9 April 2014
EMA/COMP/74734/2014
Human Medicines Research and Development Support

Committee for Orphan Medicinal Products (COMP)

Minutes of the 11 - 12 March 2014 meeting

Chair: B. Sepodes – Vice-chair: L. Greene

Note on access to documents

Some documents mentioned in these minutes cannot be released at present as they are currently in draft format or are classified as confidential. They will become public when adopted in their final form 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

The Committee welcomed new COMP members:

- Ms E. Kaisis representing Cyprus
- Ms Z. Batová representing Slovakia

and visiting guests:

- Mr Harumasa Nakamura, PMDA
- Ms Yasuko Inokuma, MHLW
- Mr Hiroshi Takeda, PMDA
- Ms Yuki Ando, PMDA
- Dr Nao Tsuchida, National Center for Child Health and Development
- Ms Irene Norstedt, Head of Innovative and personalised Medicine Unit, Research & Innovation DG, European Commission

1.1 Adoption of the agenda, EMA/COMP/74731/2014

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting held on 4 - 6 February 2014, EMA/COMP/77369/2014

The adoption 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:

- K. Kubáčková declared a potential conflict of interest on agenda point 5.3.8. B. Dembowska-Bagińska was appointed as a new coordinator for the procedure.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 Synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA that is covalently linked to a ligand containing three N-acetylgalactosamine residues

for treatment of symptomatic transthyretin mediated amyloidosis, Voisin Consulting S.A.R.L. - EMA/OD/194/13

[Co-ordinators: 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:

- Number of people affected

The prevalence calculation appears to be low particular regarding the estimate for senile systemic amyloidosis. The sponsor was invited to recalculate the overall prevalence for the new condition ATTR-amyloidosis.

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.

In the written response, the sponsor further elaborated on the prevalence of the proposed condition, and provided a recalculated estimate as requested by the Committee.

Following review of the application by the Committee, it was agreed to rename the indication to "treatment of ATTR amyloidosis".

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

The intention to treat the condition with the medicinal product containing synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA that is covalently linked to a ligand containing three N-acetylgalactosamine residues was considered justified based on pre-clinical in vivo data using a valid model of the condition as well as preliminary data in healthy volunteers.

The condition is life-threatening and chronically debilitating due to the development of polyneuropathy and cardiomyopathy. The condition was estimated to be affecting approximately 0.1 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 synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA that is covalently linked to a ligand containing three N-acetylgalactosamine residues may be of

[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).

significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vivo results and clinical data in healthy subjects that demonstrate that there was a relevant reduction in amyloid levels and production thereby offering an alternative mode of action to tafamidis. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA that is covalently linked to a ligand containing three N-acetylgalactosamine residues, for treatment of ATTR amyloidosis, was adopted by consensus.

2.1.2 Autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human beta *A-T87Q*-globin gene

for treatment of sickle cell disease, bluebird bio France - EMA/OD/184/13

[Co-ordinators: L. Gramstad]

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 sickle cell disease, the sponsor should further elaborate on the validity of the bibliographical experimental data used which is based on another similar product to support the medical plausibility of the proposed product.

- 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 further elaborate on the clinically relevant advantage this product will bring concerning its place within the standard of care currently practiced in Europe. In particular how it will be used knowing that hydroxyurea is the currently approved therapy in Europe as no preclinical or clinical data has been presented where hydroxyurea has been used either as a comparator or in combination.

In the written response, and during an oral explanation before the Committee on 11 March 2014, the sponsor further elaborated on the different vectors used in the preclinical and preliminary clinical studies to justify the medical plausibility. It was stressed that all lentiviral vectors used encode for the same gene and that they all have demonstrated expression of the beta A-T87Q-globin in vivo.

With regards to the significant benefit issue, the sponsor discussed the mechanism of action of hydroxyurea and its role in preventing significant complications of sickle cell disease such as acute chest syndrome. This was contrasted with the mechanism of action of the proposed product which targets the underlying genetic defect, and the sponsor discussed that the initial proof of concept study is designed to evaluate patients who are considered to have failed treatment with hydroxyurea. A potential use in combination with hydroxyurea was also considered.

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

The intention to treat the condition with the medicinal product containing autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human beta A-T87Q-globin gene was considered justified based on preliminary in vitro and pre-clinical data, as well as clinical data from with other β-haemoglobinopathies.

The condition is chronically debilitating and life threatening due to anaemia, vaso-occlusive ischaemic incidences, bacterial infections and reduced survival. The condition was estimated to be affecting approximately 2.16 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 CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human beta *A-T87Q*-globin gene may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical and preliminary clinical data that demonstrate that the different mode of action offers an alternative to hydroxyurea in patients who are intolerant or do not respond. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human beta *A-T87Q*-globin gene, for treatment of sickle cell disease, was adopted by consensus.

2.1.3 **Autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19** for treatment of acute lymphoblastic leukaemia, Novartis Europharm Limited - EMA/OD/187/13

[Co-ordinators: 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

The proposed orphan indication should be brought into line with the current definition in the WHO classification as B-lymphoblastic leukaemia/lymphoma; your attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

- Number of people affected

As the condition should be redefined as B-lymphoblastic leukaemia/lymphoma, the sponsor was requested to recalculate the prevalence of this condition which will be different from acute lymphoblastic leukaemia.

In the written response the sponsor agreed to revise the indication for orphan medicinal product designation to “treatment of B lymphoblastic leukaemia/lymphoma” in line with the WHO classification and the COMP recommendation. The sponsor also provided an updated prevalence calculation in light of the amended indication.

The Committee decided that the written information is sufficient for adopting of an opinion and the sponsor was informed that the oral explanation is not required.

Following review of the application by the Committee, it was agreed to rename the indication to “treatment of B-lymphoblastic leukaemia/lymphoma”.

The Committee agreed that the condition, B-lymphoblastic 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 autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19 was considered justified based on preliminary clinical data in patients.

The condition is chronically debilitating and life-threatening depending on the response to treatment, with acute leukemic forms being fatal in a few weeks if left untreated. The main manifestations of the disease such as persistent fever, infections, anaemia, fatigue, breathlessness, bone and joint pain, are linked to invasion by the tumour cells of the bloodstream, the bone marrow and/or the lymph nodes and other lymphatic organs, resulting in lack of normal blood cells, bone marrow failure, and specific organ damage. The condition was estimated to be affecting approximately less than 1 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 T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19 may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the product was efficacious in patients who relapsed or were refractory to previous treatment in the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19, for treatment of B-lymphoblastic leukaemia/lymphoma, was adopted by consensus.

2.1.4 Genetically modified serotype 5/3 adenovirus coding for granulocyte macrophage colony-stimulating factor

Genetically modified serotype 5/3 adenovirus coding for granulocyte macrophage colony-stimulating factor for treatment of ovarian cancer, Oncos Therapeutics Oy - EMA/OD/186/13 *[Co-ordinators: 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 ovarian cancer, the sponsor should further elaborate on the effects of the specific product as applied for designation in any relevant preclinical model of ovarian cancer or in preliminary clinical settings in ovarian cancer patients.

In particular the sponsor was requested to present in detail the existing preliminary clinical data in the the ovarian cancer population and discuss the characteristics of patients, treatments received, assessments performed and results obtained.

- Significant benefit

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

The sponsor was requested to present in detail the existing preliminary clinical data in the ovarian cancer population and discuss the characteristics of patients, treatments received, assessments performed and results obtained.

In the written response, and during an oral explanation before the Committee on 11 March 2014, the sponsor has provided further clarifications on the two raised issues, starting with a justification of why similar products and not the specific product as applied for designation had been used in the preclinical part of the application. With regards to the preliminary clinical data, the sponsor clarified that in the open access program (ATAP) 23 patients with ovarian cancer patients have been included and those patients were refractory to conventional therapies with progressive disease and performance score of

less than 3. Based on imaging data, the sponsor reported 4 Minor responses and 4 Stable diseases in the 11 patients that were evaluated from this program. In addition sponsor also reported two patients with refractory ovarian cancer in a phase clinical study. In these two patients, at three months after the start of treatment, two Stable Disease (SD) were reported on the basis of evaluation by RECIST criteria.

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 genetically modified serotype 5/3 adenovirus coding for granulocyte macrophage colony-stimulating factor was considered justified based on preliminary clinical data in patients affected by the condition that responded to treatment with the proposed 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 less than 3 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 genetically modified serotype 5/3 adenovirus coding for granulocyte macrophage colony-stimulating factor may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing responses in patients with ovarian cancer refractory to existing therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for genetically modified serotype 5/3 adenovirus coding for granulocyte macrophage colony-stimulating factor, for treatment of ovarian cancer, was adopted by consensus.

2.1.5 Product for treatment of aneurysmal subarachnoid haemorrhage - EMA/OD/171/13

[Co-ordinators: L. Gramstad]

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:

- Condition

The sponsor was requested to further elaborate on the exclusion of other types of subarachnoid haemorrhage including non-aneurysmal and traumatic aetiologies. In case of an amended indication, the prevalence estimate should also be recalculated.

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of aneurysmal subarachnoid haemorrhage, the sponsor should further elaborate on:

  - any available preclinical data or preliminary clinical studies with the proposed product as applied for designation in valid model(s) of the condition or in patients affected by the proposed condition;
  - 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 extrapolation of observations made using other products and not the one subject of this procedure.

- Significant benefit

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

Given that extrapolation from preclinical or early clinical studies cannot predict the safety of a product in its clinical setting, 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 current authorised medicinal products for the same condition.

Furthermore, it would be useful to obtain more information on the on-going study/planned development.

In the written response, and during an oral explanation before the Committee on 12 March 2014, the sponsor elaborated on the exclusion of other types of haemorrhage on the basis of the involvement of clinically relevant angiospasm. With reference to non-aneurysmal subarachnoid haemorrhage, the sponsor asserted that in about half of patients with perimesencephalic haemorrhage there are indeed signs of vasospasm, but these are without any sign of clinical manifestation. As for the cases of traumatic brain injury, the sponsor argued that it is the trauma that drives morbidity and mortality and that the relationship between quantity of blood in the subarachnoid space and vertebral vasospasm is less granular.

As for the medical plausibility, the sponsor confirmed that no studies have been performed yet with the proposed product as applied for designation, and presented a comparative discussion on the product as applied for designation versus a surrogate product with reference to literature.

Lastly, with regards to the significant benefit issue raised by the COMP, the sponsor argued on the assumption for improved efficacy based on the profile of the a surrogate product, and also discussed the possibility for continuous and local delivery of the new product in CNS.

The COMP considered that in line with the existing guideline on the format and content of the applications for designation, benefit/risk considerations may not be used for the purpose of defining a distinct medical entity valid for orphan designation. In addition, the Committee understood that data with the proposed product as applied for designation in any relevant preclinical or clinical setting, which would be needed to support the proposal and provide the basis of the comparative discussion versus authorised counterparts was missing from the application.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 March 2014, prior to final opinion.

2.1.6 Product for treatment of systemic sclerosis - EMA/OD/165/13

[Co-ordinators: V. Saano]

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 is invited to discuss the significant benefit of the proposed product in terms of possible clinically relevant advantage or major contribution to patient care, taking into account the existing

authorised medicinal products both at centralised and at national level. An assumption of significant benefit should be as much as possible be supported by data with the proposed product.

Based on the available pre-clinical and clinical data the sponsor is asked also to discuss whether the product would be of significant benefit only in interstitial lung disease related to SSc or in other manifestations of SSc.

In the written response, and during an oral explanation before the Committee on 12 March 2014, the sponsor postulated a clinically relevant advantage on the basis of an alternative mechanism of action, with the proposed product combining anti-fibrotic and anti-inflammatory properties, while the authorised counterparts exerted their effects through different mechanisms.

The Committee considered that the data presented to support the significant benefit of the applied product compared to the standard of care and authorised products for the proposed condition was limited. In conclusion, the Committee was of the opinion that the assumption on significant benefit was not fullfilled. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 March 2014, prior to final opinion.

2.1.7 Product for treatment of osteonecrosis of the jaw - EMA/OD/177/13
[Co-ordinators: A. Corrêa Nunes]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation on 21 February 2014, prior to responding to the list of issues.

2.1.8 Product for treatment of mobilisation of progenitor cells prior to stem cell transplantation - EMA/OD/192/13
[Co-ordinators: J. Torrent-Farnell]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation on 24 February 2014, prior to responding to the list of issues.

2.1.9 Product for treatment of argininosuccinic aciduria - EMA/OD/189/13
[Co-ordinators: I. Bradinova]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation on 19 February 2014, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1 Product for treatment of biliary tree cancer - EMA/OD/199/13
[Co-ordinators: B. Bloechl-Daum]

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

- Proposed condition

The sponsor is invited to elaborate on the proposed condition as applied for designation vis a vis the ICD classification system or other internationally accepted classifications.

- 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".

As it seems that the sponsor has excluded part of the population affected by intrahepatic disease, the sponsor should indicate on which population the prevalence calculation is based on, and amend the estimate accordingly.

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

2.2.2 Product for treatment of follicular lymphoma - EMA/OD/200/13
[Co-ordinators: F. Naumann-Winter]

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

- Medical plausibility

In order to establish the medical plausibility the sponsor is invited to clarify the relevance of the cell lines used in the generation of the in vitro and in vivo preclinical data to the proposed condition follicular lymphoma.

In addition the sponsor is asked to provide the results of the positive control group in the preclinical study and to comment on the survival of the control group.

- Significant benefit

In order to support the significant benefit, the sponsor is asked to provide more details on the preliminary clinical data, including the baseline parameters of the patients with follicular lymphoma, the time since last treatment, the number of doses and the concomitant treatments.

The sponsor is also invited to further discuss the response criteria applied for evaluating treatment success in these patients.

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

2.2.3 Product for treatment of inherited retinal disease caused by lecithin: retinol acyltransferase (*LRAT*) or retinal pigment epithelium protein 65 (*RPE65*) mutations - EMA/OD/197/13
[Co-ordinators: K. Westermark]

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

- Intention to diagnose, prevent or treat

"Inherited Retinal Disease based on mutations in retinol acyltransferase (*LRAT*) or retinal pigment epithelium protein 65 (*RPE65*)"should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; your attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

The sponsor is invited to:

- ✓ elaborate with regards to the definition of the condition 'Inherited Retinal Disease based on mutations in retinol acyltransferase (*LRAT*) or retinal pigment epithelium protein 65 (*RPE65*)' and how this fulfils the requirements for a distinct condition as stated in the Guideline on Format and Content of the applications (ENTR/6283/00);
- ✓ explain why treatment with the proposed product should be restricted only to mutations in LRAT and RPE65 considering that it seems to work outside Inherited Retinal Diseases caused by mutations in *LRAT* and *RPE65;*
- ✓ refer to any new, generally agreed classification of Inherited Retinal Diseases supporting the condition as applied for designation.

- 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 and further elaborate on the derivation of the conclusion as proposed for the purpose of designation.

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

2.2.4 **Humanised monoclonal antibody against CD38** for treatment of plasma cell myeloma, Sanofi-Aventis Groupe - EMA/OD/198/13

[Co-ordinators: 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 humanised monoclonal antibody against CD38 was considered justified based on preclinical in vivo and preliminary clinical data in patients with 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 an overall survival of up to approximately 45 months for newly diagnosed patients. The condition was estimated to be affecting approximately 1.8 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 humanised monoclonal antibody against CD38 may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vivo and preliminary clinical data that demonstrate a prolongation of tumour free survival in the pre-clinical models when used in combination with other anti-neoplastic agents and the efficacy in patients with the condition who have relapsed or refractory disease when they have received the current standard of care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised monoclonal antibody against CD38, for treatment of plasma cell myeloma, was adopted by consensus.

2.2.5 **Ibrutinib** for treatment of Waldenström's Macroglobulinemia, Janssen-Cilag International N.V. - EMA/OD/185/13
[Co-ordinators: F. Naumann-Winter]

Following review of the application by the Committee, it was agreed to rename the indication to "lymphoplasmacytic lymphoma".

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

The intention to treat the condition with the medicinal product containing ibrutinib was considered justified based on preliminary clinical data in patients affected by the condition who responded to treatment with the product.

The condition is chronically debilitating and life-threatening due to bone marrow dysfunction, lymphadenopathy, splenomegaly and paraproteinaemia resulting in hyperviscosity, autoimmunity, cryoglobulinaemia, coagulopathies and neuropathies.

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 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 ibrutinib 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 have relapsed or were refractory to available products and responded to treatment with the product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for ibrutinib, for treatment of lymphoplasmacytic lymphoma, was adopted by consensus.

2.2.6 Product for treatment of gastro-entero-pancreatic neuroendocrine tumours - EMA/OD/196/13
[Co-ordinators: B. Bloechl-Daum]

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 gastro-entero-pancreatic neuroendocrine tumours, the sponsor should further elaborate on the compassionate use data submitted with particular focus on the length of time of exposure of the Gep-net patients described as well as their disease characteristics (stage, relapsed or refractory) and previous oncological therapy. The sponsor should also identify the patients who received their product in the publications submitted clearly describing the stage of the disease, previous oncological therapy given, comparisons made and outcome.

- 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 is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the compassionate use study and the specific publications to justify the

assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

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

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

2.2.7 Product for treatment of dystrophic epidermolysis bullosa - EMA/OD/201/13
[Co-ordinators: F. Naumann-Winter]

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 dystrophic epidermolysis bullosa, the sponsor should elaborate on:

- the transport from blood to the skin basal membrane (and not to organs other than the skin), taking into account the size of the product and the potential to form higher order aggregates;
- the interaction of the proposed product with the different constituents of the dermis
- the possible generation of antibodies against the proposed product.

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

2.3. Follow-up on the COMP opinions adopted at the last meeting

2.3.1 Caffeine citrate for prevention of bronchopulmonary dysplasia, Viridian Pharma Ltd - EMA/OD/161/13
[Co-ordinators: K. Westermark]

The COMP revised their positive opinion adopted on 6 February 2014, by amending the number of the population of patients eligible for prevention of the condition, bronchopulmonary dysplasia, from 1 to between 1 and 3 in 10,000 people in the European Union.

2.3.2 Recombinant human surfactant protein D for prevention of bronchopulmonary dysplasia in premature neonates of less than 32 weeks of gestational age, Dr Ulrich Granzer - EMA/OD/172/13
[Co-ordinators: K. Westermark]

The COMP revised their positive opinion adopted on 6 February 2014, by renaming the indication to “prevention of bronchopulmonary dysplasia” and amending the number of the population of patients eligible for prevention of the condition, bronchopulmonary dysplasia, from 3 to between 1 and 3 in 10,000 people in the European Union.

2.4. COMP appeal opinion adopted via written procedure following previous meeting

2.4.1 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

The COMP noted the final COMP opinion as adopted via written procedure on 17 February 2014.

2.5. Evaluation on-going

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

2.6. Validation on-going

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

3. Requests for protocol assistance

3.1. Letters

3.1.1 Product for treatment of follicular lymphoma

The protocol assistance advice letter was discussed for adoption via written procedure.

3.1.2 Product for treatment of acute lymphoblastic leukaemia

Adoption of the protocol assistance advice letter was postponed to the following COMP meeting.

4. Overview of applications

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

COMP co-ordinators were appointed for 2 applications submitted and 28 upcoming 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 Vimizim (Recombinant human N-acetylgalactosamine-6-sulfatase) for treatment of mucopolysaccharidosis, type IVA (Morquio A syndrome); BioMarin Europe Ltd (EU/3/09/657) [Co-ordinators: J. Torrent-Farnell]

The COMP noted the CHMP opinion on MA adopted at 17-20 February 2014 meeting.

The COMP concluded that:

The proposed therapeutic indication "treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages" falls entirely within the scope of the orphan indication of the designated orphan medicinal product, treatment of mucopolysaccharidosis, type IVA (Morquio A syndrome).

The prevalence of mucopolysaccharidosis, type IVA (Morquio A syndrome) was estimated to be 0.03 in 10,000 and thus 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 in particular due to cervical instability and cardiorespiratory failure. There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

An opinion not recommending the removal of Vimizim (Recombinant human N-acetylgalactosamine-6-sulfatase) (EU/3/09/657) 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 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) [Co-ordinators: B. Bloechl-Daum]

The Committee considered that the following issue requires clarification by the sponsor:

- Currently approved diagnostics

Additional information should be provided to support the use of the product in the context of the currently used diagnostics for ovarian cancer. A discussion on the currently endorsed diagnostic techniques which are available and used within the context of the condition should be further elaborated.

- Justification of significant benefit

Additional argumentation should be provided to justify the potential significant benefit of the product over the currently used diagnostics for ovarian cancer. The clinically relevant advantage should be supported with data with the product used within the context of the condition.

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

5.2.2 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) [Co-ordinators: B. Bloechl-Daum]

The Committee considered that the following issue requires clarification by the sponsor:

- Justification of significant benefit

Additional argumentation should be provided to justify the potential significant benefit of folic acid used in combination 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 over folic acid used as a diagnostic for ovarian cancer. This should be supported with data with the product within the context of the condition. The sponsor should also explain how this form of folic acid shows significant benefit over other forms of folic acid licenced, used and or available for this purpose in this condition.

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

5.2.3 Sorafenib tosylate; Bayer HealthCare AG
Nexavar – MA extension of indication

a) treatment of follicular thyroid cancer (EU/3/13/1199)

b) treatment of papillary thyroid cancer (EU/3/13/1200)

5.2.4 Pasireotide for treatment of Cushing's disease; Novartis Europharm Limited (EU/3/09/671) Signifor **-** MA type II variation opinion

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

5.2.6 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)

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

5.3. On-going procedures

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

5.3.2 (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)

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

5.3.4 Ramucirumab for treatment of gastric cancer; Eli Lilly Nederland B.V. (OD/030/12)

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

5.3.6 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)

5.3.7 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)

5.3.8 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)

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

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

5.3.11 Ketoconazole for treatment of Cushing's syndrome; Laboratoire HRA (EU/3/12/965)

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

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

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

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

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

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

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

5.3.19 (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)

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

5.4. Appeal procedure

5.4.1 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-ordinators: N. Sypsas]

Following the COMP negative opinion adopted at the January 2014 meeting, the sponsor submitted the grounds for appeal on 25 February 2014.

In the written grounds for appeal and during the oral explanation on 11 March 2014, the sponsor discussed the data from the studies that have been presented as part of the MA application, and further elaborated on the predictive value of the results of the pivotal clinical study and the available long-term observations.

The following studies were discussed: a) the main study 204 which is the randomised, controlled trial in MDR-TB where the primary endpoint was 2-month sputum conversion b) study 208 which is the open-label extension of the previous study c) study 116, the non-interventional registry for patients who had previously participated in Trial 204 and d) the on-going 213 study from which data are not available, notwithstanding that information was presented by the sponsor during the oral explanation relating to the proportion of negative cultures in a blind analysis of data form patients from this study.

The grounds of appeal revolved around the following two points:

1. First, the sponsor emphasised the importance of the 204 study results, namely the sputum conversion rate (SCC) at 2 months in the treated patients with Deltyba as an add-on, compared to those with the optimised background regimen (OBR) alone. The proportions of patients achieving 2-month SCC in Deltyba treatment groups: 100 mg BID + OBR and 200 mg BID + OBR were higher compared to placebo + OBR (45% and 42% respectively compared to 30%) and the differences were statistically significant. In addition, the sponsor stressed that over 40% of all MDR-TB patients with bilateral cavitation treated with Deltyba achieved 2-month SCC compared with only 15% achieving 2-month SCC among those receiving placebo, and that the corresponding figures for XDR-TB are 25% vs none.

Importantly, it was discussed that conversion of SCC at two months is correlated with improved relapsed rates and mortality as per literature references. With reference to a meta-analysis of MDR-TB that was conducted by the Collaborative Group for the WHO Stop TB Department, two co-authors analysed a subset of 2,942 patients from the original total group with baseline culture data at the request of the sponsor. The sponsor reports that of those patients that converted at month 2 of their MDR-TB therapy, approximately 4.0% died compared to 16% of the patients that did not convert early at month 2. The sponsor stressed that this is in line with follow-up observations of patients from study 204 which showed that mortality rates during the 2 year follow up, independently of the treatment received, was 2.4% vs 13.8% for converters and non-converters at 2 months respectively as per the oral explanation presentation.

2. At a second level of argumentation, the sponsor discussed the available long-term observations, by comparing patients who chose to enter study 208 and received 6m treatment versus those who did not

receive 6m of Delamanid treatment. It was reported that vital status at 24 months after treatment initiation was collected for 464 (96.5%) of the 481 patients randomised in 204. Mortality at 24 months was significantly lower for patients treated with 6m Delamanid + OBR(2.9%), compared to patients treated with OBR alone (12%). It was also reported that, 130 of 143 patients (91%) treated with Deltyba for 6 months had a higher frequency of sustained SCC compared to those not treated with full course of 6 month Deltyba (112 of 158, 71%). Patients in study 204 who did achieve 2-month SCC and then enrolled in Trial 208 achieved the highest level of sustained SCC (98.7%) among all groups and no patient died. In contrast, patients who did not achieve 2-month SCC in Trial 204 and did not receive a full course of 6 months Deltyba treatment demonstrated the lowest level of sustained SCC (56.3%) among all groups and the highest mortality (15.4%).

The Committee, having examined the grounds of appeal considered that there is a limitation in that the only randomised controlled data comes from the 2-month 204 study. The existing treatment for MDR-TB comprises an initial period of 6 months of intensive therapy and a total of at least 24 months of treatment, while there is an absence of a properly designed, controlled comparison of delamanid versus placebo over a continuous 6 month treatment period. It was particularly discussed that the data from the open extension studies are not of the same bearing and may be subject to unknown bias. Nevertheless, it was agreed that the sponsor has submitted data on both the predictive value of the results of the 204 study, linking them to expected improved survival and conversion rates, and provided 24 months observations on mortality that are in line with literature references on 2-month sputum culture converted patients.

Based on 1) the improvement of 2-month sputum conversion rates in MDR patients treated with the product when added to optimised background regiment, and 2) the 2 year follow up observations regarding sustained sputum conversion and mortality in patients who received at least 6 months of treatment, the Committee considered that a clinically relevant advantage has been justified.

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 (see sections 4.2, 4.4 and 5.1).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, treatment of tuberculosis.

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 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 still holds. Based on the main clinical study completed by the sponsor, there are data in patients with multi-drug resistant tuberculosis, showing a higher sputum conversion rate at 2 months of treatment as compared to placebo when the product was added to a background regimen. This improvement in 2-month sputum conversion rates was considered by the Committee as predictive of improved relapse rates and mortality in patients affected by the Condition. In addition, the sponsor has provided observational open label uncontrolled data from multi-drug resistant tuberculosis patients that have received treatment with the product for 6 months, and showed improved survival and

sustained sputum conversion at 24 months, compared to patients who did not receive 6 months of treatment. The Committee considered that this constitutes a clinically relevant advantage.

The final opinion not 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) for treatment of tuberculosis (EU/3/07/524) from the EC Register of Orphan Medicinal Products was adopted by majority.

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

6. Procedural aspects

6.1 European Medicines Agency Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP)

The Draft Agenda of the 25 February 2014 PCWP meeting, EMA/19425/2014 was circulated for information.

6.2 European Medicines Agency Human Scientific Committees' Working Party with Healthcare Professionals' Organisations (HCPWP)

The Draft Agenda of the 25 February 2014 HCPWP meeting, EMA/13760/2014 was circulated for information.

6.3 Joint PCWP and HCPWP Workshop on regulatory and methodological standards to improve benefit/risk evaluation of medicines

The Draft Agenda of the 26 February 2014 Workshop, EMA/796225/2013 was circulated for information.

7. Any other business

7.1 3rd presentation on the EMA move to 30 Churchill Place

Following the presentation give in the previous meeting, the COMP was briefed further on the conference rooms' equipment in the new building.

7.2 Call for nominations for the Inter-Committee Oncology SAG (to replace the existing SAG Oncology)

The Mandate, objectives and rules of procedure for the Inter-Committee Scientific Advisory Group (SAG) for Oncology, EMA/684918/2012 was circulated for information and potential proposals of expert for the COMP nomination to the Inter-Committee Oncology SAG.

7.3 COMP meeting dates

The COMP meeting dates for 2016-2018 were adopted.

7.4 COMP Information Pack

The revised COMP Information Pack was circulated for information.

7.5 COMP publications strategy

The topic was briefly summarised by the Chair.

7.6 Significant Benefit at time of MA – working group

The Committee discussed creation of the working group.

7.7 COMP/PDCO interactions

The COMP was briefed on the topic.

7.8 Update on Similarity Assessment inter-committee discussions

The topic was briefly summarised by the Chair.

7.9 Update on the International Rare Diseases Research Consortium (IRDiRC)

M. Mavris from EURORDIS presented the topic.

7.10 EU Research funding for rare disease research

I. Norstedt from the European Commission presented the topic.

List of participants

Chair:

Bruno Sepodes

Vice-Chair:

Lesley Greene	Volunteer patient representative for Eurordis

COMP Members:

André Lhoir	België/Belgique/Belgien
Irena Bradinova	Бълга̀рия
Kateřina Kubáčková	Česká Republika
Frauke Naumann-Winter	Deutschland
Vallo Tillmann	Eesti
Geraldine O'Dea	Éire/Ireland
Nikolaos Sypsas	Ελλάδα
Josep Torrent Farnell	España
Annie Lorence	France
Adriana Andrić	Hrvatska
Sigurdur B. Thorsteinsson	Iceland
Armando Magrelli	Italia
Elena Kaisis	Κύπρος
Dainis Krievins	Latvija
Aušra Matulevičienė	Lietuva
Henri Metz	Luxembourg
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
Flavia Saleh	Romãnia
Martin Možina	Slovenija
Zuzana Batová	Slovensko
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

Visiting attendees:

Irene Norstedt	European Commission
Harumasa Nakamura	Japan
Yasuko Inokuma	Japan
Hiroshi Takeda	Japan
Yuki Ando	Japan
Nao Tsuchida	Japan