Itolizumab, a Novel Anti-CD6 Therapy, in Systemic Lupus Erythematosus Patients: Interim Safety Results from the Phase 1b EQUALISE Dose Escalation Study

POSTER 1750

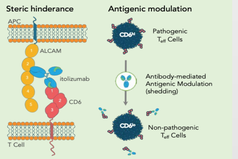
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Introduction

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 (T_{eff}) 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 lupus nephritis (LN),[1] and levels of urinary ALCAM have been shown to be a predictor of disease activity as well.[2] Animal models of LN have demonstrated that anti-CD6 treatment improves glomerular and tubular histology and decreases immune cell infiltration and improves cytokine expression.[3]

Here we present results from Type A in EQUALISE (NCT04128579), which is a Phase 1b, multiple ascending-dose study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of subcutaneous doses of itolizumab in subjects with systemic lupus erythematosus (SLE).

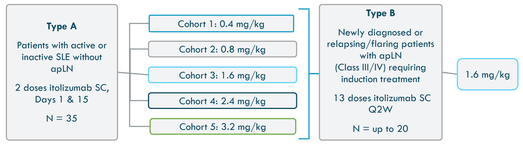


Methods

Primary Objective

- Assess the safety and tolerability of itolizumab in subjects with SLE with or without active proliferative LN (apLN)

Study Design



- In Type A, 35 subjects with active or inactive SLE, who did not have apLN, were studied in 5 dose escalation cohorts (0.4 to 3.2 mg/kg itolizumab subcutaneous [SC] Q2W x 2 doses).
- After the initial screening period of up to 4 weeks, subjects were dosed on itolizumab on Days 1 and 15 and then followed for an additional 6 weeks.
- Data are current from 30 July 2021.
- Up to 20 subjects with apLN are anticipated to be studied with itolizumab 1.6 mg/kg SC Q2W x 13 doses in the Type B Cohort (currently enrolling).

Type A utilized a cohort dose escalation design

- An independent data review committee endorsed dose escalation between cohorts to ensure the safety of the subjects.
- Patients were to be discontinued from study drug if a dose-limiting toxicity occurred:
  - Any ≥ Grade 3 AE considered by investigator at least possibly related to study drug during Days 1-29 (including Grade 3 lymphopenia that does not recover to ≥ 500 cells/mm^3 prior to next schedule dose and/or any Grade 3 injection-related reaction).

Primary Endpoint

Safety and tolerability of itolizumab

Secondary Endpoints

1. PK of itolizumab
2. PD of itolizumab including CD6 receptor occupancy
3. PK/PD relationship of itolizumab
4. Clinical activity of itolizumab in subjects with apLN (Type B only)

Key Eligibility Criteria

Type A Cohort Key Inclusion Criteria:

1. Documented to have met Systemic Lupus International Collaborating Clinics (SLICC) and/or American College of Rheumatology (ACR) criteria for SLE
2. Received at least 1 immunosuppressive or immunomodulatory treatment (including antimalarials) for SLE at any time in the past or currently
3. Dose of prednisone (or equivalent glucocorticoid) ≤ 10 mg per day and stable for at least 2 weeks prior to Screening (if subject taking prednisone)
4. Elevation of antinuclear antibodies (ANA) in the past or during Screening
5. Adequate hematologic function and eGFR ≥ 40 mL/min/1.73 m^2

Type A Cohort Key Exclusion Criteria:

1. Active central nervous system (CNS) lupus requiring therapeutic intervention within 60 days of Screening
2. Acute or chronic infections requiring systemic antibacterial, antifungal, or antiviral therapy within 21 days of Screening or active infection during Screening
3. History of antiphospholipid syndrome within 12 months of Screening

Statistical Methods

All safety, PK, PD, and efficacy endpoints will be tabulated with descriptive statistics by cohort for Type A. Baseline is the last value prior to dosing except for urine protein-to-creatinine ratio (UPCR) and albumin-to-creatinine ratio (ACR) which are the mean of Screening and Day 1 values.

Results

Patient Demographics and Baseline Characteristics

Subjects were predominantly female and white. SLE was stable with subjects taking low dose corticosteroids and antimalarial treatments. All the cohorts were generally similar in baseline characteristics (TABLE 1).

TABLE 1. DEMOGRAPHICS AND BASELINE CHARACTERISTICS BY COHORT

Baseline	0.4 mg/kg N=6	0.8 mg/kg N=7	1.6 mg/kg N=7	2.4 mg/kg N=6	3.2 mg/kg N=9	Total N=35
Age mean (SD) years	59.5 (12.9)	44.6 (16.2)	47.1 (6.8)	48.2 (11.6)	55.0 (12.6)	51.4 (12.5)
Sex (F/M)	6/0	7/0	6/1	6/0	8/1	33/2
Race (White/Black or African American)	3/3	5/2	6/1	5/1	7/2	26/9
Ethnicity: Hispanic or Latino (Y/N)	4/2	5/2	3/4	4/2	0/9	16/19
SLEDAI-2K mean (SD)	8.7 (3.9)	7.1 (4.3)	7.1 (1.6)	5.3 (2.7)	8.0 (4.1) n=8	7.3 (3.5) n=34
Time from SLE diagnosis to first dose mean (SD) years	12.0 (10.5)	15.4 (10.4)	8.7 (4.4)	11.0 (8.1) n=5	11.2 (7.9)	11.7 (8.2) n=34
Current use of low dose corticosteroids yes (%)	5 (83.3%)	1 (14.3%)	1 (14.3%)	2 (33.3%)	1 (11.1%)	10 (28.6%)
Current use of antimalarial yes (%)	2 (33.3%)	3 (42.9%)	4 (57.1%)	5 (83.3%)	4 (44.4%)	18 (51.4%)
Current use of methotrexate yes (%)	2 (33.3%)	1 (14.3%)	0	0	1 (11.1%)	4 (11.4%)
Body mass index mean (SD) (kg/m2)	29.0 (2.2)	34.9 (9.0)	30.9 (7.0)	29.4 (8.5)	30.8 (5.5)	31.1 (6.8)
C3 level mean (SD) mg/dL Normal: 81-157 mg/dL	138 (22)	132 (31)	123 (37)	141 (28)	129 (22) n=7	132 (27) n=33
C4 level mean (SD) mg/dL Normal: 13-39 mg/dL	26 (10.8)	33 (12.0)	29 (9.7)	37 (16.8)	28 (6.4) n=8	30 (11.3) n=34
Anti-DS DNA mean (SD) IU/mL Positive: ≥ 36 IU/mL	23.7 (32)	33.3 (44) n=4	8.3 (6)	37.2 (43)	18.1 (9)	22.5 (28) n=32

Baseline: Last pre-dose value.
Abbreviations: C complement; **F** female; **M** male; **max** maximum; **min** minimum; **SD** standard deviation; **SLEDAI 2K** Systemic Lupus Erythematosus Disease Activity Index 2000, **SLE** systemic lupus erythematosus, **anti-DS DNA** anti-double-stranded DNA

Patient Disposition

In Cohorts 1-4, subjects had high study and treatment completion rates. Cohort 5 (3.2 mg/kg), subjects were less likely to complete study treatment due to tolerability (TABLE 2).

TABLE 2. PATIENT DISPOSITION BY COHORT

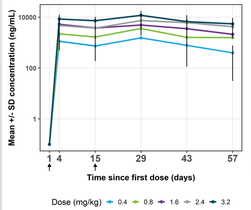
	0.4 mg/kg N=6	0.8 mg/kg N=7	1.6 mg/kg N=7	2.4 mg/kg N=6	3.2 mg/kg N=9	Total N=35
Subjects who completed study treatment	6 (100%)	6 (86%)	6 (86%)	5 (83%)	4 (44%)	27 (77%)
Subject prematurely ended study treatment	0	1 (14%)	1 (14%)	1 (17%)	5 (56%)	8 (23%)
• Lost to follow up	0	0	0	0	0	0
• Adverse event	0	0	1 (14%)	1 (17%)	2 (22%)	4 (11%)
• Withdrawal by subject	0	0	0	0	3 (33%)	3 (9%)
• Protocol deviation	0	1 (14%)	0	0	0	1 (3%)
Subjects who completed the study	6 (100%)	5 (71%)	7 (100%)	6 (100%)	8 (89%)	32 (91%)
• Lost to follow up	0	1 (14%)	0	0	0	1 (3%)
• Withdrawal by subject	0	0	0	0	1 (11%)	1 (3%)
• Protocol Deviation	0	1 (14%)	0	0	0	1 (3%)

Pharmacokinetics & Pharmacodynamics

FIGURE 1. SC ADMINISTRATION OF ITOLIZUMAB RESULTS IN DOSE-DEPENDENT PK (LEFT) AND PD (RIGHT) RESPONSES

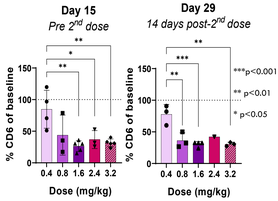
PHARMACOKINETICS[2]

- Dose-dependent increases in exposures observed
- Preliminary data suggest no impact of ADA on PK[1]



PHARMACODYMANICS[2]

- Reductions in surface levels of CD6 on CD4 cells observed
- Magnitude of decrease is comparable at 1.6 mg/kg and higher



[1] Baseline ADA only: 4/19 (21%); low titer (≤200) ADA observed in 3/19 (16%), at 2 (n=1) and 6 (n=2) weeks after the last dose of study drug; arrows indicate itolizumab dosing
[2] Some missing data points due to inadequate sample collection and/or pending analysis
Abbreviations: ADA anti-drug antibodies

Disease Assessments

TABLE 3. DISEASE MARKERS, ASSESSMENTS, AND PATIENT-REPORTED OUTCOMES REMAINED STABLE THROUGHOUT THE STUDY.

	n	Baseline	n	FU1 (4 weeks after last dose)
C3 (mg/dl) mean (SD)	33	132 (27.7)	29	130.1 (30.1)
C4 (mg/dl) mean (SD)	33	30.2 (11.3)	32	28.7 (9.9)
UPCR Geometric mean (gCV%) median (min, max)	33	115.54 (83.4) 98.8 (47.55, 1505)	31	100.9 (75.2) 90.3 (39.2, 1420)
eGFR (ml/min/1.73m^2) mean (SD)	35	99.0 (20.1)	33	95.4 (20.4)
SLEDAI 2K# mean (SD)	34	7.3 (3.5)	33	5.5 (3.2)
FACIT Fatigue mean (SD)	34	22.4 (10.9)	33	28.1 (11.6)

Baseline: Last pre dose value, with exception of UPCR and eGFR which are the mean of Day 1 and Screening values. Missing data due to assessments not done or visit not attended.
#SLEDAI 2K factors that changed over time include pyuria, alopecia, mucosal ulcers, and rash.
Abbreviations: C complement; **eGFR** estimated glomerular filtration rate; **FU** follow up; **max** maximum; **min** minimum; **SD** standard deviation; **SLEDAI 2K** Systemic Lupus Erythematosus Disease Activity Index 2000, **UPCR** urine protein-to-creatinine ratio, **gCV** geometric coefficient of variation, **FACIT** Functional Assessment of Chronic Illness Therapy

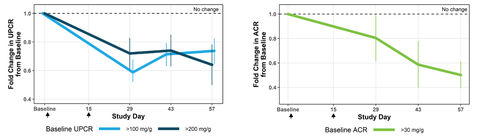
Proteinuria Subgroup Analysis

Exploratory subgroup analyses were performed on subjects with proteinuria or albuminuria at Baseline: UPCR > 100 mg/g, UPCR > 200 mg/g, or ACR > 30 mg/g. At Day 57, there was a mean change in UPCR of 34% to 42% and ACR of 54%. (TABLE 4 and FIGURE 2).

TABLE 4. REDUCTION IN URINE MARKERS IN SUBSETS BY BASELINE URINE PARAMETERS

Subset	n	Geometric Mean UPCR or ACR (mg/g) Baseline	Geometric Mean Change in UPCR or ACR (%) Day 29	Day 57	Figure 2 Panel
Baseline UPCR > 100 mg/g	16	200	-45	-34	Left (light blue)
Baseline UPCR > 200 mg/g	6	378	-33	-42	Left (dark blue)
Baseline ACR > 30 mg/g	4	97.3	-22	-54	Right (green)

FIGURE 2. SUBSET ANALYSIS OF SLE PATIENTS WITH ELEVATED PROTEINURIA AND ALBUMINURIA AT BASELINE: FOLD CHANGE IN UPCR (>100 OR > 200 MG/G; N=16 AND N=6; LEFT) & ACR (>30 MG/G; N=4; RIGHT)[1]



[1]missing data: UPCR, n=1 (D57); UACR, n=2 (D29); arrows indicate itolizumab dosing; **UPCR** urine protein-to-creatinine ratio, **ACR** albumin-to-creatinine ratio

Safety

Two SC doses of itolizumab 0.4 to 2.4 mg/kg (n=26) were safe and well tolerated (reduced tolerability seen in the 3.2 mg/kg dose group), with 35% of subjects reporting a treatment-emergent adverse event (TEAE), mostly mild and comprised of injection site reactions (TABLE 5.)

- Across all cohorts, 30 Preferred Terms were noted; the most common System Organ Classes were General Disorders and Administration and Skin and Subcutaneous Tissue Disorders.
- The most frequently reported adverse events were injection site erythema and headache.
- One dose limiting toxicity of lymphopenia was reported in the 2.4 mg/kg cohort.
- At the high dose of 3.2 mg/kg (which required 2 injections), 89% of subjects reported TEAEs, mostly moderate in severity, including injection site reactions and headache/chills.
- One subject had 2 serious adverse events (SAEs) unrelated to treatment (hypotension and syncope) in the follow-up period after dosing was complete.
- No treatment-related SAEs were reported, and no deaths were reported in the study.

TABLE 5. OVERALL SUMMARY OF TREATMENT EMERGENT ADVERSE EVENTS (TEAES)

TEAEs	0.4 mg/kg (N=6) n (%)	0.8 mg/kg (N=7) n (%)	1.6 mg/kg (N=7) n (%)	2.4 mg/kg (N=6) n (%)	3.2 mg/kg (N=9) n (%)	Total (N=35) n (%)
Subjects with Any TEAEs	0	2 (28.6%)	4 (57.1%)	3 (50.0%)	8 (88.9%)	17 (48.6%)
Subjects with Serious TEAEs (TESAEs)	0	0	0	0	1 (11.1%)	1 (2.9%)
Subjects with Treatment-Related TEAEs	0	2 (28.6%)	4 (57.1%)	3 (50.0%)	6 (66.7%)	15 (42.9%)
Subjects with Treatment-Related TESAEs	0	0	0	0	0	0
Subjects with TEAEs by Maximum CTCAE Severity Grade						
Grade 1 - Mild	0	2 (28.6%)	2 (28.6%)	2 (33.3%)	0	6 (17.1%)
Grade 2 - Moderate	0	0	2 (28.6%)	0	7 (77.8%)	9 (25.7%)
Grade 3 - Severe	0	0	0	1 (16.7%)	1 (11.1%)	2 (5.7%)
Grade 4 - Life-threatening	0	0	0	0	0	0
Grade 5 - Death	0	0	0	0	0	0
Subjects with DLTs	0	0	0	1 (16.7%)	0	1 (2.9%)
Subjects with TEAEs Leading to Withdrawal of Treatment	0	0	1 (14.3%)	1 (16.7%)	2 (22.2%)	4 (11.8%)
Subjects with TEAEs Leading to Death	0	0	0	0	0	0

Conclusions

- In the EQUALISE Study (NCT04128579), two SC doses of itolizumab up to 2.4 mg/kg in SLE subjects were well tolerated (reduced tolerability seen in the 3.2 mg/kg dose group).
- Consistent with the mechanism of action of itolizumab, the target receptor on CD4 cells (CD6) decreased significantly.
- Exploratory analyses showed reduction in proteinuria and albuminuria.
- This novel MOA and clinical data support continued evaluation of itolizumab in SLE/apLN and other chronic autoimmune diseases.

Acknowledgments

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References

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Disclosures

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