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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 atacept clinical studies across multiple indications to date.

Objectives: To characterize the overall safety profile of atacept.

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 atacept 25, 75 and 150 mg. Overall, baseline characteristics were balanced across treatment arms. Treatment exposure in patient-years (py) was similar with PBO and atacept 75 and 150 mg but was lower with 25 mg (Table). Exposure-adjusted TEAE rates were generally higher with atacept vs PBO; serious TEAE and infection rates were similar with atacept and PBO (Table). TEAE-related discontinuation rates were higher with atacept vs PBO (16.1 vs 10.9/100 py). In the SLE-S and DBPC-S, pharmacodynamic effects of atacept (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 atacept 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 atacept 150 mg and 0.78 (0.29–2.07) across all atacept-treated patients. The underlying disease and other causes were potential confounders in most cases.

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

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

	Placebo, n=483	Atacept			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	0	0	2 (0.9)	4 (1.4)	6 (1.1)
hypogammaglobulinemia (IgG <3 g/L)					
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<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

respiratory tract infections were observed in patients treated with DZP vs PBO; the majority were mild. We observed four thromboembolic events: one in the 24 mg/kg DZP group and three in the PBO group.

Full analysis set		Week 12				Week 24			
		PBO n=43	DZP 6 mg/kg n=43	DZP 24 mg/kg n=43	DZP 45 mg/kg n=43	PBO n=43	DZP 6 mg/kg n=43	DZP 24 mg/kg n=43	DZP 45 mg/kg n=43
BICLA*	Responders, n (%)	11 (25.6)	21 (48.8)	29 (67.2)	20 (46.5)	16 (37.2)	21 (48.8)	29 (67.2)	24 (55.8)
	Difference vs PBO (95% CI)	–	23.3 (3.4, 43.1)	31.2 (11.6, 50.8)	17.9 (–1.5, 37.3)	–	11.6 (–8.2, 31.4)	19.6 (–1.0, 40.2)	15.0 (–5.5, 35.4)
SRI-4†	Responders, n (%)	12 (30.2)	23 (53.5)	21 (47.7)	27 (58.7)	22 (51.2)	29 (67.4)	23 (52.3)	29 (67.0)
	Difference vs PBO (95% CI)	–	23.3 (3.5, 43.1)	17.5 (–2.7, 37.7)	26.5 (6.7, 46.3)	–	16.3 (–4.2, 36.8)	1.1 (–19.9, 22.1)	11.9 (–6.6, 30.3)
SLEDAI-2K‡	Change in total score from baseline, mean (SD)	–2.7 (3.8)*	–3.7 (3.2)	–3.8 (3.1)	–3.9 (2.7)*	–4.3 (4.1)*	–5.2 (3.4)*	–5.2 (3.5)*	–5.4 (3.4)*
	Patients with daily CS dose ≥ 7.5 mg/day prednisone equivalent§	n (%)	32 (76.7)	31 (72.1)	36 (81.8)	36 (78.3)	37 (86.0)	36 (81.8)	37 (86.4)
Safety set		n=45	n=45	n=45	n=47	n=45	n=45	n=45	n=47
Anti-dsDNA (SLEDAI-2)¶	n	17	23	18	19	17	23	18	19
	Change from baseline, mean (SD)	–27.4 (101.4)	–36.4 (100.4)	–43.4 (100.9)	–132.5 (142.7)	–132.3 (142.7)	–132.3 (142.7)	–99.4 (100.3)	–296.3 (100.3)
	Patients with 50% reduction in anti-dsDNA¶	n (%)	3 (18.8)	11 (52.4)	7 (41.2)	9 (50.0)	4 (25.0)	10 (45.5)	11 (58.8)
C3 (g/L) in patients with C3 < 0.9 g/L at baseline	n	18	18	16	17	17	18	16	17
	Change from baseline, mean (SD)	0.01 (0.12)*	0.04 (0.11)*	0.03 (0.13)	0.03 (0.13)	0.03 (0.11)	0.03 (0.13)	0.12 (0.11)	0.12 (0.11)
C4 (g/L) in patients with C4 < 0.1 g/L at baseline	n	26	26	23	26	26	23	23	26
	Change from baseline, mean (SD)	–1.6 (27.0)	–1.8 (22.9)	–23.9 (36.8)	–30.8 (28.9)	–2.9 (31.3)*	–26.2 (43.5)	–15.5 (33.2)*	–42.0 (35.0)

BICLA, BILAG 2004-Based Composite Lupus Assessment; BILAG, British Isles Lupus Assessment Group; CS, corticosteroids; dsDNA, deoxyribonucleic acid; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI-4, SLE Responder Index 4; TEAE, treatment-emergent adverse event.

*P-value (modified non-responder imputation): patient was deemed a non-responder if ≥ 2 items were missing. If 1 item was missing, it could be imputed from the previous visit for one-sided only. †Observed cases; n=42; n=42; n=42; n=42. ‡LOCF (last observation carried forward). §Percentage of patients with baseline CS ≥ 7.5 mg/day prednisone equivalent. ¶PBO: 37.2%, DZP 6 mg/kg: 54.5%, DZP 24 mg/kg: 40.9%, DZP 45 mg/kg: 47.8%. ¶Anti-dsDNA measured by the Farr assay. n=18; n=21; n=17; n=18; n=22; n=17; n=22; n=17; n=22; n=22.

	PBO n=45	DZP 6 mg/kg n=45	DZP 24 mg/kg n=45	DZP 45 mg/kg n=47
Serious TEAEs, n (%)	5 (11.1)	1 (2.2)	4 (8.9)	3 (6.4)
TEAEs of interest, n (%)	9 (20.0)	8 (17.8)	11 (24.4)	9 (19.1)
Thromboembolic events	3 (6.7)	0	1 (2.2)	0
Moderate to severe infections	6 (13.3)	8 (17.8) ^a	11 (24.4)	8 (17.0)

DZP, dapirolizumab pegol; PBO, placebo; TEAE, treatment-emergent adverse event.
^a One TEAE was of mild intensity but was deemed to be a TEAE of interest by the investigator for the interim analysis.

Conclusion: DZP appeared to be well tolerated as TEAEs were generally balanced across the treatment groups. Numerically greater improvements relative to PBO were observed consistently across multiple efficacy endpoints and biomarkers; however, for the primary endpoint no pre-specified dose-response relationship model fit the observed BICLA response rates at Week 24 with statistical significance. The potential for deriving clinical benefit from DZP in patients with SLE warrants further investigation.

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TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS WITH THE IMMUNOPROTEASOME INHIBITOR KZR-616: RESULTS FROM THE FIRST 2 COHORTS OF AN OPEN-LABEL PHASE 1B DOSE ESCALATION TRIAL

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Background: Nonspecific proteasome inhibitors, e.g., bortezomib (BTZ), target both the constitutive and immuno- proteasomes and are standard of care for multiple myeloma. While BTZ has been used to treat refractory systemic lupus erythematosus (SLE) and lupus nephritis (LN), it is associated with adverse events (AEs) that limit its broad use. KZR-616, a first-in-class selective inhibitor of the immunoproteasome, is highly active and well tolerated in murine SLE¹. In a Phase (Ph) 1 healthy volunteer (HV) study, KZR-616 subcutaneously (SC) at 30 and 45 mg weekly (QW) was shown to be safe, be well tolerated and achieve the target level of immunoproteasome inhibition². We report here the preliminary safety and efficacy of KZR-616 in the Ph 1b portion of Study KZR-616-002 in active SLE patients (pts) (NCT03393013).

Objectives: The 1^o objective of this first-in-patient study is to assess the safety and tolerability of KZR-616. The 2^o objectives are to evaluate pharmacokinetics (PK) and determine the KZR-616 doses for the Ph 2 portion of the study. Pharmacodynamics (PD) and efficacy are also being assessed.

Assessments	Mean (SD)	Timepoint	Cohort 1 n=6	Cohort 2 n=3
SLEDAI		BL	9.7 (1.97)	10.0 (2.00)
		W13	7.2 (3.35)	6.0 (2.83)
CLASI		BL	5.5 (2.07)	7.3 (1.16)
		W13	3.6 (1.95)	4.5 (2.12)
TJC		BL	14.3 (8.14)	11.7 (4.93)
		W13	7.6 (6.99)	8.5 (3.54)
SJC		BL	11.0 (6.03)	9.3 (3.06)
		W13	4.4 (6.07)	3.5 (4.95)
PhGA		BL	58.3 (19.24)	63.3 (26.50)
		W13	39.8 (24.67)	40.0 (14.14)
PtGA		BL	57.5 (25.79)	73.3 (11.59)
		W13	43.6 (31.64)	35.0 (7.07)

Methods: This open-label multicenter dose escalation trial enrolled SLE pts (per Systemic Lupus International Collaborating Clinics Classification Criteria) with SLE Disease Activity Index (SLEDAI) ≥ 4 despite stable background immunosuppressant, antimalarial, and/or corticosteroid (≤ 20 mg prednisone equivalent) therapy. Patients received KZR-616 at 45 mg (Cohort 1) or 60 mg (Cohort 2) SC QW through Week 13 (W13) with 12 weeks of follow up. Cohort 2a is currently enrolling pts using intrapatient dose escalation from 30 to 60 mg. Safety data include AEs, vitals, electrocardiograms and laboratory tests. Efficacy measures include the SLEDAI, Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), 28 tender (T) and swollen (S) joint counts (JC), Physician Global Assessment (PhGA), and Patient Global Assessment (PtGA) in evaluable pts (receive ≥ 1 month of KZR-616; non-evaluable pts can be replaced).

Results: We enrolled 13 pts: 8 in Cohort 1, 5 in Cohort 2. The pts were 100% female; Baseline (BL) median SLEDAI was 10.0. All pts received at least 1 dose of KZR-616. In each cohort, 3 pts withdrew due to withdrawal of consent prior to W13. Overall, the 45 mg dose was well tolerated with no SAEs; all AEs were mild in intensity. The most common AEs were injection site erythema (62.5%), nausea (25%), and injection site pruritus (25%). Cohort 2 (60 mg) enrollment was halted, as all pts experienced vomiting within 8-24 hours (h) of their first dose, which typically resolved within 24 h. One pt had an SAE of thrombotic microangiopathy. Two pts permanently reduced their dose to 45 mg. After 2 doses at 45 mg, another pt successfully re-escalated to 60 mg. In