Background and Objectives

- Orphan designation is a status assigned to a drug intended to treat a rare condition. The drug must fulfill criteria for designation as an orphan medicine so that it can benefit from incentives such as prolonged protection from competition once marketed.
- In France, HAS (French National Authority for Health) has increasingly reinforced its requests for post-registration studies, providing a better understanding of innovative drugs in the clinical or real-world settings.
- This study aims to analyze their impact on reassessment with a specific focus on orphan medicines.

Methods

- A search was performed on the EMA (European Medicines Agency) and Orphanet websites to identify all authorized drugs with an orphan status, a marketing authorization under exceptional circumstances, or an indication in at least one rare disease.
- A search of the HAS (French Health National Authority) website was then performed to check whether or not these products had been assessed and reimbursed in France.
- For products having received a positive opinion for reimbursement, the search was extended to identify reassessment or renewal opinions.
- An analysis of the ASMR (level of added medical benefit determined by HAS) was carried out for those drugs having been reassessed between 2005 and may 2016. For each product, we also appraised the indication/therapeutic area, health authority requests, post-marketing study types and study methodology.
- The findings of the variable "indication/therapeutic area" do not support the conclusion that there is a class effect; analyses will therefore not be presented by indication.

Results

Evolution of the ASMR appraisal

- The analysis of ASMR ratings given between 2005 and 2016 showed that there was no ASMR IV or V given until 2007 while in 2015 more than 70% of orphan drug assessments resulted in an ASMR IV or V (figure 8).
- The results of the analysis clearly showed that achieving an ASMR I and II at initial reimbursement registration has become increasingly difficult, even for orphan drugs.
- The results shown in the figures 8 and 9 demonstrate a marked decline in ASMR I and II ratings for both orphan and all products.

Change in ASMR following reassessment

- Of the 105 orphan medicinal products having been assessed for initial reimbursement registration or for an extension of indication, the ASMR of 21 products was reassessed over the study period (for 22 indications).
- Seven of the 22 reassessments resulted in a decrease in the ASMR rating, 6 resulted in an increase and 9 maintained the same ASMR.
- For increases in the ASMR rating not due to reassessment of a therapeutic class (2), the HAS granted an upgrade of the ASMR for companies providing new real-world data (1) or an additional comparative study (2).
- Furthermore, we observed a positive correlation between providing exhaustive data (real-world data or indirect comparison), good study methodology and complying with and providing the type of data requested at initial registration, and a positive opinion from HAS.
- For 7 of the 9 products having maintained their ASMR rating, real-world data were taken into consideration by HAS and contributed to confirming the product's value in the French clinical setting.
- Among the decreases in ASMR rating upon reassessment, the HAS had initially challenged the drug's effectiveness (1 product) or had requested more exhaustive real-world data in a post-inscription study (3 products), and also reappraised and decreased the therapeutic benefit recognized for all treatments of a therapeutic area (2 products).
- For decreases despite the submission of new post-inscription study data (4), HAS criticized the lack of a control group, not reaching the initial inclusion objectives, the limited number of patients included and followed up in studies, and the variable effect size of seen from one study to another, which make it difficult to interpret the results.
- In addition, the lack of information about a large number of patients treated with the orphan drug (patients changing to other treatments, those lost to follow-up, etc.) was seen as being unacceptable since these patients suffer from very rare diseases which by definition require careful monitoring.

Discussions

- HAS expects both efficacy and safety data in a real-world setting to limit uncertainties around a product's value, especially given the fact that orphan drugs are often expensive.
- HAS is therefore more attentive to the use and safety/efficacy profile of the product in French clinical practice. Nevertheless, one limitation of this study is that it is not possible to determine whether HAS prefers one type of data over the other (cohort versus registry).
- The main limitations of this study are that it does not take into account the competitive environment (arrival of new treatments that could impact reassessment of older products) and the low number of reassessments.
- Additionally, further analysis revealed that 9 out of the 21 products assessed are registered on the "liste en sus", of which 6 currently have an ASMR IV or V.
- These products are likely to be removed due to the stipulations of the decree "liste en sus".
- An interesting area for further research would be to evaluate the impact of the reassessment of these orphan products ASMR level on pricing conditions in terms of price cuts or increases.

Conclusion

- Post-inscription studies can remove uncertainties about the transposability of the use of orphan drugs from a clinical trial to a real-world setting.
- In 9 out of 13 cases with real-world post-inscription studies, the ASMR rating of the product was maintained or improved.
- Real-world evidence is increasingly required by payers, including for drugs with a particular status such as orphan designation. Therefore, it is necessary to consider and anticipate the implementation of these studies in order to maintain optimal reimbursement and price conditions for medicinal products.