21 March 2019
EMA/COMP/126402/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 19-21 February 2019

Chair: Violeta Stoyanova-Beninska – Vice-Chair: Armando Magrelli

19 February 2019, 08:30-19:30, room 03-E

20 February 2019, 08:30-18:00, room 03-E

21 February 2019, 08:30-15:00, room 03-E

Disclaimers

Some of the information contained in this set of minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also vary during the course of the review. Additional details on some of these procedures will be published in the COMP meeting reports once the procedures are finalised.

Of note, this set of minutes is a working document primarily designed for COMP members and the work the Committee undertakes.

Further information with relevant explanatory notes can be found at the end of this document.

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction 5

1.1. Welcome and declarations of interest of members and experts 5

1.2. Adoption of agenda 5

1.3. Adoption of the minutes 5

2. Applications for orphan medicinal product designation 5

2.1. For opinion 5

2.1.1. - EMA/OD/0000001908 5

2.1.2. - EMA/OD/0000001901 6

2.1.3. - EMA/OD/0000002181 6

2.1.4. codon-optimised human cystic fibrosis transmembrane conductance regulator messenger ribonucleic acid complexed with lipid-based nanoparticles - EMA/OD/0000002333 8

2.1.5. adeno-associated viral vector serotype rh10 containing the human cholesterol 24-hydroxylase gene - EMA/OD/0000002264 9

2.1.6. - EMA/OD/0000002429 10

2.2. For discussion / preparation for an opinion 11

2.2.1. marzeptacog alfa (activated) - EMA/OD/0000002304 11

2.2.2. 1-[(3S)-3-{4-amino-3-[(3,5-dimethoxyphenyl)ethynyl]- 1H-pyrazolo[3,4-d]pyrimidin-1-yl}pyrrolidin-1-yl]-2-propen- 1-one - EMA/OD/0000002457 12

2.2.3. 2-[3-(2-chloro-4-{[5-cyclopropyl-3-(2,6-dichlorophenyl)-1,2-oxazol-4-yl]methoxy}phenyl)-3-hydroxyazetidin-1-yl]pyridine-4-carboxylic acid—2-amino-2-(hydroxymethyl)propane-1,3-diol (1/1) - EMA/OD/0000002498 13

2.2.4. - EMA/OD/0000002526 13

2.2.5. - EMA/OD/0000002530 13

2.2.6. - EMA/OD/0000002559 14

2.2.7. - EMA/OD/0000002563 14

2.2.8. - EMA/OD/0000002735 14

2.2.9. - EMA/OD/0000002754 14

2.2.10. 4-hydroxy-6-{2-[4-(trifluoromethyl)phenyl]ethyl}pyridazin-3(2H)-one - EMA/OD/0000002821 14

2.2.11. - EMA/OD/0000002861 15

2.3. Revision of the COMP opinions 15

2.4. Amendment of existing orphan designations 15

2.5. Appeal 15

2.6. Nominations 15

2.6.1. New applications for orphan medicinal product designation - Appointment of COMP rapporteurs 15

2.7. Evaluation on-going 15

3. Requests for protocol assistance with significant benefit question 15

3.1. Ongoing procedures 15

3.1.1. -..... 15

3.1.2. -..... 15

3.1.3. -..... 16

3.1.4. -..... 16

3.1.5. - - 16

3.1.6. -..... 16

3.2. Finalised letters 16

3.2.1. - - 16

3.2.2. -..... 16

3.3. New requests 16

3.3.1. -..... 16

4. Review of orphan designation for orphan medicinal products at time of initial marketing authorisation 17

4.1. Orphan designated products for which CHMP opinions have been adopted 17

4.2. Orphan designated products for discussion prior to adoption of CHMP opinion 17

4.2.1. – Pegvaliase – EMEA/H/C/004744, EMEA/OD/112/09, EU/3/09/708..... 17

4.2.2. - Autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human betaA-T87Q-globin gene – EMEA/H/C/003691, EMA/OD/146/12, EU/3/12/1091 17

4.2.3. - pacritinib - EMEA/H/C/004793 17

4.3. Appeal 17

4.4. On-going procedures 17

4.5. Orphan Maintenance Reports 17

5. Review of orphan designation for authorised orphan medicinal products at time marketing authorisation extension 18

5.1. After adoption of CHMP opinion 18

5.2. Prior to adoption of CHMP opinion 18

5.2.1. Imnovid – pomalidomide – Type II variation – EMEA/OD/053/09, EU/3/09/672, EMEA/H/C/002682/II/0031/G 18

5.3. Appeal 18

5.4. On-going procedures 18

6. Application of Article 8(2) of the Orphan Regulation 18

7. Organisational, regulatory and methodological matters 18

7.1. Mandate and organisation of the COMP 18

7.1.1. Strategic Review & Learning meetings..... 18

7.1.2. Protocol Assistance Working Group (PAWG) 18

7.1.3. Non-Clinical Working Group 18
7.1.4. Prevalence Working Group 18
7.2. Coordination with EMA Scientific Committees or CMDh-v 19
7.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups 19
7.3.1. Working Party with Patients' and Consumers' Organisations (PCWP) 19
7.3.2. Working Party with Healthcare Professionals' Organisations (HCPWP) 19
7.3.3. SAWP/COMP joint membership 19
7.4. Cooperation within the EU regulatory network 19
7.4.1. European Commission 19
7.5. Cooperation with International Regulators 19
7.5.1. Food and Drug Administration (FDA) 19
7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA) 19
7.5.3. The Therapeutic Goods Administration (TGA), Australia 19
7.5.4. Health Canada 19
7.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee 19
7.7. COMP work plan 20
7.8. Planning and reporting 20
7.8.1. List of all applications submitted/expected and the COMP rapporteurships distribution of valid applications submitted in 2019 20
7.8.2. Overview of orphan marketing authorisations/applications 20
8. Any other business 20
8.1. Concepts of significant benefit (follow-up to COMP Work Plan 2017) 20
8.2. Presentation on Study to support the evaluation of the EU Orphan Regulation 20
***List of participants* 21**

1. Introduction

1.1. Welcome and declarations of interest of members and experts

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some meeting participants in upcoming discussions as included in the pre-meeting list of participants and restrictions. Participants in this meeting were asked to declare any changes, omissions or errors to their declared interests and/or additional restrictions concerning the matters for discussion. No new or additional interests or restrictions were declared. Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 23 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

The agenda for 19-21 February 2019 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 4-6 December 2018 were adopted with amendments and will be published on the EMA website.

The COMP minutes for 22-24 January 2019 were adopted with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. - EMA/OD/0000001908

Treatment of Polycythemia Vera

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the non-clinical studies and preliminary clinical observations, to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

In particular:

- The sponsor should justify the dose of ruxolitinib as a comparator used in the non-clinical studies.
- The sponsor should discuss the results of the *in vivo* study, including the effects on splenomegaly, Hb (haemoglobin) and Htc (haematocrit).
- The sponsor should detail the results of any clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients.

The sponsor should further elaborate on the potential risks with the product and how this compares with the safety profile of currently authorised medicinal products for the same condition.

In the written response, and during an oral explanation before the Committee on 19 February 2019, the sponsor elaborated on the raised issues, noting that the total dose of ruxolitinib of 180mg/Kg once daily has been considered in line with the literature (Quintas-Cardama A, *et al.* Blood. 2010;115(15):3109-3117.) In this context, a more pronounced statistically significant effect was observed by treatment with the product versus ruxolitinib, as well as a numerical trend of improved spleen size. No dose-response of the comparator has been described.

The sponsor also reported the corresponding experience from five patients with PV (Polycythemia Vera) and rheumatoid arthritis or vasculitis, who were under treatment with a combination of methotrexate and hydroxyurea. No clear comparisons versus ruxolitinib could be made from these narratives.

The COMP considered that while the medical plausibility in the sought indication may be supported by the non-clinical data, the preliminary clinical observations were difficult to interpret on the basis of co-morbidities and concomitant treatments. Therefore a comparative discussion versus the authorised counterparts in PV could not be made for the purpose of justifying the assumption of significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 20 February 2019, prior to final opinion.

2.1.2. - EMA/OD/0000001901

Treatment of Duchenne muscular dystrophy

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 14 February 2019, prior to responding to the list of issues.

2.1.3. - EMA/OD/0000002181

Treatment of endophthalmitis

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

Endophthalmitis should be justified as a distinct medical entity as opposed to an iatrogenic complication. Note that this is for the purposes of orphan medicinal product designation; the

sponsor's attention was drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

- Number of people affected

Notwithstanding the acceptance of the orphan condition, the current prevalence calculation should be updated.

For the calculation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation". More transparency is needed if figures are derived from commercial databases where the COMP has no access. The sponsor was asked to exclude epidemiological figures that do not stem from valid data sources, e.g. newspaper articles etc.

The sponsor should perform a sensitivity analysis for all underlying assumptions and provide a conservative estimate of prevalence. Representative figures and subsequent extrapolations could be useful.

The COMP requests a more comprehensive prevalence calculation that adequately covers all aetiologies of endophthalmitis. All aetiologies must be covered including all forms of non-infectious endophthalmitis, endophthalmitis occurring in other underlying conditions like diabetes, all types of post-operative endophthalmitis (chronic POE, POE after glaucoma surgery, POE after vitrectomy, POE after keratoplasty), post-injection endophthalmitis after all types of injection (e.g. corticosteroids), fungal endogenous endophthalmitis.

Without full knowledge of the prevalence of the condition, orphan designation cannot be granted.

- Significant benefit

Notwithstanding the acceptance of the orphan condition, significant benefit needs to be demonstrated. As outlined by the sponsor, intravitreal vancomycin is currently considered to be the best standard of care in clinical practice. It is currently produced as officinal or magistral formulation. In line with the sponsor's argumentation these preparations could be considered well-known and safe. Therefore a significant benefit assessment was required and a data-driven discussion over officinal/magistral formulations of intravitreal vancomycin produced in the EU should be provided. Significant benefit could be established as improved efficacy, improved safety or major contribution to patient care.

In the written response, and during an oral explanation before the Committee on 19 February 2019, the sponsor requested a change of the condition to "bacterial endophthalmitis". This change was proposed to more accurately reflect the mechanism of action and clinical use of the proposed product. The COMP disagreed and explained that the definition of the condition would need to be based on pathophysiology, histopathology, clinical characteristics and consensus classifications of the condition. The COMP agreed that "endophthalmitis" could be accepted as orphan condition.

An updated prevalence calculation was presented, however the sponsor acknowledged that it was not comprehensive in nature and did not contain epidemiological data of all underlying aetiologies. The COMP concluded that a more comprehensive prevalence figure would be necessary to ascertain with certainty that endophthalmitis due to all potential causes meets the prevalence criterion for orphan designation.

The proposed product in its intravitreal pharmaceutical form is currently part of the best standard of care as per European consensus guidelines. For the demonstration of significant benefit, the sponsor on one hand acknowledged the use of magistral formulations of the active substance, on the other hand the sponsor claimed that there is also off-label use of the active substance by healthcare professionals preparing formulations outside of the hospital pharmacy. The COMP noted that the sponsor had not provided sufficient evidence on the current practice in Europe regarding the use of magistral and off label preparations of the active substance. The COMP highlighted the possibility of extensive use of magistral formulations of the proposed product without reported safety concerns. The COMP therefore requested significant benefit argumentation over magistral formulations of the proposed product. The sponsor was not able to provide any data-driven arguments of significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 21 February 2019, prior to final opinion.

2.1.4. codon-optimised human cystic fibrosis transmembrane conductance regulator messenger ribonucleic acid complexed with lipid-based nanoparticles - EMA/OD/0000002333

Real Regulatory Limited; Treatment of cystic fibrosis

COMP rapporteur: Ingeborg BarisicAs agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of cystic fibrosis, the sponsor should further elaborate on the methodology of the study in knockout (KO) rats in which nasal potential difference was measured. In particular, the sponsor is invited to explain why the product was administered intranasally and via the oropharynx and whether this type of administration may lead to different results than the intended administration via inhalation.

In the written response, the sponsor further detailed the methodology of the non-clinical studies in relation to the methodology of the measurement of nasal potential difference. The applicant clarified that administration by aerosol, while being ideal for delivery to the lungs, would have not been effective at delivering sufficient mRNA to the nose, where the potential is measured. This was acknowledged, since systems for administration via inhalation are designed in order to minimize deposition in the nose while maximizing delivery to the lungs. The COMP considered the responses of the applicant satisfactory and concluded for a positive opinion without the need of an oral explanation.

The Committee agreed that the condition, cystic fibrosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing codon-optimised human cystic fibrosis transmembrane conductance regulator messenger ribonucleic acid complexed with lipid-based nanoparticles was considered justified based on non-clinical studies showing the production of a functional CFTR (Cystic fibrosis transmembrane conductance regulator) protein and improvement in chloride transport across respiratory cells membranes in valid models of the condition.

The condition is life-threatening and chronically debilitating due to recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure.

The condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing codon-optimised human cystic fibrosis transmembrane conductance regulator messenger ribonucleic acid complexed with lipid-based nanoparticles will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate improvement of chloride transport across cell membranes, which is further enhanced when used in combination with ivacaftor, currently authorised for the condition. In addition the proposed product has the potential to be used in cystic fibrosis patients with mutations resulting in absence of the CFTR protein, for which currently no medicinal product is authorised. The Committee considered that the above constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for codon-optimised human cystic fibrosis transmembrane conductance regulator messenger ribonucleic acid complexed with lipid-based nanoparticles, for treatment of cystic fibrosis, was adopted by consensus.

2.1.5. adeno-associated viral vector serotype rh10 containing the human cholesterol 24-hydroxylase gene - EMA/OD/0000002264

Brainvectis; Treatment of Huntington's disease

COMP rapporteur: Fernando Mendez HermidaAs agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for Treatment of Huntington's disease the sponsor should further elaborate on:

  - the clinical relevance of impaired cholesterol homeostasis in the pathophysiology of the proposed condition,
  - the pre-symptomatic timing of treatments, given that the product is proposed for the treatment of an already established disease,
  - the available data in the zQ175 model,
  - present any available data with the proposed product as applied for designation, containing the non-tagged transgene.

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action that would translate into a clinically relevant advantage. The sponsor was invited to elaborate on the pre-symptomatic timing of treatment in the *in vivo* studies, and further elaborate on the results to establish significant benefit.

In the written response the sponsor further elaborated on the raised issues. With regards to the relevance of impaired cholesterol homeostasis in the pathophysiology of the condition, it was pointed out that this is observed both in non-clinical models and patients with HD (Huntington's disease).

With regards to the timing of treatments in the non-clinical models, the hallmark features and disease onset in the models were discussed. In view of arguments made by the sponsor it was considered that treatment was started in early symptomatic setting, rather than a pre-symptomatic setting, which was in line with the early intervention intended in the clinical application of the proposed treatment. Importantly the sponsor also shared data with the product as proposed for designation, which had the same efficacy as the surrogate product used in initially submitted studies.

It was further considered that the sponsor has also addressed the issue of significant benefit, because the authorised products target different manifestations of the condition than the proposed product.

As the designation criteria were considered met and the oral explanation was cancelled.

The Committee agreed that the condition, Huntington's disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype rh10 containing the human cholesterol 24-hydroxylase gene was considered justified based on nonclinical data suggesting that treatment with the product may delay the deterioration of motor function.

The condition is life-threatening and chronically debilitating due to severe behavioural and cognitive disturbances, progressive motor dysfunction and potentially fatal complications.

The condition was estimated to be affecting approximately 1.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing an adeno-associated viral vector serotype rh10 containing the human cholesterol 24-hydroxylase gene will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical data suggesting that treatment with the product may delay the deterioration of motor function. This treatment therefore intends to improve manifestations of the condition that are currently not addressed by the authorised products. The Committee considered that this constitutes a clinically relevant advantage. Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

A positive opinion for adeno-associated viral vector serotype rh10 containing the human cholesterol 24-hydroxylase gene, for treatment of Huntington's disease, was adopted by consensus.

2.1.6. - EMA/OD/0000002429

Treatment of Essential Thrombocythemia

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

Essential Thrombocythemia was proposed as a distinct medical entity or a valid subset. The COMP noted, when examining the data submitted for medical plausibility, that the condition to be designated is myelofibrosis. The sponsor should consider amending the condition therefore to myelofibrosis from essential thrombocythaemia. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention was drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

- Number of people affected

The COMP considered that the condition was myelofibrosis and not essential thrombocythaemia. The sponsor should therefore provide a prevalence calculation for myelofibrosis.

For the calculation and presentation of the prevalence estimate, the sponsor was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

- Significant benefit

The arguments on significant benefit were based on a new mechanism of action and the potential improved efficacy in the condition which the COMP considered to be myelofibrosis.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the non-clinical *in vivo* studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

The sponsor should detail the results of any clinical data to support the significant benefit assumption in the context of the current therapeutic management of myelofibrosis patients.

In the written response, and during an oral explanation before the Committee on 20 February 2019, the sponsor requested to maintain the condition as essential thrombocythaemia. The COMP agreed to this and accepted the non-clinical data presented in support of the medical plausibility.

The sponsor presented clinical data based on one patient who had had essential thrombocythaemia which then had transformed into myelofibrosis at the time of treatment with the sponsor's product. The COMP considered that the data was too limited to be able to establish a real clinically relevant advantage. The fact that the patient had transformed from essential thrombocythaemia to myelofibrosis made establishing significant benefit more difficult. During the plenary meeting it was discussed that a few more patients with regards to essential thrombocythaemia could be acceptable and that at that stage there was insufficient data to establish the clinically relevant advantage.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 20 February 2019, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. marzeptacog alfa (activated) - EMA/OD/0000002304

Voisin Consulting S.A.R.L.; Treatment of haemophilia B

COMP rapporteur: Armando MagrelliThe Committee agreed that the condition, haemophilia B, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing marzeptacog alfa (activated) was considered justified based on improved bleeding times in non-clinical models of the proposed condition and affected patients.

The condition is life-threatening and chronically debilitating due to spontaneous bleeding episodes and substantially prolonged bleeding upon injury. Bleeding starts early in life and can include life threatening haemorrhages, such as intracranial and gastrointestinal haemorrhages. Adult patients are at risk for cerebral- or gastric haemorrhage, which can be life-threatening.

The condition was estimated to be affecting approximately 0.3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing marzeptacog alfa (activated) will be of significant benefit to those affected by the condition. The sponsor has provided clinical data in haemophilia patients supporting that the product may be used as a regular prophylaxis in patients who have developed inhibitors to exogenous coagulation factors. The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for marzeptacog alfa (activated), for treatment of haemophilia B, was adopted by consensus.

2.2.2. 1-[(3S)-3-{4-amino-3-[(3,5-dimethoxyphenyl)ethynyl]- 1H-pyrazolo[3,4-d]pyrimidin-1-yl}pyrrolidin-1-yl]-2-propen- 1-one - EMA/OD/0000002457

Taiho Pharma Europe Limited; Treatment of biliary tract cancer

COMP rapporteur: Bozenna Dembowska-BaginskaThe Committee agreed that the condition, biliary tract cancer, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 1-[(3S)-3-{4-amino-3-[(3,5-dimethoxyphenyl)ethynyl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}pyrrolidin-1-yl]-2-propen-1-one was considered justified based on preliminary clinical observations in relapsed/refractory patients, who responded to treatment with the product as a monotherapy.

The condition is life-threatening and chronically debilitating due to the development of liver insufficiency, cholestasis, cholangitis, weight loss and cachexia. Patients with unresectable tumours die between 6 and 12 months following diagnosis. Death usually occurs from liver failure or infectious complications accompanying the progressive biliary obstruction.

The condition was estimated to be affecting approximately 1.5 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for 1-[(3S)-3-{4-amino-3-[(3,5-dimethoxyphenyl)ethynyl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}pyrrolidin-1-yl]-2-propen-1-one, for treatment of biliary tract cancer, was adopted by consensus.

2.2.3. 2-[3-(2-chloro-4-{[5-cyclopropyl-3-(2,6-dichlorophenyl)-1,2-oxazol-4-yl]methoxy}phenyl)-3-hydroxyazetidin-1-yl]pyridine-4-carboxylic acid—2-amino-2-(hydroxymethyl)propane-1,3-diol (1/1) - EMA/OD/0000002498

Gilead Sciences Ireland UC; Treatment of primary sclerosing cholangitis

COMP rapporteur: Dinko VitezicThe Committee agreed that the condition, primary sclerosing cholangitis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 2-[3-(2-chloro-4-{[5-cyclopropyl-3-(2,6-dichlorophenyl)-1,2-oxazol-4-yl]methoxy}phenyl)-3-hydroxyazetidin-1-yl]pyridine-4-carboxylic acid—2-amino-2-(hydroxymethyl)propane-1,3-diol (1/1) was considered justified based on preliminary clinical data showing an improvement in surrogate end-points specific for the condition.

The condition is chronically debilitating and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased risk of developing hepatocellular cancer. Common findings include pruritus, hyperlipidaemia, hypothyroidism, deficiency of fat-soluble vitamins and osteopenia.

The condition was estimated to be affecting approximately 2.7 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 2-[3-(2-chloro-4-{[5-cyclopropyl-3-(2,6-dichlorophenyl)-1,2-oxazol-4-yl]methoxy}phenyl)-3-hydroxyazetidin-1-yl]pyridine-4-carboxylic acid—2-amino-2-(hydroxymethyl)propane-1,3-diol (1/1) will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate an improvement in surrogate endpoints in patients who were intolerant to UDCA (ursodeoxycholic acid). The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2-[3-(2-chloro-4-{[5-cyclopropyl-3-(2,6-dichlorophenyl)-1,2-oxazol-4-yl]methoxy}phenyl)-3-hydroxyazetidin-1-yl]pyridine-4-carboxylic acid—2-amino-2-(hydroxymethyl)propane-1,3-diol (1/1), for treatment of primary sclerosing cholangitis, was adopted by consensus.

2.2.4. - EMA/OD/0000002526

Treatment of Stargardt's Disease

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the March meeting.

2.2.5. - EMA/OD/0000002530

Treatment of Invasive Aspergillosis

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the March meeting.

2.2.6. - EMA/OD/0000002559

Treatment of Spinal cord injury

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond in writing before the Committee March meeting.

2.2.7. - EMA/OD/0000002563

Treatment of Fragile X Syndrome

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond in writing before the Committee March meeting.

2.2.8. - EMA/OD/0000002735

Treatment of Hepatocellular carcinoma

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the March meeting.

2.2.9. - EMA/OD/0000002754

Treatment of Mucopolysaccharidosis type III (Sanfilippo syndrome)

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the March meeting.

2.2.10. 4-hydroxy-6-{2-[4-(trifluoromethyl)phenyl]ethyl}pyridazin-3(2H)-one - EMA/OD/0000002821

Takeda Pharma A/S; Treatment of Friedreich's ataxia

COMP rapporteur: Robert NisticoThe Committee agreed that the condition, Friedreich's ataxia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 4-hydroxy-6-{2-[4-(trifluoromethyl)phenyl]ethyl}pyridazin-3(2H)-one was considered justified based on non-clinical data showing significant improvement of motor coordination in valid model of the condition.

The condition is chronically debilitating and life threatening due to ataxia, progressive disability that requires the use of wheelchair, and cardiac involvement in the form of hypertrophic cardiomyopathy.

The condition was estimated to be affecting approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for 4-hydroxy-6-{2-[4-(trifluoromethyl)phenyl]ethyl}pyridazin-3(2H)-one, for treatment of Friedreich's ataxia, was adopted by consensus.

2.2.11. - EMA/OD/0000002861

Treatment of follicular lymphoma

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the March meeting.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

2.6.1. New applications for orphan medicinal product designation - Appointment of COMP rapporteurs

COMP rapporteurs were appointed for twenty submitted applications.

2.7. Evaluation on-going

Eleven applications for orphan designation were not discussed as evaluation is on-going.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of diffuse large B-cell lymphoma

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

3.1.2. -

Treatment of ATTR amyloidosis

The Committee was briefed on the significant benefit issues in preparation of the March meeting.

3.1.3. -

Treatment of congenital adrenal hyperplasia

The Committee was briefed on the significant benefit issues in preparation of the March meeting.

3.1.4. -

Treatment of gastric carcinoid

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

3.1.5. - -

Treatment of beta-thalassaemia intermedia and major

The Committee was briefed on the significant benefit issues in preparation of the March meeting.

3.1.6. -

Treatment of hyperargininaemia

The discussion was postponed.

3.2. Finalised letters

3.2.1. - -

Treatment of multiple myeloma

The finalised letter was circulated for information.

3.2.2. -

Treatment of diffuse large B-cell lymphoma

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of adenosine deaminase-deficient-severe combined immunodeficiency

The new request was noted.

4. Review of orphan designation for orphan medicinal products at time of initial marketing authorisation

4.1. Orphan designated products for which CHMP opinions have been adopted

None

4.2. Orphan designated products for discussion prior to adoption of CHMP opinion

4.2.1. – Pegvaliase – EMEA/H/C/004744, EMEA/OD/112/09, EU/3/09/708

Treatment of hyperphenylalaninaemia

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond in writing before the Committee March meeting.

4.2.2. - Autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human betaA-T87Q-globin gene – EMEA/H/C/003691, EMA/OD/146/12, EU/3/12/1091

Treatment of beta-thalassemia intermedia and major

The status of the procedure at CHMP was noted.

4.2.3. - pacritinib - EMEA/H/C/004793

a) Treatment of post-essential thrombocythaemia myelofibrosis EMA/OD/058/10, EU/3/10/767

b) Treatment of primary myelofibrosis EMA/OD/019/10, EU/3/10/768

c) Treatment of post-polycythemia vera myelofibrosis EMA/OD/057/10, EU/3/10/769

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP rapporteurs were appointed for four applications.

4.5. Orphan Maintenance Reports

Documents were circulated in MMD.

5. Review of orphan designation for authorised orphan medicinal products at time marketing authorisation extension

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Imnovid – pomalidomide – Type II variation – EMEA/OD/053/09, EU/3/09/672, EMEA/H/C/002682/II/0031/G

Celgene Europe Limited; Treatment of multiple myeloma

CHMP rapporteur: Greg Markey

The status of the procedure at CHMP was noted.

5.3. Appeal

None

5.4. On-going procedures

COMP rapporteurs were appointed for one application.

6. Application of Article 8(2) of the Orphan Regulation

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. Strategic Review & Learning meetings

None

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 19 February 2019.

7.1.3. Non-Clinical Working Group

The working group on Non-Clinical met on 20 February 2019.

7.1.4. Prevalence Working Group

The working group on Prevalence met on 20 February 2019.

7.2. Coordination with EMA Scientific Committees or CMDh-v

None

7.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

7.3.1. Working Party with Patients' and Consumers' Organisations (PCWP)

None

7.3.2. Working Party with Healthcare Professionals' Organisations (HCPWP)

None

7.3.3. SAWP/COMP joint membership

A call for interest to replace the COMP alternate representative at SAWP was circulated with a deadline for expression of interest on 8 March 2019.

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. The Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

7.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee

None

7.7. COMP work plan

None

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP rapporteurships distribution of valid applications submitted in 2019

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2019 were circulated.

7.8.2. Overview of orphan marketing authorisations/applications

An updated overview of orphan applications for Marketing Authorisation was circulated.

8. Any other business

8.1. Concepts of significant benefit (follow-up to COMP Work Plan 2017)

The discussion was postponed.

8.2. Presentation on Study to support the evaluation of the EU Orphan Regulation

The COMP discussed following the presentation on the findings of the 'Study to support the evaluation of the EU Orphan Regulation.'

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 19-21 February 2019 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Chair	Netherlands	No interests declared	
Brigitte Blöchl-Daum	Member	Austria	No interests declared	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Nectaroula Cooper	Member	Cyprus	No interests declared	
Lenka Kovarova	Member	Czech Republic	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Annie Lorence	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member (Vice-Chair)	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Elizabeth Rook	Member	Netherlands	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Fernando Mendez Hermida	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Angelo Brunetta	Member	Patients' Organisation Representative	No participation in discussion, final deliberations and voting on:	3.1.1 5.2.1. Imnovid – pomalidomide Type II variation – EMEA/OD/053/09, EU/3/09/672, EMEA/H/C/002682/II/0031/G
Bruno Sepodes	Member	Expert recommended by EMA	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert - in person*		No restrictions applicable to this meeting	
A representatives from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the agenda topics or activities they participated in.

Explanatory notes

The notes below give a brief explanation of the main sections and headings in the COMP agenda and should be read in conjunction with the agenda or the minutes.

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

EC: European Commission

OD: Orphan Designation

PA: Protocol Assistance

PDCO: Paediatric Committee

PRAC: Pharmacovigilance and Risk Assessment Committee

SA: Scientific Advice

SAWP: Scientific Advice Working Party

Orphan Designation *(section 2 Applications for orphan medicinal product designation)*

The orphan designation is the appellation given to certain medicinal products under development that are intended to diagnose, prevent or treat rare conditions when they meet a pre-defined set of criteria foreseen in the legislation. Medicinal products which get the orphan status benefit from several incentives (fee reductions for regulatory procedures (including protocol assistance), national incentives for research and development, 10-year market exclusivity) aiming at stimulating the development and availability of treatments for patients suffering from rare diseases.

Orphan Designations are granted by Decisions of the European Commission based on opinions from the COMP. Orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products.

Protocol Assistance *(section 3 Requests for protocol assistance with significant benefit question)*

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

Sponsor

Any legal or physical person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

Maintenance of Orphan Designation *(section 4 Review of orphan designation for orphan medicinal products for marketing authorisation).*

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu