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Case Number: T 0072/23 - 3.3.07

Application Number: 14735770.1

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IPC: A61K9/28, A61K9/48, A61K31/472

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL FORMULATIONS OF A HIF HYDROXYLASE INHIBITOR

Patent Proprietor:
Fibrogen, Inc.

Opponents:
Teva Pharmaceutical Industries Ltd.
SANDOZ AG

Headword:
Photostable roxadustat formulation/FIBROGEN

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

Decisions cited:
T 0393/18, T 2591/18, T 0814/19, T 1349/19, T 0091/22, T 0783/22

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Case Number: T 0072/23 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 23 January 2025

Appellant: (Opponent 1)	Teva Pharmaceutical Industries Ltd. 124 Dvora HaNevi'a St. Tel Aviv 6944020 (IL)
Representative:	D Young & Co LLP 3 Noble Street London EC2V 7BQ (GB)
Appellant: (Opponent 2)	SANDOZ AG Centralbahnstrasse 4 4051 Basel (CH)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Respondent: (Patent Proprietor)	Fibrogen, Inc. 409 Illinois Street San Francisco, CA 94158 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 9 December 2022 concerning maintenance of the European Patent No. 3003284 in amended form**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Molina de Alba
	Y. Podbielski

Summary of Facts and Submissions

I. The decision under appeal is the opposition division's interlocutory decision concluding that the European patent as amended in accordance with the main request, and the invention to which it relates, met the requirements of the EPC.

Claim 1 of the main request held allowable by the opposition division read as follows:

"*1. A tablet comprising [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid, a pharmaceutically acceptable excipient, and an effective amount of a photostabilizing agent, wherein the photostabilizing agent comprises titanium dioxide and at least one additional dye selected from the group consisting of, a red dye, an orange dye, a yellow dye, and combinations thereof, and wherein*

(i) the photostabilizing agent is blended into the tablet; or

(ii) the tablet comprises a tablet core and a coating and the photostabilizing agent is blended into the tablet core; or

(iii) *the tablet comprises a tablet core and a coating and the tablet core comprises [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid and the pharmaceutically acceptable excipient, and the coating comprises the photostabilizing agent*."

The compound [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid is also known as roxadustat.

II. The following documents cited in the decision under appeal are mentioned in this decision:

D1 WO 2012/097331 A1

D4 J. Swarbrick, Encyclopedia of Pharmaceutical Technology, Informa Healthcare, vol. 5, 3rd edn., 2007, 2859-65

D5 ICH Harmonised Tripartite Guideline, "Stability testing: photostability testing of new drug substances and products Q1B", 6 November 1996

D6 J.T. Piechocki et al., Pharmaceutical Photostability and Stabilization Technology, Informa Healthcare, 2007, 323-43

D8 R.C. Rowe et al., Handbook of Pharmaceutical Excipients, 6th edn., 2009, 741-4

D9 M. Litvić et al., Journal of Photochemistry and Photobiology A: Chemistry, 2013, 252, 84-92

D11 K. Thoma et al., International Journal of Pharmaceutics, 1991, 67, 169-75

D16 Note for guidance on the photostability testing of new active substances and medicinal products, European Medicines Agency, January 1998

D26 J.W. McGinity et al., Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, Informa Healthcare, 3rd edn., 2008, 171-202

III. In the decision under appeal, the opposition division concluded, among other things, that the subject-matter of the main request was inventive starting from D1 as the closest prior art.

IV. Opponent 1 (appellant 1) and opponent 2 (appellant 2) each filed an appeal against the decision. The patent proprietor is the respondent in these appeal proceedings.

V. In their statements of grounds of appeal, the appellants requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

VI. With its reply to the statements of grounds of appeal, the respondent filed 23 sets of claims as its main request and auxiliary requests 1 to 12, MR-A and 3-A to 11-A.

VII. The Board scheduled oral proceedings, in line with the parties' requests, and gave its preliminary opinion on the case.

VIII. At the respondent's request and with the agreement of the appellants, the oral proceedings were held by videoconference. During the oral proceedings, the respondent withdrew all the claim requests then on file except the main request and auxiliary requests 3-A and 5-A.

The main request was identical to the main request held allowable by the opposition division.

Claim 1 of auxiliary request 3-A differed from claim 1 of the main request in that the additional dye was limited to a red dye.

Claim 1 of auxiliary request 5-A differed from claim 1 of auxiliary request 3-A in that the red dye was specified to be Allura Red AC aluminum lake.

At the end of the oral proceedings, the board announced its decision.

IX. The appellants' arguments relevant to the present decision can be summarised as follows.

Admittance of the argument from appellant 2 relating to the technical effect shown in Table 7 of the patent

Appellant 2 had argued in its notice of opposition that the data in Table 7 of the patent did not demonstrate that the selection of dyes in claim 1 as granted provided a technical effect. The argument that this was also the case for the selection of dyes in claim 1 of the request held allowable by the opposition division was not an amendment of its case. It was merely a development of the original argument following the amendment of claim 1 as granted. The argument also addressed the conclusion in the decision under appeal that the selection of yellow, orange and red dyes provided a technical effect. In addition, the argument could not take the respondent by surprise because it merely analysed the data disclosed in the patent. Therefore the argument should be admitted.

Inventive step - main request

Starting from D1 as the closest prior art, the subject-matter of claim 1 differed in that the roxadustat composition contained titanium dioxide and at least one red, orange or yellow dye. The technical effect provided by this difference was that the composition was stable to light. Therefore the objective technical problem was to provide a photostable roxadustat composition.

The solution proposed in claim 1 was obvious. Photostability testing was an essential step in the development of new drugs. Contrary to the respondent's contention, photostability testing was an uncomplicated routine task that could be carried out, for instance, by the protocol described in D5. Therefore, the skilled person would necessarily have found that roxadustat was degraded by light, and would have sought to block light from reaching it. Using the information obtained from photostability testing and bearing in mind common general knowledge (e.g. D6 and D4), they would have added a UV-VIS absorbent and an opacifier as defined in claim 1 as an obvious measure. UV-VIS absorbents were commonly added to absorb problematic wavelengths and were generally selected by applying the basic principle of spectral overlay. Following this principle, the skilled person would have found that yellow, orange or red dyes were suitable stabilisers for roxadustat. With regard to the use of an opacifier, this was a common measure to absorb and scatter light to prevent it from reaching the photosensitive drug. Titanium dioxide was a typical opacifier. The fact that it had an absorption gap between 400 and 420 nm did not lead away from it. The skilled person knew from the photostability tests to what extent the wavelengths in this gap were relevant, and the gap could be covered by the additional dyes if needed. The combination of a dye with a UV-VIS absorption spectrum overlapping that of the photosensitive drug and titanium dioxide was usual. The effect of the combination was merely a juxtaposition of the individual effects.

The respondent had argued that the obvious solution was to protect the drug by putting it into light-resistant packaging, as suggested in the flow chart of D5 and

D16. However, the flow chart in D5 and D16 did not deal with the photostability of drug substances but of final drug products. That option did not negate the usefulness of adding photostabilising agents upstream when photodegradation was identified at the outset of drug formulation. Photostability had to be tested again at a late stage because the final product could contain excipients acting as sensitisers. At that stage, light-resistant packaging was a preferred solution because a reformulation of the final product would require repeating the clinical tests with the reformulated product. The adding of photostabilising agents at pre-formulation stage and the packaging under light-resistant conditions at pre-marketing stage did not exclude each other. They were two obvious solutions depending on the circumstances.

The respondent had cited several decisions to support its case on obviousness, but T 393/18 reflected better the circumstances of the case at hand.

Inventive step - auxiliary request 3-A

The selection of a red dye was not associated with any unexpected effect and was obvious for the reasons outlined for the main request. The application of the spectral overlay principle rendered a red dye as obvious as a yellow or an orange dye. Furthermore, Table 7 of the patent showed that red dyes were not as good as yellow or orange ones.

Inventive step - auxiliary request 5-A

Allure Red AC aluminum lake was a well-known dye and there was no evidence on file that it produced any

unexpected effect. Table 7 did not even conclusively demonstrate that it was better than other red dyes.

X. The respondent's arguments relevant to the present decision can be summarised as follows.

Admittance of the argument from appellant 2 relating to the technical effect shown in Table 7 of the patent

Appellant 2 contested for the first time in its statement of grounds of appeal that the data in Table 7 of the patent demonstrated that yellow, orange and red dyes provided better photoprotection of roxadustat than blue dyes. Appellant 2 had failed to identify this new argument as an amendment to its case and had not explained why the argument should be admitted into the appeal proceedings. The argument could and should have been raised earlier since, in the opposition proceedings, the respondent had relied on the technical effect in Table 7 of the patent for inventive step. Therefore the new argument should not be admitted into the appeal proceedings.

Inventive step - main request

The closest prior art, D1, dealt primarily with the therapeutic effect of roxadustat. It disclosed a long list of possible formulation types but no specific dosage form. The subject-matter of claim 1 differed from D1 in that it related to a tablet comprising an effective amount of a photostabilising agent comprising titanium dioxide and a yellow, orange or red dye or a combination thereof. The photostabilising agent was blended into the tablet or tablet core or was in the coating.

The technical effect provided by these differences was improved stability of roxadustat. The data in Tables 2, 3, 5 and 7 of the patent showed that roxadustat photodegradation was reduced in compositions containing the photostabilising agent of claim 1 compared with compositions containing no photostabilising agent. Furthermore, Table 7 showed that the selection of a yellow, orange or red dye in claim 1 was purposive since a photostabilising agent containing a blue dye did not effectively protect roxadustat against photodegradation. Therefore the objective technical problem was to provide a composition comprising roxadustat having improved stability. The problem should not refer to a solid formulation nor to photostability since these pointed to the solution.

The solution proposed in claim 1 was not obvious. The appellants' arguments on this point were based on an *ex post facto* analysis tracing backwards the steps taken by the respondent to arrive at the invention. Such arguments were unacceptable according to T 1349/19 (Reasons 1.27). The prior art did not suggest that roxadustat could degrade when exposed to light. In D1, roxadustat was not identified as being photosensitive in spite of having been tested in clinical studies. Therefore the skilled person had no reason to formulate roxadustat together with a photostabilising agent, let alone one as defined in claim 1.

The appellants' argument that the skilled person would arrive at the claimed composition in the light of common general knowledge by routine experimentation was flawed and introduced unacceptable hindsight. Photostability was one of a large number of properties that needed to be studied for marketing authorisation. Thus photostability testing was part of a research

project for drug development that involved extensive experimentation rather than routine work. Separating photostability from the many other aspects of drug development introduced hindsight.

Even if the skilled person tested photostability and found that roxadustat was photosensitive, the immediate solution was not to add a photostabilising agent but to use light-resistant packaging, as proposed in D5 and D16. Reformulation was an option of last resort and, even if this option was chosen, there was no suggestion in the prior art that the combination of titanium dioxide with a red, orange or yellow dye would be successful in protecting roxadustat. Photostability could be influenced by many factors (D4, Table 2), and multiple reformulation techniques other than adding photostabiling agents, e.g. cyclodextrin complexation, microencapsulation, use of liposomes, etc., could be tried to improve it. The skilled person would not necessarily apply the principle of spectral overlay, which was not a universal approach with a predictable outcome for formulations. Analysing the photostability of a formulation was a complex task because each component in the formulation could influence photostability, e.g. by photosensitisation. In addition, it was known that titanium dioxide could be incompatible with some substances due to its photocatalytic effect. Thus selecting the appropriate technique to achieve photoprotection required a research programme. Furthermore, the appellants had not provided the absorption spectrum of roxadustat so that any conclusion on what the skilled person would have derived from it was speculative.

The view that preparing a roxadustat formulation with improved photostability as defined in claim 1 was not

obvious was also supported by T 814/19, T 2591/18, T 91/22, T 783/22 and T 1349/19.

Inventive step - auxiliary request 3-A

In claim 1 the additional dye was now limited to a red dye. The skilled person would have selected a yellow dye to protect roxadustat because the latter was yellow and because a yellow dye covered the absorption gap of titanium dioxide at 400 to 420 nm (Figure 12 of D6). The skilled person would not have selected a red dye, which nevertheless provided good photoprotection.

Inventive step - auxiliary request 5-A

In claim 1 the additional dye was now limited to the specific red dye Allura Red AC aluminum lake. As for auxiliary request 3-A, the skilled person would not have chosen a red dye, let alone this specific one. The patent showed that this dye provided excellent photoprotection. Comparing the results obtained for Orange#3 and Orange#4 in Table 7 of the patent, Allura Red AC aluminum lake was better than other red dyes.

XI. The parties' final requests were as follows:

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

- The respondent requested that the appeals be dismissed (main request). In the alternative, it requested that the patent be maintained as amended in accordance with auxiliary request 3-A or 5-A, both filed with the reply to the statements of grounds of appeal.

The respondent also requested that the argument from appellant 2 relating to the technical effect shown in Table 7 of the patent not be admitted into the appeal proceedings.

Reasons for the Decision

1. Admittance of the argument from appellant 2 contesting the technical effect shown in Table 7 of the patent (Article 12(4) and (6) RPBA)

1.1 Appellant 2 argued in its statement of grounds of appeal that the data in Table 7 of the patent did not conclusively demonstrate that red, orange and yellow dyes imparted better photoprotection of roxadustat than blue dyes. This was because, according to Table 6, the blue dye tested in Table 7 was present at a lower concentration than the yellow, orange and red dyes.

The respondent requested that this argument not be admitted into the appeal proceedings under Article 12(4) or (6) RPBA. In the opposition proceedings, the appellants had not contested the respondent's position that the data in Table 7 of the patent demonstrated that red, orange and yellow dyes were advantageous over blue dyes.

1.2 In the decision under appeal (page 12, first and second paragraphs), the opposition division concluded that a photostabilising agent comprising titanium dioxide and at least one dye selected from red, orange and yellow dyes reduced roxadustat photodegradation. This

conclusion was derived from the data in the patent: Tables 2, 3, 4, 5 and 7 showed that roxadustat was less susceptible to photodegradation in compositions containing photostabilising agents as defined in claim 1 than in compositions with no photostabilising agent. Therefore the opposition division defined the objective technical problem as the provision of a solid pharmaceutical composition comprising roxadustat with improved photostability. The definition of the problem as an improvement was justified by the fact that the composition contained a photostabilising agent; the opposition division did not analyse the data in Table 7 specifically nor assess whether the selection of a red, orange or yellow dye over a blue dye was purposive.

In these appeal proceedings, the respondent has also defined the objective technical problem as an improvement. However, in contrast to the opposition division, the respondent has not justified the improvement only by the presence of a photostabilising agent. According to it, the improvement results from the selection of a photostabilising agent which contains a red, orange or yellow dye rather than a blue dye (reply to the statements of grounds of appeal, point 4.30). This technical effect was, it claimed, demonstrated by the data in Table 7 of the patent.

1.3 In view of the respondent's analysis of inventive step, the Board considered that it might be necessary, as an essential step for establishing the correct objective technical problem, to assess whether the data in Table 7 of the patent supported the allegation that the selection of a red, orange or yellow dye was advantageous. As the considerations from appellant 2 in that respect were not complex and were not detrimental to procedural economy, the Board decided to admit them.

Nevertheless, the new argument ultimately had no bearing on the Board's conclusion on inventive step (see points 2.4 and 2.5 below). Like the opposition division, the Board acknowledged that the composition of claim 1 showed improved roxadustat photostability based on the presence of the photostabilising agent alone.

2. Main request - inventive step (Article 56 EPC)

2.1 Roxadustat is an inhibitor of hypoxia inducible factor (HIF) prolyl hydroxylase. It is a useful drug for treating or preventing conditions associated with HIF, such as anaemia, or ischaemia- and hypoxia-related disorders. The invention according to the patent is based on the observation that roxadustat degrades when exposed to light. Thus, the patent proposes protecting roxadustat with a photostabilising agent that comprises titanium dioxide and at least one additional dye (patent, paragraphs [0002] to [0004] and [0010]). In claim 1 of the main request, the additional dye is selected from a red dye, an orange dye, a yellow dye, and combinations thereof. The photostabilising agent is incorporated into a tablet comprising roxadustat and a pharmaceutically acceptable excipient.

2.2 The parties agreed that D1 can be taken as the closest prior art. D1 is directed to the use of roxadustat to increase or maintain the reticulocyte haemoglobin content in a subject in need thereof (page 2, first paragraph, and claim 1). It generally refers to oral formulations including tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and emulsions. The formulations contain roxadustat and excipients, e.g. colourants (page 7, lines 11 to 16 and 21 to 24). However, apart from the compositions used in

Examples 1 and 2 for the oral administration of roxadustat, D1 does not disclose any actual formulation. As to the compositions used in Examples 1 and 2, D1 does not give any details beyond the roxadustat dose.

2.3 The parties did not dispute that the subject-matter of claim 1 differs from the teaching of D1 at least in that roxadustat is formulated together with a photostabilising agent that comprises titanium dioxide and a dye selected from a red dye, an orange dye, a yellow dye and combinations thereof.

The respondent correctly noted that the formulation of roxadustat in a tablet also constitutes a difference since D1 does not disclose any specific formulation.

2.4 The examples in the patent show that the technical effect associated with the photostabilising agent of claim 1 is the protection of roxadustat against photodegradation. It is apparent from Tables 2, 3 and 7 that the photodegradation of roxadustat in a formulation containing a photostabilising agent as defined in claim 1 is reduced compared with a formulation containing no photostabilising agent (uncoated formulation in Tables 2 and 3 or light control in Table 7).

With regard to the formulation of roxadustat as a tablet, the respondent has not alleged any particular technical effect.

2.5 Based on the improved photostability conferred by the photostabilising agent of claim 1, the respondent defined the objective technical problem as providing a composition comprising roxadustat having improved

stability. The respondent contended that the problem should not refer to photostability or to a solid composition since this would point at the solution. As photostability was part of the total stability, improving photostability also implied improving stability in general.

The appellants did not agree with the respondent's definition of the problem. In their view, the objective technical problem should be to provide a photostable roxadustat composition. Nevertheless, at the oral proceedings before the Board, the appellants considered that this point was not critical because the subject-matter of claim 1 was also an obvious solution to the problem proposed by the respondent.

The Board decided to accept the respondent's definition of the objective technical problem. Given the conclusion on inventive step here below, the appellants were not negatively affected by this decision (see point 2.6.3, last paragraph).

2.6 The solution proposed in claim 1 is a tablet comprising roxadustat and an effective amount of a photostabilising agent comprising titanium dioxide and at least one dye selected from a red dye, an orange dye, a yellow dye and combinations thereof.

The formulation of roxadustat in a tablet is a customary choice that has not been shown to be associated with any surprising technical effect. It is also one of the options proposed in D1 (page 7, line 12). Therefore, the fact that roxadustat is formulated in a tablet does not involve any inventive step.

The parties focused their discussion on obviousness on the question of whether using a phostostabilising agent as defined in claim 1 to stabilise roxadustat was obvious. For the reasons set out in the following paragraphs, the Board agrees with the appellants that the answer to this question must be in the affirmative.

2.6.1 It was common ground that D1 provides no information on the photostability of roxadustat and is silent on the need to take photostability into account for roxadustat formulations. Although D1 mentions that colouring agents may be added to roxadustat formulations, it does not associate colouring agents with photostability (page 7, lines 15 and 23). The matter of dispute between the parties was whether the skilled person would arrive at the formulation of claim 1 in the light of common general knowledge.

2.6.2 The appellants cited common general knowledge which demonstrates that photostability testing is an essential part of drug development and that it has to be performed for each new drug and drug product.

D4, which is an excerpt from an encyclopedia of pharmaceutical technology, stresses the importance of testing the photostability of drugs and drug products because photodegradation during storage or use may lead to a loss of drug potency or even the occurrence of toxic degradation compounds (page 2859, left-hand column, first paragraph).

This common general knowledge is confirmed by D5 and D16. D5 is a guideline for photostability testing of new drugs and drug products proposed by the ICH Expert Working Group for adoption by the regulatory bodies of the European Union, Japan and the USA. D16 is the note

issued by the European Medicines Agency implementing D5. These two documents teach the importance of testing the photostability of new drugs and drug products as an integral part of stress testing in the proceedings leading to regulatory approval to demonstrate that light exposure does not result in unacceptable change (D5, page 1, first and second paragraphs; D16, page 3, first and second paragraphs).

Thus the skilled person would necessarily test the photostability of roxadustat. By doing so, they would find that roxadustat degrades upon exposure to certain wavelengths in the UV-VIS range.

Against this conclusion, the respondent argued that developing a product for marketing authorisation required a research project and involved far more than routine testing. The data that had to be submitted to the regulatory authorities involved extensive experimentation on multiple aspects of drug development and focusing on photostability distorted the whole picture introducing unacceptable hindsight. Furthermore, even if photostability was tested, identifying whether a product was sensitive to light degradation was not a routine task but, rather, a complex one.

These arguments are not convincing. The Board accepts that developing a product for marketing authorisation generally requires a research project. However, photostability testing is an essential step for each new drug to be developed and, contrary to the respondent's submissions, does not require extensive experimentation. The tests are routine and, as indicated in D4 (page 2862, right-hand column, penultimate paragraph) a basic protocol proposing a

reasonably simple test is provided in D5 (page 2). The test basically requires exposing the drug to a standard source of UV and visible light under controlled conditions and observing whether the drug shows degradation.

2.6.3 Considering that the skilled person would necessarily find that roxadustat degrades when exposed to light, the next question to be answered is whether the addition of a photostabilising agent comprising titanium dioxide together with a red dye, an orange dye, a yellow dye or a combination thereof was an obvious measure to reduce photodegradation.

D6, which is an excerpt from a textbook on pharmaceutical photostability, sets out the basic principles for the photostabilisation of tablet formulations (section "Photostabilisation of Tablets" starting on page 329). It states that, in order to protect photosensitive drugs, the amount of undesirable radiation penetrating the drug molecules must be reduced. One way of doing this is photostabilisation by spectral overlay. This method relies on the principle that excipients with absorption spectra similar to that of the photosensitive drug can be added to the formulation to reduce the amount of radiation interacting with the drug molecules (paragraph bridging pages 329 and 330 and Figure 12). D6 also indicates that in pharmaceutical practice food colorants can be used as photostabilising excipients for oral dosage forms (sentence bridging pages 330 and 331). In addition to excipients with UV-VIS spectra overlapping the UV-VIS spectrum of the photosensitive drug, tablets may contain opacifiers as photostabilising agents. Opacifiers are compounds that scatter and absorb light. A typical example is titanium dioxide, although it is

known that it has an absorption gap between 400 and 420 nm (page 332, first paragraph).

The principles in D6 are confirmed by D9 which teaches in its introduction that photosensitive substances are usually protected by additives which have an absorption spectrum that overlaps that of the substance to be protected, e.g. food colourants (page 85, left-hand column, fourth paragraph). D9 also teaches that titanium dioxide is a very good photostabilising agent but that its absorption gap between 400 and 420 nm has to be considered prior to use. Similarly, D11 discloses the usefulness of the principle of photoprotection by spectral overlay and the use of food colourants for that purpose (abstract, last sentence; conclusion, first paragraph and Figure 9).

Thus it follows from common general knowledge that the use of photostabilising agents to reduce the photodegradation of a drug was obvious. Typical photostabilising agents are dyes with a UV-VIS absorption spectrum overlapping that of the drug and an opacifier which absorbs and scatters light, preventing it from penetrating into the formulation. Furthermore, it appears that these two types of photostabilising agents were commonly combined to improve the photoprotection provided by each. For instance, D6 refers to nifedipine, which is a drug sensitive to wavelengths between 290 and 450 nm (page 333, first paragraph). Nifedipine was protected using the spectral overlay principle by a combination of tartrazine (a yellow dye) and titanium dioxide. This combination reduced light transmittance in the relevant wavelength range and imparted greater protection than either of the individual photostabilising agents did. Similarly, D26, which is a chapter from a textbook and also

represents common general knowledge, refers to nifedipine and other cases in which the combination of a yellow dye (iron oxide) and titanium dioxide provided the best photoprotection (page 189, last paragraph and page 190).

Consequently, once the photostability problems and the UV-VIS absorption spectrum of roxadustat were known from the mandatory photostability testing at the outset of drug development, it was obvious which dyes could be used for stabilising it in accordance with the principle of spectral overlay. The UV-VIS spectra of the dyes commonly used for photoprotection were known and the respondent never contested that the UV-VIS spectra of red, orange and yellow dyes greatly overlap with the UV-VIS spectrum of roxadustat. In other words, the respondent did not contest that the dyes in claim 1 protected roxadustat in accordance with the principle of spectral overlay. Furthermore, it was known that titanium dioxide is broadly used as a photostabilising opacifier and that it is commonly combined with dyes to enhance photostabilisation. Therefore the solution proposed in claim 1 does not involve an inventive step.

2.6.4 The respondent contended that the addition of a photostabilising agent as defined in claim 1 was not obvious for two reasons. First, the addition of a photostabilising agent was not the solution of choice against photodegradation. D4 stated that the method used most commonly to protect photosensitive drugs is to place the drug product in a protective market pack or in a coloured or amber immediate container (page 2862, right-hand column, second paragraph, first sentence). This teaching was in line with the flow chart in D5 (page 3) and D16 (page 4), which shows that the immediate solution against photodegradation was

putting the drug product into light-resistant packaging. A reformulation of the product to add a photostabilising agent was a last-resort measure and should be avoided because reformulation implied repeating a large number of the tests required by the regulatory authorities for the reformulated product. Second, the principle of spectral overlay was not reliable because a formulation could contain photosensitising excipients, i.e. excipients which absorb energy at wavelengths outside the absorption range of the drug but which subsequently transfer the absorbed energy to the drug causing its degradation. Therefore the photostability of a drug in a formulation could not be predicted only from the absorption spectrum or the stability studies of the drug in a pure solvent (D4, page 2859, right-hand column, first paragraph). Furthermore, titanium dioxide would not be selected as the opacifier because it has an absorption gap at the range between 400 and 420 nm. Other opacifiers would be preferred, e.g. iron oxides.

The Board disagrees.

With regard to the first argument, D4 teaches that it is essential to obtain information about the photoreactivity of a drug as early as possible in the formulation process. D4 also refers to D5 as a document providing a reasonably simple photostability test (D4, page 2862, right-hand column, penultimate paragraph). Thus routine photostability testing is performed at the pre-formulation stage. It is at that stage that, if needed, the principle of spectral overlay is applied and photostabilising agents are added. The flow chart in D5 and D16 does not deal with the photostability testing of drugs. Instead, it relates to the photostability testing of drug products. This means

that the flow chart does not deal with photostability testing at the outset of drug development but at the final stage, shortly before marketing. At that stage, photostabilising agents have already been added to the product if initial photostability testing revealed that the drug was photosensitive. The late photostability testing of drug products depicted in D5 and D16 is required because, as argued by the respondent, the formulated product might contain excipients that act as sensitisers, in which case additional photostabilising measures would need to be taken. A reformulation of the product at a late stage would be undesirable because extensive testing would need to be repeated for the reformulated product. As indicated in the flow chart of D5 and D16, the immediate solution would be to use light-resistant packaging. However, the fact that light-resistant packaging is a preferred solution when photostability issues are detected shortly before marketing does not negate that adding photostabilising agents is an obvious measure when a drug is found to be photosensitive at the pre-formulation stage.

With regard to the second argument, the principle of spectral overlay is applied at the outset of drug development based on the results of routine photostability testing on the drug rather than the drug product. Therefore, the respondent's arguments on the photostability testing of drug products and the possible presence of photosensitising excipients are not convincing.

With regard to the use of titanium dioxide, it is known that titanium dioxide has an absorption gap between 400 and 420 nm, but this does not make it unsuitable for photoprotection, especially if combined with a dye absorbing in the gap range, e.g. a yellow dye (see

Figure 12 in D6). Such combinations are known in the art (see e.g. D6, page 333, first paragraph; D26, page 190). The respondent also referred to the fact that titanium dioxide might be incompatible with some active compounds, as stated in D8 (paragraph bridging pages 8742 and 8743). However, this does not point away from titanium dioxide either. The incompatibility described in D8 was the exception rather than the rule. Titanium dioxide was a broadly used opacifier and the fact that other opacifiers might be preferred depending on the circumstances does not render titanium dioxide a less-obvious option.

2.6.5 The respondent cited several decisions to argue that the solution proposed in claim 1 could not be obvious. It referred in particular to T 814/19, T 2591/18 and T 91/22 to argue that identifying and overcoming the photostability problems of roxadustat was not a matter of routine and that the skilled person had no incentive to combine roxadustat with the photostabilising agent of claim 1. These decisions, however, do not support the respondent's case.

T 814/19, T 2591/18 and T 91/22 deal with several aspects of drug formulation but not with the particular issue of drug photostability. In T 814/19 (Reasons 2.6 and 2.7) and T 2591/18 (Reasons 3.7.2) the competent boards, taking into consideration the circumstances of the case, came to the conclusion that an undue amount of experimentation was required to identify and overcome the formulation issues arising in each case. This was the case even if the tests that had to be performed were part of the process of drug development. In T 91/22 (Reasons 6.6), the competent board held that the skilled person had no incentive to combine the drug of the closest prior art with an anti-nucleating agent

because it was not known that the drug converted to a less-soluble form under certain acidic conditions.

In the present case, the Board has explained that the skilled person would necessarily have found that roxadustat was photosensitive. Once this was known, combining roxadustat with the photostabilising agent of claim 1 was an obvious measure in the light of common general knowledge. Thus, unlike in the cases dealt with in T 814/19, T 2591/18 and T 91/22, in the present case the skilled person would arrive at the claimed invention without conducting undue experimentation and prompted by common general knowledge. The Board agrees with the appellants that the circumstances of the present case are closer to those of T 393/18 (Reasons 2.3.1 and 2.3.2). In T 393/18, the Board agreed with the parties that stability testing was part of the pre-formulation studies of new drugs and that the skilled person would identify stability issues as a matter of routine.

At the oral proceedings before the Board, the respondent also referred to decision T 783/22, which relates to the photostability of a drug in a tablet formulation. As noted by the appellants, this decision was based on different facts and the conclusions therein are not applicable to the case at hand. In particular, the parties to T 783/22 never discussed the principle of spectral overlay, which is a crucial aspect in the present appeal proceedings.

The respondent also cited T 1349/19 (Reasons 1.27) to argue that holding the invention obvious would introduce unacceptable hindsight because it implied working backwards the steps taken by the respondent to arrive at the invention. Points 2.6.2 and 2.6.3 above

make it clear that the claimed invention is obvious because the skilled person would inevitably find that roxadustat is photosensitive and, therefore, they would be prompted by common general knowledge to add a photostabilising agent as defined in claim 1. Thus, the circumstances of T 1349/19 are not applicable, either.

3. Auxiliary request 3-A - inventive step (Article 56 EPC)

Claim 1 of auxiliary request 3-A differs from claim 1 of the main request in that the additional dye has been limited to a red dye.

At the oral proceedings before the Board, the respondent stated that roxadustat is yellow and therefore, in accordance with the principle of spectral overlay, the skilled person would have selected a yellow dye for the photoprotection of roxadustat. In addition, it was generally known that yellow dyes had a maximum absorbance at wavelengths covering the range of 400 to 420 nm at which titanium dioxide had its absorption gap (see D6, Figure 12). Therefore the skilled person would have chosen a yellow dye rather than a red dye. It was unexpected that the combination of titanium dioxide with a red dye was suitable to improve roxadustat photostability.

The Board disagrees. The fact that roxadustat is yellow does not mean that the UV-VIS absorption spectrum of a red dye does not substantially overlap with that of roxadustat or, at least, that it does not absorb at the problematic wavelengths. As explained for the main request, the skilled person would find the suitable dyes by knowing the problematic wavelength range and comparing the absorption spectrum of roxadustat with that of the commonly used dyes. The respondent has not

denied that the spectra of red dyes and roxadustat substantially overlap, especially at the problematic wavelength range. The respondent may be right that a yellow dye could have been regarded as a better option. Indeed, Table 7 of the patent shows that the combination of titanium dioxide with a red dye provides less protection than the combination with a yellow dye. However, there are no apparent reasons why the skilled person would discard a red dye as a suitable photoprotecting agent.

Therefore the subject-matter of claim 1 of auxiliary request 3-A does not involve an inventive step either.

4. Auxiliary request 5-A - inventive step (Article 56 EPC)

Claim 1 of auxiliary request 5-A differs from claim 1 of auxiliary request 3-A in that the red dye has been specified to be Allura Red AC aluminum lake.

The respondent argued that the spectral overlay principle may suggest a colour range, but not a specific dye within that colour range. There were different dyes of each colour and each dye produced a different result. According to the respondent, a comparison of the results for Orange#3 and Orange#4 in Table 7 of the patent, which differ only in that Orange#3 contains red iron oxide and Orange#4 contains Allura Red AC (see Table 6), demonstrated that the latter was advantageous over other red dyes. There was no pointer in the prior art suggesting that Allura Red AC might have a higher photostabilising effect on roxadustat than other red dyes.

The respondent's arguments are not convincing. On the one hand, it cannot be conclusively derived from a

comparison of the results of Orange#3 and Orange#4 in Table 7 that Allura Red AC provides greater photoprotection of roxadustat than red iron oxide. In addition to titanium dioxide and the red dye, Orange#3 and Orange#4 contain a yellow dye. It is uncertain whether the difference in photoprotection between Orange#4 and Orange#3 comes from the red dye alone or whether there are interactions between the different components of the photostabilising agent. On the other hand, different dyes have different absorption spectra and can be expected to provide different degrees of photoprotection within a certain range. There is no evidence that the photoprotection provided by Allura Red AC is surprisingly better than that conferred by other red dyes.

Therefore, the subject-matter of auxiliary request 5-A does not involve an inventive step, either.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated