EQUATE, a Phase 1b/2 study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and clinical activity of a novel targeted anti-CD6 therapy, itolizumab, in subjects with newly diagnosed acute graft versus host disease

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Background

Clinical need:

- Acute graft versus host disease (aGVHD) is a significant contributor to morbidity and non-relapse mortality (NRM), occurring in ~50% of patients receiving allogeneic hematopoietic stem cell transplant (HSCT) with standard GVHD prophylaxis regimens
- There are currently no FDA approved therapies for the initial treatment of newly diagnosed aGVHD.

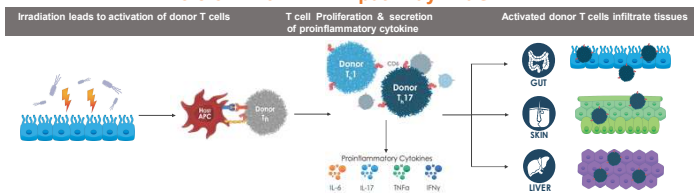
T cells are a driver of aGVHD:

- T effector cells (T_{eff}), particularly CD4+ T helper cells, play a central role in the pathogenesis of aGVHD
- **CD6** is a co-stimulatory receptor, predominantly expressed on CD4+ T helper cells, that binds to activated leukocyte cell adhesion molecule (ALCAM), a ligand expressed on antigen presenting cells and various epithelial and endothelial tissues.
- The CD6-ALCAM pathway plays an integral role in modulating T cell activation and trafficking and is central to immune mediated inflammation.

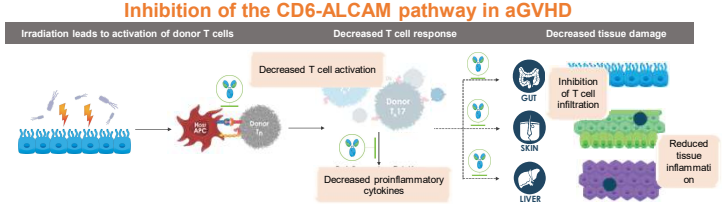
EQ001 (itolizumab):

- Itolizumab is a humanized IgG1 mAb that binds to CD6 and blocks the interaction with ALCAM, thereby inhibiting both the activity and trafficking of T cells without T cell depletion.
- Itolizumab has previously been approved for the treatment of psoriasis in India[1].

Role of CD6-ALCAM pathway in aGVHD



Inhibition of the CD6-ALCAM pathway in aGVHD

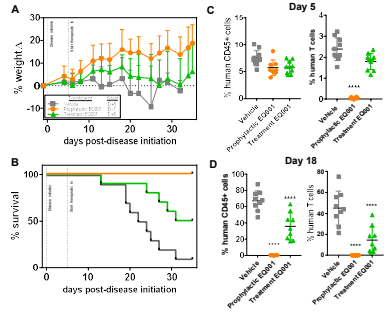


Rationale for evaluation of itolizumab in aGVHD

- **Human validation of target**: Previous studies by Soiffer et al. in patients receiving allogeneic bone marrow transplants had shown that depleting CD6+ T cells ex-vivo in donor bone marrow using T-12, an anti-CD6 monoclonal antibody, as the sole method for GVHD prophylaxis lowered the incidence of acute and chronic GVHD[2].

- **Preclinical support for itolizumab**: In an aggressive xenogeneic humanized model of GVHD, itolizumab demonstrated significant reductions in GVHD-associated weight loss, mortality, and presence of reactive human T cells[3].

Itolizumab treats disease in a humanized model of aGVHD



EQUATE

Trial Design & Endpoints

Study Objective:

To evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of EQ001 in subjects with newly diagnosed aGVHD.

Study Design:

Table 1. Summary of Study

	Phase 1b	Phase 2
Trial Design	Open-label, dose escalation (3X3 design)	Double-blind, placebo-controlled Randomization at 2:1 (drug:placebo)
Primary Objectives	1. Assess safety and tolerability 2. Determine optimal IV dose level	1. Define the clinical activity
Secondary Objectives	To characterize the following: 1. Pharmacokinetics (PK) 2. Pharmacodynamics (PD) 3. PK/PD relationship 4. Clinical activity	To further characterize: 1. Safety and tolerability 2. Pharmacodynamics (PD)
Sample Size	Up to 24 patients	60 patients
Dosing Regimen	EQ001 administered intravenously Q2W for 2 months (5 doses) with additional 10 months of follow-up	

Study Schematics

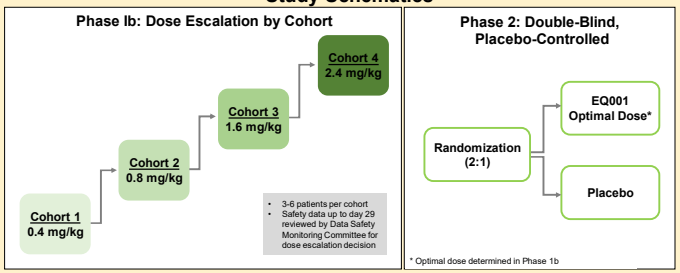


Table 2. Key Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
• Age: ≥ 18yrs (Phase 1b), ≥ 12yrs (Phase 2) • First allogeneic hematopoietic stem cell transplant (alloHSCT) • Clinical diagnosis of acute GVHD requiring systemic immune suppressive therapy **1) Phase 1b: aGVHD grades III to IV** **2) Phase 2: aGVHD grades II to IV**	• Relapse of malignancy • Graft failure • Post-transplant lymphoproliferative disease • Prior therapy for aGVHD, except for alloHSCT prophylaxis regimens or systemic corticosteroids • Initial dose of systemic corticosteroids for aGVHD more than 72 hours prior to initial dose of study drug • Severe organ dysfunction • Active, uncontrolled infection

Sample Size:

- **Phase 1b:** The sample size of up to 24 subjects includes a sufficient number to meet the primary and secondary objectives in adult subjects with aGVHD.
- **Phase 2:** 60 subjects randomized in a 2:1 ratio provides ~80% power to detect the assumed difference when the null hypothesis of no difference is tested using a 2-sided Fisher's exact test (alpha level = 0.05).
  - Assumptions: At Day 29, an overall response rate (partial response or better) of 40% in the placebo group and 80% in the EQ001-treated group. The sample size may be recalculated based on revised assumptions on effect size after Phase 1b is completed

Concomitant Medications:

- All subjects will receive systemically administered corticosteroid therapy, prednisone initiated at 2 mg/kg/day (or equivalent).
- Following stabilization of aGVHD, tapering of corticosteroids may be initiated according to the recommended treatment tapering schedule, however, the investigator can adjust dosing as clinically indicated during the study.
- All subjects may remain on their GVHD prophylactic immunosuppressant regimens.

Study Endpoints:

Summary of Assessments

Safety

- Physical examinations, vital signs, 12-lead ECGs, laboratory tests (clinical chemistries, complete blood count, coagulation panel and urinalysis), ADA, and AE monitoring.
- Adverse Events of Interest based on prior clinical experience with EQ001 (lymphopenia, infusion-related reactions, and fever)

Pharmacokinetics:

- PK parameters assessed: T_{max}, C_{max}, AUC_{0-t}, C_{min}, AUC_{0-inf}, $t_{1/2}$, Cl, and Vd
- CD6 receptor occupancy

Pharmacodynamics:

- Inflammatory markers and cytokines (including IL-1β, IL-2, IL-6, IL-17, IL-21, IL-22, IL-23, IFN-γ, TGF-β, C-reactive protein)
- Immunophenotyping
- T cell stimulation
- Disease related markers (ST2 and Reg3α)

Efficacy

- Overall response rate (PR, VGPR,CR)
- Change from baseline in aGVHD organ stages and overall clinical grading
- aGVHD Activity Index
- Concomitant medication use including steroid exposure
- Disease Progression
- Incidence of chronic GVHD
- Overall mortality and non-relapse mortality

Patient Safety Review:

An independent Data & Safety Monitoring Committee will review all available clinical, laboratory and safety data, for each cohort in Phase 1b and periodically for Phase 2, to make recommendations regarding the continuation or modification of the study, advancement to next dose cohort and progression to Phase 2.

Dose-Limiting Toxicities (DLT window Study Days 1–29):

- Any ≥ Grade 3 infusion reaction or other clinical finding associated with hypersensitivity
- Any ≥ Grade 3 AE that is not related to the underlying disease (aGVHD)

Subject Stopping Criteria	
Phase 1b	**Phase 2**
Any dose limiting toxicity	Study drug related toxicity that cannot be controlled with supportive care, despite 1 dose reduction and/or delay of treatment for up to 1 week
Clinically significant disease progression	Clinically significant disease progression
During any part of the study: • Withdrawn consent • Investigator or Sponsor considers that the subject will not benefit from further investigational drug • Pregnancy • Subject is not able to comply with the study requirements • Sponsor terminates the study • A regulatory authority mandates study dosing cessation	

Study Progress:



1) The trial is currently open and enrolling patients at US centers.
2) Itolizumab been awarded FDA FastTrack Designation for the treatment of aGVHD

Summary

- Inhibiting the CD6-ALCAM pathway with EQ001 (itolizumab) represents a unique and promising approach for the treatment of aGVHD following HSCT by inhibiting both the activity and trafficking of T cells.
- This is the first clinical study to examine the effects of an anti-CD6 therapy for the treatment of patients with newly diagnosed aGVHD.
- **The EQUATE trial is currently open at US Centers; more information can be found on clinicaltrials.gov (NCT# 03763318).**

Acknowledgements & References

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1. Krupashankar et al. J Am Acad Dermatol. 2014 Sep;71(3): 484-92
2. Soiffer et al., J Clin Oncol. 2001 Feb;19(4): 1152-9
3. Ng et al. Blood. 2019 Nov; 134(Supplement_1): 5603