A PHASE II OPEN LABEL STUDY OF NEIHULIZUMAB, AN ANTI-CD162 (PSGL-1) ANTIBODY, IN PATIENTS WITH MODERATE TO SEVERE ACTIVE, ANTI-TNFα AND/OR ANTI-INTEGRIN REFRACTORY ULCERATIVE COLITIS

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INTRODUCTION

- **Neihulizumab** (**ALTB-168,** former name AbGn-168H) represents a novel immune checkpoint agonistic antibody that binds to human CD162 (PSGL-1), leading to downregulation of activated T cells. Results of early-phase trials of neihulizumab have suggested a benefit in patients with treatment refractory auto-immune conditions, including psoriasis, psoriatic arthritis and steroid-refractory acute graft-versus-host disease.

- **Ulcerative colitis (UC)** is a lifelong, chronic inflammatory disease affecting the colorectal mucosa, which is characterized by the hallmark clinical symptoms of bloody diarrhea, rectal urgency, and tenesmus. Anatomically, UC involves the rectum in about 95% of cases and may extend to the proximal portion of the large intestine. The pathological process that causes mucosa damage in UC is substantially involved with T cell accumulation and T cell mediated immune-inflammatory response. The important role of T cells in the pathogenesis of UC has been suggested in the literature and therapies that target T cell mediated inflammatory response and T cell trafficking have demonstrated efficacy to treat UC. Therefore, we conducted a Phase II trial to evaluate the efficacy and safety of neihulizumab in UC.

STUDY DESIGN

This is a single arm, open label, multiple dose study to assess neihulizumab in patients with moderate to severe active, anti-TNFα and/or anti-integrin refractory UC.

- Dose: 9 mg/kg, intravenously (i.v.)
- Two regimens were tested
  - 5 weekly doses plus 3 bi-weekly doses (5+3 regimen)
  - 8 weekly doses plus 2 bi-weekly doses (8+2 regimen)

STUDY OBJECTIVES

Primary Objective:
- To evaluate the efficacy of ALTB-168 administered intravenously in patients with moderate-to-severe active UC who are refractory or intolerant to anti-TNFα and/or anti-integrin treatments

Secondary Objective:
- To investigate the safety, tolerability, and immunogenicity of intravenous ALTB-168 administration

Exploratory Objective:
- To explore the change of biomarkers (fecal calprotectin and C-reactive protein) after intravenous ALTB-168 administration.

KEY ELIGIBILITY CRITERIA

- Diagnosis of UC ≥ 12 weeks prior to screening.
- Moderate-to-severe active UC, at time of screening, defined as:
  a) Mayo Clinic Score (MCS) of 6 points or higher, AND
  b) a centrally read MCS endoscopic subscore of grade 2 or higher, AND
  c) MCS rectal bleeding subscore of 1 point or higher, AND
  d) disease extending 15 cm or more from the anal verge
- Having previously received anti-TNFα and/or anti-integrin therapy for UC and demonstrated an inadequate response, loss of response, or intolerance.

EFFICACY ENDPOINT

Primary efficacy endpoint: **Clinical response at Week 12**
A ≥ 3-point reduction in MCS, a 30% or greater decrease from the baseline score, and with a ≥ 1-point decrease of the rectal bleeding subscore or an absolute rectal bleeding score of 0 or 1 at Week 12.

Key Secondary efficacy endpoints:
(1) Clinical response at Weeks 6, 7, 9 and 11 defined as a ≥2-point decrease in pMCS, and with a 1-point or greater decrease of the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1.
(2) Clinical remission, defined as MCS of 2 or lower (or pMCS of 1 or lower) and no subscore higher than 1 at Weeks 6, 7, 9, 11 and 12.
(3) Mucosa healing, defined as an absolute subscore for endoscopy of 0 or 1 at Weeks 12 and 26.
(4) Histological remission, defined as histological grade <2 at Weeks 12 and 26.
(5) IBDQ response, defined as an increase from baseline of at least 16 points at Weeks 12 and 26.

RESULTS

Demographic and Baseline Characteristics

	5+3 Regimen N=10	8+2 Regimen N=14
Age, y, median (Min-Max)	37 (21-65)	35.5 (22-61)
Male, n (%)	6 (60%)	7 (50%)
Duration of UC (yrs) , median (Min-Max)	3.8 (1.4-13.5)	7.4 (0.9-15.3)
Use of Corticosteroids, n (%)	4 (40%)	5 (36%)
Number of prior biologics usage, n (%)		
1	6 (60%)	3 (21%)
2	0	2 (14%)
≥3	4 (40%)	9 (64%)
Complete Mayo score, median (Min-Max)	9.5 (7-12)	9 (6-12)
Endoscopy Subscore, median (Min-Max)	3 (1-3)	3 (2-3)
IBDQ score, median (Min-Max)	133 (63-172)	139 (66-197)
Fecal calprotectin (µg/g), median (Min-Max)	543 (198-2,001)	1366 (16-2181)
CRP (mg/L), median (Min-Max)	1.5 (1-17)	6.5 (1-81)

Efficacy

Assessment	5+3 Regimen	8+2 Regimen
Week 12	N=9	N=14
cMayo score clinical response	2 (22%)	7 (50%)
cMayo score clinical remission	0	4 (29%)
Mucosal healing	2 (22%)	4 (29%)
Histological healing (Geboes score = 0)	0	0
Histological Improvement	0	2 (14%)
IBDQ response	2 (22%)	9 (64%)
Week 26	N=9	N=14
cMayo score clinical response	1 (11%)	5 (36%)
cMayo score clinical remission	0	3 (21%)
Mucosal healing	0	3 (21%)
Histological healing (Geboes score = 0)	0	0
Histological Improvement	1 (11%)	4 (29%)
IBDQ response	1 (11%)	7 (50%)

Adverse Events

	5+3 Regimen N = 10 (%)	8+2 Regimen N =14 (%)
Any Adverse Event	9 (90.0)	13 (92.9)
TEAEs[a]	9 (90.0)	13 (92.9)
Related	7 (70.0)	2 (14.3)
Not related	9 (90.0)	12 (85.7)
Severity of TEAEs		
Mild	5 (50.0)	7 (50.0)
Moderate	3 (30.0)	5 (35.8)
Severe	1 (10.0) [b]	1 (7.1)[c]
Serious TEAEs		
Related	0	0
Not related	1 (10.0)[b]	0
Early Withdrawal	1 (10,0)	0
AE Leading to Death	0	0

[a] Treatment Emergent Adverse Event
[b] UC flare
[c] Worsening headache

Treatment-Related TEAEs by System Organ Class

Treatment-related TEAEs	5+3 Regimen, N = 10 (%)	8+2 Regimen, N = 14 (%)
Any Adverse Event	**7 (70.0)**	**2 (14.3%)**
Gastrointestinal Disorders	**1 (10.0)**	
Constipation	1 (10.0)	
General Disorders And Administration Site Conditions	**2 (20.0)**	
Chills	1 (10.0)	
Fatigue	1 (10.0)	
Pyrexia	1 (10.0)	
Infections And Infestations		**1 (7.1)**
Vulvovaginal Candidiasis		1 (7.1)
Nervous System Disorders	**5 (50.0)**	
Headache	5 (50.0)	
Respiratory, Thoracic And Mediastinal Disorders	**1 (10.0)**	
Cough	1 (10.0)	
Skin And Subcutaneous Tissue Disorders	**1 (10)**	
Rash	1 (10.0)	
Uncoded		**1 (7.1)**

SUMMARY

Efficacy:
- Primary efficacy endpoint:
  - 5+3 regimen: Two (22.2%) achieved clinical response at Week 12.
  - 8+2 regimen: Seven (50.0%) achieved clinical response at Week 12.

- Secondary efficacy endpoint:
  - 5+3 regimen: One (11.1%) achieved clinical response at Week 26.
  - 8+2 regimen: Five (35.7%) achieved clinical response at Week 26.

- Secondary endpoint clinical remission:
  - 5+3 regimen: None achieved clinical response at Week 12 or Week 26.
  - 8+2 regimen: Four (28.6%) and three (21.4%) achieved clinical remission at Week 12 and Week 26, respectively.

Pharmacokinetics:
- 5+3 regimen: Mean maximum neihulizumab plasma concentrations ranged from 304233.3 ng/mL to 533375.0 ng/mL between Week 0 and Week 10 and appeared to reach steady-state by Week 3.
- 8+2 regimen: Mean maximum neihulizumab plasma concentrations ranged from 316071.4 ng/mL to 548000.0 ng/mL between Week 0 and Week 11 and appeared to reach steady-state by Week 3.
- For biomarkers, only a moderate inverse relationship between peak neihulizumab concentration and decreases in fecal calprotectin levers was observed under 8+2 regimen.

Safety:
- 5+3 regimen: 90.0% patients reported TEAEs, and 70.0% is related to the study treatment.
- 8+2 regimen: 92.9% patients reported TEAEs, and 14.3% is related to the study treatment.
- There was one SAE (not related). One AE led to early withdrawal of patient from the study. There was no serious TEAEs that resulted in death.
- There were no clinically meaningful findings in the vital sign measurements, ECG measurements, physical examination assessment, or quality of life IBD score related to safety in this study.

CONCLUSIONS

✓ In this phase 2 study of patients with moderately to severely active UC refractory to prior biologic therapies, neihulizumab demonstrated efficacy at week 12, with the 8+2 regimen more effective than the 5+3 regimen.

✓ Neihulizumab was safe and well-tolerated.

✓ These data support further development of neihulizumab as a novel mechanism of action for patients with ulcerative colitis.

CONTACT INFORMATION

- This study was sponsored by AltruBio, Inc.
- Clinical trial identification: NCT03298022
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