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Datasheet for the decision of 6 June 2023

Case Number: T 0559/19 - 3.3.04

Application Number: 09810708.9

Publication Number: 2337575

IPC: A61K38/14, A61P31/04, A61P17/00

Language of the proceedings: EN

Title of invention:
Methods of treatment using single doses of oritavancin

Patent Proprietor:
Melinta Therapeutics, Inc.

Opponent:
Prüfer & Partner mbB

Headword:
Single dose oritavancin/MELINTA

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

Keyword:
Inventive step - (no)
Late-filed evidence - could have been filed in first instance proceedings (yes)
Amendment after summons - taken into account (no)

Decisions cited:
T 0715/03

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Beschwerdekammern

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Case Number: T 0559/19 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 6 June 2023

Appellant: (Opponent)	Prüfer & Partner mbB Sohnckestrasse 12 81479 München (DE)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Patent Proprietor)	Melinta Therapeutics, Inc. 300 George Street, Suite 301 New Haven, CT 06511 (US)
Representative:	Dehns St. Bride's House 10 Salisbury Square London EC4Y 8JD (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 20 December 2018 concerning maintenance of European patent No. 2337575 in amended form.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	O. Lechner
	L. Bühler

Summary of Facts and Submissions

I. The appeal of the opponent (appellant) lies from the interlocutory decision of the opposition division that the patent in amended form, specifically in the version of the main request filed during the oral proceedings, and the invention to which it related met the requirements of the EPC.

II. The patent is based on European patent application No. 09 810 708.9, which had been filed as an international application and published as WO 2010/025438 A2.

III. In its decision, the opposition division held that the main request filed during the oral proceedings complied with
Articles 123(2) and (3), 83, 84, 87, 54(2) and 56 EPC.

IV. In its statement of grounds of appeal, the appellant raised objections under
Articles 123(2), 87, 54 and 56 EPC.

V. In reply, the patent proprietor (respondent) filed sets of claims of a new main request and of three auxiliary requests, as well as new documents D29 and D30.

VI. With further letters, the appellant referred to document D31 (corresponding to document D22 submitted by letter dated 12 January 2018 in the opposition proceedings) and the respondent submitted new documents D32 and D33.

VII. Oral proceedings before the board took place as scheduled on 6 June 2023.

At the end of the oral proceedings, the Chairwoman announced the board's decision.

VIII. The independent claims of the requests dealt with in this decision read as follows:

(a) Main request

"1. A pharmaceutical composition comprising oritavancin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent, for use in treating a Complicated Skin and Skin Structure Infection (cSSSI) in a human subject, wherein the bacteria causing the cSSSI is a gram-positive bacteria, and wherein said treating is by intravenous administration of one dose of a therapeutically effective amount of said pharmaceutical composition, over a course of therapy, to a human subject having a cSSSI, which thereby treats said cSSSI in said human subject, wherein said one dose comprises 800 or 1200 mg of oritavancin or a pharmaceutically acceptable salt thereof."

(b) Auxiliary request 1 (with amendments as compared to the main request highlighted by the board)

"1. A pharmaceutical composition comprising oritavancin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent, for use in treating a Complicated Skin and Skin Structure Infection (cSSSI) in a human subject, wherein the bacteria causing the cSSSI is a gram-positive bacteria, and wherein said treating is by intravenous administration of one dose of a therapeutically effective amount of said pharmaceutical

composition, over a course of therapy, to a human subject having a cSSSI, which thereby treats said cSSSI in said human subject, wherein said one dose comprises ~~800 or~~ 1200 mg of oritavancin or a pharmaceutically acceptable salt thereof."

(c) Auxiliary request 2 (with amendments as compared to the main request highlighted by the board)

"1. A pharmaceutical composition comprising oritavancin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent, for use in treating a Complicated Skin and Skin Structure Infection (cSSSI) in a human subject, wherein the bacteria causing the cSSSI is a gram-positive bacteria, and wherein said treating is by intravenous administration of ~~one~~ a single dose of a therapeutically effective amount of said pharmaceutical composition~~, over a course of therapy,~~ to a human subject having a cSSSI, which thereby treats said cSSSI in said human subject, wherein said ~~one~~ single dose comprises 800 or 1200 mg of oritavancin or a pharmaceutically acceptable salt thereof."

(d) Auxiliary request 3 (with amendments as compared to the main request highlighted by the board)

"1. A pharmaceutical composition comprising oritavancin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent, for use in treating a Complicated Skin and Skin Structure Infection (cSSSI) in a human subject, wherein the bacteria causing the cSSSI is a gram-positive bacteria, and wherein said treating is by intravenous administration of ~~one~~ a single dose of a therapeutically effective amount of said pharmaceutical

composition~~,over a course of therapy,~~ to a human subject having cSSSI, which thereby treats said cSSSI in said human subject, wherein said ~~one~~ single dose comprises ~~800 or~~ 1200 mg of oritavancin or a pharmaceutically acceptable salt thereof."

IX. Reference is made to the following documents:

D2: Targanta Therapeutics Inc., "Targanta Initiates Phase 2 Oritavancin Infrequent Dosing Study", press release, 13 September 2007; 3 pages

D4: G.J. Fretterly et al., "Abstract A-18", 43rd Annual ICAAC Chicago, 14-17 September 2003, Sunday, Session 3(A); cover page and 1 page

D9: US Securities and Exchange Commission, "Annual report pursuant to section 13 or 15(d) of the securities exchange act of 1934 for the fiscal year ended: December 31, 2007: Targanta Therapeutics Corporation", File Number 1-33730, 27 March 2008, EDGAR search results page, title page and pages 1 to 12 of the document: https://www.sec.gov/Archives/edgar/data/1398161/000119312508067341/d10k.htm accessed on 22 December 2016, SEC; Accession No. 0001193125-08-067341

D14: E. Seltzer et al., "Clinical Infectious Diseases" 37, 2003, 1298-1303

D16: C.M. Rubino et al., "Abstract No. O152", Abstract of 18th European Congress of Clinical Microbiology and Infectious Diseases, Barcelona, Spain, 19-22 April 2008, pages S31 and S32

D22: Declaration by Dr Heidi Kabler, dated 11 January 2018; 10 pages including CV

D23: Declaration by Dr Christopher Lucasti, dated 10 January 2018; 28 pages including CV dated 4 December 2016

D24: Declaration by Gregory Moeck, PhD, dated 11 December 2012; 18 pages including CV

D29: BIO, Biomedtracker and Amplion, "Clinical Development Success Rates 2006-2015", June 2016; 28 pages

D30: Office Director Memo published by the FDA Center for Drug Evaluation and Research in respect of NDA 206,334, Reference ID: 3605749; 11 pages

D31: M. Ashford, "Introduction to Biopharmaceutics", in M.E. Aulton, "Pharmaceutics: The Science of Dosage Form Design", 2nd edn., Churchill Livingstone, 2002, ISBN 0 443 05517 3, chapter 15, pp. 213-216

D32: Novartis Pharma, "Information for the patient concerning the study42446 02 041", version 2, 5 January 1998; 6 pages

D33: T0096/20 (ECLI:EP:BA:2021:T009620.20210422)

X. The appellant's arguments, in so far as they are relevant to the decision, can be summarised as follows:

(a) Admittance of document D30

Document D30 could and should have been filed during the opposition proceedings. In its reply to the notice

of opposition, the respondent had already formulated the objective technical problem as being the provision of an improved dosage regime for oritavancin in the treatment of cSSSI, i.e. the question of whether a dose of 1200 mg oritavancin was superior to the "old" dose of 200 mg had already been discussed early in the opposition proceedings. The patent taught that single or infrequent oritavancin doses had a "*non-inferior*" effect (see paragraph [0088]). The burden was on the respondent to show that the new dose led to an improvement. The opponent's argument challenging the statistical significance of the data in the patent could not have come as a surprise to the respondent. This argument was submitted within the time limit set under Rule 116 EPC. A reaction by the respondent was possible. Moreover, if it was considered to be an important part of the proceedings, the respondent could have asked for a postponement of the oral proceedings before the opposition division.

(b) Main request

Inventive step - Article 56 EPC - claim 1

Closest prior art

Document D9 represented the closest prior art.

Difference and objective technical problem to be solved

Document D9 comprised all of the claimed features, but it did not disclose any results of the trial. Therefore, the distinguishing feature was that the safety and efficacy of the single 800 and 1200 mg doses for treating a cSSSI were not confirmed.

Paragraph [0077] of the patent explained that the daily 200 mg dose of the trial of Example 1 had been known to have "demonstrated efficacy" against cSSSI. The primary hypothesis had been that the 800 and 1200 mg single doses would be "non-inferior" to this known regimen, which was confirmed by the trial results provided in the patent (see paragraph [0092]).

Starting from the single doses of 800 or 1200 mg oritavancin, the objective technical problem was the provision of an effective treatment for cSSSI.

Starting from the daily 200 mg oritavancin dosage regimen, the objective technical problem was the provision of an alternative, non-inferior treatment for cSSSI.

Obviousness

Based on mere knowledge of such an ongoing clinical trial, the skilled person was not certain but had a reasonable expectation that these doses would be effective. Clinical trials such as those discussed in document D9 were not even approved unless there was sufficient evidence to suggest that a favourable outcome could be expected.

Document D9 also provided some background information on why success was to be expected, such as extensive pharmacokinetic/pharmacodynamic modelling, the long plasma and tissue half-life of oritavancin, and the high level of potency (see page 6, second full paragraph). The patent itself provided a direct and explicit link between half-life and single dosing (see paragraph [0019]). This prolonged half-life had also

been confirmed by prior-art document D16 (see "Discussion/Conclusion" starting on page S31 thereof).

(c) Auxiliary request 1

Inventive step - Article 56 EPC - claim 1

Admittance of the respondent's new line of argument

The respondent's line of argument represented a non-allowable amendment to the appeal case, which should not be admitted under Article 13(2) RPBA 2020. In its reply to the appeal, the respondent had defined the objective technical problem as being the provision of a superior dosage regime for the treatment of cSSSI relative to the regimen of 200 mg/day for 3 to 7 days as taught in document D9.

The respondent based its assessment on Table 3 of the patent, which allegedly showed a higher cure rate for the 1200 mg single dose compared to the daily 200 mg dose. However, as admitted by the respondent in paragraph 7.4.3 of its reply letter, the difference in cure rates between the two doses was not shown to be statistically significant in the patent. Hence, the respondent had based its further reasoning on document D30 (see paragraphs 7.4.4. and 7.4.5 of the reply and pages 10 to 12 of the letter dated 19 April 2021), which the board had decided not to admit into the proceedings.

In the discussion of the results of Example 1, the patent itself referred to a non-inferior dose of oritavancin (see paragraph [0099]).

The discussion of the significance of the isolated finding reported in paragraph [0097] of the patent in favour of the overall treatment was only put forward during the oral proceedings and did not justify a reformulation of the objective technical problem.
The conclusion of Example 2 (see paragraph [0108] of the patent) also referred to the single dose of 1200 mg oritavancin as being "equivalently efficacious" (compared to 3 daily doses of 100, 200 or 400 mg, see paragraph [0107] of the patent).

Obviousness

Given that the patent disclosed a non-inferior efficacy but not a superior efficacy, the subject-matter of claim 1 of auxiliary request 1 lacked an inventive step for the same reasons as those provided with respect to the subject-matter of claim 1 of the main request.

(d) Auxiliary requests 2 and 3

Inventive step - Article 56 EPC - claim 1

The same reasons as those discussed with respect to the main request and auxiliary request 1 applied *mutatis mutandis* to claim 1 of auxiliary requests 2 and 3, respectively.
Thus, auxiliary requests 2 and 3 did not involve an inventive step within the meaning of Article 56 EPC.

XI. The respondent's arguments, in so far as they are relevant to the decision, may be summarised as follows:

(a) Admittance of document D30

Document D30 showed that the 1200 mg dose of oritavancin had an improved effect. Objections to the statistical analysis reported in the patent had only been raised in the opponent's letter dated 20 December 2017. Therefore, D30 could not have been filed during the opposition proceedings. Document D30 was *prima facie* relevant as it supported the improved effect of the 1200 mg dose of oritavancin already shown in the application as filed.

(b) Main request

Inventive step - Article 56 EPC - claim 1

Closest prior art

The closest prior-art regimen of document D9 was the 200 mg/day for 3 to 7 days control regimen, as the most promising starting point for an effective treatment regimen for cSSSI was a regimen that was already known to be effective.

Difference and objective technical problem to be solved

There was no evidence that the two investigational single doses of 800 and 1200 mg oritavancin disclosed in document D9 constituted an effective treatment. The difference between the claimed treatment regimes and the effective daily 200 mg treatment regimen taught in document D9 was in the structure of the dosing regimens.

The objective technical problem was the provision of an alternative, non-inferior treatment for cSSSI.

Obviousness

Starting from the teaching in document D9 and the objective technical problem as defined, the skilled person would not have selected an oritavancin dosing regime of a single dose of 800 or 1200 mg with a reasonable expectation of success.

Considering the uncertainty of success in clinical trials and considering that the majority of phase 2 clinical trials failed, the skilled person would not have had a general expectation that any or all of the clinical trials would succeed.

There was no requirement to provide evidence of efficacy or likely efficacy in order to obtain approval to conduct a phase 2 clinical trial. Clearly the drug had to be sufficiently safe to be tested, but this did not indicate that it would be effective. Moreover, a phase 2 clinical trial might be approved before the termination of a corresponding phase 1 clinical trial and in some cases the level of supporting evidence might be low, e.g. when using a known therapeutic for a new indication. Therefore, assumptions of the existence of comparable efficacy data for each phase 2 clinical trial could not be made.
The risk-benefit analysis performed for allowing a phase 2 clinical trial was not the same as a reasonable expectation of success. Daily doses of 200 mg of oritavancin had been known to be effective, and there had also been some testing of an 800 mg dose, however some safety issues had been reported.

The skilled person would also not have expected the clinical trials treating a cSSSI with a single dose of oritavancin to be successful since a similar trial of a

single dose of the antibiotic dalbavancin, which, like oritavancin, is a glycopeptide antibiotic, had been found to be inferior to a two-dose regimen (see document D14). The results of document D14 had to be considered more predictive of the likely outcome of the proposed treatment than a phase 1 clinical trial, which had not tested for efficacy. Declaration D23 (see paragraph 2.2) reinforced the fact that a skilled person would have been very sceptical that a single dose of any antibiotic would be effective in treating cSSSI - as confirmed by the data in document D14.

Clinical efficacy could not be easily predicted based on the results of pharmacokinetics/pharmacodynamics studies. Documents D4 and D16 were examples of such studies of oritavancin performed prior to the phase 2 clinical trial. Neither of these documents would have caused the skilled person to have a reasonable expectation that the phase 2 clinical trial would be successful.

Document D16 provided simulations based on data obtained from the administration to healthy volunteers of 800 mg oritavancin daily for 5 days, which was not equivalent to efficacy data. Levels of the antibiotic in plasma rather than tissue had been calculated. Thus, the skilled person could not draw efficacy conclusions from the snapshot simulation results provided in document D16.

Although the underlying facts in T 715/03 differed from those of the current case, the fundamental conclusion was applicable: namely that the existence of a phase 2 clinical trial could not be taken to inherently indicate a reasonable expectation of success of the

trialled therapy, and that in such an instance a case had to be considered based on the facts alone.

On the basis of a successful phase 1 clinical trial, it could only be concluded that the safety and tolerability results in humans as well as the pharmacokinetic studies were positive - not whether the treatment has any beneficial effect on patients (see T 715/03, Reason 2.2).

(c) Auxiliary request 1

Admittance of the respondent's new line of argument concerning inventive step

The significance of the data in the patent had been discussed at length in the passages cited by the appellant. The passages in the patent cited for the first time during the oral proceedings, i.e. paragraphs [0097], [0107] and Table 5, were referred to in order to show that the improved efficacy of a single dose of 1200 mg oritavancin was credible from the application as filed alone, i.e. the demonstration of an improved effect was not only based on the new data in document D30. This line of argument could not be considered surprising since it was based on the arguments put forward by the appellant in its statement of grounds of appeal and the reply thereto. It was perfectly allowable and was not a new argument.

Inventive step - Article 56 EPC - claim 1

Closest prior art

Document D9 represented the closest prior art.

Difference and objective technical problem to be solved

While document D9 did not disclose whether or not a single 1200 mg dose of oritavancin was effective, the patent made it credible that there was an improved effect over the known 200 mg dosing regimen for this single dose, as shown in Tables 3 and 5 and as discussed in Example 2 and especially in paragraph [0107] of the patent. There were also fewer serious adverse events in this group, as discussed in paragraph [0097] of the patent.

Starting from the dose of 200 mg oritavancin daily, which was the only dose known to be therapeutically effective, the technical problem to be solved was the provision of an improved treatment for cSSSI.

Obviousness

As none of the prior-art documents disclosed such an improved effect for a single 1200 mg dose of oritavancin, the claimed subject matter was not obvious and was therefore inventive.

(d) Auxiliary requests 2 and 3

Inventive step - Article 56 EPC - claim 1

The dosage regimes claimed in auxiliary request 2 were the same as those claimed in the main request. Accordingly, the objective technical problem solved by auxiliary request 2 was the same as that solved by the main request, and the claims were therefore inventive for the same reasons as those set out with respect to the main request.

The dosage regime claimed in auxiliary request 3 was the same as that claimed in auxiliary request 1. Accordingly, the objective technical problem solved by auxiliary request 3 was the same as that solved by auxiliary request 1, and the claims were therefore inventive for the same reasons as those set out with respect to auxiliary request 1.

XII. The parties' requests, where relevant to the decision, were as follows:

(a) The appellant (opponent) requested that
- the decision under appeal be set aside and that the patent be revoked
- document D31 be admitted into the proceedings
- document D30 not be admitted into the proceedings
- the respondent's new inventive-step argument based on paragraphs [0097] and [0107] and Table 5 of the patent as put forward at the oral proceedings during the discussion of the inventive step of auxiliary request 1 not be admitted into the proceedings.

The request that documents D22 to D24 not be admitted was withdrawn.

(b) The respondent (patent proprietor) requested that
- the appeal be dismissed and that the patent be maintained on the basis of the set of claims according to the main request or one of auxiliary requests 1 to 3 filed with the reply to the appeal
- documents D22 to D24, D29 and D30 be admitted into the proceedings and
- documents D16 and D17 not be admitted in case documents D22 to D24 were not admitted.

Reasons for the Decision

1. Admittance of document D30

1.1 As set out in the transitional provisions of Article 25(2) RPBA 2020, the admittance of document D30 is governed by Article 12(4) RPBA 2007, as the statement of grounds of appeal was filed before the RPBA 2020 entered into force.

1.2 The course of events during the opposition proceedings, where relevant to the admittance of document D30, can be summarised as follows:

In its reply to the notice of opposition, the patent proprietor pointed to paragraph [0092] and Tables 3 and 4 of the patent as showing higher cure rates for the 1200 mg and 800 mg dose groups and argued that the technical problem consisted in the provision of an improved dosage regimen (see points 8.1.3 and 8.1.4 of the letter dated 27 June 2017). The opponent replied thereto, arguing that the estimated difference between the single dose of 1200 mg and 200 mg/day was "insignificant" and that there was "no difference" between the infrequent dose of 800 mg and the 200 mg/day dosage regimen (see points 3.1 to 3.3 of the letter dated 12 January 2018). The patent itself did not mention an "improvement", but rather classified the single and infrequent doses as "non-inferior" compared to the daily dose regimen (see paragraph [0092], first and second sentences as well as the comments on the data of Table 3; paragraph [0099]).
The patent proprietor reacted by filing new auxiliary claim requests but did not file any further experimental evidence or inform the opposition division

and the opponent of its intention to do so. Moreover, the patent proprietor did not request the opposition division to postpone the oral proceedings.

1.3 The data contained in document D30 (dated 2014), which the respondent held to be *prima facie* relevant to its case, were available well before the oral proceedings in opposition.

1.4 With reference to the Case Law of the Boards of Appeal, 9th ed., 2019, V.A.4.13.2, the respondent argued that the late-filed evidence in the form of document D30 should be admitted into the appeal proceedings since it was *prima facie relevant*.
However, the relevance of late-filed submissions is only one criterion to be considered by the board under Article 12(4) RPBA 2007. Other criteria to be considered include, *inter alia,* fairness and procedural economy and, foremost, whether the submission could and should have been filed during the opposition proceedings.

1.5 As follows from points 1.3 and 1.4 above, document D30 was available to the respondent from the beginning of the opposition proceedings. The respondent hence could have filed this document in the opposition proceedings and should have done so in reaction to the opponent's letter of 12 January 2018. The board considers that it is not within the remit of the appeal board to re-start a case in view of evidence which could and should have been provided in the response to the notice of opposition or at the latest in reply to the opponent's written submissions in preparation for the oral proceedings before the opposition division.

Consequently, document D30 is held to be inadmissible (Article 12(4) RPBA 2007).

2. Main request

Inventive step - Article 56 EPC - claim 1

2.1 The object of the patent is to provide a treatment for Complicated Skin and Skin Structure Infection (cSSSI) caused by gram-positive bacteria, by intravenous administration of one dose of a pharmaceutical composition comprising at least 800 mg oritavancin, or a pharmaceutically acceptable salt thereof. The patent reports in paragraph [0092] that oritavancin single (1200 mg oritavancin) and infrequent doses (800 mg oritavancin with optionally 400 mg on day 5) demonstrated non-inferiority to the oritavancin daily dose of 200 mg (see Table 3).

Closest prior art

2.2 The parties started their inventive-step reasoning based on document D9 as the closest prior art. The board has no reason to deviate from this.

Document D9 (see page 6) discloses that extensive pharmacokinetic/pharmacodynamic modelling had been performed for oritavancin. These data suggest, according to document D9, that due to the long half-life of oritavancin in plasma and tissue and its high level of potency, it should be possible to treat gram-positive cSSSI with a single administration of a higher dose of oritavancin. The document goes on to state that as a result of this suggestion, a phase 2 clinical study entitled SIMPLIFI was commenced to evaluate the use of a higher total dose in a single or two-part

administration for treating patients with gram-positive cSSSI.
The study comprises three arms, administering
i) a single 1200 mg dose of oritavancin;
ii) an 800 mg dose of oritavancin on the first day of treatment and a 400 mg dose of oritavancin, if necessary, on the fifth day of treatment; and
iii) a 200 mg daily dose of oritavancin for three to seven days, as necessary, corresponding to a previously established dosage regimen.
Document D9 also mentions that in several previously conducted clinical trials, oritavancin had been administered in daily doses of 800 mg or higher (see page 6, third to fifth full paragraphs). No results of the SIMPLIFI trial are disclosed.

2.3 The respondent argued that within the disclosure of document D9, the assessment of inventive step should start from the control regimen (200 mg/day for 3 to 7 days), since the most promising starting point for an effective treatment regimen for cSSSI was the regimen taught by document D9 to be effective.

The appellant argued that the investigational treatment regimens of 800 or 1200 mg oritavancin were the most promising starting points because they required the fewest modifications to yield the claimed regimens.

2.4 Each of the study arms in document D9 (i.e. the known regimen as well as the investigational regimens) are suitable staring points: the control arm is the benchmark, while the other arms have been selected based on scientific evaluation. The relevant question for obviousness is whether the skilled person would have had a reasonable expectation that a single dose of

800 or 1200 mg of oritavancin would be effective for the treatment of cSSSI.

Thus, the board considers that any of the dosage regimens disclosed in document D9 can be considered as an appropriate starting point and starts its inventive step analysis from a single dose of 1200 mg oritavancin.

Difference and objective technical problem to be solved

2.5 The difference between the subject-matter claimed and the investigational treatment arm of document D9 in terms of disclosure is the effectiveness of the treatment of a single dose of 1200 mg oritavancin.

2.6 Starting from the single dose of 1200 mg oritavancin as the closest prior art, the objective technical problem is to provide an effective treatment for cSSSI.

Obviousness

2.7 The skilled person knew, for example from document D9 (see page 5, paragraph entitled "*Development of Oritavancin for cSSSI*"), that oritavancin had already been approved by the FDA for the treatment of cSSSI on the basis of phase 3 clinical trials with 200 mg daily doses.
Document D9 also discloses an ongoing phase 2 clinical trial, approved by an institutional review board, evaluating oritavancin using a higher total dose in a single or two-part administration of therapy for patients with gram-positive cSSSI, namely the administration of a single 1200 mg dose of oritavancin and the administration of an 800 mg dose of oritavancin on the first day of treatment and a 400 mg dose of

oritavancin, if necessary, on the fifth day of treatment (see page 6, paragraph "*Single/Infrequent Dosing for cSSSI*").

2.8 The respondent argued that in the present case there was no evidence that the approval of the phase 2 clinical trial was linked to likelihood of efficacy. Moreover, a phase 2 clinical trial might be approved before a phase 1 clinical trial has been concluded and in some cases the level of supporting evidence might be low, for example when using a known therapeutic for a new indication. Reference was also made to decision T 715/03 in support of the respondent's line of argument.

The board is not persuaded by these arguments. In T 715/03, the board found that there was no information about a possible beneficial effect for the specific drug tested on the condition to be treated. The condition to be treated, Tourette's Syndrome, was considered very complex and no animal models for preclinical studies existed in this field (see Reasons 2.2).

In the present case, however, a daily dose of 200 mg of oritavancin was already known to be effective and safe in treating cSSSI in phase 3 clinical trials (see document D9, page 5, penultimate paragraph) and daily doses of 800 mg oritavancin had been used previously in other clinical trials (see document D9, page 6, paragraph 5). The results of these trials and extensive pharmacokinetic and pharmacodynamic modelling were relied on in support of investigating single and infrequent dosing of oritavancin for treating cSSSI in the further on-going trial reported in document D9.

2.9 The respondent also argued that document D9 reported some safety concerns in terms of a higher rate of phlebitis than expected in healthy patients. Thus, safety could not be inferred from previous clinical trials with 200 mg daily doses.

The board considers that the higher rate of occurrence of phlebitis is not presented as raising safety concerns in respect of a single 1200 mg dose of oritavancin, since the reported issues concern daily doses of 800 mg or higher of oritavancin. Indeed, the incidence of phlebitis is attributed to multiple factors (normal subject *versus* patients, the frequency of dose administration, the drug concentration, and the infusion rate). The authors of D9 suggest administering the single or infrequent dose of oritavancin at a slower rate of infusion to substantially lower the incidence of phlebitis. Hence, the incidence of phlebitis reported for daily doses of 800 mg or higher of oritavancin neither discounts a single dose of 1200 mg of oritavancin nor teaches away from such a regime.

2.10 The respondent further argued that the skilled person would not have expected the clinical trials treating a cSSSI with a single dose of oritavancin to succeed, because a similar trial of a single dose of the related antibiotic dalbavancin for cSSSI had been found to be inferior to a two-dose regimen, as disclosed in document D14. The results obtained in document D14 had to be considered more predictive of the likely outcome of the treatment proposed than a phase 1 clinical trial (see document D9, page 6, paragraph entitled Single/ Infrequent Dosing for cSSSI) which was not known to have tested efficacy.

The board notes that although dalbavancin, like oritavancin, is a lipoglycopeptide antibiotic with a long half-life, it is a different molecule and therefore cannot be considered predictive for oritavancin. Thus, the skilled person would not have considered the teaching of document D14 as evidence suggesting the failure of the clinical trial with oritavancin.

2.11 A cautious skilled person would also have looked for the pharmacokinetic/pharmacodynamic data mentioned in document D9 and found document D16 reporting recent results.

The board does not agree with the respondent that the data provided in document D16 are unreliable.
The scientific conference abstract D16, presented at the 18th European Congress of Clinical Microbiology and Infectious Diseases, teaches that a population pharmacokinetic (PK) model was developed using pharmacokinetic data from 20 intensively sampled subjects who received 800 mg of oritavancin intravenously Q24h x 5 days. Based on simulations evaluating daily and cumulative free-drug plasma area under the curve (AUC) values following front-loaded oritavancin regimens (i.e. the majority of the AUC is delivered on day 1) as a single dose of 1200 mg or of 800 mg on day 1 followed by 400 mg on day 5, the authors predict that front-loaded oritavancin regimens would result in improved response rates for patients with cSSSI relative to those regimens previously studied with a 200 mg daily dose (see also the table on page S32, left-hand column, of document D16). It is also mentioned that these data were used to support dose selection for a Phase 2 cSSSI study.

Document D4, which investigates the deposition of oritavancin in skin structures, also provides some expectation of success by reporting that oritavancin tested in healthy volunteers at 200 mg/day for three days or 800 mg as a single dose exceeded the MIC90 of *S. aureus* of 2 µg/ml in canthariде-induced skin blisters by several fold, supporting the potential use of oritavancin in the treatment of cSSSI.

2.12 The board considers that based at least on the combination of the teaching in the closest prior art document D9 and document D16, the skilled person would have envisaged using the claimed single dose of 1200 mg (or 800 mg) of oritavancin for treating cSSSI and would have had a reasonable expectation of success.

Thus, the subject-matter of claim 1 lacks an inventive step within the meaning of Article 56 EPC.

3. Auxiliary requests 1 to 3

3.1 Admittance of the respondent's new line of argument under inventive step for claim 1 of auxiliary request 1

3.1.1 In the written appeal proceedings, the respondent referred to paragraph [0099] and Table 3 of the patent, and itself stated that the patent did not show the reported difference to be statistically significant (see paragraph 7.4.3 of the respondent's reply to the statement of grounds of appeal). The subsequent comments on an improved effect were all based on document D30 (see paragraphs 7.4.4 to 7.4.7 of the same letter), which, however, the board has found to be inadmissible (see paragraph 1.5 above).

During the oral proceedings, the respondent attempted to support an improved effect on a different factual basis by referring for the first time in the appeal proceedings additionally to Table 5 and paragraphs [0097] and [0107] of the patent as showing an improved/ advantageous effect for the single 1200 mg dose.

3.1.2 The line of argument in favour of an improved effect of the single dose of 1200 mg of oritavancin, based exclusively on Tables 3 and 5 and paragraphs [0097] and [0107] of the patent, is considered to be a change of case because it introduces new facts. However, this amendment is not justified by exceptional circumstances. Nothing has been presented and no change in the proceedings is apparent that could have given rise to a change in the respondent's case on appeal. Consequently, the board has decided not to admit this line of argument into the appeal proceedings under Article 13(2) RPBA 2020.

Inventive step - Article 56 EPC -claim 1

3.2 The same reasoning as that provided with respect to the main request (see points 2.7 to 2.12 above) applies *mutatis mutandis* to claim 1 of auxiliary requests 1 to 3 which all relate to a single dose of 1200 mg of oritavancin. The amendments made in these auxiliary requests have no effect on the finding on inventive step.
Therefore, auxiliary requests 1 to 3 do not involve an inventive step within the meaning of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

L. Stridde M. Pregetter

Decision electronically authenticated