Clinical study of Netherton syndrome treated topically with a *Staphylococcus epidermidis* strain expressing recombinant human LEKTI-D6 (ATR12-351)

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Abstract

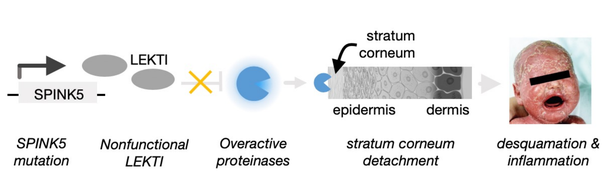
Netherton syndrome (NS) is a rare autosomal recessive disorder caused by mutations in the serine protease inhibitor of Kazal type 5 (*SPINK5*) gene, which encodes the serine protease inhibitor lympho-epithelial Kazal-type-related inhibitor (LEKTI). Loss-of-function mutations in the SPINK5 gene lead to unregulated kallikrein (KLK) proteolysis and activation of the KLK cascade, resulting in skin desquamation and increased transepidermal water loss. Microbial and allergen penetration trigger the release of antimicrobial peptides and activation of inflammatory pathways. There are no approved therapies for NS.

ATR12-351 is a live biotherapeutic topical ointment comprised of an auxotrophic strain of *Staphylococcus epidermidis* (SE351) engineered to express domain 6 (D6) of the human LEKTI protein. Delivery of recombinant human LEKTI-D6 in the lower layers of the stratum corneum restores normal KLK activity levels. ATR12-351 is expected to inhibit skin serine protease activity, improve skin barrier function, and reduce underlying cutaneous inflammation, reducing the signs and symptoms (skin appearance, pain, and pruritus) of NS.

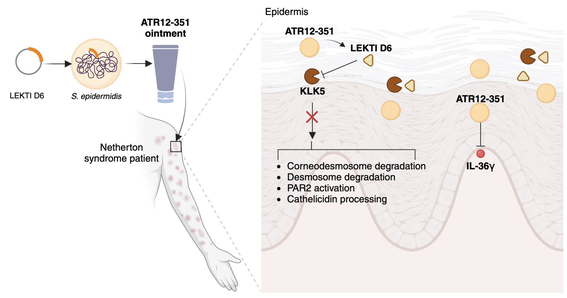
This proof-of-concept, randomized, double-blind, multicenter, vehicle-controlled study (NCT06137157) assesses the safety, tolerability, and pharmacokinetics of topical ATR12-351 in approximately 12 adult patients with NS. ATR12-351 ointment is applied twice daily to a defined area of affected skin on one side of the body, and its vehicle is applied to similarly affected skin contralaterally during a 14-day treatment period. Throughout the study, including a 70-day follow-up period, clinical assessments include safety and local tolerability, the severity of the signs and symptoms of NS, local biomarkers (including KLK activity), and the presence of LEKTI-D6 in skin. The results of this clinical study will establish an initial safety and efficacy profile of ATR12-351 in NS patients to potentially support further clinical development.

ATR12-351 Overview

Etiology of Netherton syndrome



ATR12-351 mechanism of action



- **ATR12-351 is a live biotherapeutic product,** comprised of an **auxotrophic strain** of *Staphylococcus epidermidis* (SE351) engineered to express domain 6 (D6) of the human LEKTI protein. SE351 has the following preclinical properties:
  - Nanomolar IC_{50} values to inhibit KLK5, a key driver of Netherton syndrome
  - Delivers functional LEKTI and reduces protease activity to normal levels
  - Delivers LEKTI in significantly more effective quantities and skin depths than topical LEKTI delivery alone
  - Is formulated as a topical ointment (ATR12-351)
- **Mechanism of action:** Delivery of recombinant human LEKTI-D6 (rhLEKTI) in the lower layers of the stratum corneum restores KLK activity, while the *S. epidermidis* strain reduces IL-36γ. Auxotrophic ATR12-351 inhibits the overactive proteases through LEKTI fragment secretion.
  - Inhibits skin serine protease activity, improves skin barrier function, reduces underlying cutaneous inflammation, and improves the cutaneous signs and symptoms (appearance, pain, and pruritus) of Netherton syndrome

Clinical Study Objectives

- **Primary objective**:
  - Assess the safety and tolerability of topical application of ATR12-351
- **Secondary objectives:**
  - Evaluate efficacy signals including investigator and patient global assessments, and NS-modified SCORAD
  - Evaluate the skin pharmacokinetics of rhLEKTI-D6
- **Exploratory objectives:**
  - Evaluate pharmacodynamic parameters, including anti-rhLEKTI response, cytokine responses, biomarkers such as KLK5, KLK7, IL-36γ, TARC/CCL17, trypsin-like activity, and chymotrypsin-like activity

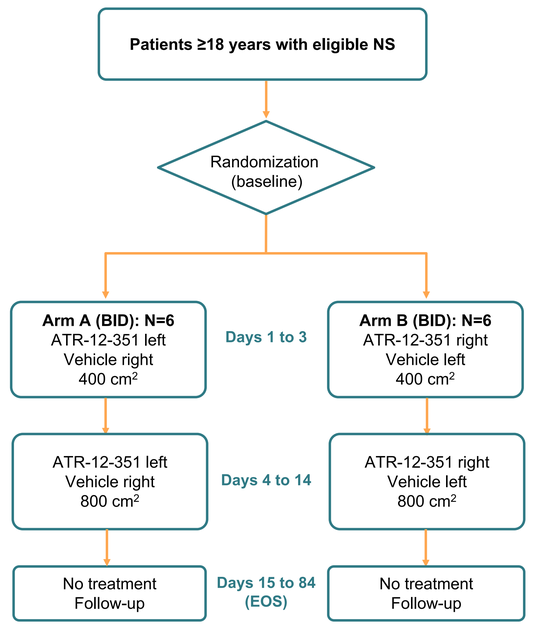
Clinical Study Design

Multicenter, randomized, double-blind, intra-patient, vehicle-controlled study in adults with Netherton syndrome

- Dose level: 10^9 CFU / g ATR12-351
- Applied twice daily for 14 days

Key Eligibility Criteria:

- Confirmed mutation of the serine protease inhibitor of Kazal type 5 (SPINK5) gene
- Involvement of ≥20% of body surface area with skin changes consistent with Netherton syndrome
- No concurrent use of biologic therapies, antibiotics, antihistamines, corticosteroids, retinoids, disease-modifying antirheumatic drugs (DMARDs), immunosuppressive agents, phosphodiesterase-4 (PDE4) inhibitors, topical calcineurin inhibitors, or topical Janus kinase (JAK) inhibitors
- No open wounds or extensive areas of excoriation precluding identification of appropriate application sites



Summary

- ATR12-351 is a topical ointment containing a lyophilized version of a live biotherapeutic product, *Staphylococcus epidermidis* strain designated SE351. This strain has been modified to be auxotrophic and to express recombinant human LEKTI protein.
- ATR12-351 is intended to address the underlying cause of Netherton syndrome by replacing deficient/dysfunctional LEKTI at affected areas, countering the dysregulated skin serine protease activity.
- The Phase 1b, first-in-human clinical study aims to establish the safety and tolerability, as well as the initial efficacy of ATR12-351 application in patients with Netherton syndrome.

More information about this clinical trial is available at clinicaltrials.gov (identifier: NCT06137157).