Preclinical pharmacokinetics, pharmacodynamics and safety of BION-1301, a first-in-class antibody targeting APRIL for the treatment of multiple myeloma

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INTRODUCTION

BION-1301 is a first-in-class humanized antibody targeting A PRoliferation Inducing Ligand (APRIL, TNFSF13). APRIL is a ligand for the receptors BCMA and TACI and mediates important B-cell functions including activation, survival and maturation. APRIL serum levels are enhanced in patients diagnosed with multiple myeloma (MM), chronic lymphocytic leukemia (CLL), and Colorectal Carcinoma correlates with poor prognosis[1,2]. APRIL critically triggers BCMA to drive proliferation and survival of human MM cells. Importantly, APRIL induces resistance to lenalidomide, bortezomib and other standard-of-care drugs[3]. Furthermore, APRIL drives expression of PD-L1, IL-10, VEGF and TGFβ forcing an immunosuppressive phenotype on BCMA+ cells[3]. MM survival, resistance to treatment and the immunosuppressive phenotype can be blocked by BION-1301, the first-in class humanized antibody neutralizing APRIL. BION-1301 blocks APRIL binding to the MM relevant receptors BCMA and TACI in contrast with anti-BCMA bispecifics, ADC and CAR T-cells which use only BCMA for MM cell killing. In addition, BION-1301 inhibits immune suppressive effects of regulatory T-cells via TACI which differentiates it from BCMA targeting cytotoxic approaches[4]. In vivo, BION-1301 was shown to suppress T cell-independent B cell responses to NP-Ficoll[4]. Furthermore, APRIL blockade demonstrated single agent anti-MM activity in a humanized SCID model confirming its activity in vivo targeting MM cells in the tumor-protective bone marrow microenvironment[3]. Here, we report on the preclinical pharmacokinetics (PK)/ pharmacodynamics (PD) relationship and safety analysis of BION-1301.

Fig.1 Study design single and multiple dose IV BION-1301 in non human primates; no BION-1301 related Toxicity

A)

Group	Treatment	No. of Females	Dose Level (mg/kg)
1	Control	3	0
2	BION-1301	3	0.3
3	BION-1301	3	3
4	BION-1301	3	30
5	Control	3	0
6	BION-1301 and TNP Ficoll	3	0.3
7	BION-1301 and TNP Ficoll	3	3
8	BION-1301 and TNP Ficoll	3	30

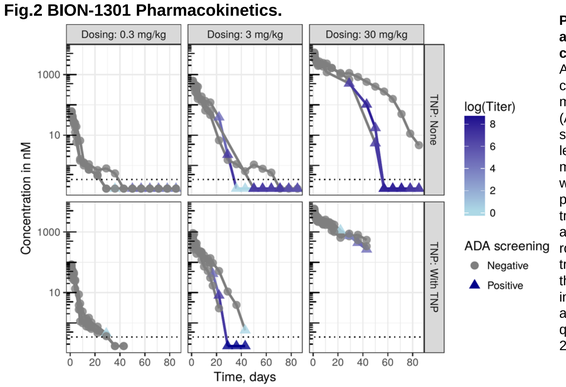
Single dose PK/PD study in NHP (A).
BION-1301 was dosed as a single dose via IV injection to female cynomolgus monkeys. After dosing, Groups 1 to 4 (Phase 1 - PK) were observed post-dose for 84 days (Day 85 phase termination) and animals in Groups 5 to 8 (Phase 2 - PK/PD) were observed post-dose for 42 days (Day 43 phase termination) to assess the reversibility, persistence, or delayed occurrence of effects. The inclusion of TNP-Ficoll in Groups 5 to 8 was to assess the PK/PD effect of BION-1301 on the T cell-independent B-cell response (Ref 3.). Results are presented in Fig. 2 and 3A.

B)

Group	Treatment	No. of Animals Male	Female	Dose Level (mg/kg)
1	Control	5	5	0
2	BION-1301	5	5	10
3	BION-1301	5	5	30
4	BION-1301	5	5	100

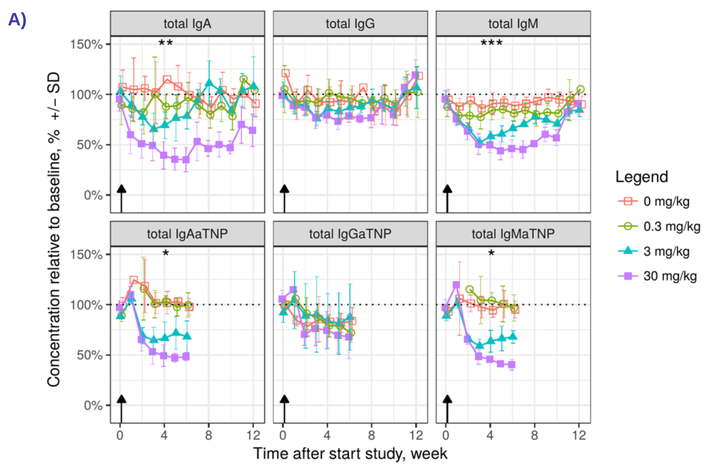
GLP tox. multiple dose study in NHP (B).
BION-1301 was dosed IV for 4 weeks (5 doses). Animals for terminal necropsy (3/sex/group) were euthanized on Day 31 of the dosing phase. Animals designated for recovery necropsy (2/sex/group) underwent 4 weeks of dosing (5 doses) followed by 12-week recovery period following dosing. Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic observations, electrocardiographic (ECG) measurements, physical examinations, pulse oximetry, blood pressure measurements, neurological examinations, dermal observations, clinical and anatomic pathology. Blood samples were collected for PK, PD, and immunogenicity evaluations. There were no BION-1301-related changes in organ weights, macroscopic findings or microscopic findings in animals sacrificed at the terminal necropsy.

Fig.2 BION-1301 Pharmacokinetics.

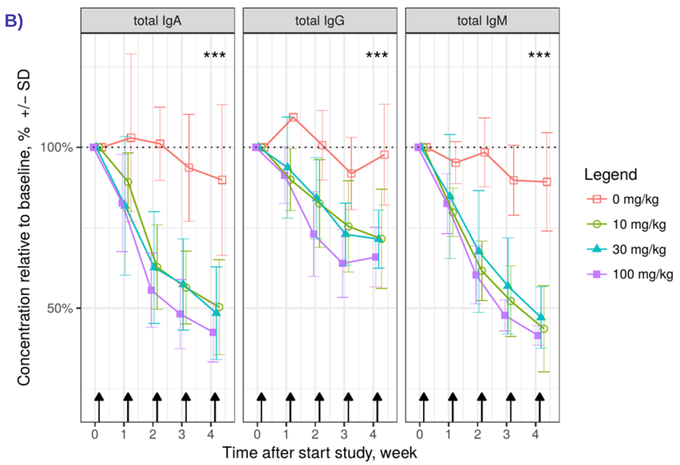


Pharmacokinetics (PK) and anti-drug antibodies (ADA) after a single intravenous dose of BION-1301 to cynomolgus monkey.
A colorimetric ELISA method was utilized to measure the concentration of BION-1301 in serum from cynomolgus monkey serum samples. For detection of anti-drug antibodies (ADA) directed against BION-1301 in cynomolgus monkey serum, a bioanalytical method (ELISA) was developed. From left to right, PK is shown at doses increasing from 0.3 to 30 mg/kg; the lower panels are from animals co-treated with TNP while for the upper panels, a vehicle co-treatment was provided. PK of BION-1301 was not sensitive to TNP treatment and was generally characterized by a low clearance and limited distribution, as typical for antibodies. Circles (gray; round) show samples that were negative for ADA and (blue; triangle) triangles shows samples that were positive where the intensity of the color indicates the ADA titer. Light blue indicates that ADA was not confirmed and dark blue indicates a high ADA titer. The dotted line indicates the lower limit of quantification. A clear impact of ADA on PK was only visible in 2 out of 3 animals at the highest dose group, 30 mg/kg.

Fig. 3 BION-1301 suppresses IgA, IgM and IgG level in NHP

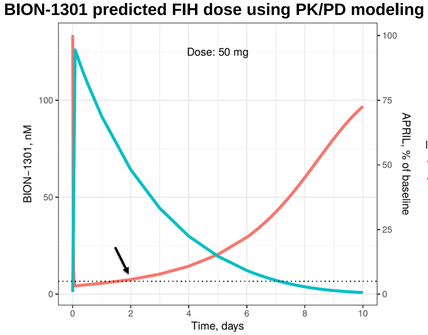


Total and anti-TNP Ig level in single dose PK/PD study in NHP (A) .
Total and anti-TNP specific immunoglobulin type A (IgA), G (IgG) and M (IgM) levels were measured with ELISA after a single intravenous dose of BION-1301 in cynomolgus monkey at 0.3 (green circles), 3 (green triangles) and 30 mg/kg (purple squares) or control (red squares), as a percentage of pre-dose levels. For clarity, only measurements at whole weeks after dosing are shown. Arrows denote time of dosing and asterisks, if present, indicate P-value (*: P<0.05; **: P<0.01; ***: P<0.001) for differences among treatment groups by non-parametric Kruskal-Wallis tests at 4 weeks after dosing. The upper panel contains immunoglobulin levels in BION-1301 only treated NHP, whereas the lower panel regards anti-TNP specific levels. Symbols were placed along the x-axis for clarity.



Total IgA, IgG and IgM level in multiple dose study in NHP (B) .
Total Immunoglobulin type A (IgA), G (IgG) and M (IgM) levels were measured with ELISA during 4-week repeated intravenous dosing of BION-1301 at 0.3 (green circles), 3 (green triangles) and 30 mg/kg (purple squares) or control (red squares), as a percentage of pre-dose levels. For clarity, only measurements at whole weeks after dosing are shown. Arrows denote time of dosing and asterisks, if present, indicate P-value (***: P<0.001) for differences among treatment groups by non-parametric Kruskal-Wallis tests. Symbols were placed along the x-axis for clarity.

Fig.4
BION-1301 predicted FIH dose using PK/PD modeling



PK/PD pharmacometric modeling using MABEL approach.
Serum concentrations of BION-1301 in NHP were determined using a validated ELISA assay. Serum samples were added to a 96-well microtiter plate coated with anti-idiotype antibody. The captured analyte (BION-1301) was detected by biotinylated anti-idiotype followed by streptavidin-HRP and TMB. The color intensity, after stopping the reaction, is proportional to the quantity of BION-1301 in the analytical sample. Calculations of results were conducted using 4-parameter regression.
The detection of free APRIL in serum samples obtained from cynomolgus monkeys treated with BION-1301 was performed using ELISA. Recombinant human B-cell maturation antigen (BCMA) coated onto a plate was used to capture free APRIL present in diluted cynomolgus monkey serum. Free APRIL bound to the plate was detected by mouse anti-human APRIL antibody as a primary antibody, followed by addition of biotinylated goat anti-mouse IgG antibody. The amount of free APRIL bound to the plate was subsequently visualized by adding streptavidin-HRP and TMB. After stopping the reaction, data is acquired using a microplate reader. The color intensity was proportional to the quantity of APRIL.
Anticipated exposure and target inhibition after a 50-mg intravenous flat dose in human (blue) exposure/ PK and (red) APRIL inhibition to BION-1301 in human, obtained by translating the PK-PD model developed on cynomolgus monkey BION-1301 and APRIL data to human using allometric principles.

CONCLUSION

In summary, BION-1301 showed no toxicity in NHP and binding of APRIL resulted in decreased IgA, IgG and IgM levels. Furthermore, BION-1301 suppresses the T-cell independent (TI) B-cell response in NHP, confirming its suppressive activity in the TI mouse model. PK and target engagement biomarkers predict the first in human dose using PK/PD pharmacometric modeling. A first-in-human study is ongoing to characterize safety and PK/PD relationship of BION-1301 in heavily pretreated MM patients.

References:

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