FcRn Blockade with SYNT001 for the Treatment of Pemphigus

Werth, VP[1], Culton, DA[2], Blumberg, LJ[3], Humphries, JE[4], Blumberg, RS[3,5], Hall, RP[6]

[1]University of Pennsylvania, Philadelphia, PA, [2]University of North Carolina, Chapel Hill, NC, [3]Syntimmune, Inc., Boston, MA, [4]Biologics Consulting, Alexandria, VA, [5]Brigham and Women's Hospital/Harvard Medical School, Boston, MA, and [6]Duke University Medical Center, Durham, NC

INTRODUCTION

In pemphigus foliaceus (PF) and pemphigus vulgaris (PV) IgG autoantibodies to desmogleins (DSG) 1 and 3 lead to acantholysis, causing painful cutaneous and/or mucosal lesions. The neonatal crystallizable fragment receptor (FcRn) binds to IgG and circulating immune complexes (CIC) at acidic pH to regulate their half-life and inflammatory activity. SYNT001 is a humanized IgG4 monoclonal antibody optimized to inhibit FcRn function (Fig. 1). SYNT001-103 (NCT03075904) is an ongoing, open-label phase 1b study evaluating safety and clinical effect of SYNT001 in PV or PF. Up to 3 cohorts (N=8 subjects each) assessing 5 weekly doses ≤45 mg/kg SYNT001 IV are planned. Primary objective is safety; secondary objectives include pharmacodynamics and clinical response. Follow-up is through Day 112. The study is approved by each site's IRB; all subjects provide written informed consent. Data on 7 subjects (6 PV, 1 PF) enrolled in Cohort 1 (10 mg/kg) are presented. All completed 5 doses of SYNT001 and were in varying stages of follow-up. These interim data show SYNT001 is well tolerated in PV and PF. Mean total IgG levels were reduced by 59% by Day 30 and returned to within 10% of Baseline by Day 84. Mean Pemphigus Disease Area Index (PDAI) was reduced by 41% by Day 42, anti-DSG1 was reduced by 22% by Day 14 and anti-DSG3 was reduced by 24% by Day 33. This first-in-human study in pemphigus provides initial proof-of-concept for anti-FcRn treatment with SYNT001 in this disorder.

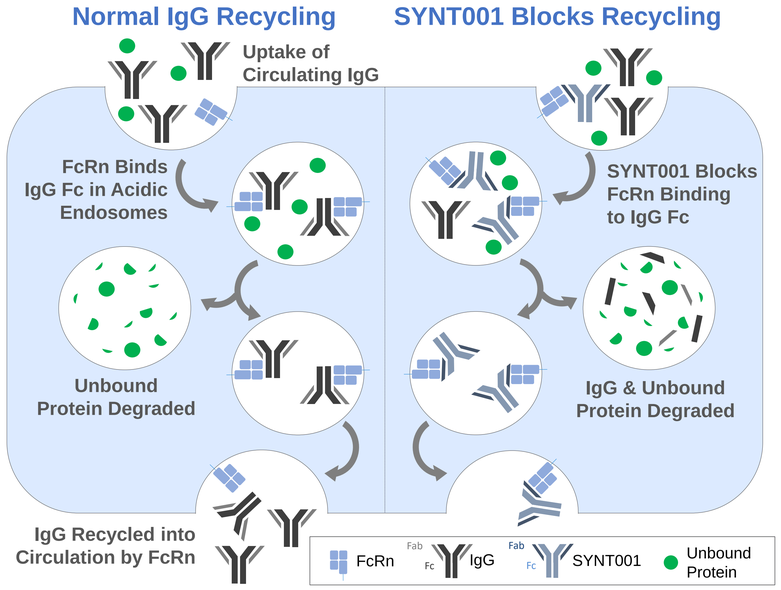

Figure 1. SYNT001 reduces serum concentrations of total IgG and CIC via inhibition of the FcRn-IgG interaction. Under normal conditions (left), concentrations of IgG are maintained via a recycling mechanism controlled by FcRn. SYNT001 inhibits this recycling (right) by preferentially binding FcRn.

METHODS

- **Study Design:** Multiple-ascending dose, multicenter, open-label, Phase 1b clinical trial
- **Primary Objective:** Safety and tolerability of SYNT001
- **Secondary Objectives:** Assessment of pharmacokinetics and pharmacodynamics, including levels of total IgG, anti-DSG1 antibodies, anti-DSG3 antibodies, CIC. PDAI was also recorded.
- **Inclusion Criteria:** Patients are ≥ 18 years of age with active pemphigus (vulgaris or foliaceus). Acceptable medications include stable doses (2-6 weeks prior to dosing) of corticosteroids, azathioprine, mycophenolate mofetil, and cyclosporine. No restrictions are placed on disease severity.
- **Exclusion Criteria:** Serum total IgG < 600 mg/dL, evidence of HIV, hepatitis antibodies, or hepatitis B surface antigen, a history of active or recurrent infection. Prohibited medications include rituximab or other anti-CD20 antibodies (the last dose of any anti-CD20 therapy must be completed > 12 months before screening), other monoclonal antibodies, unapproved immunosuppressants, topical steroids, topical tacrolimus or sirolimus, and any vaccines.

METHODS, cont'd

- **Trial Sites:** University Hospitals of Cleveland, University of Buffalo, University of Pennsylvania, Duke University, University of North Carolina, Emory University, and Stanford University. Sites pending activation: University of Southern California and Mount Sinai Hospital.
- **Ethical Concerns:** The study was approved by the IRBs of all participating sites. Informed consent was provided by all patients.

RESULTS

SYNT001 10 mg/kg (n=7)	
Age (mean ± SD, years)	51.9 ± 17.64
Sex (number, %)	
Male	3 (42.9)
Female	4 (57.1)
Race (number, %)	
White	5 (71.4)
Black or African American	2 (28.6)
Type of Pemphigus (number, %)	
Vulgaris	6 (85.7)
Foliaceus	1 (14.3)
Disease Duration (mean ± SD, years)	6.6 ± 5.91
BMI (mean ± SD, kg/m²)	30.91 ± 5.027

Table 1. Patient Demographics and Disposition. As of April 2018, 7 patients have been recruited: 6 patients have completed the 5-dose treatment period and 3 have completed the Day 112 follow-up.

No other races were reported. All patients reported their ethnicity as "Not Hispanic or Latino."

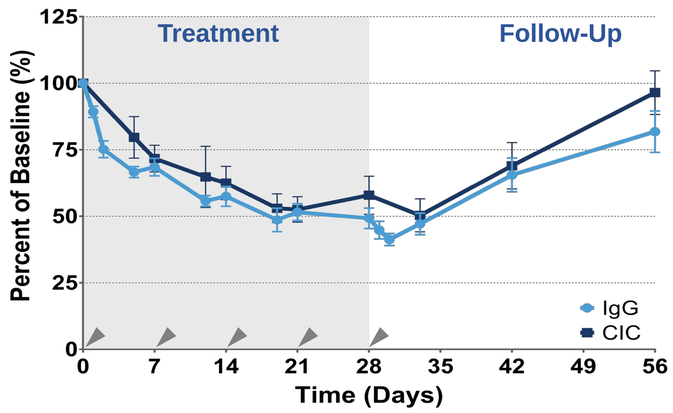

Figure 2. SYNT001 rapidly reduces serum concentrations of total IgG and CIC. Mean total IgG levels were reduced by 59% by Day 30 and mean CIC levels were reduced by 50% by Day 33. Mean total IgG and mean CIC levels returned to within 10% of Baseline by Day 84. All samples tested are included. Error bars represent Standard Error of Mean (SEM). Gray arrows indicate dosing days.

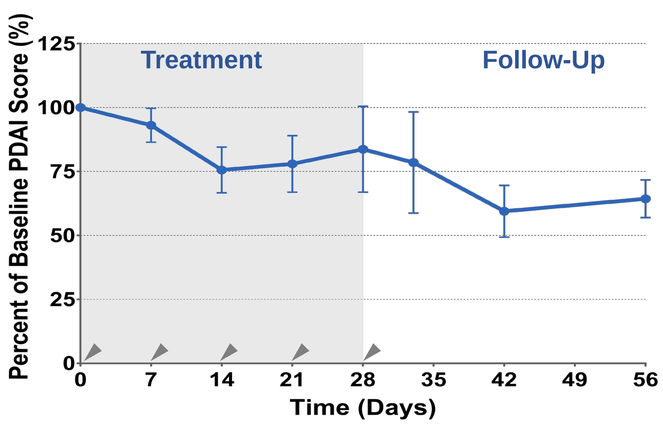

Figure 3. SYNT001 reduces PDAI, a pemphigus-specific severity marker. Mean PDAI was reduced by 41% by Day 42, decreasing from "Severe" to "Moderate." Anti-DSG1 was reduced by 22% by Day 14 and anti-DSG3 was reduced by 24% by Day 33 (not shown). Error bars represent Standard Error of Mean (SEM). Gray arrows indicate dosing days.

RESULTS, cont'd

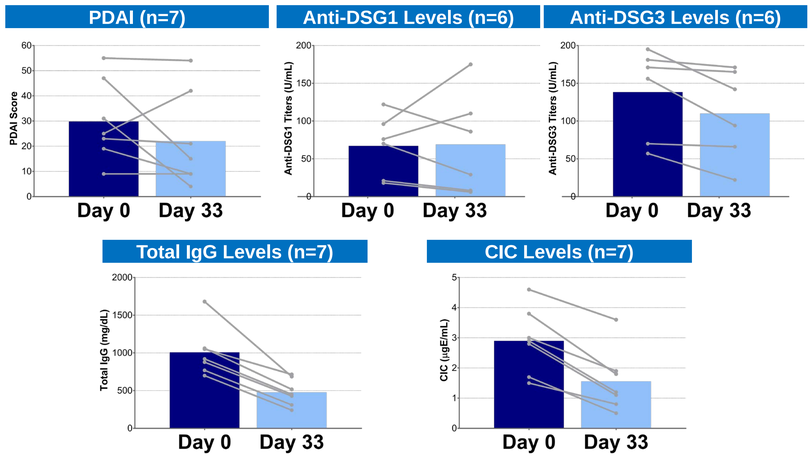

Figure 4. Mean biomarker data show clinical response with low-dose SYNT001. Dark blue bars represent mean values at Baseline (Day 0). Light blue bars represent mean values at Day 33. Gray lines indicate individual patient values at Baseline and Day 33. Mucosal PV and PF patients did not have detectable anti-DSG1 or 3 levels, respectively, and were not included in the respective graph. Repeat measurements of anti-DSG1 and 3 levels are required to verify high values due to the pro-zone/hook effect.

Study Drug-Related AE	Number of AEs (in n patients)		
	Grade 1 (Mild)	Grade 2 (Moderate)	Total
Headache	8 (3)	5 (3)	**13 (6)**
Infusion Related Reaction		2 (1)	**2 (1)**
Diarrhea	1 (1)		**1 (1)**
Vomiting	1 (1)		**1 (1)**
Malaise	1 (1)		**1 (1)**
Hyperhidrosis	1 (1)		**1 (1)**
Pallor	1 (1)		**1 (1)**
Total	**13 (3)**	**7 (4)**	**20 (7)**

Table 2. SYNT001 appears safe and well tolerated. 65% of study drug-related AEs were mild and 35% were moderate. No discontinuations, interruptions, or dose reductions occurred due to study-drug related AEs. The most common AE was headache. 46% of related headaches occurred post first infusion; all were mild (62%) or moderate (38%). The second most common AE was transient urticarial infusion reaction, which occurred twice in one patient after doses 4 and 5 and which responded to diphenhydramine. Two SAEs occurred in one patient and were unrelated to treatment (disease exacerbation and acute kidney injury).

CONCLUSIONS

- Based on these interim data, 5 weekly doses of 10 mg/kg SYNT001 appears safe and well tolerated
- SYNT001 resulted in rapid reductions in total IgG and CIC levels
  - The results support the pharmacodynamic activity of FcRn blockade
  - The effect was reversible upon cessation of therapy
- Improvement in PDAI indicates a clinical response within 30 days
  - Further work needed to elucidate the PDAI and biomarker relationship
  - Based on these interim data, 10 mg/kg SYNT001 appears effective; higher doses may demonstrate greater magnitude and duration of response

DISCLOSURES

SYNT001 is an investigational drug which has not been approved for use outside of clinical testing. VPW is a consultant to Syntimmune and is a principal investigator for this study. DAC is a principal investigator for this study. LJB is a senior advisor to, is on the Board of Directors of, and has an equity interest in Syntimmune. JEH is a consultant to Syntimmune. RSB is a consultant to, is on the Board of Directors of, has an equity interest in, and has received grant funding from Syntimmune. RPH is a consultant to and has received grant funding from Syntimmune and is a principal investigator for this study.

ACKNOWLEDGEMENTS

This work was supported by Syntimmune, Inc., Boston, MA. The authors would like to thank the study investigators: Annette Czernik, MD, Ronald Feldman, MD, PhD, Neil Korman, MD, PhD, M. Peter Marinkovich, MD, Animesh Sinha, MD, PhD, Scott Worswick, MD. The authors would also like to acknowledge Donald R. Johns, MD, Leslie E. Stolz, PhD, Stephanie Haller, Matthew Mockler, Katherine Poulin, and James S. Graydon for their contributions to this study and to this poster.