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Datasheet for the decision of 22 February 2021

Case Number: T 2517/19 - 3.3.07

Application Number: 15724638.0

Publication Number: 3151865

IPC: A61K47/68

Language of the proceedings: EN

Title of invention:
SITE-SPECIFIC CONJUGATION OF LINKER DRUGS TO ANTIBODIES AND RESULTING ADCS

Applicant:
Byondis B.V.

Headword:
Site-specific conjugation of drugs to antibodies / BYONDIS

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (yes)

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Case Number: T 2517/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 22 February 2021

Appellant: (Applicant)	Byondis B.V. Microweg 22 6545 CM Nijmegen (NL)
Representative:	van der Sterren-Mol, Josephine Synthon Biopharmaceuticals B.V. P.O. Box 7071 6503 GN Nijmegen (NL)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 3 April 2019 refusing European patent application No. 15724638.0 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Lécaillon
	P. Schmitz

Summary of Facts and Submissions

I. The appeal was filed by the appellant (applicant) against the decision of the examining division to refuse the European patent application No 15 724 638.0(hereinafter "the application").

II. The decision was based on a main request and four auxiliary requests wherein the main request and auxiliary requests 1-3 were filed on 14 February 2019 (and renumbered during examination oral proceedings) and auxiliary request 4 was filed during oral proceedings on 19 March 2019.

The independent claims of the main request read as follows:

"1. An antibody-drug conjugate compound wherein a linker drug is site-specifically conjugated to an IgG1 antibody through an engineered cysteine in said antibody at heavy chain position 41 according to Kabat numbering, wherein said linker drug comprises a duocarmycin derivative."

"11. A pharmaceutical composition comprising a compound according to any one of claims 1-10 and one or more pharmaceutically acceptable excipients, preferably in the form of a lyophilized powder."

"12. The compound according to any one of claims 1-10 or the pharmaceutical composition according to claim 11 for use as a medicament."

"13. The compound according to any one of claims 1-10 or the pharmaceutical composition according to claim 11

for use in the treatment of human solid tumours and haematological malignancies."

III. The following documents were cited in the International Search Report or submitted by the appellant during the examination proceedings:

D1: WO 2006/034488 A2
D3: WO 2007/038658 A2
D6: WO2013/093809 A1
D7: Report on the structure of the cavity in the Fab region of antibodies
D8: WO2017/089447 A1
D9: New Table 8 presenting additional hydrophobicity data and sequence alignment of the antibodies depicted in Table 8

IV. The examining division decided in particular that the subject-matter of the main request did not involve an inventive step. D1 was considered to represent the closest prior art. The claimed subject-matter differed from D1 in the position of modification of the antibody with an engineered cysteine. The reduced hydrophobicity alleged by the applicant had not been credibly substantiated as occurring over the entire scope of the claims. The problem to be solved by the application thus lay in the provision of an alternative amino acid in the heavy chain of an IgG1 antibody for cysteine engineering. Modifying an antibody at position H41 was considered to reside within the skills of a person, willing to find an alternative to position H40 of D1.

V. On 24 July 2019, with the statement setting out the grounds of appeal, the appellant filed a main request and four auxiliary requests. These requests

corresponded to the requests on which the decision was based.

VI. Oral proceedings were held *per* video conference on 22 February 2021.

VII. The appellant requested as a main request that the decision under appeal be set aside and that a patent be granted on the basis of the main request or one of the auxiliary requests 1 to 4 all filed with the statement setting out the grounds of appeal on 24 July 2019. However, the order of the auxiliary requests were to be changed. Auxiliary request 4 became auxiliary request 1 and the other auxiliary requests were to be renumbered accordingly.

VIII. The arguments of the appellant, as far as relevant for the present decision, can be summarised as follows:

The choice of the specific position H41 for engineering an IgG1 with a cysteine for further conjugation with duocarmycin, which constituted the distinguishing feature versus the closest prior art D1, was shown to lead to antibody-drug conjugates (ADCs) having reduced hydrophobicity, and thus better clearance properties, compared to ADCs based on the corresponding wild-type antibody conjugated to duocarmycin on reduced native cysteine residues. This effect would occur over the whole scope claimed as substantiated by experimental data and an *in silico* study. None of the prior art documents suggested to select said position for cysteine engineering to solve the problem of providing ADCs with improved physicochemical, pharmacological and/or pharmacokinetic properties. The main request did thus involve an inventive step.

Reasons for the Decision

Main request

1. Amendments

The subject-matter of independent claim 1 of the main request is based on original claims 1 and 4 as well as on page 19 line 14 of the original description. Claims 2-14 of the main request are based on original claims 3 and 6-17. Accordingly the main request fulfills the requirements of Article 123(2) EPC.

2. Sufficiency of disclosure and novelty

The examining division did not raise any objection of lack of sufficiency of disclosure or novelty for the present main request. The Board agrees that the subject-matter of the main request fulfills the requirements of Articles 83 and 54 EPC.

3. Inventive step

3.1 *Closest prior art*

3.1.1 In agreement with the examining division and the appellant, the Board considers D1 to represent the closest prior art.

3.1.2 D1 discloses antibody-drug-conjugates (ADCs) for use in the treatment of cancer wherein the antibody contains an engineered cysteine to which the drug moiety is linked. D1 focuses *inter alia* on the selection of the specific position at which the cysteine should be introduced. The position is to be chosen based on the

distance to the antigen binding site as well as on the thiol reactivity. Following said criteria D1 identifies potential substitution positions including H35-H45, which encompass the presently defined position H41 according to Kabat numbering. Furthermore D1 generally mentions duocarmycin in a list of chemotherapeutic agents.

3.2 *Distinguishing feature*

However D1 does not disclose any preferred embodiment nor any specific example of an ADC prepared with (i) duocarmycin and (ii) an antibody comprising an engineered cysteine at position H41 according to Kabat numbering.

3.3 *Technical effect*

3.3.1 The choice of duocarmycin as the drug moiety (distinguishing feature (i)) has no particular effect compared to D1, the drug moieties described in both in D1 as well as the application all having anti-cancer properties.

3.3.2 The experimental data provided in the original application (see table 1 and Figures 2A and 4A) as well as in D8 (see tables 3 and 5) and D9 (see table 8) substantiate that the selection of the specific position H41 (distinguishing feature (ii)) allows to reduce hydrophobicity of the thus obtained duocarmycin-containing ADCs compared to duocarmycin containing ADCs based on the wild type (wt) antibody conjugated on reduced native cysteine residues. These data further render credible that the reduced hydrophobicity avoids in turn rapid clearance of the ADCs *in vivo*.

Furthermore these experimental results reported for 26 different antibodies can be reasonably extrapolated to ADCs based on any IgG1 in view of the *in silico* study reported in the original application and in D7. This study was based on X-ray data of Fab parts of 1370 antibodies, wherein, as explained by the appellant, more than half of the antibodies are IgG1 and the remaining ones originate from IgG2 having common Fab domains with IgG1. According to this study, the primary as well as tertiary structures of said Fab domain are highly conserved amongst antibodies, especially the Fab cavity, which contains the amino acid in position H41 (Kabat numbering). The amino acid at said position is also highly conserved (over 90% proline or serine, see Appendix 2-3 of D7). Furthermore docking studies show that duocarmycin fits into said Fab cavity (see D7). Based on this conserved structure amongst antibodies, in particular IgG1, the experimental data on hydrophobicity obtained in the examples for various ADCs based on antibodies containing a cysteine at H41 (Kabat numbering) can credibly be extrapolated to any IgG1 engineered with a cysteine at said position H41. Additionally, as explained by the appellant, as the H41 position (Kabat numbering) is situated in the FR2 domain, *i.e.* not in the CDR domain providing the actual recognition of the antigen, maintenance of good antigen binding appears reasonable.

Consequently in the absence of any evidence in the prior art indicating that the effect on hydrophobicity, and thus on clearance, could not be extrapolated to any IgG1, the Board is of the opinion that there is no reason to consider that said effect would not occur over the whole breadth of the claims.

3.4 *Objective technical problem*

3.4.1 It follows that, starting from D1, the objective technical problem lies in the provision of further ADCs useful in the treatment of cancer and having good pharmacokinetic profile.

3.4.2 The Board considers that this problem has been solved by the claimed ADCs (see 3.3.2).

3.5 *Obviousness of the solution*

Duocarmycin is a well known chemotherapeutic agent already used in ADCs (see D1-D3 and D6) so that its selection is not regarded as inventive. However the prior art does not suggest that the specific position H41 (Kabat numbering) for cysteine engineering is advantageous in terms of hydrophobicity of the resulting ADC. D1 does indeed not identify any correlation between the selected residues and their position relative to the Fab pocket so as to reduce hydrophobicity compared to an ADC based on the wild type antibody. Hydrophobicity is actually not an issue in D1 as the drugs used in the examples are not as hydrophobic as the present duocarmycin. None of the other documents identifies this issue of hydrophobicity or let alone suggests a solution thereto. Therefore, when faced with the objective technical problem defined in point 3.4.1, the skilled person would not have modified the ADCs of D1 by linking duocarmycin through an engineered cysteine at position H41 (Kabat numbering).

3.6 As a result the main request fulfills the requirements of Article 56 EPC.

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 with the order to grant a patent on the basis of the set of claims of the main request filed with the letter dated 24 July 2019 and a description to be adapted thereto.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated