Synopsis of the Kick-off meeting, April 12th, 2023

Session 1 Perspectives on opportunities and challenges in EB therapy development

Sub session: EB Expert perspective – Dimitra Kiritsi and Martin Laimer

EB is a disease characterized by skin and mucosal fragility leading to blisters, erosions, and non-healing ulcers. There are four main types of EB based on this level of tissue cleavage, with overlapping but also different clinical characteristics. This disease, that manifests at birth, is chronic, progressive, painful, and disabling, often multisystemic, and sometimes even characterized by reduced life expectancy. So far, patients with EB do not have curative treatments, and they have to manage time consuming bandaging every day.

There are encouraging research efforts that provide new insights into the underlying mechanisms of the disease. Progress in the methodological and technological field has paved the way for more personalized precision medicine; we are more and more able to profile the pathogenic signature/patterns of each patient and identify key structures or mediators that may serve as therapeutic targets. The possibility to realize translational perspectives largely depends on accurate clinical testing to prove the efficacy, effectiveness, and safety of the novel or repurposed drugs. However, clinical research in rare diseases like EB comes with some challenges, including low patient numbers and disease heterogeneity, lack of repository of outcomes and outcome measures that are validated, inconsistent outcome definitions, trial design complexities, trial burden, amongst an array of other factors.

This lack of standardization hinders comparability, data consolidation and cross-study interpretability, which is particularly critical in rare diseases. There is a need to explore experience and expertise to drive the progress, and to gain high quality evidence, trial efficacy and faster translation of true innovation.

Sub session: Patient representative perspective – Rainer Riedl

Patients and their families can bring a lot to the table. They are no experts in EB biology but do have extensive experience in the daily struggle; parents observe their children growing, and thereby observe the changes and symptoms. EB means a life full of pain, but also a life full of fun. Patient organizations like DEBRA Austria are like big and reliable families. The EB House Austria is one of the great initiatives that was realized in a collective effort by clinicians and DEBRA Austria. Two important networks have been set up, including EB-CLINET that links clinical expertise around the globe, and EB-RESNET, which brings together researchers, organizations and DEBRA groups that are interested in conducting and funding research conduct and funding. It also maintains a registry of clinical trials for EB patients.

It is obvious that EB comes with a plethora of different and complex manifestations, with small patient cohorts, and patients that are limited in their mobility. In addition, there are also limited (funding) resources available. During the last decades, studies were conducted with different aims and even more different endpoints that were not always the most appropriate or relevant to patients. Therefore, patients should play a key role in study design as they have high expertise in EB that can contribute significantly to reasonableness and consequently to acceptance to potential study participants. It is essential to inform and educate patients, to address patients' questions and doubts, and to provide clear answers, which will encourage them to participate. In addition, public awareness is key, not only to the public, but also in directing regulatory agencies and fundraising initiatives.

Subsession: Regulatory perspective – Caroline Auriche and Thorsten Olski

The Scientific Advice Working Party (SAWP) is a regulatory organ that provides recommendations on the development of drugs. These recommendations are made on specific aspects of the development on which the Applicant asks feedback from the SAWP on a voluntary basis.

There are a lot of different drug products that are or have been developed to treat patients with EB, ranging from plant extracts to gene therapy, with corresponding diverse mechanisms of action and diverse routes of administration. In addition, there are various subtypes of the disease, which means that there are various prognostic factors, disease severities, and various sensitivities to a given treatment. All these sources of heterogeneity command the choice of a clinical trial's primary endpoint. Besides, the primary endpoint is also chosen to support the target claim/indication as chosen by the applicant.

When the SAWP gives recommendations, it is not an assessment of the data, it is to help to ensure that the drug development will be done in a way that will foster access to innovation for patients. To that end, the SAWP aims to ensure that the data generated throughout the development will allow drawing a conclusion, whatever the conclusion is. Specifically, in the scientific advice working party, the chosen primary and key secondary endpoints in EB trials should be consistent with the claim(s) as pursued by the Applicant, if relevant, should be workable and feasible, which means they should take into account all the above-detailed sources of heterogeneity.

Harmonization is always welcomed, and in this respect, it is stressed that, when making efforts towards harmonization, it should first be considered whether sufficient experience has been acquired through scientific advices in at least one specific linear combination of the above-detailed sources of heterogeneity (including disease subtype, mechanism of action, route of administration, applicant's claim).

Session 2 Outcome assessment in rare diseases

Sub session: Outcome reporting in EB – Eva Korte and Tobias Welponer

A scoping review was performed, analyzing and mapping the outcome domains (the 'what' to measure) and outcome measurement instruments (the 'how' to measure) reported EB studies in the past 30 years. There is an evident increase in trials, especially in the past 10 years, mostly focusing on recessive dystrophic EB. There is an even larger increase in the number of reported outcomes in the total body of included studies over time.

The authors found over twelve hundred outcomes, leading to fourteen different overarching outcome domain areas. The various outcomes reflect the heterogeneity of the disease. The two main areas were safety and skin manifestations. There were 80 different outcome domains, of which wound healing and blister formation were most prominent within the skin manifestations area. The choice of outcomes should also be dependent on the EB type, the age of the study population, the intervention that is being evaluated, and the phase of the trial. In the scoping review paper, the authors have stratified the results for all of these groups, and even within these groups they found reporting heterogeneity.

A total of 200 measurement instruments were identified to measure all the 80 outcome domains, showing the heterogeneity of the data. This might also reflect the heterogeneity of the disease with the different underlying mechanisms, the diverse needs, and distinct cultural backgrounds of the study population. The choice of the correct measurement instrument for the individual outcome is very complex when considering the validity; frequently used measurement instruments might not be suitable for all trials. For example, the Visual Analogue Scale (VAS) might be easy and good

comparable, but it lacks the individuality that would be more prominent in multidimensional scales, and vice versa.

When reporting outcomes, investigators should consider the characteristics of different EB types; recessive dystrophic EB and EB simplex might need different outcome domains. The same goes for treatment type; considering the study setting of a local or systemic treatment, we also need to choose different outcomes in the different settings. Observing the diversity of measurement instrument use in EB, it is important to consider if a measurement instrument is fit for purpose, fit for the outcome, and if it captures a clinically meaningful outcome domain.

Sub session: Outcomes in Duchenne – Elizabeth Vroom

Better patient involvement is a key topic in the rare disease field. Often in research, a patient is asked a question at the end of the research protocol development, or once the project is already running or even finished. A frequently used saying is “from bench to bed”, however, it should be turned around by starting from bed to bench, and then to the bed again.

Input from patients and patient engagement is not a must as in an obligation, but because it is useful. Funny enough the term is often: “patients want a seat at the table”. But it is the patients’ table - it is about the patients. So patient involvement is truly relevant when it comes to trial design, maybe even in the selection of the compound, the outcome and instrument, inclusion criteria, recruitment of patients, data provision and sharing, in the regulatory decision, and ultimately in the access to drugs.

In the design of relevant outcomes, patients should and could play a significant role. Outcome measurement should be patient-centric: the first question to ask with an open question is what is relevant to the patient? Above all, outcomes should be meaningful to the patients. However, many trials on rare diseases in particular, still do not include validated outcomes. It is also important to look at the actual burden to the patient, in other words: is this outcome measurement feasible for the patient?

In the rare disease field, patient data are gold. You need rigorous planning, methodology and partnership between investigators and patient organizations in order to collect data, in often very small and heterogeneous patient populations, based on appropriate well agreed-on measures.

Session 3: Consensus strategy

Sub session: Roadmap of consensus strategy – Marieke Bolling

With this initiative, we aim to bring harmonization and optimization in outcome use and reporting in EB. We suggest doing this by using the proven methodology of ‘core outcome set’ (COS) development by systematically analyzing the existing data, appreciating the vital role of the patient’s voice, and conducting objective multistakeholder voting rounds and consensus discussions. In this process, we will identify what is missing and/or needs to be optimized, with a final goal to speed up the clinical trial period of drug development to bring effective and safe therapies to EB patients.

There is no uniform use of outcome definitions in EB and there does not seem to be a consensus on which outcomes should be measured in a certain setting, or which outcome measurement instruments would be best to use. There is so much knowledge, expertise and experience within each group, each from a slightly distinct perspective. So why not join forces and try and tackle these issues together? Because in the end we all want the same: optimum and meaningful outcome measurement, to get safe and effective therapies to people living with EB as fast as possible. Therefore, we aim to set up a consortium with its first focus on better standardization of outcome

measurement in trials in EB. This starts with setting a scope, followed by developing a core domain set and a core measurement set.

All persons involved in EB research and management, primarily the patient (representative), can be part of the consortium. Everybody is invited to vote in the Delphi procedures to get to the core outcome sets. An organogram has been made in which the tasks are split into a steering group, EB type specific working groups, advisory panels, and project support groups. Based on your comments in the survey, the consensus protocol will be adjusted and optimized and will eventually be published. Everyone attending will be acknowledged in the paper based on personal preferences. After the formation of the working groups and panels the work will start to define the exact scopes of the COS within the working groups for the types of EB and prepare the initial voting lists of outcome domains.