2 June 2016
EMA/COMP/278477/2016
Procedure Management and Committees Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 19-21 April 2016

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

19 April 2016, 09:00-18:30, room 2F

20 April 2016, 09:00-18:30, room 2F

21 April 2016, 08:30-12:30, room 2F

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.

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).

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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. Arimoclomol citrate - EMA/OD/256/15 5

2.1.2. - EMA/OD/220/15 6

2.1.3. - EMA/OD/146/15 7

2.1.4. Fc- and CDR-modified humanized monoclonal antibody against C5 - EMA/OD/246/15 8

2.1.5. - EMA/OD/258/15 9

2.2. For discussion / preparation for an opinion 9

2.2.1. (R)-6-(2-fluorophenyl)-N-(3-(2-((2-methoxyethyl)amino)ethyl)phenyl)-5,6-dihydrobenzo[h]quinazolin-2-amine dihydrochloride - EMA/OD/245/15 9

2.2.2. - EMA/OD/023/16 10

2.2.3. - EMA/OD/016/16 10

2.2.4. 4-[(2E)-1-Oxo-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-propen-1-yl]-1-piperazinecarboxamide - EMA/OD/208/15 10

2.2.5. - EMA/OD/019/16 11

2.2.6. - EMA/OD/020/16 11

2.2.7. - EMA/OD/021/16 11

2.2.8. - EMA/OD/018/16 11

2.2.9. Autologous CD34+ cells transduced with lentiviral vector encoding the human beta globin gene - EMA/OD/024/16 11

2.2.10. - EMA/OD/022/16 12

2.2.11. - EMA/OD/008/16 12

2.2.12. - EMA/OD/009/16 12

2.2.13. - EMA/OD/010/16 12

2.2.14. H-Phe-Ser-Arg-Tyr-Ala-Arg-OH-Acetate - EMA/OD/011/16 13

2.2.15. - EMA/OD/014/16 13

2.2.16. - EMA/OD/004/16 13

2.2.17. - EMA/OD/007/16 13

2.2.18. - EMA/OD/001/16 14

2.2.19. - EMA/OD/005/16 14

2.2.20. Pentosan polysulfate sodium - EMA/OD/003/16 14

2.2.21. Polyethylene glycol-modified human recombinant truncated cystathionine beta-synthase - EMA/OD/025/16 14

2.2.22. Recombinant adeno-associated viral vector containing the human *RPGR* gene - EMA/OD/002/16 15
2.2.23. Rimiducid - EMA/OD/017/16 15
2.2.24. Rovalpituzumab tesirine - EMA/OD/015/16 16
2.2.25. Sodium nitrite and ethylenediaminetetraacetic acid - EMA/OD/013/16..... 17
2.2.26. Temsirolimus - EMA/OD/027/16 17
2.2.27. Vemurafenib - EMA/OD/026/16 18
2.3. Amendment of the COMP opinions 19
2.3.1. (S)-ethyl 2-amino-3-(4-(2-amino-6((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoate – EMA/OD/047/09, EU/3/09/66 .. 19
2.4. COMP opinions adopted via written procedure following previous meeting 19
2.5. Appeal 19
2.6. Nominations 19
2.6.1. New applications for orphan medicinal product designation - Appointment of COMP coordinators..... 19
2.7. Evaluation on-going 19
3. Requests for protocol assistance with significant benefit question 20
3.1. Ongoing procedures 20
3.1.1. -..... 20
3.1.2. -..... 20
3.2. Finalised letters 20
3.2.1. -..... 20
3.2.2. -..... 20
3.2.3. -..... 20
3.3. New requests..... 20
4. Review of orphan designation for orphan medicinal products for marketing authorisation 21
4.1. Orphan designated products for which CHMP opinions have been adopted 21
4.1.1. Darzalex – daratumumab - EMA/OD/038/13, EU/3/13/1153 , EMEA/H/C/004077 21
4.1.2. Empliciti - elotuzumab - EMA/OD/061/12, EU/3/12/1037, EMEA/H/C/003967 23
4.1.3. Galafold - migalastat – EMEA/OD/105/05, EU/3/06/368, EMEA/H/C/004059 23
4.1.4. Strimvelis - autologous cd34+ enriched cell fraction that contains cd34+ cells transduced with retroviral vector that encodes for the human ada cdna sequence EMEA/OD/053/05, EU/3/05/313, EMEA/H/C/003854..... 23
4.1.5. Dropcys (CYSTIRANE) – mercaptamine – EMA/OD/106/14, EU/3/14/1341, EMEA/H/C/004038..... 23
4.2. Orphan designated products for discussion prior to adoption of CHMP opinion 24
4.2.1. - chenodeoxycholic acid – EMA/OD/196/14, EU/3/14/1406, EMEA/H/C/004061..... 24
4.2.2. – obinutuzumab - Type II variation - EMA/OD/013/15, EU/3/15/1504, EMEA/H/C/002799/II/0007..... 24

4.2.3. - irinotecan- EMA/OD/051/11, EU/3/11/933, EMEA/H/C/004125 24
4.2.4. – ixazomib – EMA/OD/110/12, EU/3/12/1060, EMEA/H/C/003844 24
4.2.5. - parathyroid hormone – EMA/OD/102/13, EU/3/13/1210, EMEA/H/C/003861 24
4.2.6. - sirolimus – EMA/OD/021/11, EU/3/11/898, EMEA/H/C/003978 24
4.3. On-going procedures 24
4.3.1. List of on-going procedures 24
5. Application of Article 8(2) of the Orphan Regulation 24
6. Organisational, regulatory and methodological matters 25
6.1. Mandate and organisation of the COMP 25
6.1.1. Significant Benefit Working Group 25
6.1.2. Protocol Assistance Working Group 25
6.2. Coordination with EMA Scientific Committees or CMDh-v 25
6.2.1. CHMP guideline on Conditional Marketing Authorisation 25
6.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups 25
6.3.1. SAWP/COMP joint membership 25
6.4. Cooperation within the EU regulatory network 25
6.4.1. European Commission 25
6.5. Cooperation with International Regulators 25
6.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee 25
6.7. COMP work plan 25
6.8. Planning and reporting 26
6.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2016 26
6.8.2. Overview of orphan marketing authorisations/applications 26
7. Any other business 26
7.1. Request for clarification of the condition/indication 26
7.2. Tutorial on Cystic Fibrosis 26
7.3. - 26

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 that no restriction in the involvement of meeting participants in upcoming discussions was identified 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. 22 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

COMP agenda for 19-21 April 2016 meeting was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 21-23 March 2016 meeting 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. Arimoclomol citrate - EMA/OD/256/15

Orphazyme ApS; Treatment of inclusion body myositis

COMP coordinator: Frauke Naumann-Winter and Violeta Stoyanova

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

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of inclusion body myositis, the sponsor should further elaborate on:

– the particulars of the preclinical model used, and its relevance for the proposed condition;

– the methodology of the preclinical study regarding the symptom onset, the start of treatment and the observed outcome;

– the patient population enrolled into the clinical study and the certainty of IBM diagnosis per the Griggs diagnostic criteria ('definite or probable IBM');

– the outcome data of the clinical study contextualising the effect sizes, discussing the expected long-term effects (duration and size) during and after treatment discontinuation.

In the written response, and during an oral explanation before the Committee on 19 April 2016, the sponsor specified the transgenic in vivo model used and stressed that the model recapitulated the main pathological characteristics of inclusion body myositis. The sponsor also elaborated on the design of the study that reflected a treatment setting.

With regards to the clinical trial, the sponsor clarified the diagnostic criteria for trial enrolment, and reported improvement of functional abilities in patients in the 8-month follow up phase compared to the treatment period of 4 months. The sponsor discussed that this might be explained by the time to response for patients on a new treatment regimen, and by the time to treatment to work most effectively.

The COMP considered that the data supported the medical plausibility for the purpose of orphan designation but recommended to seek protocol assistance for the conduct of future pivotal clinical trials regarding diagnostic criteria, study duration and efficacy endpoints.

The Committee agreed that the condition, inclusion body myositis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing arimoclomol citrate was considered justified based on preclinical data demonstrating improvements in motor function upon treatment, and supported by preliminary clinical data showing a delay in the deterioration of functional abilities of patients affected by the condition as per clinical rating scales.

The condition is chronically debilitating due to the development of progressive weakness and atrophy of the distal and proximal muscles leading to disability, and the development of dysphagia.

The condition was estimated to be affecting approximately 0.05 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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for arimoclomol citrate, for treatment of treatment of inclusion body myositis, was adopted by consensus.

2.1.2. - EMA/OD/220/15

Treatment of peripheral T-cell lymphoma

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

Peripheral T-cell lymphoma (PTCL) should be justified as a distinct medical entity or a valid subset. The sponsor's attention is drawn to the Orphan regulations and guidelines (especially section A of ENTR/6283/00).

The sponsor is requested to discuss the proposed condition in the context of the 2008 classification of tumours of haematopoietic and lymphoid tissues (Swerdlow et al, 4th edition, WHO 2008). In case of an amended indication, the information provided for the justification of criteria for orphan designation is to be updated accordingly.

- Number of people affected

In case of a change in the proposed indication, the prevalence estimate should be amended to reflect the new indication.

- Seriousness

The life-threatening and /or chronically debilitating section of the scientific annex should be renamed to reflect the new indication

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The applicant is requested to discuss whether satisfactory methods of treatments exist for the treatment of the new condition and delineate the significant benefit based on the preliminary clinical or preclinical data available.

In the written response the sponsor proposed to further specify the population by "peripheral T-cell lymphoma (nodal, extra nodal, leukemic)". To support this view they quote a publication by Zinzani et al. Panoptic clinical review of the current and future treatment of relapsed/refractory T-cell lymphomas: Peripheral T-cell lymphomas (Critical Reviews in Oncology/Hematology 99 (2016) 214–227).

The sponsor further produced a point prevalence estimate for the new proposed indication, by assuming that the annual incidence is up to 1.2 per 100,000, and an overall survival of 14.5 years, yielding a prevalence of up to 1.7 per 10,000. No new information was given for the significant benefit.

The COMP reflected on the different sources that describe the classification of the related conditions. It was noted that the 2008 classification has described several underlying entities that may be followed while the older classification of 2001 (Pathology and Genetics: Tumours of Haematopoietic and Lymphoid tissues by Jaffe et al) also describes 5 overarching categories. The icd-10 classification system follows a splitting logic and describes at least some of the distinct medical entities (MF, Sezary, Anaplastic large cell lymphoma) under sub-codes of C84. Therefore it was considered that the proposed amendment did not clarify the issue raised in the list of issues

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 20 April 2016, prior to final opinion.

2.1.3. - EMA/OD/146/15

Treatment of congenital coronary artery malformation

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 4 March 2016, prior to responding to the list of issues.

2.1.4. Fc- and CDR-modified humanized monoclonal antibody against C5 - EMA/OD/246/15

Alexion Europe SAS; Treatment of paroxysmal nocturnal hemoglobinuria

COMP coordinator: Geraldine O'Dea and Armando Magrelli

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 arguments on significant benefit are based on the improved pharmacokinetics of the product versus the authorised counterpart that may result in a major contribution to patient care and a clinically relevant advantage of improved efficacy.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from any preclinical or the preliminary clinical studies to justify the assumption of significant benefit.

In the written response, and during an oral explanation before the Committee on 19 April 2016, the sponsor discussed a double argument for the justification of significant benefit: a major contribution to patient care, and a clinically relevant advantage. Both are linked to the improved PK profile versus eculizumab.

With regards to the improved PK, the applicant added new data from two ongoing clinical studies. Using data from these studies, the sponsor generated a population PK model, calculated an estimate of half-life, and a dosing frequency within the range of every 6 to 12 weeks was expected, compared to the currently available administration of eculizumab every two weeks. Based on a survey from eculizumab-treated patients, the sponsor then discussed again the drawbacks of eculizumab treatment and preferences for a reduced frequency scheme, but no data with the proposed product for designation were available in this respect.

On the other hand, data were presented by the applicant from ongoing clinical studies that supported a possible reduction of breakthrough haemolysis. This data was juxtaposed to observations from the registration study of eculizumab, which showed that while the LDH levels are not completely normalised in all patients with eculizumab, this may not be the case for the new product. The COMP considered that this supports an assumption of a clinically relevant advantage.

The Committee agreed that the condition, paroxysmal nocturnal haemoglobinuria, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing Fc- and CDR-modified humanised monoclonal antibody against C5 was considered justified based on preliminary clinical data supporting reduction of haemolysis in treated patients affected by the condition.

The condition is life-threatening and chronically debilitating due to the complications of the chronic haemolysis such as abdominal pain, infection, cytopenia, and kidney malfunction,

and due to occurrence of thrombosis and haemorrhage in different organs. Vascular complications at the level of the central nervous system are the most common cause of death.

The condition was estimated to be affecting less than 0.2 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing Fc- and CDR-modified humanised monoclonal antibody against C5 will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that support improved reduction of haemolysis compared to the authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Fc- and CDR-modified humanised monoclonal antibody against C5, for treatment of paroxysmal nocturnal haemoglobinuria, was adopted by consensus.

2.1.5. - EMA/OD/258/15

Treatment of glioma

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 arguments on significant benefit are based on the new mechanism of action and the potentially improved efficacy in the condition, by combination with anti-angiogenic therapies. The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the ongoing clinical study in particular with regards to why the effects discussed may not be attributed to the concomitant anti-angiogenic treatment.

In the written response, and during an oral explanation before the Committee on 20 April 2016, the sponsor provided updated results from the ongoing clinical study. In an effort to delineate effects attributable to the proposed product itself, these results were plotted against published studies with the concomitant anti-angiogenic treatment. The COMP considered that the results were comparable and therefore difficult to attribute any affects to the product proposed for designation.

In communicating the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 21 April 2016, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. (R)-6-(2-fluorophenyl)-N-(3-(2-((2-methoxyethyl)amino)ethyl)phenyl)-5,6-dihydrobenzo[h]quinazolin-2-amine dihydrochloride - EMA/OD/245/15

Coté Orphan Consulting UK Limited; Treatment of biliary tract cancer

COMP coordinator: Kateřina Kubáčková

The 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 (R)-6-(2-fluorophenyl)-N-(3-(2-((2-methoxyethyl)amino)ethyl)phenyl)-5,6-dihydrobenzo[h]quinazolin-2-amine dihydrochloride was considered justified based on preliminary clinical data showing antitumor efficacy of the proposed product.

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.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (R)-6-(2-fluorophenyl)-N-(3-(2-((2-methoxyethyl)amino)ethyl)phenyl)-5,6-dihydrobenzo[h]quinazolin-2-amine dihydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate clinical response in patients relapsing from previous treatments. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for (R)-6-(2-fluorophenyl)-N-(3-(2-((2-methoxyethyl)amino)ethyl)phenyl)-5,6-dihydrobenzo[h]quinazolin-2-amine dihydrochloride, for treatment of biliary tract cancer, was adopted by consensus.

2.2.2. - EMA/OD/023/16

Treatment of acromegaly

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 May meeting.

2.2.3. - EMA/OD/016/16

Treatment of diffuse large B-cell lymphoma

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 at the May meeting.

2.2.4. 4-[(2E)-1-Oxo-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-propen-1-yl]-1-piperazinecarboxamide - EMA/OD/208/15

Shire Pharmaceuticals Ireland Limited; Treatment of retinitis pigmentosa

COMP coordinator: Dinah Duarte and Armando Magrelli

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

The intention to treat the condition with the medicinal product containing 4-[(2E)-1-oxo-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-propen-1-yl]-1-piperazinecarboxamide was considered justified based on pre-clinical in vivo data demonstrating improved survival of cones and rods in the retina.

The condition is chronically debilitating due to the development of nyctalopia and tunnel vision that progresses to total blindness.

The condition was estimated to be affecting approximately 2.8 in 10,000 persons in the European Union, at the time the application was made.

A positive opinion for 4-[(2E)-1-oxo-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-propen-1-yl]-1-piperazinecarboxamide, for treatment of retinitis pigmentosa, was adopted by consensus.

2.2.5. - EMA/OD/019/16

Treatment of Fanconi anaemia

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 May meeting.

2.2.6. - EMA/OD/020/16

Treatment of severe combined immunodeficiency

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 May meeting.

2.2.7. - EMA/OD/021/16

Treatment of Wiskott-Aldrich 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 May meeting.

2.2.8. - EMA/OD/018/16

Treatment of beta thalassaemia intermedia and major

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 May meeting.

2.2.9. Autologous CD34+ cells transduced with lentiviral vector encoding the human beta globin gene - EMA/OD/024/16

Fondazione Telethon; Treatment of beta thalassemia intermedia and major

COMP coordinator: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing autologous CD34+ cells transduced with lentiviral vector encoding the human beta globin gene was considered justified based on pre-clinical data in a valid model of the condition showing a normalisation of haematological parameters associated with the condition.

The condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these, in particular in beta-thalassaemia major patients.

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.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous CD34+ cells transduced with lentiviral vector encoding the human beta globin gene will be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical data that demonstrate a normalisation of haematologic parameters which can lead to a reduction in the need for blood transfusions and subsequently reduce the need for iron chelators. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous CD34+ cells transduced with lentiviral vector encoding the human beta globin gene, for treatment of intermedia and major, was adopted by consensus.

2.2.10. - EMA/OD/022/16

Treatment of acute liver failure

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 May meeting.

2.2.11. - EMA/OD/008/16

Treatment of acute lymphoblastic leukaemia

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 May meeting.

2.2.12. - EMA/OD/009/16

Treatment of glioma

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 May meeting.

2.2.13. - EMA/OD/010/16

Treatment of glioma

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 May meeting.

2.2.14. H-Phe-Ser-Arg-Tyr-Ala-Arg-OH-Acetate - EMA/OD/011/16

QRC Consultants Ltd; Treatment of amyotrophic lateral sclerosis

COMP coordinator: Violeta Stoyanova

The Committee agreed that the condition, amyotrophic lateral sclerosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing H-Phe-Ser-Arg-Tyr-Ala-Arg-OH-acetate was considered justified based on preclinical data demonstrating treatment related improvements in motor function, supported by preliminary clinical data demonstrating treatment related improvements in the deterioration of forced expiratory volume and disability progression.

The condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure. The survival of the patients is usually limited to 2-3 years.

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

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing H-Phe-Ser-Arg-Tyr-Ala-Arg-OH-acetate will be of significant benefit to those affected by the condition. The sponsor has provided preclinical and preliminary clinical data that demonstrate that treatment with the proposed product improves motor function, breathing and disability progression. These clinically relevant aspects of the condition are not treated by the currently authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for H-Phe-Ser-Arg-Tyr-Ala-Arg-OH-acetate, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.15. - EMA/OD/014/16

Treatment of neuromyelitis optica

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 May meeting.

2.2.16. - EMA/OD/004/16

Treatment of eosinophilic oesophagitis

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 May meeting.

2.2.17. - EMA/OD/007/16

Treatment of neonatal sepsis

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 May meeting.

2.2.18. - EMA/OD/001/16

Treatment of necrotising enterocolitis

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 May meeting.

2.2.19. - EMA/OD/005/16

Treatment of acute respiratory distress 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 May meeting.

2.2.20. Pentosan polysulfate sodium - EMA/OD/003/16

Nextrasearch di Gasparetto Adolfo & C., Sas; Treatment of interstitial cystitis

COMP coordinator: Bożenna Dembowska-Bagińska

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

The intention to treat the condition with the medicinal product containing pentosan polysulfate sodium was considered justified based on clinical data in patients with the condition.

The condition is chronically debilitating due to morbidity which is associated with pain, pressure, or discomfort in the pelvic area as well as increased daytime urinary frequency.

The condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made.

A positive opinion for pentosan polysulfate sodium, for treatment of interstitial cystitis, was adopted by consensus.

2.2.21. Polyethylene glycol-modified human recombinant truncated cystathionine beta-synthase - EMA/OD/025/16

Alan Boyd Consultants Ltd; Treatment of homocystinuria

COMP coordinator: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing polyethylene glycol-modified human recombinant truncated cystathionine beta-synthase was considered justified based on preclinical data showing improved liver histology and survival with the proposed product.

The condition is life-threatening and chronically debilitating due to mental retardation, osteoporosis, stroke, myocardial infarction, and pulmonary embolism. The principal

contributors of premature death are cardiovascular complications, in particular arterial and venous thrombosis;

The condition was estimated to be affecting less than 0.2 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing polyethylene glycol-modified human recombinant truncated cystathionine beta-synthase will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing a synergistic effect of the proposed product with betaine anhydrous, currently authorised for the condition, in reducing homocysteine levels. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for polyethylene glycol-modified human recombinant truncated cystathionine beta-synthase, for treatment of homocystinuria, was adopted by consensus.

2.2.22. Recombinant adeno-associated viral vector containing the human *RPGR* gene - EMA/OD/002/16

TMC Pharma Services Ltd; Treatment of retinitis pigmentosa caused by mutations in the *RPGR* gene

COMP coordinator: Armando Magrelli

The Committee agreed that the condition, retinitis pigmentosa caused by mutations in the *RPGR* gene, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing recombinant adeno-associated viral vector containing the human *RPGR* gene was considered justified based on preclinical data in a relevant disease model with a surrogate product demonstrating that treatment improved vision.

The condition is seriously debilitating due to the development of nyctalopia and tunnel vision progressing to total blindness.

The condition was estimated to be affecting approximately 0.7 in 10,000 persons in the European Union, at the time the application was made.

A positive opinion for recombinant adeno-associated viral vector containing the human *RPGR* gene, for treatment of retinitis pigmentosa caused by mutations in the *RPGR* gene, was adopted by consensus.

2.2.23. Rimiducid - EMA/OD/017/16

QRC Consultants Ltd; Treatment of graft versus host disease

COMP coordinator: Jens Ersbøll

The Committee agreed that the condition, graft-versus-host disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing rimiducid was considered justified based on pre-clinical in vivo and preliminary clinical data showing a significant reduction in graft-vs-host disease after administration of rimiducid in patients who had received inducible caspase 9 genetically modified T cells.

The condition is chronically debilitating and life-threatening in particular due to intestinal inflammation causing diarrhoea, abdominal pain, nausea and vomiting, as well as due to hepatotoxicity, skin and mucosal damage, sicca syndrome, cholestasis, arthritis, obliterative bronchiolitis and the need for immunosuppression that increases susceptibility to infections.

The condition was estimated to be affecting approximately 0.4 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing rimiducid will be of significant benefit to those affected by the condition. The sponsor has provided preclinical and clinical data that demonstrate an elimination of the graft-vs-host disease leading to a reduction in the need for the use of corticosteroid treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for rimiducid, for treatment of graft-versus-host disease, was adopted by consensus.

2.2.24. Rovalpituzumab tesirine - EMA/OD/015/16

Aceso Biologics Consulting Ltd; Treatment of small cell lung cancer

COMP coordinator: Katerina Kubáčková

The Committee agreed that the condition, small cell lung cancer, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing rovalpituzumab tesirine was considered justified based on preclinical data demonstrating tumour volume reduction in a valid disease model, supported by preliminary clinical data demonstrating that patients affected by the condition respond to treatment.

The condition is life-threatening and chronically debilitating due to the rapid disease progression and the advanced disease at diagnosis in most cases. Overall survival at 5 years is 5-10% of those patients diagnosed.

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

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing rovalpituzumab tesirine will be of significant benefit to those affected by the condition. The sponsor has provided preclinical

and preliminary clinical data demonstrating that the product could have improved antineoplastic efficacy and a better overall response rate compared to medicinal products that are currently authorised for treating patients affected by the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for rovalpituzumab tesirine, for treatment of small cell lung cancer, was adopted by consensus.

2.2.25. Sodium nitrite and ethylenediaminetetraacetic acid - EMA/OD/013/16

Arch Bio Ireland Ltd; Treatment of cystic fibrosis

COMP coordinator: Judith Eggenhofer

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 sodium nitrite and ethylenediaminetetraacetic acid was considered justified based on preclinical data showing an effect of the proposed product on the growth of different types of bacteria relevant to the pathogenesis of cystic fibrosis.

The condition is chronically debilitating and life threatening due to the recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure, and pancreatic insufficiency leading to impaired growth.

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.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sodium nitrite and ethylenediaminetetraacetic acid will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing synergistic effect on bacterial growth when the proposed product was used in combination with some of the antibiotics currently authorized for the treatment of the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for sodium nitrite and ethylenediaminetetraacetic acid, for treatment of cystic fibrosis, was adopted by consensus.

2.2.26. Temsirolimus - EMA/OD/027/16

Centro de Investigación Biomédica en Red (CIBER); Treatment of adrenoleukodystrophy

COMP coordinator: Giuseppe Capovilla

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

The intention to treat the condition with the medicinal product containing temsirolimus was considered justified based on pre-clinical in vivo data demonstrating reduced axonal degeneration and improved locomotor function.

The sponsor has established that the condition is chronically debilitating and life threatening. Two phenotypes of adrenoleukodystrophy result in different degrees of severity. Cerebral adrenoleukodystrophy is associated with behavioral abnormalities, seizures, spastic tetraplegia and dementia. Patients usually die within several years after the onset of symptoms. The second form of adrenoleukodystrophy, adrenomyeloneuropathy is associated with primary adrenocortical insufficiency as well as progressive stiffness and gait disturbance requiring the use of a cane or a wheelchair. Patients die within 20 years after the onset of symptoms.

The condition was estimated to be affecting less than 0.4 in 10,000 persons in the European Union, at the time the application was made.

A positive opinion for temsirolimus, for treatment of adrenoleukodystrophy, was adopted by consensus.

2.2.27. Vemurafenib - EMA/OD/026/16

Groupe d'étude des histiocytoses; Treatment of Langerhans cell histiocytosis

COMP coordinator: Bożenna Dembowska-Bagińska

The Committee agreed that the condition, Langerhans' cell histiocytosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing vemurafenib was considered justified based on early clinical data from patients refractory to the standard of care demonstrating complete remission.

The condition is life-threatening and chronically debilitating due to pain, mobility limitation, skin rash, respiratory distress, liver failure and pancytopenia and risk of developing debilitating sequelae such as diabetes insipidus, growth hormone deficiency, pan hypopituitarism with hypothalamic syndrome, morbid obesity, pulmonary insufficiency, neurodegenerative histiocytosis and sclerosing cholangitis.

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

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing vemurafenib will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients refractory to the standard of care responded to the treatment with the product and achieved complete remission. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for vemurafenib, for treatment of Langerhans' cell histiocytosis, was adopted by consensus.

2.3. Amendment of the COMP opinions

2.3.1. (S)-ethyl 2-amino-3-(4-(2-amino-6((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoate – EMA/OD/047/09, EU/3/09/66

Ipsen Pharma - France; Treatment of carcinoid tumours

COMP coordinator: Frauke Naumann-Winter

The amendment procedure was requested on a voluntary basis by the sponsor of (S)-ethyl 2-amino-3-(4-(2-amino-6((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoate which had obtained an orphan designation in 2009 for carcinoid tumours. It was noted that the term carcinoid tumours has evolved as well as the classification system since 2010 part of which is covered by the term neuroendocrine tumours currently. There was concern that this would have consequences regarding the revised prevalence calculation at the time of review of the Maintenance of the Orphan Designation. As a consequence the sponsor proposed to change the condition to carcinoid syndrome which reflected more adequately the condition which they were targeting with their product. Carcinoid syndrome is clearly described in the public domain and has an ICD-10 code. The COMP discussed the proposed indication and accepted to change the original condition of carcinoid tumours to carcinoid syndrome.

A positive opinion recommending the amendment of the designation for (S)-ethyl 2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoate, telotristat, for treatment of carcinoid syndrome, was adopted by consensus.

2.4. COMP opinions adopted via written procedure following previous meeting

None

2.5. Appeal

None

2.6. Nominations

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

COMP coordinators were appointed for 1 application submitted.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 17 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of primary sclerosing cholangitis

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

3.1.2. -

Treatment of beta thalassaemia intermedia and major

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

3.2. Finalised letters

3.2.1. -

Treatment of hyperargininaemia

The finalised letter was circulated for information.

3.2.2. -

Treatment of argininosuccinic aciduria

The finalised letter was circulated for information.

3.2.3. -

Treatment of haemophilia A

The finalised letter was circulated for information.

3.3. New requests

None

4. Review of orphan designation for orphan medicinal products for marketing authorisation

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

4.1.1. Darzalex – daratumumab - EMA/OD/038/13, EU/3/13/1153 , EMEA/H/C/004077

Janssen-Cilag International N.V.; Treatment of plasma cell myeloma

COMP coordinator: Karri Penttila and Jens Ersbøll

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

- Prevalence

The sponsor is basing the prevalence estimate on the basis of 2012 data, and partial prevalence indices. Instead the sponsor is requested to provide full point prevalence at the time of the review, taking into consideration the recent advancements in the treatment of multiple myeloma that may have impacted on the duration of the condition.

- Significant benefit

The sponsor is requested to further elaborate on the issue of significant benefit, in particular by a) discussing the clinical relevance of the responses observed and b) providing data to justify a clinically relevant advantage or a major contribution to patient care versus all authorised products authorised for plasma cell myeloma.

In its written response, and during an oral explanation before the Committee on 19 April 2016, the sponsor revised the estimate upwards, by providing a 10 year partial prevalence figure of approximately 3.3 per 10,000. This was estimated on data from the five larger EU Member States, but stemming from a market intelligence platform. Similar indices from the NORDCAN and from the HMRN network were used as controls.

With regards to the significant benefit, and as a first step, the sponsor discussed the two studies already presented in the MAA dossier, in particular with regards to the background of the refractory patients studies and the responses observed therein. Among subjects treated with 16 mg/kg daratumumab in Studies MMY2002 and GEN501part2, the ORR was 31% and the background of treatments to which patients were refractory included several regiments including proteasome inhibitors, immunomodulators, and alkylating factors. In patients with refractoriness to multiple products, the ORR is still high. In addition to the ORR, the sponsor also pointed out that the estimated mOS would be 20.07 months in the total population of the two studies above. Both the ORR and the OS compare favourably when compared indirectly with other published studies in relapsed/refractory settings with other products as monotherapies, and the sponsor attributes the improved efficacy on the new alternative mode of action of the product.

As a second step, the sponsor compared the results with the proposed product as a monotherapy to “real world data” in relapsed refractory patients, and used a multivariate regression modelling to address the limitation of unadjusted cross-trial comparisons. Overall Survival HRs were favourable for daratumumab versus the three cohorts discussed.

The sponsor also presented newly available data from study MMY3004.This is a multicenter, Phase 3, randomized, open-label, active-controlled study comparing daratumumab, bortezomib, and dexamethasone (DVd) with bortezomib and dexamethasone (Vd) in subjects with relapsed or refractory multiple myeloma who had received at least 1 prior line of therapy. The hazard ratio of PFS (DVd vs. Vd) was 0.39 (95% CI: 0.28, 0.53; p<0.0001), demonstrating a 61% reduction in the risk of progression or death in subjects treated with daratumumab. The median PFS was not reached in the DVd group (12-month PFS rate: 60.7%), compared with 7.2 months in the Vd group.

Daratumumab treatment also resulted in a significantly higher ORR (83% vs. 63%; p<0.0001), a doubling of the rate of VGPR or better (59% vs. 29%; p<0.0001), and doubling of the rate of CR or better (19% vs. 9%; p=0.0012). The median duration of response was not reached in the DVd group, compared with 7.9 months in the Vd group. With a total of 65 deaths (DVd: 29; Vd: 36), median OS was not reached in either group. The hazard ratio (DVd vs. Vd) was 0.77 (95% CI: 0.47, 1.26), and the p-value was 0.297.

An indirect comparison was done of the data from Study MMY3004 in the context of other published randomized clinical studies with Vd-based controls. Subjects treated in Study MMY3004 received at least 1 prior line of treatment (range 1-10); subjects treated in the randomized studies for panobinostat, elotuzumab, or carfilzomib had received between 1-3 prior lines of treatment. In comparison of randomized bortezomib-containing studies including panobinostat+Vd, elotuzumab+Vd, PLD+V, and carfilzomib+dexamethasone, Study MMY3004 is the only study with an HR <0.5 for PFS.

The observed ORR was 83% for subjects treated with DVd compared with 61% in literature studies with panobinostat+Vd (Pano+Vd) (San Miguel 2014) and 58% in PLD+V (Orlowski 2007). In addition, the depth of response was superior in DVd with 19% of patients achieving CR or better compared with 2% in PLD+V and 11% in Pano+Vd. The rate of VGPR or better was superior in DVd compared to the other regimens. Specifically, 40% of subjects treated with DVd achieved VGPR or better compared with 17% in PLD+V and Pano+Vd each.

The sponsor also included an improved safety argument, discussing that the safety profile following treatment with daratumumab monotherapy is considerably less toxic than other approved anti-myeloma treatments in the similar indication such as pomalidomide/Dex, panobinostat+Vd. It was pointed out that based on this indirect comparison, the discontinuation due to adverse events was 4%, 9% and 35% respectively, the SAEs were 32,61, 60% and deaths due to AEs were 0, 4 and 3%.

The COMP considered that for most authorised products - including all authorised proteasome inhibitors and immunomodulators- studies MMY2002 and GEN501 confirm a clinically relevant advantage of improved efficacy, as they show responses in patients refractory to those products. In addition, the additional data provided by the sponsor with study MMY3004 allowed further indirect comparisons with published studies for the remaining authorised counterparts, including doxorubicin and panobinostat. The indirect comparisons confirm the significant benefit versus those products in terms of improved efficacy and safety.

The COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of plasma cell myeloma (hereinafter referred to as "the condition") is estimated to remain below 5 in 10,000 and was concluded to be less than 4 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating in particular due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions, and life-threatening with an overall survival of approximately 6 years.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Darzalex will be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical data with the product in relapsed and refractory patients, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. The studied population was refractory to most authorised products, and the overall response rate to treatment was approximately 31% and the estimated overall survival 20 months. Furthermore, an indirect comparison of clinical data supports that daratumumab monotherapy is more efficacious and less toxic than the authorised product panobinostat. The COMP concluded that this constitutes a clinically relevant advantage.

An opinion not recommending the removal of Darzalex, daratumumab, EU/3/13/1153 from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion will be adopted for publication on the EMA website.

4.1.2. Empliciti - elotuzumab - EMA/OD/061/12, EU/3/12/1037, EMEA/H/C/003967

Bristol-Myers Squibb; Treatment of multiple myeloma

The COMP final negative opinion after appeal of the sponsor adopted by written procedure following its March meeting was circulated.

4.1.3. Galafold - migalastat – EMEA/OD/105/05, EU/3/06/368, EMEA/H/C/004059

Amicus Therapeutics UK Ltd; Treatment of Fabry disease

The COMP opinion adopted by written procedure after its March meeting was circulated.

4.1.4. Strimvelis - autologous cd34+ enriched cell fraction that contains cd34+ cells transduced with retroviral vector that encodes for the human ada cdna sequence EMEA/OD/053/05, EU/3/05/313, EMEA/H/C/003854

GlaxoSmithKline Trading Services; Treatment of severe combined immunodeficiency (SCID) due to adenosine deaminase (ADA) deficiency

The COMP opinion adopted by written procedure after its March meeting was circulated.

4.1.5. Dropcys (CYSTIRANE) – mercaptamine – EMA/OD/106/14, EU/3/14/1341, EMEA/H/C/004038

Lucane Pharma; Treatment of cystinosis

The negative opinion on the re-examination adopted at March CHMP was noted.

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

4.2.1. - chenodeoxycholic acid – EMA/OD/196/14, EU/3/14/1406, EMEA/H/C/004061

Sigma-tau Arzneimittel GmbH; Treatment of inborn errors of primary bile acid synthesis

The status of the procedure at CHMP was noted.

4.2.2. – obinutuzumab - Type II variation - EMA/OD/013/15, EU/3/15/1504, EMEA/H/C/002799/II/0007

Roche Registration Limited; Treatment of follicular lymphoma

The COMP adopted a list of issues that will be sent to the sponsor for a written response.

4.2.3. - irinotecan- EMA/OD/051/11, EU/3/11/933, EMEA/H/C/004125

Baxter Innovations GmbH; Treatment of pancreatic cancer

The status of the procedure at CHMP was noted.

4.2.4. – ixazomib – EMA/OD/110/12, EU/3/12/1060, EMEA/H/C/003844

Takeda Pharma A/S; Treatment of systemic light chain amyloidosis

The status of the procedure at CHMP was noted.

4.2.5. - parathyroid hormone – EMA/OD/102/13, EU/3/13/1210, EMEA/H/C/003861

NPS Pharma Holdings Limited; Treatment of hypoparathyroidism

The status of the procedure at CHMP was noted.

4.2.6. - sirolimus – EMA/OD/021/11, EU/3/11/898, EMEA/H/C/003978

Santen Oy; Treatment of chronic non-infectious uveitis

The status of the procedure at CHMP was noted.

4.3. On-going procedures

4.3.1. List of on-going procedures

COMP co-ordinators were appointed for 2 applications.

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

None

6. Organisational, regulatory and methodological matters

6.1. Mandate and organisation of the COMP

6.1.1. Significant Benefit Working Group

The working group on Significant Benefit met on 21 April 2016.

6.1.2. Protocol Assistance Working Group

The working group on Protocol Assistance met on 20 April 2016.

6.2. Coordination with EMA Scientific Committees or CMDh-v

6.2.1. CHMP guideline on Conditional Marketing Authorisation

The COMP was updated on the final guideline.

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

6.3.1. SAWP/COMP joint membership

On 20 April, the COMP re-nominated Armando Magrelli as COMP representative in the Scientific Advice Working Party (SAWP) for a second 3-year term starting retrospectively on 31 January 2016 (date at which the first term expired).

6.4. Cooperation within the EU regulatory network

6.4.1. European Commission

The EC representative presented the outcome of the public consultation on the Commission Notice on the application of Articles 3, 5 and 7 of Regulation (EC) NO 141/2000 on Orphan Medicinal Products. The COMP members were invited to send their comments within 15 days to the EMA Secretariat for consolidation. The discussion will continue in the May plenary meeting.

6.5. Cooperation with International Regulators

None

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

None

6.7. COMP work plan

None

6.8. Planning and reporting

6.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2016

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2016 were circulated.

6.8.2. Overview of orphan marketing authorisations/applications

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

7. Any other business

7.1. Request for clarification of the condition / indication

The EMA received on 3 March 2016 from the sponsor a request for clarification of the condition/indication for orphan drug designation 'Chimeric monoclonal antibody against claudin-18 splice variant 2 for the treatment of gastric cancer' (EU/3/10/803).

The COMP discussed the request and agreed on the response. The sponsor was informed of the outcome of the discussion.

7.2. Tutorial on Cystic Fibrosis

The presentation on orphan aspects of cystic fibrosis that was scheduled at the Tutorial on Cystic Fibrosis scheduled on 20 April was given to the COMP for information.

7.3. -

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 April 2016 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bruno Sepodes	Chair	Expert recommended by EMA	No interests declared	
André Lhoir	Member	Belgium	No interests declared	
Irena Bradinova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No restrictions applicable to this meeting	
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	
Jens Ersbøll	Member	Denmark	No interests declared	
Karri Penttilä	Member	Finland	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	
Judit Eggenhofer	Member	Hungary	No interests declared	
Sigurdur B. Thorsteinsson	Member	Iceland	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Michel Hoffmann	Member	Luxembourg	No interests declared	
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	
Ingrid Wang	Member	Norway	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 Možina	Member	Slovenia	No interests declared	
Josep Torrent-Farnell	Member	Spain	No interests declared	
Dan Henrohn	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	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	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*	Patients' Organisation Representative	No restrictions applicable to this meeting	
A representative from the European Commission attended the meeting				

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Meeting run with support from relevant EMA staff				
A representative 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.