Measuring outcomes in epidermolysis bullosa a regulatory perspective

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COSEB: Scoping review outcome measurement in EB

Increasing number of potential **novel therapies for EB** in development

Increasing number **interventional studies in EB**

Variety of **outcomes and definitions**,
many different **instruments, heterogenous** disease

Scoping review

Korte *et al*.

BJD 2023

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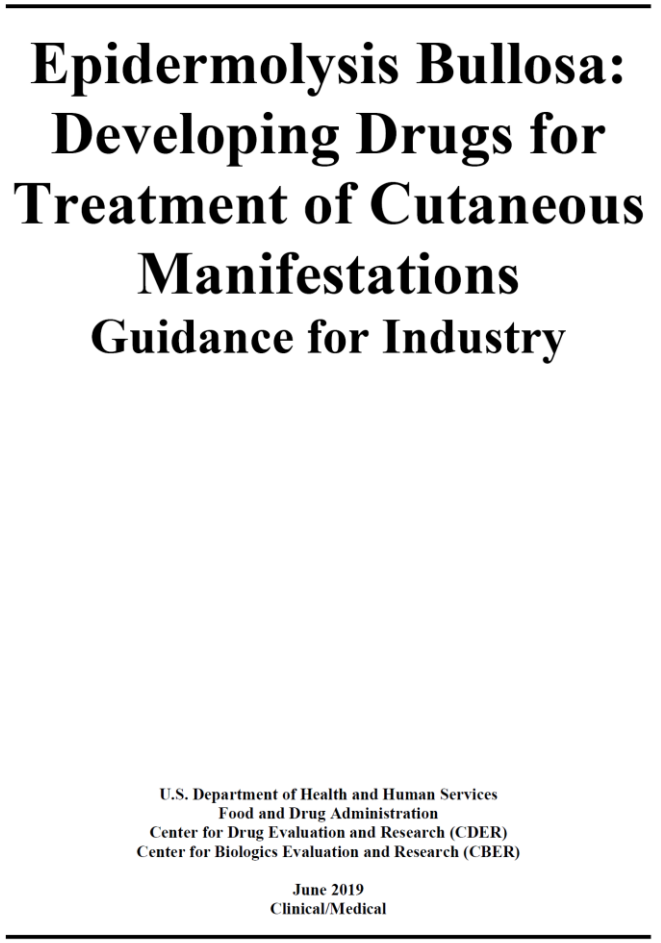
COSEB: What is the perspective of Regulators?

- FDA guidance: "*Epidermolysis Bullosa: Developing Drugs for Treatment of Cutaneous Manifestations; Guidance for Industry*", June 2019

- No EMA guidance available. Scientific advice on the drug development programme can be requested from regulators.

- EMA Scientific advice for academia will become free of charge from 2025 onwards.



Epidermolysis Bullosa: Developing Drugs for Treatment of Cutaneous Manifestations

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

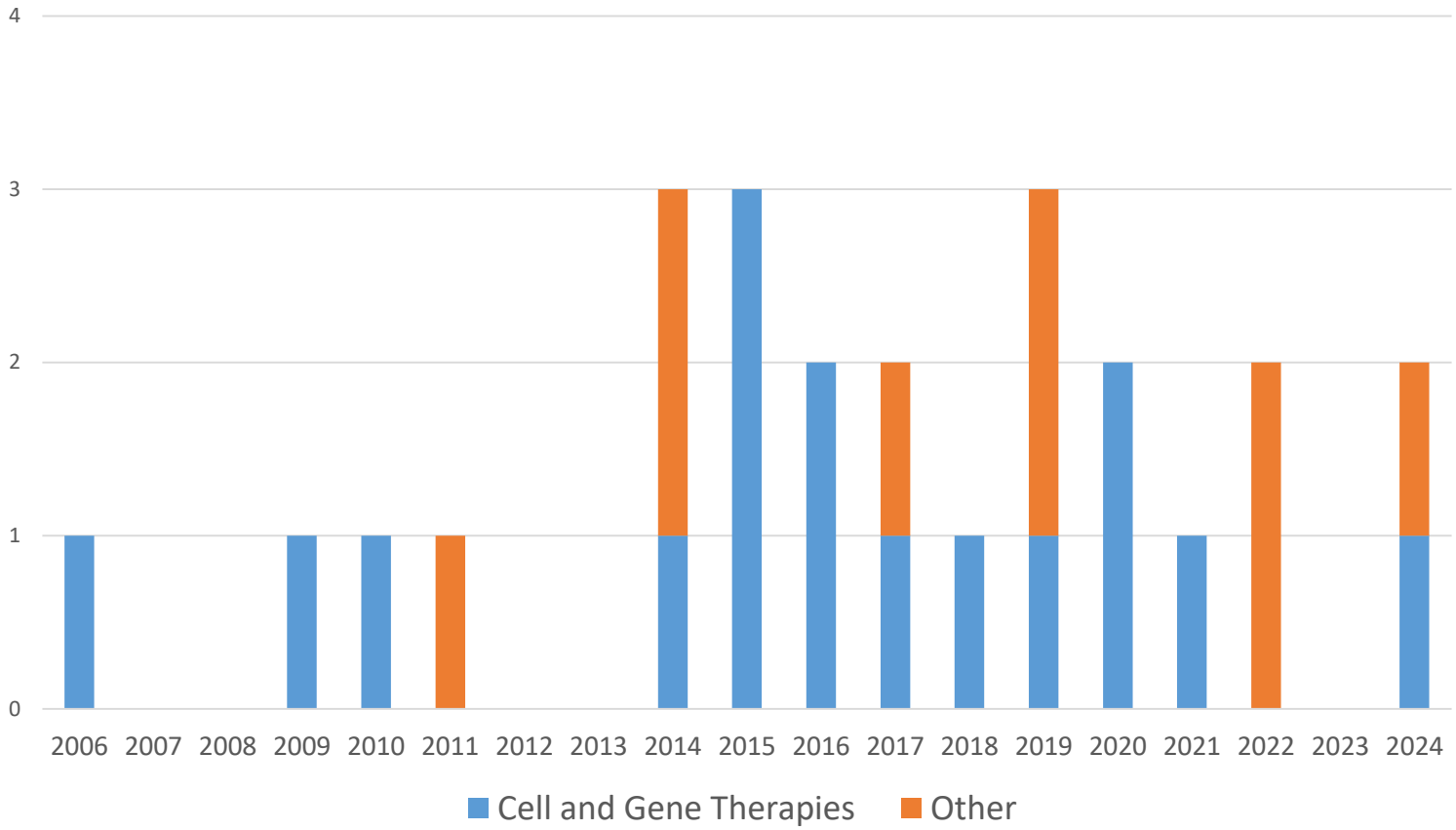
June 2019
Clinical/Medical

Research questions

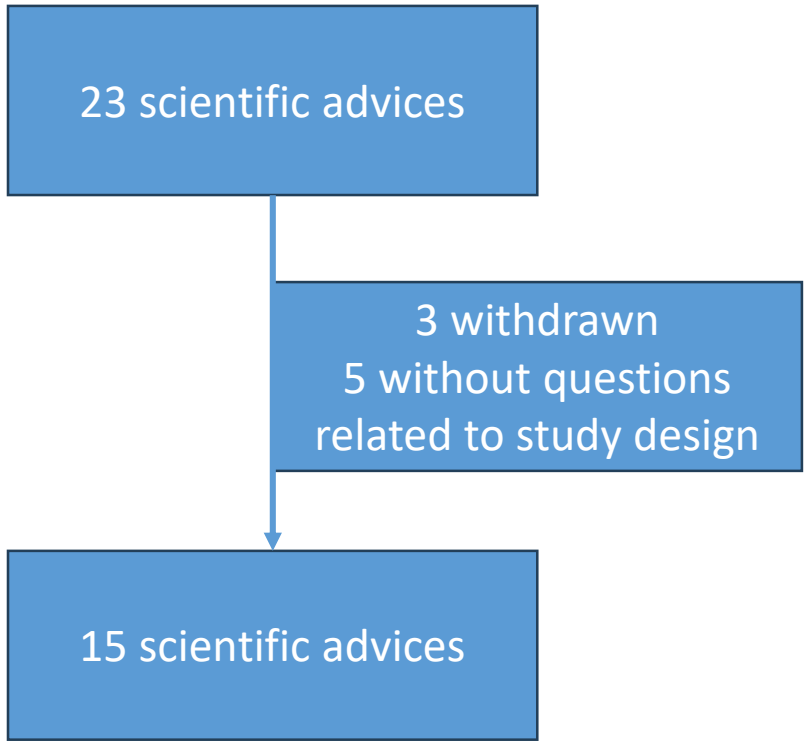
- Which Orphan Designations have been approved for EB?
- How many Scientific Advices were provided for EB?
- What where the main recommendations from the EMA regarding outcomes?

Orphan Designations for Epidermolysis Bullosa

- 28 OD's
- 3 positive outcome but withdrawn (2011, 2014, 2017)
- 64% (16/25) cell- and gene therapies
- 2 EBS, 1 JEB, 13 DEB, 9 not specified
- Filsuvez authorised in 2022 by EC (OD 2011)
- Vyjuvek authorised in 2023 by FDA



Number of Scientific Advices



Products pipeline with:

- diverse products (ATMPs, oligonucleotides, plant extracts)
- diverse mechanisms of actions (e.g., acceleration of wound healing, disease-modifiers, restoration of functional collagen)
- diverse routes of administration (systemic versus topical)
- various EB subtypes (mainly RDEB vs DEB vs EBS vs JEB)

Aim of the Scientific Advice procedures

- The EMA provide scientific advice to facilitate timely access of safe and efficacious medicinal products to patients and users of medicines by:
  - optimising Research and Development
  - reducing uncertainties in regulatory outcomes
  - accelerating time to approval of a marketing authorisation application.

- The **therapeutic indication** will reflect the population included in the main trials for which the benefit/risk balance is established to be positive.

- The Applicant's claim is supported by the **chosen primary and important secondary endpoints**.

Phase II and III trials

Primary endpoints			
Area	Domain	Example	EB type
Cutaneous Manifestations	Wound healing	Proportion of subjects with first complete closure; percentage of wounds achieving total closure;	DEB, All subtypes, JEB/DEB
	Wound characteristics and appearance	Wound closure without drainage	DEB
	Number of blisters	Reduction of the number of blisters in the treated area	EBS
Clinical Assessment	Global Assessment by Investigator	Proportion of patients achieving treatment success on the IGA	EBS
	General disease severity	Reduction of iscorEB clinician; Reduction in EBDASI	RDEB/JEB, RDEB

Comments related to the primary outcome and study design

- Importance of measuring the wound healing **maintenance**
- **Standardisation of wound evaluation** by imaging techniques and blind assessment
- Adequate definition of target wounds
- Effect on **seasonal variations** on the disease severity?
- What is the Minimal Clinically Important Difference (**MCID**)?
- **Extrapolation** from one subtype be **to other subtypes**? Is stratification needed for different subtypes?
- Recommendation to include **similar endpoints** as previous studies for the same product allowing (cautious) **comparison** across studies

"Supporting the efficacy variables for measuring the long-lasting effect to obtain a clear view on the overall risk benefit evaluation."

" The company is advised to standardize the assessment as far as possible and to apply a blinded endpoint assessment (e.g. based on imaging techniques)."

Other comments

- Suggestion on including secondary endpoints such as **quality of life, pain, itching, sleep**
- The **need for additional medications** (rescue)
- Important of **time to wound healing** as a secondary endpoint
- Inclusion of **infection rate** (with the use of antibiotics)
- Inclusion of a **lower age range**, as this is a relevant age group. But… any specific precautions?

"Even though an effect can be statistically significant, the effect that will be seen on the primary endpoint and main secondary endpoints should also be clinically relevant for patients."

"A x% reduction of wound surface as a secondary endpoint appears reasonable, however the durability of re-epithelialisation needs to be addressed."

Summary and Discussion

- **Heterogeneity in primary outcomes**, due to diverse products, mechanisms of actions, route of administration, EB subtypes
- Primary endpoints → mainly focused on **wound healing**
- "The importance of wound healing **maintenance**" and "The **standardization of wound assessment** by imaging techniques and blind assessment'' → most discussed topics in the SAs

- Bruckner- Tuderman et al. (2017) : *" **Wound closure is not synonymous with healing**, and it should be taken into consideration that wound closure may be achieved but breakdown might occur within a short time period. "*
- Gould et al. (2020) → "**reduction of wound recurrence**" among top 3 endpoints
- FDA guidance document; further specification of the important aspects about wound healing:
  - **T**he need for multiple timepoints
  - **A**dditional visits and an extended follow-up
  - **S**tandardization of wound assessment by photographic documentation

Questions?

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GOOD MEDICINES USED BETTER