 According to the objective technical problem, the skilled person was tasked with putting into practice a combination product comprising vilanterol and a specific anticholinergic agent for the treatment of COPD and/or asthma. This product should also facilitate patient compliance.

6.16 In its introductory part, D3 states that there is a clinical need for LABA agents with an advantageous profile of action. It is implied that twice-daily dosing, as required with the commercially available LABAs known at the time, is considered a drawback (see D3: page 1, lines 15 to 19):

"Although salmeterol and the other commercially available β2-adrenoreceptor agonists are effective bronchodilators, the maximum duration of action is 12 hours, hence twice daily dosing is often required. There is therefore a clinical need for compounds having potent and selective stimulant action at β2-adrenoreceptors and having an advantageous profile of action."

Further passages in D3 mention that the compounds according to D3 may be suitable for once-daily administration.

6.17 Hence, it seems fair to say that D3 acknowledges a clinical need for long-acting compounds and is optimistic about the long-acting effect of the LABA compounds proposed in D3, a preferred one being vilanterol. It was, furthermore, common general knowledge that a low dosing frequency facilitates patient compliance.

6.18 The person skilled in the art would thus have found an incentive in D3 to combine compounds with a long duration of action, in order to facilitate patient compliance by providing a combination product suitable for once-daily dosing.

6.19 It was not in dispute that tiotropium, mentioned in D3 as an example of an anticholinergic muscarinic receptor antagonist (see page 21, line 33), is suitable for once-daily administration and was the only long-acting agent of that class available at the effective date.

6.20 The appellants submitted that the person skilled in the art, after confirming the favourable duration of action of vilanterol, would have considered its combination with the equally long-acting tiotropium taught in D3 as obvious. Moreover, they would have sought to identify

further LAMA agents besides tiotropium as possible combination partners for the long-acting vilanterol. They would, therefore, have considered document D5, which was directed towards the discovery of new LAMAs as alternatives to tiotropium. Umeclidinium (compound 14o in D5) was known from D5 to have "a very long *in vivo* duration of broncho-protection" and was considered a likely candidate for achieving long duration of bronchodilation in humans (see D5: abstract, compound 14o; page 2499, left-hand column, first paragraph). Still according to the appellants, the person skilled in the art would have derived a reasonable expectation of success for the claimed combination product from the combined disclosures of D3 and D5, which at least disclosed favourable preclinical data for both compounds. While success was never guaranteed in pharmaceutical development, positive results at one stage of clinical testing would necessarily have given the skilled person a reasonable expectation of success for the next stage absent any prejudice or disincentive to proceed.

6.21 The board is not convinced by the appellants' arguments, for the following reasons.

6.21.1 The question to be answered with regard to obviousness is whether, at the effective date, there was a direct route that would have led to the development of the claimed combination with a reasonable expectation of success.

6.21.2 At the relevant date, both vilanterol and umeclidinium were still in early stages of their pharmaceutical development. While the basis for proceeding with the pharmaceutical development of a compound is favourable preclinical data, this does not necessarily give rise to a well-founded expectation of success, even less

in the case of a combination product when neither combination partner has, as yet, progressed to the clinical stage of development.

6.21.3 D3 does not disclose the practical implementation of monotherapy or combination therapy with vilanterol, which also means that efficacy and safety of the compound in actual patients had not yet been confirmed. On pages 99 to 100, preclinical results are summarised. The onset time and duration of action reported in this context (onset time: typically less than 30 minutes, duration of action: typically more than 3 hours) are not indicated for individual compounds but for the group of particularly preferred compounds. While this presumably includes vilanterol, these values do not permit the conclusion to be drawn that once-daily administration in human subjects would be possible. While the authors in D3 assert that the proposed compounds are long-acting and "may be suitable for once-daily administration", there is no data in D3 to back up this claim, apart from the *in vitro* data discussed above. Thus, it cannot be verified that this assessment is more than speculation.

6.21.4 The situation is similar in the case of D5, in relation to compound 14o (umeclidinium). D5 does not disclose putting therapy with umeclidinium into practice. As in D3, the favourable assessment by the authors of D5 is based on preclinical data only (*in vitro* and animal studies).

6.21.5 The board is, therefore, of the view that the information derivable from D3 and D5 might, at best, have provided the person skilled in the art with the hope to succeed, but that this does not amount to a reasonable expectation of success. Neither agent had been established for the treatment of patients. Each

agent's efficacy and safety as well as the duration of action was still to be established. Thus, a high level of uncertainty regarding the potential for successful dual therapy with both agents would have been involved.

6.21.6 The appellants' argument that clinical development of the monotherapies and dual therapy would necessarily have proceeded to further stages based on success in the respective preceding stages relies on information that might have been gained during further stages of development but that was not available at the effective date to establish an expectation of success.

6.21.7 The appellants' further argument that the combination of active agents with different mechanisms of action was generally considered advantageous, and in the field of pulmonary therapy, the combination of LABA and LAMA agents in particular was considered advantageous, cannot compensate for the absence of more advanced data in D3 and D5 in relation to the specific compounds.

6.22 For these reasons, the subject-matter of claim 1 as granted involves an inventive step within the meaning of Article 56 EPC. This conclusion also applies to the dependent claims.

7. Admittance of documents D73 and D74

In the debate relating to inventive step at the oral proceedings, the respondent did not rely on documents D73 and D74 (see point IX. above, see also the Minutes of the oral proceedings before the board, page 4, sixth paragraph and page 5, last paragraph), and they play no role in the board's reasoning set out in section 6 above and its outcome in the respondent's favour. Hence, it was not necessary for the board to take a decision on admittance.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated