Itolizumab, a Novel Anti-CD6 Antibody, in Systemic Lupus Erythematosus Patients with Proteinuria: An Interim Subgroup Analysis from EQUALISE a Phase 1b Study (NCT04128579)

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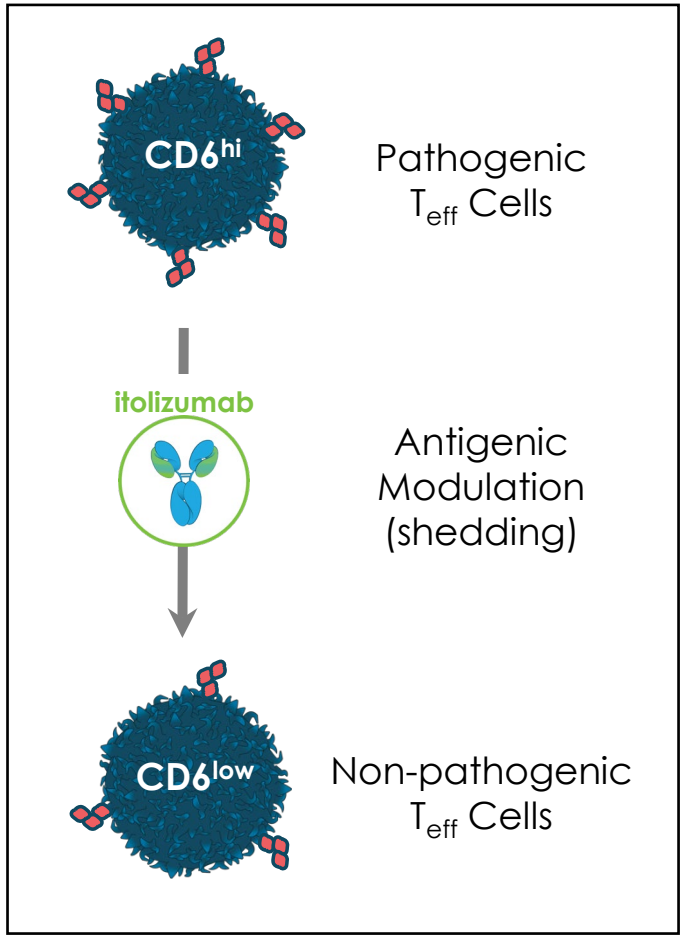
CD6-ALCAM Pathway & Itolizumab

- **CD6 is a co-stimulatory receptor** expressed on CD4 and CD8 T_{eff} cells and modulates **T cell activity and trafficking**
- CD6 ligand (ALCAM) **is expressed on APCs and endothelial tissues**
- CD6 & ALCAM are **over-expressed** in patients with LN and urinary ALCAM is a biomarker of disease activity
- CD6 is a validated target relevant to the pathogenesis of SLE and LN



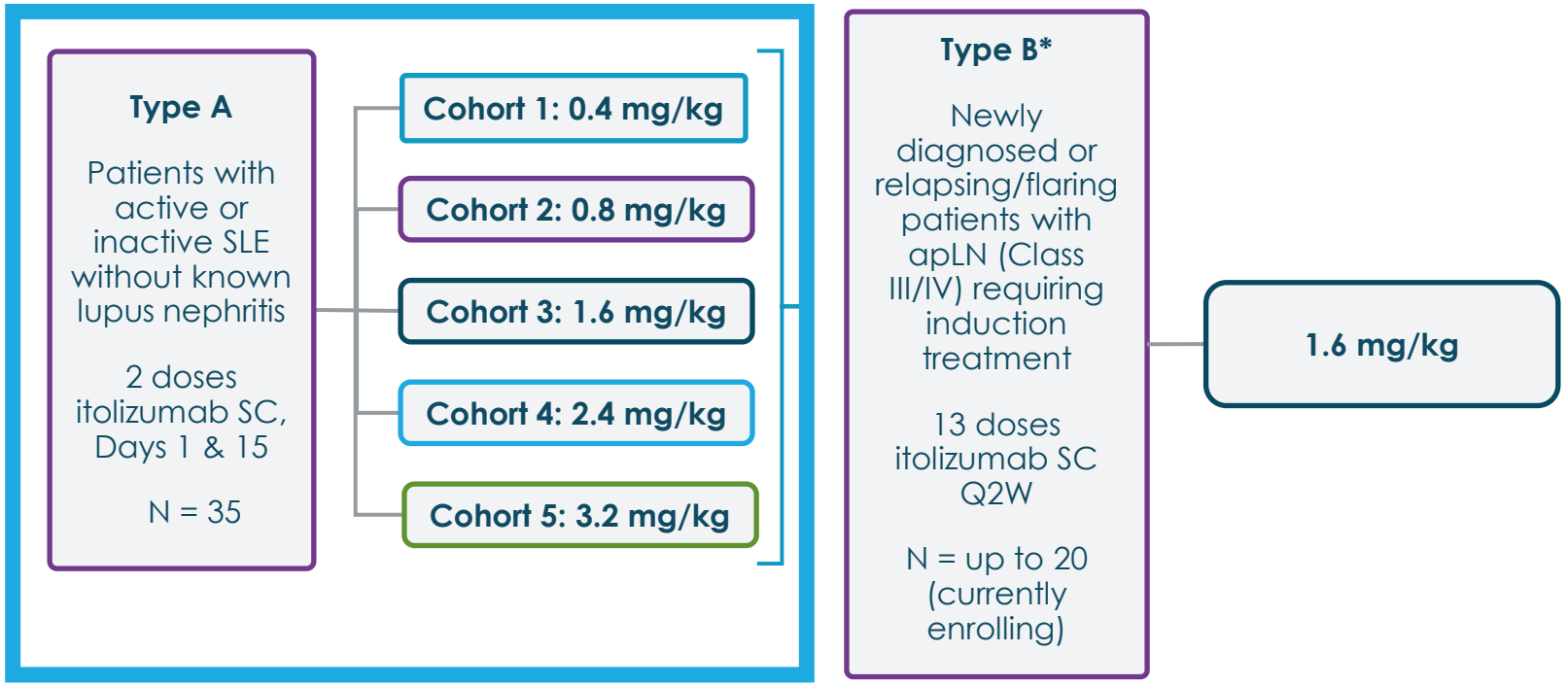
- **Itolizumab** is a first-in-class antibody therapeutic targeting the CD6-ALCAM pathway
  - Binds CD6 and induces antigenic modulation to produce $CD6^{low}$ T cells
- **$CD6^{low}$ T cells are hyporesponsive to stimulation**, exhibiting decreased activation, proliferation and cytokine production
- Itolizumab is being evaluated as a treatment for immuno-inflammatory diseases in which T_{eff} cells play a central role, including in patients with SLE and LN.

Abbreviations: ALCAM activated leukocyte cell adhesion molecule, LN Lupus Nephritis, SLE Systemic Lupus Erythematosus, T_{eff} effector T cells

Consuegra-Fernandez *et al.*, *Cell Mol Immunol* 2018; Ma *et al* Ma *et al.*, *J Crohns & Colitis* 2019; Soiffer *et al.*, *JCO* 1992; Dataset derived from AMP (Arazi et al., 2019). Analysis by Dr. Chaim Putterman, Stanley *et al.*, 2016 ACR/ARHP Annual Meeting; Chalmers et al. ACR Meeting 2020. Abstract 65; Chalmers et al. ACR Meeting 2020. Abstract: 0840.

EQUALISE Study Type A Cohorts: Evaluation of Itolizumab in Subjects with Systemic Lupus Erythematosus without Lupus Nephritis

Exploratory Subgroup Analyses in Subjects with Baseline Spot UPCR > 100 mg/g, Baseline Spot UPCR > 200 mg/g and Baseline ACR > 30 mg/g



Type A Proteinuria Subgroup Analyses

- Baseline Spot UPCR = mean of Screening and Day 1 UPCR
  - Spot UPCR > 100 mg/g (N=16)
  - Spot UPCR > 200 mg/g (N=6)
- Baseline ACR=mean of Screening and Day 1 ACR
  - ACR > 30 mg/g (N=4)

*EQUALISE is an ongoing Phase 1b study that is currently enrolling the Type B Cohort, which evaluates itolizumab 1.6 mg/kg SC Q2W x 13 doses in subjects with apLN (Class III/IV) for 24 weeks (NCT04128579).

Abbreviations: ACR albumin creatinine ratio, apLN active proliferative lupus nephritis, eGFR estimated glomerular filtration rate, Q2W every two weeks, SC subcutaneous, SLE systemic lupus erythematosus, UPCR urine protein-to-creatinine ratio

Data are interim from 30 July 2021

Baseline Demographics/Disease Characteristics by Proteinuria Subgroups Were Similar

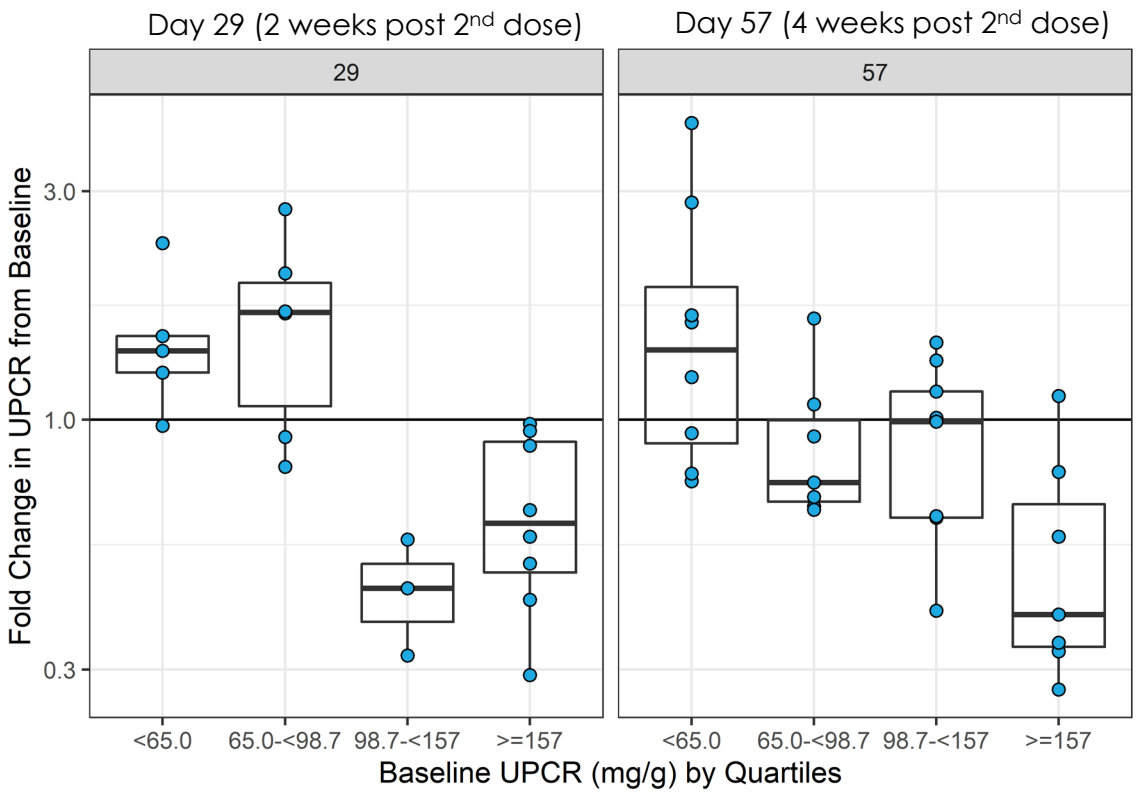
Demographics/Disease Characteristics	Proteinuria Subgroups*			
	ACR > 30 mg/g N=4	Spot UPCR > 200 mg/g N=6	Spot UPCR > 100 mg/g N=16	**All Subjects N=35**
Age: years, mean (SD)	54.0 (11.3)	58.8 (12.5)	54.5 (11.6)	**50.9 (12.6)**
Sex: Female, n (%)	3 (75%)	5 (83%)	15 (94%)	**33 (94%)**
Race: White/Black, n (%)	3 (75%)/1 (25%)	6 (100%)/0	13 (81%)/3 (19%)	**26 (74%)/9 (26%)**
SLEDAI-2K: mean (SD)	10.5 (4.1)	6.7 (3.3)	7.4 (3.5)	**7.1 (3.5)**
Time from SLE diagnosis to first dose: years, mean (SD)	12.0 (13.8)	4.6 (2.3) n=5	12.1 (9.0) n=15	**11.7 (8.2)** **n=34**
Current use of low dose corticosteroids (≤10 mg/d prednisone): yes, n (%)	1 (25%)	3 (50%)	5 (31%)	**10 (29%)**
eGFR: ml/min/1.73m^2, mean (SD)	91.6 (10.7)	95.7 (6.4)	95.3 (17.2)	**99.1 (20.1)**
Spot urine protein-creatinine-ratio (UPCR): mg/g, median (min, max) mean (SD)	255.7 (115.1, 1505.1) 532.9 (656.5)	282.8 (218.4, 1505.1) 484.4 (502.0)	172.7 (100.4, 1505.1) 271.8 (336.9)	**98.7 (47.6, 1505.1)** **164.4 (246.6)** **n=34**
Spot albumin-creatinine-ratio (ACR): mg/g, median (min, max) mean (SD)	48.9 (31.6, 1205.5) 333.7 (581.2)	15.6 (5.7, 1205.5) 253.6 (532.2) n=5	15.7 (3.2, 1205.5) 110.8 (329.3) n=13	**9.3 (3.2, 1205.5)** **50.9 (214.6)** **n=31**
C3 level: mg/dL, mean (SD) Normal: 81-157 mg/dL	133.3 (20.9)	115.3 (18.8)	130.7 (23.7)	**132.0 (27.2)**
C4 level: mg/dL, mean (SD) Normal: 13-39 mg/dL	30.4 (1.8)	23.6 (10.2)	29.1 (10.9)	**30.2 (11.2)**
Anti-DS DNA: IU/mL, mean (SD) Positive: ≥ 36 IU/mL	30.8 (38.5)	18.8 (11.3)	22.3 (21.2) n=15	**22.4 (28.3)** **n=32**

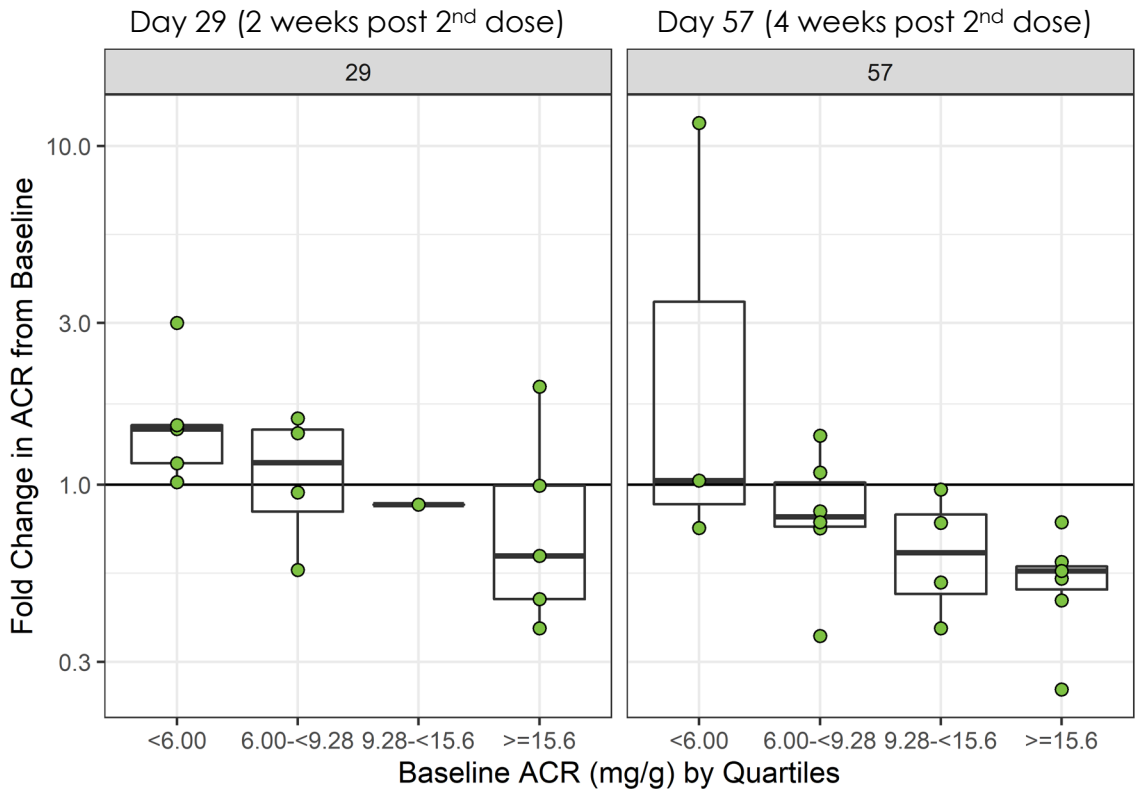
Baseline: Last pre dose value with exception of Spot UPCR, ACR, and eGFR which are the mean of all Screening and Baseline values.
*Subjects may be in more than 1 subgroup
Abbreviations: C complement, eGFR estimated glomerular filtration rate, Max maximum, Min minimum, SD standard deviation, SLEDAI 2K Systemic Lupus Erythematosus Disease Activity Index 2000

Data are interim from 30 July 2021

Greater Decreases in Spot UPCR and ACR Observed in Subjects with Higher UPCR and ACR at Baseline (All Type A Subjects, N=35)

A quartile analysis indicated that larger decreases in spot UPCR and ACR were observed at Days 29 and 57 in subjects with higher baseline spot UPCR or ACR





Itolizumab was dosed on Days 1 and 15 (not all subjects received the second dose). Dots represent subject-level data; data are not available for all subjects at all timepoints.

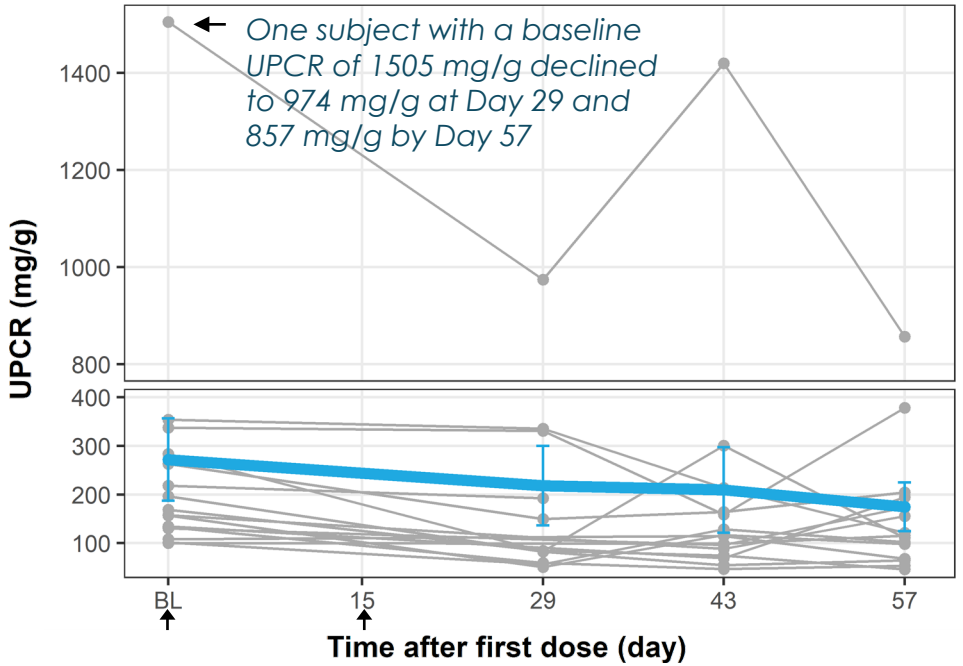
Abbreviations: ACR urine albumin-to-creatinine ratio, UPCR urine protein-to-creatinine ratio

Data are interim from 30 July 2021

Exploratory Analyses in Subjects with Baseline Spot UPCR > 100 mg/g Showed up to 40% Reduction After 2 Doses of Itolizumab

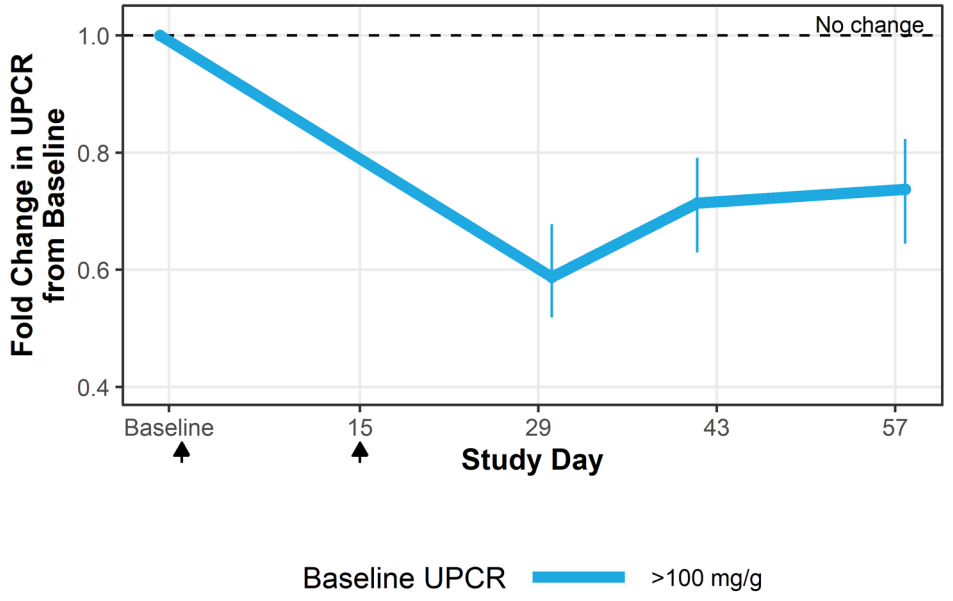
Exploratory subgroup analysis of subjects with baseline elevated proteinuria: UPCR > 100 mg/g (N=16)

Observed spot UPCR over time



Visit	N	Mean (mg/g)	SE
Baseline	16	272	85
Day 29	11	218	82
Day 57	15	183	53

Mean ± SE fold change in spot UPCR over time



Visit	N	Change from Baseline¥ (%)
Baseline	16	0.0
Day 29	11	-45
Day 57	15	-34

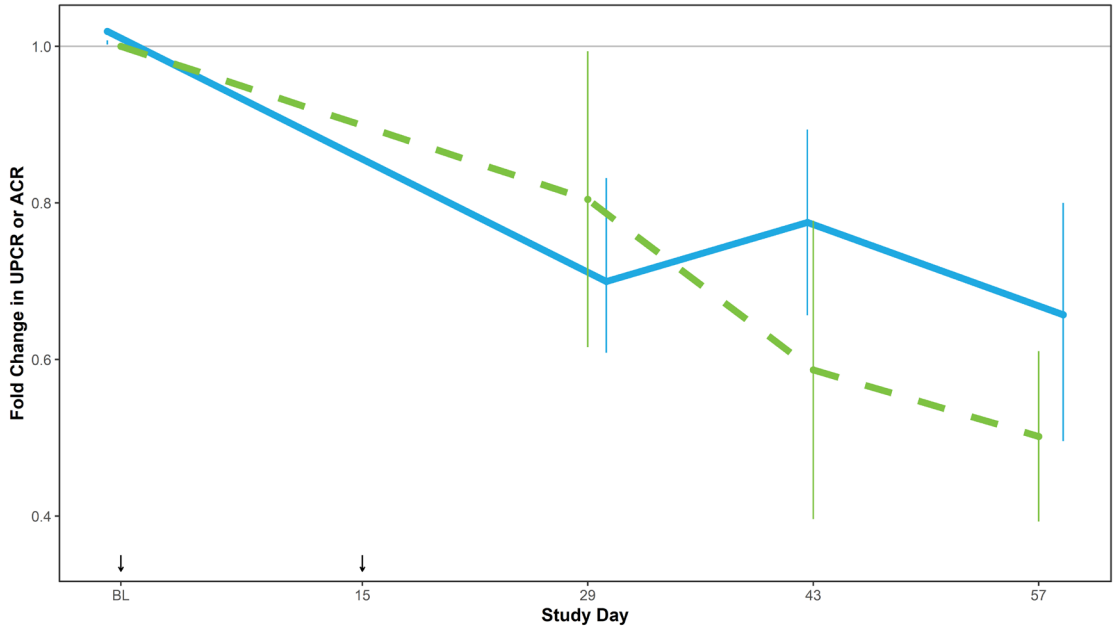
Itolizumab was dosed on Days 1 and 15 (not all subjects received the second dose). Gray lines represent subject-level data and blue lines represent means; ¥Change from baseline = (geometric mean of subject specific fold changes from baseline -1) x 100, negative values indicate % reduction from baseline, baseline is the mean of the Screening and Day 1 values; Data are not available for all subjects at all timepoints

Abbreviation: UPCR urine protein-to-creatinine ratio

Data are interim from 30 July 2021

Subgroup Analyses of Subjects with Elevated Baseline Spot UPCR and ACR Showed Reductions in Proteinuria of up to 53%

Exploratory subgroup analysis of subjects with baseline elevated proteinuria: spot UPCR (> 200 mg/g; n=6) or ACR (> 30 mg/g; n=4)



Visit	N	Spot UPCR Mean (mg/g)	SE	Change from Baseline¥ (%)	N	ACR Mean (mg/g)	SE	Change from Baseline¥ (%)
Baseline	6	484	203	NA	4	334	291	NA
Day 29	6	344	133	-33	2	387	355	-22
Day 57	5	334	139	-42	4	174	154	-54

Itolizumab was dosed on Days 1 and 15 (not all subjects received the second dose). Mean ± SE shown; ¥Change from baseline = (geometric mean of subject specific fold changes from baseline -1) x 100, negative values indicate % reduction from baseline; Data are not available for all subjects at all timepoints. Two subjects were in both subsets. Baseline is the mean of the Screening and Day 1 value

Abbreviations: ACR urine albumin-to-creatinine ratio, UPCR urine protein-to-creatinine ratio

Data are interim from 30 July 2021

Subcutaneous Itolizumab was Well Tolerated and the Majority of TEAEs Were Mild or Moderate in Severity

TEAE	Proteinuria Subgroups*			
	ACR > 30 mg/g N=4 n (%)	Spot UPCR > 200 mg/g N=6 n (%)	Spot UPCR > 100 mg/g N=16 n (%)	**All subjects N=35 n (%)**
Subjects with Any TEAEs	2 (50%)	3 (50%)	7 (44%)	**17 (49%)**
Subjects with TESAEs	0	0	0	**1 (3%)**
Subjects with Treatment-Related TEAEs	1 (25%)	3 (50%)	6 (38%)	**15 (43%)**
Subjects with Treatment-Related TESAEs	0	0	0	**0**
Subjects with TEAEs by Maximum CTCAE Severity Grade				
Grade 1 - Mild	0	1 (17%)	2 (13%)	**6 (17%)**
Grade 2 - Moderate	2 (50%)	2 (33%)	5 (31%)	**9 (26%)**
Grade 3 - Severe	0	0	0	**2 (6%)**
Grade 4 - Life-threatening	0	0	0	**0**
Grade 5 - Death	0	0	0	**0**
Subjects with DLT	0	0	0	**1 (3%)**
Subjects with Adverse Events of Special Interest	0	0	0	**1 (3%)**
Subjects with TEAEs Leading to Withdrawal of Treatment	1 (25%)	0	1 (6%)	**4 (11%)**

- The most frequently reported adverse events were injection site erythema and headache
- No treatment-related SAEs were reported, and no deaths were reported in the study
- Two TESAEs were reported in one subject (not in any of the proteinuria subgroups), and these were hypotension and syncope that occurred ~30 days after the last dose, that was deemed unrelated by the investigator.

*Subjects may be in more than 1 subgroup

Abbreviations: ACR albumin-creatinine-ratio, CTCAE Common Terminology Criteria for Adverse Events, DLT dose-limiting toxicity, TEAE treatment-emergent adverse event, TESAE treatment-emergent serious adverse event, UPCR urine protein-creatinine-ratio

Data are interim from 30 July 2021

Conclusions

- EQUALISE is a two-part, Phase 1b dose-escalation study of subcutaneous itolizumab in SLE subjects with or without active LN.
- The Type A cohorts in SLE patients without known LN has been completed. Enrollment is ongoing for the Type B cohort in apLN patients.
- Subcutaneous itolizumab was well tolerated with the majority of AEs being mild to moderate injection site reactions.
- Exploratory subgroup analysis of Type A SLE subjects without a diagnosis of active lupus nephritis but with elevated baseline levels of proteinuria or albuminuria showed a decline in proteinuria (up to 53%) following two doses of itolizumab.
- The ongoing EQUALISE Type B study (NCT04128579) will assess itolizumab safety and efficacy in SLE patients with Class III/IV active proliferative lupus nephritis.