9 April 2014
EMA/COMP/77369/2014
Human Medicines Research and Development Support

Committee for Orphan Medicinal Products (COMP)

Minutes of the 4 - 6 February 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

1.1 Adoption of the agenda, EMA/COMP/14514/2014

The agenda was adopted with no amendments.

1.2 Adoption of the draft minutes of the COMP meetings held on:

- on 10-12 December 2013 EMA/COMP/687306/2013
- on 7-9 January 2014 EMA/COMP/788104/2013

It was agreed to adopt the documents via written procedure.

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 2.1.1. Nevertheless, no direct conflicts of interest have been identified for P. Evers, who represents EGAN in the COMP.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 Recombinant human alpha-glucosidase conjugated with multiple copies of synthetic bismannose-6-phosphate-tetra-mannose glycan for treatment of glycogen storage disease type II (Pompe's disease), Genzyme Europe BV - EMA/OD/148/13
[Co-ordinator: A. Corrêa Nunes]

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

- Number of people affected

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.

In the written response, and during an oral explanation before the Committee on 4-05 February 2014, the sponsor further elaborated on the prevalence of the Condition and provided an updated estimate as requested by the Committee.

The Committee agreed that the condition, glycogen storage disease type II (Pompe's disease), is a distinct medical entity and meets the criteria for orphan designation.

[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 intention to treat the condition with the medicinal product containing recombinant human alpha-glucosidase conjugated with multiple copies of synthetic bismannose-6-phosphate-tetra-mannose glycan was considered justified based on preclinical data in a valid model of the disease.

The condition is chronically debilitating and life-threatening, in particular due to progressive weakness of muscles, respiratory and cardiac failure and limited survival. The condition was estimated to be affecting not more 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 recombinant human alpha-glucosidase conjugated with multiple copies of synthetic bismannose-6-phosphate-tetra-mannose glycan may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data supporting that the product improves the muscle function compared to the authorised treatment. The Committee considered that this could translate into a clinically relevant advantage.

A positive opinion for recombinant human alpha-glucosidase conjugated with multiple copies of synthetic bismannose-6-phosphate-tetra-mannose glycan, for treatment of glycogen storage disease type II (Pompe's disease), was adopted by consensus.

2.1.2 Product for treatment of systemic sclerosis - EMA/OD/179/13

[Co-ordinator: K. Westermark] [Expert: N. Feltelius]

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 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 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 was 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..

- 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 was 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.

In the written response, and during an oral explanation before the Committee on 4 February 2014, the sponsor further elaborated on the raised issues. With regards to the medical plausibility, the sponsor discussed the contents of the product and proposed several mechanisms by which it may have effects in the applied indication. The results from the preclinical and clinical studies, including statistical analysis used were also reiterated. In addition, significant benefit was also further elaborated by stressing that the only authorised treatment is for the digital ulcers of patients affected by the condition, while the proposed product targets other systemic aspects of the condition.

The committee considered that the mechanism of action still remains pleiotropic and highly assumptive. The argued trends in the results of the preclinical and preliminary clinical settings may not be considered plausible given the uncertainties regarding of the mode of action of the product. It was also noted during the meeting that from the quoted published paper, measurements of the endpoints do not show statistical significant differences between the groups. The significant benefit of improved efficacy may also not be considered in the absence of a justified medical plausibility.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 4 February 2014, prior to final opinion.

2.1.3 Product for treatment of amyotrophic lateral sclerosis - EMA/OD/178/13

[Co-ordinator: V. Stoyanova]

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

- Intention to diagnose, prevent or treat

The sponsor was 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;

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

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

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 was 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 was 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.

In the written response, and during an oral explanation before the Committee on 4 February 2014, the sponsor further elaborated on the raised issues. With regards to the medical plausibility, the sponsor discussed the contents of the product and proposed several mechanisms by which it may have effects in the applied indication. The results from the preclinical and clinical studies, including statistical analysis used were also reiterated. With regards to the significant benefit, the sponsor provided a discussion versus riluzole and baclofen. For riluzole, a lack of specificity and identification of additional sites of action was argued. For baclofen, the limited effects as described in some of the available literature were discussed.

The committee considered that the mechanism of action still remains pleiotropic and highly assumptive. The argued trends in the results of the preclinical and preliminary clinical settings may not be considered plausible given the uncertainties regarding of the mode of action of the product. The significant benefit may not be considered in the absence of a justified medical plausibility.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 4 February 2014, prior to final opinion.

2.1.4 **Cysteamine bitartrate** for treatment of pancreatic cancer, Raptor Pharmaceuticals Europe BV - EMA/OD/164/13

[Co-ordinator: B. Bloechl-Daum]

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

- Significant benefit

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

In the written response, and during an oral explanation before the Committee on 4 February 2014, the sponsor stressed again the assumed new mechanism of action through inhibition of matrix metallo-proteinases. It was proposed that this mechanism may be particularly important in the context of metastases, and the sponsor discussed data from the in vivo experiments pointing towards a potential for reduction in the number of metastasis. The Committee considered that this would be an acceptable assumption of a clinically relevant advantage over authorised treatments.

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

The intention to treat the condition with the medicinal product containing cysteamine bitartrate was considered justified based on data in preclinical models of the condition where treatment with the proposed product prolonged survival compared to controls.

The condition is chronically debilitating because of pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression, and life-threatening with a median survival of about 6 months. The condition was estimated to be affecting approximately 1.5 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 cysteamine bitartrate may be of significant benefit to those affected by the condition. The sponsor has provided data that demonstrate that the product has an alternative mechanism of action that may translate into improved efficacy. This is based on preclinical models that show reduction of metastases. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for cysteamine bitartrate, for treatment of pancreatic cancer, was adopted by consensus.

2.1.5 Caffeine citrate for prevention of bronchopulmonary dysplasia, Viridian Pharma Ltd - EMA/OD/161/13
[Co-ordinator: K. Westermark][Expert: N. Gullberg]

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 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 the application. In particular the sponsor was invited to discuss the level of overlap between treatment of primary apnoea of the newborn as cause of bronchopulmonary dysplasia vs. prevention of bronchopulmonary dysplasia from other causes.

- Number of people affected

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

In addition the definition of bronchopulmonary dysplasia is usually based on gestational age rather than birth weight, therefore the sponsor was invited to calculate the population at risk based on gestational age rather than birth weight.

In the written response, and during an oral explanation before the Committee on 4 February 2014, the sponsor discussed the medical plausibility taking into account the currently licenced indication of apnoea of prematurity. The discussion was focused on the results of a published clinical trial which studied prevention of bronchopulmonary dysplasia as one of the endpoints. Discussing this study the sponsor showed overall reduced incidence of bronchopulmonary dysplasia in the caffeine treated subjects, consistent through the different groups of the study and irrespective of the main indication

for treatment, therefore supporting the argument of caffeine in preventing bronchopulmonary dysplasia beyond the cases that might have been caused by apnea of prematurity. The sponsor also discussed the possible mechanism of action in the proposed indication, and in particular the effects on the lungs and argued anti-inflammatory activity and improvement of bronchial tone and respiratory muscle function. The COMP considered that the scientific rationale and medical plausibility of using caffeine for prevention is acceptable, and that this is not covered by the current existing indication of treatment of apnoea of prematurity.

In addition and with regards to the prevalence, the sponsor re-calculated the estimate as requested by the Committee.

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

The intention to prevent the condition with the medicinal product containing caffeine citrate was considered justified based on clinical data from published literature showing reduction of incidence of bronchopulmonary dysplasia from different causes in patients treated with the proposed product;

The condition is life-threatening and chronically debilitating due to inflammation and scarring in the lungs, resulting in necrotizing bronchiolitis and alveolar septal injury, which compromises the oxygenation of blood. The population of patients eligible for prevention of the condition was estimated to be approximately 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 prevention that has been authorised in the European Union for the population at risk of developing the condition.

A positive opinion for caffeine citrate, for prevention of bronchopulmonary dysplasia, was adopted by consensus.

2.1.6 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-ordinator: K. Westermark] [Expert: N. Gullberg]

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for prevention of bronchopulmonary dysplasia 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 respiratory distress syndrome, resulting in prevention of bronchopulmonary dysplasia consequently. Since surfactants are only authorised for prevention or treatment of respiratory distress syndrome, the sponsor should discuss the plausibility of using the product for bronchopulmonary dysplasia.

In addition the sponsor was 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.

In the written response, and during an oral explanation before the Committee on 4 February 2014, the sponsor discussed the differences of respiratory distress syndrome and bronchopulmonary dysplasia, as distinct medical entities. It was clarified that the product was being developed for prevention of

bronchopulmonary dysplasia based on an immunomodulatory profile and anti-inflammatory effects, as well as promotion of surfactant homeostasis. The sponsor also defended the preclinical model used, and stressed that in that model the product can attenuate the ventilator-induced inflammation which plays a central role in the pathogenesis of the condition.

The Committee agreed that the condition, bronchopulmonary dysplasia in premature neonates of less than 32 weeks of gestational age, is a distinct medical entity and meets the criteria for orphan designation.

The intention to prevent the condition with the medicinal product containing recombinant human surfactant protein D was considered justified based on preclinical data showing reduction of lung inflammation.

The condition is life-threatening and chronically debilitating due to inflammation and scarring in the lungs, resulting in necrotizing bronchiolitis and alveolar septal injury, which compromises the oxygenation of blood.

The population of patients eligible for prevention of the condition was estimated to be approximately 3 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 recombinant human surfactant protein D, for prevention of bronchopulmonary dysplasia in premature neonates of less than 32 weeks of gestational age, was adopted by consensus.

2.1.7 **Ex vivo cultured human mesenchymal stromal cells** for prevention of graft rejection following solid organ transplantation, iCell Science AB - EMA/OD/168/13

[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:

- Significant benefit

In order to establish the significant benefit of the proposed product the sponsor was 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.

In the written response, and during an oral explanation before the Committee on 5 February 2014, the sponsor discussed the immunological principles of rejection and presented the available preclinical and preliminary clinical data as per the request of the committee.

The Committee agreed that the condition, graft rejection following 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 ex vivo cultured human mesenchymal stromal cells was considered justified based on preclinical and clinical studies from the literature showing prevention of graft rejection in different models of solid organ transplantation.

The condition is life-threatening and chronically debilitating due to the loss of function and reduced survival of the transplanted organ. The population eligible for prevention of graft rejection following solid organ transplantation was estimated to be not more than 0.9 in 10,000 in the European Union, at the time the application was made.

In addition, although satisfactory methods of prevention of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ex vivo cultured human mesenchymal stromal cells may be of significant benefit to the population at risk of developing the condition. The sponsor has provided and discussed preclinical and clinical data from the literature, and sponsor's preliminary clinical data showing that administration of the proposed product in combination with the currently authorised immunosuppressive treatment resulted in prolonged survival of the transplanted organs as compared to immunosuppressive treatment alone, and that it can reduce the need of immunosuppressive treatment. The Committee considered that this constitutes a clinically relevant advantage for the patient population at risk of the condition.

A positive opinion for ex vivo cultured human mesenchymal stromal cells, for prevention of graft rejection following solid organ transplantation, was adopted by consensus.

2.1.8 **Eculizumab** for prevention of antibody-mediated rejection after solid organ transplantation, Alexion Europe SAS - EMA/OD/176/13

[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

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 was 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.

In the written response, and during an oral explanation before the Committee on 5 February 2014, the sponsor elaborated on the differences between antibody mediated rejection and T-cell mediated rejection, including the different effector mechanisms involved in solid organ rejection. Moreover, the sponsor further discussed the results of the preclinical and preliminary clinical studies and asserted that the product would be expected to prevent donor specific antibody mediated activation of the complement system, thereby allowing sensitized patients to receive transplants from donors which they would otherwise be excluded.

Following review of the application by the Committee, it was agreed to rename the indication to “prevention of rejection following solid organ transplantation”.

The Committee agreed that the condition, graft rejection following 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 data showing increased graft survival when the product was used in combination with currently authorised treatments for the condition.

The condition is chronically debilitating due to organ-specific morbidity including e.g. liver or kidney failure, lung fibrosis and lung function decline. The condition is life-threatening as the reduced survival of the transplanted organ leads to premature death. The population eligible for prevention of graft rejection following solid organ transplantation was estimated to be approximately not more than 0.9 in 10,000 in the European Union, at the time the application was made.

In addition, although satisfactory methods of prevention of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing eculizumab may be of significant benefit to the population at risk of developing the condition. The sponsor submitted preclinical data showing that administration of the proposed product in combination with some of the currently authorised immunosuppressive treatments resulted in prolonged survival of the transplanted organs as compared to immunosuppressive treatment alone. The Committee considered that this has the potential to translate a clinically relevant advantage for the patients at risk of the condition.

A positive opinion for eculizumab, for prevention of rejection following solid organ transplantation, was adopted by consensus.

2.1.9 Product for treatment of cystic fibrosis - EMA/OD/166/13

[Co-ordinator: 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 was 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 was 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.

In the written response, and during an oral explanation before the Committee on 5 February 2014, the sponsor discussed the differences of the proposed product compared to an authorised counterpart with the same mechanism of action. The sponsor, based on ex vivo generated data, expected that the product may result in an improved efficacy compared to the existing treatments. The Committee however considered, that the differences shown in these ex vivo settings were minimal and that these data may not be extrapolated to allow conclusions for the justification of significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 5 February 2014, prior to final opinion.

2.1.10 Product for treatment of small cell lung cancer - EMA/OD/094/13
[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 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 with a different protocol (e.g. in relation to start and duration of the treatment) and the methodology for analysing the groups together and normalising 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 was 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 the written response, and during an oral explanation before the Committee on 5 February 2014, the sponsor further elaborated on the available preclinical studies, including a presentation of non-normalised measurements, as well as a on the preliminary clinical observations available. With regards to the potential activity of the product in non-small cell lung cancer, the sponsor reported that expression of SSRT2 receptor does occur in a small subset of non-small cell lung cancer. The Committee discussed that the available data did not allow for establishing the intention to treat the condition as proposed for designation, given the inappropriate pooling of data from different experimental settings and the heterogeneity of results observed.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 5 February 2014, prior to final opinion.

2.1.11 Antisense oligonucleotide targeting transthyretin for treatment of Familial Amyloid Polyneuropathy, Isis USA Ltd - EMA/OD/098/13
[Co-ordinator: J. Torrent-Farnell]

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

- Proposed indication

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

- Number of people affected by the condition

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

In the written response, and during an oral explanation before the Committee on 5 February 2014, the sponsor accepted the revision of the indication to ATTR amyloidosis, and provided a new Application form and scientific Annex for the amended indication. With regards to the prevalence issue, the estimation of the prevalence of ATTR amyloidosis was based on literature, and in particular three population based studies in France UK and Italy. Some of the assumptions used were that the mean survival is 4 years and the rate of under ascertainment up to 50%. The sponsor asserted that the estimate would be approximately 1.32 /10,000 and that if the survival were to be twice as the one assumed, the conclusion would still be 2.64, well below the provisioned threshold.

The COMP reflected on the justifications provided and also took into account previous opinions for products designated for certain clinical phenotypes for ATTR-amyloidosis and concluded to less than 3 per 10,000 people in the EU at the time the application is made

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 transthyretin" and the condition originally proposed by the sponsor should be renamed as "ATTR-amyloidosis".

The intention to treat the condition with the medicinal product containing phosphorothioate oligonucleotide targeted to transthyretin was considered justified based on preclinical data showing reduction of levels of circulating TTR protein after administration of the proposed product.

The condition is life-threatening and chronically debilitating due to the development of polyneuropathy and cardiomyopathy. 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 phosphorothioate oligonucleotide targeted to transthyretin may be of significant benefit to those affected by the condition. This is based on a new mechanism of action that may result in the product being effective in more disease stages than the currently authorised product as supported by preclinical data. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for phosphorothioate oligonucleotide targeted to transthyretin, for treatment of ATTR-amyloidosis, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1 Adeno-associated viral vector serotype 8 containing the human *GUCY2D* gene for treatment of Leber Congenital Amaurosis type 1 (LCA1), Fondazione Telethon - EMA/OD/182/13
[Co-ordinator: J. Torrent-Farnell]

Following review of the application by the Committee, it was agreed to rename the indication to "Leber's congenital amaurosis".

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 8 containing the human *GUCY2D* gene was considered justified based on adequate pre-clinical in vivo data using a validated model.

The condition is chronically debilitating due to loss of visual acuity. The condition was estimated to be affecting less than 1 in 10,000 people in the European Union, at the time the application was mad.

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 adeno-associated viral vector serotype 8 containing the human *GUCY2D* gene, for treatment of Leber's congenital amaurosis, was adopted by consensus.

2.2.2 Amikacin sulfate for treatment of nontuberculous mycobacterial lung disease, Insmed Limited - EMA/OD/191/13
[Co-ordinator: N. Sypsas]

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

The intention to treat the condition with the medicinal product containing amikacin sulfate was considered justified based on the established clinical efficacy of amikacin as active substance in the proposed condition, and on preclinical data with the sponsor's liposomal formulation for inhalation showing high eradication rates of nontuberculous mycobacterial infection in the lungs.

The condition is chronically debilitating due to progressive lung damage in severe forms that respond poorly to treatment. The condition was estimated to be affecting approximately 0.6 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 amikacin sulfate may be of significant benefit to those affected by the condition. The sponsor presented early clinical data showing better lung penetration and lower incidence of side effects as compared to the existing intravenous formulation. The Committee considered that this can translate into a clinically relevant advantage for patients affected by nontuberculous mycobacterial lung disease, as there are well-known and documented side-effects of the existing intravenous

formulation that limit its use. In addition, the possibility of using amikacin by inhalation has the potential to result in a major contribution to patient care by allowing the outpatient administration of the product.

A positive opinion for amikacin sulfate, for treatment of nontuberculous mycobacterial lung disease, was adopted by consensus.

2.2.3 Autologous CD34+ cells transduced with a lentiviral vector containing a codon optimized version of the human *RAG1* gene

for treatment of Recombination Activating Gene 1 deficient Severe Combined Immunodeficiency (RAG1-SCID), Prof. F.J.T. Staal - EMA/OD/188/13
[Co-ordinator: K. Westermark]

Following review of the application by the Committee, it was agreed to rename the active substance should be renamed to “autologous CD34+ cells transduced with a lentiviral vector containing the human *RAG1* gene”.

The Committee agreed that the condition, recombination-activating gene 1 deficient severe combined immunodeficiency, 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+ cells transduced with a lentiviral vector containing the human *RAG1* gene was considered justified based on preclinical data showing the restoration of functional lymphocytes up to 6 months after treatment.

The condition is chronically debilitating and life-threatening due to the repeated and persistent opportunistic bacterial, fungal and viral infections. Pneumonia, diarrhoea and failure to thrive are the main symptoms of the disease, usually appearing around six months of life. The disease is fatal within the first two years of life if left untreated. In cases of longer survival, developmental disorders, hearing loss, skeletal dysplasia and costochondral abnormalities, and hepatic and renal dysfunction can develop. 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, based on literature and European databases.

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

A positive opinion for autologous CD34+ cells transduced with a lentiviral vector containing the human *RAG1* gene, for treatment of recombination-activating gene 1 deficient severe combined immunodeficiency, was adopted by consensus.

2.2.4 Product for treatment of sickle cell disease - EMA/OD/184/13

[Co-ordinator: L. Gramstad]

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 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.

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

2.2.5 Product for treatment of acute lymphoblastic leukaemia - EMA/OD/187/13
[Co-ordinator: B. Dembowska-Bagińska]

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

- 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 is requested to recalculate the prevalence of this condition which will be different from Acute Lymphoblastic Leukaemia.

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

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

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

- Significant benefit

The arguments on significant benefit are based on the potential for improved efficacy and safety in the condition.

The sponsor is requested to further discuss the claims provided and to elaborate on the results from the preclinical and clinical studies to justify the assumption of significant benefit, in particular over the authorised medicinal product with the same mechanism of action (plerixafor) for the proposed orphan indication.

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

2.2.7 Doxorubicin(6-maleimidocaproyl)hydrazone for treatment of soft tissue sarcoma, Eudax Srl - EMA/OD/190/13
[Co-ordinator: D. O'Connor]

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

The intention to treat the condition with the medicinal product containing doxorubicin(6-maleimidocaproyl)hydrazone was considered justified based on preliminary clinical data in patients affected by the proposed condition who had objective responses as assessed by imaging.

The condition is chronically debilitating with a high recurrence and metastasis rate, and life-threatening with an overall 5-year survival rate of approximately 60%. The condition was estimated to be affecting 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 doxorubicin(6-maleimidocaproyl)hydrazone may be of significant benefit to those affected by the condition. This is based on the assumption of improved efficacy, on the grounds of preliminary clinical data in patients affected by the condition, showing improved objective response rates compared to authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for doxorubicin(6-maleimidocaproyl)hydrazine, for treatment of soft tissue sarcoma, was adopted by consensus.

2.2.8 Fixed dose combination of (R-S) baclofen, naltrexone hydrochloride and D-sorbitol for treatment of Charcot Marie Tooth disease type 1A, Pharnext SAS - EMA/OD/193/13
[Co-ordinator: V. Stoyanova]

The Committee agreed that the condition, Charcot-Marie-Tooth disease type 1A, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing fixed dose combination of (R-S) baclofen, naltrexone hydrochloride and D-sorbitol was considered justified based on pre-clinical in vivo data obtained in a valid model of the condition as well as preliminary clinical data.

The condition is chronically debilitating due to the progressive deterioration of peripheral motor and sensory nerves which leads to functional impairment, pain, progressive disability and a reduction in the quality of life. The condition was estimated to be affecting approximately 1.4 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/for the population at risk of developing the condition.

A positive opinion for fixed dose combination of (R-S) baclofen, naltrexone hydrochloride and D-sorbitol, for treatment of Charcot-Marie-Tooth disease type 1A, was adopted by consensus.

2.2.9 Product for treatment of ovarian cancer - EMA/OD/186/13
[Co-ordinator: 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 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 is 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 is 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.

The sponsor should position the proposed treatment in the context of the currently available standard of care and the authorised products for the treatment of ovarian cancer.

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 treatment of osteonecrosis of the jaw - EMA/OD/177/13
[Co-ordinator: A. Corrêa Nunes]

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

- Proposed condition

The sponsor is requested to further elaborate on the proposed condition, and in particular to discern between the proposed condition and all other types of osteonecrosis.

- Seriousness

The sponsor should provide data regarding the morbidity and mortality of the proposed condition, supported by adequate scientific references.

- Intention to treat

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

  - the existing in vitro data and the extrapolation of these data to draw conclusions for the treatment of the proposed condition as applied for designation;
  - the absence of relevant preclinical models for the treatment of the proposed condition as applied for designation;
  - the relevance of the preliminary clinical data in the absence of patients with the proposed condition as applied for designation and the uncontrolled nature of the observations presented.

- Number of people affected

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

The sponsor is requested to supplement the document by data relating to the annual incidence of the condition as applied for designation.

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

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 argininosuccinic aciduria, the sponsor should further elaborate on the validity of the preclinical in vivo model data where an inhibitor of NOS was used and blood pressure was the end point. They should also explain how these results can be bridged to their product. A similar concern regarding the case report where a different although similar product has been used in a patient with this condition was discussed. The sponsor is also asked to elaborate on the relevance of this case to the efficacy of their product in 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.

2.2.12 Product for treatment of aneurysmal subarachnoid haemorrhage - EMA/OD/171/13
[Co-ordinator: L. Gramstad]

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

- Condition

The sponsor is 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.

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

2.2.13 Product for treatment of systemic sclerosis - EMA/OD/165/13
[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 in terms of possible clinically relevant advantage or major contribution to patient care, taking into account the existing authorised medicinal products both at centralized 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.

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 Product for treatment of symptomatic transthyretin mediated amyloidosis - EMA/OD/194/13
[Co-ordinator: A. Magrelli]

Following the initial COMP discussion the sponsor was advised to amend the indication to “treatment of ATTR-amyloidosis”. Following the submission of the revised application on 6 February 2014, the Committee considered that the following issues require clarification by the sponsor:

- Number of people affected

The prevalence calculation appears to be low particular regarding the estimate for senile systemic amyloidosis. The sponsor is 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.

The COMP adopted a list of issues for a written response only.

2.2.15 Volasertib for treatment of acute myeloid leukaemia, Boehringer Ingelheim International GmbH - EMA/OD/181/13
[Co-ordinator: B. Dembowska-Bagińska]

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

The intention to treat the condition with the medicinal product containing volasertib was considered justified based on early clinical data showing efficacy on clinical endpoints in acute myeloid leukaemia.

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

The condition was estimated to be affecting 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 volasertib may be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data that demonstrate favourable responses when the proposed product is used in addition to the current standard of care of acute myeloid leukaemia. The Committee considered that this constitutes a clinically relevant advantage for the patient population affected by the condition.

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

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] [Expert: R. Elbers]

The Sponsor submitted detailed grounds for appeal on 15 January 2014. The detailed grounds for appeal were further addressed by the sponsor at an oral explanation before the COMP on 5 February 2014.

The sponsor argued that while ALK-positive NSCLC is not listed as a distinct medical entity by an international classification system, ALK-rearranged NSCLC is a distinct subset of NSCLC that can be unequivocally identified by a variety of well-established molecular methodologies. It was argued that ALK rearrangements in NSCLC can be identified by a variety of highly sensitive and specific methods, with concordant results among them and that there is a scientific rationale to restrict the clinical

development to ALK-positive tumours. Moreover, the sponsor was of the opinion that ALK positivity is neither a degree of severity nor a stage of NSCLC and has been shown to be a stable attribute of ALK-positive NSCLC. The sponsor rejected the argument that the 15% cut-off is not sufficiently justified, as arbitrary and not based on meaningful evidence. The sponsor also referred to another product that has previously been designated for the treatment of Telomerase Reverse Transcriptase (TERT) positive NSCLC in HLA-A2 positive patients in 2007.

The Committee discussed that the applied product is an orally available ALK kinase inhibitor which inhibits ALK-mediated signalling pathways in ALK-rearranged cancer cells both in vitro and in vivo in non-clinical models. Clinically, associations with ALK-positivity have been made with younger age, never smoking history, histology with signet-cells and advanced clinical stage. However, at present, ALK-positive NSCLC is not listed as a distinct medical entity by any international classification system.

Moreover, the COMP also considered that the proposed indication for designation is a subset of a broader distinct condition, NSCLC, which is not rare. It was discussed that ALK is an oncogenic driver in some patients with NSCLC and thus a relevant therapeutic target for those who are ALK-positive. The Committee acknowledged that there exist a number of well-established molecular methodologies to detect ALK-rearrangements. The proposed cut-off level may be suitable to enrich the number of responders to the treatment, but the ALK positivity was agreed to be a continuum and in the view of the COMP any cut-off point may be considered arbitrary for the purpose of orphan designation in this case. Some members of the COMP were also of the view that the ALK-positivity may be a stage of the disease, in particular as there is only very limited information available on the tumour heterogeneity and the concordance of the ALK status in a patient as the disease progresses. The expert also questioned the biological function of ALK-positive vs. ALK-negative cells in NSCLC.

The COMP's main concern was the limited knowledge of the product's activity outside the proposed subset. The product has been studied with regard to 36 kinases, while there are 518 protein kinases in the human genome. Using a dendrogram of human protein kinases, the sponsor's view was that the tested branches were representative to allow conclusions for selectivity profile of the product. However, the COMP was of the view that this does not sufficiently exclude the activity in other non-tested kinases. Further, in the panel of 36 kinases tested, an inhibitory effect was seen in two other kinases. It is uncertain whether this activity demonstrated against INSR and IGF-1R could be clinically relevant.

During the oral explanation, it became apparent that in addition to those targets, at least two more kinases have been documented to be inhibited by the compound, although again with less potency, namely SSTKD22 and ROS1 (Published on June 6, 2013 in Journal of Medicinal Chemistry by Marsilje et al.). In addition, due to the close homology of ALK and ROS1, and given also the emerging role of ROS1 in NSCLC, the sponsor was asked to clarify if ROS1 could be inhibited by the applied product. The sponsor confirmed that this was indeed the case in some preclinical settings, but the inhibition was less potent and in the sponsor's view the effects of this inhibition were not expected to be clinically relevant for NSCLC based on in vitro cell line testing. The COMP was however of the view that this further supported that the applied product may have activity in other kinases.

The COMP concluded that the non-clinical information provided was not considered sufficient to establish that the product may not be effective in other patient subgroups of NSCLC than the one proposed. In addition, as the sponsor also referred to another previous designation for a different sub-set of the same broad condition, it was stressed that the evaluation is made on a case-by case basis and that since the previous designation in 2007 the knowledge on biomarkers in the context of orphan designation has evolved.

Having examined the grounds for appeal, and the additional considerations provided during the oral explanation the COMP considered that the sponsor has requested orphan designation for a condition that is not a recognised distinct medical entity with reference to the updated guideline ENTR6283/00 Rev 03, but a subset of non-small cell lung cancer.

The sponsor defines the proposed subset based on the presence of equal or more than 15% positive cells by the fluorescent in situ hybridization test.

The pharmacodynamic effects outside of the proposed population cannot be excluded; this is based on the inability of the proposed test to detect non-rearranged activated ALK, the insufficiently justified cut-off point of 15% positive cells, the availability of more sensitive detection tests that have not been used, and the limited number of kinases tested for inhibition by the product; hence it is not established that the product will be ineffective in the rest of the population with reference to the updated guideline ENTR/6283/00 Rev 03; therefore the sponsor has not established that the proposed condition is a valid condition for designation and the broader condition of “non-small cell lung cancer” should have been considered for the purpose of this application.

The intention to treat non-small cell lung cancer with the medicinal product containing 5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N4-[2-(isopropylsulfonyl)phenyl]-2,4-pyrimidinediamine was considered justified based on preliminary clinical studies showing relevant responses in treated patients;.

Non-small cell lung cancer is life-threatening with 5-year overall survival reported to be approximately 15%, and chronically debilitating due to local and systemic spread of the tumour to other organs. The condition was estimated to be affecting more than 5 in 10,000 people in the EU. This was based on 5-year partial prevalence data of approximately 6 in 10,000 people in the European Union, at the time the application was made.

The product is intended for treatment of a life-threatening and seriously debilitating condition, non-small-cell lung cancer. However, the sponsor did not submit the application on the basis of the second paragraph of Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products, and has not provided any data with the application that would allow an evaluation of a potential claim of insufficient return of the investment without incentives. Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are not fulfilled.

Although satisfactory methods of treatment of non-small cell lung cancer have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N4-[2-(isopropylsulfonyl)phenyl]-2,4-pyrimidinediamine may be of significant benefit to those affected by non-small cell lung cancer; the sponsor has provided preliminary clinical data showing responses in patients relapsed or resistant to other authorised products, and this might result in improved efficacy of the product compared to authorised counterparts; the Committee considered that this constitutes a clinically relevant advantage. Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

Based on the above considerations, and having examined the application and the overall data submitted, the COMP therefore recommends, by consensus, the refusal of the orphan medicinal product designation for 5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N4-[2-(isopropylsulfonyl)phenyl]-2,4-pyrimidinediamine, as an orphan medicinal product for the orphan indication: treatment of non-small cell lung carcinoma (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive.

2.4. COMP opinions adopted via written procedure following previous meeting

2.4.1 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 COMP noted final opinion as adopted via written procedure on 15 January 2014.

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

The COMP noted final opinion as adopted via written procedure on 15 January 2014.

2.5. Evaluation on-going

The Committee noted that evaluation was on-going for seven 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

The protocol assistance advice letter was adopted for the following indication:

3.1.1 Product for treatment of chronic lymphocytic leukaemia

The protocol assistance advice letter adoption was postponed to the next meeting for the following indication:

3.1.2 Product for treatment of follicular lymphoma

3.2. 1st reports

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

3.2.1 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 25 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 Adempas (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) [Co-ordinator: V. Saano]
CHMP opinion adopted in January 2014

As agreed during the previous meeting, a list of issues was adopted via written procedure on 15 January 2014 and sent to the sponsor for response. The sponsor was asked to elaborate on the following issues:

- Significant benefit

The sponsor was invited to further elaborate on the significant benefit of the proposed product versus all products authorized in the EU for the treatment of PAH and CTPH.

The discussion should be supported by any available clinical data showing the significant benefit of Adempas to the current management of the target conditions.

In its written response, and during an oral explanation before the Committee on 4 February 2014, the sponsor stressed that CTEPH and PAH are associated with endothelial dysfunction, impaired synthesis of NO, and insufficient stimulation of the NO–sGC–cGMP pathway. It was discussed that the product, could restore this pathway, though both independently activating of soluble Guanyl Cyclase as well as by increasing its sensitivity to NO. The sponsor presented the data from the available clinical studies (CHEST and PATENT) and argued that the product would be of improved efficacy in PAH patients as a monotherapy and in combination with other authorised products; it was also stressed that it would also be the first medicine for the treatment of CTEPH patients.

The COMP concluded that:

The proposed therapeutic indication:

"Chronic thromboembolic pulmonary hypertension (CTEPH)

Adempas is indicated for the treatment of adult patients with WHO functional class II to III with

- inoperable CTEPH,
- persistent or recurrent CTEPH after surgical treatment,

to improve exercise capacity

Pulmonary arterial hypertension (PAH)

Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO functional class (FC) II to III to improve exercise capacity.

Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease"

falls entirely within the scope of the orphan indication of the designated orphan medicinal product orphan indication.

The prevalence of pulmonary arterial hypertension including chronic thromboembolic pulmonary hypertension (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 at the time of the review of the designation criteria. The prevalence is still estimated at less than 2 in 10,000 in the EU.

The condition is life-threatening and chronically debilitating due to progressive dyspnoea and right hearth failure, leading to death in an average period of 2.8 years after diagnosis;

Although satisfactory methods of treatment of the condition have been authorised in the European Union for the treatment of pulmonary arterial hypertension, the assumption that riociguat may be of potential significant benefit to those affected by the orphan condition still holds. In two pivotal trials the sponsor demonstrated significant improvement of the six minute walking test, a validated functional primary endpoint, when riociguat is used on top of currently authorized treatments for pulmonary arterial hypertension in the EU. This was considered by the COMP a clinically relevant advantage for the patients affected by pulmonary arterial hypertension. Regarding chronic thromboembolic pulmonary hypertension (CTEPH), the sponsor demonstrated the clinical efficacy of riociguat in patients that are not eligible for surgery. There are at present no treatments authorized for CTEPH. The COMP considered that the possibility of treating inoperable CTEPH constitutes a clinically relevant advantage for patients affected by the condition and therefore supports the significant benefit.

An opinion not recommending the removal of Adempas, (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 (EU/3/07/518) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

5.1.2 Cholic Acid FGK, cholic acid for treatment of inborn errors of primary bile acid synthesis responsive to treatment with cholic acid; FGK Representative Service GmbH (EU/3/09/683) [Co-ordinator: A. Magrelli]

During the meeting on 23 January 2014, the CHMP adopted a revised positive opinion for granting a Marketing Authorisation under exceptional circumstances to cholic acid FGK for the following therapeutic indications: Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency; 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency; Cholesterol 7α-hydroxylase *(*CYP7A1) deficiency.

The COMP re-discussed their opinion of 12 December 2013 and concluded as follows:

The proposed therapeutic indication "Cholic acid FGK is indicated for the treatment of inborn errors in primary bile acid synthesis due to Sterol 27-hydroxylase (presenting as cerebrotendinous

xanthomatosis, CTX) deficiency, 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency or Cholesterol 7α-hydroxylase (CYP7A1) deficiency in infants, children and adolescents aged 1 month to 18 years and adults" falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product which is worded at broader terms as: "treatment of inborn errors in primary bile acid synthesis responsive to treatment with cholic acid".

The prevalence of inborn errors of primary bile acid synthesis responsive to treatment with cholic acid is estimated to remain below 5 in 10,000 at the time of the review of the designation criteria, and in particular to be affecting approximately 0.07 per 10,000 people in the EU at the time of the review.

The condition is chronically debilitating and life-threatening in particular due to the development of liver failure and cirrhosis.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification that the medicinal product containing cholic acid is of significant benefit to those affected by the condition. This is justified because the product is indicated for specific enzyme deficiencies, which are different to the enzyme deficiencies targeted by the authorised product. The Committee considered that this constitutes a clinically relevant advantage.

The revised opinion not recommending the removal of Cholic Acid FGK, cholic acid for treatment of inborn errors of primary bile acid synthesis responsive to treatment with cholic acid (EU/3/09/683), from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

The COMP noted the CHMP negative opinion adopted in January 2014.

5.1.4 Translarna (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)

The COMP noted the CHMP negative opinion adopted in January 2014.

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)

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)

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

5.2.5 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 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, EU/3/12/1004)

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

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

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

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

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

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

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

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

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

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

5.4. Appeal procedure

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

On 18 January 2014 the Sponsor submitted detailed grounds for appeal to the COMP opinion on 9 January 2014. The detailed grounds for appeal were further addressed by the sponsor at an oral explanation before the COMP on 4 February 2014.

The sponsor based the grounds for appeal on the well-established use of the product in MDR-TB, supported by a large literature in the past 40 years. This literature had already been provided with the initial application however the applicant managed to better discuss the available literature data and their relevance to the significant benefit of PAS-GR in the detailed grounds of appeal. In this view the sponsor further discussed the results from the 2 main literature pivotal trials on PAS, already presented in the original application, including around 500 subjects showing sustained sputum conversion and reduction of decline in microorganisms resistant to other TB drugs (in particular streptomycin) with PAS treatment.

As additional support the sponsor discussed more in depth the data of the two metanalysis (Ahuja 2012, Menzies 2013) on more than 9000 subjects with MDR-TB across different studies, already presented in the original submission. The results show that treatment with PAS was associated more often with the more resistant isolate, i.e. the treatment was administered when patients had very severe MDR-TB or XDR-TB. In this context, the results of PAS-GR were not statistically significant (measured as odds ratio). The sponsor presented a reasoned and detailed analysis of confounding by severe indication that explains the likely estimation of the PAS-GR effects.

The sponsor added additional discussion on the analysis of their own data from the French ATU cohort that has been on-going since May 2011. As of 31 December 2013 231 adult patients were included, many of which migrants with severe MDR-TB. Some of the baseline data of the ATU cohort are not complete in terms of previous treatments, due to that the patients were migrants and their treatment

history was not known. From the other subjects a detailed treatment history was available, with several first and second line MDRT-TB treatments at baseline. The data presented regarding efficacy in this cohort included weight, that stayed stable in the patient population over 5 consecutive semesters and sputum conversion, with median time to sputum conversion if three months (CI 1.6-4.7). Resistance to PAS was detected in only 2 cases out of the whole cohort.

The sponsor further discussed also the safety data from the cohort, already presented in the original application. In the ATU cohort 6% of patients discontinued the treatment with PAS-GR due to adverse effects as compared to data from 2005 where PAS (the non-gastro resistant formulation) was used (Torun et al, 2005). In the 2005 analysis the non-gastro resistant formulation resulted in up to 55% discontinuation due to adverse effects, most of which gastrointestinal. The better tolerability of PAS-GR as compared to the "old" formulation of PAS (still authorized but not used in a few European countries) was considered by the sponsor as an additional argument supporting the significant benefit.

The COMP discussed the analysis of the literature on PAS-GR presented by the sponsor during the re-examination, and the analysis of the data from the ATU cohort.

The data from the literature are in line with the knowledge of the COMP, i.e. that PAS treatment has been usually administered in the past most likely to patients with severe forms of MDR-TB, since its use has been always as second line or in salvage therapy.

The additional discussion on the data from the ATU cohort presented by the sponsor in the grounds of appeal and the oral explanation was carefully assessed by the COMP and several questions and clarifications were asked to the sponsor during the oral explanation. It was clear from what the sponsor presented as baseline data that most patients in the cohort had been heavily pre-treated for MDR-TB. In addition the framework of this cohort (compassionate use) is an indication of the fact that PAS was used in patients who were not responding to a number of other treatments. This included also cases resistant to second line group 4 treatments and linezolide.

The positive outcome in terms of sputum conversion in this group, sustained over time, and the lack of generation of resistance to PAS-GR in the whole cohort were considered by the COMP as a sufficient ground for significant benefit based on a clinically relevant advantage in the MDR-TB population. A clinically relevant advantage is further supported by the very low incidence of resistance to PAS consistently reported in the literature. The safety data from the ATU cohort, showing a 10 times lower discontinuation of treatment for adverse effects with PAS-GR as compared to previous studies with the PAS non gastro-resistant formulation was positively considered by the COMP as reinforcing the clinical position of PAS-GR in the treatment algorithm of MDR-TB.

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 (see section 4.4). 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 still holds. The Committee was of the opinion that there was sufficient evidence from published literature to support the efficacy of the use of para-aminosalicilic acid (PAS) as active substance when added to different types of background regimens in the treatment of multi-drug resistant tuberculosis (MDR-TB). This was further supported by data showing sputum conversion with the proposed PAS-GR formulation in a cohort including patients resistant to several treatments for MDR-TB. The COMP considered that this constitutes a clinically relevant advantage for the patients affected by MDR-TB.

The final opinion not 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.

5.5. COMP opinions adopted via written procedure following previous meeting

5.5.1 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 final opinion as adopted via written procedure on 15 January 2014.

6. Procedural aspects

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

The Committee adopted the draft Work plan for 2014, EMA/552003/2014.

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

The Committee adopted the draft Work for 2014, EMA/549571/2014.

7. Any other business

7.1 Orphan medicines survey on designation and development conducted in October-November 2012

The Committee was briefed on the survey outcome.

7.2 2nd presentation on the EMA move to 30 Churchill Place

The COMP was briefed on the conferences equipment in the new building.

7.3 COMP article *Use of biomarkers in the context of orphan medicines designation in the European Union* published in the Orphanet Journal of Rare Diseases on 24 January 2014

The Committee members noted the publication.

List of participants

Chair:

Bruno Sepodes

COMP Members:

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
Aušra Matulevičienė	Lietuva
Judit Eggenhofer	Magyarország
Albert Vincenti	Malta
Violeta Stoyanova-Beninska	Nederland
Lars Gramstad	Norway
Bożenna Dembowska-Bagińska	Polska
Ana Corrêa-Nunes	Portugal
Flavia Saleh	Romãnia
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

Observers:

Maria Mavris	Eurordis
Diederick Slijkerman	Medicines Evaluation Board, Nederland

Visiting expert:

Rembert Elbers	Federal Institute for Drugs and Medical Devices, Germany (for 2.3.1)