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# Datasheet for the decision of 29 April 2025

**Case Number:** T 0122/23 - 3.3.07

**Application Number:** 09818544.0

**Publication Number:** 2350096

**IPC:** A61K31/395, A61K31/437, A61K45/06, A61K31/352, A61K31/08, A61K31/4164, A61K31/426, A61K31/4439, A61K31/606, A61K31/7016, A61K31/785, A61K38/14, A61K38/31, A61P25/28

**Language of the proceedings:** EN

**Title of invention:**

METHODS OF TREATING HEPATIC ENCEPHALOPATHY

**Patent Proprietor:**

Salix Pharmaceuticals, Ltd.

**Opponents:**

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Aera A/S
Teva Pharmaceutical Industries Ltd
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Hollatz, Christian

**Headword:**
Hepathic encephalopathia/SALIX

**Relevant legal provisions:**
EPC Art. 56

**Keyword:**
Inventive step - reasonable expectation of success (yes)

**Decisions cited:**
T 1437/21, T 2963/19

Europäisches Patentamt
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**Case Number: T 0122/23 - 3.3.07**

# D E C I S I O N
# of Technical Board of Appeal 3.3.07
# of 29 April 2025

| | |
|---|---|
| **Appellant:**<br>(Patent Proprietor) | Salix Pharmaceuticals, Ltd.<br>400 Somerset Corporate Blvd.<br>Bridgewater, NJ 08807 (US) |
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| **Decision under appeal:** | **Decision of the Opposition Division of the European Patent Office posted on 4 November 2022 revoking European patent No. 2350096 pursuant to Article 101(3)(b) EPC.** |

**Composition of the Board:**

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| **Chairman** | A. Usuelli |
| **Members:** | M. Steendijk |
| | Y. Podbielski |

## Summary of Facts and Submissions

I. European patent 2 350 096 ("the patent") was granted on the basis of 3 claims.

Claim 1 as granted related to rifaximin for use in decreasing a subject's risk of hepatic encephalopathy breakthrough episodes in a subject suffering from hepatic encephalopathy or in a subject with a risk of hepatic encephalopathy involving long-term administration of defined daily doses of rifaximin and concomitant therapy with lactulose.

II. Eight oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step, that the patent did not sufficiently disclose the claimed invention and that the patent comprised subject-matter extending beyond the content of the application as originally filed.

The appeal was filed by the patent proprietor against the decision of the opposition division to revoke the patent. The decision was based on the claims of the patent as granted (main request) and auxiliary requests 1-4 as filed on 31 March 2021.

Claim 1 of the auxiliary request 1 defined:

"Rifaximin for use in decreasing a subject's risk of hepatic encephalopathy (HE) breakthrough episodes in a subject suffering from HE,

- wherein a Conn score and asterixis score increase of one grade each or an increase of the Conn Score

from 0 or 1 to 2 or greater is indicative of a breakthrough episode,

and wherein rifaximin is orally administered daily for a period of at least 168 days and wherein 550 mg of rifaximin is administered to the subject two times per day (BID) or wherein 275 mg of rifaximin is administered to the subject four times per day, and wherein lactulose is administered as a concomitant therapy."

Auxiliary requests 2 and 3 corresponded to auxiliary request 1 except for the deletion of dependent claims.

Auxiliary request 4 corresponded to auxiliary request 3 wherein the use was additionally defined as "for increasing the time to the first HE-related hospitalisation".

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

D3: Dig Dis Sci (2007), 52:737-741
D4: Semin Liver Dis (2007), 27 (suppl 2):18–25
D5: Aliment Pharmacol Ther (2006), 25 (Suppl. 1): 23–31
D7d: Printout from clinicaltrials.gov of clinical study no. NCT00298038 dated 25 May 2008
D8: Am J Health-Syst Pharm (2008), 65:818-822
D9: Curr Med Res Opin (1995), 13(5):274-281
D11: Chemotherapy (2005), 51(suppl 1):67–72
D14: Pharmacotherapy (2008), 28(8):1019-1032
D21: Chemotherapy (2005), 51(suppl 1):36–66
D22: BMC Gastroenterology (2008), 8:26
D23: Clinical Infectious Diseases (2006), 42:541-547
D24: Yonsei Medical Journal (2005), 46(3):399-407
D30: Am J Gastroenterology (2001), 96(7):1968-1976

D31: Metab Brain Dis (2007) 22:389-405
D43: PNAS (2008), 105(12): 4886-4891
D49: Declaration by Prof. Labenz of 7 July 2022
D50: CV Prof. Labenz
D51: Clin Gastroent Hepatol (2014), 12(8):1390-1397
D52: Eur J Gastroent Hepatol (2000), 12(2):203-208
D53: Hepatology (2003), 38(2):527-529
D54: Bass et al., Rifaximin Treatment is Beneficial for Mild Hepatic Encephalopathy, presented at the 55th Annual Meeting of the American Association for the Study of Liver Diseases, Boston, MA, October 29-November 2, 2004
D61: ICH guideline ES (R1) on general considerations for clinical studies, European Medicines Agency, 14 October 2021, EMA/CHMP/ICH/544570/1998
D62: "22 Case Studies Where Phase 2 and Phase 3 Trials had Divergent Results", FDA, January 2017
D63: ICH guideline Topic E8 General considerations for clinical trials, European Medicines Agency, 17 July 1997

The opposition division arrived at the following conclusions:

(a) Documents D49, D50 and D63 were admitted into the proceedings. Documents D51-D54 and D61-D62 were not admitted.

(b) Claim 1 as granted comprised subject-matter extending beyond the content of the application as originally filed.

(c) Auxiliary request 1 complied with Articles 123(2) and 83 EPC.

The priority was validly claimed.

The claimed subject-matter was new over the prior art. The teaching in document D7d, which described a protocol relating to a clinical phase III trial for the long-term prevention of hepatic encephalopathy with rifaximin, differed from the subject-matter of claim 1 of auxiliary request 1 in that it revealed no beneficial results.

Document D7d represented the closest prior art. The objective technical problem concerned the provision of an effective treatment for decreasing the risk of hepatic encephalopathy breakthrough episodes in patients suffering from hepatic encephalopathy. The subject-matter of claim 1 of auxiliary request 1 represented an obvious solution, because the skilled person had a reasonable expectation of a successful outcome of the trial described in document D7d, especially in view of the information in documents D9 and D31.

Auxiliary request 1 did therefore not meet the requirement of inventive step.

(d) Auxiliary requests 2 and 3 did not meet the requirement of inventive step for the same reason as auxiliary request 1.

(e) Auxiliary request 4 did not comply with Article 84 EPC.

III. With the statement of grounds of appeal, the patent proprietor filed a new main request and auxiliary requests 1-3. These requests corresponded to auxiliary requests 1-4 on which the decision under appeal was based.

IV. The following documents were *inter alia* additionally cited during the appeal proceedings:

A64: Expert opinion by Prof Labenz of 23 February 2023
A65: Journal of Hepatology (2014), 61:642–659
A66: Journal of Hepatology (2020), 73:1526–1547
A67: Z. Gastroenterol (2019), 57:611–680
A68: BMJ (2004) doi:10.1136/bmj.38048.506134.EE (Als-Nielsen B, Gluud LL, Gluud C "Non-absorbable disaccharides for hepatic encephalopathysystemic review of randomised trials")
A69: Journal of Hepatology, 2021, vol. 75:1452–1464
A70: Hepatology, 2021, vol. 74(3):1660-1673

A71: Journal of Hepatology (2005), 42:674–679

Documents A64-A70 were filed by the patent proprietor with the statement of grounds of appeal.

Document A71 was filed by opponent 4 with the reply to the appeal.

V. In its communication under Article 15(1) RPBA the Board expressed *inter alia* its preliminary opinion that claim 1 of the main request did not to involve an inventive step.

VI. Oral proceedings were held on 29 April 2025. The patent proprietor withdrew auxiliary request 3 during the oral proceedings.

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

(a) Admittance of evidence

Documents D49, D50 and D63 were to be considered part of the appeal proceedings, because the decision under appeal was based on these documents. Documents D51-D54 were cited in document D49 and should therefore be admitted into the appeal proceedings. Documents D61-D62 should be admitted, because they were relevant to the skilled person's understanding of relevance of a phase III clinical study.

Document A64 should be admitted into the appeal proceedings, because it addressed the findings in the decision under appeal regarding skilled person's expectations based on the prior art. Documents A65-A70 were cited in document A64 and should therefore also be admitted.

The relevance of document A71 was questionable, because it merely confirmed the statement in document D23 regarding the lack of efficacy of rifaximin in prevention of hepatic encephalopathy.

(b) Inventive step

As affirmed by the declarations in documents D49 and A64 the skilled person had no reasonable expectation that the use of rifaximin with concomitant treatment with lactulose would be effective in the prevention of hepatic encephalopathy breakthrough episodes as defined in claim 1 of the main request.

Document D7d only described a protocol of a trial investigating the efficacy of rifaximin in the prevention of hepatic encephalopathy without suggestion towards a positive outcome of the trial.

Taking account of the significant placebo effect in the treatment of hepatic encephalopathy as for instance mentioned in document D53 (see page 528, right column), the open-label study in document D9 involving short-term treatment of hepatic encephalopathy with rifaximin and lactulose did not convincingly demonstrate the efficacy of the described treatment. The lack of evidence for the efficacy of rifaximin and lactulose in the treatment of hepatic encephalopathy was highlighted by document A68 and confirmed in documents D5, D14, D24, D30, D31 and D52. Moreover, documents D4, D14 and D54 indicated that treatment of hepatic encephalopathy with rifaximin did in fact not allow for an improvement of mental function with respect to placebo treatment. Document D3 recognized itself the shortcomings of the reported retrospective chart review and would in this context not provide any further evidence of the efficacy of rifaximin and lactulose in the treatment of hepatic encephalopathy.

Any indication of efficacy of rifaximin and lactulose in the treatment of acute hepatic encephalopathy could anyway not provide a basis for a reasonable expectation of success for their use in the long-term prevention of breakthrough episodes. In fact, document D23 indicated with reference to the study in document A71 that neither rifaximin nor lactitol were beneficial in the

prevention of hepatic encephalopathy in patients following the placement of a transjugular intrahepatic portosystemic shunt (TIPS).

The skilled person would furthermore not expect that the prolonged daily administration of rifaximin could be effective due to the development of resistance indicated in documents D11, D21, D22, D23, D31, D43 and A68.

The skilled person would also not expect that lactulose was suitable for prolonged concomitant therapy in view of the known side effects of lactulose addressed in documents D3, D14 and D30.

VIII. The arguments of the opponents relevant to the present decision are summarized as follows:

(a) Admittance of evidence

Documents D49, D50 and D63 were late filed and should not have been admitted by the opposition division. The late filed documents D51-D54 and D61-D62 were correctly not admitted by the opposition division.

Document A64 and documents A65-A70 should have been filed during the first instance proceedings. These documents provided no relevant new information and no justification for their admittance into the appeal proceedings was evident.

Document A71 was relevant to the appeal proceedings, because it explained that the patients in the study in which prevention of hepatic encephalopathy with rifaximin had failed referred to in document D23 were

entirely different from the patients of the trial of document D7d.

(b) Inventive step

The protocol for the clinical trial described in document D7d itself already provided the skilled person with a reasonable expectation that the claimed use of rifaximin with concomitant treatment with lactulose would be effective.

This expectation would further be based on the utility of the combination of rifaximin with lactulose in the treatment of hepatic encephalopathy described in document D9.

The utility of rifaximin and lactulose in the treatment of hepatic encephalopathy was confirmed in documents D4, D5, D8, D14, D23, D30 and D31. Document D54 and A71 did not suggest that rifaximin would lack efficacy with respect to placebo in the treatment of hepatic encephalopathy or its prevention under investigation according to document D7d.

In view of documents D5, D11, D21 and D22 the skilled person would not expect that the development of resistance to rifaximin would affect its efficacy in the long-term prevention of breakthrough episodes of hepatic encephalopathy. The skilled person would in view of the known practical utility of lactulose also not be deterred by its side effects from its concomitant use in the prevention of hepatic encephalopathy. The practical utility of the long-term use of rifaximin and

lactulose in treatment of hepatic encephalopathy was furthermore confirmed by document D3.

IX. The appellant-patent proprietor requested that the decision under appeal be set aside and that the patent be maintained based on the main request or one of auxiliary requests 1-2 as filed with the statement of grounds of appeal.

The patent proprietor further requested that documents D51-D54 and D61-D62 as well as documents A64-A70 be admitted.

X. The respondents-opponents 1, 2, 4-6 and 8 requested that the appeal be dismissed.

They further requested that documents D49-D63 and A64-A70 not be admitted.

## Reasons for the Decision

1. Admittance of evidence

1.1 Documents D49, D50 and D63

Documents D49, D50 and D63 were admitted by the opposition division and form part of the reasons for the decision under appeal. Accordingly, the Board considers that documents D49, D50 and D63 are part of the appeal proceedings under Article 12(1)(a) RPBA.

1.2 Documents D51-D54

Documents D51-D54 were cited in document D49, which is part of the appeal proceedings. The Board considers that documents D51-D54 are of relevance for the

assessment of document D49. The Board has therefore admitted documents D51-D54 into the appeal proceedings under Article 12(6) RPBA.

1.3 Documents D61-D62

The opposition division did not admit the late filed documents D61 and D62 for lack of *prima facie* relevance considering that documents D61 and D62 were published well after the relevant date for the patent (priority date of 2 October 2008). The Board does not recognize a reason to overrule the decision by the opposition division with regarding the admittance of documents D61 and D62 under Article 12(6) RPBA.

1.4 Documents A64-A70

Document A64 specifically addresses the finding in the decision under appeal concerning the relevance of documents D9 and D31 taking account of the distinction between the short-term treatment of a hepatic encephalopathy episode and the long-term prevention thereof and the quality of the experimental evidence presented in documents D9 and D31. The Board considers that the filing of document A64, which does not raise new issues, is justified in reaction the findings in the decision under appeal. Documents A65 and A68 were cited and are supportive of the explanations in document A64. The Board has therefore admitted documents A64, A65 and A68 into the appeal proceedings under Article 12(4) RPBA.

Documents A66, A67, A69 and A70 were also cited in document A64. However, these documents are post-published and the Board does not recognize any justification for their admittance.

1.5 Document A71

Document A71 corresponds to reference 56 in document D23. The patent proprietor relied in the statement of grounds of appeal specifically on this reference in document D23 to argue that rifaximin was not effective in prevention of HE. The filing of document A71 thus assists in the discussion of a relevant issue in the appeal proceedings. The Board has therefore admitted document A71 under Article 12(6) RPBA.

2. Priority

The validity of priority claimed by the applicant for the patent, Salix Pharmaceuticals Ltd, was challenged, because the priority application was filed by the inventor, Mr Forbes. It was questioned whether Salix Pharmaceuticals Ltd was entitled to claim the priority from the earlier application filed by Mr Forbes.

In its communication pursuant to Article 15(1) RPBA the Board expressed the preliminary opinion that the patent as amended according to the main request enjoys the claimed priority in view of the rebuttable presumption of an applicant's entitlement to claim the priority (see G 1/22 and G 2/22).

No substantive arguments were submitted in response to the preliminary opinion expressed by the Board in its communication. The Board has therefore confirmed its opinion that the patent as amended according to the main request enjoys the claimed priority.

3. Novelty

In its communication pursuant to Article 15(1) RPBA the Board expressed the preliminary opinion that the subject-matter of claim 1 of the main request was new over the prior art, because document D7d presented a protocol for a phase III clinical trial without revealing any results from the trial.

No substantive arguments were submitted in response to the preliminary opinion expressed by the Board in its communication. The Board has therefore confirmed its opinion that the subject-matter of claim 1 of the main request was new over the prior art

4. Main request - Inventive step

4.1 Objective technical problem

The patent presents the results of a randomized controlled trial in which patients in remission from demonstrated recurrent, overt, episodic hepatic encephalopathy received 550 mg rifaximin twice daily or placebo for 6 months, optionally in combination with lactulose. The risk of a breakthrough episode of hepatic encephalitis was in the rifaximin treated group of patients 57.9% reduced in comparison to the placebo treated group of patients (see the patent paragraphs [0177]-[0179], [204] and Figure 2). The patent further reports the results of a second, on-going open-label, treatment extension study indicating the durable protective effect of rifaximin (see the patent paragraphs [0194]-[0197] and Figure 13).

Document D7d describes a protocol for a phase III randomized controlled trial for the use of rifaximin in preventing hepatic encephalopathy. According to the protocol the trial was to evaluate the efficacy and

safety of rifaximin given 550 mg twice daily as compared to placebo, optionally with concomitant use of lactulose, during a period of 6 months in subjects who are in remission from demonstrated hepatic encephalopathy.

It was not in dispute that document D7d represents a suitable starting point in the prior art for the assessment of inventive step.

The phase III clinical trial disclosed in document D7d only differs from the subject-matter of claim 1 of the main request in that document D7d does not report the actual effectiveness of the described treatment in decreasing the hepatic encephalopathy breakthrough episodes.

The objective technical problem in view of document D7d may therefore be formulated as the provision of effective long-term treatment for decreasing the risk of hepatic encephalopathy breakthrough episodes in patients who previously suffered from overt hepatic encephalopathy.

4.2 Assessment of the solution

4.2.1 The Board considers that the mere fact that document D7d reports the protocol for the evaluation of the efficacy and safety of rifaximin with optionally lactulose in a phase III clinical trial does not by itself provide the skilled person with a reasonable expectation of success of the trial.

The assessment of inventive step starting from document D7d therefore crucially depends on the question whether the skilled person had in view of the prior art, in

particular having regard to the available information on the nature of the products under investigation and the condition to be treated, a reasonable expectation that the use of rifaximin with concomitant lactulose therapy would be effective in decreasing the risk of hepatic encephalopathy breakthrough episodes.

In this context the Board relies on the considerations in T 2963/19 (see reasons 4.3.1) and T 1437/21 (see reasons 4.3.1).

4.2.2 Document D7d itself describes hepatic encephalopathy as caused by a reversible decrease in neurologic function associated with gut derived nitrogenous substances which are not adequately detoxified due to liver disease or bypass the liver due to shunting and which adversely affect brain function. Document D7d further mentions that broad-spectrum, gastrointestinal-active antibiotics, which have been used to treat hepatic encephalopathy, appear to act indirectly by inhibiting the splitting of urea by deaminating bacteria, thus reducing the production of ammonia and other potential toxins. Document D7d further describes rifaximin as a non-systemic, non-absorbed, broad-spectrum, oral antibiotic specific for enteric pathogens of the gastrointestinal tract (see D7d, under "Detailed Description").

Document D9 reports the results from an open-label study indicating clinical efficacy and tolerability of the administration of rifaximin at a dose of 1200 mg/ day in combination with lactulose during 15 consecutive days in the treatment of hepatic encephalopathy. According to document D9 the results confirm the clinical efficacy of rifaximin in controlling episodes of encephalopathy with a reduction in all clinical,

biochemical and instrumental parameters and demonstrate a synergistic effect from the combination in the reduction of ammonia-producing flora. The document specifically concludes that the reported efficacy and tolerability make rifaximin a valid alternative to the use of aminoglycoside antibiotics, particularly in the case of long-term therapy of hepatic encephalopathy in patients with chronic cirrhosis (see D9, Abstract and pages 280-281, last two paragraphs).

The Board considers that the tolerability, the clinical efficacy in treatment of hepatic encephalopathy and the efficacy in reducing ammonia-producing bacterial flora of the treatment with rifaximin combined with lactulose described in document D9 provided the skilled person with a reasonable expectation of success regarding the prevention of breakthrough episodes of hepatic encephalopathy under investigation in the trial of document D7d.

4.2.3 The patent proprietor's argument, that due to its open-label set-up and taking account of the significant placebo effect in the treatment of hepatic encephalopathy the study in document D9 did not convincingly demonstrate the efficacy of the described treatment, is not considered persuasive.

Document A68 indeed questions the evidence for the efficacy of lactulose in the treatment of hepatic encephalopathy stating that non-absorbable disaccharides seem to have been introduced into clinical practice without appropriate documentation (see A68, page 5, left column, under "Implications"). Document A68 furthermore concludes that taking account of the lack of effect of antibiotics in placebo controlled clinical trials, the risk of multi-

resistance and the potential risk of severe adverse effects, there is insufficient evidence to recommend the use of antibiotics for hepatic encephalopathy (see A68, page 5, second paragraph). The reviews in document D5 (see page 24, right column), document D14 (see page 1030, right column) and document D31 (see page 392) cite the conclusions from the study reported in document A68. The lack of rigorous evidence regarding the efficacy of lactulose or rifaximin was also observed in document D24 (see page 405, right column), document D30 (see page 1971, right column) and document D52 (see page 207, left column, under "Discussion").

The conclusions in document A68 are, however, explicitly criticized in document D31 (see D31, page 393). Moreover, documents D4 and D5 are review articles which describe the administration of non-absorbable disaccharides such as lactulose as the recommended first line treatment of hepatic encephalopathy. Documents D4 and D5 explicitly conclude that the available evidence indicates that rifaximin is better than placebo and non-absorbable disaccharides in therapeutic benefit in hepatic encephalopathy and is at least comparable with other antibiotics, demonstrating favourable tolerability with respect to lactulose (see D4, page 23, right column; see D5, Abstract and page 29, right column). The reviews in documents D8 and D14 also refer to the better efficacy and safety profile of rifaximin compared to lactulose and neomycin in treatment of hepatic encephalopathy (see D8, Abstract and page 821, right column; D14, Abstract and page 1031, left column). Similarly, the review in document D23 refers to studies favouring treatment with rifaximin over treatment with lactulose (see D23, page 544, paragraphs bridging the columns). Document D24

concludes that the reported results indicate that rifaximin is safe and as effective as lactulose in the treatment of hepatic encephalopathy despite of the limitations of the reported study (see abstract). Document D30 specifically describes the use of lactulose for treatment of acute and chronic encephalopathy in the treatment of cirrhosis (see page 1973, left column). The review in document D31 mentions that non-absorbable disaccharides such as lactulose are widely used as first line therapy (see D31, pages 392-393) and that in several countries rifaximin is used as a first line therapy which is at least as effective as lactulose or other antibiotics and better tolerated (see D31, pages 393-395). Document D52 also concludes that rifaximin may be considered as an adjuvant or alternative to non-absorbable disaccharides in treatment of patients with hepatic encephalopathy (see page 207, right column).

The results reported in document D9 are in line with the reports and reviews in documents D4, D5, D8, D14, D23, D4, D30, D31 and D52 regarding the practical utility of lactulose and rifaximin. The Board does therefore not consider that the lack of placebo-controlled evidence of the efficacy of rifaximin and lactulose in document D9 affects the reasonable expectation of success of the long-term treatment under investigation in document D7d based on document D9.

4.2.4 The Board agrees with the patent proprietor, that the effectiveness of an agent in the short-term treatment of symptoms of acute disease may not generally suggest the suitability of such an agent in long-term prevention of the recurrence of such symptoms.

However, document D9 explicitly describes the efficacy of the treatment with rifaximin and lactulose in the reduction of ammonia-producing flora (see D9, page 280, last paragraph). Document D7d (see under "Detailed Description") as well as document D9 specifically address the known role of ammonia produced by intestinal bacteria as a factor in the pathogenesis and pathophysiology of hepatic encephalopathy (see D9, pages 274-275, under "Introduction"). This known role of ammonia is also recognized in the declaration of document A64 relied on by the patent proprietor (see A64, page 3). Taking account of this role of the ammonia-producing flora the skilled person had good reason to expect that the reduction of the flora as described in document D9 would also prevent breakthrough episodes, especially since document D9 concludes that the efficacy and good tolerability of rifaximin enables it to be confirmed as a valid long-term treatment of hepatic encephalopathy in patients with chronic cirrhosis.

4.2.5 The patent proprietor's specific argument based on reports of failed efficacy of rifaximin in treatment of hepatic encephalopathy are not considered convincing.

Document D54 reports the results of a placebo-controlled study in which treatment with rifaximin and treatment with placebo were associated with similar improvement versus baseline in measures of mental function in patients with hepatic encephalopathy (see D54, under "Summary"). Documents D4 and D14 refer to the results reported in document D54 regarding the lack of improvement of mental function from rifaximin with respect to placebo (see D4, page 20, right column; D14, page 1029, right column). However, document D54 also reports that rifaximin was significantly more effective

than placebo in improving asterixis (see D54, under "Summary") and explicitly concludes that the results of the study suggest that rifaximin may be beneficial and safe for patients with mild hepatic encephalopathy (see D54, under "Conclusion"). Indeed, as mentioned in section 4.2.3 above, document D4 still concludes that the available evidence indicates that rifaximin is better than placebo and non-absorbable disaccharides in therapeutic benefit in hepatic encephalopathy (see D4, page 23, right column) and document D14 still refers to the better efficacy and safety profile of rifaximin compared to lactulose and neomycin in treatment of hepatic encephalopathy (see D14, Abstract and page 1031, left column). The results of the study in document D54 and the references to these results in documents D4 and D14 would therefore not upset the skilled person's expectations of success of the trial in document D7d.

Document D23 mentions with reference to the study in document A71 that neither rifaximin nor lactitol were beneficial in the prevention of hepatic encephalopathy in patients following the placement of a transjugular intrahepatic portosystemic shunt (TIPS)(see D23, page 544, reference [56]). Document A71 indeed reports that the results of the concerned study indicate that neither a non-absorbable disaccharide (lactitol) nor a non-absorbable antibiotic (rifaximin) were better than no treatment in reducing the incidence of post-TIPS hepatic encephalopathy, even though these drugs were widely used in the treatment of hepatic encephalopathy and were in view of their characteristics good candidates for prophylaxis. However, document A71 explicitly notes that due to the design of the study, the reported conclusions are strictly applicable to the first month after TIPS only and that advantages from

prolonged treatments and follow-ups cannot be excluded (see A71, page 678, left column). Notably, the protocol for the trial described in document D7d required that in case of patients with a history of a portal-systemic shunt, the TIPS placement or revision had to be >3 months from Screening (see D7d, under "Eligibility Criteria") and thus excluded the recently operated patients as described in the study of document A71. The results of the study in document A71 and the reference to these results in document D23 would therefore not affect the skilled person's expectations of success of the trial in document D7d.

4.2.6 The patent proprietor's further specific argument, that the skilled person would in view of the risk of the development of resistance against rifaximin not expect that prolonged daily administration of rifaximin as defined in claim 1 of the main request would be effective in the prevention of breakthrough episodes, is also not considered convincing.

Document D43 describes a mechanism of resistance against rifamycin antibiotics with the potential to negatively impact the expanded use of this class of antibiotic (see D43, Abstract and page 4890, left column). Document D21 indeed reports that the development of resistance to rifaximin in fecal strains has been observed in patients with hepatic encephalopathy following treatment with rifaximin 1200 mg/day for 5 days and refers in this context to the cyclic use of rifaximin (see D21, page 43, right column). Such development of resistance was also reported in document D11 (see page 71, right column). The risk of the development of resistance to rifaximin is furthermore addressed in document D31 (see page 395), document D22 (see page 6, right column), document

D23 (see page 542, left column) and document A68 (see page 5, left column).

However, document D21 also explicitly points out that the selection of rifaximin-resistant mutants in the gastrointestinal tract is expected to be low (see D21, page 42, left column) and that antimicrobial resistance to rifaximin is minimized by its lack of absorption (see D21, page 59, right column). Similarly, document D11 states that the available evidence does not seem to be a major concern of the therapy with rifaximin (see D11, page 71, right column). Notably, document D22 reports that no clinically significant resistance to rifaximin has been observed during the 20 years of its availability in Europe (see D22, page 2, left column) and describes effective maintenance therapy for pouchitis involving daily administration of rifaximin for up to 24 months (see D22, Abstract and page 3, left column). The skilled person's expectation of success for the trial in document D7d would furthermore not be affected by the discussion of the mere potential for the development of resistance in documents D23, D31 and A68 taking account of the explicit statement in the review of document D5 that rifaximin is not associated with clinically relevant antibiotic resistance (see D5, Abstract).

In fact, document D3 describes the results of a retrospective chart review evaluating the hospitalization, clinical status and adverse events in patients with hepatic encephalopathy who were first treated with lactulose for 6 or more months and subsequently with 400 mg rifaximin 3 times per day for 6 or more months. It is reported that the period of treatment with rifaximin was associated with a reduced need for hospital care, better clinical status and

fewer adverse events (see D3, Abstract and page 741, left column). Document D3 thereby confirms that the risk of the development of resistance did not deter the skilled person from the long-term administration of rifaximin to patients with hepatic encephalopathy.

4.2.7 The patent proprietor's further argument, that in view of the known side effects of lactulose the skilled person would not expect that its use in prolonged concomitant therapy as defined in claim 1 would be effective, is also not considered convincing.

The adverse effects of lactulose have indeed been addressed in for instance document D3 (see page 740, right column), document D14 (see page 1030, right column) and document D30 (see page 1971, right column).

However, according to documents D3 and D30 themselves the known adverse effects of lactulose have not precluded its use in therapy of hepatic encephalopathy during a prolonged period of 6 months or more and in therapy of chronic encephalopathy (see D3, page 741, left column, last paragraph; see D30, page 1973, left column). These adverse effects would therefore not affect the skilled person's expectation regarding the success of the trial as described in document D7d.

4.3 The Board has therefore concluded that the subject-matter of claim 1 of the main request does not involve an inventive step (Article 56 EPC).

5. Auxiliary requests 1-2

Claim 1 in auxiliary requests 1 and 2 is identical to claim 1 of the main request. Auxiliary requests 1 and 2

do therefore not comply with the requirement of inventive step for the same reason as the main request.

## Order

## For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Vottner A. Usuelli

Decision electronically authenticated