Clinical Safety and Efficacy Results from EQUALISE Type B: A Phase 1b Open-Label Clinical Study of Itolizumab, a Novel Anti-CD6 Therapy, in Subjects with Active Proliferative Lupus Nephritis

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Introduction

Itolizumab is a first-in-class monoclonal antibody that targets the co-stimulatory receptor CD6 and induces antigenic modulation, preventing the interaction with activated leukocyte cell adhesion molecule (ALCAM) and inhibiting T effector (Teff) cell activity and trafficking to target organs.The CD6/ALCAM pathway has been shown to be overexpressed on leukocytes and kidney cells in patients with active proliferative lupus nephritis (apLN),[1] and levels of urinary ALCAM have been shown to be a predictor of disease activity as well.[2] Animal models of apLN have demonstrated that anti-CD6 treatment improves glomerular and tubular histology and decreases immune cell infiltration and improves cytokine expression.[3]

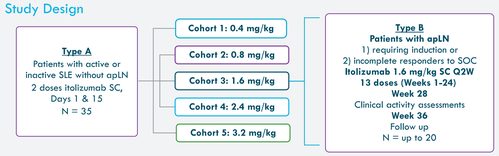
EQUALISE (NCT04128579) is a Phase 1b, multiple ascending-dose study to evaluate the safety, tolerability, pharmacokinetics (PK),pharmacodynamics (PD), and clinical activity of subcutaneous (SC) doses of itolizumab in subjects with SLE in 2 parts; Type A without apLN and Type B in those with apLN. Results from the Type A cohorts in subjects with SLE without apLN has previously been presented.[4,5] Two SC doses of itolizumab Q2weeks of up to 2.4 mg/kg in subjects were well tolerated. Consistent with the mechanism of action of itolizumab, the target receptor on CD4 cells (CD6) decreased significantly with the maximal reduction occurring at doses of 1.6 mg/kg and above. PK results showed a dose-dependent relationship. Results from the Type B subject cohort (with apLN from 01 Sept 2023 data cut-off) are presented here.

Study Design

Primary Objective (Type B)

Assess the safety and tolerability of itolizumab in subjects with SLE with active proliferative LN (apLN)

Study Design



- In Type B, 17 adult subjects with apLN (ISN/RPS class III or IV + class V) were treated with open-label itolizumab subcutaneously at 1.6 mg/kg every 2 weeks for up to 13 doses in combination with mycophenolate and systemic corticosteroids.
- Subjects were followed for an additional 12 weeks after the last dose with the key analysis at W28 (4 weeks after the final dose).

Primary Endpoint - Safety and tolerability of itolizumab

Secondary Endpoints (Type B) - Characterize the clinical activity of itolizumab:

- Proportion of subjects who meet the definition of complete response (CR) and partial response (PR) at W28/end of study (EOS)
- Change in urine protein creatinine ratio (UPCR) and urine albumin creatinine ratio (UACR) over time through W28/EOS
- Change in estimated glomerular filtration rate (eGFR) over time
- Change in daily prednisone (or equivalent) dose over time
- Exploratory endpoints- assessments of serum and urine ALCAM and CD6 as disease severity biomarkers and treatment effects (ongoing and not presented here)

Subject Disposition (as of 01 Sept 2023)



Key Eligibility Criteria (Type B)

Key Inclusion Criteria:

1. Male or female, ≥18 to ≤75 years of age, with diagnosis of SLE.
2. Elevated ANA.
3. eGFR ≥40 mL/min/1.73m².
4. Kidney biopsy ≤12 months with a histologic diagnosis of LN (ISN/RPS 2003) Classes III or IV(A/C); Subjects with concomitant Class V were permitted.
5. Urine protein to creatinine ratio (UPCR) >1000 mg/g based on the mean of two 24-hour urine collections or a single UPCR of >2000 mg/g based on a single 24-hour urine collection.
6. Subjects were required to be on MMF/MPA 2-3 g/day. For newly diagnosed subjects or relapsing/flaring disease subjects who required induction treatment, pulse systemic corticosteroids were permitted.
7. Subjects who required induction treatment were required to receive at least 2 consecutive days of pulse systemic corticosteroids of methylprednisolone (≥500 mg) or equivalent andable to receive it 12 weeks prior to Day 1 or start on Days 1 and 2; all induction subjects were required to be able to undergo a taper of systemic corticosteroids during the first 10 weeks of treatment.
8. Had adequate hematologic function, as defined by (a) ANC ≥1.5×10⁹/L, (b) ALC ≥1.0×10⁹/L, (c) platelet count >75×10⁹/L, and (d) hemoglobin >8.5 g/dL.

Key Exclusion Criteria:

1. Active CNS lupus (including seizures, psychosis, organic brain syndrome, cerebrovascular accident, cerebritis or CNS vasculitis)
2. History of rapidly progressive glomerulonephritis and/or other renal disease not directly due to LN

Statistical Methods (Type B)

Safety and efficacy endpoints were tabulated and summarized using descriptive statistics. The change in UPCR and UACR from 24-hour urine collection and spot collections up to Week 28 were summarized. Definitions for complete response (CR) and partial response (PR) included no administration of rescue medications for apLN and the following:

- CR1: UPCR < 500 mg/g, no decrease in eGFR by ≥ 20%, no rescue treatments
- CR2: UPCR of 500-700 mg/g, no decrease in eGFR by ≥ 20%, no rescue treatments
- PR: Reduction of UPCR of ≥ 50% without rescue treatments
- No response was defined as < 50% reduction or worsening UPCR

Results (01 Sept 2023 cut off; subject to change)

Key Demographics and Baseline Characteristics

The mean (SD) age of subjects was 34 (11.2) years; and the majority were female (94%) as expected in this patient population (Table 1).Subjects were predominantly Asian (82%) and had a long mean duration of SLE (9.3 years) and LN (6.5 years).The subjects had evidence of severe disease with the majority ISN/RPS Class IV+V on biopsy (41%) with a high degree of proteinuria (mean UPCR of 4.9 g/g) yet maintaining a high eGFR (mean 103.9 ml/min/1.73 m²) at baseline. [Table 1].

Table 1. Demographics and Baseline Characteristics

Baseline Characteristics	Safety Population (n=17)
Age: Mean (SD) / Range	33.8 (11.2) / 20-58
Gender: n (%)	Female: 16 (94%) / Male: 1 (6%)
Race: n (%)	White: 3 (18%) / Asian: 14 (82%)
Country: n (%)	US: 5 (29%) / India: 12 (71%)
SLE Duration (years): Mean (SD) / Range	9.3 (10.1) / 1-39
LN Duration (years): Mean (SD) / Range	6.5 (6.0) / 1-24
ISN/RPS LN class type:	
Class III only	1 (6%)
Class IV only	4 (24%)
Class III + V	5 (29%)
Class IV + V	7 (41%)
UPCR (g/g) (based on 24-hour urine collection[1,2]):	
Mean (SD)	4.9 (4.0)
Median (Range)	3.4 (1.1 - 16.3)
eGFR[2] (ml/min/1.73 m²) : Mean (SD) / Range	103.9 (31.9) / 47 – 139

Efficacy Analysis

There was a greater overall response rate (ORR= CR1+ CR2+ PR) achieved in patients receiving itolizumab by 12 and 28 weeks than expected compared to the ORR in patients receiving standard of care alone using data generated from the Accelerating Medicines Partnership® (AMP) Lupus Network (Figure 1) [6-8]. Results are comparable to those observed in the Phase 3 AURORA1 study of voclosporin (ORR 70% at 6 and 12 months in active treatment).[9] Spot and 24 hour UPCR and UACR over the course of the study are shown in Figure 2. Percent reduction from baseline in median spot UPCR is ~73%. Spot and 24 hour measures are highly correlated as are the UACR and UPCR measures, overall correlations >0.93.

Figure 1. Response rates at Week 12 and Week 28 (4 weeks post-treatment) with results from the AMP longitudinal study for patients on standard care treatments.

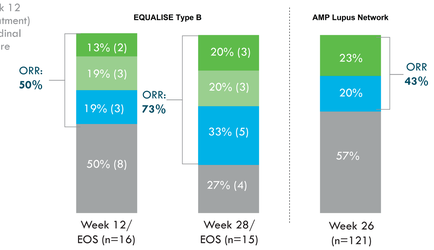
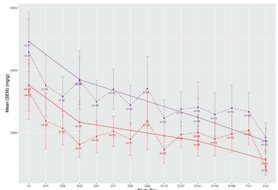


Figure 2: Change in UPCR and UACR over time during the study by Spot measures (Q2 weeks) and 24 hour measures (done sporadically). Measures are highly correlated.



eGFR remained stable throughout the treatment period and serum albumin increased over time (Figure 3). Complement levels and ds-DNA were predominantly normal at baseline and stayed stable throughout the treatment period (data not shown). Consistent with the decline in UPCR overtime, subjects were able to taper their systemic corticosteroids. Per protocol, subjects were to taper steroids to prednisone 10 mg/d by Week 10 and mean steroid use remained low through remainder of the study (Figure 4).

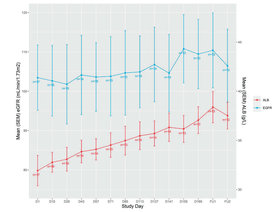


Figure 3: eGFR over time remained stable while on study (left axis), whereas there was an increase in serum albumin (right axis).

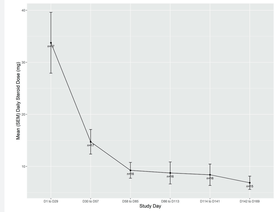


Figure 4: Consistent with the decline in proteinuria, systemic steroid use declined and remained low during the study.

Safety Analysis

- All Subjects (N=17) had at least one TEAE, with the majority of TEAEs occurred once in 1 subject (Table 2). The most commonly reported TEAE was lymphopenia (in 9 subjects).
- 9 serious TEAEs occurred in 2 (12%) subjects, 1 subject with 1 SAE and 1 subject with 8 SAEs, and no SAEs were assessed as treatment-related. There were no deaths during the study.
- 12 subjects had a treatment-related TEAEs, most common term was lymphopenia.
- Most TEAEs (77%) were assessed by the investigator as Mild (Grade 1) or Moderate (Grade 2) in severity. The majority of TEAEs assessed as Severe (in 9 subjects), including the only Grade 4 TEAEs (2 TEAEs in 2 subjects), were non-serious events of lymphopenia.
- Treatment was withdrawn due to TEAEs in 3 subjects: liver function test increased (not treatment related, Grade 2), lymphopenia (treatment related, Grade 3), and pyrexia (not treatment related, Grade 2).
- Consistent with the pharmacodynamic effect of itolizumab, there was a primary decline in absolute lymphocyte count (ALC) after the first dose of study drug. On average, ALC remained within the normal range and did not correlate with infections.

Table 2. Summary of subject incidence of treatment emergent adverse events (TEAEs).

TEAEs	Safety Population (n=17)
Any TEAE	17 (100%)
Serious TEAE (TESAE)	2 (12%)
Treatment-related TEAEs	12 (71%)
Treatment-related TESAE	0
TEAEs by Maximum CTCAE Severity Grade:	
Grade 1- Mild	3 (18%)
Grade 2 – Moderate	5 (29%)
Grade 3- Severe	7 (41%)
Grade 4- Life threatening	2 (12%)
Grade 5- Death	0
TEAEs Leading to Withdrawal of Treatment	3 (18%)
Subjects with TEAEs Leading to Death	0

Conclusions

- In the Type B cohort of the EQUALISE Study (NCT04128579), itolizumab dosed 1.6 mg/kg Q2Weeks x 13 was safe and well tolerated in subjects with apLN.
- Treatment was associated with the expected AE of lymphopenia, based on the known pharmacodynamic effect of itolizumab. There was no association with infection in subjects with lymphopenia. No other safety signals were noted.
- Use of itolizumab in subjects with apLN suggests differentiation in early, rapid, and deep responses in highly proteinuric subjects, that had a mean 24 hour UPCR of nearly 5 g/g.
- The clinical data support continued evaluation of itolizumab in apLN in a randomized controlled study.
- Itolizumab has the potential to be an important treatment for patients with severe immuno-inflammatory diseases. Continued work is ongoing in the use of ALCAM and CD6 as potential biomarkers for apLN and the response to therapy.

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Disclosures

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