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Datasheet for the decision of 26 July 2024

Case Number: T 0145/22 - 3.3.07

Application Number: 09746975.3

Publication Number: 2299984

IPC: A61K9/20, A61K9/28, A61K31/7068

Language of the proceedings: EN

Title of invention:
ORAL FORMULATIONS OF CYTIDINE ANALOGS AND METHODS OF USE THEREOF

Patent Proprietor:
Celgene Corporation

Opponents:
Teva Pharmaceutical Industries Ltd
Generics (UK) Ltd

Headword:
Oral azacytidine/CELGENE

Relevant legal provisions:
EPC Art. 123(2), 54, 111, 56
RPBA 2020 Art. 11, 12(3), 12(4), 13(1)

Keyword:

Amendments - allowable (yes)
Novelty - (yes)
Remittal - (no)
Inventive step - (yes) non-obvious modification
Amendment to case - amendment admitted (yes)

Decisions cited:

T 2201/10, G 0002/10

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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
Fax +49 (0)89 2399-4465

Case Number: T 0145/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 26 July 2024

Appellant: (Patent Proprietor)	Celgene Corporation Route 206 & Province Line Road Princeton, NJ 08543 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent: (Opponent 1)	Teva Pharmaceutical Industries Ltd 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	D Young & Co LLP 3 Noble Street London EC2V 7BQ (GB)
Respondent: (Opponent 2)	Generics (UK) Ltd Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 3 December 2021 revoking European patent No. 2299984 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 2 299 984 ("the patent") was granted on the basis of ten claims.

Claim 1 as granted defined:

"A pharmaceutical composition for use in a method of treating a subject having cancer comprising orally administering to the subject the pharmaceutical composition comprising a therapeutically effective amount of 5-azacytidine, wherein the composition is an immediate release composition and wherein the cancer is acute myelogenous leukemia."

II. Two 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 was not 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 1-3 filed on 6 August 2021.

Claim 1 of auxiliary request 1 additionally defined with respect to claim 1 of the main request that the composition releases the 5-azacytidine in the stomach following oral administration to the subject.

Claim 1 of auxiliary request 2 additionally defined with respect to claim 1 of the main request that the

composition is a non-enteric coated immediate release composition.

Claim 1 of auxiliary request 3 combined the amendments of auxiliary request 1 and 2.

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

D1: W0 2008/028193 A2
D2: US 2004/0186065 A1
D3: Journal of Clinical Oncology, 25 (18) suppl. (June 2007), Abstract 7084
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
D30: Int. J. Cancer, 2008, 123, 8-13
D41: Epigenetics, 2006, 1(1), 7-13
D43: Summary of Product Characteristics for Vidaza® (2008)

The opposition division arrived at the following conclusions:

(a) The patent as granted (main request) comprised subject-matter extending beyond the original disclosure, because the application as originally filed disclosed the combination of features of claim 1 only in the context of a composition which released the 5-azacytidine substantially in the stomach following oral administration.

(b) Auxiliary request 1 complied with the requirements of Articles 123(2) and 84 EPC.

The subject-matter of auxiliary request 1 did not benefit from the earliest priority of 15 May 2008 due to the definition of the feature of immediate release. Document D9 therefore represented prior art under Article 54(2) EPC.

Document D9 described a safety and tolerability study of escalating doses of 5-azacytidine orally administered as a film coated tablet in patients suffering from myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML) or malignant solid tumors. The pharmacokinetic data reported in Figure 1 of document D9 demonstrated for a patient with AML (patient "201") the immediate release of the 5-azacytidine in the stomach.

Document D9 did not report the actual therapeutic effect on AML in the patient. However, the claims related to treatment of patients with AML and did thereby not require effective treatment of AML. Moreover, the teaching of the patent did in this respect not go beyond the content of document D9, because the patent itself failed to present data on therapeutic efficacy.

Claim 1 of auxiliary request 1 therefore lacked novelty in view of document D9.

(c) Auxiliary request 2 did not comply with Article 123(2) EPC due to the omission of the feature concerning the release in the stomach for similar reasons as set out for claim 1 as granted.

(d) The pharmacokinetic profile of the tablets described in document D9 demonstrated that these

tablets did not comprise any enteric coating. The subject-matter of auxiliary request 3 therefore lacked novelty for the same reasons as set out for the subject-matter of auxiliary request 1.

III. With the statement of grounds of appeal, the patent proprietor upheld the main request on which the decision under appeal was based (the patent as granted) and filed 7 auxiliary requests.

IV. With the statement of ground of appeal the patent proprietor filed *inter alia* the following documents:

A51: Clinical Pharmacokinetics Concepts and Applications, 3rd ed., Rowland & Tozer, 1995, pages 11-12, 128-129 and 131-132
A52: Fibrinolytic and Antithrombotic Therapy: Theory, Practice and Management, R.Becker and F.Spencer, 2006, "Aspirin"
A53: Can. J. Gastroenterol., 1997, 11(8),663-667
A54: Am. Fam. Physician, 2002, 66, 273-280

V. In its communication pursuant to Article 15(1) RPBA the Board expressed *inter alia* the preliminary opinion that the main request complied with the requirements of novelty and inventive step.

VI. Oral proceedings were held on 26 July 2024.

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

(a) Admittance of documents

Documents A51-A54 were filed in direct response to address misinterpretations of document D9 in the

decision under appeal and should therefore be admitted into the appeal proceedings.

(b) Basis for the amendments

The combination of features defined in claim 1 as granted was adequately based on original independent claims 71 in combination with the original dependent claims 72 and 74. The omission in claim 1 as granted of the feature regarding the release in the stomach as disclosed in original claim 71 was without consequence, because the release substantially in the stomach was not an essential feature of the disclosed invention. The original disclosure in the description starting from paragraph [00108] onwards referred to formulations for oral administration without the requirement of release in the stomach,including according to paragraph [00110] oral formulations for immediate release and according to paragraph [00137] sublingual tablets. The claimed subject-matter did therefore not involve any impermissible generalisation.

The application as filed specifically disclosed in paragraph [00110]orally administered compositions for immediate release independently of the feature of the release in the stomach. The skilled person would understand that the teaching regarding the treatment of AML as specifically mentioned in paragraph [00183] of the application as filed was also applicable with respect to these orally administered immediate release compositions, especially since the combination of the features of claim 1 had been indicated as preferred in claims 71, 72 and 74 as originally filed. The definition of the subject-matter in claim 1 as granted did therefore not involve a combined selection from multiple lists of options, but merely a limitation to

what was disclosed as an individualized embodiment in the application as filed.

(c) Novelty

The claims of the patent were directed at 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 5-azacytidine and reported lower plasma levels in comparison to those resulting from the established subcutaneous dosage form without mention of any therapeutic efficacy. Document D9 even explicitly observed that high oral doses may be required to actually achieve any clinically significant effect. 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 A51 this observed delay suggested 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 A51-A54, which explained that enteric coated compositions may pass through the stomach within 0.5 hours.

(d) Inventive step

The difference of the claimed subject-matter with respect to document D1 and D9 involved at least the feature of the 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 of plasma levels with increased dosing, whereas the comparative composition with an enteric coating showed no such increase. The prior art provided no suggestion towards such an improvement from the claimed subject-matter.

Moreover, documents D1 and D9 themselves indicated in line with documents D4, D30 and D41 a technical prejudice against 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 anyway not have arrived at the defined immediate release compositions as solution to the problem of providing alternative effective treatment of AML.

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

(a) Admittance of arguments and documents

During the oral proceedings the opponents declared not to maintain any objection against the admittance of documents A51-A54.

(b) Basis for the amendments

The combination of features in claim 1 as granted involving the oral administration of 5-azacytidine in a composition for immediate release and the treatment of subjects with AML, was originally only disclosed in the context of a composition which releases the 5-azacytidine substantially in the stomach following the oral administration. The release of the drug substantially in the stomach was included in all independent claims as originally filed and was described in paragraph [00015] of the application as filed as a key feature of the claimed invention. This feature could not be regarded as implicit in the definition of an orally administered composition for immediate release taking account of the reference to promptly dissolving sublingual tablets for absorption through the oral mucosa in paragraph [00137] of the application as filed, which in accordance with document D17 represented orally administered immediate release tablets. Such sublingual tablets had been excluded by the particular combination of features defined in claims 71, 72 and 74, which required the release substantially in the stomach, but were included in claim 1 as granted due to the omission of this feature. This omission therefore generated new information which had not been disclosed in the application as filed.

The passage in paragraph [00110] of the application as filed referring to immediate release compositions without mention of the release in the stomach was subject to the general disclosure of the claimed invention of paragraph [00015] and therefore provided no basis for the omission of the feature of the release in the stomach in claim 1 as granted. In as far as this passage was nevertheless considered to disclose the feature of immediate release independently from the release in the stomach, such disclosure was not specifically linked to the feature of AML as the disease to be treated. The combination of these features in claim 1 as granted therefore anyway involved a dual selection, for which the application as filed provided no basis.

(c) Novelty

The patent provided in paragraph [00043] 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. Such a structural definition was not in keeping with the commonly accepted functional meaning of "immediate release" as a result to be achieved. In accordance with document D17 this functional meaning related to a prompt rate of direct drug release distinct from delayed or extended release without requiring a specific pharmacokinetic profile. In line with the established jurisprudence this commonly accepted broad functional meaning was decisive for the scope of the claim. Document D9 already described that the oral administration of 5-azacytidine to a patient suffering from AML in the form of a film coated tablet resulted in a

bioavailability profile which was consistent with the profile described for the formulations in the patent. The composition used according to document D9 therefore qualified as an immediate release composition.

The bioavailability of 24.5% with respect to the known clinically effective subcutaneous dose of 135 mg 5-azacytidine described in document D9 was indicative for effective treatment of the patient with AML taking account of the information in document D43, which referred to effective subcutaneous doses as low as 45 mg. The patent itself provided likewise only bioavailability data for the claimed composition for assuming its suitability for effective treatment of AML and thus presented no new teaching regarding the efficacy of the claimed composition.

(d) Inventive step

In as far as the difference with respect to documents D1 or D9 concerned the feature of the immediate release, no particular effect of the difference had been shown by direct comparison with the compositions of the prior art. Moreover, any effect demonstrated in example 6 of the patent would not apply with respect to the whole scope of the claims. The objective technical problem therefore merely concerned the provision of an alternative composition for oral administration of 5-azacytidine in the treatment of AML. As was evident from document D17 the provision of an orally administered immediate release tablet was a standard option representing the most common type of orally administered tablet and therefore lacked an inventive step. Following the publication of documents D2, D3, D4 and D9 no prejudice against immediate release compositions of 5-azacytidine existed at the filing

date for the patent. The claimed invention did anyway not overcome any 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.

Moreover, due to the omission of the feature of release in the stomach the definition of the composition in claim 1 as granted included sublingual tablets. The prior art provided no disincentive regarding the formulation of 5-azacytidine in a sublingual tablet, which according to document D17 represented a well known type of immediate release tablet. In as far as the skilled person could not have expected such a sublingual tablet to be effective on the basis of the prior art, the patent provided no relevant experimental data indicating the efficacy of sublingual tablets to support an inventive step for these formulations.

In as far as the difference with document D9 concerned the effective treatment, it would in view of the reported bioavailability of 24.5% seem obvious to increase the dose to achieve effective concentrations.

Moreover, the encouraging bioavailability from oral administration in dogs reported in documents D3 and D4 provided the skilled person with a reasonable expectation that oral formulations of 5-azacytidine for immediate release would be suitable for treatment of AML. This expectation would also be based on the reference in document D3 to ongoing clinical studies.

IX. The appellant-patent proprietor requested that the decision under appeal be set aside and that the patent be maintained as granted.

X. Respondent-opponent 1 and respondent-opponent 2 requested that the appeal be dismissed.

The opponents further requested that the case not be remitted to the opposition division, in particular in the event that the Board would hold that any of the proprietor's request meets the requirement of novelty.

Reasons for the Decision

1. Admittance of new evidence

Document A51, a textbook reference, as well as documents A52-A54 were cited by the proprietor to support the argument that contrary to the finding in the decision under appeal enteric coated compositions may pass through the stomach within 0.5 hour and that the pharmacokinetic data in document D9 were therefore not indicative for an immediate release composition.

Document A51 was further cited by the proprietor as evidence of common general knowledge that absorption is a two-step process and dissolution is often the rate-limiting step in absorption. Contrary to the finding in the decision under appeal the suggestion in document D9 regarding a delay in absorption due to the coating would therefore not refer to an effect of the coating occurring only after the dissolution.

The Board considers the filing of documents D51-D54, justified as a response by the patent proprietor to considerations in the decision under appeal, which were according to the patent proprietor not in line with the skilled person's common general knowledge. No

objections against the admittance of these documents were upheld by the opponents and the filing of documents A51-A54 raises no new issues. The Board has therefore admitted documents A51-D54 into the appeal proceedings under Article 12(4) RPBA.

Main request (patent as granted)

2. Basis for the amendments

The application as filed describes from paragraph [00108] onwards under the heading "C. Pharmaceutical Formulations" embodiments relating to pharmaceutical formulations comprising a cytidine analog such as 5-azacytidine which are prepared for oral administration, preferably for release in the stomach. In paragraph [00110] under the sub-heading "Performance of Certain Dosage Forms Provided Herein" the application as filed specifically describes that in certain embodiments the formulations comprising a cytidine analog such as 5-azacytidine are orally administered compositions for immediate release without specific reference to the release in the stomach. In paragraph [00137] the application as filed describes that in certain embodiments the composition may be a sublingual tablet for absorption through the oral mucosa, which may dissolve promptly and provide rapid release of the drug.

The application as filed furthermore specifically highlights the treatment of acute myelogenous leukemia (AML) as particular embodiment of the disorder associated with abnormal cell proliferation to be treated in accordance with the claimed invention (see paragraph [00183]).

In addition, the application as filed provides in independent claim 71 in connection with its dependent claims 72 and 74 a clear pointer to the combination of features involving immediate release of 5-azacytidine from orally administered formulations and the treatment of AML, be it with the specification in claim 71 that the active agent is released substantially in the stomach.

According to G 2/10 the assessment whether the patent comprises subject-matter extending beyond the content of the application as filed is based on what the skilled person would derive directly and unambiguously from the whole of the application as originally filed. As pointed out by the opponents all the independent claims as originally filed indeed included the feature of the release substantially in the stomach. The application as filed stated accordingly in paragraph [00015] under the heading "Summary" that pharmaceutical compositions comprising cytidine analogs are provided, wherein the compositions release the API substantially in the stomach upon oral administration. It is however evident from the embodiments mentioned in paragraphs [00108], [00110] and [00137] that the original disclosure as a whole is not restricted to the originally claimed compositions which released the active agent substantially in the stomach and expressly includes orally administered immediate release compositions comprising 5-azacytidine without the requirement regarding the release in the stomach as an alternative embodiment.

The Board therefore considers that the subject-matter of claim 1 as granted does not involve a new combination of features selected from multiple lists or otherwise results from an impermissible generalization

by omission of a crucial feature, but rather reflects the limitation to an embodiment which had been highlighted in the application as originally filed, namely the treatment of AML, by the administration a specifically disclosed composition comprising 5-azacytidine, namely by oral administration of an immediate release composition.

Accordingly, the Board concludes that the subject-matter of claim 1 as granted is directly and unambiguously derivable from the original disclosure and that the patent therefore complies with the requirement of Article 123(2) EPC.

3. Priority

The finding in the decision under appeal that the subject-matter of the claims as granted does not enjoy the priority of 15 May 2008 and that document D9 therefore represents prior art under Article 54(2) EPC was not in dispute.

4. Novelty

4.1 Effective treatment of AML

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 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. In this context the patent explains that oral administration of immediate release formulations comprising 5-azacytidine in doses up to 1200 mg allows to achieve an exposure indicative

for effective treatment from single or multiple daily dosing of 5-azacytidine based on the results in examples 4-6 (see paragraphs [00190]-[00209]).

Document D9 describes a pilot study of oral azacytidine reporting the pharmacokinetics and tolerability of single oral doses of 5-azacytidine up to 80 mg in the form of film coated tablets. Document D9 concludes that the single doses are bioavailable, safe and well tolerated. However, document D9 does not explicitly report any therapeutic efficacy from administration of the single doses and specifically states in this context (see D9, page 1683, left column): "However, high oral doses may be required to overcome potential absorptive limitations of gastrointestinal administration and reach a clinically significant therapeutic effect."

No effective therapy is implicitly derivable from the plasma levels described in document D9. The plasma levels from the oral administration (PO) reported in document D9 are substantially below the level resulting from the subcutaneous (SC) dose of 135 mg that was known to be effective (see D9, Figure 1). Document D43 only confirms on pages 2 and 12 the subcutaneous administration of 135 mg as the recommended starting dose and mentions lower doses of 67,5 and 45 mg expressly only in the context of an example of how to calculate individual doses.

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

4.2 Immediate release

Claim 1 as granted relates to a composition for the defined use, wherein the composition is defined as an immediate release composition for oral administration of 5-azacytidine. Document D17, which was relied upon by the opponents, 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 for 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. The initial observed plasma levels after about 30 minutes following administration as reported in document D9 (see page 1682, Figure 1) do not implicitly indicate that the tablets of document D9 were immediate release compositions, because even enteric coated tablets may well pass through the stomach into the intestine within 30 minutes to give rise to initial plasma levels as reported in document D9 (see A51, page 132, lines 5-6).

Document D9 actually mentions an observed delay in absorption which it attributes to the coating of the tablets (see page 1683, left column). The plasma profiles reported in document D9 (see Figure 1) reaching peak levels between 1-2 hours following administration indeed suggest a delayed release with respect to the plasma profiles presented in the patent (see Figure 11) for the exemplified immediate release compositions F3 and F6 reaching peak levels an hour

after administration. As the absorption of a solid drug is a two step process involving dissolution and actual uptake by the body (see A51, page 128) the delay in absorption as observed in document D9 is indicative for a delayed release composition rather than an immediate release composition.

The Board therefore considers that document D9 does not disclose an immediate release composition.

4.3 Accordingly, the Board concludes that the subject-matter of claim 1 as granted is new in view of document D9 and that the patent thus complies with the requirement of Article 54 EPC.

5. No remittal

In view of the Board's conclusions concerning the basis for the amendments and compliance with the requirement of novelty in relation to claim 1 of the patent as granted the decision under appeal is to be set aside.

The opponents have specifically requested the Board not to remit the case to the first instance. The patent proprietor has not requested a remittal either. Moreover, the patent proprietor and the opponents have provided their arguments regarding the ground of opposition concerning inventive step. The opponents have furthermore during the appeal proceedings not maintained that the patent lacks sufficient disclosure of the claimed invention.

In view of these circumstances the Board considers that the lack of a finding in the decision under appeal on the issues of inventive step and sufficiency of disclosure does not represent in the present case 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 ground of opposition which concerns the requirement of inventive step.

6. Inventive step

6.1 Starting point in the prior art

Examples 4-6 of the patent (see paragraphs [00190]-[00209]) report that oral administration of immediate release formulations comprising 5-azacytidine allows to achieve an exposure indicative for effective treatment from single or multiple daily dosing of 5-azacytidine.

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 4 above) document D1 describes the oral administration of a therapeutically effective amount of 5-azacytidine in 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 teaching of document D1 differs from the subject-matter of claim 1 as granted in that it relates to oral administration of delayed release compositions.

6.2 Objective technical problem

In view of the results reported in examples 4-6, 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. The opponents have questioned whether on the basis of the provided experimental data an oral formulation for immediate release in the form of a sublingual tablet could also be regarded as a solution to the mentioned objective technical problem. However, the Board finds no basis to doubt that given the demonstrated effectiveness of conventionally prepared immediate release tablets a promptly dissolving sublingual tablet intended for absorption through the oral mucosa as mentioned in paragraph [00137] should lack such effectiveness.

6.3 Assessment of the solution

6.3.1 The Board observes that document D1 itself (see pages 2-3, paragraphs [0007]-[0012]) reports that in general oral delivery of the class of cytidine analogs, including in particular 5-azacytidine, has proven difficult due to the combinations 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. This teaching in document D1 is in line with document D30 (see page 8, right column), document D41 (page 8, right column) as well as document D4 (under "Abstract", lines 8-12) and document D9 (see page 1680, Abstract and Introduction), which refer to 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

analog, 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 with the aim 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 T2201/10 (see reasons 5.1.3) not seem obvious to the skilled person to arrive at an orally administered immediate release composition, because such a solution deviates in light of the aim pursued diametrically from what was the essence of the disclosure in document D1, namely the delayed release of the 5-azacytidine disclosure to enhance its otherwise problematic systemic delivery.

6.3.2 The opponents 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 D2, D3, D4 and D9.

The Board does not consider this argument persuasive.

As explained section 4.2 above the Board is not convinced that document D9 relates to an immediate release formulation for oral administration of 5-azacytidine. 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 under "Abstract", lines 8-16). Document D4 does therefore also not dismiss but confirm the difficulty of oral administration of 5-azacytidine addressed in document D1.

Document D3 also refers to the rapid absorption with high bioavailability of 5-azacytidine following oral administration in dogs and reports that based on preclinical studies a single-treatment study of oral azacytidine is underway in subjects with MDS, AML or solid tumors to assess the safety, tolerability and pharmacokinetics of escalating single doses of orally administered 5-azacytidine. However, document D3 does not mention the actual nature of the oral administration form under investigation. Document D3 is therefore also not suitable to dismiss the difficulty of oral administration of 5-azacytidine addressed in document D1.

Document D2 envisages in a generic manner that solid state forms of 5-azacytidine may be formulated in oral administration forms such as tablets and in parenteral administration forms such as solutions for injections, and that the compound be formulated to achieve quick or

delayed release (see D2, paragraphs [0048]-[0049]). However, without any further substantiation, for instance in the form of tested examples, this mere generic reference to envisaged administration forms in document D2 cannot be considered to dismiss the difficulty of oral administration of 5-azacytidine addressed in document D1.

6.4 As explained in section 6.1 above the Board considers document D9 a less suitable starting point in the prior art than document D1, because document D9 does not even describe effective treatment of a disease with abnormal cell proliferation such as AML.

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 6.3.2 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 6.3.1 when starting from document D1 would therefore anyway apply, in case the skilled person should attempt to adjust the dose for the formulation described in document D9 in order to achieve effective treatment. The subject-matter of claim 1 as granted would thus also not be obvious to the skilled person when starting from document D9 as closest prior art.

6.5 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:

A. Vottner A. Usuelli

Decision electronically authenticated