Health by Advanced Therapies

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Proposal to establish best practice for patient follow-up and data capture

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1. Deliverable's description

Advanced Therapy Medicinal Products (ATMPs) can be defined as a new class of medical interventions and can potentially be used to treat a variety of human health issues, including neurodegenerative diseases (such as Huntington's and Parkinson's diseases), inherited diseases (such as immunodeficiency syndromes), autoimmune diseases (such as diabetes, multiple sclerosis and rheumatoid arthritis) and cancers (such as leukaemia and melanoma). On one hand, the development of new ATMPs is particularly important for severe, rare, or chronic diseases where conventional approaches have proven to be inadequate or where there is room to improve particular treatment strategies. On the other hand, however, the number of patients treated with specific ATMPs is still very low.

ATMPs are centrally regulated at the European level through various regulations. A Marketing Authorisation (MA) is needed for ATMPs to be commercially available. The European Medicines Agency's Committee for Medicinal Products for Human Use makes a recommendation for MA to the European Commission which makes the final decision. Some examples of ATMPs, which are currently commercially available, are Holoclar, which uses human corneal epithelial cells to treat the degeneration of corneal tissue resulting from chemical or physical burns to the eye, and Kymriah and Yescarta, where lymphocytes of patients with leukaemia are genetically modified to recognise the patient's own cancer cells and destroy them (see also figure 1).

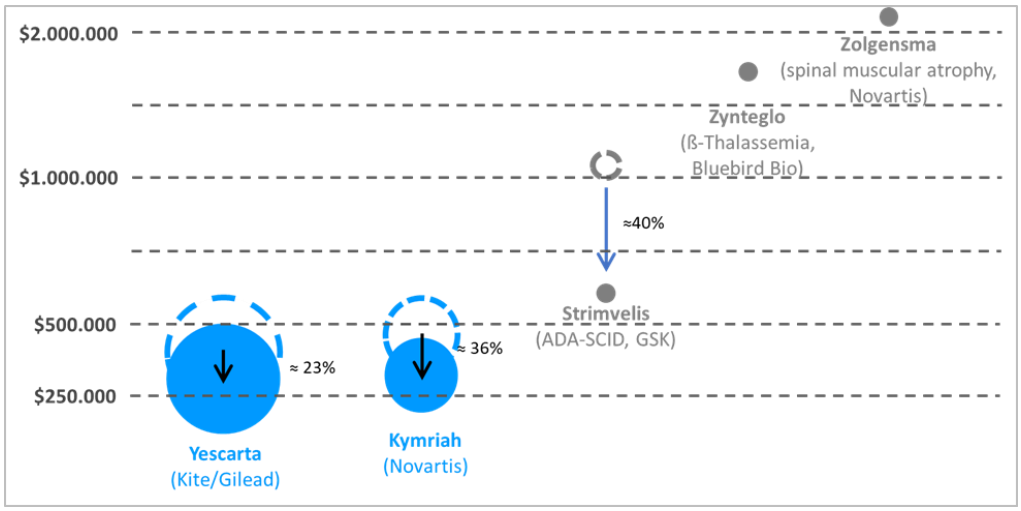

Figure 1: Pricing of current gene therapies. Costs for therapeutic cell products are illustrated in the figure as well as relative market sizes (indicated by the different contents of the circles). CAR T cell products (in blue) are compared to other gene therapy products (Strimvelis, Zynteglo, Zolgensma; in grey). Dashed circles indicate the initial prices of Yescarta, Kymriah and Strimvelis; arrows and percentages indicate drops in market prices in Germany. Initially in 2018, Novartis charged USD 475,000 for Kymriah and Gilead UDS 373,000 for Yescarta. Since then, prices have dropped significantly, i.e. in Germany to USD 304,000 for Kymriah and USD 311,000 for Yescarta (Siegmund-Schultze, 2019) – which equals pricing reductions by 36% respectively 23%.

ATMPs are very different to conventional medicines, often having complex manufacturing processes, orphan indications and tailored production, and are therefore often seen as products with a low commercial value and/or a high commercial risk. As of May 2019, 14 ATMPs have been granted a MA for the European Economic Area (EEA), however, four of them have already been withdrawn from the market for a variety of reasons. Universities are a major player in the ATMP field. Most ATMPs are initially developed by universities and more than half of the clinical studies in Europe were sponsored by universities. In part, this is because university medical centers have the necessary disease-specific expertise, the capacity for innovative research and direct access to donor and patient material. Universities dominate early stage (phase I/II) clinical research, while industry is more involved in late stage (phase III/IV) clinical development.

Next to many other ATMP-specific study requirements, which will not be discussed within this context, the long-term effects of the product may require specific arrangements for long-term follow-up of the subjects, especially for products post marketing authorization.

In this document, we will provide a proposal to establish best practice for patient follow-up and data capture. The aim of this report is to propose how the partners of the RESTORE consortium might contribute to this process further on.

2. State of the art

According to "Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products" (Revision 1, in progress, published Feb 01 2018) for long term patient follow up, wide-ranging principles by the Committee for Medicinal Products for Human Use (CHMP) are suggested as follows:

Generally, the duration of the biological activity of an applied ATMP should be taken into consideration when determining the need for patient follow-up. Where applicable, the establishment of a scheme for long-term follow-up should be described in the study-protocol and it should be undoubtedly specified, where appropriate, which follow-up activities take place after the end of the clinical trial (e.g. interventional clinical trial or non-interventional follow-up).

The length of the observation period should be based, as for all GMP-based activities, on a risk-assessment with regard to all information available to the sponsor. In assessing whether bibliographic data from other products is relevant, account has to be taken not only of the similarity of the product, but also to include the transgene expressed and the administration route. If the risk of delayed adverse events is low, long-term follow-up is not required. Where long-term follow-up is necessary, it is recommended that the sponsor considers discussing the duration of the monitoring scheme with the concerned national competent authority.

When clinical trial participants should be followed after the investigational ATMP has been approved for MA, it is recommended that the monitoring of the clinical trial patients is integrated with the mechanisms foreseen in the MA for the follow-up of patients treated with the approved product.

If the sponsor plans to collect follow-up data from sources other than visits of the participants to the clinical trial site, the process of collecting data should be clearly explained (e.g. use of digital tools or phone calls, visits of the clinical trial patient to a

local physician). The sponsor is responsible to ensure that a robust system for the collection of adverse events is in place and they should explain in the study protocol how the quality of the data collected will be ensured. Measures that could be considered include the training of local physicians, establishment of SOPs for use by local physicians/nurses/healthcare professionals, internal audits, and ensuring the preservation of samples taken from patients in case retesting becomes necessary.

The responsibilities of each of the parties involved (e.g. sponsor, investigator, local physician, nurses, other healthcare professionals involved) should be properly documented. All data collected should be centralized and be available for inspection at the clinical trial site.

When long-term follow-up is foreseen in the protocol, monitoring of patients treated should be ensured also in cases of early termination of the clinical trials. The sponsor should also ensure that there is a process in place for follow-up of the patients treated with the product in cases where the product development is discontinued or the (former) sponsor ceases to exist, for instance, by providing appropriate information to the healthcare establishments involved in the clinical trial.

3. Challenges and Limitations

Clinical trials, containing patient follow-up and data capture are crucial to determining the human safety and efficacy of new therapeutic innovations. As proposed in the previous chapter, the establishment of best practice guidelines for patient follow-up and data capture would stimulate, at the end, approvals for MAs and at the same time the access of potential ATMP-based interventions to the market and patients. Due to the higher degree of uncertainty when evaluating novel therapies such as ATMPs, post-marketing surveillance studies for these products should be designed and shared according to standards to make up the evidential shortfall and provide additional evidence to inform clinical practice. Huge amounts of human experiential data are generated over the period of any clinical trial, astonishingly, much of this data is never made publicly accessible. Improved, reliable data sharing is essential to inform clinical decisions, patient follow-up and data capture and to initiate further therapeutic improvements. Numerous current public and private changes in clinical data sharing

policies and procedures promise to increase access and data utility to reduce waste in research and increase efficiency of evidence synthesis.

4. Putative solutions

Ensuring that all patients attend follow-up visits is crucial in order to accomplish an unbiased assessment of treatment effects. Refusal to participate may result in low enrolment and therefore limit the generalizability of the findings. Patients who initially give their approval to participate but later fail to complete the trial present a major threat to the validity of clinical trials. It has been demonstrated that possible assumptions of the outcomes for participants who were lost to follow-up could change the interpretation of findings. Therefore, all researchers and involved study staff should anticipate and strive to limit the loss of follow-up at the stage of trial design, during the trial conduct and at the time of data analysis.

Next, the process of patient follow-up itself should be standardized to a certain extent, e.g. specifying the chosen method, follow-up intervals, and devices used according to certain guidelines in order to guarantee a specific level of quality. If processes during follow-up investigations are not defined or standardized, it will consequently limit the generalizability of the findings. Further it could be very time-consuming (or in the worst case impossible) to compare the findings with former studies or prospective investigations. These circumstances can significantly limit the potential presumptions, which are based on implemented meta-data analyses and may have a limiting effect on decisions needed for potential MAs of a certain product/application.

In the following, based on EMEA/149995/2008 rev. 1 three examples are given:

I) It is described: If the sponsor plans to collect follow-up data from sources other than visits of the participants to the clinical trial site, the process of collecting data should be clearly explained (e.g. use of digital tools or phone calls, visits of the clinical trial patient to a local physician). In order to be able to compare follow-up data efficiently, it would be imperative to define certain quality standards as prerequisite, e.g. that entirely used equipment to determine parameter such as temperature, weight, blood-pressure

etc. is appropriately qualified, the methods are validated, the staff is appropriately trained and access-rules to raw- and metadata are defined.

II) The sponsor should explain in the study protocol how the quality of the data collected will be ensured, it would be very efficient if best practice guidelines for patient follow-up would be available in order to define an assured standard of quality.

III) As previously described, on one hand the responsibilities of each of the parties involved should be properly documented and on the other hand, all data collected should be centralized and be available for inspection at the clinical trial site. Since documentation is a central tool of data capture, it would be more efficient if best practice guidelines for data capture would be available in order to define an assured standard of quality. It should be a prerequisite, that used hard- and software (clients, network, server, applications, access permissions etc.) are qualified and the processes are validated. Access by third parties should be strictly regulated and documented and e.g. creation, editing or changing of row- and metadata should be organized by access permissions. If technically possible, creation, editing or changing of data should be tracked by audit trail mechanisms.

5. Challenges for RESTORE

It is clear that the process of patient follow-up itself should be more precise described and standardized following best practice guidelines for patient follow-up and data capture. Only if processes during follow-up investigations are defined and standardized according to a certain degree of quality, will it directly increase the generalizability of the findings. It will be less time-consuming to compare the findings with former studies or prospective investigations. These circumstances can significantly increase the validity of potential presumptions, which are based on implemented meta-data analyses and may have a stimulating effect on decisions needed for potential MAs of a certain ATMP-based product/application. In this work package, we suggest a three-stage approach on how the RESTORE consortium could approach these goals over the next five to ten years: first through assessing currently used methodologies in the field of patient follow-up and

data capture, then by establishment of best practice guidelines and finally by managing the implementation. Within the RESTORE consortium exists a wide range of expertise in the field of execution of clinical trials until MA and therefore RESTORE is well qualified to manage the task and implement the changes.

6. Summary

As described in the previous chapters, the processes of MA of currently non-approved ATMPs may be challenged an potentially limited by recent practices in patient follow-up and data capture principles and methodologies. Defining alternative ways of eleminating increased doubts regarding effectiveness of new ATMPs, for example, by improving patient follow-up and data capture methodologies might help to recognise the true value of ATMPs. In particular, ATMPs may face a challenge in demonstrating value within current evaluative frameworks. In this work package, we suggest a three-stage approach on how the RESTORE consortium could approach these goals over the next years: first through assessing current methodologies, then by establishment of best practice guidelines and finally by managing the implementation. The proposed ways by RESTORE for optimization may be helpful in order to catalyze the dialogue around patient follow-up and data capture for ATMPs. By transforming these best practice guidelines into reality, the occasion exists to improve the principles and methodologies used for the assessment of ATMPs that would enable healthcare systems to manage some of the uncertainties and bring ATMPs closer and faster to the market.