Phase 1 Clinical Trial Evaluating the Pharmacokinetics and Pharmacodynamics of a Novel IL-17A and BAFF Dual Antagonist in Sjogren's Syndrome

#0373

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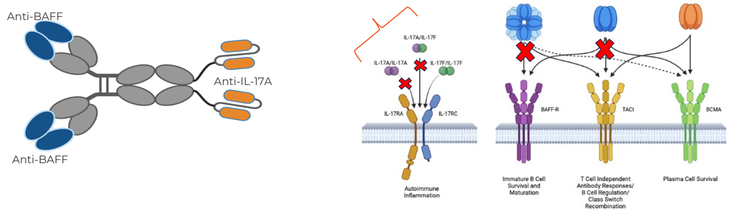
Targeting IL-17A and BAFF

- Sjogren's syndrome is a systemic autoimmune disease characterized by progressive inflammation of the glands, largely due to increased levels of activated lymphocytes (T and B cells) and autoantibodies.
- Tibulizumab (ZB-106) is an IgG-scFv engineered by the fusion of elements from TALTZ® (ixekizumab) and tabalumab that targets IL-17A and B cell activating factor (BAFF).



Study Objective

This study investigated the safety, tolerability, pharmacokinetics and pharmacodynamics of subcutaneously administered tibulizumab in Sjogren's syndrome.

Methods

Patients

- Male and female volunteers between the ages of 18 to 65.
- Confirmed diagnosis of Sjogren's syndrome using the American-European Consensus Group criteria with active disease.
- Seropositive for anti-nuclear antibodies (SSA or SSB) antibodies at screening or documented within 6 months prior to screening.

Pharmacokinetic Assessment

- Human serum samples were analyzed for levels of tibulizumab using validated IL-17A and BAFF antigen capture ELISAs.

Target Engagement Assessment

- Levels of IL-17A and BAFF were assessed in human sera using electrochemiluminescent assays.

Pharmacodynamic Assessment

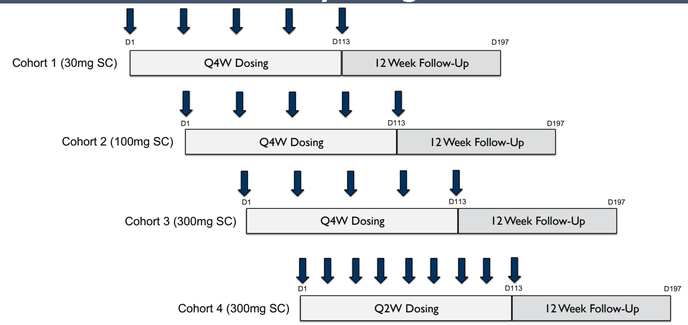
- Epiontis ID® was used to phenotype cells using cell-type specific epigenetic markers.
- OLINK® was used to assess circulating levels of inflammatory mediators.

Statistical Analysis

- Statistical differences between treatment arms were assessed using Graph Pad Prism software.

Pharmacokinetics and Pharmacodynamics of Tibulizumab

Study Design



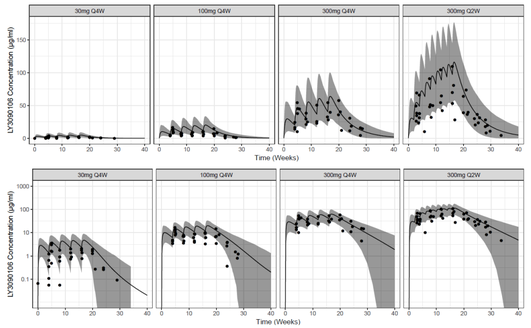
Abbreviations: D = Day; Q2W = once every 2 weeks; Q4W = once every 4 weeks; SC = Subcutaneous

Baseline Characteristics

	Placebo	30mg Q4W	100mg Q4W	300mg Q4W	300mg Q2W
Subjects	4	5	5	5	6
Female	3	5	4	5	6
Male	1	0	1	0	0
Race					
White	3	5	4	5	6
Non-White	1	0	1	0	0
Age (years)					
Mean	55.7	53.8	53.8	51.8	53.8
Standard Error	10.4	9.4	8.1	6.5	13.3
Range (Min, Max)	(41.0, 63.0)	(41.0, 65.0)	(40.0, 61.0)	(42.0, 59.0)	(36.0, 65.0)
SS Antibody Status					
SSA Positive	4/4	5/5	5/5	3/5	6/6
SSB Positive	4/4	2/5	0/5	2/5	3/6

Pharmacokinetics

Figure 1. Tibulizumab drug exposure was assessed using BAFF (Upper Panel) and IL-17A (Lower Panel) capture ELISAs. The observed and model-predicted PK profile is outlined in the figure. Based on the PK modeling, the T1/2 was calculated at 26.9 days.



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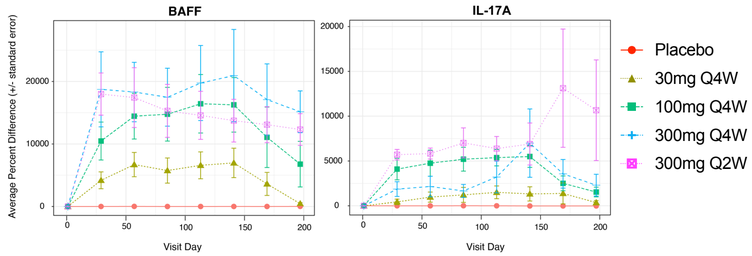
Target Engagement

Figure 2. Serological levels of total BAFF and IL-17A increased following tibulizumab administration, reflecting target engagement. At doses of 100 mg Q4W and higher, the total BAFF and IL-17A concentrations appear to plateau, suggesting near maximum target engagement has occurred.



Phenotypic Analysis

Figure 3. Total B cell counts were dose-dependently reduced in Sjogren's syndrome patients throughout the clinical trial. Additionally, treatment with tibulizumab was associated with lower levels of of Th1 cells throughout the clinical trial.

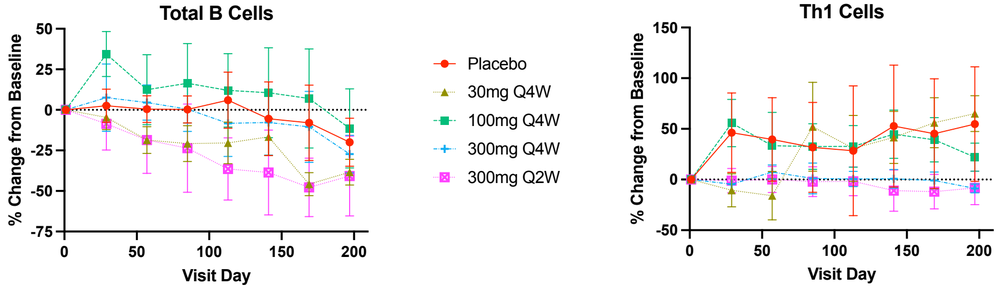


Table 1. The levels of 40 inflammatory mediators were analyzed using proteomic methods and presented as the percent change from baseline. The table below highlights some of the modulatory activity of tibulizumab on mediators associated with immune defense (serum amyloid a), Th2 biology (interleukin-5), T regulatory cells (interleukin-10) and fibroblast repair (basic fibroblast growth factor).

	Placebo	30mg Q4W	100mg Q4W	300mg Q4W	300mg Q2W
Serum Amyloid A	0.66 ± 33.40%	5.62 ± 7.47%	-3.39 ± 0.00%	-13.60 ± 7.94%	-0.30 ± 6.46%
Interleukin-5	52.64 ± 35.33%	65.46 ± 34.71%	-30.81 ± 21.17%	-41.95 ± 30.76%	-42.78 ± 15.31%
Interleukin-10	24.60 ± 122.5%	87.49 ± 99.56%	-93.27 ± 6.35%	6742 ± 4011%	6177 ± 2287%
Basic Fibroblast Growth Factor	-0.95 ± 8.16%	-1.48 ± 30.92%	43.32 ± 69.71%	334.9 ± 92.18%	-55.72 ± 20.33%

Conclusions

- Treatment with tibulizumab was well tolerated in patients with Sjogren's syndrome.
- Mechanistic reductions in total B cells and modulation of inflammatory mediators suggest the potential for tibulizumab in additional autoimmune conditions.

Acknowledgements

The authors thank the patients who volunteered to participate in the clinical trial and Emad Samani for bioinformatic support. This clinical trial was funded by Eli Lilly and Company.