Losartan for EB,

or "It takes a village to raise a child"

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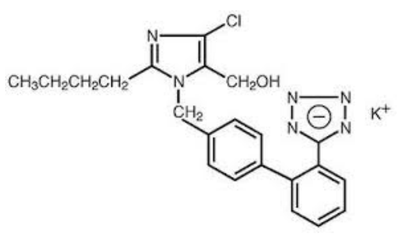
Introduction

Losartan is a well-established medication to treat hypertension and recently has shown promise for the treatment of dystrophic epidermolysis bullosa (EB), a skin blistering disease with secondary scarring and fibrosis. However, more evidence is needed whether losartan is indeed suitable for the treatment of EB and the prevention of fibrotic scarring. Furthermore, losartan is only available as tablets which are poorly suited for treatment of EB.

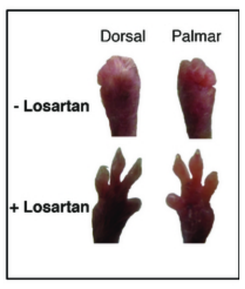
Our objective is to develop a pediatric, easy-to-swallow formulation of losartan. With this new losartan formulation we aim to create the medical evidence whether Losartan is safe and efficacious for the treatment of EB. In case of positive results the ultimate goal is to achieve regulatory approval of losartan as new medicine for treatment of EB.

A particular hurdle for this 'drug-repurposing' project is the lack of patent protection for the established active substance losartan and resulting dim commercial prospects such that pharmaceutical companies decline to sponsor the drug development effort. Instead, multidisciplinary collaboration and support by external funding are required for success.

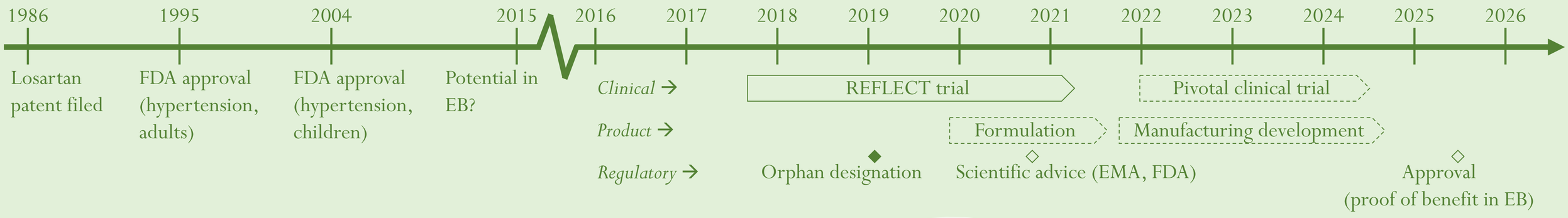
Background: A New Drug Candidate for EB is Born



Losartan was developed in the 1980's by DuPont as the first angiotensin II receptor antagonist (Timmermans et al., 1995). Further drug development led to the marketing authorization of losartan tablets (tradename Cozaar®, MSD) for treatment of hypertension in adults and later also in children 6 years and older.



In 2015, researchers in Freiburg published that losartan reduced fibrotic scarring and prevented fusion of digits in a mouse disease model of dystrophic EB (Nyström et al., 2015).



Present: First Steps have been Taken

Mice are different from men. So what does it take to know whether losartan is beneficial for the treatment of EB also in humans?

- Clinical: In Freiburg, the DEBRA-funded REFLECT trial is ongoing (2017-2021), an initial study of losartan in the treatment of EB with focus on safety. Study medication is prepared individually for each patient in this study. Interim results are now available (Monday presentation by Dr. Kiritsi).
- Nonclinical: Animal toxicology and drug safety studies have been completed previously for Cozaar®. Further animal studies are likely not required.
- Product: A new drug formulation is needed that is easier to swallow then the currently available tablets. Unfortunately, a pediatric formulation of Cozaar®, a losartan suspension previously sold in Europe, is no longer available. Initial formulation efforts have recently been started, but funding is not yet secured.
- Regulatory process: Orphan designation has been granted by both FDA (US Food and Drug Administration) and EMA (European Medicines Agency) in 2019. This provides fee reductions and support by the regulatory agencies along the development path.

Drug development requires a huge effort, even with an 'easy' development path as in the present drug repurposing example, assessing the established active substance losartan for the new indication EB. Outside of large pharmaceutical companies, drug development requires close collaboration by a multidisciplinary team and a large collaborative network. The core for such a network has been formed with the Medical Center – University of Freiburg (clinical expertise), Midas Pharma (drug formulation and manufacturing expertise) and 3R Pharma Consulting (regulatory expertise). Recruitment efforts for additional network partners are ongoing.

Aim: Proof of Maturity - Is Losartan Beneficial for the Treatment of EB?

What else does it take?

Proof of efficacy of losartan for the treatment of EB will require a larger multi-center pivotal clinical trial that uses the to-be-developed novel pediatric formulation of losartan. Only the results of such a study will provide medical evidence whether losartan is beneficial for the treatment of EB or not.

The results of such a study, if positive, can support a new regulatory application: Such approval is sought because it officially confirms an overall positive benefit-risk assessment.

Funding requirements!

Losartan faces fewer technical hurdles compared to other, novel treatments as it is an established medicine (available as tablets for the treatment of hypertension) – however, this fact poses new economic hurdles: With losartan patents expired, companies cannot expect to recoup an investment into clinical studies and alternative funding sources are needed.

Many important tasks such as the development of a study design, preliminary formulation development work, or scientific advice procedures with the regulatory agencies can be funded internally and are being performed by the present project team.

However, external funding is required for the two major development tasks:

- Development of a novel losartan medicine that is easy-to-swallow and suitable for children with EB: Full development including analytical validation and stability studies requires approximately 0.5 million Euro.
- A multi-center pivotal clinical trial will cost approximately 10 million Euro.

Conclusion

Promising drug candidates need to convince on a medical/technical level as well as on economic terms in order to attract funding by the pharmaceutical industry. For losartan for EB, only the former is currently fulfilled. Now it takes a concerted multidisciplinary effort by many parties to provide the technical expertise and the funding to turn this promising drug candidate into a new medicine for EB.

The first steps have been made. The project is advancing and growing up. But to reach maturity much more capacity and funding is needed…

For further information please contact one of us!

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Oral poster presentation: Wednesday, 22 January, at 12.55 (Park Restaurant, Station Two)

References

Nyström A, Thriene K, Mittapalli V, Kern JS, Kiritsi D, Dengjel J, Bruckner-Tuderman L. 2015. EMBO Mol Med 7:1211

Timmermans PB, Duncia JV, Carini DJ, Chiu AT, Wong PC, Wexler RR, Smith RD. 1995. J Hum Hypertens 9 Suppl 5:S3