5 March 2014
EMA/COMP/14515/2014
Human Medicines Research and Development Support

Committee for Orphan Medicinal Products (COMP)

Minutes of the 7-9 January 2014 meeting

Chair: B. Sepodes

Note on access to documents

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

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1. Introduction

1.1 Adoption of the agenda, EMA/COMP/788104/2013

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting, 10-12 December 2013 EMA/COMP/687306/2013

The adoption of the Minutes was postponed.

1.3 Conflicts of Interest

The Chair asked the Committee members to declare their potential conflict of interest.

The COMP secretariat was informed as follows:

- EGAN received a grant from the sponsors of the product under agenda point 5.1.4. Nevertheless, no direct conflicts of interest have been identified for P. Evers, who represents EGAN in the COMP.

- B. Dembowska-Bagińska declared a potential conflict of interest for agenda point 2.2.6.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 Gallium [Ga-68]-N-[(4,7,10-Tricarboxymethyl-1,4,7,10-tetraazacyclododec-1-yl)acetyl]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophanyl-L-lysyl-L-threoninyl-Lcysteinyl-L-threonine-cyclic(2-7)disulfide for diagnosis of gastro-entero-pancreatic neuroendocrine tumours, Advanced Accelerator Applications SA - EMA/OD/152/13
[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:

- Authorised treatments and significant benefit

It is the understanding of the COMP that in addition to Octreoscan, there is also another medicinal product that is authorised for the diagnosis of GEPNETs in Europe (^{99m}Tc-Tektrotyd in Poland). The sponsor should clarify which products are authorised for the diagnosis of the condition in Europe.

Based on the findings of this search over authorised products, the sponsor was asked to provide a discussion on the assumption of significant benefit of the applied product over all authorised diagnostic products, supported by any available data as far as possible.

In the written response the sponsor provided revised information about the authorised diagnostic methods for the condition in the EU. In addition, the sponsor discussed the currently authorised methods vs. the applied method in order to justify the assumption on the significant benefit over these methods.

[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, gastro-entero-pancreatic neuroendocrine tumours, is a distinct medical entity and meets the criteria for orphan designation.

The intention to diagnose the condition with the medicinal product containing gallium [Ga-68]-N-[(4,7,10-Tricarboxymethyl-1,4,7,10-tetraazacyclododec-1-yl)acetyl]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophanyl-L-lysyl-L-threoninyl-Lcysteinyl-L-threonine-cyclic(2-7)disulfide was considered justified based on preclinical and preliminary clinical data showing that the product identifies somatostatin receptor positive gastro-entero-pancreatic neuroendocrine tumours. The condition is chronically debilitating and life-threatening, in particular due to the debilitating symptoms and the poor prognosis in patients with localised advanced or metastatic disease.

The population of patients eligible for diagnosis of the condition was estimated to be less than 2.8 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of diagnosis of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing gallium [Ga-68]-N-[(4,7,10-Tricarboxymethyl-1,4,7,10-tetraazacyclododec-1-yl)acetyl]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophanyl-L-lysyl-L-threoninyl-Lcysteinyl-L-threonine-cyclic(2-7)disulfide may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that the product may improve the detection rate of somatostatin receptor positive gastro-entero-pancreatic neuroendocrine tumours compared to the authorised methods. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for gallium [Ga-68]-N-[(4,7,10-Tricarboxymethyl-1,4,7,10-tetraazacyclododec-1-yl)acetyl]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophanyl-L-lysyl-L-threoninyl-Lcysteinyl-L-threonine-cyclic(2-7)disulphide, for diagnosis of gastro-entero-pancreatic neuroendocrine tumours, was adopted by consensus.

2.1.2 11-(4-Dimethylamino-3-hydroxy-6-methyl-tetrahydro-pyran-2-yloxy)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-1-oxa-6-aza-cyclopentadecane-13,15-dione

11-(4-Dimethylamino-3-hydroxy-6-methyl-tetrahydro-pyran-2-yloxy)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-1-oxa-6-aza-cyclopentadecane-13,15-dione for treatment of cystic fibrosis, Synovo GmbH - EMA/OD/156/13
[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

The sponsor was invited to clarify the relevance of the animal model to the treatment of cystic fibrosis.

- Significant benefit

The sponsor was invited to further discuss the scientific basis of the proposed extrapolation of the beneficial clinical effects of azithromycin to the proposed product for treatment of patients affected by cystic fibrosis.

When such extrapolation was sufficiently justified, the sponsor was invited to further elaborate on the reasons for a potential clinically relevant advantage of azithromycin (and indirectly of the proposed product) in the framework of the currently authorised treatment regimen for cystic fibrosis.

In the written response, and during an oral explanation before the Committee on 7 January 2014, the sponsor discussed the relevance of the animal model to the proposed indication treatment of CF. In a

preclinical model used in this application the sponsor showed reduction of inflammatory mediators in the airways of treated mice, therefore providing a proof of concept for the anti-inflammatory activity of the product.

The COMP accepted the arguments of the sponsor on significant benefit and expressed a positive opinion on significant benefit, based on a new mechanism of action that results in reducing inflammation in preclinical models related to the inflammation that takes place in cystic fibrosis. This can translate into the possibility of using the product in combination with currently authorised products. The Committee considered that this could constitute a clinically relevant advantage for the patients affected by cystic fibrosis.

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

The intention to treat the condition with the medicinal product containing 11-(4-Dimethylamino-3-hydroxy-6-methyl-tetrahydro-pyran-2-yloxy)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-1-oxa-6-aza-cyclopentadecane-13,15-dione was considered justified based on preclinical data showing anti-inflammatory activity of the product.

The condition is chronically debilitating and life threatening due to the recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure. Cystic fibrosis was estimated to be affecting approximately 0.7 in 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 11-(4-Dimethylamino-3-hydroxy-6-methyl-tetrahydro-pyran-2-yloxy)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-1-oxa-6-aza-cyclopentadecane-13,15-dione may be of significant benefit to those affected by the condition. This is based on a new mechanism of action that results in reducing inflammation in preclinical models related to the inflammation that takes place in cystic fibrosis. This can translate into the possibility of using the product in combination with currently authorised products. The Committee considered that this could constitute a clinically relevant advantage for the patients affected by cystic fibrosis.

A positive opinion for 11-(4-Dimethylamino-3-hydroxy-6-methyl-tetrahydro-pyran-2-yloxy)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-1-oxa-6-aza-cyclopentadecane-13,15-dione, for treatment of cystic fibrosis, was adopted by consensus.

2.1.3 **Cysteamine** for treatment of cystic fibrosis, Istituto Europeo per la Ricerca sulla Fibrosi Cistica - ONLUS - EMA/OD/159/13

[Co-ordinator: A. Lorence]

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

- Number of people affected

The sponsor should describe and justify the methodology used for the prevalence calculation, taking into the consideration the duration of the condition, and to provide an updated calculation of time-point prevalence at the time the designation is made.

- 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 based on data that would justify a clinically relevant advantage or major contribution to patient care.

In the written response, and during an oral explanation before the Committee on 7 January 2014, the sponsor further elaborated on the two issues as requested. With regards to the justification of significant benefit, additional in vitro data in cystic fibrosis cell lines and in cells from CF patients were discussed.

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

The intention to treat the condition with the medicinal product containing cysteamine was considered justified based on preclinical data showing restoration of the defective chloride transport across cell membranes and reduction of inflammation in models of cystic fibrosis.

The condition is chronically debilitating and life threatening due to the recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure. The condition was estimated to be affecting approximately 0.7 in 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 cysteamine may be of significant benefit to those affected by the condition. The sponsor has provided data that demonstrate that administration of the proposed product results into improvement of the function of the defective chloride transport channel in the most prevalent mutation in cystic fibrosis, F508D. This offers the potential of treating one of the main pathogenetic events of F508D cystic fibrosis, differently from the currently authorised treatments that only act on the symptoms. The Committee considered that this could constitute a clinically relevant advantage to the patients affected by cystic fibrosis.

A positive opinion for cysteamine, for treatment of cystic fibrosis, was adopted by consensus.

2.1.4 Product for treatment of acute myeloid leukaemia - EMA/OD/150/13

[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 treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of acute myeloid leukaemia, the sponsor should further elaborate on:

- the results obtained in vitro on HL60 cell line;
- the relevance of the in vitro data for the treatment of acute myeloid leukaemia, and the interpretation of the results obtained in the experiments;
- the absence of data in relevant in vivo preclinical models of AML or preliminary clinical settings in patients affected by the proposed condition.

- Number of people affected

The sponsor should justify the duration of the disease, and clarify the methodology for drawing the final conclusion of 1 to 2 in 10,000.

- Significant benefit

The arguments on significant benefit are based on a new mechanism of action and the potential for improved efficacy in combination with de-methylating agents in patients not eligible for high intensity chemotherapy.

The sponsor was requested to elaborate on the results of the preclinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication and detail any clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, and during an oral explanation before the Committee, the sponsor further elaborated on the prevalence issue, and stated that this is in line with prevalence data appearing in Orphanet and data pertaining to the US. With regards to the medical plausibility, the sponsor discussed the possible effects of other surrogate products with the same mechanism of action in general, and outlined the strategy for developing the product. With regards to data with the specific product, some new in vitro data were discussed, and arguments on synergy with demethylating agents were reiterated as in the original application. With regards to the potential use in in vivo settings, the limitations of xenotransplantation models were mentioned, and the sponsor concluded that they are not confident that the use of such models will yield helpful observations. Finally with regards to the assumption on significant benefit, the sponsor did not provide any new data compared to the initial submission.

The COMP considered that the principle of having, as far as possible, data with the specific product in the specific indication in order to accept the intention to treat and significant benefit was not met. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 January 2014, prior to final opinion.

2.1.5 Product for treatment for acute myeloid leukaemia - EMA/OD/160/13
[Co-ordinator: D. O'Connor]

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 treat

The constituents of the proposed product were not clear. To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment for acute myeloid leukaemia, the sponsor should further elaborate on:

a) the particulars of the product in detail; the sponsor should specify any other plants that are used in its preparation, the form, solvents and excipients used, and provide as far as possible information for the herbal preparation according to the updated guideline EMA/HMPC/CHMP/CVMP/287539/2005 Rev.1

b) the details and relevance of the K562 model used for the treatment of the proposed condition as applied for designation

c) the clinical particulars and endpoints studied in the case study presented in section D3.

- Number of people affected

The sponsor should recalculate the prevalence taking into consideration the duration of the proposed condition.

- Significant benefit

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

The sponsor was requested to provide evidence that supports the proposed claims on a novel mechanism based on data with the specific product subject of this application, provide a comparative discussion vis a vis the authorised products and discuss the expected position of the product in the management of AML patients in the context of current European guidelines for the treatment of the condition.

In the written response, and during an oral explanation before the Committee, the sponsor further elaborated on a mixture of eight herbs and the case study discussed in the application, but did not provide the requested details of the experiments presented. The significant benefit was a generic discussion of safety and convenience of oral use without any support from any relevant data. The claim of a clinically relevant advantage or a major contribution to patient care was not endorsed by the Committee. The Committee was not in a position to acknowledge these claims given the absence of any data.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 January 2014, prior to final opinion.

2.1.6 **Eculizumab** for prevention of delayed graft function after renal transplantation, Alexion Europe SAS - EMA/OD/154/13

[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:

- Intention to diagnose, prevent or treat

Ischemia reperfusion injury (IRI) is a cause of delayed graft function (DGF) in kidney transplantation. In addition, the pathogenetic mechanisms of IRI and DGF are also involved in organ rejection after transplantation. The sponsor presented preclinical data on ischemia reperfusion injury and early clinical data in patients identified as having delayed graft function, within the development of the product for the prevention of antibody-mediated rejection after solid organ transplantation.

The sponsor was invited to clarify the main therapeutic target of the proposed product in this application, taking into account the mechanism of action of the product, and the current classification and case-definition of ischemia reperfusion injury and delayed graft function.

In the written response, and during an oral explanation before the Committee on 8 January 2014, the sponsor discussed the pathogenesis of delayed graft function (DGF) in relation to the pharmacological action of the product. The main cause of DGF is ischemia-reperfusion injury (IRI). Some degree of IRI occurs during all transplantations, due to the fact that the explanted organ spends a variable time outside the body before being transplanted and perfused. The COMP was of the opinion that due to the

mechanism of action of eculizumab targeting the complement cascade activated during IRI, prevention of DGF as applied for in this application covers from a scientific plausibility and a regulatory perspective indications such as prevention or treatment of IRI at the same time.

The COMP was of the opinion that the broader indication "delayed graft function after solid organ transplantation" better reflects the possible intended use of the product beyond kidney transplantation. The sponsor accepted the change of indication.

The COMP asked to the sponsor a revision of the estimated population at risk of the broadened indication "delayed graft function after solid organ transplantation". Based on the data from European transplant registries, the sponsor proposed a value for the estimated population at risk of 0.6 in 10,000 in the EU. This estimate was accepted by the COMP.

Based on all the above, the COMP issued a positive opinion for eculizumab.

The Committee agreed that the condition, delayed graft function after solid organ transplantation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to prevent the condition with the medicinal product containing eculizumab was considered justified based on preclinical models of ischemia reperfusion injury showing increased survival with the proposed product, and on clinical cases showing improved clinical outcome in delayed graft function.

The condition is chronically debilitating and life threatening due to the increased risk of graft rejection, dependence on dialysis, and increased mortality linked to organ failure. The population of patients eligible for prevention of delayed graft function after solid organ transplantation was estimated to be not more than 0.6 in 10,000 people in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of prevention that has been authorised in the European Union for the population at risk of developing the condition.

A positive opinion for eculizumab, for prevention of delayed graft function after solid organ transplantation, was adopted by consensus.

2.1.7 Diacerein for treatment of epidermolysis bullosa, Prof. Johann W. Bauer - EMA/OD/149/13 [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 epidermolysis bullosa, the sponsor should further elaborate on:

  - the preliminary clinical data in particular the trial design and the interpretability of the results in the epidermolysis patients as the therapeutic impact of the proposed product in these patients does not appear to be clearly established.

In the written response, and during an oral explanation before the Committee on 8 January 2014, the sponsor further elaborated on the relevance of the clinical data presented. The COMP concluded that the intention to treat the condition with the medicinal product containing diacerein was considered justified based on in vitro data and preliminary clinical data in patients with the condition.

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

The intention to treat the condition with the medicinal product containing diacerein was considered justified based on in vitro data and preliminary clinical data in patients with the condition.

The condition is life-threatening and chronically debilitating due to in particular severe generalised blistering resulting in poor quality of life and shortened life expectancy. The condition was estimated to be affecting approximately 0.25 in 10,000 people in the European Union, at the time the application was made; the sponsor has used a literature search to help establish the prevalence in Europe.

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 diacerein, for treatment of epidermolysis bullosa, was adopted by consensus.

2.1.8 Product for treatment of perinatal asphyxia - EMA/OD/077/13

[Co-ordinator: K. Westermark]

The application was withdrawn by the sponsor on 19 December 2013 prior to responding to the list of questions adopted at the December 2013 COMP meeting.

2.1.9 Mixture of recombinant human IgG1 monoclonal antibodies against human cytomegalovirus (CMV) envelope glycoproteins (one mAb binds to gH/gL and another mAb binds to the gH/gL/UL128/UL130/UL131 complex but not gH/gL alone) for prevention of congenital cytomegalovirus infection following primary cytomegalovirus infection, Roche Registration Limited - EMA/OD/134/13

[Co-ordinator: N. Sypsas]

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 congenital cytomegalovirus infection following primary cytomegalovirus infection due to the very early stage of development with the combination of MCMV5322A and MCMV3068A recombinant monoclonal antibodies in preventing maternal-foetal transmission of CMV in pregnant women who acquire primary CMV infection during pregnancy the sponsor should further elaborate on:

  - the results obtained in vitro cell lines with their product in the prevention of congenital cytomegalovirus infection following primary cytomegalovirus infection;
  - preliminary clinical safety data from both pre-clinical and clinical studies in healthy volunteer and renal transplant patients would indicate that the product may not be safe to use in pregnant women. The sponsor was asked to elaborate on these safety findings in view of the fact that it is this target patient population to whom the treatment is intended to be administered. The sponsor was asked to further elaborate on the reported findings of the phase II study involving 20 recipients of renal transplant.

In the written response, and during an oral explanation before the Committee on 8 January 2014, the sponsor clarified the origin of the cells used to test the properties of the product proposed. The sponsor

then further clarified the safety concerns raised by the COMP in the Loq. Following further discussion and taken into account the stage of development, the COMP considered the data to be sufficient to support a designation. It was concluded that the intention to prevent the condition with the medicinal product containing mixture of recombinant human IgG1 monoclonal antibodies against human cytomegalovirus envelope glycoproteins was considered justified based on in vitro data using foetal cell lines.

For the purpose of orphan designation, the Committee for Orphan Medicinal Products (COMP) considered that the active substance should be renamed as "mixture of recombinant human IgG1 monoclonal antibodies against human cytomegalovirus envelope glycoproteins".

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

The intention to prevent the condition with the medicinal product containing mixture of recombinant human IgG1 monoclonal antibodies against human cytomegalovirus envelope glycoproteins was considered justified based on in vitro data using foetal cell lines.

The condition is chronically debilitating and life threatening due to the high mortality rate in newborns with severe cytomegalovirus infection and neuro-sensory sequelae among survivors. The population of patients eligible for prevention of the condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for mixture of recombinant human IgG1 monoclonal antibodies against human cytomegalovirus envelope glycoproteins, for prevention of congenital cytomegalovirus infection following primary cytomegalovirus infection, was adopted by consensus.

2.1.10 Product for treatment of recent-onset Type 1 Diabetes with residual beta cell function - EMA/OD/157/13
[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:

- Intention to diagnose, prevent or treat

According to the legal basis of orphan designation and in particular guideline ENTR/6283/00 Rev03, a subset of a disease which, when considered as a whole, has a prevalence greater than 5 in 10 000, could be considered a valid condition if patients in that subset present distinct and unique evaluable characteristic(s) with a plausible link to the condition and if such characteristics are essential for the medicinal product to carry out its action.

In addition, the guideline states that "different degrees of severity or stages of a disease would generally not be considered as distinct conditions". The same applies to "subsets of patients in whom the medicinal product is expected to show a favourable benefit/risk".

It is the opinion of the COMP that the proposed indication "type 1 diabetes mellitus patients with residual beta-cell function" is a stage rather than a subset of type I diabetes mellitus type 1 diabetes mellitus patients with residual beta-cell function should therefore be justified as a distinct medical entity or a valid subset.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of recent-onset type 1 diabetes with residual beta cell function, the sponsor should further elaborate on the relevance of the preliminary clinical model used for the treatment of recent-onset type 1 diabetes with residual beta cell function, and the interpretation of the results obtained in the experiments.

- Number of people affected

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

The sponsor should justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor should describe and justify the methodology used for the prevalence calculation.

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

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

In its written responses and during the oral hearing the sponsor discussed at length the validity of the proposed indication within the framework of standard of care of type I diabetic patients. There was a discussion on the validity of the proposed condition within the framework of the Orphan legislation. The sponsor did not agree with the principle interpretation of the guidance document regarding the definition of a distinct medical entity. In this case the indication proposed was considered to be a stage of severity of type I diabetes by the COMP.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 9 January2014, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1 3-Chloro-4-fluorophenyl-[4-fluoro-4-{[(5-methylpyrimidin-2-ylmethyl) amino]methyl}piperidin-1-yl]methanone for treatment of Rett syndrome, Neurolixis UK Ltd. - EMA/OD/163/13

[Co-ordinator: I. Bradinova]

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

The intention to treat the condition with the medicinal product containing 3-Chloro-4-fluorophenyl-[4-fluoro-4-{[(5-methylpyrimidin-2-ylmethyl) amino]methyl}piperidin-1-yl]methanone was considered justified based on in vivo pre-clinical data in a validated model of the condition which showed improvement in breathing irregularities.

The condition is chronically debilitating and life-threatening particularly due to severe locomotor disability, sleep disturbances, seizures, respiratory complications, development of arrhythmias resulting in decreased life-expectancy. The condition was estimated to be affecting less than 1 in 10,000 people 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 3-Chloro-4-fluorophenyl-[4-fluoro-4-{[(5-methylpyrimidin-2-ylmethyl) amino]methyl}piperidin-1-yl]methanone, for treatment of Rett syndrome, was adopted by consensus.

2.2.2 ^{68}Ga-2,2'-(7-(4-((S)-1-((4S,7S,10S,13R,16S,19R)-4-((R)-1-amino-3-(4-hydroxyphenyl)-1-oxopropan-2-ylcarbamoyl)-10-(4-aminobutyl)-16-(4-((S)-2,6-dioxohexahydropyrimidine-4-carboxamido)benzyl)-7-((R)-1-hydroxyethyl)-6,9,12,15,18-pentaoxo-13-(4-ureidobenzyl)-1,2-dithia-5,8,11,14,17-pentaazacycloicosan-19-ylamino)-3-(4-chlorophenyl)-1-oxopropan-2-ylamino)-1-carboxy-4-oxobutyl)-1,4,7-triazonane-1,4-diyl)diacetic acid for diagnosis of gastro-entero-pancreatic neuroendocrine tumours (GEP NETs), OctreoPharm Sciences GmbH - EMA/OD/173/13
[Co-ordinator: K. Kubáčková]

The Committee agreed that the condition, gastro-entero-pancreatic neuroendocrine tumours, is a distinct medical entity and meets the criteria for orphan designation.

The intention to diagnose the condition with the medicinal product containing ^{68}Ga-2,2'-(7-(4-((S)-1-((4S,7S,10S,13R,16S,19R)-4-((R)-1-amino-3-(4-hydroxyphenyl)-1-oxopropan-2-ylcarbamoyl)-10-(4-aminobutyl)-16-(4-((S)-2,6-dioxohexahydropyrimidine-4-carboxamido)benzyl)-7-((R)-1-hydroxyethyl)-6,9,12,15,18-pentaoxo-13-(4-ureidobenzyl)-1,2-dithia-5,8,11,14,17-pentaazacycloicosan-19-ylamino)-3-(4-chlorophenyl)-1-oxopropan-2-ylamino)-1-carboxy-4-oxobutyl)-1,4,7-triazonane-1,4-diyl)diacetic acid was considered justified based on pre-clinical in vivo data using a valid model.

The condition is chronically debilitating and life-threatening, in particular due to the debilitating symptoms and the poor prognosis in patients with localised advanced or metastatic disease. The condition was estimated to be affecting approximately 2.7 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of diagnosis of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ^{68}Ga-2,2'-(7-(4-((S)-1-((4S,7S,10S,13R,16S,19R)-4-((R)-1-amino-3-(4-hydroxyphenyl)-1-oxopropan-2-ylcarbamoyl)-10-(4-aminobutyl)-16-(4-((S)-2,6-dioxohexahydropyrimidine-4-carboxamido)benzyl)-7-((R)-1-hydroxyethyl)-6,9,12,15,18-pentaoxo-13-(4-ureidobenzyl)-1,2-dithia-5,8,11,14,17-pentaazacycloicosan-19-ylamino)-3-(4-chlorophenyl)-1-oxopropan-2-ylamino)-1-carboxy-4-oxobutyl)-1,4,7-triazonane-1,4-diyl)diacetic acid may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical data that demonstrate improved imaging with their product of tumours. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for ^{68}Ga-2,2'-(7-(4-((S)-1-((4S,7S,10S,13R,16S,19R)-4-((R)-1-amino-3-(4-hydroxyphenyl)-1-oxopropan-2-ylcarbamoyl)-10-(4-aminobutyl)-16-(4-((S)-2,6-dioxohexahydropyrimidine-4-carboxamido)benzyl)-7-((R)-1-hydroxyethyl)-6,9,12,15,18-pentaoxo-13-(4-ureidobenzyl)-1,2-dithia-5,8,11,14,17-pentaazacycloicosan-19-ylamino)-3-(4-chlorophenyl)-1-

oxopropan-2-ylamino)-1-carboxy-4-oxobutyl)-1,4,7-triazonane-1,4-diyl)diacetic acid, for diagnosis of gastro-entero-pancreatic neuroendocrine tumours, was adopted by consensus.

2.2.3 A phosphorothioate oligonucleotide targeted to apolipoprotein C-III for treatment of familial chylomicronemia syndrome, Isis USA Ltd - EMA/OD/180/13
[Co-ordinator: A. Magrelli]

For the purpose of orphan designation, the Committee for Orphan Medicinal Products (COMP) considered that the active substance should be renamed as "phosphorothioate oligonucleotide targeted to apolipoprotein C-III".

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

The intention to treat the condition with the medicinal product containing phosphorothioate oligonucleotide targeted to apolipoprotein C-III was considered justified based on preclinical and preliminary clinical data in treated patients affected by the condition who responded to treatment with reduction of triglyceride levels.

The condition is life threatening and chronically debilitating due to recurrent episodes of acute pancreatitis which may lead to pancreatic insufficiency resulting in malabsorption, failure to thrive and diabetes mellitus. The condition was estimated to be affecting less than 0.1 in 10,000 people in the European Union, at the time the application was made.

In addition, although a satisfactory method of treatment of the condition has been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing phosphorothioate oligonucleotide targeted to apolipoprotein C-III may be of significant benefit to those affected by the condition. This was based on preclinical and preliminary clinical data showing that the product has an alternative mechanism of action, which is expected to be effective in a broader population affected by the condition than the authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for phosphorothioate oligonucleotide targeted to apolipoprotein C-III, for treatment of familial chylomicronemia syndrome, was adopted by consensus.

2.2.4 Product for treatment of Familial Amyloid Polyneuropathy - EMA/OD/098/13
[Co-ordinator: J. Torrent-Farnell]

The Committee considered that the following issues require clarification by the sponsor:

- Proposed indication

With a reference to the recommendations of the international society of amyloidosis (Sipe JD et al, Amyloid 2012), the sponsor is invited to amend the current proposed orphan indication to "treatment of ATTR-amyloidosis".

- Number of people affected by the condition

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

The sponsor is also invited to recalculate the prevalence for ATTR-amyloidosis.

The COMP agreed on a list of issues for a written response and during an oral explanation before the Committee at the February meeting.

Post-meeting note:

The COMP adopted the list of issues via written procedure on 16 January 2014.

2.2.5 Asp-Arg-Val-Tyr-Ile-His-Pro for treatment of Duchenne muscular dystrophy, Gregory Fryer Associates Ltd - EMA/OD/162/13
[Co-ordinator: P. Evers]

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

The intention to treat the condition with the medicinal product containing Asp-Arg-Val-Tyr-Ile-His-Pro was considered justified based on data generated in an in vivo pre-clinical study in a valid model of the condition.

The condition is life-threatening and chronically debilitating due to an inexorable progressive weakness occurring throughout the proximal musculature affecting the muscles of the hips, thighs, pelvic area and shoulders and eventually affecting all voluntary muscles. This is followed by dilated cardiomyopathy and cardiac output decrease, leading to terminal respiratory or cardiac failure often by late adolescence. Patients rarely live beyond the age of 30 years. The condition was estimated to be affecting approximately 0.5 in 10,000 people in the European Union, at the time the application was made; this was based on an extensive literature search.

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 Asp-Arg-Val-Tyr-Ile-His-Pro, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.2.6 Autologous dendritic cells pulsed with tumour antigen-derived synthetic peptides (MAGE-1, HER-2, AIM-2, TRP-2, gp-100, and interleukin-13 receptor alpha) for treatment of glioma, Diamond BioPharm Limited - EMA/OD/174/13
[Co-ordinator: K. Kubáčková]

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

The intention to treat the condition with the medicinal product containing autologous dendritic cells pulsed with tumour antigen-derived synthetic peptides (MAGE-1, HER-2, AIM-2, TRP-2, gp-100, and interleukin-13 receptor alpha) was considered justified based on preliminary clinical studies showing a favourable effect of survival in treated patients affected by the condition.

The condition is chronically debilitating due to symptoms caused by compression by the tumour on the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality and cognitive impairment, and life-threatening with 5-year survival of less than 5% for glioblastoma multiforme patients. The condition was estimated to be affecting approximately not more than 2 in 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 autologous dendritic cells pulsed with tumour antigen-derived synthetic peptides (MAGE-1, HER-2, AIM-2, TRP-2, gp-100, and interleukin-13 receptor alpha) may be of significant benefit to those affected by the condition, on the basis of improved efficacy. The sponsor has provided preliminary clinical data regarding prolonged survival in newly diagnosed patients with the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous dendritic cells pulsed with tumour antigen-derived synthetic peptides (MAGE-1, HER-2, AIM-2, TRP-2, gp-100, and interleukin-13 receptor alpha), for treatment of glioma, was adopted by consensus.

2.2.7 Product for prevention of bronchopulmonary dysplasia - EMA/OD/161/13

[Co-ordinator: K. Westermark]

The Committee considered that the following issues require clarification by the sponsor:

- Intention to prevent

To establish correctly if there exists a scientific rationale for the development of the proposed product for prevention of bronchopulmonary dysplasia, the sponsor should further elaborate on the literature studies presented in this application. In particular the sponsor is invited to discuss the level of overlap between treatment of primary apnoea of the newborn as cause of BPD vs. prevention of BPD from other causes in literature and in the other studies presented.

- Number of people affected

The sponsor calculated the point prevalence of BPD. Point prevalence is a valid epidemiologic index for a condition of short duration, however for the preventive indication the sponsor is invited to provide the estimated population at risk of BPD rather than the population affected by BPD.

In addition the definition of BPD is usually based on gestational age rather than birth weight, therefore the sponsor is invited to calculate the population at risk based on gestational age (a cut-off of 32 weeks is usually considered acceptable, according to the NIH definition of BPD) rather than birth weight.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the March meeting.

2.2.8 Product for treatment of pancreatic cancer - EMA/OD/164/13

[Co-ordinator: B. Bloechl-Daum]

The Committee considered that the following issues require clarification by the sponsor:

- Significant benefit

The arguments on significant benefit are based on a new mechanism of action. The sponsor is invited to further elaborate how this novel mechanism of action may be translated into a clinically relevant advantage over the existing authorized treatments for the condition.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the March meeting.

2.2.9 Product for prevention of antibody-mediated rejection after solid organ transplantation - EMA/OD/176/13
[Co-ordinator: K. Westermark]

The Committee considered that the following issues require clarification by the sponsor:

- Intention to diagnose, prevent or treat

Antibody mediated rejection after solid organ transplantation should be justified as a distinct medical entity or a valid subset, or amended to the broader condition "rejection after solid organ transplantation". Note that this is for the purpose of orphan medicinal product designation; your attention is drawn to the Orphan regulations and guidelines to clarify this (ENTR/6283/00). Reasons for broadening the condition are related to the lack of possibility of separating the antibody-mediated from the cell-mediated component in the pathogenesis and clinical presentation of rejection after solid organ transplantation, as the two components almost invariably coexist.

In addition, to establish correctly if there exists a scientific rationale for the development of the proposed product for prevention of rejection after solid organ transplantation, the sponsor should further elaborate on:

  - the results of the preclinical models of heart and kidney transplantation showing a seemingly similar effects of the product and the negative control, with beneficial effect of the proposed product only when added to immunosuppressive agents;
  - the clinical characteristics and concomitant medications of the patients studied in the case reports and in the ITT study.

- Number of people affected

When the sponsor broadens the indication to rejection after solid organ transplantation, revised calculations of the population at risk should be provided.

- Significant benefit

Broadening the condition to "rejection after solid organ transplantation" implies describing the existing authorised methods for prevention of solid organ transplantation and discussing the significant benefit of the proposed product in relation to such methods. The sponsor is invited to discuss these two sections of the application, and to present and discuss any available preclinical and/or clinical data supporting the significant benefit of the product.

In addition, the safety issues related to the use of the proposed product and the potential reduction of the need of the currently authorised immunosuppressants should be discussed.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the March meeting.

2.2.10 Product for prevention of graft rejection following solid organ transplantation - EMA/OD/168/13
[Co-ordinator: K. Westermark]

The Committee considered that the following issues require clarification by the sponsor:

- Significant benefit

In order to establish the significant benefit of the proposed product the sponsor is invited to further justify the extrapolation from the literature data of the published preclinical (and clinical studies) with other mesenchymal stromal cells to the sponsor's product.

In addition, the sponsor should provide any available details and results from the on-going open multi-centre clinical trial in order to further support the significant benefit assumption, in particular regarding the potential reduction of the need for concomitant immunosuppressive therapies.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the March meeting.

2.2.11 N-({Carbamoylmethyl-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-carbamoyl}-methyl)-2-[2-(2-fluoro-phenyl)-ethylamino]-N-isobutyl-acetamide for treatment of optic neuritis, Bionure Farma SL - EMA/OD/175/13
[Co-ordinator: V. Saano]

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

The intention to treat the condition with the medicinal product containing N-({Carbamoylmethyl-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-carbamoyl}-methyl)-2-[2-(2-fluoro-phenyl)-ethylamino]-N-isobutyl-acetamid was considered justified based on data obtained from a valid pre-clinical model.

The condition is chronically debilitating due to the development of partial or complete blindness dependant on the underlying aetiology. The condition was estimated to be affecting approximately 0.5 in 10,000 people 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.

Post-meeting note:

A positive opinion for N-({Carbamoylmethyl-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-carbamoyl}-methyl)-2-[2-(2-fluoro-phenyl)-ethylamino]-N-isobutyl-acetamid, for treatment of optic neuritis, was adopted by consensus via written procedure on 15 January 2014.

2.2.12 Pioglitazone for treatment of adrenoleukodystrophy, Minoryx Therapeutics S.L. - EMA/OD/170/13
[Co-ordinator: V. Tillmann]

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

The intention to treat the condition with the medicinal product containing pioglitazone was considered justified based on pre-clinical data obtained from a valid in vivo model.

The sponsor has established that the condition is chronically debilitating and life threatening. Three phenotypes of adrenoleukodystrophy result in different degrees of severity. The most severe, childhood cerebral adrenoleukodystrophy, affects only males in childhood and is associated with behavioural abnormalities, including inattention, hyperactivity, and emotional lability. The course is progressive with seizures, spastic tetraplegia, and dementia developing within months of onset. Once the neurologic manifestations appear, progression of the illness is usually rapid with death occurring

between the ages of 5 and 10 years. In the second form, adrenomyeloneuropathy (AMN), symptoms appear between 20 and 30 years of age. Patients present with stiffness and clumsiness in their legs and gait disturbance becomes severe within 10 to 15 years, requiring the use of a cane or a wheelchair. AMN patients die within 20 years of onset. The mildest form affects seventy percent of adrenoleukodystrophy patients and presents with primary adrenocortical insufficiency but, nearly all patients with this phenotype develop AMN later in adulthood.

The condition was estimated to be affecting approximately 0.35 in 10,000 people 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 pioglitazone, for treatment of adrenoleukodystrophy, was adopted by consensus.

2.2.13 Product for treatment of cystic fibrosis - EMA/OD/166/13
[Co-ordinator: V. Saano]

The Committee considered that the following issues require clarification by the sponsor:

- Significant benefit

The sponsor is invited to discuss the significant benefit of the proposed product versus the currently authorised products for the treatment of the condition, including but not limited to, dornase alpha. For the purpose of this discussion, the sponsor is invited to present and discuss the results of any available preclinical and/or clinical data in order to support the significant benefit assumption in the context of the current therapeutic management of patients.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the March meeting.

2.2.14 Recombinant human acid ceramidase for treatment of Farber disease, QOL Therapeutics EU Ltd - EMA/OD/167/13
[Co-ordinator: H. Metz]

The Committee agreed that the condition, Farber disease, 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 acid ceramidase was considered justified based on preclinical results. Patients with Farber disease have a deficiency of acid ceramidase leading to an accumulation of ceramide in tissues. The product is intended to replace the naturally deficient acid ceramidase and the preclinical results support that the product lowers the ceramide levels.

The condition is chronically debilitating due to subcutaneous nodules, painful and progressively deformed joints, and hoarseness. In addition, several organs may be affected leading to life-threatening complications in the most severe cases of the disease. The condition was estimated to be affecting less than 0.01 in 10,000 people 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 acid ceramidase, for treatment of Farber disease, was adopted by consensus.

2.2.15 Product for treatment of glycogen storage disease type II (Pompe's disease) - EMA/OD/148/13
[Co-ordinator: A. Corrêa Nunes]

The Committee considered that the following issues require clarification by the sponsor:

- Number of people affected

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

The sponsor should support the information provided on the prevalence of late-onset form of the disease with all available data. Taking this into account, the sponsor should re-calculate the final prevalence estimate based on all relevant data.

The COMP agreed on a list of issues for a written response only.

Post-meeting note:

The COMP adopted the list of issues via written procedure on 16 January 2014.

2.2.16 Product for prevention of bronchopulmonary dysplasia in premature neonates of less than 32 weeks of gestational age - EMA/OD/172/13
[Co-ordinator: K. Westermark]

The Committee considered that the following issues require clarification by the sponsor:

- 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 in premature neonates of less than 32 weeks of gestational age, the sponsor should clarify whether the mechanism of action of the product is targeting mainly treatment of RDS, resulting in prevention of BPD consequently. The sponsor should discuss the plausibility of using the product for BPD.

In addition the sponsor is invited to further elaborate on the results of the lamb model, where the proposed product reduced inflammation but did not show significant results on clinical and functional parameters.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the March meeting.

2.2.17 Ruxolitinib for treatment of Polycythaemia vera, Novartis Europharm Limited - EMA/OD/169/13
[Co-ordinator: L. Gramstad]

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

The intention to treat the condition with the medicinal product containing ruxolitinib was considered justified based on preclinical in vivo data and preliminary clinical data in patients with the condition.

The condition is chronically debilitating and life threatening due to thromboembolic and haemorrhagic complications, as well as malignant transformation and progression to myelofibrosis. The condition was estimated to be affecting less than 5 in 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 ruxolitinib may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate the use of the product in patients who were refractory to hydroxyurea which is used as a first line therapy in this condition. The Committee considered that this constitutes a clinically relevant advantage.

Post-meeting note:

A positive opinion for ruxolitinib, for treatment of polycythaemia vera, was adopted by consensus via written procedure on 16 January 2014.

2.2.18 Product for treatment of systemic sclerosis - EMA/OD/179/13
[Co-ordinator: K. Westermark]

The Committee considered that the following issues require clarification by the sponsor:

- 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 systemic sclerosis, the sponsor should further elaborate on:

Preclinical data

- the preventive settings of the models used and their relevance for the treatment of the condition as applied for designation;
- the methodology used in the pre-clinical studies including statistical analysis;
- the reported effects of the negative control serum and the differences to the product as applied for designation;
- the results from these studies and the interpretation of the results obtained in the experiments.

Clinical data

The sponsor is requested to further elaborate on the results from the preliminary clinical studies in patients affected by systemic sclerosis and particularly to present and discuss the "raw data" measurements of the primary and secondary endpoints. This includes reporting the mean values and individual data of the MRSS score.

- Significant benefit

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

The sponsor is requested to provide any data they may have to support the claims above, and provide a comparative discussion versus all authorised products for the proposed condition as applied for designation.

It is well known that extrapolation from preclinical or early clinical studies cannot predict the safety of a product in its clinical setting, thus more relevant data is mandatory to justify safety arguments in most cases. The sponsor should further elaborate on the potential risks with the product, and how this compares with the safety profile of the current authorised medicinal products for the same condition.

The COMP agreed on a list of issues for a written response and during an oral explanation before the Committee at the February meeting.

Post-meeting note:

The COMP adopted the list of issues via written procedure on 16 January 2014.

2.2.19 Product for treatment of amyotrophic lateral sclerosis - EMA/OD/178/13
[Co-ordinator: V. Stoyanova]

The Committee considered that the following issues require clarification by the sponsor:

- Intention to diagnose, prevent or treat

The sponsor is requested to elaborate on the following points:

a) the relevance of all constituents contained in the product to the treatment of the proposed condition as applied for designation, including, but not limited to, the contents within the immunoglobulin IgG range;

b) the specific mechanism of action of the product and its relevance to the proposed condition;

c) the preclinical data in the SOD1 model, in particular by comparing and contrasting the effects versus control serum;

d) the methodology of the preclinical studies, and the results of all endpoints studied;

e) the methodology of the clinical study, including e.g. duration of the treatment and outcome measures.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action. The sponsor is requested to further discuss the arguments and to elaborate on how an alternative mechanism may be translated into a clinically relevant advantage or major contribution to patient care.

The sponsor is also invited to position the proposed product in the treatment of the patients *vis a vis* all authorised products for the proposed condition as applied for designation.

It is well known that extrapolation from preclinical or early clinical studies cannot predict the safety of a product in its clinical setting, thus more relevant data is mandatory to justify safety arguments in most cases. The sponsor should further elaborate on the potential risks with the product, and how this compares with the safety profile of the current authorised medicinal products for the same condition.

The COMP agreed on a list of issues for a written response and during an oral explanation before the Committee at the February meeting.

Post-meeting note:

The COMP adopted the list of issues via written procedure on 16 January 2014.

2.2.20 Product for treatment of small cell lung cancer - EMA/OD/094/13
[Co-ordinator: K. Westermark]

The Committee considered that the following issues require clarification by the sponsor:

- Intention to treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of small cell lung cancer, the sponsor should further elaborate on the methodology and the results of the preclinical study, including:

- the reasons for treating the different groups of animals with a different protocol (e.g. in relation to start and duration of the treatment) and the methodology for analysing the groups together and normalizing the tumour volumes after treatment;

- the seemingly milder effect with the higher of the two doses of the proposed product vs. the lower dose.

- Significant benefit

One of the significant benefit grounds proposed by the sponsor is the selectivity of the product for SSTR2 positive cells, with the claim that non-small cell lung cancer cells would not express SSTR2. On the other hand, it seems that the sponsor is conducting a clinical trial with the product in non-small cell lung cancer. The sponsor is invited to clarify the claimed specificity of the product for small cell lung cancer in relation to the expression of SSRT2 receptors. The discussion on the selectivity of the product is relevant also to the establishment of the medical plausibility.

In addition the sponsor is invited to discuss the reasons for adding the proposed product to a regimen of carboplatin and taxol in the animal study, taking into account that taxol (paclitaxel) is not part of the recommended regimens for the treatment of small cell lung cancer (see ESMO guidelines).

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the March meeting.

2.3. Appeal procedure

2.3.1 5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N4-[2-(isopropylsulfonyl)phenyl]-2,4-pyrimidinediamine for treatment of non-small cell lung carcinoma (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive, Novartis Europharm Limited - EMA/OD/113/13
[Co-ordinator: D. O'Connor]

The COMP noted that the the grounds for appeal to the COMP negative opinion adopted on 18 November 2013 are pending.

2.4. Evaluation on-going

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

2.5. Validation on-going

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

3. Requests for protocol assistance

3.1. 1st reports

The protocol assistance advice was discussed for final adoption in the forthcoming meetings for the following indications:

3.1.1 Product for treatment of chronic lymphocytic leukaemia

3.1.2 Product for treatment of follicular lymphoma

3.2. On-going procedures

The Committee noted the following on-going protocol advice procedures:

3.2.1 Product for treatment of spinal cord injury

3.2.2 Product for treatment of tuberculosis

3.2.3 Product for treatment of acute lymphoblastic leukaemia

4. Overview of applications

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

COMP co-ordinators were appointed for eleven upcoming applications. Two experts were appointed for three 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 Deltyba ((R)-2-Methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole) for treatment of tuberculosis; Otsuka Novel Products GmbH (EU/3/07/524) [Co-ordinator: V. Stoyanova] [Expert: M. Ameziane]

The COMP noted the CHMP positive opinion adopted at the December 2013 CHMP meeting. 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:

- Significant benefit

The sponsor is invited to further elaborate on the significant benefit of the proposed product versus all products currently authorised in the EU for the treatment of MDR-TB and in the context of the current management of this condition. The discussion on significant benefit should be supported by any available data.

The sponsor provided a written response, and discussed the issues raised in the List of questions at an oral explanation before the Committee on 7 January 2014.

The COMP concluded that the proposed therapeutic indication "Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Consideration should be given to official guidance on the appropriate use of antibacterial agents" falls entirely within the scope of the orphan indication of the designated orphan medicinal product.

The prevalence of tuberculosis was estimated to remain below 5 in 10,000 at the time of the review of the designation criteria.

The condition is life-threatening and chronically debilitating due to pulmonary and extrapulmonary disease that can lead to irreversible lung damage and death if left untreated. The infection with drug resistant strains carries a worse prognostic and further decreases life expectancy in infected subjects.

In relation to the existence of satisfactory methods of treatment of the condition that are authorised in the European Union, the assumption that Deltyba is of significant benefit to those affected by the orphan condition does not hold. The Committee was of the opinion that the results of the Phase II clinical data presented, showing higher sputum conversion rates at 2 months of treatment as compared to placebo when the product was added to a background regimen in multi-drug resistant tuberculosis, do not sufficiently support the significant benefit of the product, due to the short duration of the controlled observation period and the lack of other data supporting the beneficial clinical effect.

An opinion recommending the removal of Deltyba, (R)-2-Methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy) piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole (R)-2-Methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy) piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole (EU/3/07/524) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The sponsor was informed about a possibility to appeal.

5.1.2 Para-aminosalicylic acid Lucane (Para-aminosalicylic acid) for treatment of tuberculosis; Lucane Pharma SA (EU/3/10/826) [Co-ordinator: V. Stoyanova] [Expert: M. Ameziane]

The COMP noted the CHMP positive opinion adopted at the December 2013 CHMP meeting. 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:

- Significant benefit

The sponsor is invited to further elaborate on the advantages of PAS-GR in the treatment of MDR-TB *vis a vis* the currently authorised treatments for this condition in Europe. The discussion on such advantages should be supported by any available data.

In relation to the significant benefit vs. the currently authorised formulation of para-aminosalicylic acid (PAS) the sponsor is invited to further elaborate on any available data supporting the existence of serious and documented difficulties with the current formulation and supporting the major contribution to patient care linked to the new proposed formulation.

The sponsor provided a written response, and discussed the issues raised in the List of questions at an oral explanation before the Committee on 7 January 2014.

The COMP concluded that the proposed therapeutic indication "indicated for use as part of an appropriate combination regimen for multi-drug resistant tuberculosis in adults and paediatric patients from 28 days of age and older when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Consideration should be given to official guidance on the appropriate use of antibacterial agents" falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of tuberculosis was estimated to remain below 5 in 10,000 at the time of the review of the designation criteria.

The condition is life-threatening and chronically debilitating due to pulmonary and extrapulmonary disease that can lead to irreversible lung damage and death if left untreated. The infection with drug resistant strains carries a worse prognostic and further decreases life expectancy in infected subjects;

In relation to the existence of satisfactory methods of treatment of the condition that are authorised in the European Union, the assumption that PAS-GR is of significant benefit to those affected by the orphan condition does not hold. The Committee was of the opinion that the claims of the sponsor of better tolerability of the product are not sufficiently justified.

The claim of a better tolerability of PAS-GR vs. PAS was not sufficiently demonstrated with data by the sponsor. In addition, the COMP was of the opinion that for establishing an improved safety or tolerability as ground for significant benefit, additional discussion and comparison would be needed between PAS-GR and other existing products used for the treatment of MDR-TB.

An opinion recommending the removal of Para-aminosalicylic acid Lucane, para-aminosalicylic acid (EU/3/10/826) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The sponsor was informed about a possibility to appeal.

5.1.3 Cometriq [Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L)-malate salt] for treatment of medullary thyroid carcinoma; TMC Pharma Services Ltd (EU/3/08/610) [Co-ordinator: B. Bloechl-Daum]

The COMP noted the CHMP positive opinion adopted at the December 2013 CHMP meeting. The oral explanation and initial COMP discussion were held in the 9-11 July 2013 COMP meeting. Additional information was provided by the sponsor on 2 January 2014.

The COMP concluded that:

The therapeutic indication "treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma. For patients in whom Rearranged during Transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision" falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of medullary thyroid carcinoma was estimated to be less than 0.7 in 10,000 and thus to remain below the limit for orphan designation at the time of the review of the designation criteria.

The condition is chronically debilitating due to the radical surgery, and life-threatening in patients with unresectable tumours or metastatic disease.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Cometriq is of significant benefit to those affected by the orphan condition still holds. The Committee agreed that there exist patients who can be treated with Comteriq but cannot be treated with Caprelsa due to cardiac risks. The sponsor has also shown that out of 25 patients with progressive disease and who had received prior Caprelsa, 7 had objective partial responses when treated with Cometriq. This was considered to further support the significant benefit of Cometriq.

Post-meeting note:

An opinion not recommending the removal of Cometriq, Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L)-malate salt (EU/3/08/610) from the EC Register of Orphan Medicinal Products was adopted by consensus via written procedure on 16 January 2014 together with the draft public summary of the COMP opinion for publication on the EMA website.

5.1.4 Sirturo ((1R,2S) 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-(1-naphthyl)-beta-phenyl-3-quinolineethano) for treatment of tuberculosis; Janssen-Cilag International N.V. (EU/3/05/314) [Co-ordinator: N. Sypsas]

The COMP noted the CHMP positive opinion adopted at the December 2013 CHMP meeting.

The COMP concluded that the proposed therapeutic indication "treatment of pulmonary tuberculosis" falls entirely within the scope of the orphan indication of the designated orphan medicinal product orphan indication.

The prevalence of tuberculosis was estimated to remain below 5 in 10,000 at the time of the review of the designation criteria. The condition is life-threatening and chronically debilitating due to pulmonary and extra pulmonary disease that can lead to irreversible lung damage and death if left untreated. The infection with drug resistant strains carries a worse prognosis and further decreases life expectancy.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Sirturo is of significant benefit to those affected by the orphan condition still holds. This appears justified based on Phase II clinical data showing significantly shorter time to sputum culture conversion (83 *vs*. 125 days) and higher and sustained conversion rates (79% *vs*. 58%) as compared to placebo when the product was added to a background regimen in multi-drug

resistant tuberculosis. Sputum culture conversion is a widely accepted endpoint of efficacy. A shorter time to sputum conversion is considered by the Committee a clinically relevant advantage as it implies earlier cure of the single patient and at the same time it lowers the risk of transmission of the infection.

An opinion not recommending the removal of Sirturo, (1R,2S) 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-(1-naphthyl)-beta-phenyl-3-quinolineethano for treatment of tuberculosis (EU/3/05/314,) 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.

5.1.5 Winfuran (-)-17(cyclopropylmethyl)-1,14 ß-dihydroxy-4,5 alpha-epoxy-6ß-[N-methyl-trans-3-(3-furyl) acrylamido] morphinan hydrochloride for treatment of uremic pruritus; Toray International U.K. Limited (EU/3/02/115).

The COMP noted the CHMP negative opinion on MA as adopted at the December 2013 CHMP meeting.

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

5.2.1 Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate for treatment of pulmonary arterial hypertension including treatment of chronic thromboembolic pulmonary hypertension; Bayer Pharma AG (EU/3/07/518)

5.2.2 N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-D-gamma-glutamyl-(2S)-2-amino-beta-alanyl-L-alpha-aspartyl-L-cysteine to be used with folic acid for diagnosis of positive folate receptor status in ovarian cancer; Endocyte Europe, B.V. (EU/3/12/1043)

5.2.3 Folic acid to be used with N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-D-gamma-glutamyl-(2S)-2-amino-beta-alanyl-L-alpha-aspartyl-L-cysteine for diagnosis of positive folate receptor status in ovarian cancer; Endocyte Europe, B.V. (EU/3/12/1044)

5.2.4 Sorafenib tosylate; Bayer HealthCare AG for:

- treatment of follicular thyroid cancer (EU/3/13/1199)
- treatment of papillary thyroid cancer (EU/3/13/1200)

5.2.5 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid for treatment of Duchenne muscular dystrophy; PTC Therapeutics Ltd (EU/3/05/278)

5.2.6 Masitinib mesilate for treatment of pancreatic cancer; AB Science (EU/3/09/684)

5.2.7 Recombinant human N-acetylgalactosamine-6-sulfatase for treatment of mucopolysaccharidosis, type IVA (Morquio A syndrome); BioMarin Europe Ltd (EU/3/09/657)

5.2.8 Vincaleukoblastin-23-oic acid, O4-deacetyl-2-[(2-mercaptoethoxy)carbonyl]hydrazide, disulfide with N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-gamma-glutamyl-L-alpha-aspartyl-L-arginyl-L-alpha-aspartyl-L-alpha-aspartyl-L-cysteine for treatment of ovarian cancer; Endocyte Europe, B.V. (EU/3/12/959)

5.3. On-going procedures

5.3.1 (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 (EU/3/07/514)

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 Ramucirumab for treatment of gastric cancer; Eli Lilly Nederland B.V. (OD/030/12, EU/3/12/1004)

5.3.4 Obinutuzumab for treatment of chronic lymphocytic leukaemia; Roche Registration Limited (EU/3/12/1054)

5.3.5 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)

5.3.6 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H- pyrazolo [3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one for treatment of mantle cell lymphoma; Janssen-Cilag International N.V. (EU/3/13/1115)

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

5.3.8 N-(methyl-diazacyclohexyl-methylbenzamide)-azaphenyl-aminothiopyrrole for treatment of malignant gastrointestinal stromal tumours; AB Science (EU/3/04/251)

5.3.9 Dexamethasone (40 mg tablet) for treatment of multiple myeloma; Laboratoires CTRS (Cell Therapies Research & Services) (EU/3/10/745)

5.3.10 Olaparib for treatment of ovarian cancer; AstraZeneca AB (EU/3/07/501)

5.3.11 [Nle4, D-Phe7]-alfa-melanocyte stimulating hormone, Afamelanotide for treatment of erythropoietic protoporphyria; Clinuvel (UK) Limited (EU/3/08/541)

5.3.12 Chimeric-anti-interleukin-6 monoclonal antibody for treatment of Castleman's disease; Janssen-Cilag International N.V. (EU/3/07/508)

5.3.13 Tobramycin (inhalation use) for treatment of *Pseudomonas Aeruginosa* lung infection in cystic fibrosis; PARI Pharma GmbH (EU/3/09/613)

6. Procedural aspects

6.1 Proposals for the COMP involvement in validation of public summaries of the COMP opinions on review of orphan designation

The Committee welcomed and approved the proposal.

7. Any other business

7.1 Similarity for orphan medicines

The COMP discussed the topic and commented on the *Reflection paper on the application of similarity for orphan medicines*, EMA/84728/2013.

7.2 Revision of the *EC Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another* ENTR/6283/00 Rev 3.

The topic was postponed.

7.3 European Conference for Rare Diseases (ECRD) to be held on 8-10 May 2014 in Berlin

The COMP noted the dates of the conference.

7.4 Presentation on the EMA move to 30 Churchill Place

The COMP was briefed on the move plan to the new location. The Committee was informed that starting from the 3-4 September 2014 meeting the COMP plenaries will be held in the new location.

List of participants

Chair:	
Bruno Sepodes	EMA representative
COMP Members:	
André Lhoir	België/Belgique/Belgien
Irena Bradinova	Бългàрия
Kateřina Kubáčková	Česká Republika
Frauke Naumann-Winter	Deutschland
Vallo Tillmann	Eesti
Geraldine O'Dea	Éire/Ireland
Adriana Andrić	Hrvatska
Nikolaos Sypsas	Ελλάδα
Josep Torrent Farnell	España
Annie Lorence	France
Sigurdur B. Thorsteinsson	Iceland
Armando Magrelli	Italia
Aušra Matulevičienė	Lietuva
Judit Eggenhofer	Magyarország
Albert Vincenti	Malta
Violeta Stoyanova-Beninska	Nederland
Lars Gramstad	Norway
Brigitte Blöchl-Daum	Österreich
Bożenna Dembowska-Bagińska	Polska
Ana Corrêa-Nunes	Portugal
Martin Možina	Slovenija
Veijo Saano	Suomi/Finland
Kerstin Westermark	Sverige
Daniel O'Connor	United Kingdom
Birthe Byskov Holm	Volunteer patient representative for Eurordis
Pauline Evers	Patient representative representing the European Genetic Alliances Network
Aikaterini Moraiti	EMA representative
Observers:	
Maria Mavris	Eurordis
Experts:	
Mohamend Ameziane via TC	College ter Beoordeling van Geneesmiddelen, Netherlands (for 5.1.1, 5.1.2)
Rembert Elbers via TC	Bundesinstitut für Arzneimittel und Medizinprodukte, Germany (for 7.1)