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Title of invention:
Fluticasone furoate in the treatment of COPD

Patent Proprietor:
GlaxoSmithKline Intellectual Property Development Limited

Opponents:
Teva UK Limited
Gill Jennings & Every LLP

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 12

Keyword:
Inventive step - (no)

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Case Number: T 2481/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 20 February 2025

Appellant: (Opponent 1)	Teva UK Limited Ridings Point Whistler Drive Castleford WF10 5HX (GB)
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Representative:	Gill Jennings & Every LLP The Broadgate Tower 20 Primrose Street London EC2A 2ES (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 11 October 2022 rejecting the oppositions filed against**

European patent No. 3148521 pursuant to Article 101(2) EPC.

Composition of the Board:

Chairwoman	M. Pregetter
Members:	R. Hauss
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 3 148 521 (patent in suit) was granted with a set of 14 claims. Independent claim 1 reads as follows:

1. A pharmaceutical product comprising fluticasone furoate for use in the treatment of COPD in a patient, wherein the patient has a blood eosinophil count of ≥150 cells/µL and wherein the pharmaceutical product reduces the rate of decline in lung function in the patient.

II. The patent in suit was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter did not involve an 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.

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

D1: Am J Respir Crit Care Med 186, 48-55 (2012)

D4: Eur Respir J 47, 1374-1382 (2016)

D9: BMJ 320, 1297-1303 (2000)

D33: GOLD Report, Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease (updated 2014)

D36: Int J Chronic Obstr Pulm Dis 14, 1063-1073 (2019)

D36a: "Online supplement", supplementary information for D36, https://spiral.imperial.ac.uk/handle/10044/1/68961

D37: Am J Respir Crit Care Med 178, 332-338 (2008)

D40: Thorax 57, 847-852 (2002)

D41: Am J Respir Crit Care Med 184, 662-672 (2011)

D42: Semin Respir Crit Care Med, 27(2), 128-133 (2006)

IV. The decision under appeal is the opposition division's decision rejecting the oppositions.

V. In the decision under appeal, the opposition division ruled as follows:

(a) The grounds for opposition under Article 100(b) and (c) EPC did not prejudice maintenance of the patent as granted.

(b) Inventive step was assessed starting from the disclosure of document D37, which relates to a study of fluticasone propionate. The objective technical problem was to find a subgroup of COPD patients in which the rate of decline in lung function was improved following treatment with fluticasone. Having regard to the state of the art, the claimed subject-matter would not have been obvious to the person skilled in the art (Articles 100(a), 52(1) and 56 EPC).

VI. Opponent 1 (the appellant) filed an appeal against this decision.

VII. The non-appealing opponent 2 is a party as of right under Article 107 EPC. It did not present any observations on the substance of the appeal case but advised the board in writing that it withdrew its request for oral proceedings, and requested a decision on the state of the file.

VIII. Oral proceedings before the board were held on 20 February 2025, in the absence of opponent 2 (Article 15(3) RPBA and Rule 115(2) EPC).

IX. The appellant's arguments may be summarised as follows:

Admittance of documents D41 and D42

The appellant had filed D41 and D42 at first instance with its Rule 116 submission, and the respondents had raised no objection to these documents' admittance at the time. Both documents were discussed substantively in the decision under appeal, which implied that they were admitted into the proceedings by the opposition division.

Inventive step

D37, which was based on data from a long-term clinical trial, disclosed that fluticasone propionate reduced the rate of decline in lung function in patients with moderate to severe COPD (chronic obstructive pulmonary disease) in comparison with placebo.

The technical features distinguishing the subject-matter of claim 1 as granted from the disclosure of D37 were the specified patient group and the use of the furoate ester of fluticasone.

As the commonly known furoate ester of fluticasone would have been an obvious alternative to the propionate ester used in D37, the key distinction to be considered for inventive step was the specified patient group, i.e. patients having a blood eosinophil count of ≥150 cells/µl.

The technical effect alleged by the respondent was that this patient subgroup responded better to fluticasone, in terms of a reduced rate of decline in lung function, than the COPD population as a whole. For support, the

respondent relied on Example 1 of the patent in suit (identically present in the application as filed) and post-published document D4.

The appellant did not contest the results of the *post hoc* analysis of clinical study data ("ISOLDE" study) as reported in Example 1 and in D4.

However, the data and conclusions from a post-published long-term observational study, presented in D36, suggested that the alleged improved efficacy in comparison with other COPD patients was not attained across the entire patient group identified in claim 1.

This was because D36 identified a division between "prevalent" patients, i.e. patients who had been prescribed an inhaled corticosteroid (ICS) at baseline, and "incident" patients, who had not. D36 showed that the blood eosinophil count biomarker was only relevant for incident patients. However, the definition of the patient group in claim 1 also covered prevalent patients.

As the alleged technical effect could not be attained in prevalent patients, and thus not across the entire group of COPD patients characterised by a blood eosinophil count of ≥150 cells/µl, the selection of this patient group had to be regarded as arbitrary. The associated objective technical problem was, therefore, the provision of an arbitrary patient group that could benefit from fluticasone treatment.

Blood eosinophil levels were a known parameter routinely measured in the art. Any arbitrary selection, including that of a patient group characterised by a specified range for this parameter, would have been obvious and could not be the basis for acknowledging an inventive step.

Moreover, D37 already taught that fluticasone reduced the rate of decline in lung function in patients with COPD. The person skilled in the art would have expected the teaching of D37 to be applicable to all patients, regardless of their blood eosinophil count.

Even on the basis of the more ambitious technical problem formulated by the respondent, the claimed subject-matter would still have been obvious in view of the common general knowledge, as represented by the review article D42 and the pertinent disclosures of, *inter alia*, D1, D40 and D41, on COPD with involvement of eosinophilic inflammation.

These prior-art disclosures suggested that the most eosinophilic patients responded better to corticosteroid treatment, which would have incentivised the skilled person to focus on this patient group.

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

Admittance of documents D41 and D42

D41 and D42 were late-filed at first instance, and the opposition division had been wrong to allow them into the proceedings. Furthermore, these documents were not *prima facie* relevant.

Inventive step

The state of knowledge in the field of COPD therapy, at the time the invention was made, was that regular treatment with inhaled corticosteroids did not modify the long-term decline in lung function, reflected by the FEV_1 parameter (forced expiratory volume in one second; see D33: page 24, right-hand column, last complete paragraph).

The finding underlying the invention was that fluticasone furoate could be used successfully to reduce the rate of decline in lung function in a specific subgroup of COPD patients, namely those having a blood eosinophil count of ≥150 cells/µl, thus providing improved treatment for this patient group. Evidence of this technical effect was provided in Example 1 and corroborated by D4, a post-published journal article on the same subject.

The disclosure of D36 was consistent with the findings in Example 1. The set-up of the ISOLDE study analysed in Example 1 and D4 included a wash-out period without ICS or oral corticosteroids before patients were started on fluticasone medication. This was similar to the situation of the "incident" patient cohort in D36 (no ICS use in the year prior to the index date). Looking at the incident data was, in fact, the correct approach to assessing the true effect of ICS on lung function without background interference of a pre-existing ICS treatment.

Thus it would be understood that the claimed subject-matter only concerned incident patients. Typically, COPD was treated initially with bronchodilators. ICS could be added later if this turned out to be necessary. Claim 1 was, in fact, focusing on the typical situation where a patient was to be initiated into ICS treatment.

D36 looked at the "prevalent" group for comparison only, as it was necessary to compare this group with the incident group to separate out the true effect of starting patients on a new ICS medication.

Furthermore, the findings in D36 related to ICS generally rather than specifically to fluticasone as they had been obtained with pooled data for several active agents. Table S5 of the supplement D36a, which

presented data separated by active agent, contained no reference to prevalent or incident users and, therefore, did not link to the main findings of D36. Thus the results reported in D36 were not conclusive on treatment with fluticasone specifically.

The objective technical problem should be defined as the provision of a subgroup of COPD patients in whom the rate of decline in lung function was improved following treatment with fluticasone. The solution to this problem involved the treatment of COPD patients having a high blood eosinophil count of ≥150 cells/µl using fluticasone furoate.

D37 was silent on eosinophil levels and did not suggest a relationship between this parameter and patient responsiveness to fluticasone treatment.

Starting from the disclosure of D37 and tasked with solving the objective technical problem, the person skilled in the art would preferentially have investigated variables mentioned in D37 itself as being associated with FEV_1 decline, such as body mass index or region of origin (see D37, page 336, right-hand column), rather than eosinophil level.

Without hindsight being involved, they would have had no incentive to consult unrelated documents such as D1 or D42 for supplementary information. D1 was concerned with oral systemic corticosteroid therapy instead of ICS therapy. D42 referred to short-term studies without relevance for the long-term decline in lung function, and did not provide conclusive teaching on blood eosinophil count. As was made clear in D33 (see page 24, right-hand column, last complete paragraph), the known acute effect of ISC on FEV_1 discussed in those documents was different from the claimed effect

on the rate of decline of FEV_1 as a measure for the long-term decline in lung function.

XI. The appellant (opponent 1) requested that the decision under appeal be set aside and that the patent be revoked.

XII. The respondent (patent proprietor) requested that the appeal be dismissed and the patent be maintained as granted. It also requested that documents D41 and D42 not be admitted.

XIII. The party as of right (opponent 2) requested in writing that the board issue an appealable decision *[sic]* based on the state of the file.

Reasons for the Decision

1. Request for non-admittance of evidence (Article 12 RPBA)

1.1 During the proceedings before the opposition division, the appellant filed documents D41 and D42, as evidence in the context of inventive step, with its submission dated 29 June 2022. This was before the final date for making written submissions under Rule 116 EPC (22 July 2022) as notified with the summons to oral proceedings dated 7 September 2021.

1.2 The appellant relied on both D41 and D42 in its statement setting out the grounds of appeal as well (points (72) to (78), (85) and (91)).

1.3 The minutes of the oral proceedings before the opposition division state that the appellant relied on D42, the respondent stated that it did not object to the admittance of D42 and the opposition division

admitted this document (see points 4.13, 4.15 and 4.16 of the minutes). Neither the minutes nor the decision under appeal mention any objection by the respondent to the admittance of D41, and no such objection was presented in writing.

1.4 In the decision under appeal, the opposition division did not discuss admittance of D41 and D42 but addressed the appellant's arguments in relation to both documents in its reasoning (see points 7.5.4 and 7.5.5 of the decision under appeal).

1.5 Thus it is apparent that the opposition division admitted documents D41 and D42 in the absence of any objection by the respondent and that these documents are part of the evidence on which the decision under appeal is based (Article 12(2) RPBA).

1.6 In its reply to the statement setting out the grounds of appeal (paragraphs (48) to (52)), the respondent objected to the appellant's reliance on D41 and D42 with the argument that these documents had been filed only at a late stage of the proceedings before the opposition division, in the context of new arguments and without any explanation as to why they had been filed only at that late stage. Moreover, the content of D41 and D42 also lacked *prima facie* relevance.

1.7 Thus it appears that the respondent's objections and request for non-admittance are not based on any new development or circumstance arising only upon appeal, and that the respondent failed to present them during the proceedings before the opposition division.

1.8 Under these circumstances, the board did not see any reason why documents D41 and D42 should not be taken into account in the appeal proceedings (Article 12(6)

RPBA). The respondent's request for non-admittance of documents D41 and D42 was thus rejected.

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

Patent in suit

2.1 The patent in suit relates to pharmaceutical products comprising fluticasone furoate for the treatment of COPD (chronic obstructive pulmonary disease). Fluticasone furoate is a corticosteroid that is administered by inhalation ("inhaled corticosteroid" or "ICS") (see paragraphs [0001] and [0015] of the patent in suit).

2.2 ICS medication is typically recommended to reduce symptoms, improve lung function and reduce the risk of exacerbations in COPD (see D33: page 24, right-hand column). In the context of the claimed invention, the administration of fluticasone furoate is intended to reduce the rate of decline in lung function, which is a long-term effect.

2.3 The description sets out that the term "lung function" refers to a patient's forced expiratory volume in one second (FEV_1). Lung function (as reflected by FEV_1) in healthy subjects declines as a result of the natural ageing process. In COPD patients, it declines at an accelerated rate. Decline in lung function may be measured in terms of millilitres (ml) per year (see paragraph [0016] of the patent in suit).

2.4 The patent in suit mentions a need for therapies that are able to modify the long-term decline in lung function seen in COPD patients, and thus slow their disease progression (see paragraph [0042]). Also, there is an interest in personalised medicine in COPD through the identification of biomarkers that can be used to

select a particular population of COPD patients that will derive most benefit from a pharmacologic treatment (see paragraph [0007]).

2.5 According to the general description of the patent in suit, it was found that COPD patients who have a blood eosinophil count of ≥150 cells/µl or *>[sic]* 2% ("responders") derive greater clinical benefit from treatment with an inhaled corticosteroid than those with lower eosinophil levels (see paragraphs [0022] and [0025]). In one embodiment, the pharmaceutical product of the patent in suit reduces the rate of decline in lung function (see paragraphs [0030], [0031] and [0043]).

2.6 Accordingly, claim 1 as granted (see point I. above) relates to a product for use in the treatment of COPD in patients having a blood eosinophil count of ≥150 cells/µl, wherein the product reduces the rate of decline in lung function.

Starting point in the prior art

2.7 In the decision under appeal, inventive step was assessed starting from the disclosure of document D37.

2.8 D37 details a *post hoc* analysis of data obtained in the "TORCH" study. This was a randomised, double-blind, placebo-controlled long-term clinical trial in COPD patients, who received the long-acting bronchodilator salmeterol (50 µg) plus fluticasone propionate (500 µg), either component alone, or placebo (see D37: abstract).

2.9 Although the development of the FEV_1 value was not a primary outcome in this study, post-bronchodilator lung function was measured every 24 weeks for three years, which provided an opportunity to evaluate how lung

function evolved in each study arm (see D37: abstract and page 337, left-hand column, penultimate paragraph).

2.10 D37 mentions that the normal rate of FEV_1 decline in healthy subjects is approximately 30 ml/year (see page 335, right-hand column, second full paragraph). The *post hoc* analysis compared the effects of the treatments on the rate of post-bronchodilator FEV_1 decline in patients with moderate or severe COPD. D37 reports that the adjusted rate of decline in FEV_1 was 55 ml/year for placebo, 42 ml/year for salmeterol, 42 ml/year for fluticasone propionate and 39 ml/year for salmeterol plus fluticasone propionate (see D37: abstract, Table 2 and page 334, right-hand column, second paragraph). Thus a significant reduction in the decline of lung function of 13 ml/year vs placebo was obtained with fluticasone ($p = 0.003$) and of 16 ml/year vs placebo with the salmeterol/fluticasone combination treatment ($p < 0.001$).

2.11 D37 does not mention blood eosinophils or their potential correlation with patients' responsiveness to fluticasone administration.

Objective technical problem and solution

2.12 It is common ground that the claimed subject-matter differs from the disclosure in document D37

(i) by the use of fluticasone furoate rather than fluticasone propionate,

(ii) by the specific patient group to be treated, namely COPD patients having a blood eosinophil count of ≥150 cells/µl.

2.13 The distinguishing features can be considered separately as there is no reason for assuming that they are functionally interdependent. Indeed, the technical

effect alleged in association with feature (ii) is based on experimental data obtained with fluticasone propionate (see point 2.15 below), hence it is unrelated to feature (i).

2.14 The technical effect of using the furoate ester of fluticasone (feature (i)) in the claimed product is that fluticasone is provided in a different (alternative) form.

2.15 The respondent contended that claim 1 furthermore provides a biomarker for improved response to fluticasone by identifying a patient group (feature (ii)) which may benefit by a decrease in the rate of decline of lung function.

2.16 In support of the alleged technical effect, the respondent relied on the evidence provided in Example 1 of the patent in suit and the corresponding evidence in the post-published journal article D4.

2.16.1 Example 1 reports on the *post hoc* analysis of data obtained in the "ISOLDE" study, a three-year study of the effects of fluticasone propionate (500 µg twice daily) on rate of decline in FEV_1 in well-characterised COPD patients.

The pre-specified analysis of ISOLDE did not show any effect of fluticasone propionate on the rate of decline of FEV_1. The data were then re-analysed by baseline blood eosinophil count (≥2% and <2%). This analysis showed that in patients with an eosinophil count of at least 2%, fluticasone propionate slowed the rate of decline of lung function by 38 ml/year in comparison with placebo ($p = 0.001$), whereas no difference was observed in patients with an eosinophil count below 2%.

Example 1 states, in conclusion (see paragraph [0087]), that a baseline blood eosinophil count of ≥2% identifies a group of COPD patients who show a slower rate of decline of FEV_1 when treated with inhaled corticosteroids.

2.16.2 D4 presents the same *post hoc* analysis of the ISOLDE data in more detail. Although D4 speaks of a 33.9 ml/year (rather than 38 ml/year) reduction in the rate of decline of FEV_1 attained with fluticasone, the order of magnitude and the conclusion are the same as in Example 1 (see D4: abstract and page 1376, last paragraph).

2.17 It appeared to be common ground among the parties that the relative proportion of 2% blood eosinophils corresponds to a concentration value of 150 cells/µl (the cut-off value used in claim 1), as also suggested by various passages in the patent in suit (see e.g. paragraph [0022]: "a responder is a COPD patient who has a blood eosinophil count of ≥150 cells/µl or >*[sic]* 2%").

2.18 The appellant did not contest the results of the *post hoc* analysis provided in D4 and in Example 1 of the patent in suit or the conclusion that a difference in the study patients' response to fluticasone that depended on baseline eosinophil count was observed.

With reference to document D36, the appellant disputed, however, that the alleged improvement could be attained for the entire patient group as defined in claim 1. As a consequence, the selection of this patient group was not, after all, linked to a specific technical effect.

2.19 The board found the appellant's line of argument persuasive, for the following reasons.

2.19.1 D36 is a post-published observational study investigating the rate of decline in lung function of COPD patients, based on general-practice electronic health records in the UK. Data between January 2004 and February 2016 were included. The outcome of interest was the rate of change of FEV_1. The authors investigated whether FEV_1 decline in patients prescribed ICS differed according to blood eosinophil levels (see D36: abstract; page 1064, right-hand column, "Methods"; page 1065, left-hand column, "Outcome").

2.19.2 According to the methodology of D36, patients were stratified according to two criteria: firstly, based on whether they had been prescribed an ICS at baseline and secondly, based on blood eosinophil count, with a cut-off concentration of 150 cells/µl (see D36: page 1066, Figure 2 and page 1064, Figure 1).

In the context of the first criterion, "prevalent" ICS use was defined as the presence of at least one ICS-containing medication in the year prior to the patient's index date, determined through recorded ICS prescriptions in the patient's data. The index date is the start of follow-up date (first FEV_1 measurement). Patients were categorised into those using an ICS-containing medication and those not using an ICS-containing medication at baseline (see D36: page 1065, left-hand column, "Exposures").

"Incident" ICS use was defined as the presence of at least one ICS-containing medication in the first year after the patient's index date and no prevalent ICS use in the year prior to their index date (see D36: page 1065, left-hand column, "Exposures"). Patients

not on ICS-containing medication at baseline were grouped into incident ICS-containing medication users or non-ICS-containing medication users based on ICS-containing medication prescriptions in their first year of follow-up (see D36: page 1065, right-hand column, "Incident ICS use").

2.19.3 The results in terms of the effect of ICS use on the rate of FEV_1 decline differed depending on whether the patients were part of the "prevalent" or the "incident" cohort.

- In the incident cohort, newly initiated ICS use slowed the rate of FEV_1 decline by 25.4 ml/year (+4.2 ml/year adjusted rate of change in FEV_1 in patients on newly initiating ICS-containing medication versus -21.2 ml/year in non-ICS users, $p < 0.001$) (see D36: Abstract, "Results" and page 1068, right-hand column, second full paragraph). While the improvement was prominent (33.0 ml/year) in the subgroup having a high blood eosinophil level of ≥150 cells/µl, no statistically significant difference between those receiving ICS and those without ICS-containing medication was seen in the patient subgroup with lower blood eosinophils (see D36: Abstract, "Results"; Table 6 and paragraph bridging pages 1068 and 1069).

- In the prevalent cohort, ICS use slowed the rate of decline in FEV_1 by 8.5 ml/year (-12.6 ml/year mean adjusted rate of change of FEV_1 in those on ICS-containing medication versus -21.1 ml/year in patients not on an ICS-containing medication; see D36: Abstract, "Results" and page 1068, left-hand column). However, no statistically significant difference was seen between patient groups when

stratified by blood eosinophil level (see D36: Table 5 and page 1068, left-hand column, "Rate of change in FEV_1 with prevalent ICS use").

2.19.4 It was not in dispute that the results reported in D36 for the incident cohort were consistent with those reported in Example 1 of the patent in suit and in D4.

Participants in the ISOLDE study taking ICS and/or oral corticosteroids had to have stopped these treatments before entry to the eight-week run-in period of the ISOLDE study (see D4: page 1375: "Overview of ISOLDE study"). As set out in D36, the findings of D4 (cited as reference [10] in D36) are similar to the incident ICS-containing medication findings, and more generally trials with an initial wash-out period are regarded as similar to the incident cohort design of D36 (see D36: page 1070, right-hand column, first full paragraph).

2.19.5 Hence, while providing data for a setting corresponding to incident fluticasone use, D4 and Example 1 do not reflect the alternative therapeutic setting involving prevalent ICS use.

2.19.6 As summarised in points 2.19.2 and 2.19.3 above, the authors of D36 also investigated a large prevalent cohort and report in this context that no difference in terms of slowing the decline in lung function was observed within the prevalent cohort between patients having a high blood eosinophil level and those with a lower blood eosinophil level. Thus the findings in D36 suggest that the blood eosinophil level does not function as a biomarker for responders in a setting characterised by prevalent ICS use; in other words, the relevance of this parameter is confined to patients with incident ICS use.

2.19.7 Claim 1 defines the patient group to be treated as having a blood eosinophil count of ≥150 cells/µl. This definition does not distinguish between incident and prevalent ICS use. The wording of claim 1 as a whole does not exclude the situation that the envisaged fluticasone therapy may correspond to the setting with prevalent ICS use described in D36. According to the data presented in D36, the blood eosinophil count would not function as a biomarker for response to fluticasone in such a setting (see point 2.19.6 above). Thus the alleged technical effect of (better) response to fluticasone in terms of slowing the decline in lung function would not be obtained for a part of the patient group defined in claim 1, namely those with prevalent ICS use. As a consequence, the alleged technical effect cannot be acknowledged in association with the patient group as defined in claim 1.

2.20 The respondent's counter-arguments did not convince the board for the following reasons.

2.20.1 The respondent pointed out that the results of D36 were not obtained exclusively with fluticasone. Rather, they were pooled results based on several ICS medicaments. The respondent contended that, therefore, D36 could not be considered conclusive on fluticasone therapy.

2.20.2 The board is of the view that the results and conclusions on the incident versus prevalent settings, which are reported in D36 as a class effect of ICS, may nevertheless be regarded as representative for fluticasone therapy, for the following reasons.

Specific information regarding the nature of the ICS agents can be found in D36a, which contains supplemental information to D36. Table S5 of D36a provides an overview for rate of FEV_1 change according to type of ICS medication (beclomethasone, fluticasone

or budesonide) and blood eosinophil level (without however distinguishing in this presentation between the incident and prevalent cohorts). According to Table S5, fluticasone was the most commonly administered of the three ICS.

The disclosure of Table S5 confirms that the data analysed in D36 could also have been stratified by type of ICS medication, as this information was indeed available and the authors looked at the ICS medicaments individually.

If the results of their analysis had differed significantly depending on the type of ICS medication used, the authors would have mentioned this in D36 as a relevant finding. Since no such differences are reported, it is reasonable to conclude that the different ICS agents, including fluticasone, based on their common anti-inflammatory mechanism, showed the same behaviour, which was accordingly presented in D36 for the ICS class as a whole. On the balance of probabilities, the board is persuaded that the conclusions reported in respect of the class apply equally to fluticasone.

2.20.3 In response to another argument by the respondent, it is not readily apparent that claim 1 can only refer to "incident" patients who are being newly introduced to ICS treatment. Firstly, as set out above, the wording of claim 1 provides no such limitation (see point 2.19.7 above). Secondly, there is also no technical reason why fluticasone should not be introduced following upon another ICS medication. Indeed, it is evident from D36, which identifies total cohort sizes of 16,601 for the prevalent cohort versus 10,074 for the incident cohort, that prevalent ICS use is a common clinical situation (see D36: Figure 2).

2.21 As a result of these considerations, the alleged technical effect cannot be acknowledged for the patient group as defined in claim 1 because this group also includes subjects with prevalent ICS use.

2.22 The established technical effect of the second distinguishing feature is thus that the claimed product will be administered to a specific subgroup of COPD patients.

2.23 In view of these considerations, the objective technical problem starting from the technical teaching of document D37 is the provision of an alternative pharmaceutical product comprising fluticasone, for use in the treatment of COPD in a specific patient group, wherein the pharmaceutical product reduces the rate of decline in lung function.

2.24 This problem is solved by the pharmaceutical product defined in claim 1 as granted, which provides fluticasone in the alternative form of fluticasone furoate, and by the envisaged use in the specific patient group characterised by a blood eosinophil count of ≥150 cells/µl.

Obviousness of the solution

2.25 It was not in dispute that the selection of a different fluticasone ester to provide an alternative product cannot render the claimed subject-matter inventive since this would have been an obvious alternative. The furoate ester was known, and the propionate and furoate esters are equivalent forms of fluticasone. Indeed, the respondent relied on Example 1, which is based on data obtained with fluticasone propionate rather than furoate, in support of its case in favour of an inventive step.

2.26 Thus the relevant aspect of the objective technical problem is the requirement for specifying a patient group.

2.27 As set out above, administering the claimed product to the patient group as defined in claim 1 is not associated with a specific technical effect.

2.28 The appellant contended that the selection of the patient group of claim 1 was arbitrary and therefore obvious.

2.29 For performing an arbitrary selection of a patient group, the person skilled in the art would not have required a particular incentive but merely the absence of disincentives.

2.30 With this criterion in mind, the following aspects would appear to be relevant for the assessment of obviousness.

2.30.1 The parameter defining the patient group of claim 1 was not unknown or new in the field. Blood eosinophil levels were routinely determined for characterising patients with COPD.

This is corroborated by D36, which is based on general-practice patient data, and also by D4, which reports that blood eosinophil levels were measured repeatedly during the ISOLDE study (see D4: page 1376, first paragraph). While both D4 and D36 are post-published, the ISOLDE study itself took place in the 1990s (see D9: page 1298, "Trial design"), and much of the observation period covered by D36 (2004-2016) is before the first priority date of the patent in suit (May 2014).

2.30.2 While COPD is typically characterised by neutrophilic inflammation and asthma by eosinophilic inflammation (D1: page 48, right-hand column, last full paragraph and D42: page 131, right-hand column, second paragraph), it was part of the common general knowledge that some patients in COPD may have an inflammatory pattern with increased eosinophils (see D33: page 6, right-hand column, penultimate paragraph).

2.30.3 D1 teaches that blood eosinophil count is a biomarker for increased eosinophilic airway inflammation which occurs during exacerbations in COPD (see D1: page 48, right-hand column, last paragraph). According to D1, peripheral blood eosinophil levels >2% are termed biomarker positive (see D1: page 49, left-hand column, "Methods"). Thus the cut-off value used in the patent in suit was also known in the prior art. D1 proposes that blood eosinophil count could be used to titrate systemic corticosteroid therapy to reduce exacerbations of COPD (see D1: page 48, right-hand column, penultimate paragraph). Moreover, frequent exacerbations in COPD had been found to accelerate the decline in long-term lung function (see D40: Abstract, "Conclusions").

D42 mentions "increasing evidence" that a significant subgroup of patients with stable COPD have chronic airway eosinophilia with a more steroid-responsive disease (see D42: abstract and page 132, first paragraph). In this context, D42 refers to studies that found higher acute responsiveness to oral or inhaled corticosteroids, in terms of acute improvement in FEV_1, in patients with a high sputum eosinophil count (see D42: page 132).

D41 teaches that blood eosinophilia is correlated to sputum eosinophilia, and also identifies a cut-off

value of 2% for blood eosinophils (see D41: page 665, right-hand column, second full paragraph).

In summary, eosinophilic inflammation in COPD, which may be characterised by the blood eosinophil count parameter, was being associated in the prior art with potentially increased responsiveness to corticosteroids, including inhaled corticosteroids, in particular with regard to the medicaments' acute effect on FEV_1 or their effect on exacerbations.

2.31 As pointed out by the respondent, there is no evidence in the cited prior art that directly suggests increased responsiveness of COPD patients with a high blood eosinophil level to ICS therapy (or specifically fluticasone therapy) in terms of reducing the long-term rate of decline in FEV_1, which is different from the acute effect of ISC on FEV_1 (see D33, page 24, right-hand column, last complete paragraph).

2.32 While the board does not dispute this, the prior-art teachings summarised in point 2.30.3 above do not suggest, either, that the envisaged therapeutic treatment would be unsuitable for the patient group specified in claim 1 - in other words, the prior art does not provide any disincentive in relation to the claimed patient group.

2.33 D37 discloses the claimed therapeutic effect of fluticasone (i.e. reducing the rate of decline in lung function) for patients with COPD in general.

Starting from D37, and seeking to define a specific patient group in accordance with the objective technical problem, the person skilled in the art would have considered the known group of subjects with a high blood eosinophil level since no disincentive or

technical prejudice against this patient group was known in the relevant therapeutic context.

In view of the prior art, the skilled person would have had no reason to be concerned that the therapeutic benefit in terms of reducing the decline in lung function might be unacceptably diminished in this patient group in comparison with the group comprising all COPD patients. Since COPD patients with eosinophilic inflammation were believed to potentially show higher responsiveness to steroid, including ICS, treatment, the skilled person might rather have had a hope of targeting the treatment to a group of potential responders. However, the decisive point in the case at hand is the absence of disincentives (see point 2.29 above).

2.34 In the circumstances set out above, the patient group defined in claim 1 as granted would have been an obvious solution to the problem of identifying a specific patient group.

2.35 As a consequence, the subject-matter of claim 1 does not involve an inventive step within the meaning of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated