Late-Breaking Oral Abstracts

LB0001 HEAD-TO-HEAD COMPARISON OF TLL-018 AND TOFACITINIB IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS: INTERIM RESULTS FROM A PHASE IIA STUDY

Topic: 16. Rheumatoid arthritis - non biologic treatment and small molecules

Keywords: Rheumatoid arthritis, Clinical Trials, Targeted synthetic drugs

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Background: None of the currently approved treatments for rheumatoid arthritis (RA) can achieve ACR50 in >50% of the patients, and ~20% of the RA patients are considered "difficult to treat", failing ≥2 targeted therapies. TLL-018 is a highly selective dual JAK1/TYK2 inhibitor. Its TYK2 activity might contribute to efficacy in RA patients.
Objectives: Compare efficacy of TLL-018 with tofacitinib in RA patients.
Methods: 101 patients with moderate-to-severe active RA who had inadequate response or were intolerant to methotrexate were randomized (1:1:1:1 ratio) to receive twice-daily oral TLL-018 10mg, 20mg, 30mg or tofacitinib 5mg. After 12-weeks of treatment, patients who achieved ACR50 continue the same treatment, and those who didn't change treatment as follows: patients on tofacitinib and TLL-018 10mg change to TLL-018 20mg; patients on 20mg and 30mg change to or continue 30mg TLL-018. The Primary endpoint is the proportion of patients achieving ACR50 at Week 12. Secondary endpoints include the proportion of patients achieving DAS28-CRP <2.6, ACR20, ACR70 at all scheduled time points, ACR50 at scheduled time points exclude week 12, CDAI and other parameters at 12 week. Safety was assessed via adverse event (AE) and laboratory examinations.
Results: 101 patients were randomized, ~50% of them also had prior bDMARDs and ~30% had prior JAK inhibitors. Demographics and baseline disease characteristics were balanced across treatment arms. At week 12, ACR50 response rates in TLL-018 treated groups [10mg, 20mg and 30mg, 48.0% (95% CI, 28.42 - 67.58), 65.4% (95% CI, 47.10 - 83.67), 72.0% (95% CI, 54.40 - 89.60), respectively] were higher than that for tofacitinib [41.7% (21.94 - 61.39)]. TLL-018 20 and 30mg were statistically superior to tofacitinib (p<0.05). Proportions of patients achieving clinical remission (DAS28-CRP<2.6) at week 12 were 39.1%, 34.8%, 54.5% and 17.4% at week 12 for the 10, 20, 30mg TLL-018 and tofacitinib, respectively. TLL-018 20 and 30mg demonstrated high efficacy in patients who had prior bDMARDs, achieving ACR50 rates of >66%. TLL-018 20mg dramatically improved responses in patients who didn't achieve ACR50 on tofacitinib at week 12. The most frequently reported treatment-emergent AEs were hyperlipidemia and respiratory infection in TLL-018 or tofacitinib-treated patients. There was one case of malignancy in tofacitinib treatment group. No death, venous thromboembolism or major adverse cardiovascular event was observed in the study. (The data cut-off time was December 19th).
Conclusion: TLL-018 20 and 30mg demonstrated superior efficacy over tofacitinib in RA patients, suggesting that inhibition of TYK2, in addition to JAK1, enhances efficacy. TLL-018 was well tolerated with most AEs being Grade 1 or 2 as expected from this class of compounds. No unexpected safety concerns were observed in the study. TLL-018 20 and/or 30mg BID warrants further studies in "difficult to treat" RA patients.
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LB0002 SAFETY & EFFICACY OF SEL-212 IN PATIENTS WITH GOUT REFRACTORY TO COVENTIONAL TREATMENT: OUTCOMES FROM TWO RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, MULTICENTER PHASE III STUDIES

Topic: 28. Crystal diseases, metabolic bone diseases other than osteoporosis

Keywords: Crystal Arthritis, Gout, Randomized control trial

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Background: Despite availability of effective therapies for gout, a small proportion of patients suffer from refractory gout and/or are intolerant to standard therapies [1]. In these patients, the inability to maintain serum uric acid (sUA) levels < 6 mg/dL may lead to severe clinical manifestations for which uricase-based therapies can be highly effective, though also immunogenic. SEL-212 is a once-monthly, novel 2-component, sequential uricase-based infusion therapy being investigated in patients with refractory gout. SEL-212 consists of an infusion of tolerogenic nanoparticles containing rapamycin (SEL-110) followed by pegadricase (SEL-037). The intent of this drug combination is to inhibit the formation of anti-uricase antibodies without the need for separate immunosuppressant therapies [2].
Objectives: DISSOLVE I and II (D1 and D2, respectively) evaluated the safety and efficacy of SEL-212 in adults with refractory gout.
Methods: D1 (US Study, 12 months) and D2 (Global Study, 6 months), were placebo-controlled, double-blind, randomized clinical trials that evaluated two dose levels of SEL-110 (0.15 mg/kg [high-dose] or 0.1 mg/kg [low-dose]) prior to SEL-037 (0.2 mg/kg) infusion in adults (19-80 years). Participants with a history of symptomatic gout were enrolled if they had ≥ 3 gout flares within 18 months prior to screening or ≥ 1 tophus or a current diagnosis of gouty arthritis, failed to normalize sUA and control symptoms with any xanthine oxidase inhibitor, and were not previously exposed to a uricase-based therapy. Participants were randomized 1:1:1 between the two doses of SEL-212 and placebo administered intravenously every 28 days for 6 treatments. D1 participants were continued in a 6-month blinded extension phase under the initial treatment conditions (Fig. 1). The primary endpoint was defined as the percentage of participants who achieved and maintained sUA < 6 mg/dL for ≥ 80% of the sixth 28-day treatment period (TP6) in the active treatment groups versus placebo (response rate). Safety and tolerability were assessed through monitoring of adverse events (AEs) and laboratory testing.
Results: A total of 265 participants (D1, n=112 (96% male, 66% ≥ 50 years); D2, n=153 (97% male, 72% ≥ 50 years) were randomized into the three treatment arms. Response rates in all treatment groups were significantly different from placebo (p ≤ 0.0015), with 56% and 47% of participants responding in the high-dose group and 48% and 41% in the low-dose group for D1 and D2, respectively (Table 1). The response rates in participants aged ≥ 50 years were 65% and 48% in the high-dose groups and 47% and 45% in the low-dose groups for D1 and D2, respectively (p ≤ 0.0044 vs placebo). Across all participants in the treatment groups, median sUA levels were reduced by ~96% and ~75% from baseline at TP6 for D1 and D2, respectively (p<0.001 vs placebo). The safety profile of SEL-212 was favorable, with 3.4% and 4.5% of participants experiencing infusion reactions in the high and low-dose groups, respectively. Reports of gout flares were comparable between treatment groups and placebo. Six participants (3.4%) in the pooled active treatment groups experienced treatment-related serious AEs (n=4 anaphylaxis, n=2 gout flares).
Conclusion: In the DISSOLVE trials, once-monthly treatment with SEL-212 demonstrated statistically significant response rates and reductions in sUA versus placebo. The safety profile of SEL-212 was consistent with that of uricase therapies. Targeted immunomodulation with SEL-212 has the potential to provide a new uricase-based treatment option for patients with gout refractory to conventional therapies without the need for traditional immunosuppressants.
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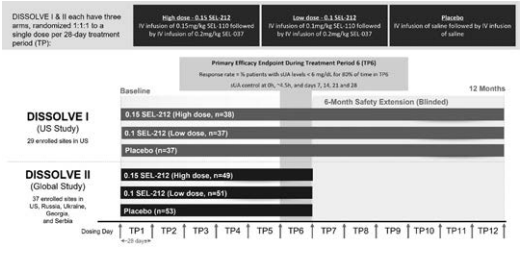

Figure 1. DISSOLVE I & II Study Design.