Study Design and Preliminary Safety and Tolerability of PCS499 for the Treatment of Necrobiosis Lipoidica

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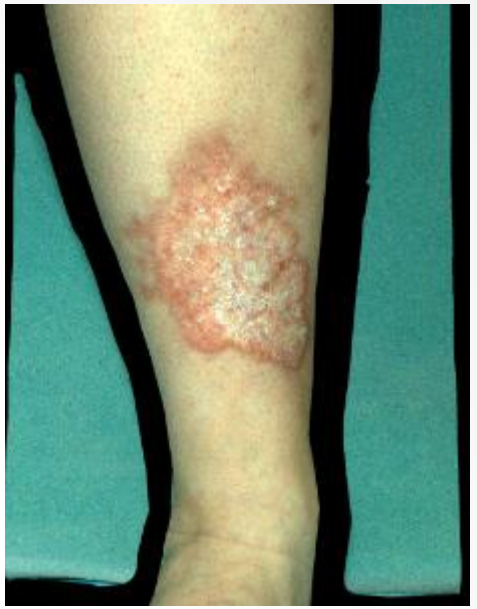
Background/Summary

- **Necrobiosis lipoidica (NL) is a chronic, disfiguring condition characterized by plaques with an atrophic yellow center, usually on the shin**
  - No FDA-approved therapies exist for NL
  - Some evidence of pentoxifylline (PTX) efficacy in NL exists; however, dose limiting adverse events at 400 mg TID (1200 mg daily) preclude administration of higher doses



- **PCS499 is a deuterated form of the primary metabolite of PTX**

- **Administration of PCS499 produces higher concentrations/exposures of active moieties compared to PTX. Active moieties inhibit the secretion of pro-inflammatory cytokines (i.e., TNF-α, IFN-γ), increase blood oxygenation, and improve blood flow.**

1800 mg daily dose of PCS499 (administered as 900 mg BID or 600 mg TID) was found to be safe & tolerable in healthy volunteers

A study to assess safety & tolerability of 1800 mg daily of PCS499 in NL patients is currently ongoing

Phase 1 – Exposure and Safety Study in Healthy Volunteers

- **Design/Methods:**
  - Open-label, 3-period sequential crossover study to assess the pharmacokinetics (PK), exposure, and safety
  - Regimens of 900 mg BID and 600 mg TID of PCS499 & 400 mg TID of PTX in fed healthy volunteers
  - Subjects received a single dose on Days 1 and 4 and multiple doses on Days 2 and 3
- **Results:**

PK Parameters (Geometric Mean) for Active Moieties (Day 4)

	PCS499 900 mg BID (n=5)	PCS499 600 mg TID (n=5)	PTX 400 mg TID (n=6)
Cmax/Dose (ng/mL/mg)	2.11	2.48	1.02
AUC(0-24)/Dose (ng.h/mL/mg)	19.3	16.2	7.32

2.6x higher

2.2x higher

Safety – Treatment emergent adverse events (TEAE)

	PCS499 900 mg BID (n=5)	PCS499 600 mg TID (n=5)	PTX 400 mg TID (n=6)
At least 1 TEAE	2	2	2
At least 1 TEAE related to drug	1 (mild nausea)	0	1 (mild headache)

1800 mg daily dose of PCS499 (administered as 900 mg BID or 600 mg TID) was well tolerated despite higher active moiety exposures on a per mg per day basis

Phase 2 - Safety and Tolerability Study in NL Patients

- **Overall Design:**
  - Open-label, study to assess the **safety and tolerability** of **daily dosing of 1800 mg PCS499** in **NL patients**
  - **6 month treatment period** (+ 6 month extension period)
  - Exploratory measures of efficacy and quality of life will also be assessed
- **Study population:**
  - Approximately **12 NL patients** (~6-9 patients without ulceration and ~3-6 patients with ulceration)
    - **Key Inclusion criteria:**
      - Biopsy-confirmed diagnosis of NL
      - Reference NL lesion with at least mild inflammation and minimum size of 10 cm^2
    - **Key Exclusion criteria:**
      - Current or previous (within 4 weeks of Baseline) treatment with:
        - Oral, topical, or intralesional corticosteroids; Oral or topical retinoid
        - Systemic pentoxifylline, theophylline, or cilostazol; Systemic or topical immunosuppressants
      - Current or previous (within 12 weeks of Baseline) treatment with any biologic therapy
      - Phototherapy/photochemotherapy (NBUVB, UVB, PUVA), skin grafting, or other surgical procedure (other than debridement) within 6 weeks prior to Baseline

- **Status:** ****Currently Enrolling** Visit** https://clinicaltrials.gov/ct2/show/NCT03698864

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