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Datasheet for the decision of 7 October 2025

Case Number:	T 1993/23 - 3.3.07
Application Number:	10164976.2
Publication Number:	2228064
IPC:	A61K31/402, A61K31/4704, A61P11/00
Language of the proceedings:	EN

Title of invention:

Pharmaceutical composition containing glycopyrrolate and a beta2 adrenoceptor agonist

Patent Proprietor:

Novartis AG

Opponents:

Hoffmann Eitle
Teva UK Limited
PGA S.P.A.
isarpatent - Patent- und Rechtsanwälte Behnisch Barth Charles Hassa Peckmann und Partner mbB
STADA Arzneimittel AG
Orion Corporation
ORION PHARMA
European Oppositions Limited
N.V. Nederlandsch Octrooibureau
Dr. Schön, Neymeyr & Partner Patentanwälte mbB
HGF Limited

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Headword:
Glycopyrrolate composition/NOVARTIS

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 12(4), 13(1), 13(2)

Keyword:
Inventive step - main request (no) - auxiliary request (no)
Amendment to case - suitability of amendment to address issues (no)
Amendment to appeal case - justification by party (no)
Amendments after summons - exceptional circumstances (no)

Decisions cited:
T 2735/19, G 0001/24, T 2027/23

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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

Case Number: T 1993/23 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 7 October 2025

Appellant: (Patent Proprietor)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Appellant: (Opponent 4)	isarpatent - Patent- und Rechtsanwälte Behnisch Barth Charles Hassa Peckmann und Partner mbB Friedrichstrasse 31 80801 München (DE)
Representative:	Isarpatent Patent- und Rechtsanwälte Barth Charles Hassa Peckmann & Partner mbB Friedrichstrasse 31 80801 München (DE)
Appellant: (Opponent 5)	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel (DE)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Appellant: (Opponent 9)	Dr. Schön, Neymeyr & Partner Patentanwälte mbB Bavariaring 26 80336 München (DE)
Representative:	Schön, Christoph Dr. Schön, Neymeyr & Partner mbB Bavariaring 26 80336 München (DE)

Appellant: (Opponent 10)	HGF Limited 1 City Walk Leeds Yorkshire LS11 9DX (GB)
Representative:	HGF HGF Limited 1 City Walk Leeds LS11 9DX (GB)
Party as of right: (Opponent 7)	European Oppositions Limited Lacon London 84 Theobalds Road London WC1X 8NL (GB)
Representative:	Kilburn & Strode LLP Lacon London 84 Theobalds Road Holborn London WC1X 8NL (GB)
Party as of right: (Opponent 8)	N.V. Nederlandsch Octrooibureau Anna van Buerenplein 21a 2595 DA The Hague (NL)
Representative:	Nederlandsch Octrooibureau P.O. Box 29720 2502 LS The Hague (NL)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 24 November 2023 concerning maintenance of the European Patent No. 2228064 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	A. Jimenez

Summary of Facts and Submissions

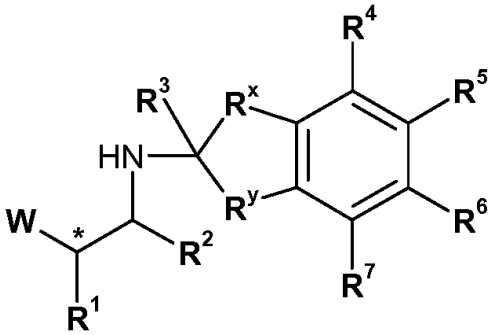
I. European patent 2 228 964 ("the patent") was granted with thirteen claims. It is derived from a divisional application of the earlier European Patent Application No. 05749635.8, originally published as PCT application WO 2005/110402.

Claim 1 of the patent as granted defines:

"A medicament comprising, separately or together,

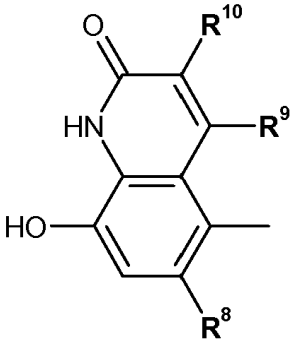
(A) glycopyrrolate; and

(B) a compound of formula I



I

in free or salt or solvate form, wherein W is a group of formula



wherein R8, R9 and R10 are each H, R1 is OH, R2 and R3 are each H, RX and RY are both -CHr, R4 and R7 are each H and R5 and R6 are each CH3CHr;

for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease."

The compound defined by its structure under (B) has become known by the International Nonproprietary Name (INN) Indacaterol.

II. Ten oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the parent and the subsequent divisional application as originally filed.

The patent proprietor and opponents 2, 4, 5, 9 and 10 filed appeals against the interlocutory decision of the opposition division that the patent as amended in accordance with auxiliary request 1 met the requirements of the EPC.

The decision was based on the patent as granted (main request) and on auxiliary request 1, filed on 6 April 2021.

Claim 1 of auxiliary request 1 defines the medicament of claim 1 as granted wherein the medicament comprises (A) and (B) together as a mixture of effective amounts of (A) and (B), optionally together with a pharmaceutically acceptable carrier.

The opposition division cited *inter alia* the following documents:

D3: WO 00/75114 A1

D4: WO 01/76575 A2
D13: Results of BLAZE phase III study
D20: Report of the BEACON study
D22: Asthma and Rhinitis, second edition, 2000, volume 2, "Mechanisms of action of β2-adrenoceptor agonists", pages 1541-1557
D24: Drugs Aging (2004), 21(6), 405-414
D25: Abstracts from the QUANTIFY phase III study
D29: International Journal of COPD (2013), 8, 501-508
D34: Declaration of Dr Thomas Storm, 2 September 2014
D55: Ultibro Breezhaler, CHMP Assessment report, EMA/CHMP/296722/2013, 25 July 2013
D96: Pulmonary Pharmacology & Therapeutics (2019), 59, 101855, 1-10
D97: Pulmonary Pharmacology & Therapeutics (2019), 59, 101841, 1-11
D98: Respiratory Medicine (2017), 126, 105-115
D109: Prescribing information dated October 2015 for the Utibron Neohaler
D110: EMA Assessment Report for Bevespi Aerosphere

The opposition division arrived *inter alia* at the following conclusions:

(a) The claims as granted differed from the closest prior art represented by document D4 by the definition of the combination of glycopyrrolate with indacaterol instead of formoterol or salmeterol.

The patent proprietor could not rely on the post-published evidence regarding an advantage of the claimed combination over the prior art. This evidence was in any case not considered to convincingly demonstrate any improvement over the prior art combination.

The claimed subject-matter was obvious as a solution to the problem of providing an alternative combination of glycopyrrolate with a long-acting beta-2 agonist in view of document D3.

(b) Auxiliary request 1 complied with the requirements of Articles 76(1), 123(2) and 83 EPC.

The closest prior art was represented by document D4. The effect from the additional distinguishing feature, the fixed-dose combination of glycopyrrolate and indacaterol, was a reduction in the required dose of indacaterol, which was demonstrated in the post-published documents D20, D29 and D34.

The objective technical problem concerned the provision of a further bronchodilator combination with glycopyrrolate which required reduced amounts of the second ingredient. The prior art provided no suggestion towards the claimed fixed-dose combination as solution to this problem. The subject-matter of the claims of auxiliary request 1 therefore involved an inventive step.

III. The following additional documents were *inter alia* filed during the appeal proceedings:

A122: International Journal of Pharmaceutics (2024), 651, 123755, 1-8,
by O4 with the grounds of appeal

A126: European Journal of Clinical Pharmacology (2023), 79, 1321-1332

by the patent proprietor with its letter of 29 August 2024

A127: Respiratory Medicine (2011), 105(6), 930-938
A128: International Journal of COPD (2018), 13, 1965-1977
A129: Respiratory Medicine (2016), 120, 16-24
by the patent proprietor with its letter of 7 August 2025

A130: International Journal of Pharmaceutics (2019), X 1, 100018, 1-9
A131: Journal of Aerosol Medicine and Pulmonary Drug Delivery (2010), 23(3), 137-148
A132: npj Primary Care Respiratory Medicine (2017), 22, 1-10
A133: BMJ Open (2025), 15, e088846, 1-6
by O9 with its letter of 5 September 2025

A134: Pulmonary Pharmacology & Therapeutics (2016), 39, 48-53
by O9 with its letter of 2 October 2025.

IV. With the statement of grounds of appeal, the patent proprietor maintained the main request relating to the patent as granted and filed auxiliary requests 1-13, which correspond to the auxiliary requests filed before the opposition division on 6 April 2021.

Claim 1 of auxiliary request 1, which was held allowable in the decision under appeal, corresponds to claim 1 as granted with the amendments that the medicament comprises (A) and (B) together ("separately or" deleted) and is defined as:

"a pharmaceutical composition comprising a mixture of effective amounts of (A) and (B), optionally together with at least one pharmaceutically acceptable carrier; for simultaneous administration in the treatment of an inflammatory or obstructive airways disease".

Claim 1 in auxiliary request 2 corresponds to claim 1 of the main request in which the definition of treatment is limited to the treatment of chronic obstructive pulmonary disease.

Claim 1 in auxiliary request 6 combines the amendments to claim 1 of auxiliary requests 1 and 2 and defines the medicament as:

"a pharmaceutical composition comprising a mixture of effective amounts of (A) and (B), optionally together with at least one pharmaceutically acceptable carrier; for simultaneous administration in the treatment of chronic obstructive pulmonary disease".

Claim 1 in auxiliary requests 3-5 and 7 is identical to claim 1 of the main request.

Claim 1 in auxiliary requests 8 is identical to claim 1 in auxiliary request 1.

Claim 1 in auxiliary requests 10-13 is identical to claim 1 in auxiliary request 2.

Claim 1 in auxiliary request 9 is identical to claim 1 in auxiliary request 6.

V. In its communication pursuant to Article 15(1) RPBA, the Board expressed *inter alia* the preliminary opinion that the assessment of inventive step for the main

request, and possibly the outcome of the appeal proceedings, depended critically on the question whether the effects relied on by the patent proprietor in support of an inventive step could be attributed to the distinguishing features of the claimed subject-matter with respect to the closest prior art. The Board further indicated that it intended not to admit documents A122 and A126 into the appeal proceedings.

VI. Oral proceedings were held on 7 October 2025.

During the oral proceedings the patent proprietor filed auxiliary request 14. This auxiliary request 14 corresponds to auxiliary request 1, in which in claim 1 the term "optionally" was omitted.

VII. The arguments of the appellant-patent proprietor relevant to the present decision are summarized as follows:

(a) Admittance documents A122 and A126-A134

Document A122 should not be admitted because it would only introduce complications without materially advancing the opponents' case.

Document A126 was filed in response to new objections by O9, filed for the first time with the reply in the appeal proceedings, that the comparison of the outcome of clinical trials in document D96 is not adjusted for variances in patient baseline characteristics and is inappropriately based on trials of short duration. Document A126 confirmed the finding in document D96 that the combination of glycopyrrolate/indacaterol

provides better prevention of exacerbations of COPD than the combination of glycopyrrolate/formoterol.

Documents A127-A129 were filed in response to the Board's preliminary opinion to confirm that the improvement from the combination of glycopyrrolate with indacaterol over the combination of glycopyrrolate with formoterol as reported in documents D96 and D97 could be attributed to the presence of indacaterol instead of formoterol and was not due to the difference in the device used for their administration or differences in the administered doses. The exceptionally precise indication of this issue as crucial to the outcome of the appeal proceedings in the Board's preliminary opinion justified the admittance of documents A127-A129.

Documents A130-A134 did not demonstrate that the improvement reported for the combination of glycopyrrolate/indacaterol over the combination of glycopyrrolate/formoterol could be due to the difference in the device used for their administration. The admittance of the late-filed documents A130-134 was not justified in view of any exceptional circumstances.

(b) Main request

The difference between the claimed subject-matter and the closest prior art represented by document D4 concerned the combination of glycopyrrolate with indacaterol instead of the combination of glycopyrrolate with formoterol or salmeterol.

Documents D96 and D97 concluded on the basis of meta-analyses of the outcomes of clinical studies that the claimed combination of glycopyrrolate with indacaterol provides improved treatment of airways disorders over the prior art combination of glycopyrrolate with formoterol. Moreover, documents D13, D25 and D55 reported for the combination of glycopyrrolate with indacaterol a significantly improved efficacy in the treatment of COPD as compared to the efficacy of tiotropium, whereas documents D98, D99 and D110 indicated that the combination of glycopyrrolate with formoterol did not provide for such a significant improvement with respect to tiotropium. Following the considerations in T 2735/19, the evaluation of the evidence should take account of the fact that comparative tests on patients cannot be carried out in a discretionary manner. The clinical studies relied on in documents D96 and D97 involved the administration of the tested combinations in the form of different types of formulations and with the use of different inhaler devices. However, the improvement observed with the use of the claimed combination could still be attributed to the difference in the active agents of the tested combinations, because the studies used for the comparison involved the authorized and thus optimized formulations for each of the compared combinations. This related in the case of the glycopyrrolate-indacaterol combination to Ultibro Breezhaler (see D55) and Ultibron Neohaler (see D109), and in the case of the glycopyrrolate-formoterol combination to Bevespi Aerosphere (see D110). The use of the dry powder inhaler (DPI) and the use of magnesium stearate as an excipient merely reflected aspects of the optimized formulations for the combination of

glycopyrrolate and indacaterol. No evidence indicated that the presence of magnesium stearate as a mere excipient in these formulations corresponded in any way to the technology involving the use of magnesium stearate to achieve controlled release as described in document D4. Moreover, document D97 stated explicitly, that potential effect modifiers, including the inhaler device, did not significantly affect the comparison across the different combinations of active agents. Any differences in the inhaler devices used would in any case favour the treatment involving the prior art combination with a pressurized metered dose inhaler (pMDI). As noted in document D98, pMDIs were recognized for their lower risk of mishandling and their suitability for patients with significant lung function impairment.

No prior art suggested the claimed subject-matter as solution to the problem of providing an improved treatment.

Even if the objective technical problem in view of document D4 was formulated as the provision of an alternative treatment, the claimed combination of glycopyrrolate with indacaterol would not be obvious. From documents D22 and D24 the skilled person was aware of the severe cardiac side effects of beta-1 agonists. Document D3 reported a very limited beta-2/beta-1 selectivity of indacaterol, in particular when compared to the selectivity of formoterol reported in document D22. The skilled person would therefore not have considered indacaterol as an alternative to formoterol for the combination with glycopyrrolate.

(c) Auxiliary request 1

Claim 1 of auxiliary request 1 defined a fixed-dose composition of glycopyrrolate with indacaterol optionally together with at least one pharmaceutically acceptable carrier. The patent reserved the term "pharmaceutically acceptable carrier" exclusively for carriers as used in the formulation of inhalable powders. Appropriately interpreted, claim 1 of auxiliary request 1 therefore related to a fixed-dose composition in the form of an inhalable dry powder.

The difference between the claimed subject-matter and the teaching of document D4 concerned the combination of glycopyrrolate with indacaterol and its formulation as fixed-dose composition in the form of an inhalable dry powder. As explained in document D34 with reference to the results reported in documents D20 and D29, the formulation of indacaterol together with glycopyrrolate in a fixed-dose composition as defined in claim 1 of auxiliary request 1 allowed for a dose reduction of the indacaterol due to an increase in the fine particle mass (FPM). The prior art provided the skilled person with no motivation to combine glycopyrrolate with indacaterol in the defined fixed-dose combination in order to achieve this dose reduction effect.

(d) The auxiliary requests complied with the requirement of inventive step for the same reasons as the main request or auxiliary request 1.

(e) Admittance auxiliary request 14

The filing of auxiliary request 14 represented a justified response to the argument raised by the opponents for the first time during the oral proceedings that claim 1 of auxiliary request 1 defines the presence of the pharmaceutically acceptable carrier only as an optional feature.

VIII. The arguments of the appellants-opponents relevant to the present decision are summarised as follows:

(a) Admittance documents A122 and A126-A134

Document A122 demonstrated that the mixing energy in the preparation of a dry powder formulation critically determines the resulting fine particle mass (FPM). Document A122 was filed in response to the finding in the decision under appeal, which relied on document D34 as evidence for the favourable FPM of the combined preparation of glycopyrrolate with indacaterol over separate preparations. Document A122 could not have been filed at an earlier stage, because it was only recently published.

Document A126 should have been filed at an earlier stage of the proceedings. The admittance of document A126 was not justified by any newly raised objections concerning document D96, because the objections regarding the comparison in document D96 had already been raised during the first-instance proceedings. Moreover, document A126 lacked a clear conclusion regarding any improvement of the combination of glycopyrrolate with indacaterol over the combination of glycopyrrolate with formoterol.

The admittance of the late-filed documents A127-A129 was not justified in view of any exceptional circumstances.

Documents A130-134 were filed in response to the late filing of documents A127-A129. The admittance of documents A130-A134 was justified if documents A127-129 were to be admitted.

(b) Main request

The claimed subject-matter differed from the closest prior art represented by document D4 in the combination of glycopyrrolate with indacaterol instead of with formoterol or salmeterol.

Documents D96 and D97 presented meta-analyses comparing the outcomes of clinical studies involving the use of combinations of glycopyrrolate with indacaterol and combinations of glycopyrrolate with formoterol in the treatment of chronic obstructive pulmonary disease (COPD). Insofar as documents D96 and D97 demonstrated any advantage from the treatment with the combination of glycopyrrolate with indacaterol, it could not be established that this improvement could be attributed to the presence of indacaterol instead of formoterol in the combination due to other potential effect modifiers, including the presence or absence of magnesium stearate in the administered formulations. The same uncertainty affected the indirect comparison based on documents D13, D25 and D55 for the claimed combination and documents D98, D99 and D110 for the prior art combination. The objective technical problem could

therefore only be formulated as the provision of a simple alternative treatment.

From document D3 it was known that indacaterol is a long-acting beta-2 adrenergic agent with rapid onset of action which can be combined with anti-muscarinic agents in the treatment of COPD. In view of this teaching it was obvious to provide the combination of glycopyrrolate with indacaterol as an alternative to the combination of glycopyrrolate with formoterol as known from document D4.

(c) Auxiliary request 1

Claim 1 of auxiliary request 1 did not define the claimed medicament as a fixed-dose composition in the form of an inhalable dry powder. A restrictive interpretation of the claim in view of the description was not appropriate. The patent did not reserve the terms "pharmaceutically acceptable carrier" for particulate carriers as used in the formulation of inhalable powders. Moreover, the claim only defined the presence of a pharmaceutically acceptable carrier as optional.

Insofar as the formulation of the combination of glycopyrrolate with indacaterol in a fixed-dose combination represented any additional distinguishing feature with respect to the teaching of document D4, no unexpected effect from this difference had been demonstrated, at least not over the whole scope of the claims.

Document D34 explained that the dose reduction effect observed with the fixed-dose combination of glycopyrrolate with indacaterol, derivable from the

so-called BEACON study reported in documents D20 and D29, was attributable to an increase in the FPM, which could only occur in compositions formulated as inhalable dry powders.

(d) The auxiliary requests 2-13 did not comply with the requirement of inventive step for the same reasons as the main request or auxiliary request 1.

(e) Admittance auxiliary request 14

The admittance of auxiliary request 14 was not justified by any exceptional circumstances.

IX. The parties as of right under Article 107 EPC, opponents O7 and O8, did not file any substantive submission nor any requests during the appeal proceedings.

X. Opponents O1 to O3 and O6 withdrew their oppositions.

XI. The appellant-patent proprietor requested, insofar as relevant to the decision, that

- the decision under appeal be set aside and the patent be maintained as granted (main request)

- the patent be maintained on the basis of one of auxiliary claim requests 1-13 filed with the statement of grounds of appeal or auxiliary request 14 filed during the oral proceedings before the board

- documents A126 and A127-A129 be admitted into the appeal proceedings

- documents A122, A130-A133 and A134 not be admitted into the appeal proceedings.

XII. The appellants-opponents requested, insofar as relevant to the decision, that

- the decision under appeal be set aside and that the patent be revoked in its entirety.

- documents A126-A129 not be admitted into the appeal proceedings

- documents A122 and A134 be admitted into the appeal proceedings

- documents A130-A133 be admitted, if documents A126-A129 were admitted into the appeal proceedings.

Reasons for the Decision

1. Admittance documents A122 and A126-A134

1.1 Document A122

Document A122 was filed by opponent O4 with the statement of grounds of appeal. Its filing thus represents an amendment to its case under Article 12(4) RPBA.

In the communication pursuant to Article 15(1) RPBA, the Board expressed its preliminary opinion that document A122 should not be admitted into the appeal proceedings due to lack of relevance. The Board considered that the teaching in document A122, that the

mixing energy during the preparation of an inhalable powder influences the fine particle mass (FPM), does not appear to contradict the effect on the FPM observed with the combined preparation of glycopyrrolate with indacaterol demonstrated in document D34 and relied on in the decision under appeal.

No substantive arguments were submitted by the opponents in response to the preliminary opinion regarding the admittance of document A122 expressed by the Board in its communication.

Accordingly, the Board has confirmed its preliminary opinion and has not admitted document A122 into the appeal proceedings.

1.2 Document A126

Document A126 represents new evidence filed by the patent proprietor after its reply to the appeals. The filing of document A126 thus constitutes an amendment to its appeal case under Article 13(1) RPBA.

The patent proprietor justified the filing of document A126 as a response to new objections that the comparison in document D96 does not take account of variances in patient baseline characteristics in the compared trials and is inappropriately based on studies of short duration. In its view document A126 confirmed the finding in document D96 that the combination of glycopyrrolate with indacaterol provided better prevention of exacerbations of COPD than the combination of glycopyrrolate with formoterol.

However, opponent O9 already raised the objections against the comparison in document D96 based on the

variance in the patient inclusion criteria and the reliance on studies of short duration during the first instance proceedings in its letter of 17 August 2023 (see pages 16 and 19). Moreover, it is not evident that the information in document A126 is suitable to overcome these objections, because in the discussion of the results document A126 classifies the combination of glycopyrrolate with indacaterol and the combination of glycopyrrolate with formoterol in the same category of fixed-dose combinations (FDC) with comparable efficacy (see A126, page 1329, right column).

The Board has therefore not admitted document A126 into the appeal proceedings.

1.3 Documents A127-A129

Documents A127-A129 were filed by the patent proprietor with its letter responding to the communication pursuant to Article 15(1) RPBA. The filing of these documents thus represents an amendment to its appeal case under Article 13(2) RPBA.

The patent proprietor justified the admittance of documents A127-A129 in view of the Board's indication that the assessment of inventive step for the main request and possibly the outcome of the appeal proceedings critically depended on the question whether improved effects relied on by the patent proprietor in support of an inventive step could be attributed to the distinguishing features of the claimed subject-matter with respect to the closest prior art. However, this issue had been raised by the opponents during the first instance proceedings and was explicitly addressed in the decision under appeal (see sections 20.2 and 20.5).

The admittance of documents A127-A129 is thus not justified by any exceptional circumstances.

The Board has therefore not admitted documents A127-A129 into the appeal proceedings.

1.4 Documents A130-A134

Documents A130-134 were filed by opponent O5 in response to the filing of document A127-A129 and thus represent an amendment to its appeal case under Article 13(2) RPBA.

Following the Board's decision not to admit documents A127-A129, no justification for the admittance of documents A130-A134 is apparent.

The Board has therefore not admitted documents A130-A134 into the appeal proceedings.

2. Main request (claims as granted) - inventive step

2.1 Starting point in the prior art

It was not in dispute that the requirement of inventive step is to be evaluated starting from document D4 as the closest prior art and that the difference between the medicament comprising glycopyrrolate and indacaterol as defined in claim 1 as granted and the teaching of document D4 concerns the combination of glycopyrrolate with indacaterol instead of formoterol or salmeterol.

Document D4 describes a long-acting inhalable formulation of glycopyrrolate for the treatment of COPD, which may involve the co-administration with a

beta-2 agonist, such as formoterol or salmeterol, and which may provide maximal effect on lung function whilst avoiding side effects (see D4, page 2, lines 13-32; page 6, lines 18-22; page 7, lines 3-7; claims 1, 2 and 8).

2.2 Objective technical problem

2.2.1 According to the established jurisprudence (see Case Law of the Boards of Appeal of the EPO, 11th edition, 2025, I.D.4.3.1), the burden of proof that the claimed invention provides an improvement over the prior art rests with the patent proprietor. Moreover, if the patent proprietor relies on comparative tests as evidence of an unexpected effect, the nature of the comparison must be such that the alleged advantage or effect is convincingly shown to have its origin in the distinguishing feature of the invention compared with the closest prior art (see Case Law of the Boards of Appeal of the EPO, *supra*, I.D.4.3.2).

The Board acknowledges, as stated in T 2735/19 (see Reasons 7.2.1), that comparative tests on patients cannot be conducted at will. Nevertheless, this does not exempt the patent proprietor from the obligation to provide convincing evidence of the effects of the claimed subject-matter relied upon to support an inventive step.

2.2.2 In the present case, the patent proprietor relied on documents D96 and D97 as evidence of the improved efficacy of the claimed combination of glycopyrrolate with indacaterol over the prior art combination of glycopyrrolate with formoterol in the treatment of chronic obstructive pulmonary disease.

Each of documents D96 and D97 presents a meta-analysis of the outcome of a multitude of clinical studies investigating the efficacy of fixed-dose combinations (FDC) of long-acting beta-2 agonists (LABA), including indacaterol and formoterol, with long-acting muscarinic antagonists (LAMA), including glycopyrrolate, in the treatment of COPD (see D96, pages 4-5, Table 1; D97, pages 3-5, Table 1). Document D96 indicates that the tested combinations of glycopyrrolate with indacaterol provide better protection against acute exacerbations of COPD than the tested combination of glycopyrrolate with formoterol (see D96, page 6, bridging paragraph between columns, page 7, Table 3, page 8 right column). Document D97 indicates a better efficacy/safety profile for the tested combinations of glycopyrrolate with indacaterol than for the tested combination of glycopyrrolate with formoterol as reflected by a higher Implemented Bidimensional SUCRA (IBiS) score (see D97, page 8, right column).

It was undisputed that the pharmaceutical compositions tested in the studies cited in documents D96 and D97 involved in the case of the glycopyrrolate–indacaterol combination inhalable dry powder formulations containing magnesium stearate administered at doses of 50/110 mg daily or 15.6/27.5mg twice daily via a dry powder inhaler (DPI) corresponding to Ultibro Breezhaler and Ultibron Neohaler, and in the case of the glycopyrrolate–formoterol combination a suspension administered at a dose of 18/9.6 mg twice daily via a pressurized metered dose inhaler (pMDI)corresponding to Bevespi Aerosphere.

Each of documents D96 and D97 consistently refer to the efficacies of the combinations of the active agent (see D96, page 7-8, "Discussion" and "Conclusions"; see D97,

pages 8-10, "Discussion"). Moreover, document D97 explicitly states that a meta-regression analysis, performed to identify factors that could have altered the comparison across the LABA/LAMA FDCs with respect to the investigated outcomes, including the inhalation device, did not reveal such potential effect modifiers (see D97, page 6, right column, page 8, left column, page 9, right column). However, documents D96 and D97 do not specifically address the presence or absence of magnesium stearate as a potential effect modifier.

Notably, the document D4, which provides the starting point in the prior art, discloses the formulation of an antimuscarinic agent, such as glycopyrrolate, in discrete microparticles of a hydrophobic matrix material such as magnesium stearate that provides for the controlled release of the agent following pulmonary delivery (see D4, page 2, lines 13-32, page 5, lines 1-15, and claims 1-4). Document D4 thereby explicitly identifies the presence of magnesium stearate in compositions for pulmonary administration comprising glycopyrrolate compared in documents D96 and D97 as a factor which affects the release of the glycopyrrolate following administration. It may therefore not be excluded that any improvement with the glycopyrrolate-indacaterol compositions observed in documents D96 and D97 may find its origin in the presence of magnesium stearate in the glycopyrrolate-indacaterol compositions and the absence of magnesium stearate in the glycopyrrolate-formoterol tested in the studies relied upon in documents D96 and D97, rather than in the replacement of formoterol by indacaterol.

The patent proprietor argued that document D4 describes the specific use of magnesium stearate as a hydrophobic matrix material for achieving a controlled release of

glycopyrrolate, whereas the tested compositions comprising the glycopyrrolate-indacator, namely the Ultibro Breezhaler described in document D55 and Ultibron Neohaler described in document D109, merely comprise magnesium stearate as an inactive excipient. In its view, the opponents had not demonstrated that the presence of magnesium stearate as an inactive excipient results in the effect described in document D4. However, given the identification of magnesium stearate as a potential effect modifier, the Board considers that the burden of proof remains on the patent proprietor to demonstrate that any improved effect of the tested compositions comprising the glycopyrrolate-indacaterol combination can be attributed to the replacement of formoterol by indacaterol and not to the presence of magnesium stearate. This proof is not established by the patent proprietor's reference to the presence of magnesium stearate in the tested compositions as a mere excipient, because it is not evident that a similar effect of magnesium stearate as described in document D4 is excluded when magnesium stearate is used as an excipient.

The Board also rejects the patent proprietor's argument that the presence of magnesium stearate in the tested compositions comprising the glycopyrrolate-indacaterol combination was directly associated with their administration by DPI and corresponded to the authorized and optimized Ultibro Breezhaler and Ultibron Neohaler formulations, in the same manner as the tested compositions comprising the glycopyrrolate-formoterol combination without magnesium stearate corresponded to the authorized and optimized Bevespi Aerosphere formulation. The reference to optimized formulations in this argument supports, rather than

contradicts, the potential influence of magnesium stearate on the efficacy of the tested compositions, as suggested by the teaching of document D4. Moreover, the assumed optimization of the authorized formulations does not necessarily indicate that all such formulations are equally balanced with respect to efficacy and tolerability.

2.2.3 The patent proprietor also referred to the significantly improved efficacy of the glycopyrrolate-indacaterol combination compared to tiotropium, as reported in documents D13, D25 and D55, in contrast to the absence of significantly improved efficacy of the glycopyrrolate-formoterol combination relative to tiotropium reported in documents D98, D99 and D110, as evidence for an unexpected advantage of the claimed subject-matter over the prior art.

However, the results reported in documents D13, D25 and D55 relate to the same formulation of the glycopyrrolate-indacaterol combination as Ultibro Breezehaler (see the explicit reference to "QVA149" as Ultibro Breezehaler in D55, page 9/97) and the results reported in documents D98, D99 and D110 relate to the same formulation of the glycopyrrolate-formoterol combination as Bevespi Aerosphere. For the same reasons as set out in section 2.2.2 above, it may therefore not be excluded that any advantage of the glycopyrrolate-indacaterol composition suggested by the indirect comparison relative to tiotropium finds its origin in the presence of magnesium stearate in the glycopyrrolate-indacaterol compositions rather than the replacement of formoterol by indacaterol.

2.2.4 The Board therefore considers that the evidence relied on by the patent proprietor does not convincingly

demonstrate that the distinguishing features of the claimed subject-matter are associated with an improvement over the prior art.

Accordingly, the Board formulates the objective technical problem as the provision of a mere alternative medicament for the treatment of an inflammatory or obstructive airways disease.

2.3 Assessment of the solution

Starting from the combination of glycopyrrolate with formoterol as described in document D4 as an example of a composition for pulmonary delivery of glycopyrrolate with a beta-2 adrenergic agent, the skilled person would take account of document D3, because it describes indacaterol as a long-acting beta-2 adrenergic agent with rapid onset of action (see D3, pages 14-15, bridging paragraph, example 2) and specifically discloses its combination with anti-muscarinic agents for the treatment of COPD (see D3, page 17, lines 1-16).

In view of this teaching in document D3, the skilled person would consider the claimed combination of glycopyrrolate with indacaterol an obvious alternative for the glycopyrrolate-formoterol combination of document D4.

The Board rejects the patent proprietor's argument that, due to the potentially severe cardiac side effects of beta-1 agonists, the skilled person would not select indacaterol for combination with glycopyrrolate based on its limited beta-2/beta-1 selectivity. Document D3 still describes indacaterol as a selective beta-2 adrenergic agent suitable for the

treatment of obstructive or inflammatory airway disease, and associated with a low incidence of side effects, including cardiac side effects (see D3, page 15, lines 12-26).

2.4 Accordingly, the Board concludes that the subject-matter of claim 1 of the main request does not involve an inventive step.

3. Auxiliary request 1

3.1 Claimed subject-matter

Claim 1 of auxiliary request 1 defines the medicament as a pharmaceutical composition comprising a mixture of effective amounts of glycopyrrolate and indacaterol, optionally together with a pharmaceutically acceptable carrier.

Contrary to the argument by the patent proprietor presented during the oral proceedings, the term "pharmaceutically acceptable carrier" does not limit the defined medicament to an inhalable dry powder composition. A skilled person would understand that the category of pharmaceutically acceptable carrier encompasses a broad range of pharmaceutical excipients and is not restricted to excipients of dry powder formulations. In line with the conclusions in T 2027/23 (Reasons 3.5.2, 3.5.6, and 3.5.8) regarding the order in G 1/24, the Board considers that claim 1 of auxiliary request 1 should not be interpreted, based on embodiments presented in the description, as having a meaning narrower than the wording of the claim as understood by the person skilled in the art. Furthermore, in contrast to the patent proprietor's argument, the patent does in any case not reserve the

terms "pharmaceutically acceptable carrier" to an excipient for a dry powder formulation. Notably, the sections of the description of the patent (see paragraphs [0017]-[0018] relating to the embodiment of an inhalable dry powder) more specifically refer to a "particulate pharmaceutically acceptable carrier".

3.2 Objective technical problem

The difference between subject-matter of claim 1 of auxiliary request 1 with the closest prior art represented by document D4 concerns the combination of glycopyrrolate with indacaterol and its formulation in a fixed-dose composition.

The patent proprietor relied on a dose reduction effect for indacaterol when administered with glycopyrrolate to achieve a given therapeutic effect in the form of a fixed-dose composition as opposed to separate formulations of these agents as reported in documents D20, D29 and D34. As explicitly stated in document D34 (see sections 7 and 16) this dose reduction effect derives from an increase in the fine particle mass (FPM) of indacaterol when it is prepared together with the glyopyrrolate in an inhalable dry powder. However, as explained in section 3.1 above, claim 1 of auxiliary request 1 is not limited to inhalable dry powder formulations. The effect relied on by the patent proprietor is therefore not achieved over the whole scope of the claim.

Accordingly, the Board formulates the objective technical problem as a mere alternative to the combination of glycopyrrolate and formoterol as described in document D4, without further qualification regarding a dose reduction effect.

3.3 For the reasons set out in section 2.3 above, the Board considers that, in the context of the identified objective technical problem, it was obvious for the skilled person to replace the glycopyrrolate-formoterol combination of document D4 by the combination of glycopyrrolate with indacaterol in view of the teaching in document D3.

Moreover, merely as an alternative, the preparation of glycopyrrolate with indacaterol as a fixed-dose combination would also be obvious to the skilled person, because fixed-dose compositions were common place in the art and indeed explicitly foreseen for treatment of respiratory disease in documents D3 (page 17, lines 1-16) and D4 (see page 5, lines 30-32).

3.4 Accordingly, the Board concludes that the subject-matter of claim 1 of auxiliary request 1 also does not involve an inventive step.

4. Auxiliary requests 2-13

The patent proprietor did not argue that, the independent claims of auxiliary requests 2-13 define with respect to claim 1 of the main request or claim 1 of auxiliary request 1 any additional distinguishing features over the closest prior art represented by document D4.

The Board therefore concludes that auxiliary requests 2-13 do not comply with the requirement of inventive step of Article 56 EPC for the same reasons set out for the main request and auxiliary request 1.

5. Admittance auxiliary request 14

Claim 1 of auxiliary request 14 corresponds to claim 1 of auxiliary request 1 in which the term "optionally" is omitted. Auxiliary request 14 was filed by the patent proprietor during the oral proceedings. The filing of this request thus represents an amendment to its appeal case under Article 13(2) RPBA.

The argument that the claim 1 of auxiliary request 1 does not define dry powder formulations and is not even limited to inhalable compositions was already raised by the opponents in their statement of grounds of appeal. In its communication pursuant to Article 15(1) RPBA, the Board indicated that, merely as an alternative to the closest prior art, the provision of a fixed-dose combination as defined in claim 1 of auxiliary request 1 would seem obvious to the skilled person. The Board therefore does not consider the fact that the opponents first referred to the optionality of the pharmaceutically acceptable carrier in claim 1 of auxiliary request 1 during the oral proceedings to represent an exceptional circumstance justifying the late filing of auxiliary request 14, particularly since it was the patent proprietor who argued for the first time during the oral proceedings that the reference to the pharmaceutically acceptable carrier qualified the composition as an inhalable dry powder. Accordingly, the auxiliary request 14 is not admitted into the appeal proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated