Statistical Analysis Plan

AARD-203

Aardvark Therapeutics, Inc.

A PHASE 2, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND EFFICACY OF ARD-101 IN PATIENTS WITH PRADER-WILLI SYNDROME

Phase 2

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Phase 2

Protocol 7.0: 28-Nov-2023

IND Number: 142288

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LIST OF ABBREVIATION

Abbreviation	Definition
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BID	Twice a day
BMI	Body mass index
CCK	Cholecystokinin
CSR	Clinical study report
[redacted]	[redacted]
ECG	Electrocardiogram
EOS	End of study
HDL	High density lipoprotein cholesterol
HQ	Hyperphagia Questionnaire
HQ-CT	Hyperphagia Questionnaire for Clinical Trials
LDL	Low-density lipoprotein cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
PI	Principal investigator
PT	Preferred team
PWS	Prader-Willi syndrome
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
WHO-DD	World Health Organization Drug Dictionary (WHO-DD)

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1 INTRODUCTION

Prader-Willi syndrome (PWS) is the leading known genetic cause of obesity and is marked by a distinctive behavioral phenotype, including hyperphagia. Hyperphagia in PWS is associated with an aberrant satiety response in affected individuals, especially a delay in satiety (Holland AJ et al. 1995; Lindgren AC et al. 2000; Harris RM and Stafford DEJ 2020). Caused by a paternal deletion or maternal uniparental disomy of chromosome 15q11-q13, PWS affects about 1 in 15,000 births and results in intellectual disabilities and salient maladaptive and compulsive behaviors such as tantrums, skin picking, hoarding, and concerns with exactness and sameness. Although people with PWS have cognitive and personality strengths (Dykens EM 2002), their drive for food remains a life-long source of stress for them and their families (Hodapp RM et al. 1997). Moreover, complications of obesity remain the leading cause of death in PWS. Death rates are six times higher in PWS subjects compared with others with intellectual disabilities (Einfeld SL et al. 2006). Deaths in children often stem from illnesses associated with high fevers and respiratory infections, whereas deaths in adults are typically related to complications of obesity that involve the cardiovascular and respiratory systems (Schrander-Stumpel CT et al. 2004). Hyperphagia is also dangerous in persons who are relatively slim, with increased risks of death caused by choking while sneaking food and gastric perforations after consuming more food than usual.



[redacted]

The purpose of this phase 2 study is to evaluate the safety and efficacy of ARD-101 in patients with Prader-Willi Syndrome.

This document provides a detailed description of the statistical methods and procedures during the analysis of AARD-203. If the data suggest and warrant a change to the proposed methods and approaches, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the clinical study report (CSR) for the study, as appropriate. Any such changes must be substantiated by sound statistical rationale.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Endpoint

- Safety of ARD-101 in subjects with PWS by assessment of the incidence of Treatment-Emergent Adverse Events (TEAEs)

2.2 Secondary Objectives and Endpoints

1. Efficacy evaluation of hyperphagia in Prader-Willi syndrome
2. Quantitative evaluation of hyperphagia via a caregiver-completed hyperphagia questionnaire administered prior to dosing and on days 8 (for the dose escalation treatment group only), 15, 28 and at Follow-up.
3. Effect on weight [time frame: baseline to day 28]

[redacted]

4. [redacted]

3 STUDY OVERVIEW

3.1 Study Design

This is a Phase 2, single-arm, open-label study of ARD-101 in subjects 17-65 years of age with PWS with a BMI ⩾ 18.5 kg/m2.

This study has a planned enrollment of approximately 18 subjects. This includes about 6 subjects receiving the escalated dose regimen under the protocol amendment, in addition to the 12 subjects previously enrolled and dosed at 200 mg BID. The study will be conducted in [redacted] centers in the United States.

Table 1 lists the schedule of events for Study AARD-203. The study will consist of a Screening Period (up to 28 days), a Treatment Period (28 days), and a Follow-up Period (EOS Visit within 14 days after receiving the last dose of ARD-101). The screening procedures will be initiated upon completion of the informed consent process. Following completion of screening procedures and confirmation of eligibility, subjects will be enrolled to receive ARD-101. The study design is depicted graphically in Figure 1.

[redacted]

Under the latest protocol amendment, subjects will be dosed for 1 week at 400 mg BID, 1 week at 600 mg BID and 2 weeks at 800 mg BID for a total of 4 weeks. Subjects will receive treatment in an outpatient setting and will be instructed to visit the clinical center periodically as scheduled in Table 1 for safety and efficacy assessments. The treatment may be discontinued due to intolerable toxicity, withdrawal of informed consent, discretion of principal investigator (PI), or end of the study.

Figure 1 Schematic Diagram of Study Design

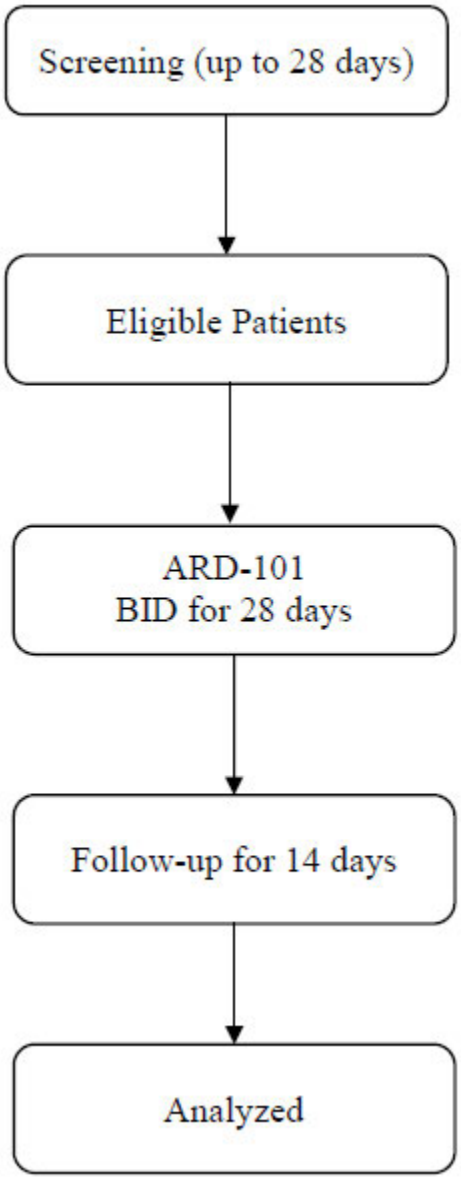


Table 1 Schedule of Assessments

Period	Screening	Treatment Period (±3 days)				Follow Up/End of Study
Study Days	**-28 to 1**	**1 (predose)[b]**	**8[e]**	**15**	**28**	**14**
Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Medical History	X					
Physical Examination[a]	X	X	X	X	X	X
Vital Signs	X	X	X	X		
12-lead ECG	X					
Hematology	X	X				
Comprehensive Serum Chemistry	X	X	X	X	X	X
Urinalysis	X					
Urine Toxicology	X					
Coagulation Parameters	X					
Pregnancy Test[c]	X	X				X
[redacted]	[redacted]	[redacted]				[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Height	X					
[redacted]		[redacted]			[redacted]	[redacted]
[redacted]		[redacted]			[redacted]	
[redacted]		[redacted]			[redacted]	[redacted]
[redacted]		[redacted]			[redacted]	[redacted]
[redacted]		[redacted]			[redacted]	
Study Drug Dispensation		X				
Concomitant Medication	X	X	X	X	X	
[redacted]		[redacted]			[redacted]	
[redacted]		[redacted]			[redacted]	
Adverse Event Monitoring	X	X	X	X	X	X
Hyperphagia Questionnaire (HQ-CT)[d]	X	X	X	X	X	X
[redacted]	[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Complete physical examination at screening, and brief physical examination for all follow-up visits.
[b] These procedures are not needed if performed within 3 days.
[c] For women of child-bearing potential only.
[d] Questionnaires obtained.
[e] Day 8 visit only conducted in the dose escalation treatment group

4 ANALYSIS POPULATIONS

The Safety Analysis Set will include all subjects who are exposed to the study investigational medicinal product. The Safety Analysis Set will be used for safety analysis and efficacy analysis.

5 STUDY SUBJECTS

5.1 Subject Disposition

Subject disposition will be summarized by treatment group [redacted] and overall, for all screened subjects. The summary will include number of subjects dosed, number and percentage of subjects completing the study, and the number and percentage of subjects who discontinued by reasons for discontinuation.

The disposition of all screened subjects will also be presented in a data listing and include: date of informed consent, study completion status, reason for discontinuation (adverse event, physician decision, pregnancy, lack of efficacy, site terminated by sponsor, participant non-compliance / protocol violation, subject withdrew consent withdrawal by parent/guardian, other), date (study day, as specified in Table 1) of study exit, and date (study day) of last dose of study drug. A listing of screening eligibility and/or the reason that subjects are excluded from the Safety Analysis Set will also be presented.

[redacted]

5.2 Demographic and Baseline Characteristics

Demographic characteristics will be summarized by treatment group and overall, for the Safety Analysis Set. Summary statistics will be generated for continuous variables [redacted] Counts and percentage of subjects within each category will be presented for categorical variables (e.g., sex, ethnicity, and race).

5.3 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Protocol deviations will be documented by the clinical monitor or the study team throughout the course of the study. All protocol deviations will be reviewed by the PI and Sponsor. The Sponsor will categorize deviations as important or non-important. An important protocol deviation is a protocol deviation that affects primary safety and assessments, the safety or mental integrity of a subject, or the scientific value of the trial project. Final decision on the important/non-important classification will be made prior to database lock and will be recorded.

Important protocol deviations will be listed by subject.

5.4 Exposure



A listing of drug accountability and daily dosing information will be presented.

5.5 Prior and Concomitant Medication and Drug Administration

Prior medications are those that started and stopped prior to the first dose of study medication. Concomitant medications are those taken after first dosing (including medications that started prior to dosing and continued after).

Prior and concomitant medication will be coded according to the B3 Sept 2023 version of the World Health Organization Drug Dictionary (WHO-DD) and Anatomical Therapeutic Chemical (ATC) classification system. Counts and percentage of participants receiving concomitant medications will be summarized by ATC classification level 2, level 4, and/or preferred term (PT), and by treatment group and overall, for the Safety Analysis Set.

Prior and concomitant medication will be listed by subject and include: reported name, PT, indication, route of administration, dose, frequency/regimen, start date, and stop date.

5.6 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA, version 27.1) and summarized with counts and percentages by system organ class (SOC) and PT, and by treatment sequence and overall, for Safety Analysis Set.

A listing will also be provided, including description of the disease/procedure, SOC, PT, start date, and stop date (or ongoing if applicable).

6 STATISTICAL METHODS OF ANALYSIS

6.1 General Considerations

Safety Analysis Set will be used for all safety analysis and efficacy analysis, and summarized by treatment group and overall, unless otherwise specified.

6.1.1 Descriptive Statistics

Continuous variables will be summarized by number of observation (n), mean, standard deviation (SD), median, minimum, and maximum. Frequency counts and percentage of subjects within each category will be provided for categorical data.

Minimum and maximum values will be rounded to the precision of the original value. Means and medians will be rounded to one decimal place greater than the precision of the original value. SDs will be rounded to two decimal places greater than the precision of the original value. Percentages for summarizing categorical data will be rounded to one decimal place.

The by-subject listings, including data collected at scheduled and unscheduled visits, will be sorted by subject number, and then by date/time of the records.

6.1.2 Hypothesis Testing

[redacted]

6.1.3 Study Baseline

[redacted]

6.1.4 Handling of Multiple Observations

[redacted]

6.1.5 Handling Missing or Partial Dates

[redacted]

[redacted]

6.2 Safety Analyses

6.2.1 Adverse Events

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational)

product. All reported terms (investigator descriptions) for AEs will be coded using MedDRA 27.1.

A TEAE is defined as an AE with a start date on or after the first dose of study drug, or that worsened following first administration of study drug.

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening; this means that the subject was at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation in existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect, or
- Is another important medical event (see below)

Important medical events that do not result in death, are not life-threatening or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or in a physician's office, blood dyscrasias or seizures that do not result in in-patient hospitalization, and the development of drug dependency or drug abuse.

The PI will assess all AEs for severity in accordance with the following standard ratings.

- Mild (Grade 1): Ordinarily transient symptoms, does not influence performance of subject's daily activities. Treatment is not ordinarily indicated.
- Moderate (Grade 2): Marked symptoms, sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Treatment may be necessary.
- Severe (Grade 3): Symptoms cause considerable discomfort. Substantial influence on subject's daily activities. May be unable to continue in the study and treatment may be necessary.
- Potentially Life Threatening (Grade 4): Symptoms require emergency room visit or hospitalization.
- Fatal (Grade 5): All deaths related to an AE are classified as grade 5.

The PI will also assess the causality/relationship between the study drug and the AE.

- Not Related

- Unlikely Related
- Possibly Related
- Probably Related
- Definitely Related

Number of events and percentages of subjects with all TEAEs will be tabulated by treatment group, SOC, and PT. TEAEs leading to study discontinuation, leading to study drug withdrawal, leading to death, related to study drug, SAEs, and TEAEs by maximum severity will also be summarized.

All AEs leading to study discontinuation, leading to study drug withdrawal, leading to death, related to study drug, and SAEs will be provided in listings. Non-TEAEs will be listed, as applicable.

6.2.2 Clinical Laboratory Evaluations

All clinical laboratory tests (hematology, serum chemistry, urinalysis, urine toxicology and fasting blood lipids) will be evaluated at Screening.

[redacted]

Lab tables will be presented by site and overall.

Listings will present all clinical laboratory test results.

6.2.3 Vital Signs, Physical Examination, and Electrocardiogram Findings

Vital signs (blood pressure, pulse, body temperature, and respiratory rate) will be assessed at [redacted] Vital sign values will be summarized descriptively by treatment group and visit for the actual values and the changes from baseline.

Physical examinations will be assessed [redacted] Abnormal physical examination results will be listed.

Standard 12-lead Electrocardiograms (ECG) will be performed at Screening. All ECG data will be included in the listing.

6.2.4 Pregnancy

A pregnancy test will be performed for women of child-bearing potential at Screening and Follow Up/End of Study. A listing will be presented.

6.3 Efficacy Analyses

6.3.1 Hyperphagia Questionnaire for Clinical Trials

The Hyperphagia Questionnaire for Clinical Trials (HQ-CT) is a 9-item questionnaire developed in 2015 for the assessment of food-seeking behaviors in PWS clinical trials. The HQ-CT 9 has been used in over a dozen clinical trials examining hyperphagia behaviors in Prader-Willi Syndrome patients. This instrument is completed by a parent/primary caregiver of the person with PWS and assesses the frequency and intensity of hyperphagic behaviors over the past two weeks. Each of the nine items is scored from 0 to 4, (0=Never, 1=Rarely, 2=Sometimes, 3=Often, 4=Never). The HQ-CT total score will be computed by summing the nine item-level responses, yielding a score ranging from 0 to 36, provided at least six items have been answered by the caregiver.

[redacted]

6.3.2 Weight and Body Mass Index

Weight will be assessed at Screening, Day 8 (dose escalation treatment group only), 15, and

[redacted]

6.4 Analyses of Exploratory Questionnaire Endpoints

[redacted]

6.4.3 [redacted]

[redacted]

6.4.4 [redacted]

[redacted]

7 [redacted]

[redacted]

8 [redacted]

[redacted]

9 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS® version 9.4.

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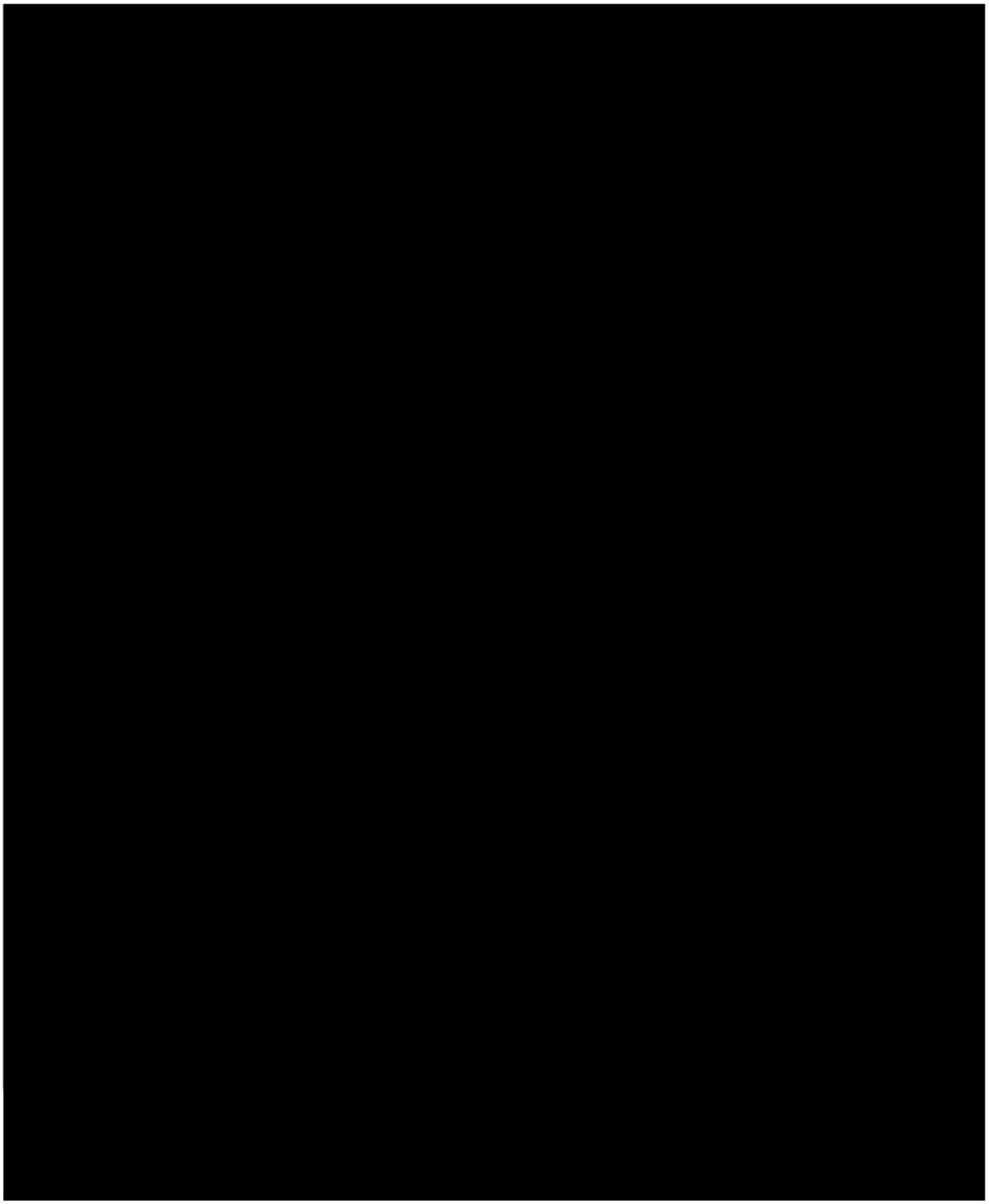
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APPENDICES

[redacted]

AARD – 2 0 ___ 1 0 ____ – ____ ____ ___ Date _____
Study Number *Patient Number* *Date YYYY-MMM-DD*

[redacted]



[redacted]

[redacted]

[redacted]

