EQUIP Interim Results: A Phase 1b Study Evaluating Itolizumab in Subjects with Moderate-to-Severe Uncontrolled Asthma

POSTER
P071

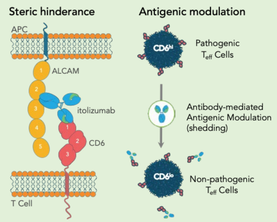
Reynold A. Panettieri Jr.[1], Peter Bremner[2], Philip Bardin[3], Stephen Connelly[4], Joel Rothman[4], Dolca Thomas[4], Cherie T Ng[4], Maple Fung[4], Jo Douglass[5]

[1]Rutgers, The State University of New Jersey, New Brunswick, NJ, [2]University of Notre Dame, Murdoch, Australia [3]Monash University, Melbourne, Australia [4]Equillium, San Diego, CA [5]University of Melbourne, Melbourne, Australia

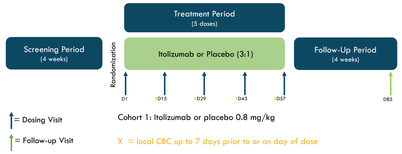
Introduction

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. It is being evaluated as a treatment for immuno-inflammatory diseases in which T_{eff} cells play a central role, including in patients with uncontrolled asthma. The CD6/ALCAM pathway is elevated in severe asthmatics and is implicated in Th2 and Th1 /Th17 driven responses.[1-3]

Here, we present results from EQUIP (NCT04007198), which is an ongoing phase 1b, randomized, double-blind, placebo-controlled study of itolizumab in subjects with moderate-to-severe uncontrolled asthma.



Study Design



Itolizumab doses of 0.8, 1.6, 2.4, or 3.2 mg/kg or placebo were administered subcutaneously every 2 weeks (SC Q2W) for a total of 5 doses. Interim blinded data from the completed Cohort 1 (itolizumab 0.8 mg/kg or placebo) is summarized (data cut off 30 Aug 2021). Cohort 2 (itolizumab 1.6 mg/kg) is ongoing in Australia and New Zealand.

Subjects were randomized in a 3:1 ratio (active:placebo). Dose escalation into Cohort 2 may occur after Cohort 1 completed and review of the data by the data review committee.

Primary Objectives

Characterize the safety and tolerability of itolizumab

Secondary Objectives

1. Characterize the pharmacokinetics (PK) of itolizumab
2. Characterize the pharmacodynamics (PD) of itolizumab
3. Characterize the PK/PD relationships of itolizumab
4. Characterize the clinical activity of itolizumab

Primary Endpoints

Safety and tolerability of itolizumab

Secondary Endpoints

1. PK and PD of itolizumab
2. Clinical activity:
   a. Change from baseline in prebronchodilator Forced Expiratory Volume -1second (FEV1)
   b. Change from baseline in Fractional Exhaled Nitric Oxide (FeNO)
   c. Change from baseline in Asthma Control Questionnaire (ACQ-6) score

Statistical Methods

Safety, PK, PD, and efficacy endpoints are tabulated using descriptive statistics with itolizumab and placebo groups combined. After database lock and unblinding, data from all placebo subjects will be pooled and itolizumab-treated subjects will be presented by dose and combined.

Patient Eligibility

Key Inclusion Criteria

1. Moderate-to-severe uncontrolled asthma requiring moderate- or high-dose inhaled corticosteroid (ICS) and one or more additional controller medications with a stable dose ≥1 month prior to the initial Screening Visit
2. Prebronchodilator FEV1 ≥ 40% and ≤ 90% of predicted value, despite use of a moderate- or high-dose ICS and one or more additional controller medications
3. FEV1 reversibility of ≥ 12% (% predicted increase) AND ≥ 200 mL (absolute increase) after administration of a short-acting beta agonist during the Screening Period or documented within the prior 2 years, or has a history of positive bronchial challenge test within the prior 2 years
4. History of ≥ 1 clinically significant asthma exacerbation in the 12 months prior to the initial Screening Visit, despite use of a moderate- or high-dose ICS and one or more additional controller medications at the time the exacerbation(s) occurred
5. ACQ-6 score ≥ 1.5 during the Screening and Study Day 1 (Baseline) Visits

Key Exclusion Criteria

1. Current or former smoker with a smoking history of ≥10 pack-years
2. Body mass index > 36 kg/m2
3. Respiratory tract infection and/or asthma exacerbation within 4 weeks before the initial Screening Visit, or during the Screening Period
4. Monoclonal antibody therapy for the management of asthma or any other condition within 3 months prior to the initial Screening Visit
5. Required an oral corticosteroid burst within 1 month prior to the initial Screening Visit or during the Screening Period (these subjects may be re-screened following the 1-month period); maintenance oral corticosteroids ≤ 10 mg/d prednisone or equivalent is permitted

Results

Baseline Characteristics

Nine subjects were enrolled in Cohort 1 after 1 subject was replaced due to an adverse event. The mean age was 52 years with 33% female, 89% white, Baseline mean FEV1 was 2.1L (SD 0.66; 62% predicted) and the mean Baseline ACQ-6 was 2.5 (SD 0.6) (TABLE 1).

TABLE 1. BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS

Baseline	Cohort 1 (0.8 mg/kg or placebo) N=9
Age- years, mean (SD)	52.2 (14.0)
Sex (Male/Female)	6/3
Race (White/non-White)	8/1
Eosinophil count, x10⁹/L, mean (SD)	0.29 (0.35)
Fractional Exhaled Nitric Oxide (FeNO) in parts per billion (ppb) mean (SD) Minimum, maximum	 36.3 (29.5) 8.5, 86.0
Asthma Control Questionnaire- 6 (ACQ-6) mean (SD)	 2.5 (0.6)
Forced Expiratory Volume-1second (FEV1), L mean (SD) % predicted, mean (SD)	2.1 (0.66) 62.4% (15.0)
Peak Expiratory Flow Rate (PEFR), L/min, mean (SD)	386.8 (117.2)

All subjects in Cohort 1 completed the study, with 1 subject discontinuing study treatment due to an adverse event/dose limiting toxicity (DLT) of lymphopenia (TABLE 2).

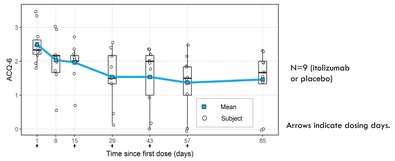
TABLE 2. COHORT 1 SUBJECT DISPOSITION

	Cohort 1 (0.8 mg/kg or placebo) N=9
Safety population	
Subjects who completed study treatment	8 (89%)
Subject prematurely ended study treatment	1 (11%)
• Lost to follow up	0
• Adverse event	1 (11%)
• Withdrawal by subject	0
Subjects who completed the study	9 (100%)
• Withdrawal by subject	0

Clinical Activity

Baseline mean ACQ-6 for Cohort 1 was 2.5, which improved to 1.5 by Day 29, and was maintained through final treatment on Day 57 and 30 days after the last dose at Day 85 (FIGURE 1).

FIGURE 1. ACQ-6 OVER TIME COHORT 1



Mean FEV1 on Day 1 was 2.1 L for Cohort 1, which improved to 2.4 L on Day 29 and was maintained after the last dose at Day 85 (Figure 2A). This corresponded to the percent predicted at Day 1 with a mean of 62.4%, which increased to 69.4% at Day 29 but was 67.1% at Day 85 (Figure 2B).

FIGURE 2. COHORT 1 FEV1 OVER TIME (FIGURE 2A) AND FEV1 % PREDICTED OVER TIME (FIGURE 2B)

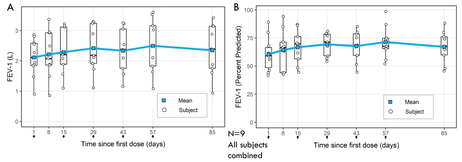
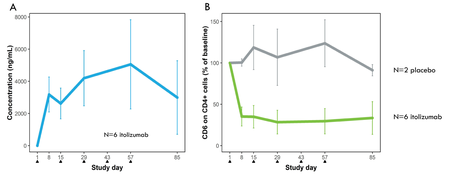
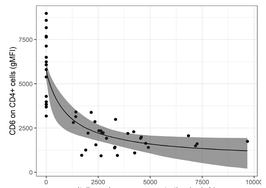


FIGURE 3. COHORT 1 MEAN ± SD ITOLIZUMAB CONCENTRATIONS (FIGURE 3A; N=6 FOR ACTIVE SUBJECTS) AND CD6 EXPRESSION ON THE SURFACE OF CD4+ CELLS EXPRESSED AS PERCENT OF BASELINE (FIGURE 3B) OVER TIME AFTER ADMINISTRATION OF 0.8 MG/KG SC Q2W (N=6) OR PLACEBO (N=2)



Interim PK findings indicate that higher itolizumab concentrations are associated with a greater loss of CD6 from the surface of T cells, with the maximal PD effect observed within the observed concentration range (FIGURE 4).

FIGURE 4. THE RELATIONSHIP OF PK WITH THE PD MARKER (N=6 FOR ACTIVE SUBJECTS) THROUGHOUT THE STUDY



Includes up to 5 measures per subject.

Safety

Although all subjects in Cohort 1 reported at least one treatment emergent adverse event (TEAE), most were mild/moderate (Grade 1 /2) in severity (TABLE 3). There was one subject who had 2 Grade 3 TEAEs, which were lymphopenia events (one was considered a DLT). The most commonly reported events were the adverse events of special interest (AESI), including injection site reactions and lymphopenia. Overall, study treatment was well tolerated.

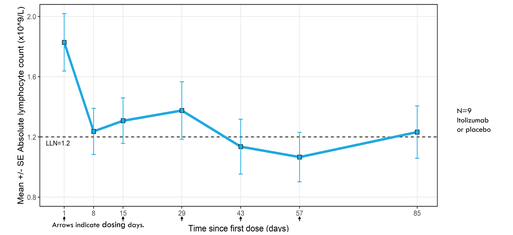
TABLE 3. COHORT 1 SUMMARY OF TREATMENT EMERGENT ADVERSE EVENTS

	Cohort 1 (0.8 mg/kg or placebo) N=9 n (%)
Subjects with Any Treatment Emergent Adverse Event (TEAE)	9 (100)
Subjects with Treatment Emergent Serious Adverse Event (TESAE)	0
Subjects with Treatment-Related TEAEs	6 (67)
Subjects with Treatment-Related TESAEs	0
Subjects with TEAEs by Maximum Common Terminology Criteria for Adverse Events (CTCAE) Severity Grade	
Grade 1 – Mild	2 (22)
Grade 2 – Moderate	6 (67)
Grade 3 – Severe	1 (11)
Grade 4 - Life-threatening	0
Grade 5 – Death	0
Subjects with Dose Limiting Toxicity (DLT)*	1 (11)
Subjects with Adverse Event of Special Interest (AESI)	6 (67)
Subjects with TEAEs Leading to Withdrawal of Treatment	1 (11)
Subjects with TEAEs Leading to Death	0

*DLT criteria: a CTCAE Grade 3 event that was considered related to study treatment by the investigator
Data cut off 30 JUL 2021

FIGURE 5 shows the absolute lymphocyte count over time in the cohort. The decline was noted after the first dose and remained stable through continued dosing. Infections were not associated with the declines.

FIGURE 5. ABSOLUTE LYMPHOCYTE COUNT OVER TIME



Conclusions

- EQUIP is a phase 1b dose-escalation study of itolizumab and placebo in subjects with moderate-to-severe uncontrolled asthma.
- Study treatment in the first dosing cohort (0.8 mg/kg) was well tolerated with most adverse events reported being mild/moderate in severity. These consisted of primarily injection site reactions and lymphopenia events.
- Interim PK/PD findings suggest the expected concentrations and CD6 receptor shedding from T cells with subcutaneous dosing.
- Preliminary findings show stability in FEV1 and ACQ-6 scores.
- Based on these interim results, additional study of itolizumab in moderate-to-severe uncontrolled asthma is warranted.

Acknowledgments

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References

1. Seon Oh et al. *Allergy Asthma Immunol Res* 2019;11(5):677-690. **2.** Km YS et al. *Clin Exp Immunol* 2018;192(2):151-164. **3.** Kim MN et al. *Am J Resp Crit Care Med* 2018;197(8): 994-1008

Disclosures

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Additional Information

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