EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Procedure Management and Business Support Division

# Committee for Orphan Medicinal Products (COMP)

## Minutes of the 9-11 December 2014 meeting

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

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# 1. Introduction

**1.1** Adoption of the agenda, EMA/COMP/706672/2014

The agenda was adopted with no amendments.

**1.2** Adoption of the minutes of the previous meeting, 11-13 November 2014 EMA/COMP/638338/2014

The minutes were adopted with no amendments.

**1.3** Declaration of conflicts of interest

In accordance with the Agency's Policy and Procedure on the handling of conflicts of interests, participants in this meeting were asked to declare any conflict of interests on the matters for discussion (in particular any changes, omissions or errors to the already declared interests). No new or additional conflicts of interest were declared.

# 2. Applications for orphan medicinal product designation[1]

## 2.1. For opinion

### 2.1.1 A lentiviral vector pseudotyped by the Indiana serotype of the vesicular stomatitis virus G protein encoding an antigen derived from the Tax, HBZ, p12I and p30II HTLV-1 proteins

**A lentiviral vector pseudotyped by the Indiana serotype of the vesicular stomatitis virus G protein encoding an antigen derived from the Tax, HBZ, p12I and p30II HTLV-1 proteins** for treatment of the Adult T-cell leukemia/lymphoma, THERAVECTYS - EMA/OD/203/14
*[COMP co-ordinator: J. 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

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of the adult T-cell leukaemia/lymphoma, the sponsor was asked to further elaborate on:

  - the lack of preclinical and /or clinical data showing any type of anti-tumour effect of the proposed product;
  - the relevance of the results obtained *in vitro* showing immunogenic response to the clinical translation in the proposed condition;
  - the relevance of using two different serotypes to the assumed clinical efficacy of the product.

- Significant benefit

In absence of an established medical plausibility the significant benefit of the product cannot be assessed. Therefore sponsor is invited to provide any available data to support the medical plausibility.

In the written response, the sponsor further elaborated in relation to the data supporting the medical plausibility and the significant benefit the sponsor further elaborated on the available preclinical data, and in particular on the clinical significance of the immunological response elicited by the product.

[1] The procedures under assessment discussed by the COMP are considered confidential. COMP meeting reports and subsequent minutes will contain additional details on these procedures once these are finalised. Access to documents in relation to these procedures is possible after marketing authorisation is granted according to the Agency policy on access to documents (EMA/127362/2006).

The Committee agreed that the condition, adult T-cell leukaemia/lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing a lentiviral vector pseudotyped by the Indiana serotype of the vesicular stomatitis virus G protein encoding an antigen derived from the Tax, HBZ, p12I and p30II HTLV-1 proteins was considered justified based on preclinical data.

The condition is life-threatening and chronically debilitating due to infiltration of the bone marrow by the tumour cells with immune suppression and development of severe and recurrent opportunistic infection. The median survival time in aggressive forms is less than 1 year.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing a lentiviral vector pseudotyped by the Indiana serotype of the vesicular stomatitis virus G protein encoding an antigen derived from the Tax, HBZ, p12I and p30II HTLV-1 proteins may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing specific anti-tumour immune response with the proposed product. The Committee considered that this can translate into a clinically relevant advantage for the patients affected by adult T-cell leukaemia/lymphoma.

A positive opinion for a lentiviral vector pseudotyped by the Indiana serotype of the vesicular stomatitis virus G protein encoding an antigen derived from the Tax, HBZ, p12I and p30II HTLV-1 proteins, for treatment of adult T-cell leukaemia/lymphoma, was adopted by consensus.

### 2.1.2 A lentiviral vector pseudotyped by the New-Jersey serotype of the vesicular stomatitis virus G protein encoding an antigen derived from the Tax, HBZ, p12I and p30II HTLV-1 proteins

**A lentiviral vector pseudotyped by the New-Jersey serotype of the vesicular stomatitis virus G protein encoding an antigen derived from the Tax, HBZ, p12I and p30II HTLV-1 proteins** for treatment of the adult T-cell leukemia/lymphoma, THERAVECTYS - EMA/OD/204/14

*[COMP co-ordinator: J. 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

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of the adult T-cell leukaemia/lymphoma, the sponsor was asked to further elaborate on:

  - the lack of preclinical and /or clinical data showing any type of anti-tumour effect of the proposed product;
  - the relevance of the results obtained *in vitro* showing immunogenic response to the clinical translation in the proposed condition;
  - the relevance of using two different serotypes to the assumed clinical efficacy of the product.

- Significant benefit

In absence of an established medical plausibility the significant benefit of the product cannot be assessed. Therefore sponsor was invited to provide any available data to support the medical plausibility.

In the written response the sponsor further elaborated in relation to the data supporting the medical plausibility and the significant benefit the sponsor further elaborated on the available preclinical data, and in particular on the clinical significance of the immunological response elicited by the product.

The Committee agreed that the condition, adult T-cell leukaemia/lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

- the intention to treat the condition with the medicinal product containing a lentiviral vector pseudotyped by the New-Jersey serotype of the vesicular stomatitis virus G protein encoding an antigen derived from the Tax, HBZ, p12I and p30II HTLV-1 proteins was considered justified based on preclinical data;
- the condition is life-threatening and chronically debilitating due to infiltration of the bone marrow by the tumour cells with immune suppression and development of severe and recurrent opportunistic infection. The median survival time in aggressive forms is less than 1 year;
- the condition was estimated to be affecting approximately 0.3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing a lentiviral vector pseudotyped by the New-Jersey serotype of the vesicular stomatitis virus G protein encoding an antigen derived from the Tax, HBZ, p12I and p30II HTLV-1 proteins may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing specific anti-tumour immune response with the proposed product. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by adult T-cell leukaemia/lymphoma.

A positive opinion for a lentiviral vector pseudotyped by the New-Jersey serotype of the vesicular stomatitis virus G protein encoding an antigen derived from the Tax, HBZ, p12I and p30II HTLV-1 proteins, for treatment of adult T-cell leukaemia/lymphoma, was adopted by consensus.

### **2.1.3** Product for treatment of Wilson's disease - EMA/OD/201/14

*[COMP co-ordinator: K. Westermark]*

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

- Significant benefit

The sponsor was invited to provide any evidence of lack of supply of an authorised counterpart in EU member states.

The sponsor was also invited to provide any available clinical data to support the claims of improved safety, convenience (especially with regard to paediatric use) and compliance to treatment. Moreover, the sponsor was invited to provide comparative stability data.

In the written response, and during an oral explanation before the Committee on 9 December 2014, the sponsor discussed that a survey on availability has been performed, however many MS have not

responded therefore the data are rather sparse. Views from experts treating Wilson disease were also presented, supporting a difficulty in obtaining the authorised alternative. The sponsor also discussed the stability of the products and compared it to an authorised counterpart.

The committee considered that in absence of data supporting the theoretical points of significant benefit, it would be difficult to conclude positively on the proposal.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 9 December 2014, prior to final opinion.

### **2.1.4** Product for treatment of systemic sclerosis - EMA/OD/207/14

*[COMP co-ordinator: J. 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

To establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of systemic sclerosis, the sponsor was asked to further elaborate on:

  - the scientific rationale taking in the context of the specific immunologic (autoimmune) pattern in systemic sclerosis;
  - the overall lack of data supporting the medical plausibility of the proposed product in systemic sclerosis;
  - the results of the only small case series in systemic sclerosis that have been defined as “non-conclusive”.

- Significant benefit

The sponsor was invited to present and discuss any available preclinical or clinical data supporting the significant benefit of the proposed product in comparison to what currently authorized for the treatment of systemic sclerosis. It was also noted that in the absence of a valid medical plausibility the significant benefit of the proposed product cannot be assessed.

In the written response, and during an oral explanation before the Committee on 9 December 2014, the sponsor elaborated the proposed mechanism of action in the context of the pathophysiology of the condition and discussed the available preliminary clinical observations in patients affected by the condition. The COMP considered that in the absence of conclusive data it would be difficult to consider that the criteria for designation are met.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 10 December 2014, prior to final opinion.

### **2.1.5 Allogeneic, umbilical cord blood-derived, ex vivo expanded, hematopoietic CD133+ cells (CF) / Allogeneic, umbilical cord blood-derived, non-expanded, hematopoietic CD133- cells (NF)** for treatment of acute myeloid leukaemia, Regulatory Resources Group Ltd - EMA/OD/188/14

*[COMP co-ordinator: F. 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

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of acute myeloid leukaemia, the sponsor was asked to further elaborate on any data with the specific product as applied for designation in AML-specific situations.

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results presented to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

The sponsor was asked to detail the results of any clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of these patients. In the absence of any data with the product as applied for in the condition the significant benefit cannot be established.

In the written response, and during an oral explanation before the Committee on 9 December 2014, the sponsor discussed data in AML patients from two preliminary clinical studies who have received their product as part of their treatment. With regards to the significant benefit, the sponsor elaborated with regards to a potential broadening of eligible patients with access to alternative stem cell sources for transplantation, and a reduction of time of neutrophil and platelet engraftment versus other sources of stem cells.

The Committee agreed that the condition, 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 allogeneic, umbilical cord blood-derived, ex vivo-expanded, haematopoietic CD133+ cells / allogeneic, umbilical cord blood-derived, non-expanded, haematopoietic CD133- cells was considered justified based on preliminary clinical data in AML patients who responded to treatment with the proposed product.

The condition is life threatening 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 allogeneic, umbilical cord blood-derived, ex vivo-expanded, haematopoietic CD133+ cells / allogeneic, umbilical cord blood-derived, non-expanded, haematopoietic CD133- cells may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that support an increase in the population of AML patients that would have access to stem cell transplantation. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic, umbilical cord blood-derived, ex vivo-expanded, haematopoietic CD133+ cells / allogeneic, umbilical cord blood-derived, non-expanded, haematopoietic CD133- cells, for treatment of acute myeloid leukaemia, was adopted by consensus.

### **2.1.6** Product for treatment of pancreatic cancer - EMA/OD/178/14

*[COMP co-ordinator: B. 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:

- 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 pancreatic cancer, the sponsor was asked to further elaborate on:

  - details on the proposed product, in particular the rationale for the proposed formulation;
  - details on the clinical studies, in particular patients' characteristics and treatment protocols.

- Significant benefit

The arguments on significant benefit are based on a potential improved efficacy in the condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on:

  - the comparison of the results for the preliminary clinical studies with the current standard of care for a similar population in the context of current European guidelines.

In the written response, and during an oral explanation before the Committee on 9 December 2014, the sponsor discussed in particular two available preliminary clinical studies in patients affected by the condition. The COMP considered in particular that the positioning of the product vis a vis the currently available products was not clear.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 December 2014, prior to final opinion.

### **2.1.7** Product for treatment of progressive supranuclear palsy - EMA/OD/141/14

*[COMP co-ordinator: V. Stoyanova]*

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of progressive supranuclear palsy, the sponsor was asked to further elaborate on:

  - the mechanism of action in the proposed condition by showing the claimed reduction of neuro-inflammation,
  - the relevance of the preclinical model used for the treatment of progressive supranuclear palsy, and the interpretation of the results obtained in the experiments,
  - submit any available data in a specific model of the condition or in preliminary clinical settings in patients affected by the condition.

It was pointed out that without data with the specific product in the specific condition the medical plausibility cannot be accepted.

In the written response, and during an oral explanation before the Committee, the sponsor discussed that even if preclinical models exist that recapitulate some aspects of the condition, there are no models that resemble the inflammatory mechanism associated with tau deposition, which appears to be the target of this product. The sponsor also discussed effects in models of other conditions in line with a reduction of inflammation.

The COMP considered that in the absence of data in the context of the specific condition as applied for designation, the criterion of medical plausibility may not be considered.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 10 December 2014, prior to final opinion.

### **2.1.8** Product for treatment of glioma - EMA/OD/181/14

*[COMP co-ordinator: F. 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

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of glioma, the sponsor was asked to further elaborate on:

  - the relevance of the results obtained in the preclinical model;
  - any further available data with the product as proposed for designation in models of the condition, or in patients affected by the condition.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition.

The sponsor was invited to provide and discuss any data with the product in relevant models of the condition or in preliminary clinical settings that may justify a clinically relevant advantage compared to the authorised treatment methods for the condition.

In the written response, and during an oral explanation before the Committee on 10 December 2014, the sponsor further elaborated on the mechanism of action, the pharmacokinetics, the relevance of the models used and the available results in preclinical settings of the condition. The sponsor also discussed the short comings of the current standard of care for glioma patients. The COMP considered that in particular with regards to significant benefit, the indirect comparative discussions provided would not allow justification of the criterion.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 December 2014, prior to final opinion.

### **2.1.9 Herpes simplex type 1 virus containing cellular B-myb gene as tumour-specific promoter** for treatment of pancreatic cancer, Karcinolys S.A.S - EMA/OD/187/14

*[COMP co-ordinator: K. Kubáčková]*

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

In order to justify the significant benefit of the proposed product the sponsor was invited to discuss the significant benefit in relation to all products authorized for the treatment of the proposed condition.

In the written response, and during an oral explanation before the Committee on 10 December 2014, the sponsor further elaborated on the issues raised and stressed the advantages of viral oncolytic therapy as a novel mechanism of action. The potential benefit from the use of the product in combination with existing treatments for pancreatic cancer was supported by the data in preclinical settings that showed reduction of tumour progression when the proposed product was used on top of gemcitabine.

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

The intention to treat the condition with the medicinal product containing herpes simplex type 1 virus containing cellular *B-myb* gene as tumour-specific promoter was considered justified based on data showing antitumor activity in different relevant preclinical models of the condition.

The condition is life-threatening and chronically debilitating due to early dissemination of the tumour to distant sites including brain, bone, soft tissues and lungs. The condition has a 5 year survival rate of 6%.

The condition was estimated to be affecting approximately 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 herpes simplex type 1 virus containing cellular *B-myb* gene as tumour-specific promoter may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate increased antitumor effects when the product is used in combination with the currently authorised product gemcitabine. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by pancreatic cancer.

A positive opinion for herpes simplex type 1 virus containing cellular *B-myb* gene as tumour-specific promoter, for treatment of pancreatic cancer was adopted by consensus.

**2.1.10 Emtricitabine** for treatment of Aicardi-Goutières syndrome, Dr Yanick Crow - EMA/OD/206/14 *[COMP co-ordinator: G. Capovilla]*

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 Aicardi-Goutières syndrome, the sponsor was asked to further elaborate on:

  - how the in vivo model supports the medical plausibility in all AGS types;
  - what the difference is in the pathogenic mechanism between AGS types 1-5 and AGS6-7, and why the latter could not be included in the OD;

- how the treatment can practically be given in the time window required to halt the neurological damage;
- whether there is a risk that the proposed treatment strategy (treatment only in the initial stages of the disease) does not abrogate but simply postpone the neurological disease process to a later time point/older age;
- whether the product crosses the blood–brain barrier (if this is indeed required).

In the written response, and during an oral explanation before the Committee on 10 December 2014, the sponsor further elaborated on the issues raised and summarised the current understanding of the disease mechanism of AGS. The sponsor discussed the existing literature data supporting the hypothesis of how inhibition of reverse transcription of RNA derived from endogenous retro-elements with an NRTI could be expected to block the triggering of the aberrant innate immune response underlying AGS.

The Committee agreed that the condition, Aicardi-Goutières syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing emtricitabine was considered justified based on current scientific understanding of the pathogenesis of the condition, as well as preliminary observations from a non-clinical model in which administration of emtricitabine in combination with other reverse transcriptase inhibitors markedly ameliorated the disease phenotype.

The condition is life-threatening and chronically debilitating due to the severe neurological damage inflicted by the initial encephalopathic phase, which causes profound intellectual disability and significant neuromuscular problems, and in most cases results in death in (early) childhood, as well as the debilitating extra-neurological symptoms, such as transitory chilblain-like skin lesions.

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 emtricitabine for treatment of Aicardi-Goutières syndrome was adopted by consensus.

**2.1.11 Tenofovir disoproxil fumarate** for treatment of Aicardi-Goutières syndrome, Dr Yanick Crow - EMA/OD/205/14
*[COMP co-ordinator: A. Corrêa Nunes]*

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 Aicardi-Goutières syndrome, the sponsor was asked to further elaborate on:

- how the in vivo model supports the medical plausibility in all AGS types;
- what the difference is in the pathogenic mechanism between AGS types 1-5 and AGS6-7, and why the latter could not be included in the OD;

- how the treatment can practically be given in the time window required to halt the neurological damage;
- whether there is a risk that the proposed treatment strategy (treatment only in the initial stages of the disease) does not abrogate but simply postpone the neurological disease process to a later time point/older age;
- whether the product crosses the blood–brain barrier (if this is indeed required).

In the written response, and during an oral explanation before the Committee on 10 December 2014, the sponsor further elaborated on the issues raised and summarised the current understanding of the disease mechanism of AGS. The sponsor discussed the existing literature data supporting the hypothesis of how inhibition of reverse transcription of RNA derived from endogenous retro-elements with an NRTI could be expected to block the triggering of the aberrant innate immune response underlying AGS.

The Committee agreed that the condition, Aicardi-Goutières syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing tenofovir disoproxil fumarate was considered justified based on current scientific understanding of the pathogenesis of the condition, as well as preliminary observations from a non-clinical model in which administration of tenofovir disoproxil fumarate in combination with other reverse transcriptase inhibitors markedly ameliorated the disease phenotype.

The condition is life-threatening and chronically debilitating due to the severe neurological damage inflicted by the initial encephalopathic phase, which causes profound intellectual disability and significant neuromuscular problems, and in most cases results in death in (early) childhood, as well as the debilitating extra-neurological symptoms, such as transitory chilblain-like skin lesions.

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 tenofovir disoproxil fumarate for treatment of Aicardi-Goutières syndrome was adopted by consensus.

### **2.1.12** Product for treatment of hypogonadotropic hypogonadism - EMA/OD/126/14

*[COMP co-ordinator: V. Tillmann]*

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:

- Medical plausibility

The proposed frequency of administration of the product may not be the most appropriate to obtain a stimulation, rather than an inhibition, of gonadotropin secretion. The applicant was asked to provide further justification and discussion of the proposed dosing schedule.

- Number of people affected

The applicant was invited to provide and discuss more data on the relative prevalence of secondary versus primary (idiopathic) HH, and of HH in general. Particularly, the impact of prevalence data from (pan)hypopituitarism on the prevalence on secondary HH.

- Significant benefit

The applicant was asked to provide a more detailed discussion of the assumed significant benefit of the product, particularly in the long-term treatment of HH in adults, versus existing treatments such as sex steroids or injectable gonadotropins.

In the written response, and during an oral explanation before the Committee on 10 December 2014, the sponsor further elaborated on the issues raised, and discussed the proposed dosing of the product, the prevalence of secondary and primary HH, as well as the proposed significant benefit as a safe alternative to already authorised treatments. The COMP noted the absence of data to confirm the assumptions proposed by the sponsor, which would make it difficult to accept this application.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 10 December 2014, prior to final opinion.

**2.1.13** Product for prevention of bronchopulmonary dysplasia - EMA/OD/183/14
*[COMP co-ordinator: B. 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:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for prevention of bronchopulmonary dysplasia, the sponsor was asked to further elaborate on:

  - any available data with the product as proposed for orphan designation, namely intra-tracheal installation in newborns (e.g. in preclinical models);
  - the safety of the product with regards to local administration to premature lungs, in particular in view of the developmental toxicity.

In the written response, and during an oral explanation before the Committee on 10 December 2014, the sponsor further elaborated on the issues raised, and discussed the available data in preclinical settings with the active substance given systemically. The sponsor also discussed the planned preclinical safety- and efficacy studies. After having discussed both with the sponsor and internally, the COMP concluded that the presented data would not allow extrapolation to draw conclusions for the justification of medical plausibility.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 December 2014, prior to final opinion.

**2.1.14** Product for treatment of respiratory distress syndrome in neonates - EMA/OD/182/14
*[COMP co-ordinator: M. Možina]*

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 respiratory distress syndrome in neonates, the sponsor was asked to further elaborate on:

- any available data with the product as proposed for orphan designation, namely intra-tracheal installation in newborns (e.g. in preclinical models);
- the safety of the product with regards to local administration to premature lungs, in particular in view of the developmental toxicity.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on any available results to justify the assumption of significant benefit over standard of care of the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 10 December 2014, the sponsor further elaborated on the issues raised, and discussed the available data in preclinical settings with the active substance given systemically. The sponsor also discussed the planned preclinical safety and efficacy studies. After having discussed both with the sponsor and internally, the COMP concluded that the presented data would not allow extrapolation to draw conclusions for the justification of medical plausibility.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 December 2014, prior to final opinion.

**2.1.15 Sodium thiosulfate** for treatment for calciphylaxis, Hope Pharmaceuticals, Ltd - EMA/OD/191/14
*[COMP co-ordinator: A. Corrêa Nunes]*

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:

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of sodium thiosulphate for the treatment of calciphylaxis, the sponsor was invited to further elaborate on:

- the availability of non-clinical studies which are validated as models for the condition to establish proof of principle that sodium thiosulphate is effective in calciphylaxis;

- the availability of case reports in calciphylaxis patients successfully treated with sodium thiosulphate.

In the absence of relevant data of this product in the disease applied for orphan designation medical plausibility cannot be established.

In the written response the sponsor further elaborated on the issues raised and discussed several published case reports in patients affected by the condition who were treated with the product.

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

The intention to treat the condition with the medicinal product containing sodium thiosulfate was considered justified based on case reports of successful treatment of calciphylaxis with sodium thiosulfate, as well as on preclinical and clinical data which give evidence that sodium thiosulfate can be expected to dissolve calcium salts, and to act as antioxidant, which may help reducing the build-up of calcium in arteries, and restore the healthy functioning of cells lining the interior walls of the arteries.

The condition is life-threatening due to the risk of sepsis and chronically debilitating due to deep and painful non-healing ulcers which are associated with a high mortality rate.

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

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 sodium thiosulfate for treatment of calciphylaxis was adopted by consensus.

**2.1.16** Product for treatment of primary biliary cirrhosis- EMA/OD/158/13
*[COMP co-ordinator: A. Corrêa Nunes]*

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 primary biliary cirrhosis, the sponsor was asked to further elaborate on:

  - the relevance of the preclinical model(s) used for the treatment of primary biliary cirrhosis, and the interpretation of the results obtained in the experiments,
  - the methodology used in the pre-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition,
  - the available human clinical data that is directly relevant to the condition.

In the written response, and during an oral explanation before the Committee on 10 December 2014, the sponsor discussed that absence of cross species reactivity of the product, does not allow for testing in available models of the condition. The sponsor also presented data with other products targeting the same pathway, or in the settings of other conditions than the one applied for. The COMP considered that the lack of data with the specific product in either specific models or in patients affected by the condition would not allow extrapolation to draw conclusions for the treatment of the proposed condition.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 December 2014, prior to final opinion.

**2.1.17 Chimeric monoclonal antibody specific to O-acetyl-GD2 antigen (ATL-301)** for treatment of neuroblastoma, Atlab Pharma SAS - EMA/OD/199/14
*[COMP co-ordinator: B. Dembowska-Bagińska]*

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 neuroblastoma, the sponsor was asked to further elaborate on:

  - The specification of the final product and on any available data with the final product as applied for designation.

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on any available data with the product as applied for designation. In the absence of data with the product as applied for designation significant benefit cannot be assessed.

In the written response, and during an oral explanation before the Committee on 10 December 2014, the sponsor clarified the specification of the product, discussed the available preclinical data and, to support their argument on significant benefit, also referred to clinical data obtained with a similar antibody. The Committee agreed that the condition, neuroblastoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing chimeric monoclonal antibody to O-acetyl-GD2 antigen was considered justified based on preclinical data demonstrating anti-neuroblastoma activity in models of the condition.

The condition is life threatening and chronically debilitating due to its aggressive nature and frequency of metastatic disease. It accounts for almost 15% of childhood cancer fatalities. The likelihood of survival is dependent on the age of the patient, the stage and biological characteristics of the disease. The poorest prognosis is seen in children diagnosed at older age (>15 months), those diagnosed at later stages of disease, and those positive for certain molecular biological markers such as myelocytomatosis viral related oncogene-Neuroblastoma derived (MYCN) amplification, which occurs in 5–10% of cases in infants up to 1 year and in 20–30% of childhood and adolescent cases.

The condition was estimated to be affecting approximately 1.1 in 10,000 persons in the European Union, at the time the application was made.

A positive opinion for chimeric monoclonal antibody to O-acetyl-GD2 antigen for treatment of neuroblastoma was adopted by consensus.

**2.1.18** Product for treatment of Pseudomonas Aeruginosa infections in cystic fibrosis patients - EMA/OD/174/14
*[COMP co-ordinator: J. Eggenhofer]*

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:

- Medical plausibility

In order to justify the medical plausibility of the proposed product the sponsor was invited to elaborate on the grounds for assuming equal efficacy of the proposed product *vis a vis* currently authorized products, taking into account the lack of in vivo data with the proposed formulation at the present stage.

- Significant benefit

In order to justify the significant benefit of the proposed product the sponsor was invited to elaborate on:

- any available data supporting an assumption of potential better tolerability than currently authorized products;

- any available data supporting the claims of major contribution to patient care with the proposed formulation, and any available data documenting difficulties and problems with the currently authorised products.

In absence of any data the significant benefit cannot be acknowledged.

In the written response, and during an oral explanation before the Committee on 11 December 2014, the sponsor further elaborated on the issues raised, in the context of the formulation of the new product and the delivery method. The COMP considered that the argument for significant benefit was not supported by data.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 December 2014, prior to final opinion.

**2.1.19 Recombinant human aspartylglucosaminidase** for treatment of aspartylglucosaminuria, ACE Biosciences A/S - EMA/OD/172/14
*[COMP co-ordinator: I. Bradinova]*

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 aspartylglucosaminuria, the sponsor was asked to further elaborate on:

  - the results obtained in in vitro fibroblast cell lines for the treatment of aspartylglucosaminuria;
  - the methodology used in the pre-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition.

In the written response, and during an oral explanation before the Committee on 11 December 2014, the sponsor elaborated on the relevance of the in vivo model used and the results obtained in the experiments.

The Committee agreed that the condition, aspartylglucosaminuria, 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 aspartylglucosaminidase was considered justified based on pre-clinical in vivo data in a valid model of the condition showing a reduction in glycoasparagines.

The condition is life-threatening due to a life-expectancy of only 40yrs and chronically debilitating due to mental retardation, epilepsy and recurrent infections.

The condition was estimated to be affecting not more 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 Recombinant human aspartylglucosaminidase, for treatment of aspartylglucosaminuria, was adopted by consensus.

**2.1.20** Product for treatment of haemolytic uremic syndrome caused by Shiga toxin-producing bacteria - EMA/OD/194/14
*[COMP co-ordinator: A. Magrelli]*

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

- Intention to diagnose, prevent or treat

The condition should be justified as a distinct medical entity or a valid subset, for the purposes of orphan medicinal product designation. The sponsor's attention was drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00). Acknowledging all infectious agents that can cause HUS as well as previous designations the COMP suggests renaming the proposed orphan indication to "treatment of infection-associated haemolytic uremic syndrome".

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of haemolytic uremic syndrome caused by Shiga toxin-producing bacteria, the sponsor was asked to further elaborate on:

- the relevance of the preclinical model used for the treatment of haemolytic uremic syndrome caused by Shiga toxin-producing bacteria and the interpretation of the results obtained in the experiments;
- any available data with the proposed product in either relevant models of the condition or preliminary clinical data in patients.

In the absence of relevant data with the product in the condition as proposed for designation medical plausibility cannot be assessed.

In the written response, and during an oral explanation before the Committee on 11 December 2014, the sponsor accepted a revision of the proposed indication and discussed ex-vivo experiments supporting inhibition of complement deposits in serum from patients with STEC and atypical HUS. They also discussed data obtained in a murine model of primary membrano-proliferative glomerulonephritis. The COMP considered that in the absence of either specific preclinical models or in patients affected by the condition, it would be difficult to extrapolate the observations seen ex-vivo or in other conditions, to establish the medical plausibility.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 December 2014, prior to final opinion.

**2.1.21 Adenoviral vector serotype 5 containing the vascular endothelial growth factor D isoform (preprocessed short form) from a CMV promoter** for treatment of placental insufficiency, Magnus Invention Management Ltd - EMA/OD/198/14
*[COMP co-ordinator: V. Tillmann] [Expert: Dr V. Odlind]*

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

Placental insufficiency should be further justified as a distinct medical entity, for the purposes of orphan medicinal product designation. The sponsor's attention was drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

- Number of people affected

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

The sponsor was asked to re-calculate the epidemiological indices based on relevant epidemiological studies and registers for the proposed orphan condition, and given the substantial uncertainty about many of the assumptions regarding the number of people affected, not least the uncertainty about the definition of the condition, the sponsor was asked to perform a sensitivity analysis of the reported calculations.

In the written response, and during an oral explanation before the Committee on 11 December 2014, the sponsor elaborated on the definition and clinical characteristics of the proposed condition, as well as the calculation of prevalence.

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

The intention to treat the condition with the medicinal product containing adenoviral vector serotype 5 containing the vascular endothelial growth factor D isoform (pre-processed short form) from a CMV promoter was considered justified based on data in preclinical models demonstrating that local administration of the proposed product had favourable effects on hallmarks of placental insufficiency, such as vasoconstriction of uterine arteries, endothelial cell proliferation, and uterine blood flow.

The condition is chronically debilitating and life-threatening to the foetus due to chronic hypoxia and under-nutrition leading to foetal growth restriction, which is associated with an increased risk of abnormal neurodevelopment, altered cardiac morphology and function, and iatrogenic preterm delivery to prevent further neonatal morbidity and mortality. Preterm delivery is associated with increased neonatal mortality and morbidity, including bronchopulmonary dysplasia, germinal matrix haemorrhage, or cystic periventricular leukomalacia, necrotising enterocolitis (NEC), or sepsis.

The condition was estimated to be affecting approximately 3.3 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 Adenoviral vector serotype 5 containing the vascular endothelial growth factor D isoform (pre-processed short form) from a CMV promoter for treatment of placental insufficiency was adopted by consensus.

**2.1.22 Pentosan polysulfate sodium** for treatment of interstitial cystitis, Dr Ulrich Granzer - EMA/OD/179/14

*[COMP co-ordinator: A. Corrêa Nunes]*

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 the sponsor was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor was asked to re-calculate the prevalence estimate based on relevant European epidemiological studies and registers for the proposed orphan condition.

In the written response the sponsor further elaborated on the issue raised.

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

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

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

The condition was estimated to be affecting not more than 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 pentosan polysulfate sodium, for treatment of interstitial cystitis, was adopted by consensus.

## 2.2. For discussion / preparation for an opinion

**2.2.1** Product for treatment of angioedema - EMA/OD/170/14
*[COMP co-ordinator: M. Možina]*

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 January meeting.

**2.2.2** Product for treatment of ovarian cancer - EMA/OD/211/14
*[COMP co-ordinator: B. Bloechl-Daum]*

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 January meeting.

**2.2.3 Adeno-associated viral vector serotype 8 containing the human factor-VII gene** for treatment of congenital factor VII deficiency, Professor Edward G. Tuddenham - EMA/OD/224/14
*[COMP co-ordinator: M. Možina]*

The Committee agreed that the condition, congenital factor VII deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 8 containing the human factor VII gene was considered justified based on pre-clinical in vivo data using a valid model of the condition which showed that endogenous factor VII increased and there was improved survival.

The condition is chronically debilitating due to recurrent bleedings in joints, gastrointestinal tract or other organs and tissues, as well as in surgery. These bleedings may be life-threatening in some patients, in particular in case of intracranial bleeding.

The condition was estimated to be affecting approximately 0.06 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 adeno-associated viral vector serotype 8 containing the human factor VII gene may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vivo data that demonstrate that this treatment will improve the production of endogenous Factor VII as well as survival. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 8 containing the human factor VII gene for treatment of congenital factor VII deficiency was adopted by consensus.

### 2.2.4 **Allogeneic peripheral blood mononuclear cells induced to an early apoptotic state** for prevention of graft versus host disease, Richardson Associates Regulatory Affairs Ltd - EMA/OD/217/14

*[COMP co-ordinator: F. Naumann-Winter]*

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

The intention to prevent the condition with the medicinal product containing allogeneic peripheral blood mononuclear cells induced to an early apoptotic state was considered justified based on preliminary clinical data showing improved effects compared to historical controls.

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

The population of patients eligible for prevention of the condition was estimated to be approximately 0.4 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 allogeneic peripheral blood mononuclear cells induced to an early apoptotic state may be of significant benefit to the population at risk of developing the condition. The sponsor has provided preliminary clinical data showing reduced severe acute GVHD compared to historical controls. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic peripheral blood mononuclear cells induced to an early apoptotic state, for prevention of graft-versus-host disease, was adopted by consensus.

**2.2.5** Product for treatment of Sjogren's syndrome - EMA/OD/235/14
*[COMP co-ordinator: Z. Batova]*

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 January meeting.

**2.2.6** Product for treatment of mantle cell lymphoma - EMA/OD/220/14
*[COMP co-ordinator: K. Kubáčková]*

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 January meeting.

**2.2.7** Product for treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma - EMA/OD/208/14
*[COMP co-ordinator: F. Naumann-Winter]*

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 January meeting.

**2.2.8 Ceftriaxone** for treatment of spinocerebellar ataxia, Ospedale San Raffaele s.r.l. - EMA/OD/216/14
*[COMP co-ordinator: G. O'Dea]*

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

The intention to treat the condition with the medicinal product containing ceftriaxone was considered justified based on pre-clinical data in a valid model of the condition showing an improvement in ataxia.

The condition is chronically debilitating due to slowly progressive incoordination of gait which is often associated with poor coordination of hands, speech, and eye movements.

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 ceftriaxone for treatment of spinocerebellar ataxia was adopted by consensus.

**2.2.9 Chimeric fusion protein of recombinant human alpha-N-acetylglucosaminidase and human insulin-like growth factor 2** for treatment of mucopolysaccharidosis type III B (Sanfilippo B syndrome), BioMarin Europe Ltd. - EMA/OD/213/14
*[COMP co-ordinator: J. Torrent-Farnell]*

The Committee agreed that the condition, mucopolysaccharidosis type IIIB (Sanfilippo B syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing chimeric fusion protein of recombinant human alpha-N-acetylglucosaminidase and human insulin-like growth factor 2 was

considered justified based on preliminary pre-clinical data using a validated model of the condition where there was a clearance of heparan sulfate.

The condition is life-threatening and chronically debilitating due to frequent infections and neurocognitive delay, that progresses to profound mental disability and vegetative state. The survival of the patients is limited to 20-30 years.

The condition was estimated to be affecting approximately 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 Chimeric fusion protein of recombinant human alpha-N-acetylglucosaminidase and human insulin-like growth factor 2 (BMN250), for treatment of mucopolysaccharidosis type IIIB (Sanfilippo B syndrome), was adopted by consensus.

**2.2.10** Product for treatment of glioma - EMA/OD/234/14
*[COMP co-ordinator: A. Lhoir]*

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 January meeting.

**2.2.11** Product for treatment of Creuztfeldt-Jacob Disease - EMA/OD/221/14
*[COMP co-ordinator: S. Thorsteinsson]*

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 January meeting.

**2.2.12** Product for treatment of Ebola viral infection - EMA/OD/250/14
*[COMP co-ordinator: J. Torrent-Farnell]*

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 January meeting.

**2.2.13** Product for treatment of non-infectious uveitis - EMA/OD/236/14
*[COMP co-ordinator: K. Westermark]*

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 January meeting.

**2.2.14 Humanised Fc engineered monoclonal antibody against CD19** for treatment of diffuse large B-cell lymphoma, MorphoSys AG - EMA/OD/215/14
*[COMP co-ordinator: F. Naumann-Winter]*

The Committee agreed that the condition, diffuse large B-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 humanised Fc engineered monoclonal antibody against CD19 was considered justified based on preliminary clinical data showing reduced tumour size in treated patients affected by the condition.

The condition is chronically debilitating due to involvement of single or multiple nodal or extranodal sites, including the gastrointestinal tract and bone marrow and life-threatening in patients not responding to treatment.

The condition was estimated to be affecting approximately 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 humanised Fc engineered monoclonal antibody against CD19 may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients affected by the condition, who had relapsed or did not respond to previous treatments. These patients showed clinically relevant responses when treated with the product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised Fc engineered monoclonal antibody against CD19, for treatment of diffuse large B-cell lymphoma, was adopted by consensus.

**2.2.15** Product for treatment of Ebola virus disease - EMA/OD/272/14
*[COMP co-ordinator: N. Sypsas]*

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 January meeting.

**2.2.16** Product for treatment of systemic sclerosis- EMA/OD/225/14
*[COMP co-ordinator: G. O'Dea]*

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 January meeting.

**2.2.17 N-methyl-4-({4-[({3-methyl(methylsulfonyl)amino]pyrazin-2- yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide hydrochloride** for treatment of ovarian cancer, TMC Pharma Services Ltd - EMA/OD/223/14
*[COMP co-ordinator: B. Bloechl-Daum]*

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

The intention to treat the condition with the medicinal product containing N-methyl-4-({4-[({3-methyl(methylsulfonyl)aminopyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide hydrochloride was considered justified based on preclinical and on preliminary clinical data showing anti-tumour activity of the product.

The condition is chronically debilitating in particular due to pain, weight loss, ascites and vaginal bleeding, and life-threatening with approximately half of the patients surviving less than five years.

The condition was estimated to be affecting not more than 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 N-methyl-4-({4-[({3-methyl(methylsulfonyl)aminopyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide hydrochloride may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing re-sensitising of paclitaxel-resistant tumours to paclitaxel with the proposed product, and reduction of ovarian cancer stem cells, in valid models of the condition. The Committee considered that this could translate into a clinically relevant advantage for the patients affected by ovarian cancer.

A positive opinion for N-methyl-4-({4-[({3-methyl(methylsulfonyl)aminopyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide hydrochloride, for treatment of ovarian cancer, was adopted by consensus.

**2.2.18 Pegylated recombinant arginine deiminase** for treatment of malignant mesothelioma, Designerx Europe Limited - EMA/OD/076/14
*[COMP co-ordinator: K. Kubáčková]*

The Committee agreed that the condition, 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 pegylated recombinant arginine deiminase was considered justified based on clinical data showing favourable response with the proposed product.

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 approximately 0.2 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 pegylated recombinant arginine deiminase may be of significant benefit to those affected by the condition. This is based on clinical data showing improved progression free survival with the proposed product, including in patients pretreated with other antineoplastic products, and on preclinical data showing an effect of the proposed product in combination with the current standard of care treatment of the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by malignant mesothelioma.

A positive opinion for pegylated recombinant arginine deiminase for treatment of malignant mesothelioma was adopted by consensus.

**2.2.19** Product for treatment of diastolic heart failure caused by hypertrophic cardiomyopathy - EMA/OD/153/14
*[COMP co-ordinator: J. Torrent-Farnell]*

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 January meeting.

**2.2.20 Ponatinib hydrochloride** for treatment of malignant gastro intestinal stromal tumors, ARIAD Pharma Ltd - EMA/OD/212/14
*[COMP co-ordinator: B. Dembowska-Bagińska]*

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

The intention to treat the condition with the medicinal product containing ponatinib hydrochloride was considered justified based on preliminary clinical data showing tumour size reduction in treated patients affected by the condition.

The condition is chronically debilitating and life-threatening, in particular due to the high rate of relapse and development of metastatic disease resulting in a poor survival.

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 ponatinib hydrochloride may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing responses in treated patients who have progressed following treatment with available products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for ponatinib hydrochloride, for treatment of gastrointestinal stromal tumours, was adopted by consensus.

**2.2.21 Recombinant human alkaline phosphatase** for treatment of hypophosphatasia, AM-Pharma BV - EMA/OD/218/14
*[COMP co-ordinator: V. Tillmann]*

The Committee agreed that the condition, hypophosphatasia, 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 alkaline phosphatase was considered justified based on pre-clinical in vivo data showing an improvement in survival.

The condition is chronically debilitating and life threatening due to impaired mineralization of bones and early mortality.

The condition was estimated to be affecting approximately 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 recombinant human alkaline phosphatase for treatment of hypophosphatasia was adopted by consensus.

**2.2.22** Product for treatment of sickle cell disease - EMA/OD/210/14
*[COMP co-ordinator: A. Moraiti]*

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 January meeting.

**2.2.23** Product for treatment of hyperornithinaemia, hyperammonaemia, homocitrullinuria syndrome - EMA/OD/228/14
*[COMP co-ordinator: L. Greene/ V. Tillmann]*

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 January meeting.

**2.2.24** Product for treatment of argininosuccinate lyase deficiency - EMA/OD/230/14
*[COMP co-ordinator: L. Greene/ V. Tillmann]*

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 January meeting.

**2.2.25** Product for treatment of N-acetylglutamate synthase deficiency - EMA/OD/227/14
*[COMP co-ordinator: L. Greene/ V. Tillmann]*

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 January meeting.

**2.2.26** Product for treatment of ornithine transcarbamylase deficiency - EMA/OD/226/14
*[COMP co-ordinator: L. Greene/ V. Tillmann]*

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 January meeting.

**2.2.27** Product for treatment of carbamoylphosphate synthetase I deficiency - EMA/OD/233/14
*[COMP co-ordinator: L. Greene/ V. Tillmann]*

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 January meeting.

**2.2.28** Productfor treatment of lysinuric protein intolerance - EMA/OD/232/14
*[COMP co-ordinator: L. Greene/ V. Tillmann]*

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 January meeting.

**2.2.29** Product for treatment of argininosuccinate synthetase deficiency - EMA/OD/229/14
*[COMP co-ordinator: L. Greene/ V. Tillmann]*

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 January meeting.

**2.2.30** Product for treatment of arginase deficiency - EMA/OD/231/14
*[COMP co-ordinator: L. Greene/ V. Tillmann]*

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 January meeting.

**2.2.31 sodium valproate** for treatment of Wolfram Syndrome, Alan Boyd Consultants Ltd - EMA/OD/222/14
*[COMP co-ordinator: A. Andrić]*

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

The intention to treat the condition with the medicinal product containing sodium valproate was considered justified based on in vitro models and a valid pre-clinical model of the condition.

The condition is life-threatening due to a life-expectancy of only 30 years and chronically debilitating due to the development of diabetes mellitus and optic atrophy.

The condition was estimated to be affecting not more than 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 sodium valproate, for treatment of Wolfram syndrome, was adopted by consensus.

**2.2.32 Synthetic signal peptide of human Mucin-1 (amino acids 1-21)** for treatment of plasma cell myeloma, Richardson Associates Regulatory Affairs Ltd - EMA/OD/214/14
*[COMP co-ordinator: K. Kubáčková]*

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

The intention to treat the condition with the medicinal product containing synthetic signal peptide of human Mucin-1 (amino acids 1-21) was considered justified based on preliminary clinical data showing biochemical responses in treated patients affected by the condition.

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

The condition was estimated to be affecting approximately 3.6 per 10,000 people 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 synthetic signal peptide of human mucin-1 (amino acids 1-21) may be of significant benefit to those affected by the condition. This was based on an alternative mechanism of action that may result in improved efficacy. The sponsor has provided preliminary clinical data that show responses in patients who had residual disease despite previous treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for synthetic signal peptide of human mucin-1 (amino acids 1-21) for treatment of plasma cell myeloma was adopted by consensus.

### 2.3. Appeal procedure

None.

### 2.4. Evaluation on-going

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

### 2.5. Validation on-going

The Committee was informed that validation was on-going for sixty one applications for orphan designation.

## 3. Requests for protocol assistance

**3.1** For treatment of glioma. [Coordinator: B. Bloechl-Daum]

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

**Post-meeting note:**

The protocol assistance letter was circulated for information.

**3.2** For prevention of graft-versus-host disease. [Coordinator: K. Westermark]

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

**Post-meeting note:**

The protocol assistance letter was circulated for information.

**3.3** For treatment of soft tissue sarcoma. [Coordinator: B. Bloechl-Daum]

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

**Post-meeting note:**

The protocol assistance letter was circulated for information.

# 4. Overview of applications

**4.1** Update on applications for orphan medicinal product designation submitted/expected

COMP co-ordinators were appointed for 5 applications submitted and 28 upcoming applications. Experts were appointed for on-going applications.

**4.2** Update on orphan applications for Marketing Authorisation

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

# 5. Review of orphan designation for orphan medicinal products for Marketing Authorisation

## 5.1. Orphan designated products for which CHMP opinions have been adopted

**5.1.1 OFEV** (nintedanib) for treatment of idiopathic pulmonary fibrosis; Boehringer Ingelheim International GmbH (EMA/OD/186/12, EU/3/13/1123) [Co-ordinators: A. Moraiti]

The COMP noted the CHMP opinion on MA adopted 17-20 November 2014.

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 sponsor was invited to justify the significant benefit of nintedanib in relation to pirfenidone, taking into account also the results of the ASCEND trial in addition to the CAPACITY trials.

Significant benefit can be established when the proposed product results in a clinically relevant advantage or a major contribution to patient care as compared to what is authorized in the EU for the treatment of the condition, therefore the sponsor was also invited to discuss any other possible grounds of significant benefit of nintedanib *vs.* pirfenidone, and to provide any available data to support these grounds.

In its written response, and during an oral explanation before the Committee on 9 December, the sponsor further elaborated on the issues raised.

The sponsor stated that the main efficacy, safety and pharmacokinetic results of the nintedanib clinical development program were reviewed and compared with the publicly available data on pirfenidone. Based on this indirect comparison, the Applicant proposed that nintedanib represents a treatment

option for patients with IPF with a significant benefit over the existing therapy with pirfenidone based on the following grounds:

Firstly, nintedanib is indicated for the treatment of adult patients with IPF without limitation based on the severity of their disease. Hence it represents a major contribution to patient care as it provides an alternative therapeutic option for patients for whom pirfenidone is not indicated, i.e. patients with severe disease. It is also a treatment option for patients who do not tolerate or do not respond to pirfenidone.

Moreover, a clinically relevant advantage in comparison to pirfenidone was argued on the basis of the following:

- Nintedanib is a tyrosine kinase inhibitor with known molecular targets that is likely to be different from pirfenidone.
- The patient population included in the nintedanib program was broader than the patient population in the pirfenidone trials and thus the nintedanib program more closely reflects clinical practice.
- The efficacy and safety profile of nintedanib is different from that of pirfenidone and indicates advantages when compared across studies.
- Nintedanib reduced the risk of acute IPF exacerbations; there is no apparent treatment effect of pirfenidone on this clinically important endpoint.
- Nintedanib demonstrated modest effects on health-related quality of life indicating less worsening in patients treated with nintedanib. In contrast, there does not appear to be any evidence for an effect of pirfenidone on HR-QoL measures.
- Nintedanib significantly reduced the risk of progression by 40% compared to placebo. Due to inconsistencies in the results between trials, and the different definition used for PFS in ASCEND, the effect of pirfenidone on this endpoint has not been shown in a consistent and conclusive manner.
- The effects of nintedanib were consistent across all subgroups confirming the applicability of the results to the broader population studied in the nintedanib program.
- In contrast to pirfenidone, photosensitivity reactions and rash are no safety concerns for nintedanib.

In relation to these claims proposed by the sponsor and discussed during the oral explanation, the COMP was of the opinion that the most relevant ground for significant benefit is the possibility of using nintedanib in patient populations not limited to mild and moderate stages of the disease, different from pirfenidone. The COMP questioned the sponsor on the data supporting the full indication of nintedanib. The patients enrolled in the trials had FVC values no lower than 50% of predicted; therefore they enrolled a patient population that was similar from the point of view of lung function to the one of the pirfenidone trials. However, with the extrapolation of the effect of nintedanib on FVC to populations with a baseline FVC lower than 50%, nintedanib obtained the marketing authorization for the full indication IPF with no restriction of severity stage. The possibility of having a product for IPF available to the whole patient population was considered by the COMP a clinically relevant advantage for the patients affected by IPF, since at present there is no product authorized for patients who do not fall into the mild and moderates spectrum of the disease.

The COMP also discussed the claims of effect on exacerbations, patient reported outcomes, and reduced worsening of the disease from nintedanib. The data presented by the sponsor are very

interesting and signal a trend towards an effect of nintedanib on these endpoints. However, the results are not consistent across the different nintedanib trials and in most instances not statistically significant. For these reasons, although the COMP acknowledged the positive trend, the claims on the secondary endpoints proposed by the sponsor were not explicitly considered as part of the grounds of significant benefit at the present stage.

The COMP concluded that:

The proposed therapeutic indication “treatment of idiopathic pulmonary fibrosis” falls entirely within the scope of the orphan indication of the designated orphan medicinal product.

The prevalence of idiopathic pulmonary fibrosis (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be not more than 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 progressive dyspnoea and loss of lung ventilator function, heavily limiting exercise capability and decreased quality of life of the affected patients and leading in many cases within months or a few years to the need of oxygen therapy. Pulmonary hypertension usually develops. Median survival is less than five years. Death ultimately occurs due to respiratory failure.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that nintedanib may be of potential significant benefit to those affected by the orphan condition still holds. This is based on the possibility to treat with the proposed product patients with idiopathic pulmonary fibrosis for whom currently no authorized treatment exists. The Committee was of the opinion that this constitutes a clinically relevant advantage for the patients affected by the condition.

An opinion not recommending the removal of OFEV, nintedanib (EU/3/13/1123), from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

**5.1.2 Cerdelga** ((1R,2R)-octanoic acid[2-(2',3'-dihydro-benzo[1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amide-L-tartaric acid salt for treatment of Gaucher disease; Genzyme Europe BV (EMA/OD/066/07, EU/3/07/514, EMA/H/C/003724) [Co-ordinators: A. Correa Nunes]

The COMP noted the CHMP opinion on MA adopted 17-20 November 2014.

The COMP concluded that:

The proposed therapeutic indication “treatment of Gaucher disease” falls entirely within the scope of the orphan indication of the designated orphan medicinal product.

The prevalence of Gaucher Disease (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be approximately 0.3 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 hepatomegaly, splenomegaly, and bone marrow dysfunction, and life-threatening with reduced life expectancy.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Cerdelga may be of potential significant benefit to those affected by the orphan condition still holds. Given that the already authorised substrate reduction therapy is indicated

only for patients for whom enzyme replacement is unsuitable, significant benefit was considered on the basis of an oral administration scheme which would offer a major contribution to patient care compared to currently available intravenous infusions of enzyme replacement therapies.

An opinion not recommending the removal of Cerdelga, (1R,2R)-octanoic acid[2-(2',3'-dihydro-benzo[1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amide-L-tartaric acid salt, eliglustat (EU/3/07/514) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

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

**5.2.1** Ex vivo expanded autologous human corneal epithelium containing stem cells for treatment of corneal lesions, with associated corneal (limbal) stem cell deficiency, due to ocular burns; Chiesi Farmaceutici S.p.A. (EU/3/08/579)

**5.2.2** Levofloxacin hemihydrate for treatment of cystic fibrosis; Aptalis Pharma SAS (EU/3/08/566)

## 5.3. On-going procedures

**5.3.1** Blinatumomab for treatment of acute lymphoblastic leukaemia; Amgen Europe B.V. (EU/3/09/650)

**5.3.2** Mifepristone for treatment of hypercortisolism (Cushing's syndrome) of endogenous origin; FGK Representative Service GmbH (EU/3/11/925)

**5.3.3** Isavuconazonium sulfate; Basilea Medical Ltd (EMEA/H/C/002734):

a) treatment of invasive aspergillosis (EU/3/14/1284)

b) treatment of mucormycosis (EU/3/14/1276)

**5.3.4** Cysteamine hydrochloride for treatment of cystinosis; Orphan Europe S.A.R.L. (EU/3/08/578)

**5.3.5** Autologous tumour-derived immunoglobulin idiotype coupled to keyhole limpet haemocyanin for treatment of follicular lymphoma; Biovest Europe Ltd (EU/3/06/394)

**5.3.6** Efmoroctocog alfa for treatment of haemophilia A; Biogen Idec Ltd (EU/3/10/783)

**5.3.7** Panobinostat for treatment of multiple myeloma; Novartis Europharm Limited (EU/3/12/1063)

**5.3.8** Human heterologous liver cells (for infusion); Cytonet GmbH&Co KG

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EU/3/10/821)

b) treatment of ornithine-transcarbamylase deficiency (EU/3/07/470)

c) treatment of citrullinaemia type 1 (EU/3/10/818)

d) treatment of hyperargininaemia (EU/3/10/819)

e) treatment of argininosuccinic aciduria (EU/3/10/820)

**5.3.9** Tasimelteon for treatment of non-24-hour sleep-wake disorder in blind people with no light perception; Vanda Pharmaceuticals Limited (EU/3/10/84)

**5.3.10** Ruxolitinib for treatment of polycythaemia vera; Novartis Europharm Limited (EU/3/14/1244)

**5.3.11** Tolvaptan for treatment of autosomal dominant polycystic kidney disease; Otsuka Pharmaceutical Europe Ltd (EU/3/13/1175)

**5.3.12** Ketoconazole for treatment of Cushing's syndrome; Agenzia Industrie Difesa-Stabilimento Chimico Farmaceutico Militare (EU/3/12/1031)

**5.3.13** Lenvatinib; Eisai Ltd

a) treatment of papillary thyroid cancer (EU/3/13/1121)

b) treatment of follicular thyroid cancer (EU/3/13/1119)

**5.3.14** Recombinant human parathyroid hormone for treatment of hypoparathyroidism; NPS Pharma UK Ltd (EU/3/13/1210)

**5.3.15** Susoctocog alfa for treatment of haemophilia A; Baxter AG (EU/3/10/784)

**5.3.16** Glyceryl tri-(4-phenylbutyrate); Hyperion Therapeutics Limited:

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EU/3/10/733)

b) treatment of ornithine carbamoyltransferase deficiency (EU/3/10/734)

c) treatment of citrullinaemia type 1 (EU/3/10/735)

d) treatment of argininosuccinic aciduria (EU/3/10/736)

e) treatment of hyperargininaemia (EU/3/10/737)

f) treatment of ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome) (EU/3/10/738)

g) treatment of citrullinaemia type 2 (EU/3/10/739)

**5.3.17** Idebenone for treatment of Leber's hereditary optic neuropathy; Santhera Pharmaceuticals (Deutschland) GmbH (EU/3/07/434)

**5.3.18** L-Asparaginase for treatment of acute lymphoblastic leukaemia; medac Gesellschaft fuer klinische Spezialpraeparate mbH (EU/3/04/258)

**5.3.19** Asfotase alfa for treatment of hypophosphatasia; Alexion Europe SAS (EU/3/08/594)

**5.3.20** Chimeric monoclonal antibody against GD2 for treatment of neuroblastoma; United Therapeutics Europe Ltd (EU/3/11/879)

**5.3.21** 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride for treatment of narcolepsy; Bioprojet (EU/3/07/459)

**5.3.22** Herpes simplex 1 virus-thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes for adjunctive treatment in haematopoietic cell transplantation; MolMed S.p.A. (EU/3/03/168)

# 6. Procedural aspects

**6.1** Significant Benefit Working group

**6.2** ITF briefing meeting, January 2015

Call for expression of interest in participation to the task force briefing meeting (for COMP members).

**6.3** Agenda - EMA Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP) meeting with all eligible organisations – 26 November (EMA/632557/2014)

The Agenda was circulated for information.

**6.4** Agenda - Training session for patients and consumers involved in EMA activities – 25 November (EMA/632556/2014)

The Agenda was circulated for information.

**6.5** Minutes of the EMA Human Scientific Committees' Working Parties with Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP) joint meeting – 16 September (EMA/563152/2014)

The minutes were circulated for information.

**6.6** Benefit-risk communication to medicines users - How can regulators best meet the information needs of patients and healthcare professionals? - Workshop report (EMA/581546/2014)

The report was circulated for information.

# 7. Any other business

None.

# Date of next COMP meeting: 7-9 January 2015

# List of participants

including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 9-11 December 2014 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 | Full involvement | |
| Brigitte Blöchl-Daum | Member | Austria | Full involvement | |
| André Lhoir | Member | Belgium | Full involvement | |
| Irena Bradinova | Member | Bulgaria | Full involvement | |
| Adriana Andrić | Member | Croatia | Full involvement | |
| Elena Kaisis | Member | Cyprus | Full involvement | |
| Katerina Kubacková | Member | Czech Republic | No restrictions applicable to the meeting | |
| Jens Ersbøll | Member | Denmark | Full involvement | |
| Vallo Tillmann | Member | Estonia | Full involvement | |
| Frauke Naumann-Winter | Member | Germany | Full involvement | |
| Nikolaos Sypsas | Member | Greece | No restrictions applicable to the meeting | |
| Judit Eggenhofer | Member | Hungary | Full involvement | |
| Sigurdur B. Thorsteinsson | Member | Iceland | Full involvement | |
| Geraldine O'Dea | Member | Ireland | Full involvement | |
| Armando Magrelli | Member | Italy | Full involvement | |
| Dainis Krievins | Member | Latvia | No restrictions applicable to the meeting | |
| Aušra Matulevičienė | Member | Lithuania | Full involvement | |
| Henri Metz | Member | Luxembourg | Full involvement | |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Violeta Stoyanova | Member | Netherlands | Full involvement | |
| Lars Gramstad | Member | Norway | Full involvement | |
| Bożenna Dembowska-Bagińska | Member | Poland | No participation in final deliberations and voting on 3.2.1 (EU/3/14/1258) | |
| Ana Corrêa Nunes | Member | Portugal | Full involvement | |
| Flavia Saleh | Member | Romania | Full involvement | |
| Zuzana Batova | Member | Slovak Republic | Full involvement | |
| Martin Možina | Member | Slovenia | No restrictions applicable to the meeting | |
| Josep Torrent-Farnell | Member | Spain | Full involvement | |
| Kerstin Westermark | Member | Sweden | No restrictions applicable to the meeting | |
| Daniel O'Connor | Member | United Kingdom | Full involvement | |
| Pauline Evers | Member | Patients' Organisation Representative | Full involvement | |
| Lesley Greene | Member (Vice-Chair) | Patients' Organisation Representative | Full involvement | |
| Birthe Byskov Holm | Member | Patients' Organisation Representative | Full involvement | |
| Aikaterini Moraiti | Member | Expert recommended by EMA | Full involvement | |
| Ingeborg Barisic | Member | Expert recommended by EMA | No restrictions applicable to the meeting | |
| Giuseppe Capovilla | Member | Expert recommended by EMA | No restrictions applicable to the meeting | |
| Virginie Hivert | Observer | Eurordis | No restrictions | |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| | | | applicable to the meeting | |
| | EC Representative | European Commission | Full involvement | |
| Meeting run with support from relevant EMA staff | | | | |

* Experts were only evaluated against the product(s) they have been invited to talk about.