8 March 2016
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Procedure Management and Committees Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 19-21 January 2016

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

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

20 January 2016, 08:30-19:00, room 2F

21 January 2016, 08:30-13:00, 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 and start of referrals will also be available.

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).

[1] Minor corrections under section 6.

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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

The agenda for 19-21 January 2016 was adopted with the addition of one topic under section 5.4.

1.3. Adoption of the minutes

The minutes for 8-10 December 2015 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/183/15

Treatment of gastric cancer

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 30 December 2015, prior to responding to the list of issues.

2.1.2. - EMA/OD/121/15

Treatment of amyotrophic lateral sclerosis

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 30 December 2015, prior to responding to the list of issues.

2.1.3. S3,S13-cyclo(D-tyrolsyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-aspartyl-L-tryptophyl-N-methyl-L-glycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-N-methyl-L-isoleucinamide) - EMA/OD/104/15

Amyndas Pharmaceuticals S.A.; Treatment of C3 glomerulopathy

COMP coordinator: Josep Torrent-Farnell

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

C3 glomerulopathy should be further justified as a distinct medical entity. The sponsor is asked to compare and contrast the new definition of the disease versus the classic classification of the disease. Specifically, the sponsor should discuss the aetiopathogenesis of the proposed condition and how it is reflected by both definitions.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of C3 glomerulopathy, the sponsor should further elaborate on the relevance of the preclinical *in vitro* cellular model used for the treatment of C3 glomerulopathy, and the interpretation of the results obtained in the experiments. In this context, the sponsor should discuss and demonstrate how the observed pharmacodynamic effect could predict clinically meaningful outcome. The sponsor is also asked to present any additional supportive data to support medical plausibility of the proposed product.

In the written response, and during an oral explanation before the Committee on 20 January 2016, the sponsor discussed the aetiology and the pathophysiology of C3 glomerulopathy versus membranoproliferative glomerulonephritis. The COMP acknowledged that the new entity is distinct from membranoproliferative glomerulonephritis by having a distinct aetiology and pathogenesis that stems from a C3 complement dysregulation, while not necessarily displaying the characteristic membranoproliferative histopathological pattern.

With regards to the medical plausibility, the sponsor pointed out that the product could not be evaluated in preclinical disease models due to species-specificity and discussed the available ex vivo studies using sera, plasma and immunoglobulins from patients affected by the proposed condition. Furthermore, it was argued that C3 glomerulopathy patients that are treated with other complement inhibitors have reduced renal inflammation and proteinuria.

The Committee agreed that the condition, treatment of C3 glomerulopathy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing S3,S13-cyclo(D-tyrolsyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-aspartyl-L-tryptophyl-N-methyl-L-glycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-N-methyl-L-isoleucinamide) was considered justified based on preclinical data demonstrating that the product can stabilise C3 dysregulation.

The condition is life-threatening and chronically debilitating due to the development of nephrotic syndrome and end-stage kidney disease leading to renal failure.

The condition was estimated to be affecting less than 1.4 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 S3,S13-cyclo(D-tyrolsyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-aspartyl-L-tryptophyl-N-methyl-L-glycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-N-methyl-L-isoleucinamide), for treatment of C3 glomerulopathy, was adopted by consensus.

2.1.4. - EMA/OD/182/15

Treatment of retinal detachment

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

Retinal detachment should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

The sponsor is requested to clearly define the scope of this application including the types of retinal detachment targeted, and justify why this does not include other retinal breaks and cysts.

Moreover the sponsor is invited to elaborate on the absence of functional endpoints studied (e.g. electroretinography).

- Number of people affected

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

The sponsor should justify:

– The duration of the condition and the use of incidence as an appropriate epidemiological index for the purpose of orphan designation.

– The use of data referring to dates up to 2009, and the absence of extrapolation for the time of this application is made.

– The absence of sensitivity analysis for all assumptions used.

The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition, and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

In the written response, and during an oral explanation before the Committee on 19 January 2016, the sponsor specified the condition to specifically include rhegmatogenous, tractional, and exudative retinal detachment, on the basis that these subclasses of retinal detachment represent the forms most associated with vision loss and amenable to treatment. As to the reason why functional data are not presented, this was attributed to

the model used which would disrupt the histological integrity of the photoreceptor layer. No additional *in vivo* data is presented with the product under evaluation.

Finally with regards to the prevalence criterion, the sponsor assumed that the duration of the condition can be calculated from the period through diagnosis, surgery, follow-up and discharge of the patient and provided an estimate of up to 3.6 per 10,000, assuming similar incidence rates for the three subsets included in the condition.

The COMP considered that the proposed condition can be viewed as a common complication of a plethora of other conditions, and that all subcategories of the ICD-10 classification would have to be considered for the purpose of prevalence calculation. Furthermore, it was considered that functional endpoints were missing, and could have been studied in several other existing models. Therefore, the intention to treat a condition had not been justified.

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

2.1.5. - EMA/OD/186/15

Prevention of necrotising enterocolitis

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 January 2016, prior to responding to the list of issues.

2.1.6. - EMA/OD/132/15

Treatment of Burkitt 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

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Burkitt lymphoma, the sponsor should further elaborate on the presented preclinical *in vivo* data, including a discussion of the endpoints studied and the controls used.

- Number of people affected

The sponsor is invited to revisit its current prevalence calculation to find and include additional epidemiological data to establish the prevalence. In this context the sponsor is recommended to also consult the Haematological Malignancy Research Network (HMRN) York epidemiological data.

For the calculation and presentation of the prevalence estimate it is 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 sponsor is requested to provide additional arguments to establish significant benefit in relation to all authorised products for the treatment of Non-Hodgkin lymphoma that are used to treat the condition.

The COMP cannot yet consider the claim for improved safety or major contribution to patient care in the absence of sufficient clinical data with the proposed product.

The sponsor is asked to clarify the intended target patient population and to justify the choice of control regimen R-CHOP over other recommended dose-intensive combination treatments both in first and second line treatment.

In the written response, and during an oral explanation before the Committee on 20 January 2016, the sponsor further discussed the issues raised. In particular with regards to prevalence, the estimate was updated by including more recent sources; this was considered acceptable by the COMP. With regards to the significant benefit, the sponsor argued improved efficacy based on *in vitro* data outlining that the product has an immune-system stimulatory effects, as well as improved safety on the basis of *in vivo* data arguing an improved toxicity profile versus platinum-containing products.

The COMP considered that the used preclinical model is immunocompromised and that the controls used were unsuitable to confirm significant benefit for the sought indication. Furthermore, it was considered that the safety, at this stage of development, remains unknown. Therefore the criterion for significant benefit could not be considered justified.

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

2.1.7. - EMA/OD/185/15

Treatment of partial deep dermal and full thickness burns

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 partial deep dermal and full thickness burns, the sponsor should further elaborate on the methodology and design of the clinical study which is being used to support the medical plausibility. The sponsor should also further elaborate on the target population and the underlying treatment.

- Significant benefit

The arguments on significant benefit are based on the alternative mechanism of action which could favourably affect the outcome of the patients with the condition.

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

In the written response, and during an oral explanation before the Committee on 20 January 2016, the sponsor further elaborated on the clinical experience of using their product, clarifying the mode of administration and observations made. The mechanism of action was also elaborated, discussing in particular an emerging anti-inflammatory effect, by interfering with cytokine expression. The COMP considered that at that point in time, there were no quantified data to confirm the argued clinical observations, and that the mechanism of action remained assumptive. Therefore the criteria for designation could not be considered met.

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

2.1.8. Methyl 3-((2R)-2-hydroxy-4-(((((S)-1-methoxy-1-oxopropan-2-yl) amino)(phenoxy)phosphoryl)oxy)-3,3-dimethylbutanamido)propanoate - EMA/OD/189/15

Retrophin Europe Limited; Treatment of pantothenate kinase associated neurodegeneration

COMP coordinator: Josep Torrent-Farnell and Dinah Duarte

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

Pantothenate kinase-associated neurodegeneration (PKHAN) should be justified as a distinct medical entity or a valid subset of neurodegeneration with brain iron accumulation (NBIA). Given the emergent nature of the proposed condition the sponsor is invited to discuss whether there exists a plausibility of the product's efficacy in the treatment of idiopathic NBIA and to further discuss the distinct pathophysiology of PKAN and other types of NBIA. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

- Prevalence

The sponsor has provided an estimate of prevalence for both the PKAN as well as the overarching NBIA disorder. Since the upper value of the proposed range is the same for both the broad condition and the subset, the sponsor should discuss the implications of potential renaming of the condition to NBIA on the prevalence estimate.

In the written response, and during an oral explanation before the Committee on 20 January 2016, the sponsor discussed the validity of the condition on the basis of the distinct underlying etiology relating to mutations in PANK2, and further elaborated on the mechanism of action of the product which would only exert beneficial effects in patients affected by this condition. With regards to the prevalence issue, the sponsor acknowledged uncertainties regarding the calculation of prevalence and proposed a refined prevalence estimate ranging between 0.015 and 0.03.

The Committee agreed that the condition, treatment of pantothenate-kinase-associated, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing methyl 3-((2R)-2-hydroxy-4-(((((S)-1-ethoxy-1-oxopropan-2-yl) amino)(phenoxy)phosphoryl)oxy)-3,3-dimethylbutanamido)propanoate was considered justified based on early clinical data in persons affected by the condition demonstrating improvement in movement on the Unified Parkinson's Disease Rating Scale.

The condition is chronically debilitating due to progressive neurological degeneration with signs of Parkinsonism and dystonia and life-threatening due to secondary complications such as aspiration pneumonia, malnutrition and status dystonicus.

The condition was estimated to be affecting less than 0.03 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 methyl 3-((2R)-2-hydroxy-4-(((((S)-1-ethoxy-1-oxopropan-2-yl) amino)(phenoxy)phosphoryl)oxy)-3,3-dimethylbutanamido)propanoate, for treatment of pantothenate-kinase-associated neurodegeneration, was adopted by consensus.

2.1.9. - EMA/OD/190/15

Treatment of globoid cell leukodystrophy (Krabbe disease)

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 globoid cell leukodystrophy, the sponsor should further elaborate on:

  - The results in the referenced pre-clinical studies in particular with regards to the absence of functional/clinically relevant outcomes.

- Number of people affected

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

The sponsor should describe and justify the methodology used for the prevalence calculation, and provide a point prevalence figure including all forms of the proposed condition.

In the written response, and during an oral explanation before the Committee on 20 January 2016, the sponsor clarified that there were no quantitative data available with regards to any functional assessments, such as grip strength or rotarod tests. With regards to the prevalence calculation, the sponsor provided further calculations taking into consideration the birth rate in Europe.

The COMP considered that in the absence of functional data a modest improvement in the histological endpoints would not suffice to justify the medical plausibility.

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

2.1.10. Humanised IgG4 monoclonal antibody against total complement component 1, subcomponent s - EMA/OD/177/15

Assign Group Development UK Ltd; Treatment of autoimmune haemolytic anaemia

COMP coordinator: Karri Penttila

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 autoimmune haemolytic anaemia, the sponsor should further elaborate on:

- The results obtained *in vitro* on sera from cold AIHA patients;
- The relevance of the preclinical *in vitro* data used for the treatment of autoimmune haemolytic anaemia, and the interpretation of the results obtained in the experiments;
- The possibility of testing the product *in vivo* in pre-clinical models or whether models other than those in rodents exist, where agents targeting the complement system could be tested.

- Significant benefit

It appears that there are authorized treatments for AIHA in the Community, such as corticosteroids. There are also multiple modes of disease management depending on whether it is primary or secondary, warm, cold or mixed type.

The sponsor is requested therefore to discuss the results from *in vitro* study on serum samples from patients to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. A comparative discussion of the proposed treatment versus all authorized products and other satisfactory treatment methods is expected. In addition, the sponsor should clearly identify the patient population which will benefit from the proposed treatment in the context of the current standard of care.

In the written response, and during an oral explanation before the Committee on 20 January 2016, the sponsor further elaborated on the issues raised. The proposed condition was limited to the cold agglutinin disease (CAD), motivated by *in vitro* data and new data from one patient from an ongoing Phase 1 study. The sponsor further argued that the product is expected to work only in a condition which is driven by complement-mediated autoimmunity. However during the oral explanation, the sponsor admitted that partial efficacy in other types of autoimmune haemolytic anaemia may also be expected.

With regards to the arguments to support significant benefit the sponsor acknowledged that there are medicinal products authorized in the EU for the treatment of autoimmune haemolytic anaemia. However, the use of corticosteroids in CAD was not considered effective, and methods like splenectomy or RBC transfusions have a short lived effect and in case of CAD there is still an unmet need for an improved treatment. It was also argued that there are also patients with mix-type and persistent warm autoimmune haemolytic anaemia, who could benefit from the proposed product, especially in the context of an acute haemolytic crisis. The committee considered this to constitute a clinically relevant advantage.

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

The intention to treat the condition with the medicinal product containing humanised IgG4 monoclonal antibody against total complement component 1, subcomponent s was considered justified based on clinical data demonstrating decreased haemolysis and increased haemoglobin levels.

The condition is chronically debilitating due to venous or arterial thrombotic events, infectious complications, requirement of red blood cell transfusion and decreased quality of life.

The condition was estimated to be affecting less than 2.3 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised IgG4 monoclonal antibody against total complement component 1, subcomponent s will be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical *in vitro* and early clinical data from persons affected by cold autoimmune haemolytic anaemia that demonstrate that the product inhibits haemolysis and improves haemoglobin levels. The immediate effect of the treatment compares favourably to the authorised treatments and methods such as corticosteroids or splenectomy. The use of the product may also have a more long-lived effect compared to red blood cell transfusion. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised IgG4 monoclonal antibody against total complement component 1, subcomponent s, for treatment of autoimmune haemolytic anaemia, was adopted by consensus.

2.1.11. Arsenic trioxide - EMA/OD/180/15

Orsenix Holdings BV; Treatment of acute promyelocytic leukaemia

COMP coordinator: Frauke Naumann-Winter

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

The COMP requests the sponsor to broaden the indication to “Treatment of acute myeloid leukaemia”, or otherwise to justify the proposed conditions as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor’s attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

- Number of people affected

With reference to the discussion on the proposed condition, the sponsor is invited to update its prevalence calculation reflecting the change in condition. Otherwise, the sponsor is invited to strengthen the prevalence calculation for the proposed condition by including additional epidemiological data.

For the calculation and presentation of the prevalence estimate it is advised to refer to the “Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation”.

In the written response, the sponsor revised the sought indication to “treatment of acute myeloid leukaemia”, while confirming that the product at this point in time is developed for the subset of patients diagnosed with acute promyelocytic leukaemia. The sponsor furthermore submitted a new prevalence calculation for the new broader condition.

Following review of the application by the Committee, it was agreed to rename the indication to “acute myeloid leukaemia”.

The Committee agreed that the condition, treatment of acute myeloid leukaemia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing arsenic trioxide was considered justified based on published literature data demonstrating anti-neoplastic efficacy of the product in a subset of patients affected by the condition.

The condition is life-threatening and chronically debilitating due the consequences of the bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated. The overall 5-year relative survival with the currently available treatments is approximately 22%.

The condition was estimated to be affecting approximately 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing arsenic trioxide will be of significant benefit to those affected by the condition. The sponsor has provided clinical data from the published literature that demonstrate that the product has anti-neoplastic efficacy in a subset of patients affected by the condition that have not been previously treated. Furthermore, this product is an oral formulation of an already authorised product that is administered intravenously and therefore it might have the potential to benefit patient care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for arsenic trioxide, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.1.12. Ex-vivo-expanded autologous fibroblasts transduced with lentiviral vector encoding COL7A1 gene - EMA/OD/188/15

Dr Waseem Qasim; Treatment of dystrophic epidermolysis bullosa

COMP coordinator: Frauke Naumann-Winter

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:

- Number of people affected

The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the revised orphan condition - epidermolysis bullosa, and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

In the written response, the sponsor provided an updated prevalence calculation for epidermolysis bullosa based on a number of citations from EU and worldwide. The estimated prevalence ranged greatly between 0.01 and 0.49 per 10,000 in selected regions of the EU. Given the substantial uncertainty regarding the prevalence and the exceeding rarity of the condition the COMP adopted the most conservative value as seen in previous applications.

Following review of the application by the Committee, it was agreed to rename the indication to “epidermolysis bullosa”, and to rename the active substance to “ex-vivo-expanded autologous fibroblasts transduced with lentiviral vector containing the *COL7A1* gene”.

The Committee agreed that the condition, treatment of epidermolysis bullosa, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing ex-vivo-expanded autologous fibroblasts transduced with lentiviral vector containing the *COL7A1* gene was considered justified based on pre-clinical data demonstrating the establishment of dermal-epidermal junctions in epidemolysis bullosa engineered skin graft treated with the proposed product.

The condition is debilitating and life-threatening because of severe blistering and associated scarring and deformities resulting in poor quality of life and reduced life expectancy.

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.

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 ex-vivo-expanded autologous fibroblasts transduced with lentiviral vector containing the *COL7A1* gene, for treatment of epidermolysis bullosa, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. 2-Ethylbutyl (2S)-2-{[(S)-{[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl]methoxy}(phenoxy)phosphoryl]amino}propanoate - EMA/OD/197/15

Gilead Sciences International Ltd; Treatment of Ebola virus disease

COMP coordinator: Josep Torrent-Farnell

The Committee agreed that the condition, treatment of Ebola virus disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 2-ethylbutyl (2S)-2-{[(S)-{[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl]methoxy}(phenoxy)phosphoryl]amino}propanoate was considered justified based on *in vivo* pre-clinical data in a model of Ebola infection showing improved survival.

The condition is life-threatening due to multi-organ failure and severe haemorrhagic complications.

The condition was estimated to be affecting less than 0.01 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 2-ethylbutyl (2S)-2-{[(S)-{[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl]methoxy}(phenoxy)phosphoryl]amino}propanoate, for treatment of Ebola virus disease, was adopted by consensus.

2.2.2. - EMA/OD/196/15

Treatment of chronic lymphocytic leukaemia / small lymphocytic 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 February meeting.

2.2.3. - EMA/OD/210/15

Treatment of Epstein-Barr Virus-associated lymphoproliferative disorder following allogeneic haematopoietic cell transplant

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 February meeting.

2.2.4. Allogeneic fetal human retinal progenitor cells expanded ex vivo - EMA/OD/213/15

Voisin Consulting S.A.R.L.; Treatment of retinitis pigmentosa

COMP coordinator: Ingeborg Barisic

The Committee agreed that the condition, treatment of 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 allogeneic fetal human retinal progenitor cells expanded ex vivo was considered justified based on preliminary clinical data showing improvements in visual acuity in treated patients, supported by preclinical *in vivo* data from a valid disease model demonstrating treatment-related enhancements in optomotor performance and electroretinography.

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

The condition was estimated to be affecting less than 3.7 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 allogeneic fetal human retinal progenitor cells expanded ex vivo, for treatment of retinitis pigmentosa, was adopted by consensus.

2.2.5. Delta-9-tetrahydrocannabinol and cannabidiol from extracts of the cannabis sativa L. plant - EMA/OD/222/15

GW Research Ltd; Treatment of glioma

COMP coordinator: Brigitte Bloechl-Daum

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

The intention to treat the condition with the medicinal product containing delta-9-tetrahydrocannabinol and cannabidiol from extracts of the *Cannabis sativa* L. plant was considered justified based on results of studies with the product in a valid xenograft model of glioma demonstrating tumour volume reduction and increased survival.

The condition is chronically debilitating due to symptoms caused by compression by the tumour on the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality and cognitive impairment. The condition is life-threatening, with poor 5-year survival of less than 5% for glioblastoma multiforme patients.

The condition was estimated to be affecting 2.6 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing delta-9-tetrahydrocannabinol and cannabidiol from extracts of the *Cannabis sativa* L. plant will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate a beneficial effect on tumour volume reduction and survival when the proposed product was added to radiation therapy and temozolomide, which is currently authorised for the treatment of glioma. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by glioma.

A positive opinion for delta-9-tetrahydrocannabinol and cannabidiol from extracts of the *Cannabis sativa* L. plant, for treatment of glioma, was adopted by consensus.

2.2.6. Diclofenamide - EMA/OD/199/15

Prof Michael Hanna; Treatment of familial periodic paralysis

COMP coordinator: Dinah Duarte and Michel Hoffmann

Following review of the application by the Committee, it was agreed to rename the indication to “periodic paralysis”.

The Committee agreed that the condition, treatment of periodic paralysis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing diclofenamide was considered justified based on preliminary clinical data, supporting a reduction in the number of attacks in patients affected by the condition.

The condition is chronically debilitating, due to permanent weakness and muscle pain in the majority of patients, and the requirement of mobility aids in about half of the patients. The condition may also be life-threatening, in particular due to the risk of cardiac arrhythmias in hypokalaemic periodic paralysis and Andersen-Tawil syndrome.

The condition was estimated to be affecting approximately 0.2 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 diclofenamide, for treatment of periodic paralysis, was adopted by consensus.

2.2.7. DNA plasmid encoding a recombinant fusion protein consisting of the extracellular domain of human TNFα p55 receptor linked to the human IgG1 Fc domain - EMA/OD/207/15

Eyevensys SA; Treatment of non-infectious uveitis

COMP coordinator: Armando Magrelli

The Committee agreed that the condition, treatment of non-infectious uveitis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing DNA plasmid encoding a recombinant fusion protein consisting of the extracellular domain of human TNFα p55 receptor linked to the human IgG1 Fc domain was considered justified based on pre-clinical *in vivo* data showing a reduction in inflammation and improvement in visual symptoms.

The condition is chronically debilitating due to development of significant visual impairment or legal blindness.

The condition was estimated to be affecting approximately 4.6 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing DNA plasmid encoding a recombinant fusion protein consisting of the extracellular domain of human TNFα p55 receptor linked to the human IgG1 Fc domain will be of significant benefit to those affected by the condition. The sponsor has provided preclinical *in vivo* data that supports a corticosteroid sparing effect when this product is used. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for DNA plasmid encoding a recombinant fusion protein consisting of the extracellular domain of human TNFα p55 receptor linked to the human IgG1 Fc domain, for treatment of non-infectious uveitis, was adopted by consensus.

2.2.8. - EMA/OD/203/15

Treatment of cutaneous T-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 February meeting.

2.2.9. - EMA/OD/176/15

Treatment of acute lymphoblastic leukemia

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 February meeting.

2.2.10. - EMA/OD/201/15

Diagnosis 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 February meeting.

2.2.11. - EMA/OD/200/15

Diagnosis 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 February meeting.

2.2.12. - EMA/OD/211/15

Treatment of gastro-entero-pancreatic neuroendocrine tumours

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 February meeting.

2.2.13. - EMA/OD/181/15

Treatment of monogenic diabetes

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 February meeting.

2.2.14. - EMA/OD/159/15

Treatment of soft tissue sarcoma

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 February meeting.

2.2.15. - EMA/OD/209/15

Treatment of graft rejection following solid organ transplantation

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 February meeting.

2.2.16. - EMA/OD/214/15

Treatment of gastro-entero-pancreatic neuroendocrine tumours

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 February meeting.

2.2.17. N-(4-Methoxyphenyl)-N,2,6-trimethylfuro[2,3-d]pyrimidin-4-amine - EMA/OD/206/15

FLAG Therapeutics Ltd; Treatment of glioma

COMP coordinator: Daniel O'Connor and Andri Andreou

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

The intention to treat the condition with the medicinal product containing N-(4-methoxyphenyl)-N,2,6-trimethylfuro[2,3-d]pyrimidin-4-amine was considered justified based on a preclinical model of the proposed condition, where treatment with the product resulted in inhibition of tumour growth.

The condition is chronically debilitating due to symptoms caused by compression by the tumour on the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality and cognitive impairment. The condition is also life-threatening, with poor 5-year survival of less than 5% for glioblastoma multiforme patients.

The condition was estimated to be affecting approximately 2.6 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing N-(4-methoxyphenyl)-N,2,6-trimethylfuro[2,3-d]pyrimidin-4-amine will be of significant benefit to those affected by the condition. The sponsor has provided data in a preclinical model of the condition supporting improved inhibition of tumour growth compared to temozolomide. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for N-(4-Methoxyphenyl)-N,2,6-trimethylfuro[2,3-d]pyrimidin-4-amine, for treatment of glioma, was adopted by consensus.

2.2.18. - EMA/OD/198/15

Treatment of acute myeloid 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 February meeting.

2.2.19. - EMA/OD/238/15

Treatment of soft tissue sarcoma

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 February meeting.

2.2.20. - EMA/OD/195/15

Treatment of primary hyperoxaluria type 1

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 February meeting.

2.2.21. Tolfenamic Acid - EMA/OD/193/15

RV Developpement; Treatment of progressive supranuclear palsy

COMP coordinator: Josep Torrent-Farnell

The Committee agreed that the condition, treatment of progressive supranuclear palsy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing tolfenamic acid was considered justified based on pre-clinical data showing a reduction in tau protein and an improvement in memory and learning.

The condition is chronically debilitating due to progressive neurological impairment including development of parkinsonism, inability to walk, progressive paralysis and cognitive deterioration. The condition is life-threatening, leading to premature death.

The condition was estimated to be affecting approximately 0.6 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 tolfenamic acid, for treatment of progressive supranuclear palsy, was adopted by consensus.

2.2.22. Tolfenamic acid - EMA/OD/194/15

RV Developpement; Treatment of behavioural variant fronto-temporal dementia

COMP coordinator: Josep Torrent-Farnell

The Committee agreed that the condition, treatment of behavioural variant fronto-temporal dementia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing tolfenamic acid was considered justified based on pre-clinical *in vivo* data showing a reduction in tau protein and an improvement in learning and memory.

The condition is life-threatening and chronically debilitating due to neurological and cognitive impairment and limited life-expectancy.

The condition was estimated to be affecting approximately 2.2 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 tolfenamic acid, for treatment of behavioural variant fronto-temporal dementia, was adopted by consensus.

2.2.23. - EMA/OD/179/15

Treatment of pulmonary arterial hypertension

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 February meeting.

2.2.24. Venetoclax - EMA/OD/205/15

Abbvie Ltd.; Treatment of acute myeloid leukaemia

COMP coordinator: Jens Ersbøll

The Committee agreed that the condition, treatment of acute myeloid leukaemia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing venetoclax was considered justified based on preclinical and preliminary clinical data showing antitumor activity.

The condition is life threatening due to the consequences of the bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections.

The condition was estimated to be affecting approximately 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing venetoclax will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing favourable responses in patients older than 65 years of age not eligible for standard induction therapy when the product was used in combination with decitabine or azacitidine. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by acute myeloid leukaemia.

A positive opinion for venetoclax, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.3. Revision of the COMP opinions

None

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 16 applications submitted.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 4 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of Niemann-Pick disease, type C

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 cytomegalovirus disease in patients with impaired cell mediated immunity

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

3.1.3. -

Treatment of advanced ovarian cancer

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

[Post meeting note: Updated proposed answers on the significant benefit issues were adopted at the February COMP 2016]

3.2. Finalised letters

3.2.1. -

Treatment of ovarian cancer

The finalised letter was circulated for information.

3.2.2. -

Prevention of oral mucositis in head and neck cancer patients undergoing radiation therapy

The finalised letter was circulated for information.

3.2.3. -

Treatment of amyotrophic lateral sclerosis

The finalised letter was circulated for information.

3.2.4. -

Treatment of ovarian cancer

The finalised letter was circulated for information.

3.2.5. -

Treatment of acute myeloid leukaemia

The finalised letter was circulated for information.

3.2.6. -

Treatment of growth hormone deficiency

The proposed COMP input to a request for Protocol Assistance clarification addressed to CHMP was adopted by written procedure on 3 February 2016.

3.3. New requests

3.3.1. -

Diagnosis of gastro-entero-pancreatic neuroendocrine tumours

The new request was noted.

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. Neofordex - dexamethasone – EMEA/OD/133/09, EU/3/10/745, EMEA/H/C/004071

LABORATOIRES CTRS; Treatment of multiple myeloma

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:

Prevalence

The sponsor is basing the revision of estimate on the basis of 2011 data. Instead the sponsor is requested to provide an estimate 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 has provided support of increased preference of the new strength tablet of dexamethasone; however increased convenience per se would not suffice to justify significant benefit.

The sponsor is requested to describe the available formulations and strengths of products containing dexamethasone authorised in the EU and provide any data they may have to document a) the serious and documented difficulties with regards to the existing formulations and the corresponding consequences, in the context of the current treatment regiments and schedules and b) to provide data that these serious limitations can be overcome with the proposed new formulation.

More specifically data should be provided on:

- The authorised formulations and strengths of dexamethasone in the respective European member states.
- Data on documented serious problems with the current formulations as experienced by patients with respect to compliance to treatment schedules.
- Any data from studies or the ATU program, documenting major contribution to patient care based on improved patient reported outcomes, improved compliance or other consequences from the use of the specific product in this application over and above the preference survey.
- Any validated data gathered by the company after the granting of the orphan drug designation to demonstrate the major contribution to patient care or a justification why these data have not been collected. The need for these data has been indicated in the COMP report at the time of orphan drug designation.

In the absence of data on the above aspects, the significant benefit may not be considered justified.

In the written response, and during an oral explanation before the Committee on 19 January 2016, the sponsor further elaborated on the issues raised as follows:

As regards the issue of prevalence, the sponsor complemented the initially proposed 5 year prevalence, with 10 and 15 years partial figures, using an extrapolation from 1, 3 and 5-year GLOBOCAN 2012 data. The final conclusion of 2.2 per 10,000 again is not a point prevalence index, and falls short of the previous considerations of the COMP accepting up to 3.6. The COMP considered that the prevalence could be accepted as less than 3.6 at the time of the review of criteria.

As regards the significant benefit question, the sponsor responded as follows (respectively to the points as raised by the COMP)

- The sponsor provided a list of authorised formulations, confirming the authorisation of several oral solutions up to 20mg/5ml (Slovenia, Cyprus, Greece, United Kingdom) and tablets up to 16mg. It was noted that for 35 percent of respective population there is no nationally authorised high strength dexamethasone formulation. The COMP noted that authorisation cannot be used as synonymous to patient's access to products, and reflected in particular on the issue of parallel imports, which was not discussed by the sponsor.
- With regards to the requested data on documented serious problems with existing formulations, two arguments were put forward: With reference to their questionnaire, and in particular in those patients that had not received Neofordex, a 3.4% of patients was taking a large number of tablets and that 8.2% used non oral formulations per os. A further 10% was being treated with parenteral formulations. The sponsor also discussed the use of dexamethasone in the overall management of patients with multiple myeloma, both at the

pre-ASCT setting of younger eligible patients, as well as in older patients as a second line treatment. It was argued that treatment for multiple myeloma typically contains 2 to 4 parenteral and 4 to 7 oral agents, which would raise the issue of polypharmacy and pill burden, especially for older patients with concomitant conditions under treatment (such as hypertension). The applicant then attempted to draw conclusions on compliance to treatment, by bridging to other diseases including, diabetes HIV, haemodialysis and an internet study on "chronic disease". The COMP pointed out that no myeloma-specific data were presented regarding compliance. Furthermore, it was considered that number of doses per day may be more important than the number of pills per dose, and that the new formulation does not change the number of medications per day. It was further considered that in the second line setting at least, once weekly administration of a certain number of pills would not pose a compliance issue.

- No further data to confirm a major contribution to patient care based on improved patient reported outcomes, improved compliance or other consequences from the use of the specific product are proposed. The applicant claimed that the ATU programs do not allow for gathering of efficacy data.

- No further data have been generated and the applicant asserted that "even though the significant benefit of Neofordex appears obvious from a clinical point of view it is difficult to prove due to methodological obstacles".

Having considered the sponsor's responses in writing and during the oral explanation, the COMP concluded that the sponsor has not provided any data in multiple myeloma patients confirming either improved compliance to treatment, improved patient reported outcomes, or consequences from the use of the specific product over and above expressed preferences.

The EMA/COMP also invited a patient expert from the Norwegian blood cancer association, in order to get feedback from the MM patients' perspective on the use of dexamethasone and any potential contribution to patient care for this new table strength. During the oral explanation, the patient expert did not report any problems with his experience using the 4 mg / tablets in Norway. Moreover, it was noted that the dose may need to be reduced and in that case the lower strengths may actually be more practical versus the high strength proposed. For example, the patient testified that he had to split his dose in two, and take it over two days instead of one, to improve tolerance of dexamethasone.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 21 January 2016, prior to final opinion.

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

Lucane Pharma; Treatment of cystinosis

The CHMP negative opinion was noted.

4.1.3. Wakix - 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride - EMEA/OD/087/06, EU/3/07/459, EMEA/H/C/002616

Bioprojet; Treatment of narcolepsy

The status of the procedure at CHMP was noted.

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

4.2.1. COAGADEX - factor X - EMEA/OD/044/07, EU/3/07/471, EMEA/H/C/003855

BIO PRODUCTS LABORATORY; Treatment of hereditary factor X deficiency

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 February meeting.

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

Bristol-Myers Squibb; Treatment of multiple myeloma

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 February meeting.

4.2.3. Uptravi - selexipag - EMEA/OD/043/05, EU/3/05/316, EMEA/H/C/003774

Actelion Registration Ltd.; Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension

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 February meeting.

4.2.4. - allogeneic T cells genetically modified to express suicide gene - EMEA/OD/041/03, EU/3/03/168, EMEA/H/C/002801

MolMed SpA; Adjunctive treatment in haematopoietic cell transplantation

The status of the procedure at CHMP was noted.

4.2.5. - albutrepenonacog alfa - EMEA/OD/117/09, EU/3/09/723, EMEA/H/C/003955

CSL Behring GmbH; Treatment of haemophilia B

The status of the procedure at CHMP was noted.

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

Amicus Therapeutics UK Ltd; Treatment of Fabry disease

The status of the procedure at CHMP was noted.

4.2.7. - 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.

4.2.8. Translarna - ataluren – Type II variation - EMEA/OD/107/04, EU/3/05/277, EMEA/H/C/002720/II/0012

PTC Therapeutics International Limited; Treatment of cystic fibrosis

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 3 applications.

5. Organisational, regulatory and methodological matters

5.1. Mandate and organisation of the COMP

5.1.1. COMP Membership

The COMP welcomed Dan Henrohn as new member representing Sweden.

5.2. Coordination with EMA Scientific Committees or CMDh-v

5.2.1. Paediatric Committee (PDCO)

Report from the COMP/PDCO Working Group meeting held in December 2015

The COMP was updated on the COMP/PDCO Working Group December meeting.

Next meetings will be via teleconference since COMP and PDCO meetings are not scheduled on the same week in 2016.Concerns were expressed that it could slow down the collaboration.

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

5.3.1. Significant Benefit Working Group

Proposed meeting time on 21 January 2016 at time 12:00, room 2F

5.4. Cooperation within the EU regulatory network

5.4.1. European Commission

Report on the Commission Expert Group on Rare Diseases meeting held on 12-13 November 2015

The minutes from the meeting will be circulated when available.

5.5. Cooperation with International Regulators

None

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

None

5.7. COMP work plan

5.7.1. Draft COMP Work Plan 2016

The Chair presented the latest version of the COMP work plan 2016 for adoption. A new action was introduced under 'Interaction with partners' after the December meeting.

The COMP adopted the proposed work plan with no modifications.

5.8. Planning and reporting

5.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2015-2016

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2015-2016 were circulated.

5.8.2. Overview of orphan marketing authorisations/applications

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

5.8.3. Report on the 'Data Gathering Initiative'

Postponed to next meeting.

6. Any other business

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

6.1.1. –

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 January 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	
Brigitte Blöchl-Daum	Member	Austria	No interests declared	
André Lhoir	Member	Belgium	No interests declared	
Irena Bradinova	Member	Bulgaria	No interests declared	
Adriana Andrić	Member	Croatia	No interests declared	
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	
Katerina Kubacková	Member	Czech Republic	No restrictions applicable to this meeting	
Jens Ersbøll	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	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	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	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	
Julian Isla	Expert - in person*	Patients' Organisation Representative	No interests declared	
Jacob Hygen	Expert - in person*	Patients' Organisation Representative	No interests declared	
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.