Committee for Orphan Medicinal Products (COMP)
Final minutes for the meeting on 21-23 March 2016

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene
21 March 2016, 09:00-19:00, room 2F
22 March 2016, 08:30-19:30, room 2F
23 March 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 ongoing 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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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 21-23 March 2016 was adopted with no amendments.

1.3. **Adoption of the minutes**

The minutes for 16-18 February 2016 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/204/15**

Treatment of pancreatic cancer

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 potential improved efficacy in the condition when used in combination with 5-Fluorouracil in patients who are gemcitabine resistant. The pre-clinical data presented does not demonstrate such efficacy. The sponsor is invited to clarify, whether the model used was indeed gemcitabine resistant. Data in the correct therapeutic context would be expected to justify the significant benefit.
The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the pre-clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 21 March 2016, the sponsor described the effects of the product on tumour growth in an in vivo immunocompetent xenograft pancreatic cancer model. In this model, the product was assumed to have an additional mechanism of action, by way of stimulating the immune system. The committee considered that a novel mechanism of action alone would not suffice to justify significant benefit and this would need to be translated into improved efficacy versus authorised products based on data. The committee expressed a negative trend for significant benefit following the discussion and the sponsor withdrew the application upon being informed about this trend.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 22 March 2016, prior to final opinion.

2.1.2. EMA/OD/212/15

Treatment of acute respiratory distress syndrome

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 acute respiratory distress syndrome, the sponsor should further elaborate on:

- the relevance of the preclinical model used for the treatment of acute respiratory distress syndrome, and the interpretation of the results obtained in the experiments. The data presented so far appear to support a preventive and not a treatment indication;
- the results on the endpoint of survival in the ALI model used.

- 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 inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor should describe and justify the methodology used for the prevalence calculation. It should be noted that the evolution of ARDS definitions has to be taken into account to ensure that all affected patients are accounted for.

In the written response, and during an oral explanation before the Committee on 21 March 2016, the sponsor further elaborated on the issues raised.

With regards to medical plausibility the sponsor argued that the development of ARDS models is challenging and several publications use similar close-to-challenge administration schemes to study potential treatments of ARDS. A bridging with effects of similar products...
(not containing the same active as applied for) as appearing in the literature was also put forward. Finally the survival data requested were further elaborated.

As for the issue of prevalence, the sponsor acknowledged that there has been a change in the classification and revised the estimate upwards. The COMP noted that some more recent literature sources should also have been considered (e.g. Bellani et al, JAMA. 2016 Feb 23;315(8):788-800).

The COMP considered that in the absence of data with the product as proposed for designation in a treatment setting of ARDS, the medical plausibility would not be considered acceptable. Further, all available sources regarding prevalence should be taken into consideration, in light of the recent change in the diagnostic criteria for the proposed condition.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 23 March 2016, prior to final opinion.


SELLAS Life Sciences Group UK, Limited; Treatment of acute myeloid leukaemia

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 acute myeloid leukaemia, the sponsor should contextualise the outcome of the clinical data presented with natural history or study data of patients affected by the condition.

- **Significant benefit**

The sponsor is invited to further elaborate on the target patient population for the product, and how this patient population is reflected by the enrolled study population of the presented trials. More detailed background information on the patients enrolled in the study/ies regarding their age and eligibility for non-intensive treatment should be given.

In the written response, and during an oral explanation before the Committee on 21 March 2016, the sponsor compared the outcome data with a published study in AML patients, which supported an increased overall survival in patients treated with the proposed product.

With regards to the patient population the sponsor provided more detail regarding the age group and the previous treatments of the patients studied. The sponsor clarified that the target patient population should not be eligible for allogeneic HSCT, as this might be the first choice regarding consolidation therapy.

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 Tyr-Met-Phe-Pro-Asn-Ala-Pro-Tyr-Leu, Ser-Gly-Gln-Ala-Tyr-Met-Phe-Pro-Asn-Ala-Pro-Tyr-Leu-Pro-Ser-Cys-Leu-Glu-Ser, Arg-Ser-Asp-Glu-Leu-Val-Arg-His-His-Met-His-Gln-Arg-Asn-Met-Thr-Lys-Leu and Pro-Gly-Cys-Asn-Lys-Arg-Tyr-Phe-Lys-Leu-Ser-His-Leu-Gln-Met-His-Ser-Arg-Lys-His-Thr-Gly was considered justified based on preliminary clinical data demonstrating improvement in overall survival of patients affected by the condition that are in complete remission after intensive induction and consolidation treatment.

The condition is life-threatening due to its rapid progression and its 5 year survival of approximately 22% with current treatments and chronically debilitating due to the consequences of 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 Tyr-Met-Phe-Pro-Asn-Ala-Pro-Tyr-Leu, Ser-Gly-Gln-Ala-Tyr-Met-Phe-Pro-Asn-Ala-Pro-Tyr-Leu-Pro-Ser-Cys-Leu-Glu-Ser, Arg-Ser-Asp-Glu-Leu-Val-Arg-His-His-Met-His-Gln-Arg-Asn-Met-Thr-Lys-Leu and Pro-Gly-Cys-Asn-Lys-Arg-Tyr-Phe-Lys-Leu-Ser-His-Leu-Gln-Met-His-Ser-Arg-Lys-His-Thr-Gly will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that maintenance treatment improved overall survival of patients affected by the condition that are in complete remission after successful treatment with currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.


### 2.1.4. EMA/OD/235/15

**Treatment of osteogenesis imperfecta**

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.

### 2.1.5. EMA/OD/217/15

**Prevention of short bowel syndrome**

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.
2.1.6. **EMA/OD/236/15**

**Treatment of Smith-Magenis syndrome**

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 sponsor is seeking an orphan designation for the treatment of Smith-Magenis syndrome. To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Smith-Magenis syndrome, the sponsor should further elaborate on:
  - the plausibility of using the product as a single agent. The sponsor is invited to discuss whether there is an intent to develop this product in combination with beta-blockers, which are currently used off-label in this indication;
  - the administration regimen scheme.

- **Number of people affected**

  The sponsor presents an estimate of prevalence based on publications, which do not contain epidemiological data per se. Instead, they refer to ‘disease frequency’, which can be interpreted either as prevalence or incidence. The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and/or registries for the proposed orphan condition and clearly state the epidemiological index used. Where incidence data is considered, the life-span of affected persons should be stated and taken into consideration when calculating the prevalence.

  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, and during an oral explanation before the Committee on 22 March 2016, the sponsor elaborated on the rationale for the development of a specific formulation of the proposed active substance. The Committee inquired whether any data existed to support the development of the proposed active as a single agent treatment. The sponsor did not present any data to support this and at the same time did not express an intention to develop the treatment in combination with other active substances as discussed in literature. The committee therefore noted the absence of data to support the medical plausibility.

  In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 23 March 2016, prior to final opinion.

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2.1.7. **Brincidofovir - EMA/OD/234/15**

Chimerix UK Ltd; Prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk

**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:
• Population eligible for prevention of CMV disease
The sponsor is invited to justify the exclusion of patients at risk for CMV disease (e.g. receiving immunosuppressive treatment) with respect to the prevalence calculation.

• Significant benefit
The sponsor is invited to confirm whether any immunoglobulin-containing product is authorised in the EU for the scope of this application, and provide a justification of significant benefit with regards to a clinically relevant advantage or a major contribution to patient care.

In the written response, and during an oral explanation before the Committee on 22 March 2016, the sponsor further elaborated on the issues raised.

With regards to the population eligible for the use of the proposed product for prevention of CMV disease, the applicant further elaborated on the choice of the four populations deemed to be at risk, and the exclusion of populations not deemed eligible for prevention. It was argued that people living with chronic autoimmune conditions, such as Rheumatoid Arthritis, Multiple Sclerosis, Crohn’s Disease, and others, who may be taking immunomodulatory therapies including monoclonal antibodies and steroids, is not a population considered to have the same level of risk as those described in the original orphan drug application. The sponsor quoted treatment guidelines such as the European Crohn’s and Colitis Organisation (ECCO) 2014 guidance Opportunistic Infections and the American College of Rheumatology guidelines 2015 which do not advise preventive management for CMV viral infection or disease. The COMP considered that the proposed populations are in line with previous considerations of the COMP in similar procedures.

As for the issue of significant benefit, the sponsor acknowledged CMV-immunoglobulin is authorised in the EU but noted that this is not recommended by the international transplant societies for prevention of CMV, stemming from the low efficacy and doubtful safety. The COMP considered that in spite of the specific regulatory authorisation for prophylaxis, a number of international treatment guidelines explicitly recommended against using immunoglobulins as primary prophylaxis or do not mentioned it at all. This was also supported by literature studies reporting no additional benefit for IVIG or CMV-IG on top of antiviral treatment in gastrointestinal CMV disease. Taking into consideration the already presented clinical data in this application, a clinically relevant advantage was considered on the basis of an assumption of improved efficacy.

Following review of the application by the Committee, it was agreed to rename the indication to “prevention of cytomegalovirus disease”.

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

The intention to treat the condition with the medicinal product containing brincidofovir was considered justified based on preliminary clinical studies showing reduced rates of cytomegalovirus disease and viraemia, in allogeneic haematopoietic stem cell transplantation recipients who were seropositive for cytomegalovirus.

The condition is chronically debilitating and life-threatening in particular due to manifestations such as pneumonia, gastrointestinal infections, central nervous system infection, retinitis, and in transplant recipients graft failure, rejection, and graft-versus-host disease.
The condition was estimated to be affecting approximately 3.2 in 10,000 persons in the European Union, at the time the application was made, based on the annual number of people eligible for prevention. This was estimated on the basis of patients with impaired cell-mediated immunity being seropositive for cytomegalovirus, or receiving grafts from seropositive donors.

In addition, although satisfactory methods of prevention of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing brincidofovir will be of significant benefit to those affected by the condition. The sponsor has provided data that demonstrate reduced rates of cytomegalovirus disease and viraemia, in allogeneic haematopoetic stem cell transplantation recipients who were seropositive for cytomegalovirus. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for brincidofovir, for prevention of cytomegalovirus disease, was adopted by consensus.

2.1.8. Human/Murine Chimeric Monoclonal Antibody to CD105 (Endoglin) - EMA/OD/215/15

Tracon Pharma Limited; Treatment of soft tissue sarcoma

COMP coordinator: Brigitte Bloechl-Daum

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

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 is proposing a prevalence estimate of 4.68 in 10,000 for the condition in the EU based on the assumption of 10 years duration of the disease. The sponsor is requested to further discuss the prevalence estimate, providing a further clarification regarding the use of 10 years disease duration in the prevalence calculation.

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the clinical study to justify the assumption of significant benefit over authorised medicinal products. In particular the sponsor is invited to further elaborate on:

- the assumption of significant benefit of the proposed product compared to pazopanib monotherapy, either referring to available clinical data or to any preclinical studies performed.

In the written response, and during an oral explanation before the Committee on 22 March 2016, the sponsor proposed that the product would be of significant benefit to the current chemotherapeutic agents, due to its potential efficacy in all the types of sarcomas and its availability for a wider population of patients. This assumption was supported by preliminary clinical data reporting ongoing complete responses in 2 patients with advanced/refractory
angiosarcoma, including one patient relapsed to previous pazopanib therapy, who responded to treatment with the product in combination with pazopanib.

Following review of the application by the Committee, it was agreed to rename the active substance to “human/murine chimeric monoclonal antibody against endoglin”.

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

The intention to treat the condition with the medicinal product containing human/murine chimeric monoclonal antibody against endoglin was considered justified based on preliminary clinical data showing durable complete responses in patients with select subtypes of sarcoma known to express endoglin, including angiosarcoma.

The condition is chronically debilitating with a high recurrence and metastasis rate, and life-threatening with an overall 5-year survival rate of approximately 60%.

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.

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 human/murine chimeric monoclonal antibody against endoglin will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing favourable activity with the proposed product in combination with standard dose pazopanib in patients previously treated with other antineoplastic agents. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for human/murine chimeric monoclonal antibody against endoglin, for treatment of soft tissue sarcoma, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. (1E,6E)-1,7-Bis(3,4-dimethoxyphenyl)-4-cyclobutylmethyl-1,6-heptadiene-3,5-dione - EMA/OD/252/15

Coté Orphan Consulting UK Limited; Treatment of X-linked spinal and bulbar muscular atrophy (Kennedy’s disease)

COMP coordinator: Dinah Duarte and Michel Hoffmann

Following review of the application by the Committee, it was agreed to rename the indication to as “X-linked spinal and bulbar muscular atrophy (Kennedy’s disease).

The Committee agreed that the condition, treatment of X-linked spinal and bulbar muscular atrophy (Kennedy’s disease), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing (1E,6E)-1,7-bis(3,4-dimethoxyphenyl)-4-cyclobutylmethyl-1,6-heptadiene-3,5-dione was considered justified based on preclinical data showing improvement of muscle function in models of the condition.
The condition is chronically debilitating due to progressive muscle weakness, with difficulty in walking, with some patients requiring a wheelchair 15-20 years after the onset of the disease. Advanced cases develop dyspnea, laryngospasm, and dysphagia that may result in aspiration and choking leading to death;

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.

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 (1E,6E)-1,7-bis(3,4-dimethoxyphenyl)-4-cyclobutylmethyl-1,6-heptadiene-3,5-dione, for treatment of X-linked spinal and bulbar muscular atrophy (Kennedy's disease), was adopted by consensus.

2.2.2. **2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate - EMA/OD/253/15**

Celgene Europe Limited; Treatment of acute myeloid leukaemia

COMP coordinator: Bożenna Dembowska-Bagińska

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 2-methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate was considered justified based on clinical data demonstrating improved overall response duration in persons affected by relapsed/refractory acute myeloid leukaemia.

The condition is life-threatening and chronically debilitating 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 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 2-methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data demonstrating a novel mechanism of action and tumour growth inhibition. The sponsor also presented early clinical data that demonstrate an improved overall response in relapsed/refractory acute myeloid leukaemia. The duration of responses in the on-going clinical trial compared favourably to the standard of care. The Committee considered that this constitutes a clinically relevant advantage.
A positive opinion for containing 2-methyl-1-\{(4-\{(6-(trifluoromethyl)pyridin-2-yl)6-\{(2-(trifluoromethyl)pyridin-4-yl)amino\}-1,3,5-triazin-2-yl)amino\}propan-2-ol methanesulfonate, for treatment of acute myeloid leukaemia, was adopted by consensus.

**2.2.3. EMA/OD/146/15**

Treatment of congenital coronary artery malformation

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 April meeting.

**2.2.4. Antisense oligonucleotide complementary to the exonic splicer enhancer sequence at intron 26 of the Centrosomal Protein 290 pre-mRNA - EMA/OD/255/15**

ProQR Therapeutics BV; Treatment of Leber’s congenital amaurosis

COMP coordinator: Ingeborg Barisic and Armando Magrelli

The Committee agreed that the condition, treatment of Leber’s congenital amaurosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing antisense oligonucleotide complementary to the exonic splicer enhancer sequence at intron 26 of the centrosomal protein 290 pre-mRNA was considered justified based on pre-clinical data in patient cells harbouring homozygous splicing mutation in CEP290 demonstrating a correction in mRNA splicing and restored wild type protein levels.

The condition is chronically debilitating due to nyctalopia, loss of visual fields, tunnel vision, and eventually vision loss.

The condition was estimated to be affecting 0.4 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 antisense oligonucleotide complementary to the exonic splicer enhancer sequence at intron 26 of the centrosomal protein 290 pre-mRNA, for treatment of Leber’s congenital amaurosis, was adopted by consensus.

**2.2.5. EMA/OD/256/15**

Treatment of inclusion body myositis

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 April meeting.

**2.2.6. Autologous dermal fibroblasts genetically modified ex vivo with a lentiviral vector containing the human COL7A1 gene - EMA/OD/218/15**

Intrexon Actobiotics N.V.; Treatment of epidermolysis bullosa

COMP coordinator: Josep Torrent-Farnell
Following review of the application by the Committee, it was agreed to rename the active substance to "autologous dermal fibroblasts genetically modified ex vivo with a lentiviral vector containing the human 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 autologous dermal fibroblasts genetically modified ex vivo with a lentiviral vector containing the human COL7A1 gene was considered justified based on preclinical data showing production of trimetric collagen and deposition of collagen at the derma-epidermal junction in models of the condition.

The condition is life-threatening and chronically debilitating due to blister formation in response to minor friction or trauma, leading to the development of multiple complications including life-threatening infections, failure to thrive, and predisposition to the development of squamous cell carcinoma.

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.

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 autologous dermal fibroblasts genetically modified ex vivo with a lentiviral vector containing the human COL7A1 gene, for treatment of epidermolysis bullosa, was adopted by consensus.

2.2.7. Autologous stromal vascular cell fraction from adipose tissue - EMA/OD/257/15

Cytori Ltd; Treatment of systemic sclerosis

COMP coordinator: Dan Henrohn and Daniel O'Connor

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

The intention to treat the condition with the medicinal product containing autologous stromal vascular cell fraction from adipose tissue was considered justified based on preclinical and on preliminary clinical data showing efficacy of the product on relevant endpoints.

The condition is chronically debilitating and life-threatening due to the deposition of collagen in the skin and in internal organs such as kidneys, heart, lungs and gastrointestinal tract, leading to severe complications such as pulmonary hypertension, progressive dysphagia, scleroderma renal crisis and cardiac failure.

The condition was estimated to be affecting approximately 3.5 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 autologous stromal vascular cell fraction from adipose tissue will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing an effect on relevant endpoints in
patients that had not responded to previous treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous stromal vascular cell fraction from adipose tissue, for treatment of systemic sclerosis, was adopted by consensus.

### 2.2.8. Cannabidiol - EMA/OD/248/15

Richardson Associates Regulatory Affairs Ltd; Prevention of graft versus host disease

COMP coordinator: Frauke Naumann-Winter

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

The intention to prevent the condition with the medicinal product containing cannabidiol was considered justified based on preliminary clinical data in patients affected by the condition showing that treatment with the proposed product reduced the incidence and the time to onset of acute graft-versus-host disease.

The condition is life-threatening and chronically debilitating 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 population of patients eligible for prevention of the condition was estimated to be approximately 0.3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of prevention of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing cannabidiol will be of significant benefit to the population at risk of developing the condition. The sponsor has provided clinical data that demonstrate that treatment with the proposed product on top of standard of care, including already authorised products, was able to reduce the incidence and time to onset of acute graft-versus-host disease. The Committee considered that this constitutes a clinically relevant advantage.

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

### 2.2.9. Combination of 4-hydroxyandrostenedione Serenoa Serrulata fruit extract Alpha lipoic acid - EMA/OD/251/15

Dr. Regenold GmbH Development-Regulatory-Market Access; Treatment of multiple symmetric lipomatosis

COMP coordinator: Vallo Tillmann

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

The intention to treat the condition with the medicinal product containing combination of 4-hydroxyandrostenedione, *Serenoa serrulata* fruit extract and alpha lipoic acid was
considered justified based on early clinical data demonstrating significant reduction of fat deposits in patients.

The condition is life-threatening due to reduced life expectancy and chronically debilitating due to disfigurement, somatic neuropathy, paraesthesias, muscular cramps, tachycardia at rest, segmental hyperhidrosis, erectile dysfunction, achrocianosis, trophic ulcers and Dupuytren contracture.

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

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 combination of 4-hydroxyandrostenedione, *Serenoa serrulata* fruit extract and alpha lipoic acid, for treatment of multiple symmetric lipomatosis, was adopted by consensus.

### 2.2.10. EMA/OD/246/15

**Treatment of paroxysmal nocturnal hemoglobinuria**

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 April meeting.

### 2.2.11. EMA/OD/220/15

**Treatment of peripheral T-cell 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 April meeting.

### 2.2.12. Fluocinolone acetonide - EMA/OD/219/15

Campharm Ltd; Treatment of non-infectious uveitis

COMP coordinator: Ingeborg Barisic

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 fluocinolone acetonide was considered justified based on clinical data showing that treatment with the product resulted in reduced recurrence of posterior uveitis in patients affected by the condition.

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

The condition was estimated to be affecting less than 4.8 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 fluocinolone acetonide will be of
significant benefit to those affected by the condition. This was considered justified on the basis of a prolonged duration of the treatment effect of the proposed product that would allow a reduced number of intravitreal injections and control of inflammation over 3 years. This would compare favourably to the currently authorised intravitreal product. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for fluocinolone acetonide, for treatment of non-infectious uveitis, was adopted by consensus.

2.2.13. Humanised recombinant IgG4 anti-human tau antibody - EMA/OD/239/15

Abbvie Ltd.; Treatment of progressive supranuclear palsy

COMP coordinator: Violeta Stoyanova and 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 humanised recombinant IgG4 anti-human tau antibody was considered justified based on preclinical in vivo data demonstrating that treatment improved cognition and motor function in a valid disease model, supported by preliminary clinical data demonstrating improvements and stabilisations of clinically relevant rating scales.

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

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

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

A positive opinion for humanised recombinant IgG4 anti-human tau antibody, for treatment of progressive supranuclear palsy, was adopted by consensus.

2.2.14. EMA/OD/258/15

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 April meeting.


QRC Consultants Ltd.; Treatment of beta thalassaemia intermedia and major

COMP coordinator: Irena Bradinova and Karri Penttila

The Committee agreed that the condition, treatment of beta thalassaemia 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 N-carboxymethyl-glycyl-L-threonyl-L-histidyl-L-3,3-diphenylalanyl-L-piperidincarboxy-3-yl-L-arginyl-L-S-methylthio-cystyl-L-arginyl-L-tryptophyl-aminohexanyl-N-carboxamidomethyl-glycine N-hexadecylamide was considered justified based on results obtained showing an improvement in transferrin levels in a valid pre-clinical model of 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 0.5 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-carboxymethyl-glycyl-L-threonyl-L-histidyl-L-3,3-diphenylalanyl-L-piperidincarboxy-3-yl-L-arginyl-L-S-methylthio-cystyl-L-arginyl-L-tryptophyl-aminohexanyl-N-carboxamidomethyl-glycine N-hexadecylamide will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate a reduction in serum iron associated with an increase in transferrin levels. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for N-carboxymethyl-glycyl-L-threonyl-L-histidyl-L-3,3-diphenylalanyl-L-piperidincarboxy-3-yl-L-arginyl-L-S-methylthio-cystyl-L-arginyl-L-tryptophyl-aminohexanyl-N-carboxamidomethyl-glycine N-hexadecylamide, for treatment of beta thalassaemia intermedia and major, was adopted by consensus.

2.2.16. Recombinant adeno-associated viral vector serotype 9 carrying the gene for the human E6-AP ubiquitin protein ligase - EMA/OD/249/15

Voisin Consulting S.A.R.L.; Treatment of Angelman syndrome

COMP coordinator: Armando Magrelli and Giuseppe Capovilla

The Committee agreed that the condition, treatment of Angelman syndrome, 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 serotype 9 carrying the gene for the human E6-AP ubiquitin protein ligase was considered justified based on data in a preclinical model of the proposed condition showing expression of the missing enzyme and restoration of memory function.

The condition is chronically debilitating due to developmental delay, motor impairment, hyperactivity and epileptic seizures that are often pharmaco-resistant.

The condition was estimated to be affecting approximately 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 recombinant adeno-associated viral vector serotype 9 carrying the gene for the human E6-AP ubiquitin protein ligase, for treatment of Angelman syndrome, was adopted by consensus.
2.2.17. Recombinant human cerebral dopamine neurotrophic factor - EMA/OD/241/15

Herantis Pharma Plc; Treatment of amyotrophic lateral sclerosis

COMP coordinator: Dinah Duarte and Violeta Stoyanova

The Committee agreed that the condition, treatment of 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 recombinant human cerebral dopamine neurotrophic factor was considered justified based on preclinical data showing motor function improvement with the proposed product.

The condition is life-threatening due to progressive muscle weakness, with difficulty speaking, swallowing, and breathing. Median survival time from onset to death is less than 40 months.

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 recombinant human cerebral dopamine neurotrophic factor will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing improvement in motor function compared to the published preclinical data of the currently authorised product for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for recombinant human cerebral dopamine neurotrophic factor, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.18. Resiquimod - EMA/OD/254/15

Galderma R&D; Treatment of cutaneous T-cell lymphoma

COMP coordinator: Bożenna Dembowska-Bagińska

The Committee agreed that the condition, treatment of cutaneous T-cell lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

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

The condition is chronically debilitating due to the development of cutaneous lesions, generalised erythroderma, and lymphadenopathy. Ulceration of tumours, with secondary bacterial infections, is linked to morbidity and death. The overall five-year survival rates vary between 24% and 68% according to the subtype of cutaneous T-cell lymphoma.

The condition was estimated to be affecting less than 2.5 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 resiquimod will be of significant benefit to
those affected by the condition. The sponsor has provided preliminary clinical data showing favourable clinical responses in patients that had not responded to treatment with the currently authorised methods. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for resiquimod, for treatment of cutaneous T-cell lymphoma, was adopted by consensus.

2.2.19. **S-acetyl-(S)-4’-phosphopantetheine, calcium salt - EMA/OD/250/15**

Acies Bio d.o.o.; Treatment of pantothenate kinase-associated neurodegeneration (PKAN)

COMP coordinator: Josep Torrent-Farnell

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

The intention to treat the condition with the medicinal product containing S-acetyl-(S)-4’-phosphopantetheine, calcium salt was considered justified based on pre-clinical data demonstrating improved cell survival and locomotor function.

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 0.1 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 S-acetyl-(S)-4’-phosphopantetheine, calcium salt, for treatment of pantothenate-kinase-associated neurodegeneration, was adopted by consensus.


SELLAS Life Sciences Group UK, Limited; Treatment of malignant mesothelioma

COMP coordinator: Bożenna Dembowska-Bagińska and Armando Magrelli

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

The intention to treat the condition with the medicinal product containing Tyr-Met-Phe-Pro-Asn-Ala-Pro-Tyr-Leu, Ser-Gly-Gln-Ala-Tyr-Met-Phe-Pro-Asn-Ala-Pro-Tyr-Leu-Pro-Ser-Cys-Leu-Glu-Ser, Arg-Ser-Asp-Glu-Leu-Val-Arg-His-His-Asn-Met-His-Gln-Arg-Asn-Met-Thr-Lys-Leu and Pro-Gly-Cys-Asn-Lys-Arg-Tyr-Phe-Lys-Leu-Ser-His-Leu-Gln-Met-His-Ser-Arg-Lys-His-Thr-Gly was considered justified based on preliminary clinical data demonstrating that maintenance treatment with the proposed product improved overall survival in patients who completed previous treatments, including complete resection of the tumour.
The condition is life-threatening due to the invasion of the pleura leading to pleural effusions, dyspnoea and malignant ascites. Local invasion may also result in obstruction of the superior vena cava, cardiac tamponade, and spinal cord compression. Patients with pleural mesothelioma usually die due to increasing tumour bulk that gradually fills the hemithorax causing progressive respiratory compromise (“incarceration” of the lungs), pneumonia, or myocardial dysfunction with arrhythmias. In patients with peritoneal mesothelioma, distension due to ascites, abdominal pain, and organ impairment such as bowel obstruction are observed.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing Tyr-Met-Phe-Pro-Asn-Ala-Pro-Tyr-Leu, Ser-Gly-Gln-Ala-Tyr-Met-Phe-Pro-Asn-Ala-Pro-Tyr-Leu-Pro-Ser-Cys-Leu-Glu-Ser, Arg-Ser-Asp-Glu-Leu-Val-Arg-His-His-Ala-Tyr-Met-Thr-Lys-Leu and Pro-Gly-Cys-Asn-Lys-Arg-Tyr-Phe-Lys-Leu-Ser-His-Leu-Gln-Met-His-Ser-Arg-Lys-His-Thr-Gly will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate improved overall survival with maintenance treatment with the proposed product in patients who have completed previous treatments, including complete resection of the tumour. There are currently no authorised products for maintenance treatment of patients after a completed treatment with currently authorised products, surgery and/or radiotherapy. The Committee considered that this constitutes a clinically relevant advantage.


### 2.3. Amendment of an existing orphan drug designation

#### 2.3.1. S)-ethyl 2-amino-3-((2-amino-6((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoate – EU/3/09/661

Ipsen Pharma – France; Treatment of carcinoid tumours

COMP coordinators were appointed.

### 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 20 applications submitted.

2.7. **Evaluation on-going**

The Committee noted that evaluation was on-going for 27 applications for orphan designation.

**Action:** For information

**Notes:**

3. **Requests for protocol assistance with significant benefit question**

3.1. **Ongoing procedures**

3.1.1. **Treatment of hyperargininaemia**

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues by written procedure following its March meeting.

3.1.2. **Treatment of argininosuccinic aciduria**

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues by written procedure following its March meeting.

3.1.3. **Treatment of haemophilia A**

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues by written procedure following its March meeting.

3.2. **Finalised letters**

3.2.1. **Diagnosis of gastro-entero-pancreatic neuroendocrine tumours**
The finalised letter was circulated for information.

### 3.3. New requests

#### 3.3.1. Treatment of primary sclerosing cholangitis

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. ALPROLIX - eftrenonacog alfa – EMEA/OD/012/07, EU/3/07/453, EMEA/H/C/004142

Biogen Idec Ltd; Treatment of haemophilia B

COMP coordinator: Armando Magrelli and Karri Penttila

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:

The applicant is basing the argumentation of significant benefit on the improved PK of the product which results in a more convenient dosing for the prophylactic setting. The improved PK is endorsed.

What is not evident from the sponsor’s maintenance report and provided justifications, is the existence of any available data to substantiate how this improved regiment shall translate into consequences further and above convenience, such as quality of life measurements, complications of central access catheters and ports, or improved compliance to treatment with the new product versus the authorised counterparts for the same therapeutic indication.

The sponsor is asked to provide data to support the above points. In the absence of data to document a major contribution to patient care significant benefit cannot be considered.

In its written response, and during an oral explanation before the Committee on 21 March 2016, the sponsor performed a pre-study versus an on-study analysis for participants in the pivotal studies and stressed that the improved PK resulted in approximately 50% reduction in the number of injections, factor consumption reduction, and “similar or slightly lower” annualised bleeding rates in the prophylactic settings.

In order to further translate this into a major contribution to patient care and document the expected significant benefit the sponsor provided data pertaining to a) Quality of life using the Haem-A-QoL score and b) adherence to medication using a Medication Possession Ratio (MPR).

With regards to Quality of life, the sponsor provided the full analysis set of the Haem-A-Qol total score from study 0098HB102, which were in line with the initially provided tables.
With regards to the MPR measurements provided, a retrospective analysis was performed using aggregate, de-identified data records for the period of November 2013 to September 2015 from US Specialty Pharmacy Provider. The 596 haemophilia B patients included in this analysis had received ≥1 shipment of FIX for a prophylactic treatment regimen and had ≥60 days of supplied therapy. These patients had dispensing records available for their previous FIX therapies, which allowed longitudinal analysis of these patients’ prophylactic regimens prior to and after switching to the product in question. Treatment adherence was measured by medication possession ratio. The median MPR for rFIXFc was significantly higher for rFIXFc compared with conventional therapies (p<0.0005), indicating higher treatment adherence with rFIXFc.

The COMP reflected on the limitations of the studies design (open and uncontrolled) to allow for robust conclusions on the quality of life data provided, but accepted that there was a clear trend of improvement in the measured scores in favour of the proposed product. Furthermore, the data also provided support that the improved PK translates into improved adherence to treatment.

The COMP concluded that:

The proposed therapeutic indication “treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency)” falls entirely within the scope of the orphan indication of the designated orphan medicinal product “treatment of haemophilia B (congenital factor IX deficiency)”.

The prevalence of haemophilia B (congenital factor IX deficiency) (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in approximately 0.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating and life-threatening, in particular due to haemorrhagic complications and decreased overall survival.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Alprolix will be of potential significant benefit to those affected by the orphan condition still holds. This was considered on the basis of clinical data supporting improved quality of life and increased adherence to treatment versus other available products authorised in the proposed condition. The COMP concluded that this constitutes a major contribution to patient care.

An opinion not recommending the removal of Alprolix, recombinant fusion protein consisting of human coagulation factor IX attached to the Fc domain of human IgG1 (EU/3/07/453).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.  **Idelvion - albutreponacog alfa – EMEA/OD/117/09, EU/3/09/723, EMEA/H/C/003955**

CSL Behring GmbH; Treatment of haemophilia B

COMP coordinator: Karri Penttilä 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 elaborate on the following issues:

The applicant is basing the argumentation of significant benefit on both improved efficacy and a major contribution to patient care on the grounds of a reduced infusion frequency compared to authorised FIX products.

With regards to improved efficacy, the sponsor is requested to present the data on which this is argued, and discuss the comparability of study design and population of any indirect comparisons made.

With regards to a major contribution to patient care, while the improved PK is endorsed the COMP is interested in any documented consequences of the improved infusion frequency, such as quality of life measurements, complications of central access catheters and ports, or improved compliance to treatment with the new product versus the authorised counterparts for the same therapeutic indication.

The sponsor is asked to provide data to support the above points. In the absence of data to document a clinically relevant advantage or major contribution to patient care, the significant benefit criterion will not be maintained. In its written response, and during an oral explanation before the Committee on 21 March 2016, the sponsor further elaborated on the two issues raised.

As regards the argument on improved efficacy, the following justifications were supplemented:

- The applicant discussed the high trough FIX activity levels with the new product (median 13.8% for adults and 13.4% for children on weekly prophylaxis, and 6.8% for adults on 14-day prophylaxis). Based on an exposure-response analysis, the sponsor anticipates reduced bleeding risk by increasing maintenance FIX activity above the 1%. However, the committee considered that this is an indirect assumption that is not documenting increased efficacy.

- A second argument is improved efficacy in management of bleeding episodes. It is presented that based on data from the 3001 study, 93.6% of bleeding episodes can be treated by one injection, which is contrasted to 81% or 64% of other authorised factors IX. This is again not directly affecting control of bleeding, which may be equally satisfactory regardless of the number of injections.

- A third very similar argument to the one above is decreased consumption perioperative. It was considered that the limitation is again that the overall outcome of the bleeding control is not directly assessed.

- A fourth argument for improved efficacy is improved annual bleeding rates (ABR). The sponsor provided a table juxtaposing results for adults from study 3001, and the studies for other factor IX containing products, namely BeneFIX and Rixubis. In this table there is a trend of improvement in ABR, but this trend is not clear in the annualised spontaneous bleeding rates. It was considered that ABRs were comparable and do not support improved efficacy but similar control regardless of the prophylaxis regimen.

As for the issue of major contribution to patient care, the Quality of life data from study 3002 was further elaborated on. It was clarified that there was a significant difference between baseline and End of study for the Haemo-QoL total score (p < 0.037) for children completing the 8-12 year old questionnaire (8-11 years, n = 7). Improvement in the
quality of life was seen in all domains, including 100% of subjects reporting improvement in “sports and school” and “dealing with haemophilia” after prophylaxis treatment with rIX-FP. Similar results are reported when the parents are completing the scale. The COMP reflected on the limitations of quality of life data in the setting of open uncontrolled studies, but at the same time acknowledged consistent improvements in relevant fields, and both in patients and parents.

During the oral explanation the sponsor also discussed in more detail that the reduction of number of injections would lead to fewer complications. When asked to document this claim, the applicant reported that two paediatric patients that had central venous access ports had those ports removed when they changed to the new product.

The COMP considered overall that while the efficacy claim based on annual bleeding rates was not documented, data have been included to support a major contribution to patient care.

The COMP concluded that:

The proposed therapeutic indication “treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency)” falls entirely within the scope of the orphan indication of the designated orphan medicinal product “treatment of haemophilia B”.

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

The prevalence of haemophilia B (congenital factor IX deficiency) (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in approximately 0.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating and life-threatening, in particular due to haemorrhagic complications and decreased overall survival.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Idelvion will be of potential significant benefit to those affected by the orphan condition still holds. This was considered on the basis of clinical data supporting improved quality of life and reduced central venous access port use, versus the authorised products for the proposed condition. The COMP concluded that this constitutes a major contribution to patient care.

An opinion not recommending the removal of Idelvion, recombinant fusion protein linking human coagulation factor IX with human albumin (EU/3/09/723) 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.

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

Bristol-Myers Squibb; Treatment of multiple myeloma

COMP coordinator: Daniel O’Connor and Jens Ersboll
Following the opinion recommending the removal of Empliciti from the EC Register of Orphan Medicinal Products that was adopted in February by the COMP, the sponsor appealed against the COMP opinion.

In its written grounds of appeal, and during an oral explanation before the Committee on 22 March 2016, the sponsor elaborated on the issue of significant benefit.

The applicant highlighted that a different mode of action to currently approved treatments offers the possibility of no cross-resistance to immune modulators and proteasome inhibitors thereby offering a clinically meaningful option for patients relapsed or refractory to prior treatments.

A discussion in particular versus carfilzomib ensued by performing an indirect comparison of the registrational studies. The COMP noted that the overall survival in the indirect comparison appeared comparable, and in fact the progression free survival appeared to be worse for the elotuzumab 18.5 months compared to 26.3 months for carfilzomib. A subgroup analysis provided by the sponsor showed similar progression free survival between the two products and the confidence intervals were too broad to allow for conclusions of improved efficacy in particular subpopulations. The sponsor proposed that significant benefit is based on the effects seen in a more vulnerable patient population of senior patients (over 65yrs), having received prior lenalidomide treatment, refractory to prior bortezomib and those with a high risk, poor-prognosis myeloma. However, improved PFS in that population could not be established and therefore the COMP was of the opinion that the sponsor had not provided sufficient evidence to overturn the prior conclusions of the COMP.

The sponsor also discussed a claim for significant benefit due to better safety profile of elotuzumab, highlighting its lack of cardiac toxicity which is an adverse effect associated with proteasome inhibitors. The COMP in their discussion highlighted the need to consider other toxicities of elotuzumab which the sponsor did not consider in the data submitted. For example, no discussion on comparative renal toxicities was presented. The sponsor claimed that the safety profile regarding lower cardiac toxicity with elotuzumab was well characterised and that this substantiated that it was safer that in patients > than 65yrs of age. The sponsor did not however elaborate on the observed increased toxicity in patients with severe or end-stage renal impairment with elotuzumab. Such a risk could offset any gain in terms of cardiac toxicity versus carfilzomib. The sponsor did not elaborate either on the increase in infections seen when their product was used with lenalidomide versus the control arm in study CA204004 which would also be considered in order to establish the clinically relevant advantage based on safety. Furthermore, there was no data in patients over 85yrs so the claim that elotuzumab is safer in patients over 65 could only be limited to those between 65 and 85yrs. The COMP concluded that the criterion for establishing a clinically relevant advantage was inconclusive and that the sponsor had not provided sufficient evidence to overturn the prior conclusions of the COMP.

In addition to the sponsor’s specific grounds for appeal the COMP discussed the changing nature of treatment algorithms associated with different stages of multiple myeloma. The COMP noted that the current triple combination proposed is elotuzumab in combination with lenalidomide and dexamethasone which is offered as another option to the multitude of triplets available to clinicians treating these patients. Apart from a different mode of action nothing differentiates it from other triplets available for the proposed condition and
therefore it is not possible to establish what the significant benefit could be without more data than the two studies offered by the sponsor.

The COMP concluded that:

The proposed therapeutic indication "Empliciti is indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy" falls entirely within the scope of the designated orphan indication "treatment of multiple myeloma" of the designated Orphan Medicinal Product.

The prevalence of multiple myeloma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in 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 up to approximately 6 years.

Satisfactory methods of treatment have been authorised in the European Union; the assumption that Empliciti may be of potential significant benefit to those affected by the orphan condition does not hold.

Significant benefit versus carfilzomib has not been justified; the Overall Survival was similar in both studies: 2yr survival of 73% vs 73.3%, median Overall Survival with elotuzumab was 43.7 months and not reported for carfilzomib but from the Kaplan Meier plots Overall Survival seems to be longer in the carfilzomib trial.

An indirect comparison of the results from studies CA204004 and ASPIRE pertaining to subgroup analysis, did not justify a clinically relevant advantage, such as improved efficacy or safety in the approved identical indication; Progression free survival is analysed in several subgroups. Although the hazard ratio appears better for elotuzumab to carfilzomib the confidence intervals presented were too broad making the interpretation difficult. It was also not clear whether carfilzomib subgroups were prospectively defined, which does not support the indirect comparison made between the two products.

The data from study CA204004 showing improved outcome in patients over 65 who were resistant to bortezomib versus the indirect comparison to a similar population in the ASPIRE trial did not justify a clinically relevant advantage such as an improved efficacy.

The effect on safety was not considered substantial enough in the subgroups selected by the sponsor to conclusively establish a clinically relevant advantage to support a significant benefit claim at the time of Marketing Authorisation by the COMP.

Therefore, the sponsor has not established that elotuzumab is still of significant benefit to those affected by the condition.

An opinion recommending the removal of Empliciti, elotuzumab (EU/3/12/1037) from the EC Register of Orphan Medicinal Products was adopted by consensus.

[Post-meeting note: The COMP opinion was adopted by written procedure following its March meeting.]
4.1.4. **Revlimid – Lenalidomide - Type II variation - EMA/OD/078/11, EU/3/11/924, EMEA/H/C/000717/II/0079**

Celgene Europe Limited; Treatment of mantle cell lymphoma

The status of the procedure at CHMP was noted.

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

BIO PRODUCTS LABORATORY; Treatment of hereditary factor X deficiency

COMP coordinator: Karri Penttilä and Josep Torrent-Farnell

The COMP opinion was adopted by written procedure following its February meeting. The final summary report was circulated for information.

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

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

Amicus Therapeutics UK Ltd; Treatment of Fabry disease

COMP coordinator: Pauline Evers and Josep Torrent-Farnell

The status of the procedure at CHMP was noted. The COMP discussed whether the product would be still fulfilling the criteria for orphan designation at the time of marketing authorisation.

*Post-meeting note: After the CHMP adopted a positive opinion granting a marketing authorisation to Galafold, the COMP adopted by written procedure and by consensus an opinion not recommending the removal of Galafold - migalastat (EU/3/06/368) from the EC Register of Orphan Medicinal Products. The grounds for opinion are summarised below:

The proposed therapeutic indication “treatment of patients with Fabry disease” falls entirely within the scope of the orphan condition of the designated orphan medicinal product “treatment of Fabry disease”.

The prevalence of Fabry disease (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be less than 2.3 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating due to recurrent episodes of severe pain not responding to standard analgesics and is life-threatening due to renal failure or cardiovascular and/or cerebrovascular complications.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Galafold will be of significant benefit to those affected by the orphan condition as defined in the granted therapeutic indication still holds. Galafold offers a major contribution to patient care as it is an oral formulation which can be used by patients with amenable mutations instead of currently approved enzyme replacement therapies which involve intravenous infusions and the intervention of healthcare professionals.

The draft public summary of the COMP opinion will be published on the EMA website.*
4.2.2. 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

COMP coordinator: Josep Torrent-Farnell and Armando Magrelli

The status of the procedure at CHMP was noted. The COMP discussed whether the product would be still fulfilling the criteria for orphan designation at the time of marketing authorisation.

[Post-meeting note: After the CHMP adopted a positive opinion granting a marketing authorisation to Strimvelis, the COMP adopted by written procedure and by consensus an opinion not recommending the removal of Strimvelis - autologous cd34+ enriched cell fraction that contains cd34+ cells transduced with retroviral vector that encodes for the human ada cdna sequence (EU/3/05/313) from the EC Register of Orphan Medicinal Products. The grounds for opinion are summarised below:

The COMP concluded that:

The proposed therapeutic indication “treatment of severe combined immunodeficiency (SCID) due to adenosine deaminase (ADA) deficiency” falls entirely within the scope of the orphan condition of the designated orphan medicinal product “treatment of severe combined immunodeficiency (SCID) due to adenosine deaminase (ADA) deficiency”.

The prevalence of severe combined immunodeficiency (SCID) due to adenosine deaminase (ADA) deficiency (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be 0.04 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating and life threatening due to severe infections and poor overall survival.

There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

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

4.2.3. Darzalex (previously known as Daratumumab Janssen-Cilag) – daratumumab - EMA/OD/038/13, EU/3/13/1153, EMEA/H/C/004077

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

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

Lucane Pharma; Treatment of cystinosis

The status of the procedure at CHMP was noted.
4.2.5. 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 CAT/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. Application of Article 8(2) of the Orphan Regulation

5.1.1. Plenadren – Hydrocortisone (modified release tablet) - EU/3/06/372

Shire Services BVBA; Treatment of adrenal insufficiency;

COMP coordinator: Karri Penttilä and Daniel O’Connor

The COMP reviewed the designation EU/3/06/372 for Plenadren (hydrocortisone) as an orphan medicine. Plenadren has been authorised in the European Union for the treatment of adrenal insufficiency since 3 November 2011. At the request of the United Kingdom, the COMP re-assessed whether the medicine still met the criteria for orphan designation. The Committee looked at the seriousness and prevalence of the condition, and the existence of other methods of treatment. As other methods of treatment are authorised in the EU, the COMP also considered whether the medicine is of significant benefit to patients with adrenal insufficiency.

The COMP concluded that:

The prevalence of adrenal insufficiency (hereinafter referred to as “the condition”) is estimated to be 4.85 in 10,000 persons in the European Union, at the time of the review of market exclusivity.

The condition is chronically debilitating due to impaired health-related quality of life in case of inadequate substitution treatment and life-threatening with decreased life expectancy in particular due to unrecognised adrenal crisis and other underlying illnesses.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Plenadren will be of potential significant benefit to those affected by the orphan condition still holds. Significant benefit was considered justified in particular based on improvements in adiposity, glucose control and aspects of quality of life, as evidenced in recent literature studies.

As the criteria for orphan designation continue to be met, the COMP recommended that the 10-year period of market exclusivity granted to Plenadren in 2011 for the treatment of adrenal insufficiency should not be reduced.
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 22 March 2016.

6.1.2. Protocol Assistance Working Group

The working group on Protocol Assistance met on 22 March 2016.

6.1.3. New internal guidance on management of confidentiality and declarations of interests for observers participating in EMA scientific meetings

The Agency has developed internal guidance on observers participating in EMA scientific meetings, focusing on management of confidentiality and declarations of interests.

Observers from a non-EEA authority or organisation with no Confidentiality Arrangement in place with EMA require a personal Confidentiality undertaking only (no Declaration of Interests (DoI) / Curriculum vitae (CV)).

The following do not require a personal Confidentiality undertaking (no DoI/CV): Observers from European Institutions and European Union; Observers from non-EEA authorities or organisations with a Confidentiality Arrangement (CA) in place with EMA.

EEA National Competent Authorities (NCAs) staff members are considered as European experts: a DoI including a Confidentiality Undertaking and CV is required. Exception: non-scientific administrative staff from NCAs attending EMA meetings on a one off / ad hoc basis: a personal CU is required, but no DoI/CV.

6.1.4. COMP Membership

The COMP welcomed Olimpia Neagu as new member representing Romania.

The COMP welcomed Eva Malikova as new member representing Slovak Republic.

6.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

6.3.1. SAWP/COMP joint membership

Daniel O’Connor was appointed as SAWP/COMP member for a 3 years term.
6.3.2. Patient Data Plateform

The COMP was updated on the project and was informed that qualification procedures involving experts from COMP were ongoing at SAWP level.

6.4. Cooperation within the EU regulatory network

6.4.1. European Commission

Revision of the Commission Regulation (EC) No 847/2000 of April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concept 'similar medicinal product' and 'clinical superiority'

Upon request from the European Commission, the EMA worked on the definition for ‘principal molecular structural features’ as referred to in Art 3(3)c of Reg (EC) No 847/2000 on similar active substance. The COMP was informed of the proposal before adoption by CHMP.

6.4.2. European Commission

Orphan medicinal product accessibility

The Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products was circulated to the COMP for information.


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.

6.8.3. COMP meeting dates for 2017-2018

The meeting dates for 2017-2018 were circulated and endorsed.

7. Any other business

7.1.1. Request for clarification for 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 topic was postponed to April.
**List of participants**

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 21-23 March 2016 meeting.

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
<th>Member state or affiliation</th>
<th>Outcome restriction following evaluation of e-DoI</th>
<th>Topics on agenda for which restrictions apply</th>
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<td>Bruno Sepodes</td>
<td>Chair</td>
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<td>André Lhoir</td>
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<td>Jens Ersbøll</td>
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<td>Karri Penttilä</td>
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<td>Annie Lorence</td>
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<td>Frauke Naumann-Winter</td>
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<td>Daniel O’Connor</td>
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<td>Pauline Evers</td>
<td>Member</td>
<td>Patients’ Organisation Representative</td>
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<tr>
<td>Lesley Greene</td>
<td>Member (Vice-Chair)</td>
<td>Patients’ Organisation Representative</td>
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<td>Ingeborg Barisic</td>
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<td>Virginie Hivert</td>
<td>Expert - in person*</td>
<td>Patients’ Organisation Representative</td>
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<td>Brian O’Mahony</td>
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<td>Adrianus Jacobus van Iperen</td>
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<td>Kerstin Westermark</td>
<td>Expert - via telephone*</td>
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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.