**Internal distribution code:**

(A) [ - ] Publication in OJ
(B) [ - ] To Chairmen and Members
(C) [ - ] To Chairmen
(D) [ X ] No distribution

## Datasheet for the decision of 13 January 2026

**Case Number:** T 0986/24 - 3.3.04

**Application Number:** 20765071.4

**Publication Number:** 4017525

**IPC:** A61K38/50, A61K47/60, A61P35/02

**Language of the proceedings:** EN

**Title of invention:**
Therapeutic conjugate

**Applicant:**
Porton Biopharma Limited

**Headword:**
Erwinia L-Asparaginase/PORTON BIOPHARMA

**Relevant legal provisions:**
EPC Art. 83, 111(1)

**Keyword:**
Sufficiency of disclosure - (yes)

Europäisches Patentamt
European Patent Office
Office européen des brevets

**Beschwerdekammern**

**Boards of Appeal**

**Chambres de recours**

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0

**Case Number: T 0986/24 - 3.3.04**

# D E C I S I O N
# of Technical Board of Appeal 3.3.04
# of 13 January 2026

| | |
|---|---|
| **Appellant:** (Applicant) | Porton Biopharma Limited<br>Manor Farm Road<br>Porton Down<br>Salisbury, Wiltshire SP4 0JG (GB) |
| **Representative:** | Titmus, Craig Edward<br>Mathys & Squire<br>The Shard<br>32 London Bridge Street<br>London SE1 9SG (GB) |
| **Decision under appeal:** | **Decision of the Examining Division of the European Patent Office posted on 8 February 2024 refusing European patent application No. 20765071.4 pursuant to Article 97(2) EPC.** |

**Composition of the Board:**

| | |
|---|---|
| **Chairwoman** | M. Pregetter |
| **Members:** | O. Lechner |
| | M. Blasi |

## Summary of Facts and Submissions

I. The applicant (appellant) filed an appeal against the examining division's decision to refuse European patent application No. 20 765 071.4.

II. The examining division held that the invention defined in the set of claims of the main request (filed on 5 June 2023) and the auxiliary request (filed on 23 January 2024 during oral proceedings before the examining division) was not disclosed in the patent application in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC). The decision under appeal also contains an *obiter dictum* (page 7) in which the examining division states that no inventive step could be acknowledged (Article 56 EPC).

III. According to the minutes of the oral proceedings before the examining division, inventive step was discussed at the beginning of the oral proceedings (points 4 to 19). However, the discussion shifted to sufficiency of disclosure under Article 83 EPC without the examining division taking a decision on inventive step.

IV. With the statement of grounds of appeal, the appellant resubmitted sets of claims of a main request and an auxiliary request (identical to the requests in the decision under appeal), resubmitted documents D6 and D7, and filed new document D8. The appellant provided arguments concerning the disclosure of the invention under Article 83 EPC and also addressed inventive step under Article 56 EPC.

V. The appellant was summoned to oral proceedings as requested. In the communication pursuant to Article 15(1) RPBA, the board set out its preliminary opinion on several issues.

VI. The appellant reacted by filing the set of claims of a new main request and making the previous main request and auxiliary request new auxiliary requests 1 and 2.

VII. The oral proceedings before the board took place on 13 January 2026 by videoconference.

During the oral proceedings, the appellant replaced the main request with a new main request and withdrew auxiliary requests 1 and 2.

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

VIII. Reference is made to the following documents.

D6: R. Rau et al., Pediatr Blood Cancer, published online on 1 November 2017, doi:10.1002/pbc.26873:1-7

D8: "Package leaflet: Information for the user Oncaspar 750 U/ml powder for solution for injection/infusion, pegaspargase", 10/2022, 7 pages

IX. Claim 1 of the main request reads:

"1. A conjugate comprising L-asparaginase and a water-soluble polymer, for use in treating a disease treatable by L-asparagine depletion in a patient, wherein:
(a) the L-asparaginase is from a source other than *E. coli*;

(b) the L-asparaginase is expressed in a host cell other than *E. coli*; and
(c) the patient has previously been administered *E. coli*-derived L-asparaginase;

wherein the water-soluble polymer comprises polyethylene glycol (PEG);

wherein the patient has been identified as having a hypersensitivity to *E. coli*-derived L-asparaginase;

wherein the L-asparaginase is *Erwinia* L-asparaginase; and

wherein the disease treatable by L-asparagine depletion is cancer."

X. The appellant's arguments, where relevant to the decision, are summarised as follows.

*Admission of document D8*

*Document D8, the Oncaspar® package leaflet, should be admitted because it had been presented during the oral proceedings before the examining division and subsequently emailed to the examining division on 29 January 2024, but it did not appear to have been added to the file. Document D8 had been (re)filed at the earliest stage of the appeal proceedings and was directly relevant to the issues under Article 83 EPC as it evidenced that Oncaspar® did not list PEGylated medicinal products among the contraindicated or interacting medicines.*

*Main request*

*Admission - Article 13(2) RPBA*

The main request had been filed in direct reaction to objections raised for the first time during oral proceedings before the board.

*Disclosure of the invention - Article 83 EPC*

*Use of Erwinia L-asparaginase expressed in a host cell other than E. coli*

It was well known that host cell proteins (HCPs) are species- and even strain-specific. Accordingly, *Erwinia* L-asparaginase expressed in a host cell other than *E. coli* could be expected to be devoid of *E. coli* HCPs.

The patent application provided a plausible and technically sound therapeutic concept for the claimed patient subgroup. It identified highly immunogenic *E. coli* HCPs in Oncaspar® using ELISA and NetMHCIIpan binding predictions, providing a credible explanation for hypersensitivity upon re-exposure to *E. coli*-derived L-asparaginase. If any doubt arose as to whether a particular non-*E. coli* host cell was suitable, the skilled person could readily verify the absence of *E. coli* HCPs using the assays disclosed in the patent application, a task well within routine capabilities. By avoiding expression of *Erwinia* L-asparaginase in *E. coli*, the claimed invention credibly enabled treatment of cancer patients hypersensitive to *E. coli*-derived L-asparaginase.

*Use of PEGylated Erwinia L-asparaginase*

PEGylation (the process of attaching polyethylene glycol (PEG) chains to molecules) was a well-established strategy for extending half-life and reducing the antigenicity of therapeutic proteins, as described in the patent application and also acknowledged in document D6. The presence of anti-PEG IgG antibodies in patients was not a reliable indicator that these patients would elicit a hypersensitive immune response to subsequently administered PEG. Anti-PEG antibodies were widely circulating in the population due to the widespread use of PEG. If the presence of anti-PEG IgG antibodies truly predisposed patients to a hypersensitive immune response, the ongoing clinical use of PEGylated drugs and the widespread non-clinical use of PEG, e.g. in cosmetics, would have been severely constrained, which was clearly not the case.

Moreover, the ongoing regulatory approval and clinical use of PEGylated L-asparaginase (Oncaspar®), as set out in document D8, demonstrated that the use of PEG to extend the half-life of a therapeutic protein could not be regarded as inherently unsuitable or unsafe.
The examining division had improperly treated document D6's teaching as establishing a technical prejudice against the use of PEGylated L-asparaginase, requiring direct clinical evidence to counter it. This conflated Articles 83 and 56 EPC and set an unreasonably high burden of proof for enablement.

The examining division's reliance on document D6's small cohort and the correlation between anti-PEG IgG and hypersensitivity did not exclude an HCP-based explanation, nor did it undermine the patent

application's teaching. Moreover, the established clinical practice of switching patients with hypersensitivity to *E. coli*-derived L-asparaginase to native *Erwinia* L-asparaginase further supported the plausibility of the invention as claimed.

*Remittal - Article 111(1) EPC*

*If the objections under Articles 83 and 84 EPC were resolved, the case should be remitted to the examining division for further prosecution.*

XI. The appellant requested that:
- the decision under appeal be set aside and a patent be granted on the basis of the set of claims according to the main request filed at the oral proceedings before the board on 13 January 2026
- document D8 be admitted
- the case be remitted to the examining division for further prosecution

## Reasons for the Decision

*Admission of document D8 - Article 12(4) RPBA*

1. The appellant's assertion that document D8 had been submitted during the examination proceedings cannot be verified as no request was made to have the minutes or the decision corrected to record such a submission.

2. Document D8 was (re)filed at the earliest stage of the appeal proceedings and constitutes a direct reaction to the decision under appeal regarding disclosure of the invention under Article 83 EPC.

General doubts as to compliance with Article 83 EPC had been raised in point 5 of the examining division's communication accompanying the summons dated 10 August 2023. However, the objection based on an alleged technical prejudice against the use of PEGylated L-asparaginase appears to have been raised for the first time only during the oral proceedings (see minutes, point 26).

3. In view of these circumstances, the board admitted document D8 into the appeal proceedings pursuant to Article 12(4) RPBA.

*Main request*

*Admission - Article 13(2) RPBA*

4. The set of claims of the main request was filed during oral proceedings before the board.

The objections that elicited the amendments were raised and explained by the board for the first time during the oral proceedings and could not, therefore, have been anticipated or addressed earlier by the appellant. The amendments made to the main request were limited to overcoming these newly raised objections. They represent a direct and immediate reaction to developments during the oral proceedings and did not give rise to any new issues under the EPC.

5. The board was thus satisfied that exceptional circumstances, justified with cogent reasons, were present. In exercise of its discretion under Article 13(2) RPBA, the board therefore decided to admit the main request.

*Disclosure of the invention - Article 83 EPC*

6. *The examining division's reasoning*

The examining division decided that the claimed invention was not sufficiently disclosed under Article 83 EPC because document D6 provided a direct and unambiguous teaching-away from pursuing PEGylated asparaginase conjugates, for the treatment of patients who have developed hypersensitivity to *E. coli*-derived asparaginase. Document D6 explicitly implicated the PEG moiety of JZP-416 in the failure of trial AALL1421. An analysis based on the predicted immunogenicity of expression system-derived host cell protein (HCP) impurities present in a different PEG-asparaginase composition, comprising a structurally different asparaginase conjugate, was considered insufficient to overcome the serious technical prejudice deriving from the teaching of document D6.

The skilled person, comparing the level of evidence as well as the gravity of the adverse events, would still have considered extremely dangerous to administer to hypersensitive patients, a PEG-conjugate of the type used in document D6, even if expressed in a different expression system. The examining division considered that the burden to prove the suitability of the claimed PEGylated asparaginases for administration in the claimed subgroup of patients had not been discharged by the appellant (points "*A) II.1.12*" and "*A) II.1.13*" of the decision under appeal).

7. *Mechanism proposed by the patent application and supporting evidence*

7.1 The patent application reports on page 2, paragraph 2 that conjugation to polyethylene glycol (PEG) was a long-established strategy for improving pharmacokinetic and immunological properties of proteins. Well-known advantages of PEGylation included improved residual enzymatic activity, improved thermal stability, improved pH stability, increased resistance to proteolysis, increased *in vivo* half-life and reduced antigenicity.
*E. coli*-derived PEGylated asparaginase (EcASNase; pegaspargase; marketed as Oncaspar®) had been approved since 2006 for first-line treatment of acute lymphoblastic leukaemia (ALL) in children and adults.

7.2 The patent application proposes that, contrary to the conclusion drawn in document D6 (referred to as "Rau et al. (2018)"), hypersensitivity to PEGylated *E. coli*-derived L-asparaginase preparations, such as Oncaspar®, arose not primarily from immune reactions to PEG but from pre-existing immunity against *E. coli* host cell protein (HCP) impurities in the Oncaspar® preparation. Administration of *E. coli* HCPs primed patients immunologically, leading to a hypersensitivity response upon subsequent administration of *E. coli*-derived L-asparaginase (page 5, last paragraph ff).

7.3 The patent application provides evidence that Oncaspar® contains detectable amounts of *E. coli* HCP impurities (Example 1, Table 1). Example 2 further shows that the *E. coli* HCPs identified in Oncaspar® comprise peptides predicted to bind to major histocompatibility complex class II receptors with high to medium affinity, which

indicates potential immunogenicity of these *E. coli* HCP impurities (Example 2).

This evidence supports that immune responses against *E. coli* HCP contaminants could contribute to hypersensitivity in patients previously treated with *E. coli*-derived L-asparaginase. However, the evidence remains indirect as the immunogenicity of the identified HCPs is based solely on *in silico* prediction.

7.4 Example 6 of the patent application, although not involving a PEGylated *Erwinia chrysanthemi* L-asparaginase, shows that two patients who had developed immunological reactivity upon repeated administration of Oncaspar® tolerated a recombinant *Pseudomonas fluorescens*-expressed conjugate of *Erwinia chrysanthemi* L-asparaginase and a conformationally disordered polypeptide chain comprising proline, alanine and serine and achieved serum L-asparaginase activity within the therapeutic range at 48 hours after dosing. The patent application does not experimentally assess whether PEG itself may have contributed to the hypersensitivity observed with Oncaspar®.

7.5 Nevertheless, the data in Example 6 show that at least some patients with hypersensitivity to *E. coli*-derived L-asparaginase may benefit from treatment with *Erwinia* L-asparaginase expressed in a host cell other than *E. coli*. By identifying immunogenic *E. coli* HCP contaminants in Oncaspar® and reporting *in silico* indications of their potential immunogenicity (Examples 1 and 2), the patent application provides a credible mechanistic explanation for *E. coli* HCP-mediated effects.

8. *Teaching of document D6*

8.1 *Document D6 reports that although PEGylation was a widely used strategy to increase the half-life and reduce the immunogenicity and antigenicity of therapeutic agents, data from the AALL1421 phase 2 clinical trial raised concerns about PEG immunogenicity (Abstract, page 5, left-hand column, paragraph 2 ff; page 6, left-hand column, first full paragraph).*

In the reported clinical trial, PEGylated *Erwinia* asparaginase (pegcrisantaspase) was used as a replacement for *E. coli*-derived PEGylated L-asparaginase (pegaspargase) in patients hypersensitive to pegaspargase. Three of the four treated patients experienced hypersensitivity to (patients #3 and #4) and/or rapid clearance of (patients #1 and #4) pegcrisantaspase. The only patient without pre-existing anti-PEG serum IgG antibodies (patient #2) tolerated three doses of pegcrisantaspase without any clinical complications and maintained therapeutic serum asparaginase activity at day 15 after each infusion (Abstract; Results subsections 3.1 to 3.3; first paragraph of the Discussion).

The authors of document D6 concluded that these observations implied anti-PEG antibodies in the development of pegaspargase-induced hypersensitivity in a subset of patients. They questioned the use of PEGylation as an effective strategy for optimising *Erwinia* asparaginase administration (abstract; last two paragraphs of the Discussion).

In its introductory part, document D6 further discloses, with reference to the literature, that JZP-416, i.e. *Erwinia chrysanthemi*-derived

L-asparaginase expressed in *E. coli*, has minimal antigenic cross-reactivity with asparaginase derived from *E. coli*, thereby supporting the rationale for switching enzyme sources in patients with hypersensitivity to *E. coli*-derived L-asparaginase (page 2, left-hand column, paragraph 3).

8.2 However, the evidential value of the concerns in document D6 is limited since the underlying clinical study involved only four participants (page 3, point 3.1) and the administration protocols and patient histories differed greatly (page 3, point 3.2).

Moreover, the conclusion in document D6 that PEG was the immunogenic trigger is based solely on clinical correlations, i.e. pre-existing anti-PEG IgG antibodies, associated complement activation and the absence of anti-*Erwinia* asparaginase antibodies, and lacks any direct mechanistic experimental evidence.

The disclosure of document D6 does not address any potential contribution of *E. coli*-derived HCPs, let alone consider them immunogenic triggers.

8.3 The patent application, on the other hand, does address this aspect, i.e. the presence of other protein-based immunogens in the PEGylated L-asparaginase preparations. The patent application shows that PEGylated *E. Coli*-derived L-asparaginase preparations contain HCP impurities originating from the *E. coli* expression system.

The relevance of these HCP impurities is underscored by the identification of highly immunogenic HCP species in Oncaspar®, which, according to the patent application, provided a credible explanation and a mechanistic

concept for how prior exposure to such HCP impurities may prime the immune system and thereby contribute to subsequent hypersensitivity reactions.

8.4 The teaching of document D6 is furthermore insufficient to establish a technical prejudice. As established in the case law (see Case Law of the Boards of Appeal of the of the European Patent Office, 11th edn., 2025, I.D.10.2.1), a technical prejudice requires a prevailing but incorrect school of thought widespread throughout the technical field. Isolated reports or preliminary clinical observations do not meet this standard.

8.5 Moreover, the authors of document D6 expressly acknowledge that the small number of patients treated limited the ability of the study to determine the extent to which anti-PEG antibodies contribute to hypersensitivity reactions and silent inactivation of pegaspargase and that further detailed analysis of large populations would be required to determine the actual incidence of anti-PEG-mediated pegaspargase hypersensitivity (paragraph bridging pages 5 and 6). These explicit reservations make clear that the findings were considered preliminary and do not represent a prevailing technical opinion in the field.

8.6 In summary, document D6 does not provide conclusive evidence that PEG itself is the sole or primary trigger of hypersensitivity. Moreover, the disclosure of document D6 cannot establish a technical prejudice. It indicates at most a potential issue in a narrow study population under specific circumstances and therefore does not undermine the plausibility or credibility of the therapeutic concept underlying the claimed invention.

9. *Use of PEGylated Erwinia L-asparaginase*

The covalent attachment of PEG was, as noted in document D6 (see page 5, left-hand column, second paragraph) and also in the patent application (page 2, first full paragraph), a widely used strategy to increase the half-life and reduce the immunogenicity and antigenicity of therapeutic proteins. Moreover, PEGylated L-asparaginase (Oncaspar®) remained on the market for the treatment of ALL in children and adults as of October 2022 (document D8, page 1), several years after publication of document D6 in 2017. This continued regulatory approval indicates that the overall efficacy and safety profile of PEGylated L-asparaginase was regarded as acceptable by the competent regulatory authorities.

10. *Use of a host cell other than E. coli*

10.1 The appellant argued that hypersensitivity to *E. coli*-derived L-asparaginase arose primarily from immune responses against *E. coli* HCPs, with HCP repertoires being species- and strain-specific. Consequently, expressing *Erwinia* L-asparaginase in a host cell other than *E. coli* would avoid re-exposure to the relevant *E. coli* HCPs in sensitised patients. The patent application provided the skilled person with sufficient guidance to implement this therapeutic concept, including established methods for detecting HCPs and a detailed list of suitable non-*E. coli* host microorganisms for expression.

10.2 In addition to the credible mechanistic explanation for *E. coli* HCP-mediated effects discussed in point 7.5 above, the patent application also discloses methods for detecting HCPs, including ELISA-based assays, which are described as the current gold standard and were commercially available for *E. coli* HCPs (pages 25 to 26). The patent application also provides an extensive list of suitable non-*E. coli* microbial host cells, bacterial and fungal, capable of expressing *Erwinia* L-asparaginase (page 16 ff). This disclosure provides the skilled person with practical tools to verify the absence of *E. coli* HCPs in the final preparation and to select appropriate host cells for expressing *Erwinia* L-asparaginase for the indicated therapeutic use.

11. Thus, the patent application provides suitable *E. coli* HCP-detection tests as well as a detailed list of alternative host cell microorganisms other than *E. coli* on which the skilled person could rely when necessary. There is no evidence on file casting doubt on the appellant's mechanistic explanation linking the

immunological response to L-asparaginase to the species- and strain-specific HCP repertoire of the production host. Similarly, there is no evidence on file that the use of closely related non-*E. coli* host cells would, in practice, generate HCP profiles immunologically cross-reactive with those of *E. coli*.

12. *Conclusion*

Based on the evidence on file, it is credible that cancer patients with hypersensitivity to *E. coli*-derived L-asparaginase could benefit from treatment with a conjugate comprising PEG and *Erwinia* L-asparaginase expressed in a host cell other than *E. coli*. The requirements of Article 83 EPC are therefore met.

*Remittal - Article 111(1) EPC*

13. Inventive step was not conclusively dealt with by the examining division. According to the minutes of the oral proceedings, discussion of Article 56 EPC began but was not brought to a conclusion as the discussion during oral proceedings shifted to sufficiency of disclosure under Article 83 EPC, which ultimately formed the sole basis for the refusal. Accordingly, the decision under appeal only deals with the issue of sufficiency of disclosure in an appropriate manner. Although the decision also contains a section entitled *Obiter dictum*, this section has no further impact on the issue of remittal as it merely contains suggestions ("*seems to have consequences* [...] *in the assessment of inventive step*"), questions or statements on inventive step without proper reasoning.

14. In these circumstances, the board finds special reasons within the meaning of Article 11 RPBA justifying remittal.

The board, exercising its discretion under Article 111(1) EPC in conjunction with Article 11 RPBA, decided to remit the case for further prosecution.

**Order**

**For these reasons it is decided that:**

1. The decision under appeal is set aside.

2. The case is remitted to the examining division for further prosecution.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated