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# Imsidolimab, a novel high affinity IgG4 IL-36 Receptor Antagonist, was Effective and Well-Tolerated in Patients with Generalized Pustular Psoriasis: Results from Phase 3 trials, GEMINI-1 and GEMINI-2

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**Introduction & Objectives:**

Generalized pustular psoriasis (GPP) is a rare, severe disease characterized by debilitating flares of non-infectious pustular and erythematous skin lesions, with systemic impacts that can be life threatening. The pathogenesis of GPP is mainly attributed to excessive activity of interleukin-36 (IL-36) pathway, often caused by mutations in the *IL36RN* gene encoding IL36Ra. Imsidolimab is a novel highaffinity humanized immunoglobulin IgG4 mAb that specifically binds the IL-36 receptor (IL36R) and antagonizes IL36 signaling. The efficacy and safety of imsidolimab was investigated in GPP patients in two global, Phase 3 studies, GEMINI-1 and GEMINI-2.

**Materials & Methods:**

In GEMINI-1, a randomized, double-blind, placebo (PBO)-controlled study, GPP patients were randomized in a 1:1:1 ratio to receive a single intravenous (IV) dose of 300mg imsidolimab, 750mg imsidolimab, or PBO. Primary efficacy at Week 4 was achievement of a GPP Physician Global Assessment (GPPPGA) score of clear (0) or almost clear (1) across GPP disease attributes. Responders (GPPPGA 0 or 1), partial responders (GPPPGA >1), or those needing rescue therapy (RT) had the option to enroll in GEMINI-2, a long-term extension study. Responders were re-randomized to receive a subcutaneous (SC) 200mg dose of imsidolimab or PBO every 4 weeks (Q4W) and all partial responders received a SC 200mg dose of imsidolimab. Patients who received PBO in GEMINI-1 and needed RT crossed into GEMINI-2 and received imsidolimab 750mg IV, followed by imsidolimab 200mg SC Q4W.

**Results:**

Forty-five GPP patients received study treatment in GEMINI-1, 42 of which enrolled in GEMINI-2. In GEMINI-1, the primary endpoint of GPPPGA 0 or 1 was achieved in 53.3% of patients in the 750mg group and 53.3% in the 300mg group, vs 13.3% of PBO patients. Among PBO patients that received imsidolimab as RT in GEMINI-2, 55.6% attained GPPPGA of 0 or 1 at Week 4. No responders re-randomized to imsidolimab had a GPP flare through Week 24, and all maintained GPPPGA 0 or 1, while in the PBO group 62.5% flared and 75.0% lost GPPPGA 0 or 1 response. No PBO cross-over patients had a flare, and all maintained GPPPGA 0 or 1. No serious adverse events led to discontinuation or were treatment-related.

In GEMINI-1, the most common treatment emergent AE (≥2 and more frequent than PBO) observed in 2 patients (4.4%) in the 750mg treatment group was headache. Additionally, only 1 case of anti-drug antibodies (ADAs) (1/30, 3.3%) was reported. In contrast, 23 cases of ADAs (23/60, 46%) were reported among patients who had received at least one dose of spesolimab.

**Conclusion:**

Single IV imsidolimab doses (300mg and 750mg) and monthly SC doses (200mg) demonstrated clinically meaningful results for the treatment of GPP flares. Across both GEMINI-1 and GEMINI-2, imsidolimab was proven to be safe and well tolerated. Targeting IL-36 signaling with imsidolimab represents a promising therapeutic option for GPP patients.