JUDGMENT

**COURT OF APPEAL THE HAGUE**

Civil law team

Case number : 200.195.459/01

Case number district court : C/09/508351/ KG ZA 16-404

**judgment of 7 November 2017**

in the action between

**LEO PHARMA A/S**,

having its registered office in Ballerup, Denmark,

appellant in the appeal on the merits, respondent in the cross-appeal,

hereinafter to be called: Leo,

attorney: *Mr.* T.M. Blomme in Amsterdam, the Netherlands,

and

**SANDOZ B.V.**,

having its registered office in Weesp, the Netherlands,

respondent in the appeal on the merits, appellant in the cross-appeal

hereinafter to be called: Sandoz,

attorney: *Mr.* J.A. Dullaart in Naaldwijk, the Netherlands.

**1. The Dispute**

1.1. With the writ of 7 June 2016 Leo appealed against a judgment of 11 May 2016 rendered between the parties by the preliminary relief judge of the district court The Hague. In its statement of appeal with exhibits, Leo has advanced seven numbered grounds and a general ground of appeal. In its statement of defence as also statement of grounds of cross-appeal with exhibits, Sandoz has disputed the grounds of appeal and has also lodged a cross-appeal and has formulated a ground for this. Leo has responded to this in its statement of defence on the cross-appeal. In his e-mail message of 19 June 2017, Leo’s attorney communicated that the parties had made an arrangement on the costs of the proceedings on appeal. According to this arrangement, these are in total € 200,000, fully to be attributed to the main appeal.

1.2. Subsequently, the parties had the case argued on 29 June 2017, Leo by its abovementioned attorney and *Mr.* W.A. Hoyng, attorney in Amsterdam, assisted by patent attorney dr. J.H.J. den Hartog and Sandoz by *Mr*. D.F. de Lange and *Mr.* R. Broekstra, attorneys in Amsterdam, all on the basis of submitted pleading notes. On this same date, Leo submitted a document containing additional exhibits, with the exhibits 24 up to and including 27, and Sandoz submitted a document containing exhibits, with the exhibits 31 up to and including 35, and an additional exhibit 36. Finally, the parties requested that judgment would be rendered.

**2. The Facts**

2.1. The facts established by the preliminary relief judge in the judgment of 11 May 2016 are not in dispute. The court of appeal will also depart from them.

2.2. Leo is a globally operating producer of medicinal products. It *inter alia* markets medicinal products for the external treatment of psoriasis with calcipotriol as active component. Psoriasis is a disease in which cells in the skin are produced too rapidly, as a result of which red spots and flakes develop. One of the medicinal products marketed by Leo in the Netherlands is Dovobet, an ointment of a combination of the active components calcipotriol and betamethasone (in the form of the diproprionate salt) and a solvent (Arlamol-E).

2.3. Sandoz is part of the Novartis group and producer of generic medicinal products in the Netherlands.

2.4. Leo is the proprietor of the European patent EP 2 455 083 B1 (hereinafter EP 083 or the patent). This patent is entitled "*Pharmaceutical composition for dermal use comprising calcipotriol and betamethasone for treating psoriasis".* The patent was granted on 18 September 2013 further to an application of 27 January 2000, invoking the priority on the basis of the national Danish application of 23 April 1999 with number DK 1999 00561 (hereinafter: DK 561). The patent *inter alia* applies in the Netherlands. The claims are the following in the original English language:

1. A non-aqueous topical pharmaceutical composition in the form of an ointment, a cream, a lotion, a liniment or other spreadable liquid or semi-liquid preparation for dermal use in the treatment of psoriasis, sebopsoriasis or seborrheic dermatitis in humans and other mammals, said composition comprising a first pharmacologically active component A consisting of calcipotriol and a second pharmacologically active component B consisting of betamethasone or an ester thereof and at least one pharmaceutically acceptable carrier, solvent, or diluent.

2. A pharmaceutical composition for use according to claim 1, wherein component B consists of a betamethasone ester, such as the 17-valerate or 17,21-dipropionate.

3. A pharmaceutical composition for use according to any one of the preceding claims in the form of a mono-phase composition.

4. A pharmaceutical composition for use according to the preceding claim which is an ointment.

5. A pharmaceutical composition for use according to claim 1 characterised in that the difference between the optimum stability pH of said first component A and the optimum pH of said second component B is at least 1 further comprising at least one solvent component C selected f r om the group consisting of:

(i) compounds of the general formula R3(0CH2C(R1 )H)xOR2 (I) wherein x is in the range of 2-60, R1 in each of the x units independently is CH3, R2 is straight chain or branched C1 -20 alkyl or benzoyl, and R3 is H or phenylcarbonyloxy;

(ii) di-(straight or branched)-C4-10 alkyl esters of C4-C8 dicarboxylic acids;

(iii) straight or branched C12-18-alkyl benzoates;

(iv) straight or branched C2-4-alkyl esters of straight or branched C10-18-aikanoic or alkenoic acids;

(v) propylenglycol diesters with C8-14-alkanoic acids; and

(vi) branched primary C I 8 - 2 4 alkanols.

6. A composition for use according to the preceding claim, wherein said component C is selected from compounds of the general formula H(OCH2C(R1)H)xOR2 (II) where R l , x, and R2 are as defined in claim 5, and mixtures thereof.

7. A composition for use according to claim 6. wherein said component C is polyoxypropylene-15-stearyl ether.

8. A pharmaceutical composition for use according to claim 5, containing 0.0001 to 0.025% w/w of said component A, 0.005 to 0.1% w/w of said component B, and 1 to 20% w /w of said solvent component C.

9. A pharmaceutical composition for use according to claim 1, wherein, in the treatment, the composition is applied topically once or twice daily in a medically sufficient dosage.

2.5. The claims are the following in the undisputed Dutch translation:

1. Niet-waterig topisch farmaceutisch preparaat in de vorm van een zalf, een crème, een lotion, een smeersel of ander smeerbaar vloeibaar of half-vloeibaar preparaat voor dermaal gebruik bij de behandeling van psoriasis, sebopsoriasis of seborroïsche dermatitis bij mensen en andere zoogdieren, welk preparaat omvat een eerste farmacologisch actieve component A bestaande uit calcipotriol en een tweede farmacologisch actieve component B bestaande uit betamethason of een ester daarvan en ten minste een farmaceutisch aanvaardbare drager, oplosmiddel of verdunningsmiddel.

2. Farmaceutisch preparaat voor gebruik volgens conclusie 1, waarbij component B bestaat uit een betamethasonester, zoals het 17-valeraat of 17,21-dipropionaat.

3. Farmaceutisch preparaat voor gebruik volgens een van de voorgaande conclusies in de vorm van een monofasepreparaat.

4. Farmaceutisch preparaat voor gebruik volgens de voorgaande conclusie, dat een zalf is.

5. Farmaceutisch preparaat voor gebruik volgens conclusie 1, met het kenmerk dat het verschil tussen de pH voor optimale stabiliteit van de eerste component A en de optimale pH van de tweede component B ten minste 1 is, verder omvattende ten minste een oplosmiddelcomponent C gekozen uit de groep bestaande uit:

(i) verbindingen met de algemene formule R3 (OCH2C(R1)H)xOR2 (I) waarin x ligt in het traject van 2-60, R1 in elk van de x eenheden onafhankelijk CHS is, R2 recht of vertakt C1 – 20 -alkyl of benzoyl is, en R3 H of fenylcarbonyloxy is;

(ii) di- (recht of vertakt) -C4-10-alkylesters van C4-C8dicarbonzuren;

(iii) rechte of vertakte C12-18-alkylbenzoaten;

(iv) rechte of vertakte C2-4 -alkylesters van rechte of vertakte C10-18-alkaan- of alkeenzuren;

(v) propyleenglycoldiesters met C8-14 alkaanzuren; en

(vi) vertakte primaire C18 - 24 alkanolen.

6. Preparaat voor gebruik volgens de voorgaande conclusie, waarbij de component C gekozen is uit verbindingen met de algemene formule H(OCH2C(R1 )H)xOR2 (II) waarin R l , x en R2 zijn zoals gedefinieerd in conclusie 5, en mengsels daarvan.

7. Preparaat voor gebruik volgens conclusie 6, waarbij de component C polyoxypro-pyleen-15-stearylether is.

8. Farmaceutisch preparaat voor gebruik volgens conclusie 5, dat 0,0001 tot 0,025% w/w van de component A, 0,005 tot 0,1% w/w van de component B en 1 tot 20% w /w van de oplosmiddelcomponent C bevat.

9. Farmaceutisch preparaat voor gebruik volgens conclusie 1, waarbij het preparaat bij de behandeling een of twee maal per dag in een medisch voldoende dosering wordt aangebracht.

2.6. The description of EP 083 *inter alia* contains the following passages:

[0002] In the treatment of a number of conditions using dermal application, e.g. in the treatment of psoriasis, it is often indicated to employ a combination treatment incorporating two or even more different pharmacologically active compounds. Thus, in the treatment of e.g. psoriasis, it is common to use a combination treatment involving a steroid compound, such as a corticosteroid compound, and a vitamin D analogue such as calcipotriol, and where each of the active compounds are formulated in separate preparations.

[0003] Clinical studies have been conducted in psoriasis patients wherein calcipotriol was administered in the morning and betamethasone dipropionate or valerate in the evening. Combination therapy was more effective than monotherapy. (...)

[0004] Until now a topical pharmaceutical composition comprising a combination of a vitamin D analogue and a topical steroid has not been described. Moreover, these two types of compounds often have optimum stability values of pH that differ significantly from one another making it non-obvious to attempt to prepare a topical pharmaceutical preparation containing a steroid compound together with a vitamin D analogue. (...)

[0005] The following example describes the difficulties encountered when the skilled person wishes to prepare a combination composition for topical use comprising both a vitamin D or a vitamin D analogue or derivative and a topical steroid: The vitamin D analogue calcipotriol, as well as other examples of vitamin D analogues, requires a pH value above 8 for maximum stability, whereas-corticosteroids such as Betamethasone (9- fluoro-11, 17, 21- trihydroxy - 16- methylpregna- 1, 4- diene- 3, 20- dione) require p H values in the range of 4- 6 for maximum stability. Since the base auxiliary materials and additives traditionally used in preparing topical formulations , such as creams and/or ointments, involve having some kind of acid or alkaline nature or reaction ability, it has therefore hitherto not been possible to combine the two active compounds in one single formulation while maintaining good stability of the active compounds.

[0006] Consequently, physicians have had to resort to letting patients under this type of two- component regimen perform sequential application of two creams/ointments, each containing one of the compounds formulated at its maximum stability pH. This may lead to incompatibility of the preparations so that patients must, e.g., apply one cream/ointment in the morning and the other in the evening. Needless to say, patient compliance as well as correct administration dosage is a problem under such circumstances. Richards, H.L. et al. report in J Am Acad Dermatol 1999 Oct; 41(4):581-3 on a study of patients with psoriasis and their compliance with medication. They report that poor compliance with treatment advice in chronic conditions, such as psoriasis, represents a major challenge to health care professionals: Thirty-nine percent of participants reported that they did not comply with the treatment regimen recommended. The noncompliant group had a higher self-rated severity of psoriasis, were younger, and had a younger age at onset than those who w e r e compliant. The noncompliant group reported that psoriasis had a greater impact on daily life.

(...)

[0012] Fig. 1 is a graphic illustration of the percentage change in PASI score obtained during 4 weeks of clinical trial where the efficacy of a preparation according to the invention containing calcipotriol hydrate *(*52.2µ.g/g*)* and betamethasone dipropionate (0.643mg/g) is compared to that of a preparation in the same vehicle containing only calcipotriol hydrate (52.2µg/g) and a preparation in the same vehicle of betamethasone dipropionate (0.643mg/g). Fig. 1 shows an efficacy of the preparation of the invention which by far exceeds the efficacy obtainable by the two single component preparations. The change in PASI score reflects in the group of patients treated with the preparation of the invention a success of treatment of psoriasis hitherto unattainable by treatment with commercial preparations containing either calcipotriol or betamethasone, or by alternating treatment with such commercial preparations (cf.) thus proving the advantage of having the t w o active components present in the same preparation. (EOT=end of treatment).

Fig. 2 is a table showing the figures for percentage change in PASI score at each visit and end of treatment for the same clinical trial as described for Fig. 1. (...)

**(…)**

[0020] The composition according to the invention provides the following therapeutic advantages in the treatment of skin diseases, such as psoriasis, sebo-psoriasis and related disorders, compared to the single compound therapy or combination therapy of the prior art:

[0021] A clinical investigation has showed that treatment of psoriasis patients with a composition according to the invention comprising calcipotriol and betamethasone resulted in a faster onset of healing and a more effective healing of plaques than patients treated with only one of the active compounds.

[0022] The composition of the invention, which combines a vitamin D analogue and a topical steroid, provides synergy in the form of additional benefit to the patient apart f r om the direct therapeutic value of the active substances. It has been shown that the skin irritative side effects of a vitamin D analogue, such as calcipotriol, is alleviated by the simultaneous application of a steroid, such as betamethasone, onto psoriatic skin, an effect that is only attainable using a two- component or multi- component treatment regimen where a vitamin D analogue and a steroid cannot be applied simultaneously to affected skin due to incompatibility of the praparations. When both a vitamin D analogue and a topical steroid are used in a combination treatment of psoriasis it has hitherto been necessary to use separate applications, typically one in the morning and the other in the evening, making it impossible to obtain any synergistic effect of the two types of active compounds (cf. Ortonne, J.P., Nouv. Dermatol., 1994, 13 (10), p. 746- 751). or where a certain degree of synergistic effect, such as less skin irritation, has been reported for a two- component regiment (cf. Kragballe, K. et al. Br J Dermatol 1998 Oct; 139 (4): 649- 54, and Ruzicka, T. et Lorenz, B. Br J Dermatol 1998, 138 (2), 254- 58) a substantial proportion of psoriasis patients will not benefit due to non- compliance with the treatment regimen.

[0023] Satisfactory medical treatment of skin disorders, such as psoriasis, can be attained in a shorter period of time using the composition according to the invention resulting in a reduction of steroid side effects, such as skin atrophy and rebound. Besides, it can be anticipated that even a milder acting steroid of group I, such as hydrocortisone which is presently not administered for psoriasis treatment, will be efficient in reducing or even eliminating the skin irritation which often follows calcipotriol treatment.

[0024] Thus, the tolerance of the treatment will be considerably improved due to reduction of side effects of the active compounds.

2.7. EP 083 *inter alia* contains the following figures 1 and 2:





2.8. EP 083 has been granted further to a divisional application of EP 1 178 808 (hereinafter: EP 808) which was granted on 30 May 2012. EP 808 pertains to a '*Non-aqueous pharmaceutical composition for dermal use to treat psoriasis comprising a vitamin D, a corticosteroid and a solvent component'.*

2.9. After opposition proceedings conducted against EP 808, the opposition division of the European Patent Office (OD) maintained the patent according to the first auxiliary request, in which the definition of the solvent was limited to Arlamol-E. The OD *inter alia* considered the following:

(3.3.2)

The selection of the solvent component C as defined in claim 1 (this is the same solvent component C as in claim 5 of EP 083, court of appeal) of the contested patent is however obvious in view of the teaching of D12 in combination with D20a for solving the problem posed. In D20a, the skilled person finds a clear indication to use the compounds C(ii), (iv) and (v), in particular isopropyl myristate, for dissolving calcipotriol in non-aqueous formulations in order to provide stable formulations of the vitamin D analogue with a lipophilic base. Isopropyl myristate belongs to the group of compound C(iv) of claim 1 as granted and is used in all the examples of D20a.

Compound C of claim 1 comprises six large groups of solvents, each belonging to a different group of compounds. Even if experimental data have been provided for embodiments falling within the groups of compound C(i),(ii),(iv),(v) and (vi) to show that the problem has been solved, the skilled person would have been prompted to try, according to the teaching of D20a, any of the proposed solvents falling within the definition of compound C(ii), (iv) and (v) and to select the preferred isopropyl myristate as solvent for providing a stable composition comprising components A and B with a reasonable expectation of success and without the involvement of an inventive merit.

Thus, the requirements of art. 56 EPC of claim 1 of the MR are not fulfilled.

And furthermore with regard to the first auxiliary request with the limitation to Arlamol-E:

(4.2.2.2)

It is common general knowledge that combining corticosteroids and vitamin D analogues in a single formulation for treating psoriasis provides better patient compliance and results in less side effects (in D11 and in D60, page 132). Moreover, it is known that calcipotriol is instable in acidic media (D20a and D12). In D20a, it is further suggested to formulate the instable vitamin D analogue in a hydrophobic or anhydrous solvent selected from fatty acid esters, higher alcohols and propylene carbonate and a lipophilic base such as white petrolatum or a mixture of white petrolatum and liquid paraffin (claim 1 of 020a). The examples show stable non-aqueous ointments using isopropyl myristate as solvent.

2.10. Leo and a number of opponents have appealed against this decision. This appeal has not been decided on yet.

2.11. The applications for both EP 083 and EP 808 are based on the application WO 00/64450 (hereinafter WO 450). Claim 1 of WO 450 is the following:

1. A pharmaceutical composition for dermal use, said composition comprising a first pharmacologically active component A consisting of at least one vitamin D or vitamin D analogue and a second pharmacologically active component B consisting of at least one corticosteroid.

2.12. In subsequent claim 6 of WO 450 component A is limited to calcipotriol (or the hydrate), in subsequent claim 7 betamethasone is *inter alia* mentioned for component B. In claim 18 of WO 450 the same 6 groups of solvent C are mentioned for the stabilisation as in claim 5 of EP 083. Just like the patent, WO 450 contained figure 1 with the results of a comparative trial and the same explanation of figure 1 as in [00012] of the patent.

2.13. In DK 561, filed on 23 April 1999 and in EP 083 designated as the priority document, a solution is claimed for the stability problem that occurs in the production of a combined application of a vitamin D analogue and a corticosteroid. DK 561 provides in claim 1 a non-aqueous composition with the abovementioned components (A and B) and at least one solvent from some six designated classes (C, again see claim 5 of EP 083). In the subsequent claims, calcipotriol and betamethasone are specifically mentioned. DK 561 did not contain a figure 1 with the results of a comparative trial or the explanation as referred to in [0012] of the patent either. Claim 1 of DK 561 is the following:

1. A non-aqueous pharmaceutical composition for dermal use, said composition comprising a first pharmacologically active component A consisting of at least one vitamin D analogue; a second pharmacologically active component B consisting of at least one corticosteroid, the difference between the optimum stability pH of a first pharmacologically active compound A and the optimum stability pH of a second pharmacologically active component B being at least 1; and at least one solvent component t selected from the group consisting of:

(i) compounds of the general formula R3(OCH2C(R1)H)xOR2 (I) wherein x is in the range of 2-60, R1 in each of the x units independently is CHS, R2 is straight chain or branched C1-20 alkyl or benzoyl, and R3 is H or phenylcarbonyloxy;

(ii) di-(straight or branched)-C4-10 alkyl esters of C4-C8 dicarboxylic acids;

(iii) straight or branched C12-18-alkyl benzoates;

(iv) straight or branched C2-4-alkyl esters of straight or branched C10-18-alkanoic or alkenoic acids;

(v) propylenglycol diesters with C8 - 14 - alkanoic acids ; and

(vi) branched primary C1 8 - 24 alkanols .

2.14. Opposition was filed with the EPO against EP 083. In April 2016 Sandoz intervened in these proceedings. In its written decision of 6 October 2016, the OD maintained the patent in unamended form. The relevant considerations on inventive step by the OD are the following:

6.1 The invention concerns a non-aqueous topical pharmaceutical composition for dermal use in the treatment of psoriasis, sebo-psoriasis or seborrheic dermatitis which comprises calcipotriol (component A) and betamethasone or an ester thereof (component B) and at least one pharmaceutically acceptable carrier, solvent, or diluent.

6.2 The problem defined in the patent is the provision of stable combination therapy of psoriasis (sebopsoriasis or seborrheic dermatitis) in the form of a pharmaceutical composition for dermal use comprising calcipotriol (comp. A) and betamethasone (comp. B). According to the patent, said composition has a higher patient compliance (page 4, [0022]) and results in a substantial improvement in quality of life of the patients treated by this therapy (page 2, [007]). In addition, it is stated that the composition provides therapeutic advantages over single compound therapy or combination therapy disclosed in the art (page 4, [020]).

6.3 In view of the technical problem defined in the patent, 08 and 021 are the most relevant documents cited in the proceedings which can equally qualify as closest prior art for assessing inventive step. They address the same purpose as the present patent and has the two active components of claim 1: only these two documents disclose an effective topical treatment of psoriasis using calcipotriol and an ester of betamethasone (betamethasone valerate in 08, betamethasone dipropionate in 021). Documents D7, D9-D10, D12, D16-D17 cannot qualify as closest prior art for the following reasons: D9 is not dedicated to the treatment of psoriasis and has a different purpose. D7, D10, D12, D16-D17 have the same purpose (treatment of psoriasis) but less features in common with the present invention than D8 or D21. D7, D10, D12 disclose a treatment by monotherapies. D16 and D17 disclose combination therapies which do not explicitly include the two specific active agents defined in the claims.

*6.4 Problem solution approach starting from D21*

The distinguishing features, with D21 is the use of same components A and B (betamethasone dipropionate) administered as a single topical formulation (first difference) which is non aqueous (second difference). The effect identified in the patent is linked to the provision of a better treatment of psoriasis using a fixed administration of components A and B. Starting f r om D21 as closest prior art, the technical problem to be solved may be formulated as the provision of an improved topical combination treatment of psoriasis.

The solution as proposed in claim 1 is characterized by the use of components A and B administered as a single topical formulation (first difference) which is non aqueous (second difference).

6.4.1 First, it has to be assessed whether the subject-matter of claim 1 plausibly solves the problem identified above. Example 1 of the patent discloses the preparation of a non-aqueous ointment comprising calcipotriol as hydrate (A) and betamethasone as dipropionate (B) and specific excipients.

Drawings 1-4 comprise the results of a clinical trial wherein a composition comprising betamethasone dipropionate and calcipotriol (hydrate) was more effective than the respective monotherapies in patients suffering from psoriasis. The percentage change in PASI score (psoriasis area and severity index) was very high for the fixed combination. Therefore it is already credible f r om the disclosure of the application that an effect is linked to the administration of A and B as a fixed (single) composition.

Post published document D11 is regarded to be relevant to back-up the teaching already present in the original application concerning an improved therapeutic effect in the treatment of psoriasis. The data of D11 are not a direct comparative data over the prior art D21 (e.g. based on a randomised clinical trial) but provide a "meta-analysis" which compares the results of a phase III clinical trial with a two-compound formulation product ("TCP" in D11) with the results of known topical treatment of psoriasis (including monotherapies and combination treatment) and based on different clinical trials reported in the literature. An improvement over the combination used in D21, namely sequential administration of calcipotriol (Daivonex in the morning) and betamethasone dipropionate (Diprosone in the evening) is derivable from D11 (page 232, table 3, 12th column).

The Patentee made plausible that this meta-analysis is a valid model for comparing existing clinical trials based on the declaration of Dr. Ryttov (D31, page 2, section 6). Concerning the outcome of this analysis, D11 provides sufficient evidence that the once daily use of the fixed composition (TCF) has a greater efficacy than all the other common topical treatment of psoriasis involving calcipotriol and/or betamethasone esters as mono or combination therapies, including these of D21 (see i.a. page 236, conclusion together with figure 4, page 233 and figure 6, page 234).

As indicated by the parties, no synergy can be attributed to the composition claimed over the combination known from D21. The OD, in the present case, is of the opinion that a synergy is not required. In the present case, the unexpected effect is linked to a better efficacy using the fixed composition, either once or twice daily, over all the existing therapies over 4 weeks of use (see D11, figures 4 and 6; page 235, left-hand col., lines 6-9). Concerning the arguments that the improvement is not statistically significant due to the very slight improvement obtained or to the margin of errors present in the data, the OD cannot agree. There is no serious reason to question the statistically significance of the data analyzed in D11. On the contrary, a clear trend to a therapeutic improvement is confirmed by D11, namely a better and unpredictable efficacy combined with a simpler treatment when using the fixed composition over all the existing therapies. As the result of this improvement, a better patient compliance is plausibly obtained. The effect cannot be seen as a mere bonus effect and D11 backs up all the preliminary teaching originally disclosed in the application.

For sake of completeness, the feature "non-aqueous" does not contribute to the solution of the posed problem. The posed problem can still be solved by immediate application of any fresh (aqueous or non-aqueous) preparation comprising the two active agents.

6.4.2 Concerning the scope of the claims, there are no sound reasons to doubt that the results can be transferred to combinations comprising betamethasone or other betamethasone esters than betamethasone dipropionate as corticosteroid component, or to the treatment of the other related diseases (sebo-psoriasis, seborrhoeic dermatitis).

Moreover, the OD is satisfied that the claims contain all the essential features which contribute to the solution of the posed problem. It was contested that specific solvent component C was mandatory to stabilize the fixed composition. This view cannot be followed since it appears that component C improves the long-term stability of the fixed compositions, but does not contribute to the enhanced antipsoriatic efficacy. This feature is therefore not essential and the posed problem can still be solved without solvent C (e.g. by immediate application of a fresh preparation comprising the two incompatible active agents).

As a conclusion, claim 1 comprises all the essential features which are necessary to solve the problem defined previously over its whole scope.

6.4.3 The present solution is inventive since it was not rendered obvious by any of the cited prior art documents taken alone or in combination, that the simultaneous administration of calcipotriol and betamethasone as a fixed (non-aqueous) composition as covered by claim would provide a therapeutic effect which is superior to a treatment wherein both components are administered sequentially at different times of the day. A fortiori further restriction of the compositions claimed to "non aqueous"compositions was not suggested in the art.

P pointed out that D28 discouraged a skilled practitioner to combine the two active agents of D21 into a single formulation due to the instability of the fixed composition comprising a corticosteroid and a vitamin D analogue/derivative. Although not necessary in the present assessment of the obviousness of the solution, D28 could be seen as a further pointer that a skilled person facing the problem defined previously would not have chosen the fixed composition of the claims as an obvious solution to the problem mentioned above.

The same reasoning applies mutatis mutandis to claims 2-9.

2.15. For the month of April 2016, Sandoz had included its generic medicinal product “*Calcipotriol/Betamethason Sandoz 50 microgram/g + 0,5 mg/g, zalf*” for the treatment of psoriasis in the G-standard. This product contains another solvent than Arlamol-E, i.e. oleyl alcohol.

2.16. In its letter of 17 March 2016, Leo pointed out to Sandoz that the abovementioned product was infringing EP 083. Hereupon, in its letter of 22 March 2016 Sandoz replied to Leo that it takes the position that EP 083 is null in the Netherlands and that, also if the nullity of EP 083 is remedied, its product would not infringe it.

2.17. In the document registered on 5 April 2016 Leo partially waived the Dutch part of the patent. Herein, the patent’s claim 2 was limited to betamethasone diproprionate. Claim 2 is currently as follows:

2. Farmaceutisch preparaat voor gebruik volgens conclusie 1, waarbij component B bestaat uit de 17,21- dipropionaatester van betamethason.

2.18. The publications quoted in paragraph [0022] of the description and in these proceedings are – as far as relevant here – as included below:

2.18.1. With reference to the option to combine calcipotriol with other components, the quoted publications include the following:

Patel et al: (June 1998)

Specifically, hydrocortisone- 17-valerate 0,2% ointment, 12% ammonium lactate lotion and 6% salicylic acid can result in its degradation. Refrigeration may slow the degradation of calcipotriene but does not prevent it completely.

Lebwohl: (1997)

In combining calcipotriene with other agents, it should be stressed that both medications should be applied at different times. If calcipotriene is mixed with other agents, the two must be proven to be compatible because calcipotriene is easily inactivated.

Kragballe (1995):

Because calcipotriol, like other D3 vitamins, requires a relatively high pH to be stable, the topical calcipotriol formulations in general should not be mixed with other drugs or vehicles.

2.18.2. The publication by Ruzicka et al. (1998) describes a study, in which calcipotriol monotherapy is compared to a combination treatment with calcipotriol and betamethasone valerate. This publication contains the following passages:

The combination therapy was more effective, as assessed by all evaluated variables; moreover, patients showing insufficient response to calcipotriol alone after 2 weeks showed a regression of psoriatic lesions using the combination regimen. Thus, the combination of calcipotriol and topical steroids is recommended as the therapy of first choice for patients who do not respond well to treatment with 2 weeks of calcipotriol alone. Furthermore, this combination reduces the hazards associated with the long-term use of topical corticosteroids (atrophy and rebound) as well as the irritation associated with calcipotriol.

(...)

As calcipotriol and betamethasone valerate work by interacting with different receptor subtypes (vitamin D or glucocorticoid receptors), an additive or synergistic effect could theoretically be expected.

Therefore, the combination of topical calcipotriol and betamethasone valerate was assessed to determine whether there is such an effect in those patients who do not respond to calcipotriol alone. The results clearly show that the combination of both drugs leads to an additive clinical effect in terms of reduced psoriatic symptoms.

2.18.3. The publication by Ortonne et al. (1994) describes a study, in which an alternating monotherapy (calcipotriol ointment in the morning and betamethasone diproprionate ointment in the evening versus calcipotriol ointment in the morning and in the evening) of psoriasis was evaluated. This publication includes the following with respect to the medical patient compliance observed in the study in question in the French and English translation:

Observance thérapeutique:

Pour l’ensemble des patients, il n'a pas été observé d'écarts au schéma thérapeutique. Aucune différence n’a été mise en évidence entre les groupes en ce qui concerne le nombre de grammes de pommade utilises. En aucun cas, leur utilisation n’a dépassé 100g par semaine."

Medical Adherence:

All patients adhered to the treatment regimen, with no deviations in the study protocol. There was no statistical difference highlighted between the two groups with regard to the number of grams of ointment used. There were no instances where their use exceeded 100 g per week.

2.18.4. In 2011 Van de Kerkhof et al. (2011) published the results of a literature study, in which the effectivity of various treatments of psoriasis were compared to each other. Herein, the abbreviation PASI is short for ‘Psoriasis Area and Severity Index’, in which the index indicates the scope and seriousness of the disease. TCP (‘Two-Compound Formulation’) refers to the combination treatment with calcipotriol and betamethasone. This publication *inter alia* contains figure 6 with the accompanying passage (the line at “calcipotriol od + betamethasone dipropionate od” is particularly important):



2.19. The English parts of EP 808 and EP 083 were the subject of proceedings in the United Kingdom between Teva and Leo. In the proceedings in the first instance, the court assessed in the judgment of
6 October 2014 that both patents are null because of lack of inventive step. This judgment was reversed on appeal on 28 July 2015. In those proceedings, claim 1 of EP 083 was only defended in a restricted manner to also containing the component C according to a subgroup of (i).

2.20. Sandoz has meanwhile brought its generic calcipotriol/betamethasone product on the market in the Netherlands.

**3. The Dispute**

3.1. In the first instance, Leo demanded that the preliminary relief judge, in a judgment with immediate effect:

I. forbid Sandoz to infringe patent EP 083, in particular by its Calcipotriol/Betamethason Sandoz 50 microgram/g + 0,5 mg/g, zalf, subject to an immediately due penalty sum of € 500.000 for every violation of this order, to be increased with a further penalty of € 50.000 for every day or part of a day that a violation continues, with a maximum of € 5.000.000 per event;

II. order Sandoz to provide, within four (4) weeks after the serving of the order that will be rendered in this case, to the legal counsel of LEO Pharma, a report approved by a registered accountant of all companies and/or persons to which it has sold and/or delivered the infringing products Calcipotriol/Betamethason Sandoz 50 microgram/g + 0,5 mg/g, zalf, with a specification of the income received and the profits made, all subject to an immediately due penalty sum of
€ 50.000 for every violation of this order, to be increased with a further penalty sum of € 10.000 for every day or part of a day that a violation continues, with a maximum of € 100.000 per event;

III. order Sandoz to send, within one (1) day after the serving of the order that will be rendered in this case, a rectification letter and thereby recalling all infringing products, with exclusively the following content (or any other text to be determined by the Preliminary Provisions Judge in good justice), printed on the company paper of Sandoz in the usual company format, without any further additions, to all companies and/or persons to which it has sold or offered the present products Calcipotriol/Betamethason Sandoz 50 microgram/g + 0,5 mg/g, zalf, addressed to their board, all subject to an immediately due penalty sum of € 50.000 for every violation of this order, to be increased with a further penalty sum of € 10.000 for every day or part of a day that this violation continues; as well to send the evidence of the sending thereof at the same instance to the lawyer of LEO Pharma, subject to an immediately due penalty sum of € 10.000 for a violation of this latter order; all together with a maximum of € 150.000 per event:

[date]

URGENT!

Dear Sir, Madam,

The Preliminary Provisions Judge of the Court of The Hague has ordered in his decision of [date] that we have infringed the patent EP 2 455 083 B1 of the company LEO Pharma, inter alia by offering and/or selling to your company Calcipotriol/Betamethason Sandoz 50 microgram/g + 0,5 mg/g, zalf. We have been ordered to cease this infringement with immediate effect and to recall said products. We will fully compensate you for any damages suffered.

Sandoz B.V.

The Board”

IV. orders Sandoz to pay the reasonable and proportional procedural costs on the basis of Article 1019h DCCP, to be increased with the statutory interest as of fourteen days, or at least as of a term to be deemed reasonable by the Preliminary Provisions Judge, after the decision that will be rendered in this case, if Sandoz has not paid the costs by that term;

V. orders Sandoz to pay the aftercosts of € 131 without serving of the decision or € 199 with serving of the decision, the latter amount to be in-creased with statutory interest if Sandoz has not paid this amount within the (statutory term) of two days, or at least within a term that is deemed reasonable by the court, after serving of the decision that is rendered in this case.

3.2. Leo based these claims on Sandoz infringing the claims 1, 2, 3, 4 and 9 of EP 083 with the trade in its generic product. As Sandoz has meanwhile entered the (Dutch) market with its generic product, Leo Pharma has an urgent interest in the allowance of its claims.

3.3. Sandoz has *inter alia* advanced the following defences. Claim 1 and the other claims of EP 083 invoked by Leo are null because of lack of inventive step. As Leo has abandoned the stability problem, it merely invokes a combination product that would have an improved effect. This effect can (at least partially) be traced to (expected) improved patient compliance. The fact that the patient compliance improves by a combination product was generally known though. The synergistic effect invoked by Leo may at best be a bonus effect of a non-inventive measure and is furthermore not made plausible in the original documents nor in the patent. The study by Van de Kerkhof dates from 11 years after the relevant dates and may not count as substantiation of the claimed effect. Furthermore, the improved/synergistic effect cannot be deduced from it either. Not only is Van de Kerkhof unable to link the cause of a possible improvement to a synergistic effect, it is not even certain that there is an improvement and the extent of this possible improvement is also insignificant.

3.4. In the judgment of 11 May 2015, the preliminary relief judge rejected Leo’s claims. He was of the preliminary opinion that it is open to serious doubt whether EP 083 would survive proceedings on the merits to be initiated or the opposition proceedings that were already pending. In his assessment, the solution of claim 1 and 2 of EP 083 to combine calcipotriol and betamethasone (dipropionate) in an ointment was obvious to the average skilled person to improve patient compliance. He provisionally rejected Leo’s argument that there is also a synergistic effect that contributes to the technical effect and thus to the patent’s inventive step, because this effect has not been made plausible in the patent and is also not an established fact on the basis of the study by Van de Kerkhof.

3.5. In the main appeal, Leo requests that the court of appeal reverse the judgment by the preliminary relief judge and allow its claims after all, ordering Sandoz to pay the costs of the appeal, including the subsequent costs, to be increased by the statutory interest. Leo has advanced one general ground and seven numbered grounds of appeal against the judgment. The grounds will be described in more detail below as far as important. Sandoz has disputed the grounds in a substantiated manner.

3.6. In the cross-appeal, Sandoz requests that the court of appeal quashe the judgment by the preliminary relief judge to the extent that it concerns the order to pay costs and order Leo to pay
€ 121,658, ordering Leo to pay the reasonable and proportionate costs of the appeal in conformity with section 1019h DCCP, to be increased by the statutory interest pursuant to article 6:119 Dutch Civil Code over this amount from 14 days after the date of judgment until the day of full payment. Sandoz has advanced one ground, implying that the preliminary relief judge was wrong not to award an amount of € 30,000 on the basis that Sandoz had made it insufficiently clear that these costs had been incurred in the scope of these proceedings. Leo has disputed the ground in a substantiated manner.

**4. The Assessment**

*ground 1: novelty*

4.1. Leo was right to submit a ground against the assessment by the preliminary relief judge that the invoked claims are not new over the parent patent WO 450. Leo has advanced undisputedly that this nullity argument cannot be maintained in view of the decision by the Enlarged Board of Appeal on partial priority (decision by EBA of 29 November 2016, G 0001/15, ECLI:EP:BA:2016:G000115.20161129). This cannot lead to a nullification of the challenged judgment because, as will be explained below, Sandoz’ inventive step attack is successful. To this extent, also Leo’s ground 1 fails.

*grounds 2 and 5: inventive step*

4.2. The court of appeal shares the conclusion of the preliminary relief judge that Leo’s claims must be rejected because a fair chance exists that the TBA, different from the OD, will revoke the claims of the patent invoked by Leo on appeal. For, in our provisional assessment, the subject matter claimed in these claims is obvious for the average skilled person from Ortonne (see above no. 2.18.3). This will be explained below on the basis of the so-called *problem-and-solution-approach,* which both parties also employ in their arguments. For this, the court of appeal assumes with the parties that the reference date for the assessment of the inventive step is the application date of the patent in this case (in the scope of the inventive step attack Leo does explicitly not invoke the priority). For that matter, it has not been asserted or proven that in this case it would be relevant for the assessment of the inventive step whether the application date or priority date is departed from.

4.3. The fact that Ortonne forms a suitable starting point for the assessment of the inventive step of EP 083 is not in dispute. Leo itself assumes that Ortonne is the closest prior art (paragraph 6.5 of the originating summons and paragraph 22 of the pleading notes on appeal).

4.4. Nor is it in dispute that there are two differences between Ortonne and the matter claimed in the claims 1 and 2 of EP 083. First, the active substances calcipotriol and betamethasone (dipropionate) are administered in one combination product instead of alternatingly, i.e. an ointment with only one active substance in the morning and another ointment with exclusively the other active substance in the evening. Secondly, this combination product is non-aqueous.

4.5. In addition, it is beyond dispute that there a positive effect of the first distinguishing feature mentioned (the combination product) is that it increases patient compliance. The parties also agree that this same distinguishing feature has a negative effect. The choice for a combination product leads to a stability issue. For, as also described in the patent specification, it was known on the application date that calcipotriol and betamethasone (dipropionate) are stable in different pHs (paragraph [0005] of the patent specification). This is why the monoproducts applied in the alternating regimen used various vehicles with a pH adjusted to the substance in question (paragraph [0006] of the patent specification). In the combination product, one vehicle must be chosen. Without further measures, the choice for a combination product will therefore lead to the instability of at least one of the active substances.

4.6. It is not in dispute either that the application of the second distinguishing feature, i.e. the claimed product being non-aqueous, does not provide any advantage over the alternating regimen, but does offer a short-acting solution for the stability problem that is inherent in the choice for a combination product. The non-aqueous character of the claimed product does thus contribute to the preservation of the stability of the active substances in the short term. However, the parties agree that this measure is insufficient to warrant the stability of the active substances in the long run. The measure that according to the patent does warrant the stability of the active substances in the long run, i.e. the solvent as referred to in claim 5, does not form part of the claims 1 and 2. This means that with the measures of the claims 1 and 2 the stability problem in the long run is not solved.

4.7. Leo has argued that the claimed combination product has another effect, i.e. – in summary – an improved treatment of psoriasis. As will be explained below in the discussion of ground 3 (see ground 4.14 and further), this effect must be disregarded in the assessment of inventive step because it has not been made plausible. This is why the objective definition of the problem must exclusively be based on the effects of the distinguishing features established above. Departing from this, the objective problem that the claimed product solves must in our provisional assessment be formulated as: the improvement of the patient compliance with the preservation of the stability in the short term. It fits in with this definition of the problem that the average skilled person consists in a team consisting of a dermatologist and a formulation expert.

4.8. It must be provisionally assumed that a skilled person who is faced with the problem formulated above, departing from the alternating regimen disclosed in Ortonne, would arrive at the matter claimed. It is an established fact that it was common general knowledge that a combination product increases patient compliance. Sandoz has explicitly argued that this was common general knowledge by referring to declarations of its experts, the decision by the OD on EP 808 and the assessment of the British court based on expert evidence. Leo has not disputed this assertion, or at least in an insufficiently substantiated manner. In addition, as Sandoz has asserted undisputedly with reference to *inter alia* the description of EP 083, patient compliance was a particularly big problem in the treatment of psoriasis. In view hereof, it must be assumed that the skilled person was particularly motivated to find a solution for the objective problem. Finally, Sandoz has advanced, not or at least insufficiently disputed, that it formed part of the common general knowledge of the average skilled person that the use of a non-aqueous product is a logical first step to prevent stability problems related to a difference in pH.

4.9. The factors that Leo has advanced to substantiate that the matter claimed is nevertheless inventive cannot lead to a different assessment. Leo has argued that, mainly due to the stability problem in the long run, there were reservations to combine calcipotriol and betamethasone (dipropionate) into one medicinal product. However, the solution to this stability problem does not form part of the objective definition of the problem as formulated above, because the claimed product does not solve this problem either. In other words, in the scope of the assessment of the inventive step of the claimed product it must be assumed that the average skilled person exclusively focuses on the improvement of the patient compliance and the preservation of stability in the short term and that he thus ignores any stability problems in the long run. Otherwise, inventive step could be derived from the non-solving of a known problem. The court of appeal is of the opinion with Sandoz that this would not do justice to the – in this respect limited – contribution of the patent to the prior art.

4.10. In addition, Leo has advanced that the formulation of a combination product is complex because both active substances must be soluble in the excipients such that the active substance is released in a sufficient manner to the skin. As substantiation, Leo has submitted a declaration by a formulation expert, Professor Brown. Also in this respect, the patent claims invoked by Leo in this case do not contain any measures that offer a solution to the asserted problem. Furthermore, the objections of Professor Brown are contradicted by Sandoz’ expert, Professor Crowley, who mentions a number of known topical combination products in his declaration. In view of this, it must be provisionally assumed that the objections made are in any case not such that they will deter the average skilled person from developing a combination product to solve the pressing problem of poor patient compliance.

4.11. Leo’s assertions that calcipotriol and betamethasone were being administered alternatingly for seven years and the idea to combine them into one medicinal product had never even been suggested cannot lead to another conclusion either. The fact that (the idea of the development of) a combination product had remained forthcoming can be explained by the abovementioned stability problem in the long run. As long as this problem had not been solved, it was meaningless to make a combination product, because it is impractical to always immediately administer a product after its preparation (also see the second declaration by Professor Brown, Leo’s exhibit 27, paragraph 16). Secondly, Sandoz has advanced that the prior art does disclose a combination product of calcipotriol and betamethasone, with reference to Serup’s example 8 (Sandoz’ exhibit 19, p. 23). The fact that this product is an aqueous composition, does not specifically contain betamethasone dipropionate and is not used for the treatment of psoriasis is irrelevant in this regard. The relevant point is that this example substantiates that the average skilled person contemplated the combination of calcipotriol and betamethasone in one product.

4.12. Finally, Leo has advanced that its product is a success and has become the standard treatment. This alone is insufficient to assume inventive step in view of the above. Furthermore, the invoked claims are not limited to the product that Leo offers and it is plausible that the products also covered by the scope of the claims in which the stability problem has not been solved, would be unsuccessful.

4.13. On the basis of the above, it must be concluded that the claims 1 and 2 are in any case not inventive over the full range of these claims. This is why Leo’s grounds 2 and 5 on the identical assessment by the preliminary relief judge must be rejected.

*ground 3: plausibility synergistic effect*

4.14. Leo has argued that the claimed combination product also leads to an improved treatment of psoriasis apart from the improved patient compliance. For this, it explicitly took the position in first instance that this improved treatment is explained by the fact that the two active substances work synergistically in the combination product (writ of summons, paragraph 3.7). This implies that the effectivity of the active substances in the combination product, contrary to the alternating regimen, is more than a sum of the effectivity of the substances apart from each other (1+1=3). The court of appeal understands that Leo, different from what Sandoz has suggested, has not abandoned this position on appeal. For, also in its statement of appeal Leo explicitly asserts that in the alternating administration of the two active substances merely an additive effect would occur (1+1=2) and that in the combination product claimed there is a more than additive effect (statement of appeal, paragraph 32) and also at the hearing on appeal its arguments are based on the assertion that replacement of the alternating regimen by the combination product leads to the active substances having a synergistic effect (pleading notes on appeal, among other the paragraphs 16, 18, 32, 61 and 69).

4.15. The parties agree that the abovementioned effect may only be taken into account in the assessment of the patent’s inventive step if the average skilled person had found the effect plausible on the basis of the patent description. The parties have a different opinion on the answer to the question whether in this case this condition is met. Sandoz argues that this is [not] the case. Leo disputes this and complains with its third ground about the assessment by the preliminary relief judge of the lack of plausibility. In this respect, the parties also argue about the burden of proof and the interpretation of the concept of plausibility.

4.16. With respect to the burden of proof, in the opinion of the court of appeal Leo rightfully advanced that Sandoz bears the burden to assert and in preliminary relief proceedings make preliminarily plausible that the abovementioned effect is not plausible. For, Sandoz invokes the nullity of the patent because of lack of inventive step and this is why it must advance the facts and circumstances that can substantiate this. In view of Leo’s defence that Sandoz has failed to take the abovementioned effect into account in the formulation of the objective problem, this implies that Sandoz will have to assert and must make it plausible in preliminary relief proceedings that this effect need not be taken into account because it is implausible on the basis of the patent specification. Sandoz’ argument that the TBA uses another distribution of the burden of proof cannot lead to another assessment, already alone because the court of appeal is bound to the rules of Dutch procedural law instead of the procedural rules of the TBA.

4.17. With reference to the interpretation of the requirement of plausibility it comes first that it forms an elaboration of the principle that the scope of the patent monopoly must correspond to the contribution that the patent makes to the art (see the decision by the TBA of 12 September 1995, T-939/92, ECLI:EP:BA:1995:T093992.19950912, *Agrevo,* paragraph 2.4.2). This principle first implies that (substantially) all the products covered by the scope of the patent claim must be inventive and must therefore distinguish themselves from the products known from the prior art by showing the advanced technical effect (idem, paragraph 2.5.3 and 2.5.4). Secondly, it is important that the contribution to the art and inventive step must be assessed from the perspective of the average skilled person on the application date. This implies that effects that the average skilled person would not have read in the patent on the application date or that he would not have found plausible on the basis of the patent specification must be disregarded in the assessment of inventive step. In our preliminary assessment, the required degree of plausibility of the effect cannot be indicated in general terms. On the one hand it is of importance that it cannot be expected from the inventor that he already furnishes full evidence of an effect on the application date. This is why it is referred to as a low threshold. On the other hand, the threshold must be sufficiently high to prevent that inventive step is assessed on the basis of an invention that was only made or disclosed after the application date, like when the patent’s inventive step is derived from assertions about effects that the average skilled person would have found speculative on the application date. It must be taken into account though that the average skilled person reads the patent in view of his common general knowledge. On the one hand, this implies that an effect and the substantiation thereof need not be explicitly mentioned in the patent specification if the effect and the plausibility hereof were obvious to the average skilled person on the application date on the basis of his common general knowledge. For example, it is beyond dispute in this case that it was plausible for the average skilled person on the application date anyhow that the claimed combination product improves patient compliance, even though the patent specification does not provide any substantiation of this effect. On the other hand, stricter requirements must be set to the substantiation of an effect in the patent specification in the opposite situation that an effect for the average skilled person was precisely not obvious on the basis of his common general knowledge on the application date.

4.18.    For the following reasons, provisionally, Sandoz has made it sufficiently credible that on the application date the average skilled person would not have read in the patent or would have assumed on the basis of his common general knowledge that the combination products causes a synergistic effect of the two active substances and that the average skilled person would not find this effect plausible either on the basis of the patent specification or his common general knowledge.

4.19.    Firstly, the asserted synergistic effect is at odds with the status quo in the opposition proceedings. As Sandoz has remarked (statement of defence on appeal, paragraph 23), the opposition division explicitly ruled that ‘*as indicated by the parties, no synergy can be attributed to the composition claimed over the combination known from D21* [Ortonne, court of appeal]’. The court of appeal understands from this assessment that in the opposition proceedings Leo itself also indicated that a synergistic effect cannot be attributed to the combination product, let alone that this effect is plausible for the average skilled person on the basis of the patent specification. Leo has not made it clear why it takes the opposite position in these proceedings and why the assessment in the opposition proceedings cannot be followed on this point.

4.20.    Secondly, it is important that it is an established fact between the parties that the asserted synergistic effect is an unexpected effect, i.e. an effect that the average skilled person would not have expected on the application date on the basis of the prior art. Leo itself for example explicitly argued in the writ of summons that there was ‘not a single pointer’ that with the combination product the effectiveness of the formulation could be increased (writ of summons, paragraph 6.5). Sandoz also takes this as a starting point.

4.21.    Thirdly, in our provisional assessment Sandoz was right to point out that the patent does not mention that calcipotriol and betamethasone (dipropionate) have a synergistic effect in the combination product. The description *inter alia* mentions that the application of the claimed combination product compared to the monoproducts results in ‘*higher efficacy* (paragraph [0009]), ‘*a* *success of treatment of psoriasis hitherto unattainable’* (paragraph [0012]), ‘*therapeutic advantages’* (paragraph [0020]), ‘*faster onset of healing and a more effective healing of plaques*’ (paragraph [0021]) and that ‘*satisfactory medical treatment of skin disorders, such as psoriasis, can be attained in a shorter period of time’* (paragraph [0022]). However, the improvements mentioned in these passages can also point to an additive effect and to the improved patient compliance obtained by the combination product. The only time that the patent does explicitly mention ‘*synergy*’ (paragraph [0022]), this pertains to the reduction of side effects. As Leo itself has also emphasised (pleading notes on appeal, footnote 27) the reduction of side effects is irrelevant for the synergistic effect of the active substances meant by Leo.

4.22.    Leo’s remark that on the basis of the information about the effect of the monotherapies disclosed in the patent an additive effect can be calculated that can be compared to the date on the effect of the combination product cannot lead to another assessment. Also this calculation and comparison is not stated in the patent specification. In our provisional assessment, the average skilled person will not execute any calculations to establish whether a claimed product has an unexpected effect that is not designated in the patent specification. In addition, the results of the calculation proposed by Leo do not unequivocally point to a synergistic effect of the combination product. For example, the calculations demonstrate that the combination product precisely scores lower on week 4 of the treatment than the calculated additive effect of the monotherapies, whereas – as Sandoz has advanced, not or at least insufficiently disputed – in the literature measurements to establish the effect of a treatment are frequently made on week 4.

4.23.    Furthermore, the assertion that the two active substances in the combination product have a synergistic effect does not necessarily imply that this is an effect of the distinguishing feature (the combination of the two active substances in a product). To deem it plausible that the synergistic effect is caused by the substitution of the alternating regimen by a combination product, the average skilled person should also deem it plausible that the synergistic effect did *not* already occur in the known alternating regimen. However, the patent specification does not disclose any information about the effect of the alternating regimen. The fact that the average skilled person could calculate a ‘theoretical additive effect’ on the basis of the information in the patent specification about monotherapies is, different from what Leo thinks, irrelevant. With this calculation it is only established what the scope of the effect of the therapy would be *if* the substances in the alternating regimen have an additive effect. However, it must be made plausible *that* the substances in the alternating regimen have an additive effect at most.

4.24.    In addition, Sandoz’ expert Professor De Rie, has convincingly explained for the time being that the average skilled person would expect that if a synergistic effect occurs in the administration of the combination product, this effect will also occur in the alternating regimen (Sandoz’ exhibit 27, paragraph 19), because a dermatologist would expect that also in the alternating regimen the substances are always present in a sufficient concentration in the skin to let the substances interact. Leo has not disputed this in a convincing manner. With reference to a declaration by its expert Professor Segaert (Leo’s exhibit 24), Leo has argued that calcipotriol and betamethasone metabolise in such a rapid manner that after half a day the concentration of a substance is insufficiently high to realise a synergistic effect. However, this rapid metabolisation is, as Professor De Rie has remarked, contradicted by the SmPC of Leo's

Dovobet product, which precisely mentions that ‘because of the formation of a deposit in the skin, the elimination after dermal application [is] in the order of days’ (annex 2, to Sandoz’ exhibit 27; also see Sandoz’ exhibit 36, paragraph 4). Leo has also not submitted any documents to the court that can substantiate that the asserted rapid metabolisation occurs, let alone that the average skilled person was aware of this. In addition, Leo’s argument is based on the presumption of Professor Segaert that a high joint peak concentration is required for the synergistic effect. It has not been asserted or shown that on the application date the average skilled person was familiar with the asserted necessity of a high peak concentration.

4.25.    Finally, Leo has advanced that the publications about the alternating regimen (Ortonne, Ruzicka and Kragballe) that were available on the application date only speak of an additive or complementary effect of the alternating regimen and not of a synergistic effect. However, Sandoz is right to remark that the publications in question did not intend to establish whether the effect was additive or synergistic and that they could not do this either because they did not contain any information about the effect of both monoproducts. Ruzicka and Ortonne did not study the effect of the betamethasone monoproduct. Kragballe does not contain any trial information at all. This means that the average skilled person would not deduce from these publications that in the alternating regimen *no* synergistic effect will occur.

*grounds 3 and 6: plausibility improved treatment over the full range*

4.26.    At some places, Leo does not seem to base the patent’s inventive step on the asserted synergistic effect of the active substances in the application of the combination product, but on the improved treatment of psoriasis as such, which is expressed in advantages like a lower PASI-score, the more rapid onset of the therapy, a bigger group of patients in whom the therapy has a good effect and the even stronger reduction of side effects. Sandoz has also interpreted Leo’s argument this way. The court of appeal understands that this position on the effect of the combination product differs in that way from the argument discussed above, that it focuses on the result (an improved result of the treatment) instead of the specific manner in which this is reached (the synergistic effect of the two active substances). This different focus changes the debate about plausibility in two ways. Firstly, as Sandoz has argued, it is possible that the improved treatment is caused by the improved patient compliance made possible by the combination product (see ground 4.5 above). In that case, the effect meant by Leo would coincide with the effect of patient compliance discussed above. The parties agree that this is why the improved treatment must be disregarded to the extent that it is a result of improved patient compliance. Secondly, the focus on the result implies that knowledge of circumstances that have a negative effect on reaching an improved treatment, like stability problems, may be a reason for the average skilled person to find this effect implausible or less plausible.

4.27.    It also applies to the asserted improved treatment result not caused by improved patient compliance that it is not in dispute that on the application date the average skilled person did not have any positive pointers for this effect. Furthermore, it is an established fact between the parties that the scope of the claims also covers compositions with stability problems. Sandoz has pointed out that instability means that calcipotriol is degraded and that in this light it was implausible for the average skilled person that administration of these compositions leads to an improved treatment of psoriasis over the alternating regimen (statement of defence on appeal, paragraph 161). To the extent that Leo has wanted to dispute this with its remark that the kind of solvent and the instability of the composition are irrelevant for the occurrence of an improved treatment, this argument must provisionally judging fail in view of the declaration by its own expert, Professor Brown. He confirms that the choice for a combination product, because of the stability problems caused by it, may lead to the absorption of the active substance being negatively affected and the effectiveness of the product being changed (Leo’s exhibit 23, paragraph 32).

4.28.    Leo’s defence that in the answer to the question whether the claims are inventive over the full range is about whether in each embodiment of the claimed invention the effect occurs and not whether each embodiment has a better effect than Ortonne’s concrete alternating therapy is correct in our provisional assessment to the extent that it is about Leo’s primary position that the effect reached with the invention is that the combination product causes a synergistic effect (see ground 4.14). In that case, it suffices that it is plausible that the synergistic effect occurs over the full range of the claims and it need not be demonstrated that each product also has a better effect. If, however, the effect is defined as an improved treatment result, as the court of appeal understands Leo’s alternative position, it will have to be plausible that this effect occurs over the full range of the claims and thus that application of the products covered by the claims 1 and 2 results in an improved treatment of psoriasis than is achievable with Ortonne’s alternating regimen. As on the one hand these claims also cover unstable products, whereas on the other hand it is an established fact that this instability problem is introduced by the choice for the combination product and therefore not occurred in Ortonne’s alternating regimen (see ground 4.5), it is not necessarily plausible that substitution of the alternating regimen by one of the combination products covered by the claims 1 and 2 leads to an improved treatment of psoriasis. To the extent that with its reference to paragraph 6.4.2. of the decision of the opposition division Leo has wanted to argue that an improved treatment is plausible in '*immediate application of a fresh preparation*', this cannot lead to another outcome. The claims 1 and 2 are not limited to freshly prepared products that must be administered immediately. The claims also contain unstable products that are stored for a longer time, in which – different from Ortonne’s alternating regimen – the stability problem thus actually leads to degradation of the active substance.

4.29.    In view of the above, the average skilled person will not have found it necessarily plausible that administration of a combination product over the full range of the patent’s claims 1 and 2 leads to an improved treatment of psoriasis. This means that the average skilled person can only deduce the potential plausibility of this effect from the patent specification. However, the improved effect is not made plausible for the average skilled person in the patent specification. The specification does *state* that the claimed combination product offers therapeutic advantages over alternating administration (see the paragraphs quoted above in ground 4.21), but the patent specification does not substantiate this statement. For example, the patent specification does not disclose any results of trails in which the effect of the combination product is compared to the effect of an alternating administration of calcipotriol and betamethasone (dipropionate). Nor does the patent specification disclose a mechanism that makes it comprehensible for the average skilled person why the combination product would have a better effect than alternating administration.

4.30.    Leo’s remark that a ‘theoretically additive effect’ of the alternating therapy may be calculated and compared to the information about the effect of the combination product cannot lead to another assessment. As the court of appeal has already concluded above, this reasoning wrongly departs from the average skilled person assuming that the effect of the alternating regimen cannot be more than additive and the calculation does not unilaterally demonstrate an improvement.

4.31.    In addition, the calculation proposed by Leo assumed that the effect of the vehicle on the effectiveness of the treatment may be completely disregarded when assessing the plausibility of a difference in treatment of psoriasis caused by the combination product. This is incorrect. As has been determined above, the skilled person on the application date would assume that the application of a combination product may have a negative effect on the effect because of stability problems. This negative effect is not included in the trial results disclosed by the patent specification. In this trial, the same vehicle has been applied in the monoproducts as in the combination product. The calculation proposed by Leo does thus not give a definite answer to the question whether a potential positive effect of the choice for the combination product is fully negated by its known negative effect.

4.32.    The lack of plausibility also applies to the reduction of side effects that may, according to Leo, be realised with the combination product. It comes first that Sandoz, with reference to various publications from the prior art (Ortonne, Kragballe, Ruzicka and Lebwohl) and paragraph [0022] of the patent specification, has advanced that it was known on the application date that the alternating regimen results in less side effects than the monotherapies. Sandoz has also pointed out that the patent specification teaches that a part of the patients do not profit from this because of a lack of patient compliance (patent specification, paragraph [0022]) and emphasises that a combination product has favourable effects on patient compliance (patent specification, paragraphs [0006], [0007], [0025] and [0026]). In that view, it is implausible provisionally judging that the average skilled person reads in the patent specification that the application of the claimed combination product leads to less side effects than the alternating regimen apart from the effect of patient compliance. Furthermore, the patent specification does not contain any trial information about side effects, also not about the side effects of the claimed product. Nor does the patent specification disclose a mechanism that makes it comprehensible to the skilled person why the combination product would result in less side effects.

4.33.    Pursuant to the above, it must be concluded that the effects meant by Leo were not plausible for the average skilled person over the full range of the claims 1 and 2 on the basis of the patent specification or his common general knowledge and that this is why the preliminary relief judge was right to disregard these effects in the assessment of the inventive step.

4.34.    As the inventive step attack succeeds, what Leo assesses in ground 6 on the replicability can be left undiscussed. This means that the grounds 3 and 6 fail.

*ground 4: substantiation effect in post-published evidence*

4.35.    In view of the fact that the effects on the application date advanced by Leo were implausible for the average skilled person, these effects must be disregarded in the assessment of the inventive step, also if evidence from after the application date shows that these effects do occur. This is why Leo’s ground 4 against the assessment by the preliminary relief judge on this *post-published evidence* cannot lead to the reversal of the challenged judgment and no assessment must be given about Sandoz’ argument that these effects are not shown by the evidence with a sufficient degree of certainty.

*ground 7: subclaims*

4.36.    Leo has not disputed on appeal that if the claims 1 and 2 lack inventive step, the subclaims 3, 4 and 9 that it invokes are also invalid. This means that the preliminary relief judge was right to conclude that none of the claims invoked by Leo may form a basis for an injunction. Ground 7, aimed against this conclusion, must be rejected.

*general ground: decision OD*

4.37.    In its ‘general ground of appeal’ Leo has rightly argued that when assessing the nullity grounds that Sandoz advanced the fact that it must be taken into account that in its decision of 6 October 2016 the OD maintained the patent in its unamended form. This fact implies that an infringement injunction should only then be omitted in connection with the chance of revocation in opposition or nullification in proceedings on the merits if a serious chance exists that the Technical Boards of Appeal (hereinafter: TBA), different from the OD, will revoke the patent on appeal (judgments by the Dutch Supreme Court of 26 October 2001, ECLI:NL:HR:2001:AB2774, *Tetra Laval/Meyn,* ground 3.4.2 and of 21 April 1995, ECLI:NL:HR:1995:ZC1705, *Boehringer/Kirin Amgen,* ground 3.4). On the one hand, this implies that the mere repetition of arguments already assessed and rejected by the OD and the mere possibility of another assessment of these arguments by the TBA are insufficient. It will at least have to be plausible that the TBA will render another decision than the OD *(Boehringer/Kirin Amgen* judgment***,*** ground 3.4). On the other hand, there is not only room for the assessment that a serious chance exists that the TBA will revoke the patent in the event that Sandoz makes it plausible that the OD has made such errors or has ignored (or could ignore) such important material that it is to be expected that, if these errors had not been made or if the material had been taken into account, the patent would not have been maintained *(Tetra Laval/Meyn* judgment, ground 3.4.2). A manifest error or new fact is therefore not required.

4.38.    In view of the abovementioned assessments on the patent’s inventive step, a serious chance exists in this case that the TBA, different from the OD, will revoke the claims of the patent invoked by Leo. Firstly, in the current proceedings Leo has primarily based the patent’s inventive step on the assertion that the two active substances have a synergistic effect. In its decision, the OD endorses that the defence of the inventive step of the invoked claims cannot be maintained on this ground. Secondly, the OD bases its assessment on the plausibility of the improved treatment merely on the trial information mentioned in the patent specification with respect to the monotherapies. On the basis of the arguments and evidence advanced before the court of appeal, it is plausible that the TBA will render a different decision on this, also in view of the fact that in its assessment the OD has not clearly taken account of the absence of information about the effect of the alternating regimen. Nor does the court of appeal deem it plausible that the TBA will follow the OD in its assessment that the effect of the improved treatment occurs over the full range of the claims, apart from the stability problems in the long run. Fourthly, in the opposition proceedings the OD assessed with respect to EP 808 that a combination product consisting of a Vitamin D analogue, like calcipotriol, and a corticosteroid, like betamethasone (dipropionate), was *not* inventive, not even in combination with a particular solvent. Also this negative assessment on the inventive step of a combination product of calcipotriol and betamethasone (dipropionate) must be taken into account.

*foreign judgments*

4.39.    The decisions by foreign courts on the foreign parts of EP 083 do not bring the court of appeal to another assessment either. In nullification proceedings initiated by a third party in England, Leo limited the English part of EP 083 to one of the solvents mentioned in claim 5 of EP 083. The fact that the English court has maintained the patent with this limitation on appeal does not conflict with the assessment of this court of appeal that a serious chance exists that the court deciding on the merits of the case or the TBA will come to the assessment that the patent is not inventive without this limitation.

4.40.    In Germany and Sweden, a provisional injunction has been imposed on (a party related to) Sandoz. Due to procedural rules, the validity of EP 083 was assessed as regards its contents to a limited extent. Furthermore, the parties have not submitted the German judgment. This means that the court of appeal cannot assess which nullification defences were advanced before the German court and how these were assessed. The Swedish judgment has been submitted (Leo’s exhibit 16). In this judgment, the Swedish court assesses that it does not seem unfounded that the claimed invention results in a better treatment than the alternating regimen. If this assessment pertains to the plausibility of this effect on the basis of the patent specification, the court of appeal cannot endorse it on the basis of the arguments and evidence advanced in the current proceedings.

4.41.    In Denmark, Sandoz has voluntarily complied with the claimed injunction in provisional relief proceedings and this is why the court needed not assess the validity of EP 083.

**on the cross-appeal**

4.42.    The cross-appeal must be rejected. The preliminary relief judge deduced an amount of € 30,000 from the costs claimed by Sandoz in the first instance because Sandoz had made it insufficiently plausible that these costs had been incurred in the scope of the current proceedings, in view of the fact that the costs pertained to work with respect to *‘pre-launch documents’* that had been performed amply before the initiation of the preliminary relief proceedings. In its statement of appeal on the cross-appeal. Sandoz has advanced that it pertains to advisory work that Sandoz had performed prior to the market introduction of its product *inter alia* in connection with the pending opposition against the parent patent and the patent. It has not been asserted or shown that at the moment at which this work was performed, there were already threatening enforcement actions by Leo, let alone unlawful (threatening with) enforcement actions.

On the contrary, Leo has pointed out that the advisory work was performed prior to its demand letter of 17 March 2016. All this confirms that the work cannot be designated as (the preparation of) a defence against the claims advanced in these preliminary relief proceedings. That the work, after the preliminary relief proceedings had been initiated, also turned out to be useful for Sandoz’ defence against these claims, does not make - different from what Sandoz thinks - that the costs have changed colour and can be qualified as ‘introductory costs’ incurred from that moment in the scope of these proceedings.

**on the appeal on the merits and the cross-appeal**

4.43.    On the basis of the above, it must be concluded that the appeal on the merits and the cross-appeal must be rejected and that the challenged judgment must thus be upheld.

4.44.    Leo being the unsuccessful party will be ordered to pay the costs of the appeal on the merits. Sandoz being the unsuccessful party will be ordered to pay the costs of the cross-appeal. The parties have agreed that the costs of the proceedings may be estimated at € 200,000 and that this amount may be attributed in full to the appeal on the merits. In this case, the court of appeal does not see any reason to deviate from this estimate.

**5.    The Decision**

The court of appeal

5.1.    upholds the judgment rendered between the parties by the preliminary relief judge in the district court The Hague of 11 May 2016;

5.2.    orders Leo to pay the costs of the appeal on the merits, until today estimated on Sandoz’ side at
€ 200,000, to be increased by the statutory interest pursuant to article 6:119 Dutch Civil Code over this amount from 14 days after today until the day of payment;

5.3.    orders Sandoz to pay the costs of the cross-appeal, until today estimated at nil;

5.4.    declares the order to pay the costs of the proceedings to have immediate effect.

This judgment was rendered by *Mr*. P.H. Blok, *Ms*. R. Kalden and *Mr*. C.J.J.C.van Nispen and was pronounced in open court of 7 November 2017 in the presence of the court clerk.