A DOUBLE BLIND, PLACEBO CONTROLLED, SINGLE ASCENDING DOSE (SAD) AND MULTIPLE ASCENDING DOSE (MAD) STUDY OF ALPN-101, A FIRST-IN-CLASS DUAL ICOS/CD28 ANTAGONIST, IN HEALTHY VOLUNTEERS (HV)

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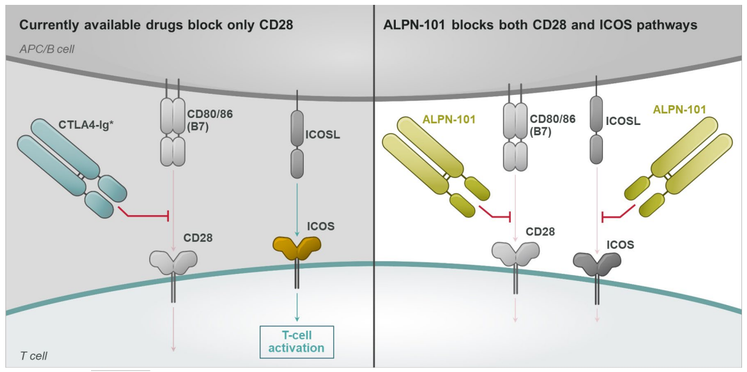
INTRODUCTION

- ALPN-101 (ICOSL vIgD-Fc) is an Fc-fusion protein of a human inducible T cell costimulatory ligand (ICOSL) variant immunoglobulin domain (vIgD™) designed to inhibit simultaneously the CD28 and ICOS inflammation pathways.
- ALPN-101 is effective in preclinical studies of graft versus host disease (GVHD), lupus, arthritis, and Sjögren's, and shows greater activity than single pathway inhibitors.

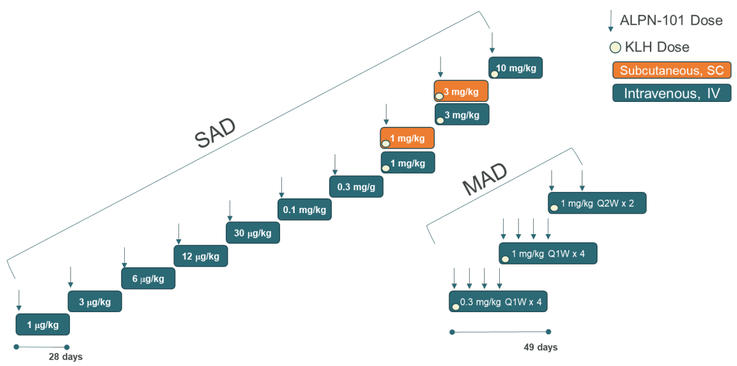
Figure 1: ALPN-101 is a first-in-class dual CD28/ICOS antagonist



OBJECTIVES and METHODS

- A Phase 1 single center study of ALPN-101 (NCT03748836) was conducted to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ALPN-101 in HV.

Figure 2: Phase 1 healthy volunteers study schema



RESULTS

TABLE 1: Baseline demographics

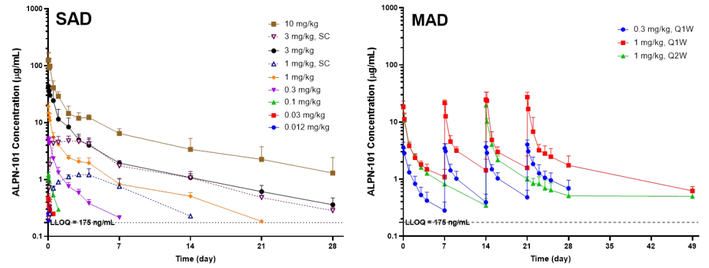
		SAD (N=72)		MAD (N=24)	
	Overall (N=96)	Placebo (N=24)	ALPN-101 (N=48)	Placebo (N=6)	ALPN-101 (N=18)
Age, years mean (min-max)	26.3 (18-60)	23.9 (18-43)	26.4 (19-60)	26.5 (19-40)	29.1 (19-51)
Sex, n male: female	49: 47	14:10	21:27	3:3	11:7
Race, n					
Asian	11	2	6	1	2
Black or African American	2	1	1	0	0
Native Hawaiian/Other Pacific Islander	1	0	1	0	0
White	79	21	39	5	14
Other	3	0	1	0	2
Weight, kg Mean (SD)	69.9 (10.1)	71.7 (9.3)	68.0 (10.4)	66.9 (8.6)	73.7 (9.6)

TABLE 2: Summary of AEs

Category / Number of Subjects, n (incidence, %)	Total	Pooled SAD		Pooled MAD	
		Placebo (N=24)	ALPN-101 (N=48)	Placebo (N=6)	ALPN-101 (N=18)
Any AE	69 (71.9%)	14 (58.3%)	34 (70.8%)	6 (100%)	15 (83.3%)
Treatment-Related AE	27 (28.1%)	4 (16.7%)	14 (29.2%)	2 (33.3%)	7 (38.9%)
Grade 1 AE	66 (68.8%)	14 (58.3%)	31 (64.6%)	6 (100%)	15 (83.3%)
Grade 2 AE	20 (20.8%)	2 (8.3%)	11 (22.9%)	3 (50%)	4 (22.2%)
Grade 3-5 AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

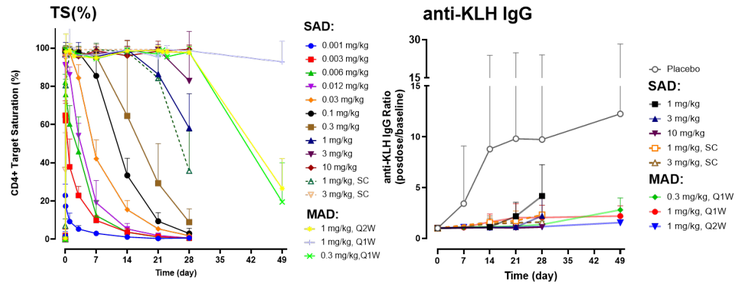
- ALPN-101 was well tolerated. There were no adverse events (AEs) related to clinical immunogenicity, including ALPN-101-related infusion-related or significant injection site reactions. No cytokine release in blood was identified among 30 cytokines (CytokineMAP® A & B).
- AEs observed in > 5% of ALPN-101-treated subjects included headache, upper respiratory tract infection, aphthous ulcer, administration site (of KLH injection) recall reaction, and back pain, observed in 20 (30%) vs 6 (20%), 12 (18%) vs 2 (6.7%), 5 (7.6%) vs 0, 4 (6.1%) vs 0, and 4 (6.1%) vs 0 of all ALPN-101- vs placebo-treated subjects, respectively.
- C_{max} and AUC_{inf} increased in a dose-proportional manner. Mean terminal $t_{1/2}$ ranged from 4 to 8.6 days. Bioavailability of SC dose was 60% at 3 mg/kg.

Figure 3: ALPN-101 demonstrates dose-dependent PK



- Minimal to modest accumulation of C_{max} and AUC_T (mean ratios ≤1.66 x) was observed with repeat weekly IV dosing.
- Duration of high TS (>95%) increased with increasing dose. The duration of suppression of anti-KLH IgG response paralleled the duration of high TS.

Figure 4: ALPN-101 demonstrates dose-dependent target saturation and potent inhibition of anti-KLH responses.



CONCLUSIONS

- ALPN-101, a first-in-class dual CD28/ICOS inhibitor, was well tolerated in healthy volunteers with dose-dependent PK and PD consistent with the known biology of these costimulatory pathways.
- Further study of ALPN-101 is warranted in multiple autoimmune or inflammatory diseases regulated by CD28 and/or ICOS.
- An open label study of ALPN-101 for the treatment of acute GVHD has recently been initiated (NCT04227938). Studies for the treatment of other autoimmune and inflammatory diseases are being planned.