

Soluble Adenylyl Cyclase (sAC) Inhibitors for the Treatment of Psoriasis

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Background & Unmet Need

- Inflammatory diseases of the skin, including psoriasis and atopic dermatitis, affect millions of people every year
- These diseases cause significant morbidity and increase the risk of other diseases such as diabetes, heart disease, and depression
- Whereas biologics and other systemic therapies are effective for patients with severe disease, those with mild to moderate disease are limited to topical anti-inflammatories
- However, corticosteroids, the most effective topicals, have significant skin and systemic side effects
- Soluble adenylyl cyclase (sAC) is an important source of the second messenger cAMP, which is critical for the activation of T cells during the inflammatory response
- **Unmet Need:** Broadly effective non-steroidal anti-inflammatory for topical treatment of psoriasis

Technology Overview

- **The Technology:** sAC inhibitors that prevent the induction of Th17-mediated psoriasis when topically administered
- **The Discovery:** Th17 cell polarization and growth were prevented by loss of sAC activity
- Based on previous high throughput screening studies that identified LRE1 as an allosteric inhibitor of sAC, TDI chemists developed a series of potent analogs with <100 nM EC₅₀ and attractive PK characteristics
- **PoC Data:** In a 7-day murine imiquimod (IMQ) induced psoriasis model, topically administered TDI-11861 (EC₅₀=1 nM) showed comparable efficacy to steroid control clobetasol but without induction of weight loss
- **Safety:** No overt toxicity was observed in in vivo studies, and TDI-11861 showed no significant activity against >310 kinases or 47 other well-known targets

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Developed in collaboration with the Tri-I TDI

Patents:

PCT Application Filed

Publications:

Fushimi et al. *ACS Med Chem Lett.* 2021.
You et al. *Exp Dermatol.* 2023.

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Technology Applications

- Treatment and prevention of psoriasis and related inflammatory skin diseases
- Combination therapy with topical steroids or systemic biologics
- The sAC inhibitor compounds are also actively being developed for contraception and ocular hypotony

Technology Advantages

- No overt toxicity was noted in *in vivo* studies, despite high dosages
- Demonstrated efficacy via topical administration
- Comparable efficacy to topical steroids but with superior safety profile

Supporting Data / Figures

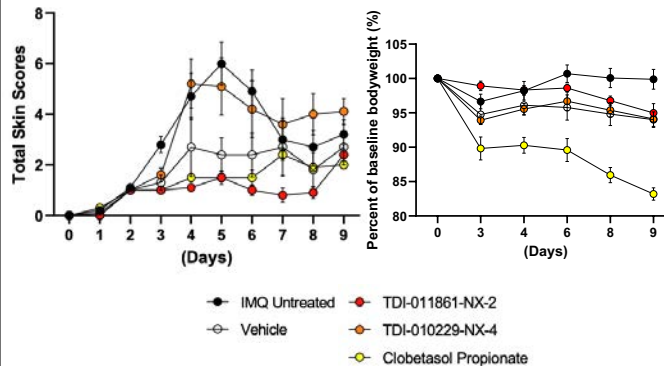


Figure 1: Topical treatment with TDI-11861 significantly ameliorates total skin scores similarly to the group treated with the positive control clobetasol propionate, but without a substantial change in baseline body weight.

The Tri-I TDI has produced an extensive preclinical data package that is available under CDA

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