A Phase 1, Open Label, Randomized, Single Dose, Parallel Group Safety and Bioavailability Study of BION-1301 Administered by Intravenous (IV) and Subcutaneous (SC) Routes

Abstract # WCN21-0706

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CHINOOK THERAPEUTICS

Introduction and Background

Chinook Therapeutics is developing BION-1301, a novel humanized blocking antibody targeting APRIL, for the treatment of IgA nephropathy (IgAN). IgAN, the leading cause of primary glomerulonephritis, is an autoimmune disease with no approved treatments.[1] Progression to end stage-renal disease occurs in up to 45% of IgAN patients, requiring dialysis or kidney transplant to manage.[2-4] As shown in **Figure 1**, a critical step in IgAN pathogenesis is the production of galactose-deficient IgA1 (Gd-IgA1) (Hit 1 in the 4 Hit Hypothesis) leading to the generation of anti-Gd-IgA1 autoantibodies and the formation of immune complexes that result in kidney inflammation and damage.[5]

BION-1301 offers disease modifying potential by targeting the underlying multi-hit immune pathogenesis of IgAN

APRIL: A Proliferation Inducing Ligand
- TNF-family cytokine involved in B-cell signaling[6]
- Drives B cell differentiation, proliferation and survival of IgA-secreting plasma cells[6]
- Shown to increase Gd-IgA secretion
- Elevated in IgAN patients, and higher APRIL levels correlated with higher Gd-IgA1 and proteinuria and lower eGFR[7]
- APRIL gene variants confer increased risk of IgAN[8]

BION-1301: APRIL blockade for treatment of IgA Nephropathy
- Humanized IgG4 monoclonal antibody that blocks APRIL binding to its receptors BCMA and TACI on B cells and plasma cells
- No adverse effects reported in NHP tox studies of IV BION-1301 for up to 6 months and SC for up to 1 month[9]
- Well-tolerated in single IV doses up to 1350mg and multiple IV doses up to 450mg in phase 1 study of healthy volunteers[10]

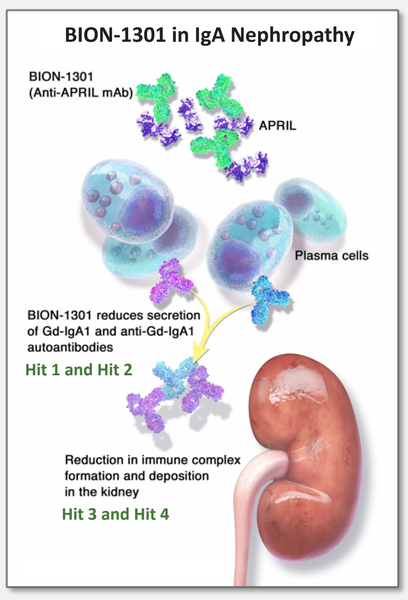

Figure 1: BION-1301's Unique MOA Directly Impacts Hit 1 by Reducing Gd-IgA1 Secretion, a Critical Step in the Pathogenesis of IgAN

Key Clinical Data To-Date

- **ADU-CL-19 Ph1 Single and Multiple Ascending Dose Study in Healthy Volunteers & IgAN Patients (ADU-CL-19)**
  - To date, BION-1301 has been assessed in a 3-part Phase 1 study (ADU-CL-19). In Parts 1 and 2 of the Phase 1 study in HV, we previously reported that BION-1301 was well-tolerated with no serious adverse events (SAEs), a pharmacokinetic (PK) half-life > 30 days and demonstrated dose-dependent pharmacodynamic (PD) effects characterized by durable reductions in serum levels of IgA, IgM, and to a lesser extent IgG[10].
  - ***Recently analyzed from this study also demonstrated that BION-1301 drove a dose-dependent reduction in serum Gd-IgA1 levels in HVs, as shown in Figure 2.***
  - Part 3 of study this study is ongoing and is currently evaluating BION-1301 in patients with IgAN. Preliminary data from part 3 will be presented at subsequent nephrology conferences in 2021.
- Based on promising preliminary results from ADU-CL-19 and the aim to reduce patient burden with a more convenient alternative administration route, BION-1301 was further studied in a single-dose Phase 1 study (ADU-CL-21) to determine safety and bioavailability of BION-1301 administered via IV infusion or SC injection in HVs.

BION-1301 drives dose-dependent & proportional reductions in serum IgA and Gd-IgA1 levels in healthy volunteers

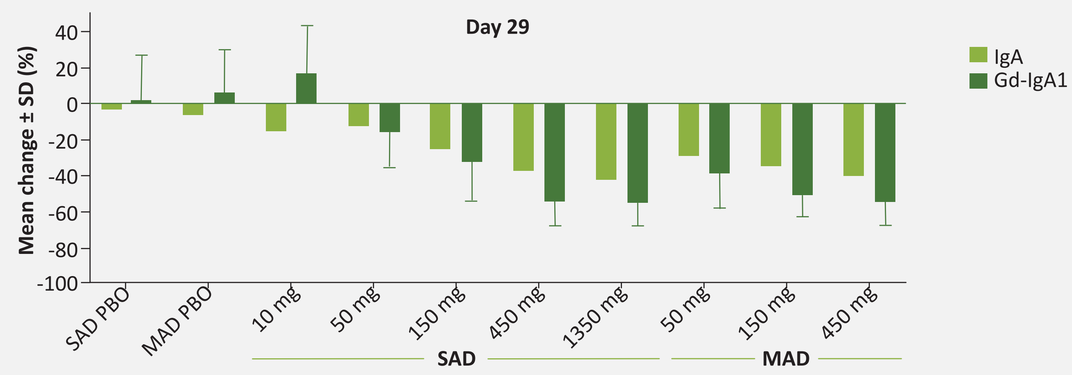

Figure 2: Mean Change in IgA and Gd-IgA1 by Dose in a Phase 1 Single Ascending and Multiple Ascending Dose Study in Healthy Volunteers (ADU-CL-19).

- MAD data reflects PD response (from D29 pre-dose sample) after subjects received 2 of 3 Q2W doses

Study Design, Objectives, & Methodology

- Study ADU-CL-21 was a Phase 1, open-label, randomized, parallel group, safety and bioavailability study of 300 mg BION-1301 administered intravenously or subcutaneously to adult healthy volunteers in the United States. The study had 3 periods, Screening (up to 6 weeks), Treatment (1 day), and Safety Follow-Up (57 days), for a total study duration of up to approximately 100 days per participant. The study schema is provided in **Figure 3**.

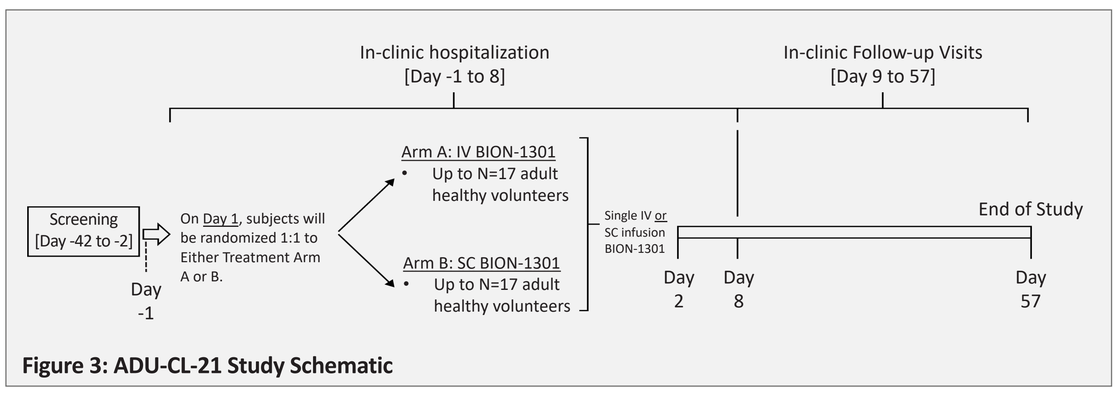

Figure 3: ADU-CL-21 Study Schematic

- **Primary objective:** estimate the bioavailability of BION-1301 administered via SC injection compared to IV infusion by assessing the relative exposure ($AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$) via each route
- **Secondary objectives:** safety and tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity.
- **Methodology** for the assessment of primary and secondary endpoints are as follows:
  - PK analyses performed on serum concentration data using non-compartmental analysis and nominal sampling times and fixed doses with Phoenix® WinNonlin® Version 8.1. Serum PK concentrations that were below the lower limit of quantitation (LLOQ) were reported as BQL (below quantification limit = 0.01 µg/ml) and excluded from the PK analyses.
  - Levels of BION-1301 in serum were quantitated using ELISA-based immunoassays under GLP.
  - Immunogenicity was assessed from serum samples for presence of anti-drug antibodies (ADA) and neutralizing ADAs (Nabs) under GLP.
  - Serum levels of IgA, IgG, and IgM were measured using an immunoturbidimetric ECL assay on the Roche Cobas 8000 analyzer (lower limit of quantitation: IgA 0.25 g/L, IgG 0.70 g/L, IgM 0.2 g/L).
  - Safety and tolerability was assessed by the incidence and severity of TEAEs and SAEs and changes from baseline in other safety parameters (e.g., safety labs, ECGs, etc.).

Results

BION-1301 was well tolerated when administered by both IV and SC routes in healthy volunteers

In this phase 1 safety and bioavailability study (ADU-CL-21) comparing IV and SC administration in HVs (N = 17 each IV and SC):
- No serious adverse events (SAE's) were reported
- No Grade 3 or greater adverse events (AE's) were reported
- No healthy volunteers terminated early due to a treatment-related adverse event (TRAE)
- No injection site or infusion-related reactions were reported
- One subject developed COVID while on drug; had mild course and recovered uneventfully
- Anti-drug antibodies (ADA) were reported in two HVs receiving IV BION-1301 with no impact on the overall safety profile. No ADAs were reported in the SC cohort

Cohorts were demographically well-matched (age, BMI, race, ethnicity, sex)

The PK profile of BION-1301 was consistent with previous clinical studies and minimal differences in drug concentration were observed between administration routes after 1 week

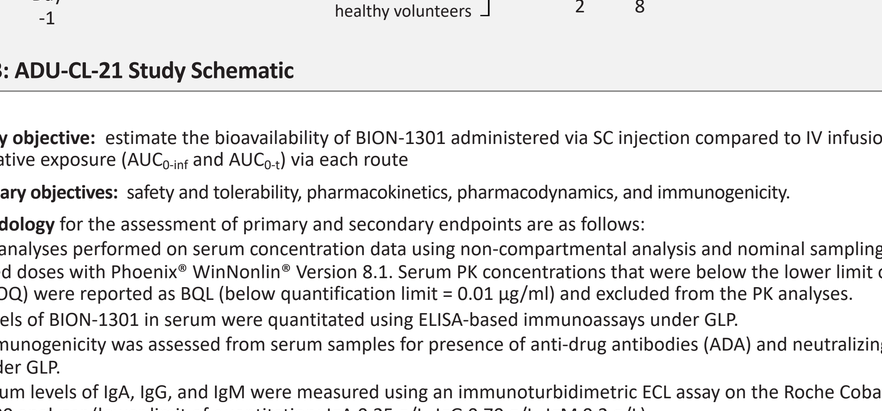

Figure 4: Mean (±SD) Serum Concentrations of BION-1301 in Healthy Volunteers After Single-Dose IV or SC Administration

- Overall variation within dose group was minimal
- In the SC group, measurable drug concentrations were observed in all subjects by 4 hours post-dosing on day 1
- ADA observed in 2 subjects: 1 low titer neutralizing antibody in the IV arm with no apparent effect on PK; no ADA observed in SC arm

Results (cont'd)

After SC administration, BION-1301 absorption rate is typical of a mAb with bioavailability of approximately 50%

Route	Subject	C_{max} (ng/mL)	T_{max} (day)*	AUC_{last} (day*ng/mL)	$AUC_{1\text{-}15day}$ (day*ng/mL)	$AUC_{1\text{-}29day}$ (day*ng/mL)	Cl (mL/day)	Vss (mL)	F (by AUC_{last}) (%)	k_a (day^{-1})
IV	N	17	17	17	16	16	17	17	0	0
	Mean	111000	1.04	1270000	764000	1070000	238	3670	NC	NC
	SD	21400	0.0369	404000	155000	219000	67.3	635	NC	NC
SC	N	17	17	17	16	15	0	0	17	17
	Mean	32300	5.08	631000	361000	584000	NC	NC	49.7	0.523
	SD	4540	1.97	195000	52200	85700	NC	NC	NC	0.225

** Dosing completed on day 1.00*

Table 1: Mean Pharmacokinetics of BION-1301 in Serum After Single-Dose IV or SC Administration

- C_{max} after the SC dose was 29% of the IV dose. SC dose C_{max} occurred at a mean T_{max} of 4 days and 2 hours post-dose compared with T_{max} of 1-hour post-dose for IV infusion
- IV mean clearance (Cl) was 238 mL/day, and the volume of distribution at steady state (V_{ss}) was 3670 mL, in line with previous clinical results
- The mean bioavailability, calculated by dividing individual SC by mean IV AUC_{last}, was 49.7%
- The mean absorption rate (k_a) was 0.523 day^{-1}, corresponding to an absorption half-life of 31.8 hours

Comparable reduction in serum fAPRIL as a result of exposure to BION-1301 was observed after dosing via both routes, with near maximal reductions evident within 1 week

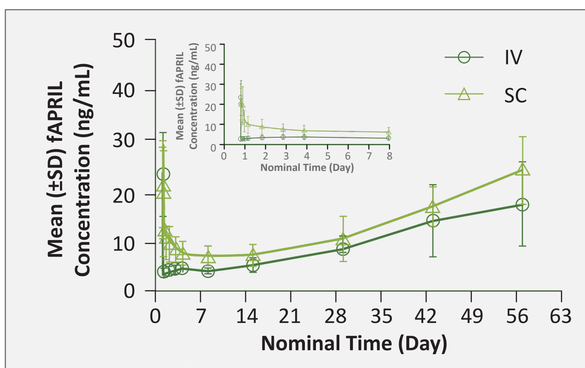

Figure 5: Mean (±SD) fAPRIL Concentrations After Single-Dose IV or SC Administration

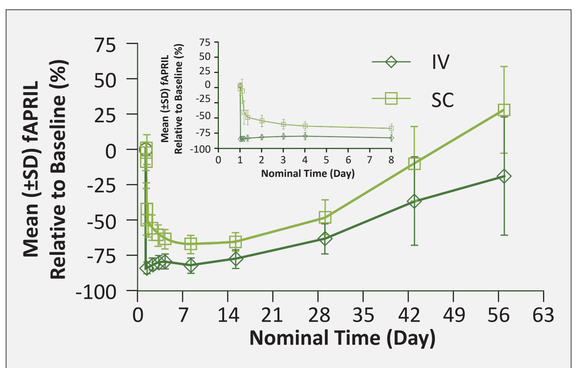

Figure 6: Mean (±SD) Percent Changes Relative to the Baseline of fAPRIL After Single-Dose IV or SC Administration

- Decrease in fAPRIL was apparent immediately after dosing in the IV group and within 4 hours in the SC group
- Consistent and slightly greater overall reductions in fAPRIL in IV group vs SC group
- Generally, the maximum reduction in the IV group was observed on Day 1 of sampling, and by Day 10.7 for the SC group
- Near-maximal reductions were maintained for approximately 2 weeks, with partial recovery to baseline by the end of the study

SC route retains 81% of the maximum fAPRIL reduction demonstrated with IV route

Route	Subject	C_{min} (ng/mL)	$\%RTB_{min}$ (%)	T_{min} (day)	AUEC 1-7day (day*ng/mL)	AUEC 1-14day (day*ng/mL)	AUEC 1-29day (day*ng/mL)
IV	N	17	17	17	17	17	17
	Mean	3.13	-85.9	2.71	25.4	54.6	147
	SD	1.01	3.83	3.02	7.21	15.9	47.4
SC	N	17	17	17	17	17	17
	Mean	6.29	-69.5	10.7	49.1	96.0	215
	SD	2.24	6.94	6.64	16.9	32.4	77.8

Table 2: Mean Pharmacodynamics of fAPRIL in Serum After Single-Dose IV or SC Administration of BION-1301

- fAPRIL max reduction is greater and reached sooner in the IV route versus SC route
- Over time SC administration can achieve 81% ($\%RTB_{min}$) of the reduction in fAPRIL relative to IV administration, with only 50% bioavailability

A single 300mg SC or IV dose of BION-1301 provides similar reductions in immunoglobulins

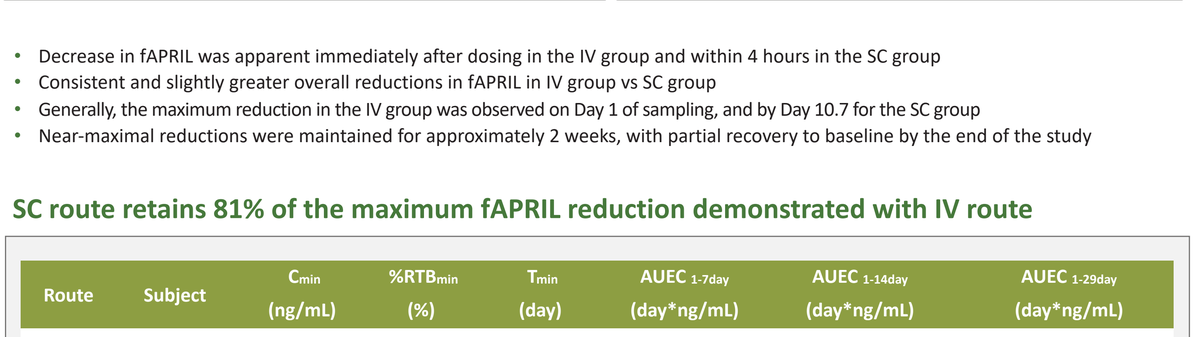

Figure 7. Mean % Change ± SD (Relative to Baseline) in Serum Immunoglobulin Levels Over Time (Days)

- Magnitude and kinetics of immunoglobulin reductions are consistent with range of dose-dependent responses previously observed in a clinical study of healthy volunteers (ADU-CL-19). Baseline sample taken on Day 1 pre-dose.
- BION-1301 provides a PD window that maximizes IgA reductions while tempering effects on IgG. No increase in infection correlated with BION-1301 treatment has been reported in clinical studies, and IgG levels remain within normal ranges for most subjects.

SC administration generates 81% of the maximum fAPRIL reduction and 75% of the maximum IgA reduction compared to IV infusion

		IV (n=17)	SC (n=17)	SC/IV proportion
PK Bioavailability:	AUC_{last} (day*ng/ml)	1270000	631000	50%
PD Markers:				
	max fAPRIL reduction (%, day)	86%, Day 3	70%, Day 11	81%
	max IgA reduction (%, day)	40%, Day 43	30%, Day 43	75%
	max IgG reduction (%, day)	14%, Day 57	7%, Day 57	50%
	max IgM reduction (%, day)	57%, Day 57	42%, Day 43	74%

Table 3: Reduction in Free APRIL and Immunoglobulins Relative to Baseline for SC vs IV Administration

Conclusions

- BION-1301's unique MOA offers disease modifying potential by directly targeting the underlying multi-hit immune pathogenesis of IgAN
- BION-1301 drives dose-dependent & proportional reductions in serum IgA and Gd-IgA1 levels (Hit 1) in healthy volunteers
- BION-1301 was well tolerated when administered by both IV and SC routes in healthy volunteers
- The PK profile of BION-1301 was consistent with previous clinical studies in HVs and minimal differences in drug concentration were noted between administration routes after 1 week
- After SC administration, the absorption rate of BION-1301 is typical of a mAb with bioavailability of ~50%
- Magnitude of pharmacodynamic responses were largely retained with SC dosing relative to IV dosing
  - SC administration generates ~ 81% of the maximum fAPRIL reduction
  - SC administration generates ~ 75% of the maximum IgA reduction
- Data from this study will be used to enable SC administration of BION-1301 in ongoing and future clinical studies

References

1. Selvaskandan H, et al. Monitoring Immune Responses in IgA Nephropathy: Biomarkers to Guide Management. *Front Immunol*. 2020.
2. Barratt J., et al.. 2005. IgA nephropathy, *J Am Soc Nephrol*, 16: 2088-97.
3. Moriyama T, et al. Prognosis in IgA nephropathy: 30-year analysis of 1,012 patients at a single center in Japan. *PLoS One*. 2014;9(3):e91756. Published 2014 Mar 21. doi:10.1371/journal.pone.0091756.
4. Komatsu H, et al. Multivariate analysis of prognostic factors and effect of treatment in patients with IgA nephropathy. *Ren Fail.* 2005; 27(1):45-52.
5. Suzuki H, et al. The pathophysiology of IgA nephropathy. *J Am Soc Nephrol*. 2011.
6. Guadagnoli M, et al. Development and characterization of APRIL antagonistic monoclonal antibodies for treatment of B-cell lymphomas. *Blood.* 2016.
7. Han SS, et al. The Role of TNF Superfamily Member 13 in the Progression of IgA Nephropathy, *JASN.* 2016.
8. Xie J, et.al. Genetic studies of IgA nephropathy: what have we learned from GWAS. *Contrib Nephrol.* 2013.
9. Kreijtz J et al. BION-1301, a Fully Blocking Antibody Targeting APRIL for the Treatment of IgA Nephropathy: Assessment of Safety, Toxicokinetics and Pharmacodynamics in Long-Term Nonclinical Studies, *ERA-EDTA 2020, Poster # P0379.*
10. Lo J, et al. Results of a Phase 1 Trail to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BION-1301 in Healthy Volunteers, *ERA-EDTA 2020, Poster #P0500.*