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Datasheet for the decision of 22 July 2025

Case Number: T 0056/24 - 3.3.07

Application Number: 19213148.0

Publication Number: 3692983

IPC: A61P1/00, A61K9/20, A61K9/28, A61K31/7068, A61P1/18, A61P15/08, A61P35/00, A61P35/02, A61P43/00, A61K47/26

Language of the proceedings: EN

Title of invention:

ORAL FORMULATIONS OF CYTIDINE ANALOGS AND METHODS OF USE THEREOF

Patent Proprietor:

Celgene Corporation

Opponents:

Lotus Pharmaceutical Co., Ltd.
SANDOZ AG
TEVA PHARMACEUTICAL INDUSTRIES, LTD.
Hoffmann Eitle Patent- und Rechtsanwälte Partnerschaftsgesellschaft mbB
STADA Arzneimittel AG
Generics [UK] Limited

Headword:

Oral azacytidine III/CELGENE

Relevant legal provisions:
EPC Art. 54, 111(1), 76(1), 123(2), 83, 56
RPBA 2020 Art. 12(4), 12(6), 11

Keyword:
Novelty - (yes) - implicit disclosure (no)
Remittal - (no)
Divisional application - added subject-matter (no)
Sufficiency of disclosure - (yes)
Inventive step - non-obvious modification
Late-filed evidence - admitted (no)

Decisions cited:
T 0230/18, T 2201/10, T 0145/22, T 0237/15

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Beschwerdekammern

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Case Number: T 0056/24 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 22 July 2025

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 17 October 2023 revoking European patent No. 3692983 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent 3 692 983 ("the patent") was granted with a single claim. It derived from the application EP19213148.0, wich was filed as divisional application of the application EP13182721.4, which in turn was a divisional application from the original application EP09746975.3 published as WO 2009/139888 A1.

Claim 1 as granted defined:

"A pharmaceutical composition comprising a therapeutically effective amount of 5-azacytidine for use in a method of treating a subject having acute myelogenous leukemia, wherein said method comprises orally administering said pharmaceutical composition and wherein the composition is an immediate release composition and releases the 5-azacytidine substantially in the stomach following oral administration to the subject."

II. Six oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention had not been sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as filed. The patent proprietor filed the appeal against the decision of the opposition division to revoke the patent.

The decision was based on the patent as granted (main request) and auxiliary requests 1-7 filed on 7 October 2022.

In its decision the opposition division cited *inter alia* the following documents:

D1: W0 2008/028193 A2
D2: US 2004/0186065 A1
D4: Blood (ASH Annual Meeting Abstracts) 2006, 108: Abstract 4850
D9: Leukemia, 2008, 22, 1680-1684
D17: Aulton's Pharmaceutics: The Design and Manufacture of Medicines, 3rd edition, 2007, 454-455
D29: Aulton's Pharmaceutics: The Design and Manufacture of Medicines, 2nd edition, 2002, 222-223
D32: WO 2006/034154 A2
D41: Adv. Drug Deliv. Rev., 1999, 36:125-141
D56: Summary of Product Characteristics for Vidaza® (2008)
D61: Clinical Pharmacokinetics Concepts and Applications, 3rd ed., Rowland & Tozer, 1995, pages 11-12, 128-129 and 131-132
D62: Fibrinolytic and Antithrombotic Therapy: Theory, Practice and Management, R. Becker and F. Spencer, 2006, "Aspirin"
D63: Can. J. Gastroenterol., 1997, 11(8),663-667
D64: Am. Fam. Physician, 2002, 66, 273-280

The opposition division arrived at the following conclusions:

(a) Claim 1 as granted related to the treatment of patients with acute myelogenous leukemia (AML) and did thereby not require the effective treatment of AML.

Claim 1 of auxiliary request 1 specified that the claimed composition was for use in a method of treating AML.

Auxiliary requests 2 and 3 additionally defined with respect to claim 1 as granted and auxiliary request 1 that the composition is a non-enteric coated immediate release composition.

Auxiliary requests 4 and 5 additionally defined with respect to claim 1 as granted and auxiliary request 1 that the composition is in the form of a tablet or capsule.

Auxiliary requests 6 and 7 combined the amendments of auxiliary requests 2/4 and 3/5.

(b) The claimed subject-matter did not benefit from the earliest priority of 15 May 2008. Document D9 therefore represented prior art under Article 54(2) EPC.

Document D9 described a study of escalating single doses of 5-azacytidine orally administered as a film-coated tablet in four patients suffering from cancer, including a patient with AML. The pharmacokinetic data reported in D9 demonstrated the immediate release of the active ingredient and the absence of an enteric coating. Documents D17 and D41 confirmed that such immediate release resulted in the release of the 5-azacytidine substantially in the stomach.

The subject-matter of claim 1, as granted as well as claim 1 according to auxiliary requests 1-7, therefore lacked novelty in view of document D9.

III. With its reply to the appeal opponent 2 filed the following document:

A67: Aliment. Pharmacol. Therap. (1989) 3, 223-232.

IV. In its communication pursuant to Article 15(1) RPBA the Board expressed the preliminary opinion that

- document A67 should not be admitted
- the subject-matter of the claims as granted is new over the prior art
- the case should not be remitted
- no other ground of opposition prejudices the maintenance of the patent as granted.

V. Oral proceedings were held on 22 July 2025.

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

(a) Admittance of document A67

The issue allegedly addressed by document A67 had already been raised by the patent proprietor in its response to the opposition. The filing of document A67 during the appeal proceedings therefore was not justified.

(b) Basis for the amendments

The subject-matter of claim 1 as granted found an adequate basis in the originally filed claims.

(c) Sufficiency

The patent credibly substantiated the suitability of the defined composition for effective treatment of the defined therapeutic indication in view of the reported bioavailability of 5-azacytidine from oral immediate release compositions. No serious doubts substantiated by verifiable facts were raised to support the opponents' objection regarding the sufficiency of disclosure of the claimed invention.

(d) Novelty

Contrary to the finding in the decision under appeal, claim 1 as granted was to be understood as defining the utility of the defined composition comprising 5-azacytidine for the effective treatment of AML.

Document D9 merely described a study regarding the safety and tolerability of single doses of up to 80 mg orally administered 5-azacytidine without mention of any therapeutic efficacy. Document D9 reported substantially lower plasma levels from the administration of these oral doses compared to the levels resulting from the established subcutaneous administration of a 135 mg dose and explicitly acknowledged that high oral doses may be required to actually achieve any clinically significant effect. Document D56 mentioned reduced subcutaneous doses of 5-azacytdine of 50% or 33% for the treatment of patients experiencing specific side effects. However, it had not been established that these reduced doses were therapeutically effective, let alone that with a bioavailability of 24.5% from

a single oral dose relative to 135 mg subcutaneous 5-azacytidine as described in document D9 any therapeutic benefit had been achieved. In contrast, the examples in the patent showed that adequately high serum levels for therapeutic efficacy could be achieved with the oral administration of the immediate release compositions as defined in claim 1 as granted.

Document D9 did furthermore not describe the investigated coated tablets to be immediate release compositions. Document D9 stated instead that the coating of the used tablets may have caused the delay in absorption observed after administration. In line with the common knowledge from document D61 this observed delay indicated the delayed release of the 5-azacytidine from the tablets. Such delay was also apparent from a comparison of the concentration profile presented in Figure 1 of document D9 with the concentration profiles reported for the exemplified immediate release compositions in the patent. The concentration profiles presented in Figure 1 of document D9 showing initial plasma values after about 30 minutes following administration were furthermore not indicative of an immediate release composition in view of documents D61-D64, which explained that enteric coated compositions may pass through the stomach within 0.5 hours. The profiles in Figure 1 of document D9 actually corresponded to the profiles reported in Figure 5 of document D1 for tablets with an enteric coating.

- Document D1 disclosed compositions with an enteric coating and did therefore not anticipate the subject-matter claim 1 as granted.

(e) Inventive step

The difference of the claimed subject-matter with respect to document D1 and D9 involved at least the feature of immediate release. The patent substantiated in examples 4-6 that oral administration of immediate release compositions comprising 5-azacytidine provided for effective treatment of AML. Example 6 of the patent demonstrated that the claimed immediate release compositions allowed for an increase in plasma levels with increased dosing, whereas the comparative composition with an enteric coating showed no such increase. The prior art provided no suggestion of such an improvement from the claimed subject-matter.

Furthermore, documents D1 and D9 themselves, along with *inter alia* documents D4 and D32, demonstrated a technical prejudice against the oral administration of 5-azacytidine in the form of immediate release compositions, or at least taught away rather than towards such compositions. Following the considerations in T 2201/10 the skilled person would therefore in any case not have arrived at the defined immediate release compositions as a solution to the problem of providing alternative effective treatment of AML.

The feature in granted claim 1 concerning the release of the 5-azacytidine substantially in the stomach merely further limited the scope of the defined composition for immediate release of the 5-azacytidine. This additional feature, compared to the claims examined in T 145/22, did not change the

meaning of the feature that the composition was for immediate release, which according to the patent excludes components that delay the release beyond the stomach.

VII. The arguments of the opponents relevant to the present decision are summarised as follows:

(a) Admittance of document A67

Document A67 represented common general knowledge that, when a delayed release tablet with an enteric coating passes the stomach, the coating slowly dissolves causing swelling and disintegration due to moisture entering the tablet core by capillary action and wicking (see A67, page 228, "The Mechanisms of Disintegration"). Document A67 was filed to address the appellant's argument that the skilled person would not be motivated to formulate 5-azacytidine as an immediate release composition, because 5-azacytidine was known to be unstable.

(b) Basis for the amendments

Claim 1 as granted comprised subject-matter extending beyond the original disclosure due to the combination of the selected features of the immediate release and AML as the disease to be treated.

(c) Sufficiency

The patent did not sufficiently disclose the suitability of the defined composition for effective treatment of the defined therapeutic indication. The formulations 1-3 of the patent,

which were tested for a clinical benefit all included a combination of 5-azacytidine with vitamin E. Moreover only Formulation 1 having a "leaky" enteric coating was used for patients with AML. The patent furthermore did not demonstrate the release in the stomach, which raised doubts whether the feature of the release in the stomach could be achieved, in particular when taking account of the short gastric residence time of only 5 minutes mentioned in document D29.

(d) Novelty

- Claim 1 as granted did not enjoy the priority of 15 May 2008. Document D9 thus represented prior art under Article 54(2) EPC.

  Document D9 already described a study in which 5-azacytidine was orally administered as a film-coated tablet to cancer patients, including a patient suffering from AML.

  The bioavailability profile reported in document D9 was in view of the common general knowledge represented by documents D17 and D41 indicative of an immediate release formulation. The reported profile was furthermore consistent with the bioavailability of the exemplified immediate release formulations 3 and 6 presented in Figure 11 of the patent. The delay in absorption following oral administration observed in document D9 was a delay relative to subcutaneous administration and did not indicate that the tested composition was a formulation for delayed release.

The patent provided a structural definition of the expression "immediate release" in terms of the absence of components that delay the release of the active agent beyond the stomach following oral administration. This structural definition did not correspond to the commonly accepted functional meaning of "immediate release" as a result to be achieved reflected in document D17. This functional meaning related to a prompt rate of direct drug release as opposed to delayed or extended release and did not imply a particular structural requirement.

In any case, the patent permitted that the claimed composition comprised a coating and even included an example of a composition with a "leaky" enteric coating. The patent further explained that the feature of the release "substantially in the stomach" meant that at least 10% of the 5-azacytidine was released in the stomach, allowing for up to 90% of the 5-azacytidine to be released from the claimed immediate release composition beyond the stomach. In this respect claim 1 of the patent differed from the claims of the parent patent in T 145/22, which did not comprise the feature of "substantially in the stomach". The composition used according to document D9 therefore also represented an immediate release composition within the definition of the patent.

In view of the release profiles for immediate release and controlled release formulations presented in document D41 and on account of the variable gastric residence times of 5 minutes to 20 hours reported in document D29 the bioavailability profile reported in document D9 also implied that

the 5-azacytidine was released substantially in the stomach.

Document D56 indicated that the recommended subcutaneous dose of 135 mg 5-azacytidine for the treatment of AML may be reduced by up to 33% to a still effective dose of only 45 mg. The concepts of "treating" and "therapeutically effective amount" were defined broadly in the patent. In line with the considerations in T 230/18, the bioavailability of 24.5% with respect to the known clinically effective subcutaneous dose of 135 mg 5-azacytidine described in document D9 therefore also implied effective treatment of AML.

Claim 1 as granted therefore lacked novelty in view of document D9.

- Document D1 described in Example 3 a dosage form corresponding to the immediate release composition described as Formulation 1 in the patent. Example 5 of document D1 described a study evaluating the safety and bioavailability of single oral doses of 5-azacytidine (60 mg and 80 mg) formulated according to Example 3. The subjects were cancer patients, including one patient with AML. Document D1 explicitly confirmed that the observed pharmacokinetic profile of the orally administered 5-azacytidine was sufficient for therapeutic use. Claim 1 as granted therefore also lacked novelty in view of document D1.

(e) Inventive step

- Insofar as the difference of the claimed subject-matter with respect to documents D1 or D9 concerned

the feature that the composition was for immediate release, no particular effect of the difference had been shown in comparison with the compositions of the prior art. The objective technical problem in view of document D1 or D9 therefore merely concerned the provision of an alternative composition for oral administration of 5-azacytidine in the treatment of AML.

No prejudice against immediate release compositions of 5-azacytidine had been established at the filing date of the patent. Document D4 already reported high bioavailability of 5-azacytidine from oral administration in dogs and document D9 reported adequate bioavailability following oral administration in cancer patients.

Moreover, claim 1 as granted defined an immediate release composition for release of the 5-azacytidine substantially in the stomach. The thereby defined amount of 5-azacytidine to be released in the stomach was according to the patent at least 10%, which left up to 90% of the 5-azacytidine for release in the intestine beyond the stomach. Document D1 described controlled release compositions for 5-azacytidine intended to release at least about 20% thereof beyond the stomach. In view of the overlap in the relative amount of 5-azacytidine that may be released beyond the stomach according to document D1 and the patent, document D1 could not be considered to teach away from the subject-matter of claim 1, at least not with regard to the whole scope of the claim. In this respect the case differed from the case decided in T 145/22, in which the claims did

not comprise the feature "substantially in the stomach".

The claimed invention did furthermore not overcome a prejudice, but merely tolerated the disadvantage of degradation as demonstrated by the low bioavailability of only up to 30% relative to subcutaneous administration reported in Figure 14 of the patent.

D17 and D61 demonstrated that immediate release formulations were commonplace. Document D2 further confirmed that the oral administration of 5-azacytidine had been envisaged. The considerations in T 237/15 also applied in the present case. The claimed subject-matter therefore lacked an inventive step.

- The claimed immediate release composition also lacked an inventive step in view of document D32 as the starting point in the prior art, because this document already described the utility of 5-azacytidine in the form of liquid formulations for oral administration.

VIII. In as far as relevant to the decision, the appellant-patent proprietor requested that

- the decision under appeal be set aside and that the patent be maintained as granted.

- document A67 not be admitted into the appeal proceedings.

IX. In as far as relevant to the decision, the respondents-opponents requested that the appeal be dismissed.

Reasons for the Decision

1. Admittance of document A67

In its communication pursuant to Article 15(1) RPBA the Board indicated that it intended not to admit document A67, because it should have been filed during the first instance proceedings and did not seem to address the issue that led to the decision under appeal. The patent proprietor had already argued in its response to the oppositions that the skilled person would not formulate 5-azacytidine for immediate release in view of its known instability. Moreover, the Board did not recognize how the reference to A67 by opponent 2 addressed that argument.

No substantive arguments were submitted by the opponents in response to the preliminary opinion expressed by the Board in its communication.

The Board has therefore confirmed the opinion expressed in the communication pursuant to Article 15(1) RPBA and has not admitted A67 into the appeal proceedings under Article 12(4) and 12(6) RPBA.

Main request (patent as granted)

2. Novelty

2.1 Document D9

2.1.1 The finding in the decision under appeal that the subject-matter of claim 1 as granted does not enjoy the

priority of 15 May 2008 was not in dispute. Document D9 therefore represents prior art under Article 54(2) EPC.

2.1.2 Effective amount / treatment

The Board considers that the utility defined in claim 1 as granted, which is formally directed to the use of the defined composition in a method of treating a subject having acute myelogenous leukemia (AML) with an effective amount of 5-azacytidine, will be understood by the skilled reader as directed to the effective treatment of AML in the defined subject.

Document D9 describes a pilot study concerning the oral administration of azacytidine. The document reports the pharmacokinetic profile and tolerability of single oral doses of 5-azacytidine up to 80 mg in the form of film-coated tablets administered to cancer patients, including one patient with AML (see D9, Abstract). Document D9 concludes that the single doses are bioavailable, safe and well tolerated (see D9, page 1683, left column).

However, document D9 does not explicitly report any therapeutic efficacy from the administration of the single doses. To the contrary, document D9 explicitly observes: "However, high oral doses may be required to overcome potential absorptive limitations of gastrointestinal administration and reach a clinically significant therapeutic effect" (page 1683, left column).

The plasma levels from oral administration (PO) reported in document D9 remain substantially below the levels resulting from the subcutaneous (SC) dose of 135 mg that was known to be effective in the treatment

of AML (see D9, page 1682, Figure 1). Whilst document D56 mentions that the generally recommended subcutaneous dose of 135 mg (75mg/m²) may be reduced to 50% or 33% thereof for a particular sub-group of patients experiencing certain side effects (see D56, page 3), the relative bioavailability of 24.5% for the oral administration in the patient with AML compared to a 135 mg subcutaneous dose reported in document D9 (see page 1682, Table 3, patient 3) still remains substantially below the dose reductions of 50% and 33% recommended in document D56 for a particular sub-group of patients. Any effective therapy is therefore also not implicitly derivable from the plasma profiles and the relative bioavailability described in document D9 for the orally administered doses of 5-azacytidine.

The Board distinguishes the situation in the present case, in which document D9 does not disclose any therapeutic effect, from the situation in T 230/18, in which the credibility of a disclosed therapeutic effect was addressed.

The Board therefore considers that document D9 does not disclose the utility of the described tablets for effective treatment of AML.

2.1.3 Immediate release / release substantially in the stomach

Claim 1 as granted defines an immediate release composition which releases the 5-azacytidine substantially in the stomach following oral administration. Paragraph [0043] of the patent explains that the immediate release feature means that the composition does not comprise any component, including a coating, which delays the release of some or all of

the active compound beyond the stomach. Paragraph [0045] of the patent defines the release substantially in the stomach independently from the immediate release feature as requiring that at least 10% of the 5-azacytidine is released in the stomach. The definition of the feature of the release substantially in the stomach therefore only restricts the definition of the immediate release compositions in claim 1 as granted.

Document D17 confirms that immediate release tablets are intended to release the drug rapidly directly after administration, which distinguishes immediate release tablets from prolonged and delayed release tablets, which are formulated to provide the release of the drug over an extended period of time or only after a delay (see D17, page 454 right column to page 455 left column).

Document D9 does not explicitly describe the investigated tablets as immediate release formulations, nor does it explicitly describe the release of the 5-azacytidine in the stomach.

As indicated by documents D61-D64, enteric coated compositions may pass through the stomach within 0.5 hours (see D61, page 132; D62, page 1; D63, page 666, Table 1; D64, page 274, Table 1). Document D29 confirms that gastric residence times may vary from as short as 5 minutes up to 2 hours. The release from an enteric formulation after 2 hours, as suggested in document D41, thus corresponds to the longer transit times within that range. However, in view of the possible shorter transit times the initial plasma values reported 30 minutes after administration for the tablets in document D9 do not exclude that the administered tablets still comprised an enteric coating

preventing the release in the stomach. Moreover, document D9 explicitly points out that a delay in absorption was observed, which it attributed to the coating of the tablets (see D9, page 1683, left column). The plasma profiles in Figure 1 of document D9 indeed appear to imply a delay when compared to the plasma profiles of the exemplified immediate release compositions presented in Figure 11 of the patent. Notably, the plasma profiles described in document D9 correspond to those reported in a similar study in document D1 for tablets with an enteric coating (see D1, Example 3 paragraph [00130]; Example 5, paragraphs [0142]-[0163]; Figure 5).

The Board thus concludes that it cannot be derived from document D9 that the tablets described in this document are immediate release compositions, nor that these tablets release the 5-azacytidine substantially in the stomach as defined in claim 1 as granted.

2.2 Document D1

Document D1 relates to controlled release compositions for oral administration of a cytidine analogue which release the agent primarily in the large intestine (see D1, paragraphs [0020]). The compositions typically comprise an enteric coating which allows them to pass the stomach intact (see D1, paragraph [0043]). As mentioned in section 2.1.3 above document D1 describes in Example 3 tablets containing 5-azacytidine provided with such an enteric coating which demonstrated a similar bioavailability profile as the tablets of document D9. In view of the purpose of controlled release of the compositions in document D1 the Board is not convinced that the tablets of example 3 of document

D1 comprised a "leaky" coating as mentioned for "Formulation 1" in the patent (see paragraph [0167]).

The Board therefore considers that document D1 does not describe immediate release compositions for oral administration of 5-azacytidine as defined in claim 1 as granted.

2.3 Accordingly, the Board concludes that the patent as granted complies with the requirement of novelty (Article 54 EPC).

3. No remittal

In view of the Board's conclusions concerning the novelty of claim 1 of the patent as granted the decision under appeal is to be set aside.

The decision under appeal does not deal with the raised grounds of opposition regarding the basis for the amendments, inventive step and sufficiency of disclosure. However, the patent proprietor has addressed these issues in its statement of grounds of appeal and the opponents have responded by at least providing their replies with respect to the issue of inventive step. Notably, no party to the appeal proceedings has requested the Board to remit the case to the first instance.

In view of these circumstances the Board considers that in the present case the fact that the decision under appeal did not deal with the issues of the basis for the amendments, inventive step and sufficiency of disclosure does not represent a special reason justifying remittal under Article 11 RPBA. The Board has therefore decided to continue the procedure in

accordance with Article 111 EPC to reach a conclusion on the only remaining grounds of opposition.

4. Basis for the amendments / Sufficiency

The Board expressed in the communication pursuant to Article 15(1) RPBA the preliminary opinion that claim 1 as granted was, for instance, adequately based on claims 71, 72 and 74 of the original PCT application which defined the use of 5-azacytidine in a composition intended for release substantially in the stomach for treating a disease associated with abnormal cell proliferation, specifying AML as the disease to be treated and characterizing the composition as prepared for immediate release.

The Board further expressed the preliminary opinion that the patent credibly disclosed the suitability of the claimed composition for the treatment of AML in view of the oral bioavailability of the exemplified immediate release compositions reported in the patent and that the opponents had not raised any serious doubts to substantiate their objection.

Notably, it was not in dispute that adequate exposure to 5-azacytidine following subcutaneous administration is effective in treatment of AML. Moreover, no evidence suggests that the exemplified formulations did not release the 5-azacytidine substantially in the stomach, or that the skilled person would face undue burden when formulating oral immediate release formulations for the release the 5-azacytidine substantially in the stomach.

No substantive arguments were submitted by the opponents in response to the preliminary opinion expressed by the Board in its communication.

Accordingly, the Board has confirmed the preliminary opinion that the patent as granted does not comprise subject-matter extending beyond the original disclosure (Articles 76(1) and 123(2) EPC) and sufficiently describes the claimed invention (Article 83 EPC).

5. Inventive step

5.1 Starting point in the prior art

Examples 4-6 of the patent (see paragraphs [00190]-[00198] and Figures 10-20) report that the oral administration of immediate release formulations comprising 5-azacytidine allows for achieving a similar exposure as that achieved with the recommended dose for subcutaneous administration, which is indicative of effective treatment of AML.

The Board considers document D1 to represent a more suitable starting point in the prior art than document D9, because in contrast to document D9 (see section 2 above) document D1 describes the oral administration of a therapeutically effective amount of 5-azacytidine in the treatment of a disease with abnormal cell proliferation such as AML (see D1, paragraphs [0020], [0023], [0082], [0094], [0142] and [00191]) and claim 1). The subject-matter of claim 1 as granted differs from the teaching of document D1 in that it relates to an immediate release composition for oral administration instead of a controlled release composition (see D1, paragraph [0020]).

Document D32 describes salt formation of cytidine analogues such as azacytidine to overcome the difficulties associated with the development of this

type of drugs (see D32, page 6, lines 28-36). This document therefore represents a less suitable starting point in the prior art than document D1.

5.2 Objective technical problem

In view of the results reported in examples 4-6 of the patent, in which conventionally prepared immediate release tablets comprising 5-azacytidine were used, the Board is satisfied that the claimed subject-matter may be considered to represent at least a solution to the objective technical problem of providing an alternative formulation for the oral administration of 5-azacytidine for use in the treatment of AML.

5.3 Assessment of the solution

5.3.1 The Board observes that document D1 itself (see pages 2-3, paragraphs [0007]-[0012]) reports that in general the oral delivery of the class of cytidine analogs, including in particular 5-azacytidine, has proven to be difficult due to a combination of chemical instability, enzymatic instability, and/or poor tissue permeability, and that various strategies have been proposed to improve the oral bioavailability of this class of drugs. Documents D4 ("Abstract", lines 8-12), document D9 (see page 1680, Abstract and Introduction), and document D32 (see page 6, lines 28-34) confirm the problematic stability of 5-azacytidine and the challenge this represents for the formulation of effective oral dosage forms. It is in this context that document D1 presents a controlled release pharmaceutical composition for oral administration to provide enhanced systemic delivery of a cytidine

analogue, in particular 5-azacytidine, to achieve effective therapy (see D1, paragraph [0020]).

The Board is of the opinion that starting from document D1 as closest prior art and aiming at a solution to the problem of providing an alternative formulation for the oral administration of 5-azacytidine for effective use in the treatment of AML, it would in line with the considerations in T 2201/10 (see reasons 5.1.3) and T 145/22 (see reasons 6.3.1) not seem obvious to the skilled person to arrive at an orally administered immediate release composition, because such a solution deviates diametrically from what was the essence of the disclosure in document D1, namely the delayed release of the 5-azacytidine intended to enhance its otherwise problematic systemic delivery.

The Board distinguishes the situation in the present case, in which the closest prior art specifically teaches away from the claimed immediate release compositions for oral administration, from the situation in T 237/15, in which the skilled person had a reasonable expectation of the effective oral administration of an agent based on its known oral bioavailability demonstrated in animal studies and its known efficacy human treatment when introduced directly into the blood stream (see T 237/15, reasons 4.6.1).

5.3.2 The opponents argued that document D1 did not teach away from the claimed subject-matter, because, unlike the claims evaluated in T 145/22, claim 1 as granted defined the feature of the release substantially in the stomach. According to the description of the patent this feature required the release of at least 10% in the stomach. This permitted in their view for the claimed composition the release of similar relative

amounts of 5-azacytidine beyond the stomach as described for the compositions of document D1.

However, as explained in section 2.1.3 above, the feature of the release substantially in the stomach only further limits the immediate release compositions as defined claim 1 as granted. Claim 1 as granted therefore excludes, in the same manner as the claims evaluated in T 145/22, any component serving to delay the release beyond the stomach. In contrast, document D1 specifically requires controlled release to achieve release of the 5-azacytidine primarily in the large intestine, for instance by including an enteric coating (see D1, paragraphs [0020] and [0043]). The release of at least 10% in the stomach, as specified in paragraph [0045] of the patent, does in any case not suggest that the claimed immediate release composition may realistically release a similar amount of 20% or more of its 5-azacytidine in the large intestine, as described for the controlled release compositions of document D1 (see D1, paragraph [0031]).

The Board therefore considers the opponents' argument not convincing.

5.3.3 The opponents further argued that no general prejudice or other consideration preventing the skilled person from providing oral administration of immediate release formulations of 5-azacytidine could be considered to have persisted following the publication of documents D4 and D9.

The Board also considers this argument not persuasive.

As explained in section 2.1.3 above the Board is not convinced that document D9 relates to an immediate

release formulation for oral administration of 5-azacytidine releasing the 5-azacytidine substantially in the stomach. In fact, document D9 specifically refers to the development of a film-coated formulation to circumvent the difficulty of rapid enzymatic catabolism and hydrolysis of 5-azacytidine in aqueous environments (see D9, page 1680, Abstract). Document D9 does therefore not dismiss, but confirm the difficulty of oral administration of 5-azacytidine addressed in document D1 and proposes a similar solution.

Document D4 mentions a study in which orally administered 5-azacytidine was absorbed rapidly with high bioavailability in dogs (see D4, Abstract, lines 22-24). However, document D4 further confirms the challenges that are associated with oral administration of 5-azacytidine and explicitly states that non-clinical testing is hampered by the difficulty of inappropriate animal models for representing human gastrointestinal tract conditions reported in document D4 (see D4, Abstract, lines 8-16). Document D4 does therefore also not dismiss, but confirms the difficulty of oral administration of 5-azacytidine addressed in document D1.

5.4 As explained in section 5.1 above the Board considers documents D9 and D32 less suitable starting points in the prior art than document D1, because document D9 does not describe effective treatment of a disease with abnormal cell proliferation such as AML and because document D32 relates to salts of cytidine analogues.

The opponents have argued that the skilled person would in view of the results reported in document D9 as a matter of obviousness increase the dose to achieve effective concentrations.

However, as mentioned in section 5.3.2 above document D9 specifically refers to the development of a film-coated formulation to circumvent the difficulty of rapid enzymatic catabolism and hydrolysis of 5-azacytidine in aqueous environments (see D9, page 1680, Abstract). Document D9 thus refers to the same difficulty of oral administration of 5-azacytidine as addressed in document D1 and suggests a similar solution. The very same considerations as set out in section 5.3.1 when starting from document D1 would therefore still apply if the skilled person were to attempt to adjust the dose for the formulation described in document D9 in order to achieve effective treatment.

The opponents have further argued that the skilled person would in view of the reference in document D32 to liquid pharmaceutical compositions for oral administration as a matter of obviousness arrive at the claimed immediate release compositions for use in the treatment of AML.

However, the compositions of document D32 are for salts of cytidine analogues to overcome the hydrolytic degradation, low solubility and minimal oral bioavailability otherwise associated with this type of drug (see D32, page 6, lines 28-36). This document thus also teaches away from the claimed immediate release composition for treatment of AML as defined in granted claim 1.

The subject-matter of claim 1 as granted would thus also not be obvious to the skilled person when starting from document D9 or document D32.

5.5 Accordingly, the Board concludes that the subject-matter of claim 1 as granted involves an inventive step and that the patent thus complies with the requirement of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is maintained as granted.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated