

PS-1001: A NOVEL PAN-INFLAMMASOME INHIBITOR TARGETING ASC FOR THE TREATMENT OF HIDRADENITIS SUPPURATIVA

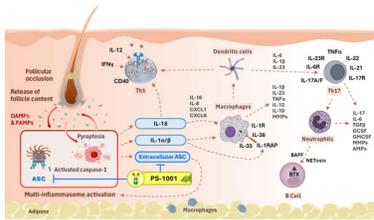
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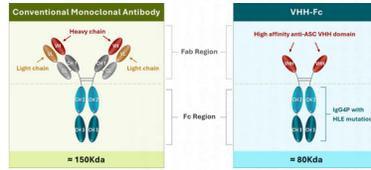
Background & Rationale

Therapeutic Rationale in HS

High levels of DAMPs/PAMPs in HS lesions drive chronic inflammasome activation. By targeting ASC, PS-1001 delivers pan-inflammasome blockade, preventing the release of both IL-1 β and IL-18 and arresting the inflammatory cascade at its source.

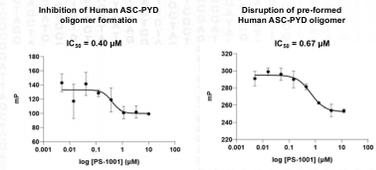


PS-1001 Molecule Profile



- Structure:** PS-1001 is a bivalent VHH-Fc fusion protein (80 kDa) consisting of a high affinity anti-ASC VHH domain fused to a human IgG4P Fc backbone engineered with half-life extending mutations.
- Tissue Penetration:** PS-1001's smaller format (compared to mAbs) facilitates deep tissue penetration into fibrotic, indurated HS lesions.
- Intracellular Delivery:** PS-1001 was engineered for intracellular uptake and cellular potency, ensuring potent target engagement.

Dual Mechanism of Action



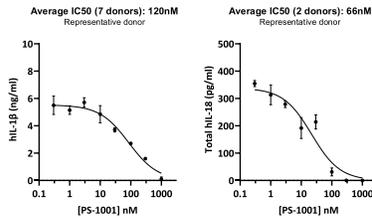
PS-1001 is a pan-inflammasome inhibitor that targets ASC via two distinct modes of action:

- Inhibition of Speck Formation:** Inhibits nucleation of productive ASC filament formation, preventing inflammasome activation, pyroptosis, and cytokine release (IL-1 β and IL-18).
- Disruption of Pre-formed Specks:** Actively disassembles existing ASC filaments—both intracellular and extracellular—dampening the spread of inflammation.

Pharmacologic Profile and In Vivo Proof-of-Concept

Potent Cellular Activity

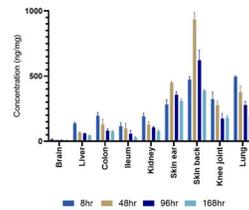
PS-1001 potently inhibits IL-1 β and IL-18 release in inflammasome-activated (LPS/ATP) human PBMCs.



Biodistribution and Skin Bioavailability

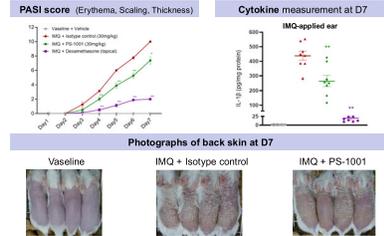
Following systemic administration (30mg/kg IV) in C57BL/6 wild type mice, PRT-000112* exhibits extensive tissue distribution, achieving high concentrations in the skin, the primary target tissue for HS.

*PRTa-000112 retains the same VHH sequence of PS-1001 without half-life extended mutations in Fc backbone



Efficacy in Inflammatory Models

In Vivo Efficacy. Efficacy in Skin Inflammation Model: PS-1001 significantly reduced disease pathology and inflammation in the Imiquimod (IMQ)-induced psoriasis model.

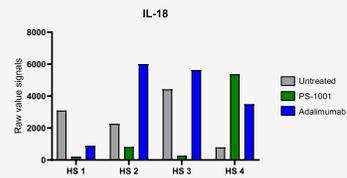


Broad Activity: Efficacy was also observed in Gout (reduced joint swelling/pain) and Colitis models (reduced DALI score), confirming robust anti-inflammatory activity in different disease contexts.

Efficacy in Patient-Derived HS 3D-SeboSkin Model

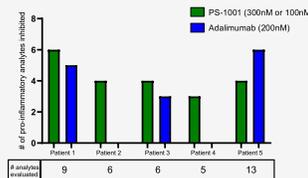
Preclinical Proof-of-Concept in Human Tissue: PS-1001 was evaluated in the HS 3D-SeboSkin model, an *ex vivo* system derived directly from lesional skin of HS patients. This model preserves the native immune architecture and inflammatory milieu of the disease.

Potent IL-18 Inhibition



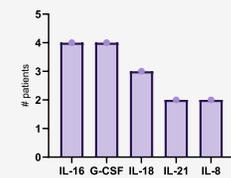
- Robust Response:** PS-1001 achieved a >60% reduction in IL-18 secretion compared to vehicle in 3/4 patient donors.
- Target Engagement:** Significant suppression of IL-18 confirms PS-1001 effectively penetrates HS tissue and inhibits inflammasome activity in HS skin.
- Distinct Mechanism:** IL-18 is a key inflammatory driver in HS that is not addressed by IL-1 inhibitors or adalimumab (TNF- α blockade).

Broader Inflammatory Activity than Adalimumab



- Superior Breadth:** PS-1001 suppressed a significantly broader repertoire of pro-inflammatory analytes compared to the standard of care, adalimumab.
- Upstream vs Downstream:** While adalimumab targets a single downstream cytokine (TNF- α), PS-1001 inhibits the inflammasome upstream, abrogating the release of multiple DAMP/PAMP-driven cytokines simultaneously.

Dampening of Distinct Innate and Adaptive Pathogenic Axes

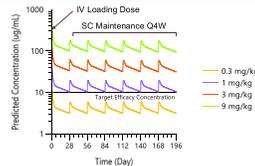


- Neutrophil Axis (IL-8, G-CSF):** Suppressing these chemoattractants limits neutrophil infiltration, a key driver of abscess formation and purulence.
- Chronicity Signals (IL-21, IL-16):** Inhibition of these cytokines limits T-cell recruitment and maintenance, potentially disrupting the Th17 axis associated with disease persistence.
- Th1/IFN- γ Axis (IL-18):** Reduction of IL-18 disrupts a critical driver of IFN- γ production and the Th1 inflammatory loop.

Safety, PK & Clinical Readiness

- Non-Clinical Safety:** No adverse findings observed during a single-dose (30 mg/kg) NHP PK study over the 28-day observation period.
- CMC and Developability:** High-concentration (>100 mg/mL) liquid formulation exhibits low viscosity and excellent stability, supporting a low-volume subcutaneous (SC) autoinjector presentation.
- Immunogenicity Risk:** Favorable profile observed in *in vitro* assays (50 donors), demonstrating low T-cell activation potential comparable to approved biologics.

Predicted Human PK Supports Q4W Dosing Regimen



- Modeling Strategy:** Human PK profiles were projected based on NHP PK parameters.
- Half-Life Extension:** Engineered Fc backbone confers a predicted human half-life ($t_{1/2}$) of ~1180 hours (~49 days), validating the molecular design for chronic dosing.
- Regimen Optimization:** Modeling confirms that an IV loading dose followed by SC maintenance supports a Q4W dosing interval, maintaining target trough coverage (C_{trough}) projected to be efficacious.

Conclusion

- Novel Mechanism of Action:** PS-1001 validates ASC as a tractable therapeutic target, delivering potent pan-inflammasome inhibition.
- Ex Vivo Proof of Mechanism in HS:** In patient-derived HS tissue, PS-1001 demonstrated a broader anti-inflammatory profile compared to adalimumab. By blocking ASC, the central component of the inflammasome complex, PS-1001 inhibits both IL-1 β and IL-18, distinguishing it from selective IL-1 blockers that leave IL-18 unaddressed.
- Candidate Profile:** Favorable PK and developability characteristics support a patient-friendly Q4W subcutaneous regimen.
- Path to Clinic:** IND-enabling studies are currently underway to support the initiation of First-in-Human (FIH) clinical trials in late 2026.