Annex

Scientific conclusions and grounds for refusal presented by the European Medicines Agency

Overall summary of the scientific evaluation of Exondys after re-examination

- **Quality issues**

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the proposed SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At time of Opinion, there are no outstanding issues on the quality of the active substance or the medicinal product.

- **Efficacy issues**

For this application clinical data were provided from a randomized, double-blinded, placebo controlled 24-week Phase IIb study (study 201) and its open label extension Study 202 in a total of 12 DMD patients. The primary analysis of this pivotal trial provided a 24-week comparison of only 4 patients on eteplirsen exposed to the proposed dose of 30mg/kg/week versus placebo (n=4), and additionally 4 patients exposed to 50 mg/kg/week, in which no difference was observed in the 6MWD. Longer comparisons (up to 4 years) with 12 DMD patients on eteplirsen were subsequently performed versus two post-hoc defined, external and non-concurrent cohorts (Italian Telethon DMD Registry and Leuven Neuromuscular Reference Center Registry) in an open label extension study. Both groups (eteplirsen treated patients and untreated external controls) experienced a decline in ambulation. A more pronounced deterioration was observed in the external control groups (both the amenable to exon 51 skipping control group and the one including amenable to any exon skipping patients) than in eteplirsen treated patients. Separation between curves is apparent at Year 3 (Year 3 - 144 metres, p=0.0055; Year 4 - 161 metres, p=0.0007). At individual level the variability between patients is evident and separation between groups is not so clear. A trend favouring eteplirsen treated patients was observed in loss of ambulation (2/12 in eteplirsen treated patients vs. 10/13 in external controls at Year 4), North Star Ambulatory Assessment and ability to rise from supine.

The main limitations in the dataset arise from the limited number of patients by arm (which hinder the interpretability of the study results), and from the duration of the placebo-controlled phase (6 months). The additional data provided from the open-label phase, a 4-year period of treatment, do not allow to convincingly conclude on a relevant effect of eteplirsen in this population. Without an appropriate concurrent control it is not possible to conclude that the results are reflecting a true and clinically meaningful change (slowing the progression) in the course of the condition. The comparison with external control cohort from natural history databases presents with methodological deficiencies, and its results can only be considered as exploratory or supportive. The Applicant has defined post-hoc several external controls that have been used for different comparisons. The potential sources of bias, using this strategy, seriously affect the reliability of the subsets and comparisons, and the conclusions made thereof. This is even more relevant when the external controls are retrospectively selected. In general, this strategy increases the uncertainty about the results rather than providing reassuring comparisons.

During the initial CHMP assessment, three additional clinical studies were being conducted, in order to provide additional data to support the application. Interim analysis became available for one of them, the PROMOVI (study 301) an open-label, multicentre study performed in DMD patients with genetically confirmed DMD with exon deletions amenable to exon 51 skipping. The comparison was done with an untreated control arm of DMD patients amenable to exon skipping of an exon other than exon 51. There were no significant differences in the clinical endpoints between eteplirsen treated and untreated patients. The limitation derived from the small numbers is acknowledged, but the fact that it is a result of the small number of patients does not reduce the uncertainty related to the results observed. Additional post-hoc comparisons with other external controls also have their limitations, as previously mentioned. A comparison versus a different external and non-concurrent cohort was provided (DMD patients on placebo

from the pivotal trial of another medicinal product) for both the whole population and that restricted to those DMD patients walking between 300 and 450 m., and similar shortcomings regarding the comparison groups were identified there.

In terms of the pharmacodynamic proof of concept, a modest increase in dystrophin (truncated) production has been shown in some patients, while in a number of them no production was detected. As the minimum amount of truncated dystrophin expression that is needed to achieve a clinically relevant benefit remains unknown, the value of these data is mainly to serve as supportive for the proposed mechanism of action of the product.

The applicant requested a Conditional marketing authorisation based on their claim that their application fulfils all the requirements from in Regulation (EC) No 507/2006. However, the CHMP concluded that the medicinal product did not fulfil all of the criteria set out in Article 4(1) of the Regulation, such as, the current benefit-risk balance could not be considered positive based on the available, submitted data.

- **Safety issues**

The assessment of the safety profile of eteplirsen was hampered by the limitations of the safety database. The only comparative data comes from study 201 (n=12) in which 4 subjects were randomized to 30 mg/kg, 4 to 50 mg/kg and 4 to placebo for 24 weeks. There are data available from the extension study 202 in which only 6 patients were treated with eteplirsen, 30 mg/kg and 6 with eteplirsen 50 mg/kg for approximately 3 additional years. This small and acquired in a non-comparative manner, dataset makes the assessment of the long-term safety impossible. Therefore, safety data have to be interpreted with caution, precluding any firm conclusions on the safety profile of the product.

All patients (100%) included in the pivotal trial and around 50% of all patients treated with any dose of eteplirsen reported AEs, mainly hypokaliemia, dermatitis contact, oropharyngeal pain, procedural pain, vomiting, balance disorder and cough. Comparison with untreated patients is challenging as only 4 patients were on placebo for 24 weeks.

For the long-term safety assessment, safety data are available only for a small set of patients (6 on eteplirsen 30 mg/kg and 6 on 50 mg/kg). The lack of a placebo controlled arm prevent from drawing any conclusions. One myocardytis event with an atypical presentation was identified in one patient on eteplirsen 30 mg/kg.

Regarding the laboratory findings the main concern is proteinuria that has already been observed in non-clinical studies. Other findings already seen for other antisense oligonucleotides, like elevation of transaminases have also been identified.

In conclusion, the safety profile of eteplirsen has not been thoroughly characterized. The limitation of the database size does not allow for the identification of frequent AEs (≥10%) and the lack of a comparator placebo arm makes it impossible to distinguish between AEs related to the disease or the age of the population and those related to the drug.

- **Grounds for refusal**

Whereas,

The CHMP considered that with the currently available data it is not possible to conclude that the benefit/risk balance of eteplirsen is positive in DMD patients with mutations amenable to exon 51 skipping, since:

- Efficacy of eteplirsen remains not demonstrated. There are no comparative data with patients on placebo beyond 24 weeks, and the available data for patients on treatment are derived from only a limited number of patients (n=12). There was no difference in 6MWD between eteplirsen and placebo during this 24 week treatment period.
- The provided additional comparative data from a variety of external controls, derived from different studies and populations, suffer from important limitations related to the nature of the methodology used (non-concurrent, retrospectively selected, post-hoc defined). This increases the uncertainty about the reliability of such comparisons rather than providing confirmatory data for efficacy.
- It remains unknown whether expression of the observed very low amount of truncated dystrophin after treatment with eteplirsen can translate into any clinical benefit to patients. Although the evidence of truncated dystrophin production may support the mechanism of action of the product, convincing demonstration of sustained functional effect is necessary to support the claim for efficacy of the medicinal product in the intended indication.
- Due to the limited number of patients exposed to eteplirsen the safety profile remains not thoroughly characterised.

The CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the efficacy and the safety of the above mentioned medicinal product is not properly or sufficiently demonstrated.

Therefore, the CHMP has recommended the refusal of the granting of the conditional marketing authorisation for Exondys.