#125 Expedited Development of AVB-S6 through the use of a Proprietary Biomarker in Healthy Volunteers to Guide Dosing in Oncology Studies

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Abstract

Aravive is developing AVB-S6, an AXL 'decoy receptor' that binds AXL's activating ligand Growth Arrest Specific 6 (GAS6) with higher affinity than endogenous AXL, effectively sequestering GAS6 and abrogating AXL signaling. AVB-S6 has been shown to reduce invasion/migration of highly metastatic cells in vitro and inhibit metastatic disease in aggressive preclinical models of human pancreatic, renal, breast, and ovarian cancers. Due to the observed preclinical relationship between serum GAS6 (sGAS6) depletion and anti-metastatic activity, Aravive has developed a proprietary pharmacodynamic [PD] biomarker assay to assess sGAS6 levels throughout development. Use of this PD assay in combination with establishing the human safety and PK/PD profile in healthy volunteers streamlined the clinical program, guiding dose selection for oncology studies.

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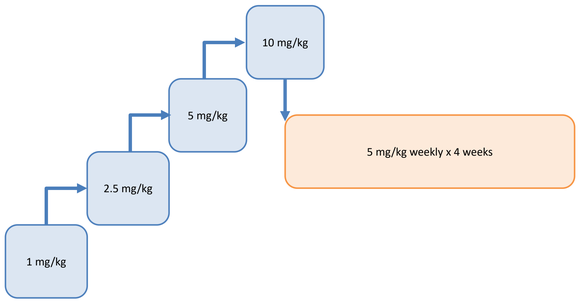
First in Human Study Design

- Single ascending dose (blue) and repeat dose (orange) study in healthy volunteers
- Single-blind, randomized, placebo-controlled



- 43 subjects participated; 42 dosed, 40 completed (2 discontinuations due to personal reasons)
- Safety and maximum drug levels were assessed prior to allowing next escalation to ensure safety and that drug levels did not exceed those at the no adverse effect levels in toxicology studies
- Serum GAS6 levels assessed between cohorts
- Anti-drug antibodies assessed

Pharmacokinetic parameters were calculated, and summary tables and figures were generated, using a validated version of PhoenixTM WinNonlin®7.0

The effect of GAS6 on the clearance of AVB-S6 was incorporated into a target-mediated drug disposition (TMDD) model, providing parallel linear and nonlinear clearance of AVB-S6.

Simulations of human GAS6 suppression were performed for the dose levels of 1, 2.5, 5, and 10 mg/kg using monkey data and then updated with human data. Considering potentially higher sGAS6 levels in cancer patients and dosing regimens of combination chemotherapies, different AVB-S6 dosing regimens were modeled to predict target coverage with doses to be used in the oncology studies.

Integration of Proprietary PD Biomarker into Development

Preclinical
- Mouse studies established relationship between depletion of sGAS6 (drug target) and antimetastatic effect
- sGAS6 used as biomarker (PD) for all nonclinical studies, including GLP toxicology; very consistent PK/PD
- Assessed sGAS6 levels from cancer patients to understand differences from healthy volunteers
- Modeling of animal PK/PD used to guide dosing in human studies considering elevated sGAS6 seen in cancer patients

P1, HV
- Nonclinical toxicology profile supports FIH study of AVB-S6 in healthy volunteers
- GLP toxicology studies combined with PD guided dose selection for first in human study
- PK/PD profile established in humans and consistent with preclinical data and modeling
- PK/PD-modeling identified dose selection for ovarian study that would suppress target by >90% and multiple dosing regimens that were compatible with chemotherapeutic dosing regimens, limiting the number of patient visits

P1b/2 Patients
- P1b portion using combination with chemotherapy facilitated by understanding of safety profile of AVB-S6 alone from P1
- P1b design included assessment of tolerability and PK/PD to ensure best dose for P2 portion
- PD-guided dosing in P1b allows preliminary efficacy read because active doses being tested in P1b

Results

Safety:
- AVB-S6 was well tolerated across all doses tested.
- There were no serious adverse events.

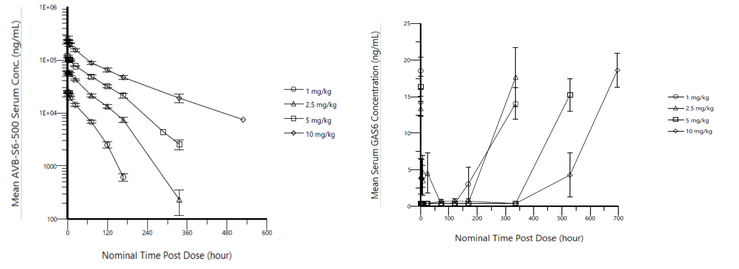
PK/ADA:
- Following single IV infusions, the PK of AVB-S6 displayed characteristics similar to other protein therapeutics such as monoclonal antibodies, displaying generally small volumes of distribution and biphasic elimination (Table 1 and Fig 1). The AVB-S6 C_{max} and AUC increased with increasing dose. The increase in C_{max} was approximately proportional across this dose range, while the increase in AUC was slightly greater than proportional with dose, suggesting nonlinear elimination kinetics consistent with TMDD.
- With repeat weekly dosing, the increase in the last measured concentration immediately prior to the subsequent infusion (C_{trough}) was approximately 2-fold between doses 1 and 4, suggesting modest accumulation in agreement with the single dose mean half-life of 59 hours.
- Among all single and repeat dose cohorts, no subjects tested positive for anti-AVB-S6 antibodies. Further, the prolonged suppression of serum GAS6 during repeat administration of AVB-S6 was reflective of the lack of any subjects testing positive for anti-AVB-S6 antibodies.

Table 1: Geometric Mean (Geometric Mean CV%) of Serum Pharmacokinetic Parameters of AVB-S6 Following a Single and Repeat IV Infusions of AVB-S6 in Healthy Subjects

Parameter	1 mg/kg	2.5 mg/kg	5 mg/kg	10 mg/kg	RD 5 mg/kg WK 1	RD 5 mg/kg WK 4
$AUC_{0-\infty}$ (hr*ng/mL)	1,204,800 (14.7)	4,506,800 (16.3)	9,950,600 (14.0)	24,184,000 (23.8)	9,269,800 (15.9)	17,372,400 (27.7)
C_{max} (ng/mL)	25,401 (13.6)	63,669 (15.2)	120,490 (8.3)	252,080 (22.9)	115,600 (14.3)	152,100 (9.9)
T_{max} (hour) [min, max]	1.5 [1.0,4.0]	1.5 [1.0, 8.0]	1.0 [1.0, 2.0]	1 [1.0, 1.0]	1.0 [1.0,2.0]	1.5 [1.0, 4.0]
Vz (L)	38.9 (14.7)	40.7 (18.6)	42.8 (13.1)	67.2 (8.2)	51.5 (11.7)	41.2 (9.1)
CL (mL/hour/kg)	0.83 (14.7)	0.55 (16.3)	0.50 (14.0)	0.41 (23.8)	0.54 (15.9)	0.29 (27.2)
$T_{1/2}$ (hours)	32.5 (12.6)	50.9 (29.4)	59.0 (29.4)	112.6 (21.2)	66.2 (16.9)	99.2 (24.6)

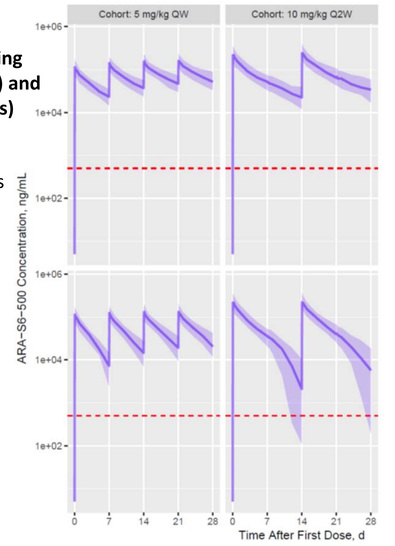
Biomarker Results

Fig 1: Mean (+SE) Concentrations of Serum AVB-S6 and GAS6 Following Single IV Doses of AVB-S6 in Healthy Subjects (N=6 per dose level)



- The average serum GAS6 level across subjects was 15.7± 3.9 ng/mL. A single infusion of 1, 2.5, 5, or 10 mg/kg AVB-S6 in healthy subjects resulted in an immediate maximal reduction in circulating serum GAS6 concentrations to below levels of quantitation (BLQ; 2 ng/mL; Fig. 1).
- Suppression of GAS6 was maintained for 168 h post infusions of 1 and 2.5 mg/kg AVB-S6.
- Serum GAS6 remained suppressed to BLQ levels until sampling times at 528 hours or 696 hours post infusion of the 5 and 10 mg/kg groups, respectively.
- Weekly infusions of 5 mg/kg AVB-S6 in healthy subjects resulted in an immediate and sustained maximal reduction in circulating sGAS6 to BLQ levels. Suppression of GAS6 was maintained at BLQ levels in all subjects until 504 h following the final infusion, when GAS6 was measurable above the LLOQ in 2 out of 6 subjects. The GAS6 concentrations remained BLQ in all other subjects (4/6).

Fig 2: Model Predictions for Repeat Dosing AVB-S6 in Healthy Volunteers (top panels) and Ovarian Cancer Patients (bottom panels)



- GAS6 is overexpressed in various cancers including ovarian cancer. Analysis of sGAS6 levels from 48 patients who had ovarian cancer suggested levels were 2-fold higher than those from the normal healthy volunteer study.
- Updating the monkey PK/PD model using Phase 1 healthy volunteer data and simulating increases in sGAS6, suggested that dosing regimens of 5 mg/kg every week or 10 mg/kg every other week would abrogate sGAS6 levels in cancer patients.

Conclusion

Use of a proprietary PD assay in combination with the PKPD modeling expedited the AVB-S6 development program by guiding dose selection for cancer patients using healthy volunteer data. This minimizes the number of cancer patients administered potentially pharmacologically inactive doses and identifies different dosing regimens to complement those of combination chemotherapy. The ability to test pharmacologically active doses in Phase 1b offers the potential to assess efficacy much earlier in development.

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