

## STATISTICAL ANALYSIS PLAN

### (Part 2)

**PROTOCOL NUMBER:** 1102-DMD-CT02

**TITLE:** A Phase 2 open label study to determine the safety, efficacy and pharmacokinetic profile of weekly dosing of ATL1102 in patients with non-ambulatory Duchenne Muscular Dystrophy (DMD).

**STUDY DRUG:** ATL1102 (CD49d antisense oligonucleotide)

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**DATE DRAFT:** 30<sup>th</sup> March 2020

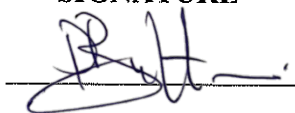
**DOCUMENT VERSION:** Final V1.0

**SIGNATURES**

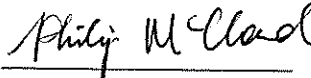
**STATISTICAL ANALYSIS PLAN (Part 2 V1.0)**

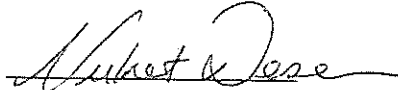
**TITLE:** A Phase 2 open label study to determine the safety, efficacy and pharmacokinetic profile of weekly dosing of ATL1102 in patients with non-ambulatory Duchenne Muscular Dystrophy (DMD).

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## VERSION HISTORY

<b>Document</b>	<b>Summary of Change</b>	<b>Date of Issue</b>
Draft Version 0.1		15 <sup>th</sup> October 2018
Draft Version 0.2	Update VAD Specs	29 <sup>th</sup> October 2019
Draft Version 0.3	Include Output Templates in separate document	24 <sup>th</sup> November 2019
Draft Version 0.4	Update to include MRI data Tables and Listings	19 <sup>th</sup> February 2020
Draft Version 0.5	Update to include output templates for PedsQL Parent and Teens data	20 <sup>th</sup> February 2020
Draft Version 0.6	Include Section 6.4.2. to specify convention for handling repeat assessment data, and update Section 10.2 to specify which efficacy analyses will be repeated with the Per-Protocol population.	27 <sup>th</sup> February 2020
Final V1.0	Consistent with Part 1 V1.0 date	30 <sup>th</sup> March 2020

## LIST OF ABBREVIATIONS

<b>Abbreviation</b>	<b>Definition</b>
6MWT	6-minute walk test
AE	Adverse Event
ADA	Anti-drug antibodies
ADME	Absorption, distribution, metabolism and excretion
A/G	Albumin/globulin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibodies
ANCA	anti-neutrophil cytoplasmic antibodies
APTT	Activated Partial Prothrombin Time
ASO	Antisense Oligonucleotide
AST	Aspartate aminotransferase
ATL	Antisense Therapeutics Limited
AUC	Area under (concentration-time) curve to last time-point
AUC <sub>inf</sub>	Area under (concentration-time) curve to infinity
CIC	circulating immune complexes
CK	Creatinine kinase
C <sub>max</sub>	Maximum observed plasma concentration
C <sub>min</sub>	Minimum observed plasma concentration
CRA	Clinical Research Associate
CRF	Case Report Form
CPF	Cough peak flow
CRP	C-reactive protein
DNA	Deoxyribonucleic acid
DMD	Duchenne Muscular Dystrophy
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EK	Egen Klassifikation
FEV1	Forced expiratory volume in 1 second

FVC	Forced vital capacity
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	Gamma glutamyl transferase
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
INR	International Normalised Ratio
IP	Investigational product
ITT	Intent-to-Treat
IUD	Intra-uterine device
IV	Intravenous
LDH	Lactate dehydrogenase
LOAEL	Low observed adverse effect level
MCP1	Monocyte chemotactic protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Maximum expiratory pressure
MIP	Maximum inspiratory pressure
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MS	Multiple Sclerosis
NOAEL	No observed adverse effect level
PD	Pharmacodynamic
PedsQL	Pediatric quality-of-life instrument
PEF	Peak expiratory flow
PICF	Patient Information and Consent Form
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
PUL	Performance of the Upper Limb

RBC	Red blood cell
RNA	Ribonucleic acid
RRMS	Relapsing remitting multiple sclerosis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	subcutaneous
SNIP	Sniff nasal inspiratory pressure
SOC	System Organ Class
STIR	Short Tau Inversion Recovery
T <sub>1/2</sub>	Terminal elimination half-life
TEAE	Treatment emergent adverse event
T <sub>max</sub>	Time to maximal concentration
ULN	Upper Limit of Normal
VLA-4	Very Late Antigen 4
WBC	White blood cell

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## 1. INTRODUCTION

This document describes the data displays to be produced planned statistical analyses for the safety, efficacy and pharmacokinetic endpoints for the Protocol 1102-DMD-CT02. This includes underlying populations and templates. The templates will provide an overview and guidance of available information and layout schemes, but do not necessarily need to be an exact match with outputs produced.

This SAP supplements the study Protocol 1102-DMD-CT02 Final Version 6.0 dated 20<sup>th</sup> September 2019. If the protocol is amended, this SAP will be revised as required. The plan will be finalized before the study database is locked.

## 2. STANDARD HEADER AND FOOTER

The following standard header and footer will be included on all tables and listings:

### **Header**

<Table, Listing and Figure Title>

**Antisense Therapeutics Limited**

**Protocol: 1102-DMD-CT02**

<Subtitle, if needed>

Population: < >

### **Footer**

Program: < filename of the program> Report: < filename of the report> Run Date: <Date of production DDMMYYYY>

Footnote requirements to explain specifics for the output

## 3. PROGRAMMING NOTES

Notes for programmers' will be stated as "Notes" below the table templates or written directly within a table as annotations. Notes for programming should not necessarily appear in any outputs.



## 4. VALUE ADDED DATASETS SPECIFICATIONS

### Laboratory Data VAD

Laboratory Ranges dataset [has Age specific normal ranges – need Age from Demo]

Notes:

- Set lower/upper limits for CRP to 0, 7.99
- If value (lborresc) is <5 set value to 4.99
- If value (lborresc) is <10 set value to 9.99
- Determine AG Ratio as  $AG\_Ratio = (albumin / (total\_protein - albumin))$ ;
- Determine H, L flags after merging ranges

### FACS Tube VADs

Approach used to determine FACS parameters:

Using the lymphocyte counts from the Haematology lab results (FBC) calculate the cell numbers (as  $10^9/L$ ) utilising the cell subset percentages determined by the FACS analysis as these cell subset percentages will be accurate. This applies to the T lymphocytes (CD3+) and the subsets of T lymphocytes (CD4+, CD8+), B lymphocytes (CD19+), the NK Cells and the Th1, Th2 and Th17 cells. The same is also applicable for the Monocytes. where the monocyte counts from the FBC can be used to calculate the cell numbers for the cell subsets including the M1 cell subsets based on the cell subset percentages determined by the FACS analysis.

### MYOSET Data VAD

Include Grip, Pinch and Moviplate Total Scores – and for each Score the Dominant/Non-Dominant Side and the Right/Left Hand Side

And need to determine Percent Predicted Values for Grip and Pinch Scores:

For Average (Left and Right Hand), Right Hand and Left Hand

Percent Predicted Pinch

If Age < 17 then

- Percent Predicted =  $(Pinch\ Score \times 100) / (1.956 \times (Exp(0.088 \times Age)))$
- Percent Predicted =  $(Grip\ Score \times 100) / (3.3996 \times (Exp(0.1527 \times Age)))$

If Age  $\geq$  17 then

- Percent Predicted = (Pinch Score x 100)/(8.206 x (Exp(-0.001 x Age)))
- Percent Predicted =(Grip Score x 100)/(45.662 x (Exp(-0.001 x Age)))

Age should be based on patient's Age at a particular visit (so formula used for a patient may change during the study (if they Age < 17 to Age  $\geq$  17

### **PUL2.0 Measure VAD**

Three Dimension and one Total Score

High Level Shoulder Dimension Score: Sum responses to Items 1-6

Mid Level Elbow Dimension Score: Sum responses to Items 7-15

Distal Wrist & Hand Dimension Score: Sum responses to Items 16-22

Total Score: Sum responses to Items 1-22

### **PedsQL VAD for Teens and Parent**

Description of the Duchenne Muscular Dystrophy Module:

Dimensions	Number of Items	Cluster of Items	Reversed Scoring	Direction of Dimensions
Daily Activities	5	1-5	1-5	Higher scores indicate lower problems
Treatment	4	1-4	1-4	
Worry	6	1-6	1-6	
Communication	3	1-3	1-3	

Scoring of Dimensions:

Item Scaling	5-point Likert scale from 0 (Never) to 4 (Almost always)
Weighting of Items	No
Extension of the Scoring Scale	Scores are transformed on a scale from 0 to 100.

Scoring Procedure	<p><b><u>Step 1: Transform Score</u></b></p> <p>Items are reversed scored and linearly transformed to a 0-100 scale as follows:</p> <p>0=100, 1=75, 2=50, 3=35, 4=0</p> <p><b><u>Step 2: Calculate Scores by Dimensions</u></b></p> <p>If more than 50% of the items in the scale are missing, the scale scores should not be computed</p> <p>Mean score= Sum of the items over the number of items answered</p>
Interpretation and Analysis of Missing Data	<p>No Total Score:</p> <p>If more than 50% of the items in the scale are missing, the Scale Scores should not be computed.</p> <p>If 50% or more items are completed: Impute the mean of the completed items in a scale.</p>

## 5. REFERENCES

1. SAS/STAT Software. 9.4 ed. Cary, NC: SAS Institute

## 6. LIST OF OUTPUTS

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## **7. OUTPUT TEMPLATES**

In Document SAP Part 2 V1.0 LTF Templates