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INTEGRATED SAFETY PROFILE OF ATACEPT FROM ALL CLINICAL STUDIES TO DATE

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Background: We conducted an integrated analysis of pooled safety data from all 17 atacicept clinical studies across multiple indications to date.

Objectives: To characterize the overall safety profile of atacicept.

Methods: Analyses were based on 3 pooled datasets: double-blind placebo (PBO)-controlled set (DBPC-S) (n=1568; key endpoint: treatment-emergent AEs [TEAEs]); systemic lupus erythematosus set (SLE-S; n=761; key endpoints: IgG change and serious infection rates, and mortality); and full analysis set (FA-S; n=1845; key endpoint: exposure-adjusted mortality).

Results: Of 1568 patients (DBPC-S), 30.8% received PBO, and 8.2%, 24.5% and 36.5% received atacicept 25, 75 and 150 mg. Overall, baseline characteristics were balanced across treatment arms. Treatment exposure in patient-years (py) was similar with PBO and atacicept 75 and 150 mg but was lower with 25 mg (Table). Exposure-adjusted TEAE rates were generally higher with atacicept vs PBO; serious TEAE and infection rates were similar with atacicept and PBO (Table). TEAE-related discontinuation rates were higher with atacicept vs PBO (16.1 vs 10.9/100 py). In the SLE-S and DBPC-S, pharmacodynamic effects of atacicept (eg on IgG) were not associated with an increase in infection rates. Across all studies (FA-S), 11 patients died during treatment. Across all indications, exposure-adjusted mortality rates/100 py (95% CI) were 3.60 (0.90–14.38), 0.34 (0.05–2.43), 1.18 (0.49–2.82) for atacicept 25, 75 and 150 mg, and 0.44 (0.06–3.12) for PBO. In SLE patients, exposure-adjusted mortality rates/100 py were 1.45 (0.54–3.87) with atacicept 150 mg and 0.78 (0.29–2.07) across all atacicept-treated patients. The underlying disease and other causes were potential confounders in most cases.

Conclusion: In this integrated safety analysis of atacicept, no consistent association was found between atacicept dose and specific TEAEs or mortality. These results support further development and evaluation of atacicept in patients in whom potential benefits may outweigh risks.

Table. Exposure-adjusted TEAE rates by dose (DBPC-S)

	Placebo, n=483	Atacicept			Total, n=1568
		25 mg, n=129	75 mg, n=384	150 mg, n=572	All, n=1085
Total number of py	278.3	51.5	225.0	286.7	563.2
TEAE, n (rate per 100 py)					
Hypersensitivity	37 (13.9)	8 (15.7)	40 (19.1)	55 (20.4)	103 (19.4)
Infections	211 (107.8)	43 (104.4)	180 (118.7)	281 (141.3)	504 (121.7)
Serious infection	20 (7.3)	1 (1.9)	23 (10.5)	22 (7.7)	46 (8.3)
Severe infection	9 (3.2)	0	11 (4.9)	16 (5.6)	27 (4.8)
Herpes zoster	13 (4.7)	2 (3.9)	10 (4.5)	17 (6.1)	29 (5.2)
Injection site reactions	54 (20.9)	27 (64.8)	109 (63.0)	156 (72.4)	292 (67.9)
Severe hypogammaglobulinemia (IgG <3 g/L)	0	0	2 (0.9)	4 (1.4)	6 (1.1)
Cardiac arrhythmias [all]	18 (6.6)	11 (22.4)	23 (10.6)	25 (8.9)	59 (10.8)
Ventricular arrhythmias	5 (1.8)	0	4 (1.8)	6 (2.1)	10 (1.8)
Ischemic heart disorders	11 (4.0)	3 (5.9)	13 (5.9)	11 (3.9)	27 (4.9)
Embolic and thromboembolic events	11 (4.0)	1 (2.0)	6 (2.7)	9 (3.2)	16 (2.9)
Vestibular disorders	19 (7.0)	5 (9.9)	18 (8.3)	26 (9.3)	49 (8.9)
Demyelination	1 (0.4)	1 (1.9)	0	5 (1.7)	6 (1.1)
Depression	14 (5.1)	3 (5.8)	8 (3.6)	11 (3.9)	22 (3.9)
Malignant tumor	0	1 (1.9)	1 (0.4)	3 (1.1)	5 (0.9)
Serious TEAE	51 (18.9)	15 (30.0)	51 (23.9)	61 (21.8)	127 (23.4)
Severe TEAE	28 (10.2)	10 (19.6)	45 (20.9)	56 (20.0)	111 (20.3)
Discontinuation of treatment due to TEAE	30 (10.9)	14 (27.6)	30 (13.4)	46 (16.1)	90 (16.1)
Infection-related deaths, n (%)					
Deaths	0	0	0	2 (0.3)	0

*Acute respiratory failure and probable leptospirosis (n=1); pneumonia and pulmonary alveolar hemorrhage (n=1)

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EFFICACY AND SAFETY OF DAPIROLIZUMAB PEGOL (DZP) IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS (SLE): A RANDOMISED, PLACEBO (PBO)-CONTROLLED STUDY

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Background: CD40 ligand (CD40L) regulates interactions between T cells and CD40-expressing cells including antigen-presenting cells (APC) and B cells, thereby playing a critical role in autoimmune disease pathogenesis. DZP, a PEGylated monovalent Fab' antibody fragment with specificity for CD40L, prevents CD40L engagement of CD40 and thus blocks intracellular signalling and APC activation.

Objectives: To report the 24-week efficacy and safety interim data of DZP in a phase IIb, randomised, double-blind, PBO-controlled, dose-ranging study in patients with SLE (NCT02804763).

Methods: Patients with moderately to severely active SLE (SLEDAI-2K score ≥ 6 ; ≥ 1 BILAG grade A or ≥ 2 BILAG grade B organ domain scores at screening) despite stable non-biologic standard of care treatment were randomised 1:1:1 to receive iv DZP 6, 24 or 45 mg/kg or PBO every 4 weeks for 20 weeks. Patients receiving corticosteroids (CS) ≥ 10 mg/day prednisone equivalent were required to start tapering CS by Week 4; guidance was provided, but tapering schedules were ultimately determined by the investigators. The primary objective was to establish a dose-response relationship across three doses of DZP and PBO based on BICLA response rates at Week 24. Four pre-specified dose-response models were tested by a statistical method (MCP-Mod), to determine whether any of the models fit the observed data with statistical significance (at a one-sided $p \leq 0.05$). The secondary endpoint was a pairwise comparison of BICLA response rates at Week 24. Other endpoints included the SRI-4 and BICLA response rates at 12 and 24 weeks, mean changes from baseline in SLEDAI-2K scores at 12 and 24 weeks, percentage of patients with daily CS dose ≤ 7.5 mg/day at 12 and 24 weeks, pharmacodynamic (PD) markers and safety.

Results: 182 patients were randomised; 167 (91.8%) completed Week 24 of the study. Baseline demographics were similar across treatment groups. The primary endpoint was not met as none of the pre-specified dose-response models fit the observed BICLA response rates at Week 24 with statistical significance ($p=0.06$ for the most applicable model). BICLA response rates and other efficacy outcome measures at Weeks 12 and 24, were numerically higher for all DZP groups vs PBO (Table 1). Favourable biological effects were observed with improvements in relevant PD markers, including anti-dsDNA antibody levels, in DZP groups vs PBO. Treatment-emergent adverse events (TEAEs) and serious TEAEs were generally balanced across treatment groups (Table 2). More upper