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Phase II open label, single arm, multiple dose 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

David T. Rubin[1], Scott Lee[2], Lucky Flores[3], Gustavo Albizu-Angulo[4], Ellen Scherl[5], Surinder Saini[6], Shipra Patel[7], Yi-Lin (Irene) Cheng[8], Ting-Ying (Hazel) Cheng[9], and Shih-Yao Lin[8]

[1] University of Chicago, IL, U.S.; [2] University of Washington Medical Center - Digestive Disease Center, WA, U.S.; [3] Wellness Clinical Research, FL, U.S.; [4] Wellness Clinical Research, P.R.;
[5] Weill Cornell Medical College, NY, U.S.; [6] Surinder Saini M.D., Inc, CA, U.S.; [8] AbGenomics B.V., Taiwan; [9] AbGenomics International, U.S.

Background

- **Neihulizumab** is a humanized monoclonal antibody which binds to human CD162 (PSGL-1) and preferentially induces apoptosis of late stage activated T cells, and has been/is being tested in T-cell mediated inflammatory diseases including psoriasis, psoriatic arthritis and graft-versus-host disease.
- The pathogenesis of ulcerative colitis (UC) includes an overly aggressive T cell mediated inflammatory response. Therefore we conducted a Phase II trial to evaluate the efficacy and safety of Neihulizumab in ulcerative colitis.

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 ulcerative colitis
• Dose: 9 mg/kg
• Two regimens 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 Neihulizumab administered intravenously in patients with moderate-to-severe active ulcerative colitis (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 AbGn-168H 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.

Patient Enrollment

Table 1. Demographics and baseline characteristics

Characteristic	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%)
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 (9-12)	9 (6-12)
Endoscopy Subscore, median (Min-Max)	3 (2-3)	3 (2-3)
Fecal calprotectin (μg/g), median (Min-Max)	612 (197-2,000)	1365 (15-2180)
CRP (mg/L), median (Min-Max)	1.5 (1-17)	6.5 (1-81)

Safety Overview

Table 2. Overall treatment emerged adverse events (TEAE)

	5+3 Regimen Case No. = 36	8+2 Regimen Case No. =35
TEAEs		
Related	12 (33%)	5 (14%)
Not related	24 (37%)	30 (86%)
Severity of TEAEs		
Mild	30 (83%)	27 (77%)
Moderate	5 (14%)	7 (20%)
Severe	1 (3%)*	1 (3%) **
Serious TEAEs		
Related	0	0
Not related	1*	0
Deaths	0	0

* UC flare **Worsening headache

Table 3. Common TEAEs (occurred in > 10% subjects)

Adverse events	5+3 Regimen N = 10	8+2 Regimen N = 14
All	8 (80%)	13 (93%)
Abdominal Pain		3 (21%)
Headache	5 (50%)	6 (43%)
Fatigue	2 (20%)	
Cough	2 (20%)	
High Calprotectin Level		2 (14%)

Table 3. Related TEAEs

Adverse events	5+3 Regimen N = 10	8+2 Regimen N = 14
All	7 (70%)	2 (14%)
Headache	5 (50%)	1 (7%)
Chills	1 (10%)	
Constipation	1(10%)	
Cough	1(10%)	
Fever	1(10%)	
Joint pains in elbows and knees		1 (7%)
Light Fatigue	1(10%)	
Rash to right and left forearms, stomach, and bilateral thighs	1(10%)	
Vaginal candida		1 (7%)

Efficacy Endpoint

Primary 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

Key Secondary 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.

Efficacy Overview

Figure 1. Continuous improvement after cessation of treatment in 3 subjects

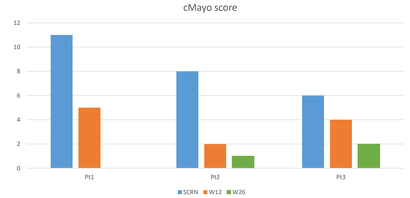

Figure 2. summary of efficacy assessments

Assessment	5+3 Regimen	8+2 Regimen
Week 12	N=9	N=14
cMayo score clinical response	1 (11%)	7 (50%)
cMayo score clinical remission	0	4 (29%)
Mucosal healing	1 (11%)	4 (29%)
Histological remission	0	1 (7%)
IBDQ response	2 (22%)	9 (64%)
Week 26	N=9	N=10
cMayo score clinical response	1 (11%)	5 (50%)
cMayo score clinical remission	0	3 (30%)
Mucosal healing	0	3 (30%)
Histological remission	0	1 (7%)
IBDQ response	1 (11%)	5 (50%)

Note: 2 subjects in 8+2 regimen did not perform W12 endoscope due to Covid-19 pandemic

Conclusions and Future Directions

- Preliminary results suggest that the 10 dose regimen (8+2) is more effective than the 8 dose regimen (5+3).
  (1) In 8 dose regimen, 1 out of 9 (11%) evaluable subjects is responder at W12, 1 out of 9 (11%) evaluable subjects showed mucosa healing at W12.
  (2) In 10 dose regimen, 7 out of 14 (50%) subjects that reached W12 are responders (4 subjects are in remission), 4 out of 14 (29%) subjects showed mucosa healing at W12.
  (3) Most of clinical responders showed improvement in histological assessment as well as IBDQ assessment.
  (4) Durable responses as well as continuation of clinical improvement after cessation of treatment is observed in some patients, consistent with the proposed MOA.
- Safety data up to date suggested that AbGn-168H is well tolerated:
  (1) Most drug-related TEAEs observed are mild to moderate in severity.
  (2) The most frequent drug-related AE observed is mild headache.
  (3) No cytokine release syndrome or local/systemic hypersensitivity or drug-related SAEs were reported.
  (4) No significant CBC changes were observed throughout the study.
  (5) No death.
- This study demonstrate the efficacy and safety of the first anti-CD162 therapy in biologics refractory UC. Studies to further support the clinical development is warranted.

Other Information/ Acknowledgements

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- Clinical trial identification: NCT03298022
- Contact information: shihyao.lin@abgenomics.com