A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Gusacitinib (ASN002) in Subjects with Moderate-to-Severe Chronic Hand Eczema

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Introduction

Chronic hand eczema (CHE) is an often-debilitating condition that affects approximately 10% of the U.S. population and millions of people worldwide. Patients with CHE suffer greatly from this disease, which limits their ability to work and perform activities of daily living. Disease drivers of CHE are multifactorial with genetics, atopy, contact allergens and irritating substances playing a role in 'triggering' the disease. Gusacitinib is an oral inhibitor of SYK and JAK signaling including Tyk2. SYK-JAK inhibition with gusacitinib modulates Th2, Th22, Th1 and Th17 cytokines, and regulates keratinocyte IL17 mediated signaling and proliferation/differentiation. Hence gusacitinib can simultaneously target both the immune cells and epithelial cells involved in CHE and other dermatologic and inflammatory conditions.

Gusacitinib was evaluated in moderate to severe CHE patients in a 16-week Phase 2b randomized, double-blind, placebo-controlled study (NCT03728504). Study objectives included efficacy, safety/tolerability, and pharmacokinetic measurements.

Material and Methods

Patients were randomized 1:1:1 placebo or gusacitinib at 40 or 80 mg oral once daily for 16-weeks (n=97). Inclusion criteria included a Physician Global Assessment (PGA) of moderate to severe and be refractory to moderate, high or ultra-high potency topical corticosteroids, or systemic corticosteroids. No concomitant administration of topical corticosteroids or other immunosuppressants was permitted during or prior to study. The primary endpoint was the percent reduction in mean modified total lesion severity score (mTLSS) at week 16. A secondary measure was the proportion of subjects to achieve a PGA score of clear or almost clear with a 2-grade decrease over placebo.

Results

Gusacitinib achieved a dose-dependent, clinically meaningful, and statistically significant improvement relative to placebo in both the primary and secondary efficacy endpoints. Gusacitinib 80 mg resulted in an overall decrease of 69.5% ($p<0.005$) in mTLSS from baseline, compared to a 49.0% decrease for 40 mg and 33.5% decrease for placebo. Both 40 and 80 mg doses resulted in 50% and 66% improvement, respectively, in the mTLSS pruritus sub-score at week 16. Topline results also showed significant improvement in key secondary measures such as Physician's Global Assessment (PGA) with a 5-fold increase ($p<0.005$) in subjects achieving clear or almost clear with a 2-grade decrease over placebo at 80 mg dose (6.3%; 31.3%). Rapid reductions in mTLSS ($p<0.005$), PGA ($p<0.05$) and pruritus were observed as early as 2 weeks and sustained for the duration of the study. Gusacitinib plasma concentration increased in a dose-related manner. Gusacitinib was well tolerated at both dose levels. The most common treatment-emergent adverse events were upper respiratory tract infection, headache, nausea, and nasopharyngitis. Adverse events were typically mild to moderate and of short duration. No thromboembolic events or opportunistic infections were reported.

Discussion

Gusacitinib, a novel dual inhibitor of SYK and JAK kinases, demonstrated clinically significant and rapid efficacy in percent reduction in mTLSS and proportion of subjects achieving a PGA of clear or almost

clear with a 2-grade decrease after 16 weeks in moderate and severe CHE patients and was well tolerated. Gusacitinib represents a potential new oral treatment for patients with moderate to severe CHE and other inflammatory dermatological diseases.