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Very-High Dose Dexamethasone Mobilizes Endogenous Bi-Specific Gamma Delta+ NKT Cells

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Abstract

Dexamethasone has been widely used since its initial approval by the FDA in 1958, either individually or as part of a therapeutic regimen for a variety of diseases and disorders, including lymphoma and leukemia and most recently, COVID-19 mediated disease.

During a preclinical experiment with A20 B-cell lymphoma bearing mice, a suprapharmacologic dose of dexamethasone phosphate, equivalent to a Human (Equivalent) Dose of 17.5 mg/kg, was inadvertently administered. Blood samples were collected and analyzed by flow cytometry, revealing the presence of a new cell 48 hours after dosing. Subsequent experiments confirmed this finding following a single dose of AVM0703. This cell has since been identified as a bi-specific gamma-delta+ NKT cell, or AVM-NKT cell.

One of the challenges of being able to deliver suprapharmacologic dexamethasone doses was the drug product itself. These limitations led to the development of a new drug product, AVM0703, which permits the safe administration of the doses necessary to mobilize these cells. AVM0703 is supplied as a sterile, single-use 50 mL, 24 mg/mL solution for infusion, without preservatives.

The ability to rapidly mobilize and activate these cells following a single dose of AVM0703 in as little as 6 hours is the subject of an on-going clinical trial, in patients with lymphoid malignancies (NCT04329728), specifically no-option, R/R ALL, MCL, DLBCL, Primary Mediastinal Large B-cell, Burkitt, CLL/SLL and B-or T-ALL. The study consists of 2-parts, dose-escalation to determine the Phase 2 dose, followed by an adaptive-design, expansion cohort study in the same patient population. Concurrently, clinical data has also been obtained from Expanded Access-Single Patient INDs.

Based on the murine model, a theoretically effective HED was determined to be at least 18 mg/kg. Because the maximum dose approved for generic injectable dexamethasone is 6 mg/kg, the starting dose for the clinical trial was set at 6 mg/kg. The dose escalation study design is a 3 x 3 design, originally consisting of cohorts escalating by 3 mg/kg to 21 mg/kg (6, 9, 12, 15, 18 and 21 mg/kg). Since that time and based on safety data (see below), the FDA has permitted a revision to the study, in which the 12 and 15 mg/kg cohorts are skipped. **Table 1** provides the original and current study design, with the corresponding total dose for a 70 kg patient. For example, 18 mg/kg is 1.26 g for a 70 kg patient.

The trial also incorporates a validated Quality of Life questionnaire and a 12-month follow-up period.

In Expanded Use, Single-Patient IND setting, 4 patients received at least one AVM0703 dose: glioblastoma: one 6 mg/kg; B-cell ALL: one 18 mg/kg dose; and two prostate cancer patients: one 18 mg/kg dose and patient #2: repeat doses for the past year as depicted in **Table 2.**

Figure 1 depicts the flow cytometry analysis 24 hours following an 18 mg/kg AVM0703 dose.

From a safety perspective, there have been no reports of drug-related or treatment emergent SAE's. The murine model safety findings correlate to the human experience. Adverse events reported to date have been self-limiting and mild to moderate. Frequent AEs include slight elevations of blood pressure, glucose and BUN that resolve without treatment in < 1 week post dose. Leukocytosis and lymphocytosis were reported 24 hours post infusion from the B-cell ALL patient but resolved by 7-days without reported intervention.

Because a single AVM0703 dose triggers the rapid mobilization and activation of an endogenous bi-specific gamma-delta+ NKT cell with a favorable emerging safety profile, AVM0703 shows promise as a therapeutic agent in treating this serious disease.

Figure 1

Cohort	AVM0703 Dose*			Status
	Protocol		Total dose-mg (per 70 kg Patient)	
	Original	*Revised*		
1	6 mg/kg	6 mg/kg	420	Completed – no DLT
2	9 mg/kg	9 mg/kg	630	Completed – no DLT
3	12 mg/kg	~~12 mg/kg~~	840	Eliminated
4	15 mg/kg	~~15 mg/kg~~	1,050	Eliminated
5	18 mg/kg	18 mg/kg	1,260	Enrolling
6	21 mg/kg	21 mg/kg	1,470	Not open
*Expressed as dexamethasone phosphate				

Table 1 – Protocol Dosing Evolution

Infusion Date	AVM0703 Dose Level	Total Dose (Approx.)
8/19/20	6 mg/kg	550 mg
9/16/20		
10/14/20		
11/18/20		
12/22/20	9 mg/kg	830 mg
1/25/21		
2/23/21	18 mg/kg	1655 mg
4/10/21		
5/10/21		
6/7/21		
7/19/21		

Table 2 – Patient JR, 72 YO Male

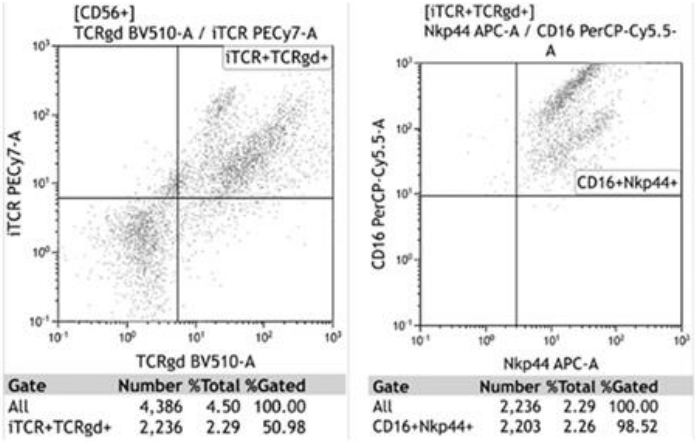

Figure 1. *Lysed whole blood flow cytometry results from an AVM0703-dosed (18 mg/kg) patient demonstrating double positive γδTCR and iTCR cells from the live cell CD56+ gate. CD56+ cells are shown on a scattergram for γδTCR and iTCR (left): 51% of the CD56+ cells are positive for both γδ TCR and iTCR. The γδTCR + iTCR quadrant (AVM-NKT) was then evaluated for CD16 and NKp44 expression (right). CD16 and Nkp44 were expressed on almost 100% of the AVM-NKT cells, indicating the activated state.*

Disclosures

Rea: *AVM Biotechnology, LLC:* Current Employment. **Deisher:** *AVM Biotechnology, LLC:* Current Employment. **Jarzyna:** *AVM Biotechnology, LLC:* Current Employment. **Zahid:** *AVM Biotechnology, LLC:* Ended employment in the past 24 months. **Suwito:** *AVM Biotechnology, LLC:* Current Employment. **Poulin:** *AVM Biotechnology, LLC:* Current Employment.