Clinical Study Protocol

A Phase 2, Single-Arm, Open-Label Study to Evaluate the Safety and Efficacy of ARD-101 in Patients with Prader-Willi Syndrome

Sponsor:	Aardvark Therapeutics
	
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IMP Name:	ARD-101
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Amendment 3	4.0 (May 9, 2022)
Amendment 4	5.0 (October 10, 2022)
Amendment 5	6.0 (April 12, 2023)
Amendment 6	7.0 (November 28, 2023)

This clinical study will be conducted in accordance with the International Council for Harmonization Tripartite Guideline for Good Clinical Practice (GCP) E6(R2), the protocol and with other applicable regulatory requirements.

Confidentiality Statement

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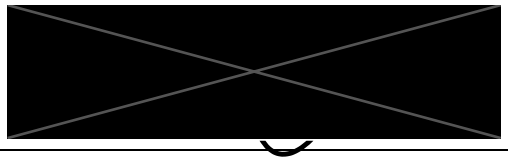
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Declaration of Sponsor

Protocol Title: A Phase 2, Single-Arm, Open-Label Study to Evaluate the Safety and Efficacy of ARD-101 in Patients with Prader-Willi Syndrome

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product (IMP), as well as with the moral, ethical and scientific principles governing clinical research as set out in the guidelines on GCP applicable to this clinical study.

Sponsor Signatory



28NOV2023

Date

Chief Medical Officer

Aardvark Therapeutics, Inc.

SIGNATURE PAGE

Declaration of the Principal Investigator

Protocol Title: A Phase 2, Single-Arm, Open-Label Study to Evaluate the Safety and Efficacy of ARD-101 in Patients with Prader-Willi Syndrome

This clinical study protocol was subjected to critical review and has been released by the Sponsor. The information it contains is consistent with current risk and benefit evaluation of the IMP, as well as with the moral, ethical and scientific principles governing clinical research as set out in the guidelines on GCP applicable to this clinical study.

Principal Investigator

Principal Investigator	Signature
Date	Site Number

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

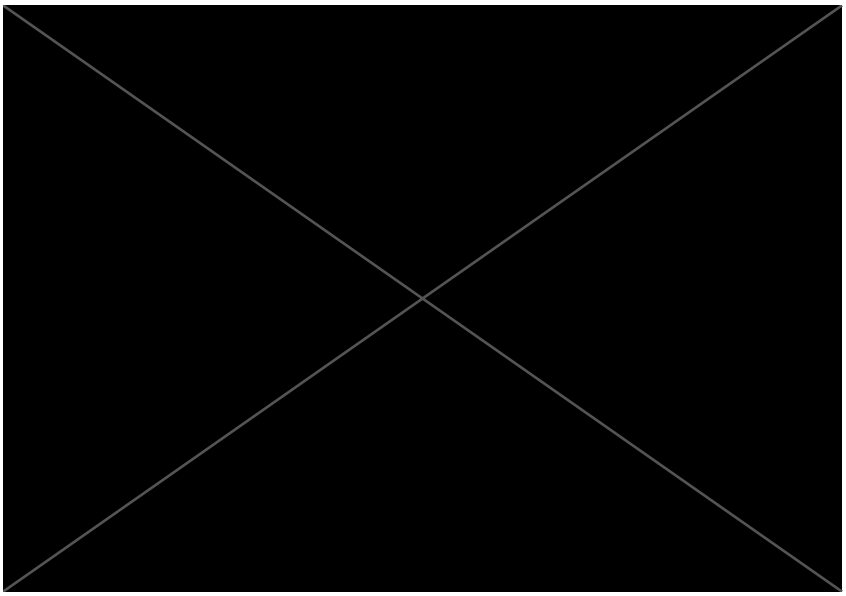
Abbreviation	Definition
AE	Adverse event
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0-\tau}$	Area under the plasma concentration versus time curve from time zero to time τ
b.i.d.	Twice a day
BLQ	Below the quantitation limit
BMI	Body mass index
bpm	Beats per minute
CBC	Complete blood count
CCK	Cholecystokinin
CFR	Code of Federal Regulations
CL	Systemic clearance
C_{max}	Maximum observed concentration
CNS	Central nervous system
[redacted]	
CRO	Contract research organization
CSR	Clinical study report
[redacted]	
DBP	Diastolic blood pressure
DEXA	Dual-energy X-ray absorptiometry
DOA	Drugs of Abuse
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EOS	End of Study
FIH	First-in-Human
F%	Oral bioavailability
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice

Abbreviation	Definition
GI	Gastrointestinal
[redacted]	
GLP	Good Laboratory Practice
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated hemoglobin
[redacted]	
HQ-CT	Hyperphagia Questionnaire for Clinical Trials
HR	Heart rate
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council on Harmonization
IC_{50}	Half maximal Inhibitory Concentration
IEC	Independent ethic committee
i.g.	Intragastric
IgE	Immunoglobulin E
IMP	Investigational medicinal product
IL	Interleukin
IP	Intraperitoneal
IND	Investigational new drug
IRB	Institutional review board
i.v.	Intravenous
[redacted]	
MedDRA	Medical Dictionary for Regulatory Activities
NASH	Nonalcoholic steatohepatitis
NOAEL	No observable adverse effect level
[redacted]	
OTC	Over-the-counter

Abbreviation	Definition
PK	Pharmacokinetics
p.o.	*per. os* (orally)
PWS	Prader-Willi Syndrome
[redacted]	
QTcB	QT interval corrected for heart rate using Bazett's correction
QTcF	QT interval corrected for heart rate using Fridericia's correction
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SMC	Safety Monitoring Committee
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal elimination half-life calculated as: ln2/λz
t_{max}	Time of the maximum observed concentration
TEAEs	Treatment-emergent adverse events
TNF	Tumor necrosis factor
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
V_d	Volume of distribution
V_{ss}	Volume of distribution at steady state
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary

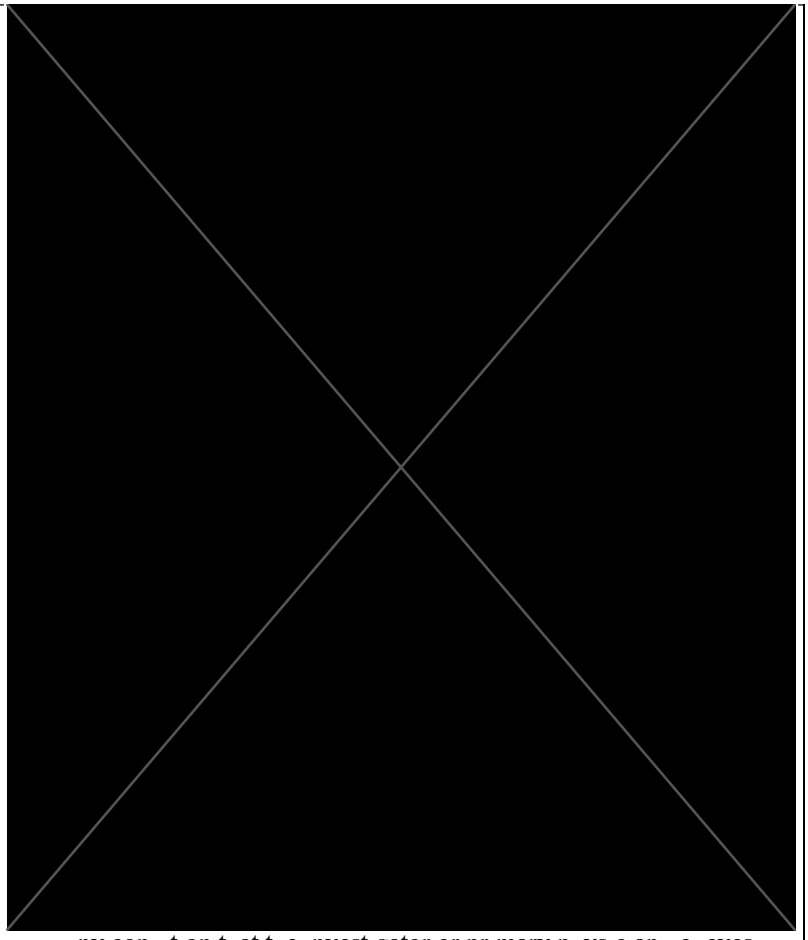
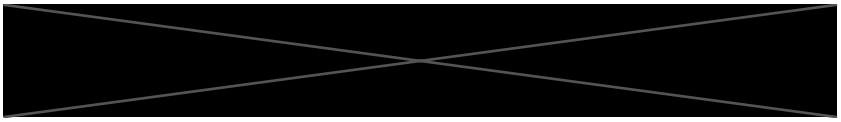
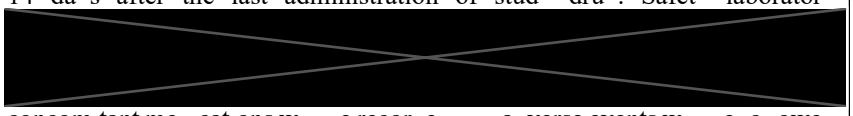
1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title	A Phase 2, Single-Arm, Open-Label Study to Evaluate the Safety and Efficacy of ARD-101 in Patients with Prader-Willi Syndrome (PWS)
Study Number	AARD-203
Development Phase	Phase 2
Sponsor	Aardvark Therapeutics, Inc.
Study Center	The study will be conducted at [redacted] centers in the United States (US)
Study Endpoints	**Primary Endpoint:** • Safety of ARD-101 in subjects with PWS by assessment of the incidence of Treatment-Emergent Adverse Events (TEAE) **Secondary Endpoints:** • Efficacy evaluation of hyperphagia in Prader-Willi syndrome ○ Quantitative evaluation of hyperphagia via the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) obtained prior to dosing and on days 15, and 28. Score will range from 0 (no hyperphagia behaviors) to 36 (most severe hyperphagia behaviors) • Effect on weight [time frame: baseline to day 28] 
Study Design	This is an open label Phase 2, single arm study of ARD-101 in subjects 17-65 of age with PWS. A total of approximately 18 subjects will be enrolled in the clinical study. This includes about 6 subjects receiving the escalated dose regimen under the current amendment, in addition to the 12 subjects previously enrolled and dosed at 200 mg BID.

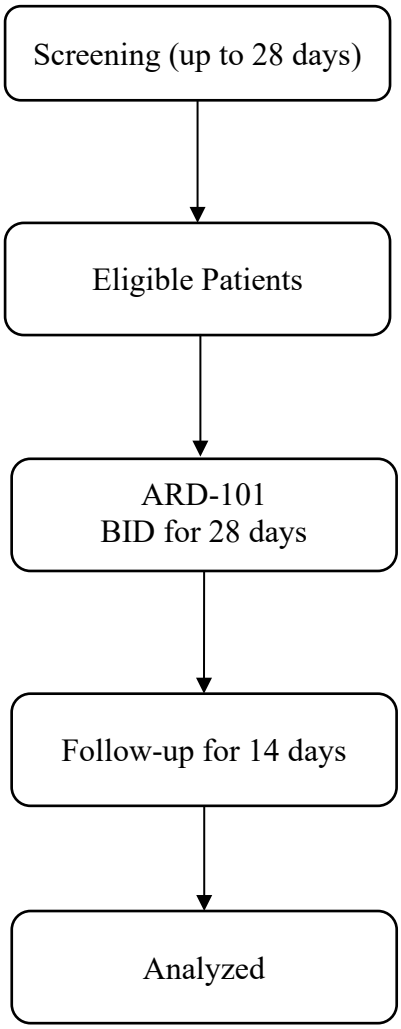
	A screening process will be initiated upon completion of the informed consent process. Subjects will be assessed for eligibility through screening tests conducted within 28 days prior to enrollment. Following completion of screening tests and confirmation of eligibility, subjects will be enrolled to complete pre-dosing requirements and questionnaires during screening window as per protocol and then continue on to receive ARD-101. Patients 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. All available safety and tolerability data will be evaluated throughout study conduct. Subjects will be receiving treatment in an outpatient setting and will be instructed to visit the clinical center periodically as assessment 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, or end of the study. All subjects will be followed for approximately 14 days after the last dose of study drug.
Test Product, Dose, and Mode of Administration	ARD-101 at 200, 400, 600 and 800 mg BID administered orally
Inclusion Criteria	Subjects must meet all the following criteria to be eligible for participation in this study: 1. Male and female subjects, 17-65 years of age 2. Provide voluntary, written informed consent (parent(s) / legal guardian(s) of participant); provide voluntary, written assent (participants, as appropriate) 3. PWS due to chromosome 15 micro-deletion, maternal uniparental disomy, or imprinting defect, confirmed by fluorescent in situ hybridization, chromosomal microarray, and/or methylation studies 4. [redacted] 5. 6. If a subject has a diagnosis of type 2 diabetes, the following criteria must be met: a. [redacted] b. c. 7. Stable or well-controlled blood ressure BP and vital si ns. [redacted]

	[redacted] 8. [redacted] 9. [redacted] 10. Parent or guardian is able to communicate well with the investigator, to understand and comply with the requirements of the study, and be able to understand and sign the written informed consent. Assent is to be provided for the patient who cannot consent for himself or herself 11. Results of screening clinical laboratory tests [complete blood count (CBC) with differential and platelets and chemistry profile] and vital signs must be within normal range or, if outside of the normal range, must be accepted by the investigator and sponsor as not clinically significant 12. [redacted] 13. [redacted] 14. [redacted] 15. [redacted] 16. [redacted]
Exclusion Criteria	Subjects who meet **any** of the following criteria will be excluded from study participation: [redacted]

	 . ny con t on t at t e nvest gator or pr mary p ys c an e eves may not be appropriate for participating the study
Duration of Study	The duration of participation for each subject will be up to 84 days • Screening Period: Up to 28 days (4 weeks) • Treatment Period: 28 days on ARD-101 • Follow-up Period: 14 days (2 weeks). The End of Study (EOS) Visit will occur within 14 days after receiving the dose of ARD-101
	
Safety Evaluations	Adverse events (AE) will be collected from the time of informed consent until 14 da s after the last administration of stud dru . Safet laborator  concom tant me cat ons w e recor e . a verse events w e o owe to resolution or stabilization. Only TEAE will be summarized.
Efficacy Evaluations	Please refer to “Endpoints”
Statistical Analysis	All safety and efficacy data will be summarized and presented overall for the study, using descriptive statistics where appropriate. Mean, median, standard

	deviation, minimum, and maximum will be presented for continuous variables and frequencies and percentages for discrete variables.

1.2. Schema



Patients 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.

1.3. Schedule of Assessments, Time Points, and Window Allowance

Details on procedures and timing of assessments are presented in Table 1.

Please note: All screening assessments may be performed at day 1 (predose).

Table 1 Scheduled Assessment

Period	Screening	Treatment Period (±3 days)				Follow Up/End of Study
Study Days	**-28 to 1**	**1 (predose)[b]**	**8**	**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]						
Height	X					
[redacted]						
Study Drug Dispensation		X[e]				
Concomitant Medication	X	X	X	X	X	
[redacted]						
Adverse Event Monitoring	X	X	X	X	X	X
Hyperphagia Questionnaire (HQ-CT)[d]	X	X	X	X	X	X
[redacted]						

Period	Screening	Treatment Period (±3 days)				Follow Up/End of Study
Study Days	**-28 to 1**	**1 (predose)[b]**	**8**	**15**	**28**	**14**
[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

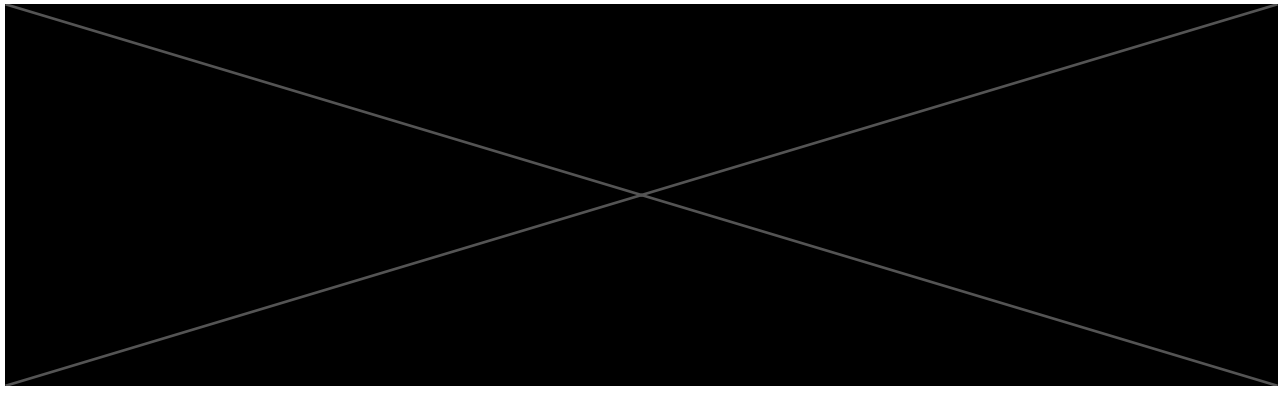
2. INTRODUCTION

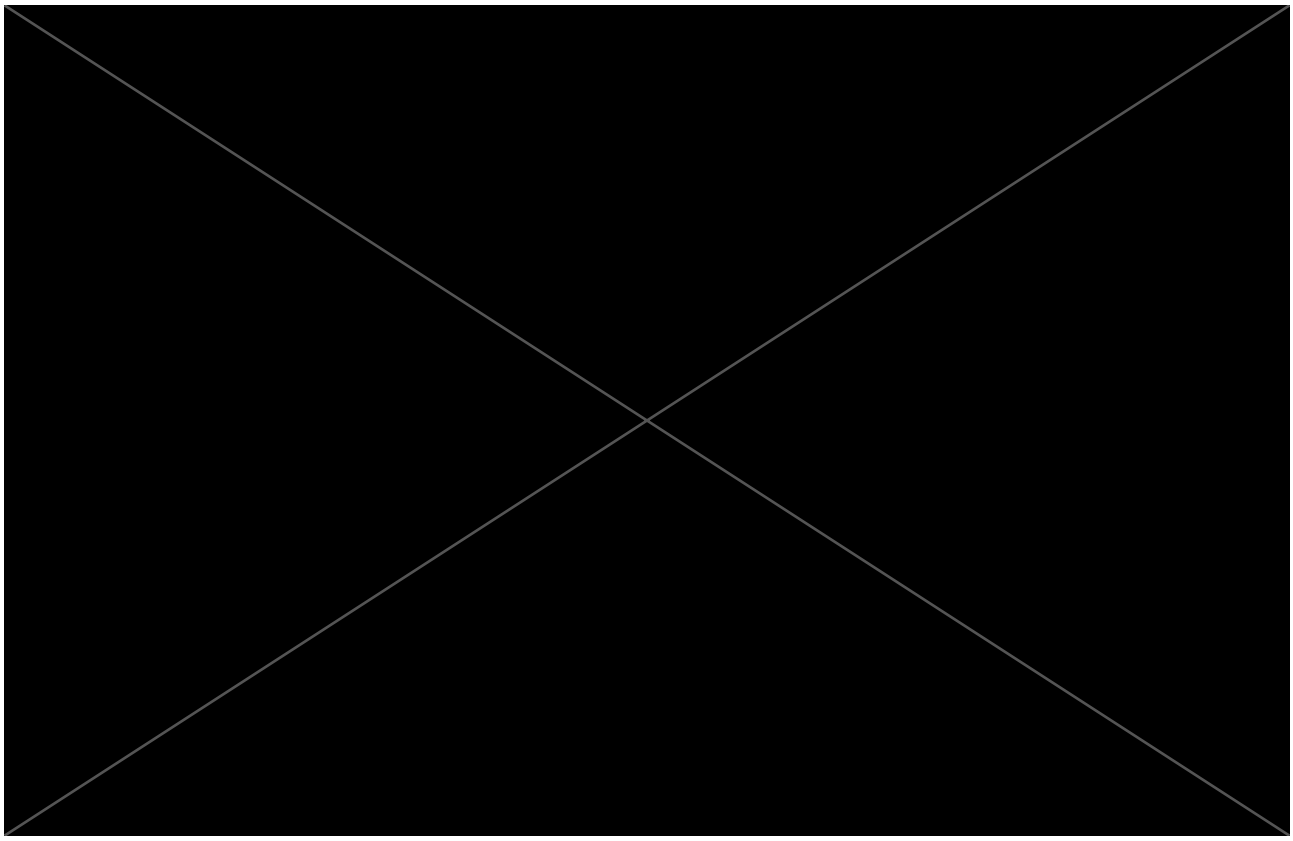
2.1. Background

Prader-Willi Syndrome and Hyperphagia

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.

In a global survey conducted by the Foundation for Prader-Willi Research, 96.5% of respondents (parent and caregivers) rated hyperphagia as the most important or a very important symptom to be relieved by a new medicine. There are currently no approved therapies to treat the hyperphagia/appetite, metabolic, cognitive function, or behavioral aspects of the disorder.

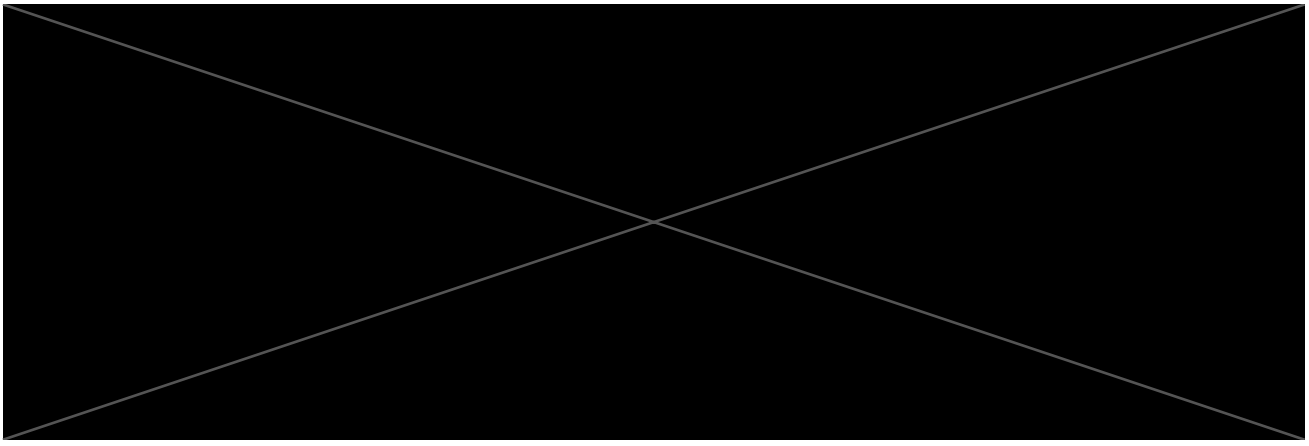




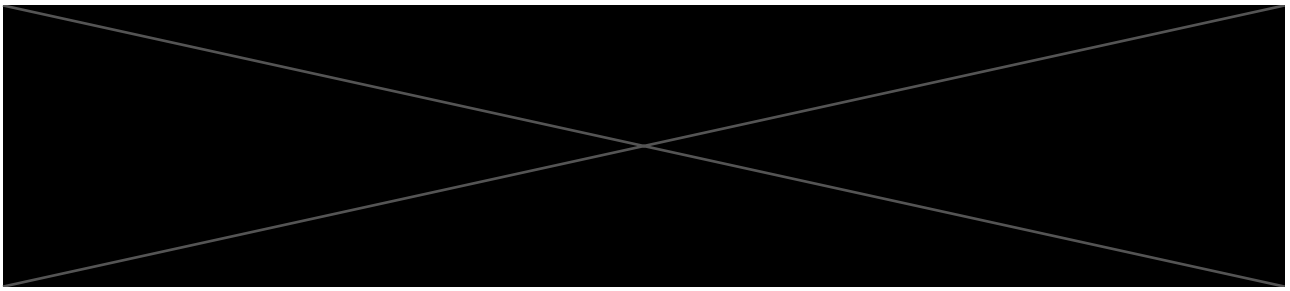
Rationale of the Study

ARD-101

In addition, ARD-101 is minimally absorbed into the circulation through the GI epithelium cells



Aardvark Therapeutics, Inc., the Sponsor, has demonstrated the efficacy and safety of oral ARD-101 in multiple preclinical animal models of metabolic disorders and weight management.



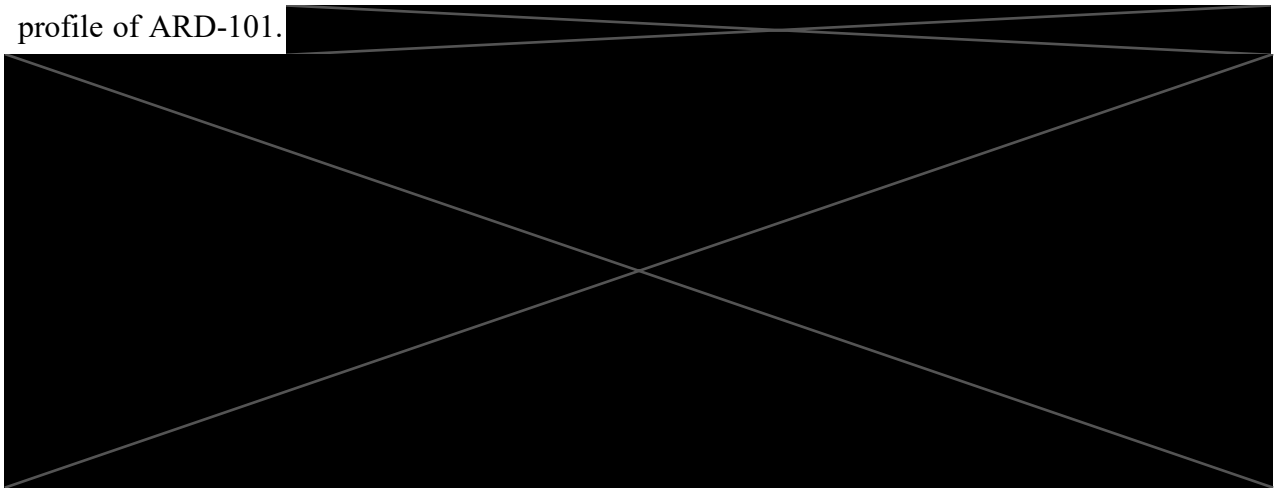
Taken together, ARD-101 has demonstrated promising preclinical activity in models of metabolic syndrome relevant to PWS and a favorable safety profile in humans.

For details of the preclinical results, please refer to the Investigator Brochure (IB).

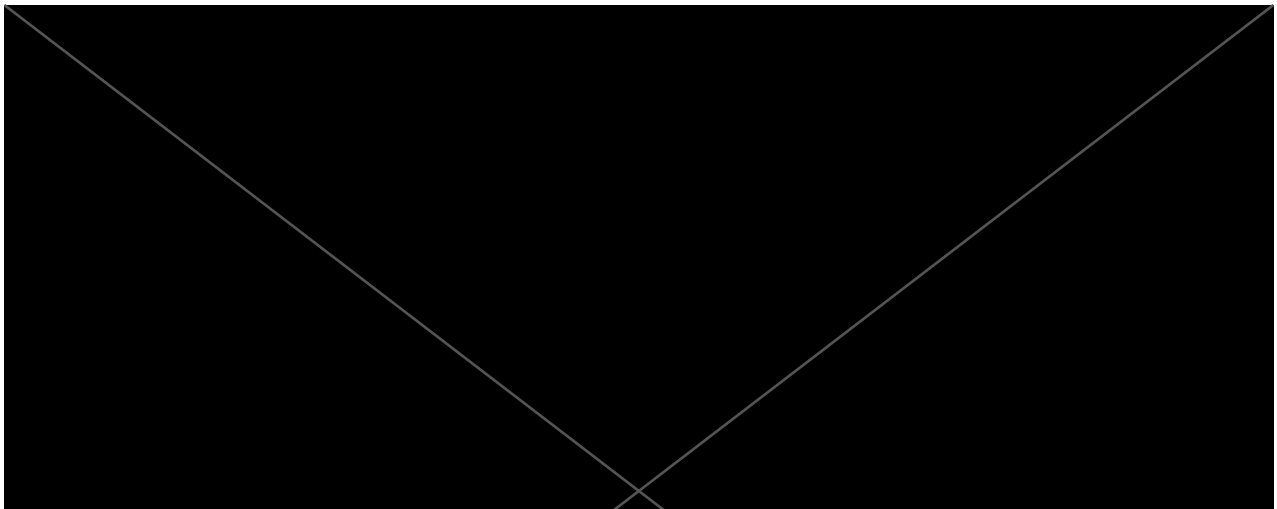
2.2. Risk-benefit Assessment

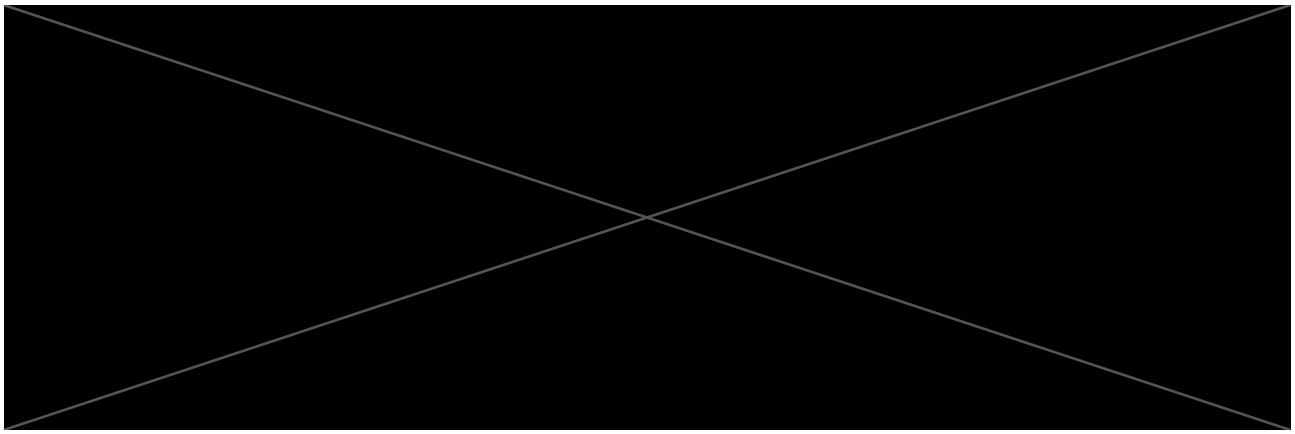
2.2.1. Known Potential Risks

Comprehensive non-clinical toxicology studies have been performed to establish the toxicity profile of ARD-101.

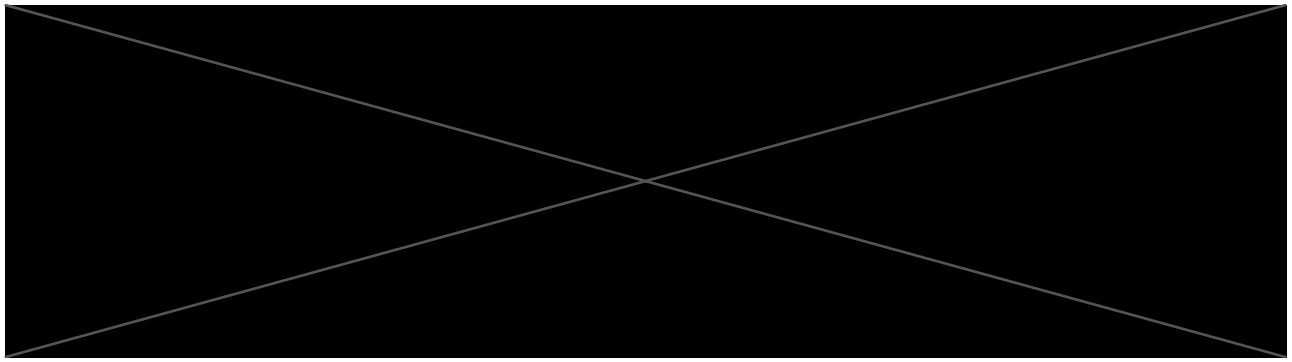


2.2.2. Known Potential Benefits

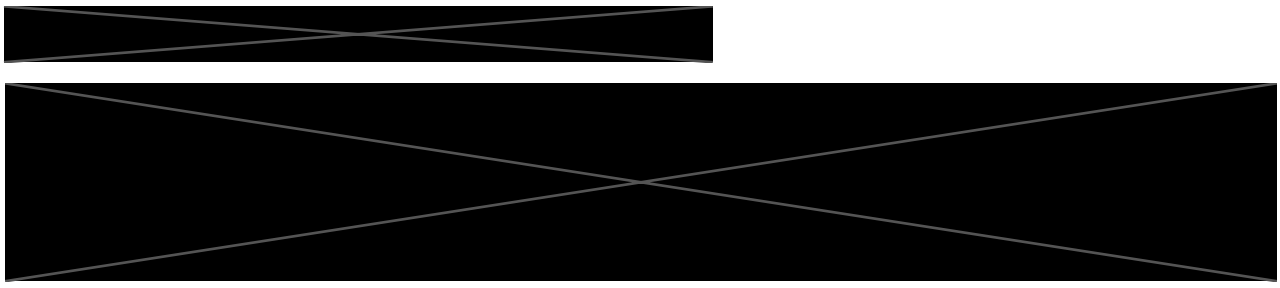




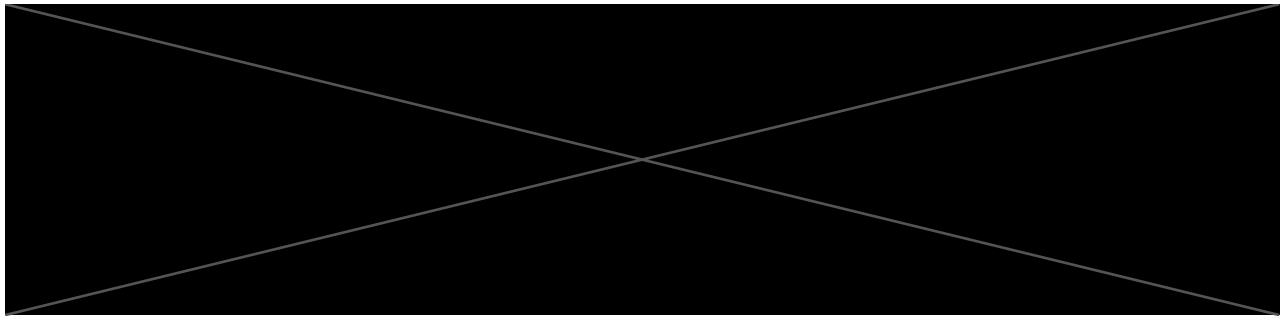
2.3. Summary of Findings from Non-clinical, in vitro Studies with Potential Clinical Relevance

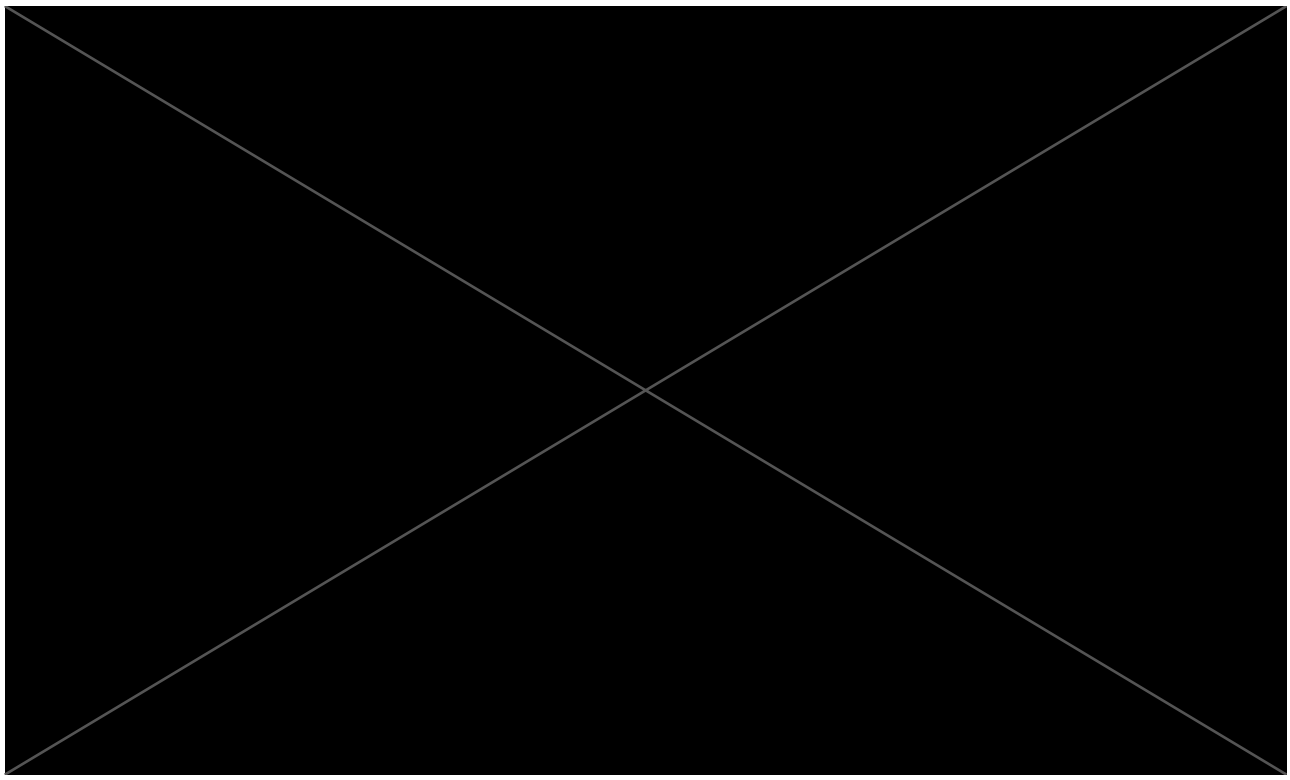


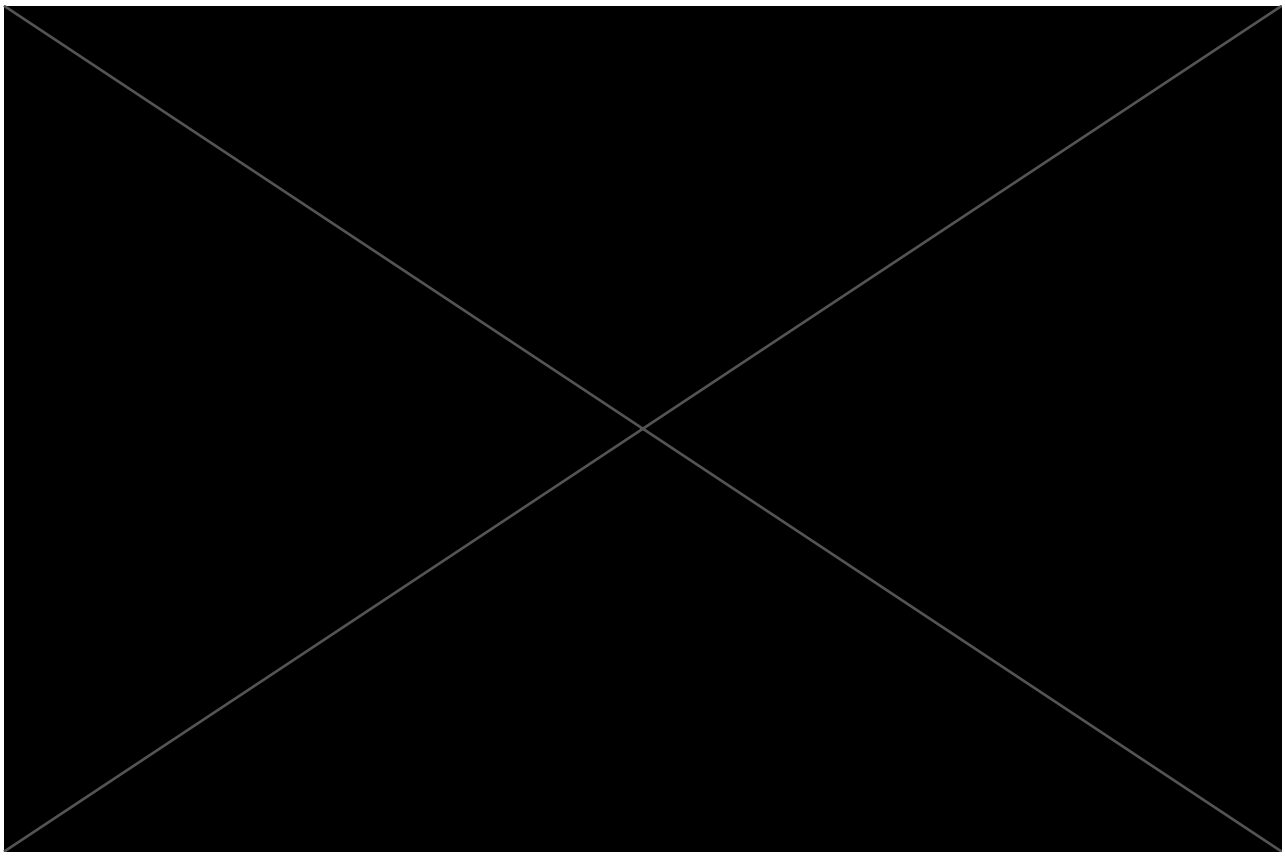
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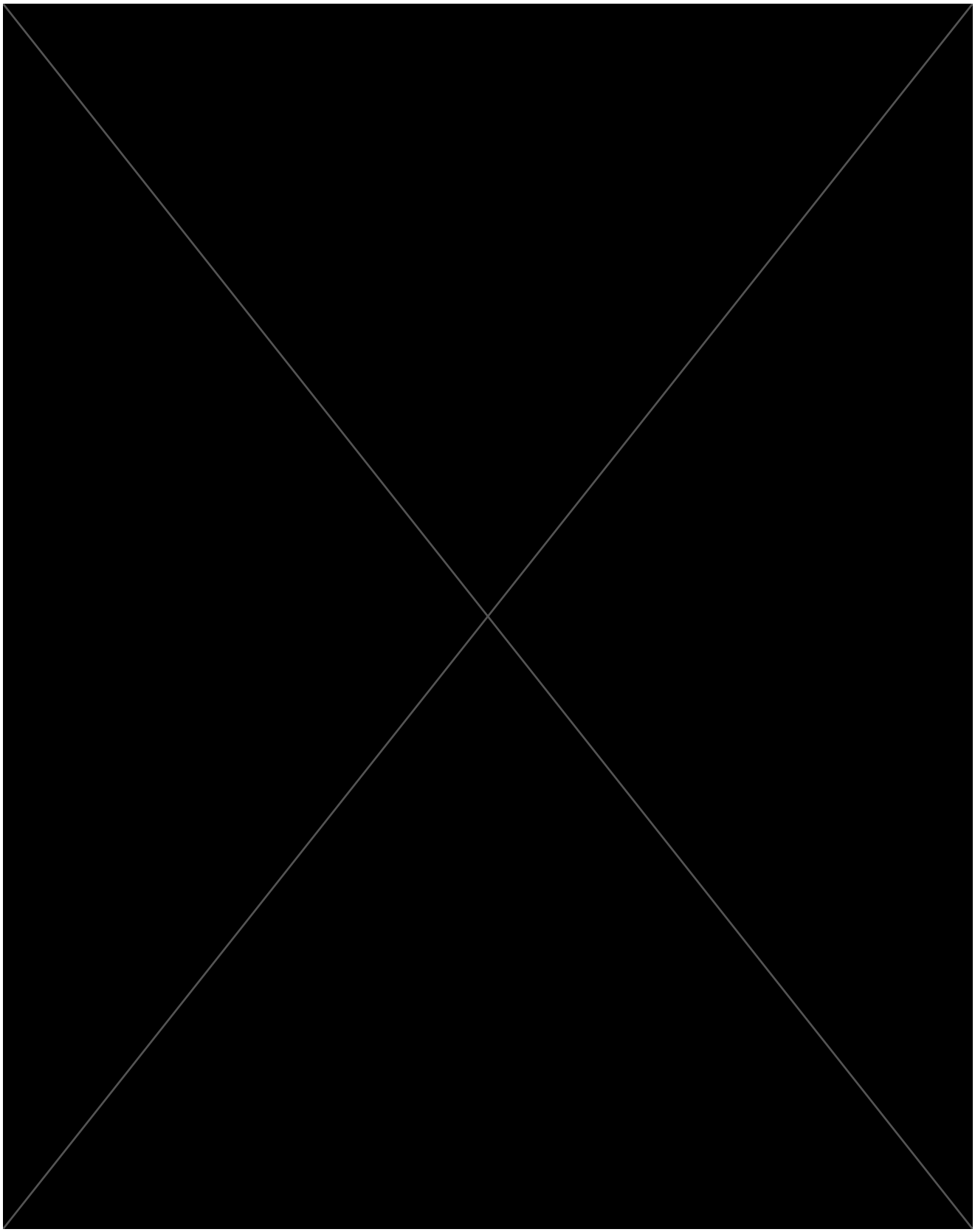


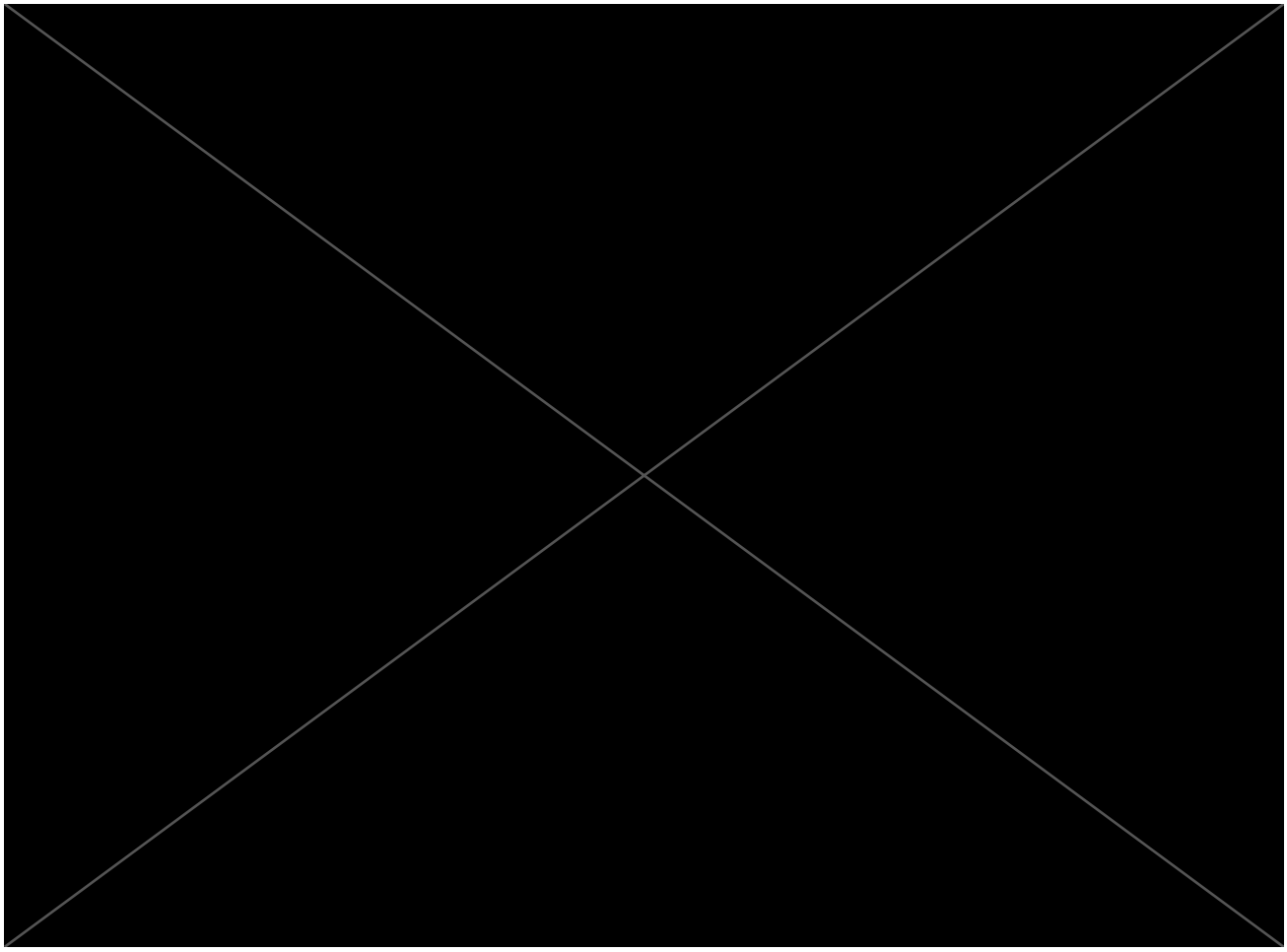
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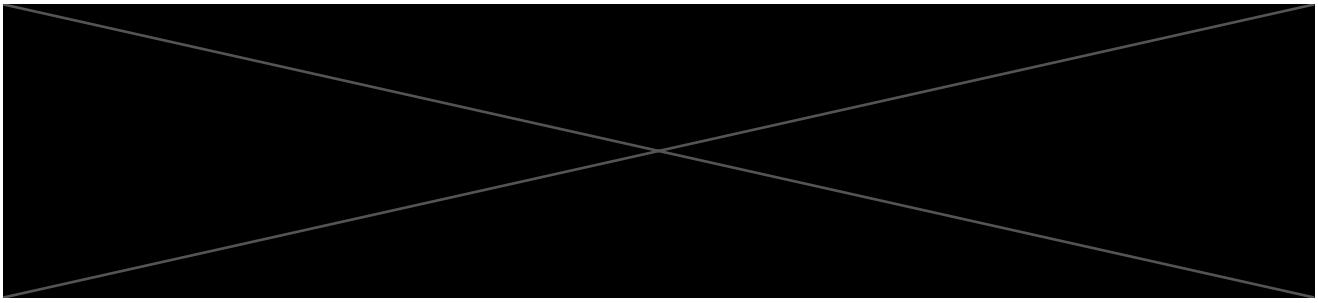












Further details can be found in the Investigator's Brochure.

2.4. Summary of Findings from Previous Clinical Studies

A FIH clinical trial with the study drug has been performed in healthy volunteers to interrogate safety and pharmacokinetics of multiple dose levels.

The study consisted of 2 parts: A single ascending dose part (SAD) and a multiple ascending dose part (MAD), dosing subjects for 14 days BID. Each part tested three dose levels (40 mg, 100 mg

and 240 mg) consecutively in a randomized, double-blinded manner. Forty-three subjects were dosed in total, 23 females and 20 males, of which 31 received ARD-101.

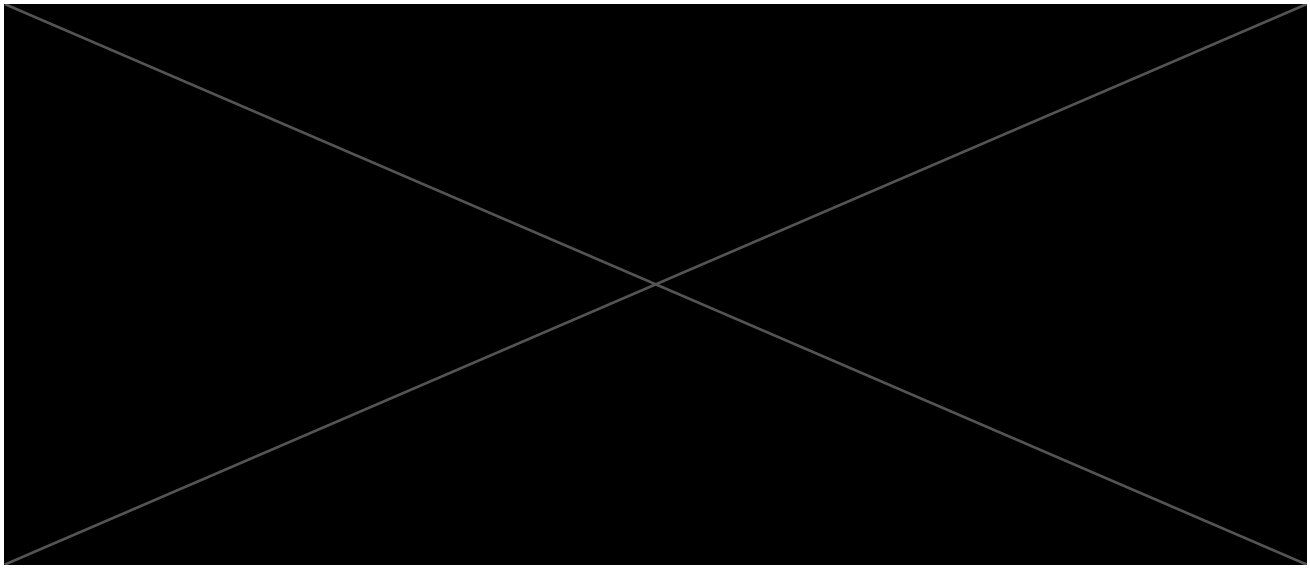
The results are summarized below:

2.4.1. Overview of Clinical Pharmacology

2.4.1.1. Single Ascending Dose

The SAD study evaluated PK parameters following administration of a single oral dose of ARD-101 at 40 mg, 100 mg, or 240 mg in healthy adult subjects. Eligible subjects were 18-55 years of age, with a body mass index between 18-30 kg/m^2 and a minimum weight of 50 kg. Subjects were orally dosed in 3 escalating cohorts of 40, 100, and 240 mg of ARD-101 or matching placebo capsules. For each dose cohort, 6 subjects received ARD-101 and 2 subjects received placebo. The study medication was administered to eligible subjects after a minimum of 8 h of fasting.

Group PK analyses have been conducted for all dose cohorts in Part 1 of the study. PK parameters for all doses are presented in Table 4 . Based on the area under the curves (AUCs) and maximum serum concentration (C_{max}) between-subject variability (Geometric CV%) was high, ranging from 45.8 to 53.7%. CV% for $t_{1/2}$ values increased with increases in ARD-101 dose level.



Following administration of a single 240 mg ARD-101 dose, quantifiable concentrations for all subjects were observed at 48 hours post dose, with 3 of 6 subjects having quantifiable concentrations at 72 hours post dose. There was a 2.4-fold increase in dose level from 100 to 240 mg ARD-101. This resulted in increases in C_{max}, AUC_{last}, and AUC_{inf} (4.08-, 3.34-, and 3.18-fold, respectively).

The geometric mean and highest peak plasma concentrations (C_{max}) following single oral administration at these doses were 0.999 and 9.59 ng/mL (40 mg), 3.04 and 10.4 ng/mL (100 mg), and 12.4 and 29.7 ng/mL (240 mg) respectively, which represented 0.12% and 1.20%, 0.380% and 1.30%, and 1.55% and 3.71% of the PK stopping criteria (800 ng/mL) for this Phase 1 study.

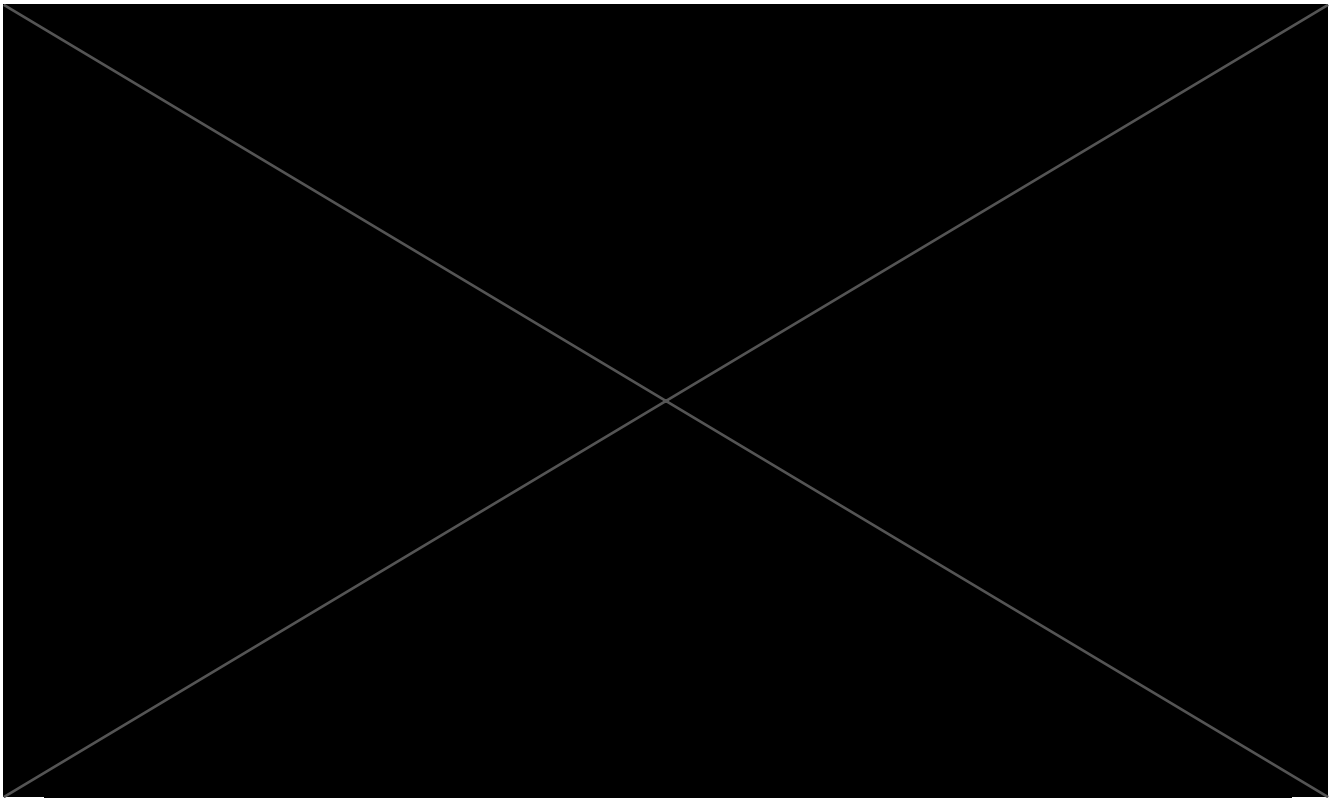
2.4.1.2. Multiple Ascending Dose

The MAD study evaluated PK parameters following repeated administration to date of oral doses of ARD-101 at 40 mg, 100 mg, or 240 mg BID in healthy adult subjects. Eligible subjects were 18-55 years of age, with a body mass index between 18-30 kg/m^2 and a minimum weight of 50 kg. Subjects were orally dosed BID, for 14 days, or matching placebo capsules. Four subjects received ARD-101 and 2 subjects received placebo in each dose level. From Day 1 to Day 14, the study medication was administered twice daily with approximately 12 h between doses.

PK results are listed below (Table 5).

The geometric mean (on Day 14) and highest individual systemic exposure (on Day 1), based on C_{max}, represented 1.14% and 2.55% of PK stopping criteria, respectively, at the 240 mg BID dose level.

Accumulation after BID dosing for 14 days was 1.20-fold for C_{max} and 1.68-fold for AUC_{tau} at 240 mg BID. Steady state appears to have been reached by Day 11 at all tested dose levels.



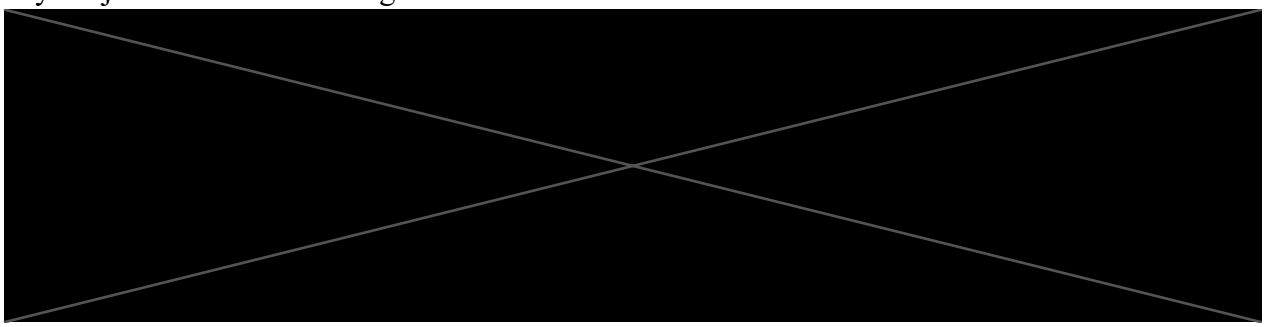
2.4.2. Overview of Clinical Efficacy

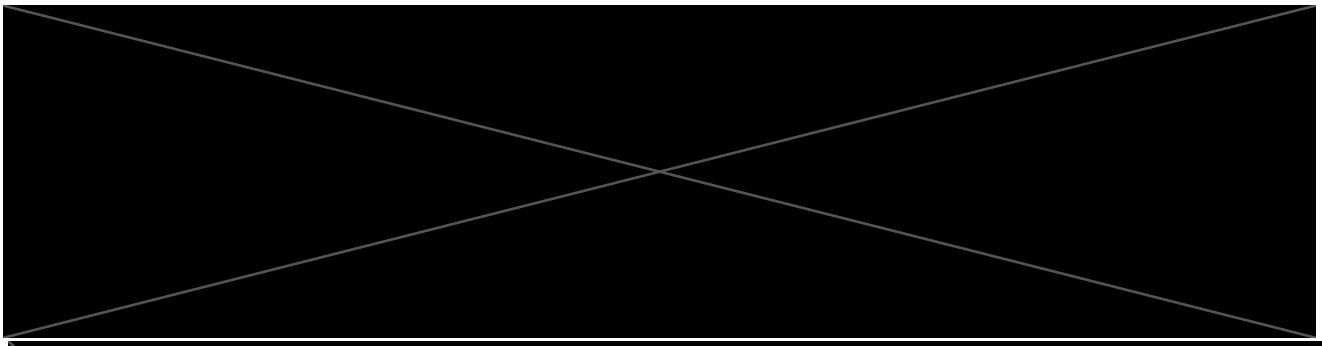
At the time of the submission of this IND, no clinical study has been conducted to investigate the efficacy of ARD-101.

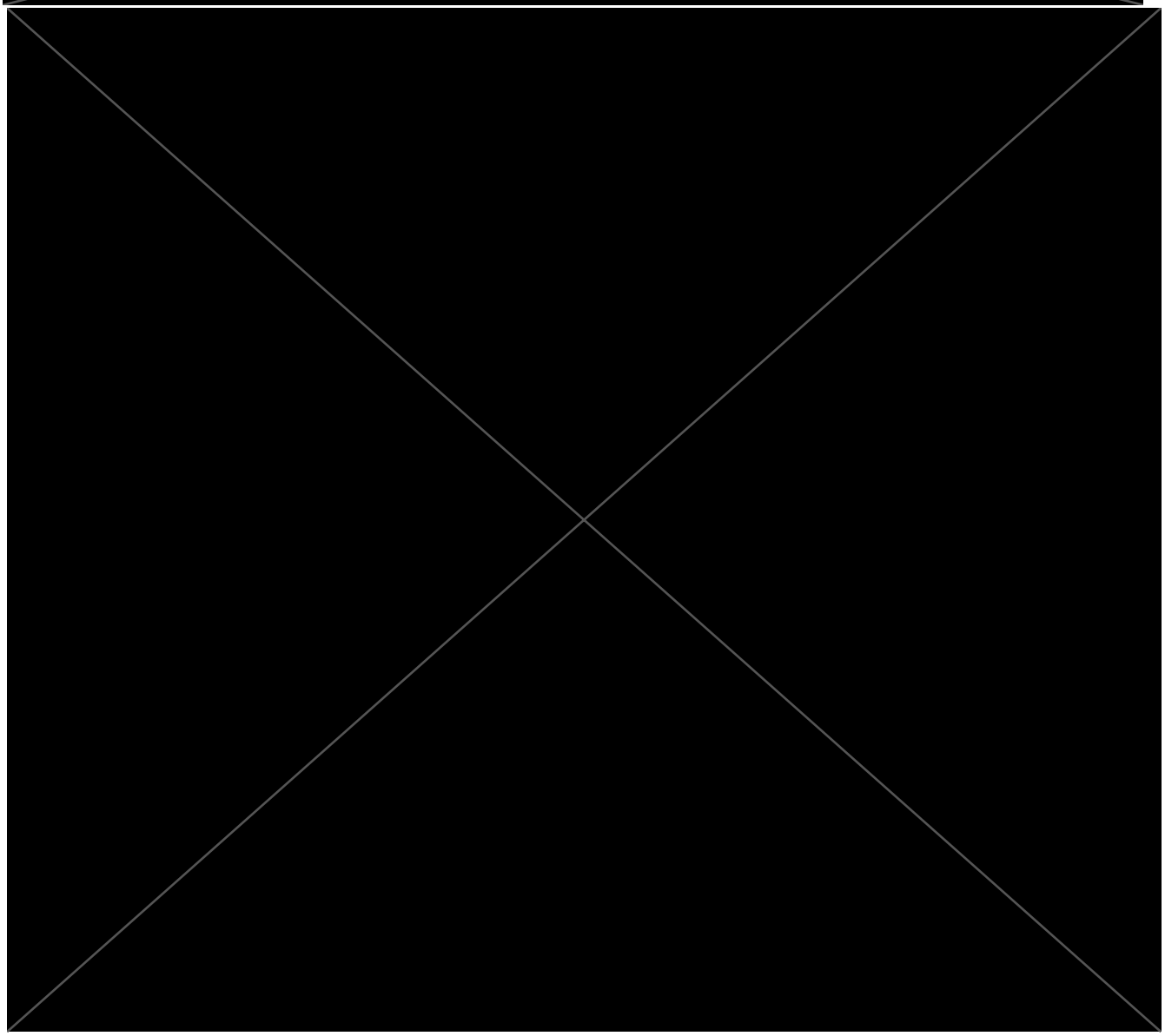
2.4.3. Overview of Clinical Safety

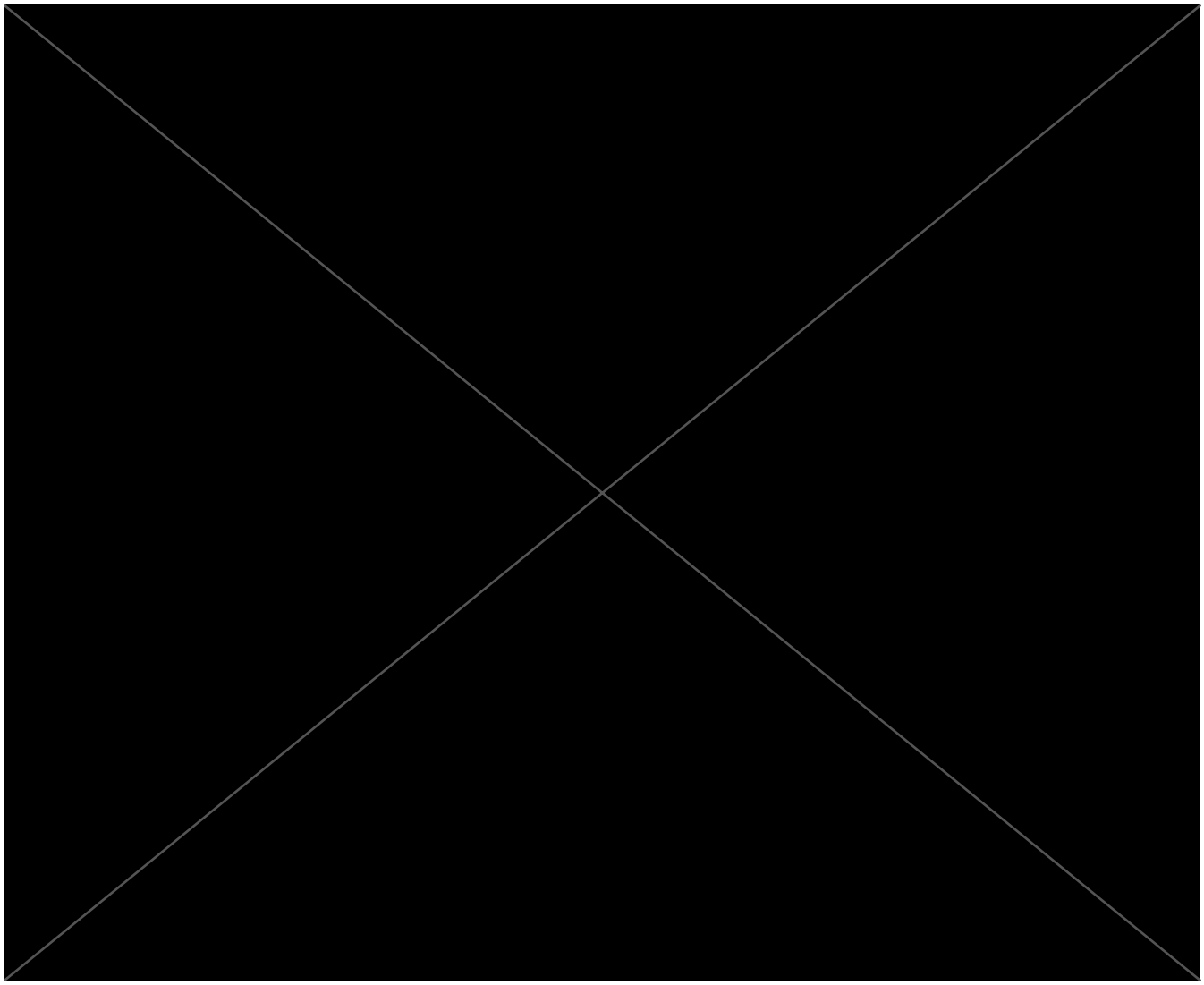
Clinical safety is based on, three dose cohorts of the SAD part and three dose cohorts of the MAD part.

In the SAD part of the study, ARD-101 was well-tolerated by subjects after single administration of the three assigned doses (40, 100, and 240 mg). No adverse effects (AEs) were reported for any subject in the three dosing cohorts.









2.4.4. Phase 2 Experience

As off February 2023, 25 subjects have been dosed in two separate Phase 2 trials at 200 mg, BID for 28 days. AEs possibly related were all grade 1 (mild) and consisted of nausea (n=2), reflux (n=2), dyspepsia (n=1), and constipation (n=1).

No SAEs or grade 2 and higher AEs were reported. All subjects finished the 28 day course.

For details, please refer to the Investigator Brochure.

2.4.5. Experience in Ongoing Trial to Date

[redacted]

2.4.6. Benefits and Risks Conclusions

According to our nonclinical studies, clinical data, and reported clinical studies o [redacted] RD-101 has demonstrated a well-tolerated safety profile and potential clinical benefit in the treatment of several metabolic disorders, including PWS. This safety profile supports the choice of the dose and dosing regimen to be used in the Phase 2 trial in PWS patients.

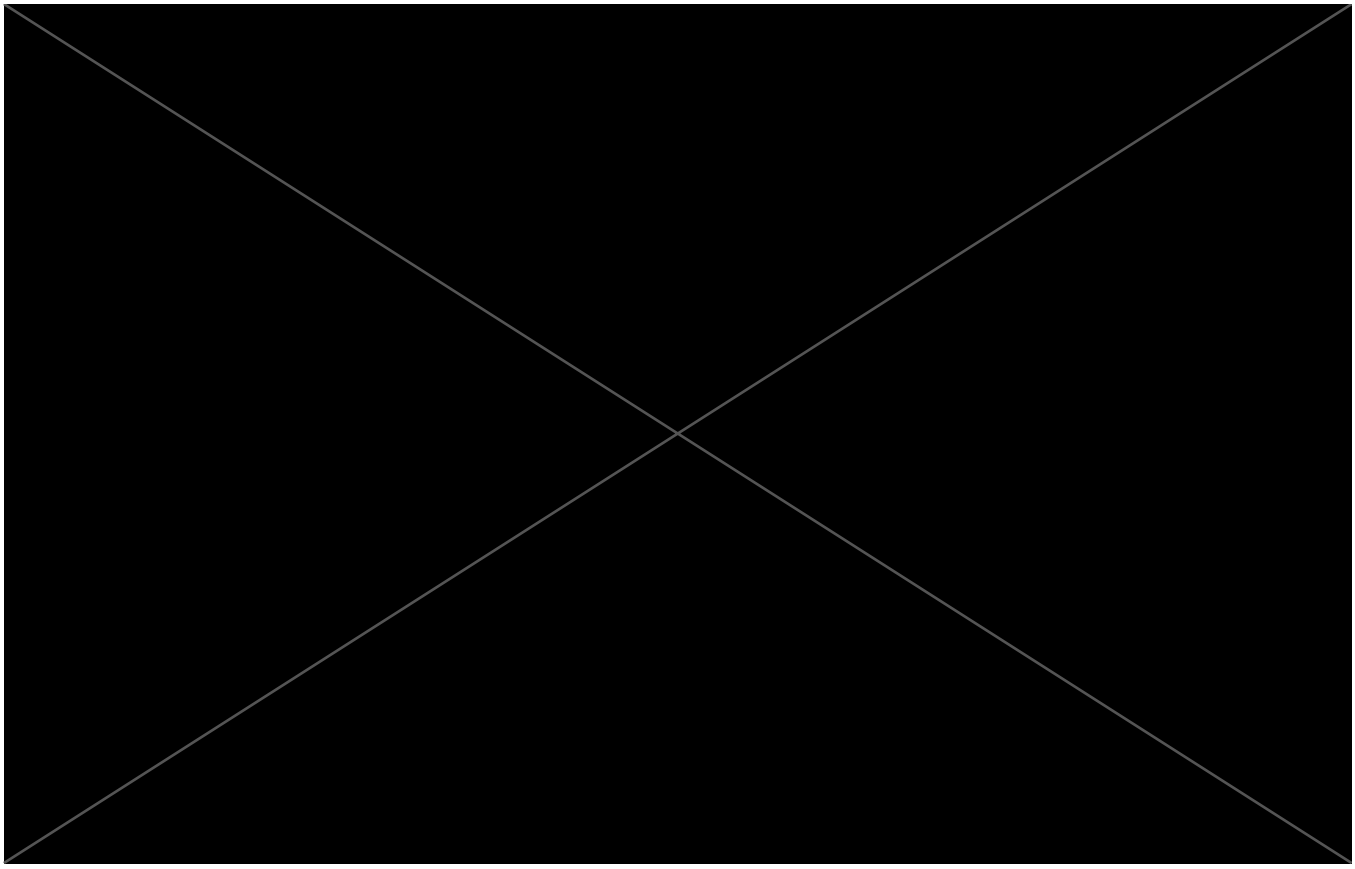
3. STUDY ENDPOINTS

3.1. Primary Endpoint:

- Safety of ARD-101 in subjects with PWS by assessment of the incidence of TEAE

3.2. Secondary Endpoints:

- Efficacy evaluation of hyperphagia in PWS
    - Quantitative evaluation of hyperphagia via the HQ-CT obtained prior to dosing and on days 15, and 28 as well as on follow-up. Score will range from 0 (no hyperphagia behaviors) to 36 (most severe hyperphagia behaviors)
- Effect on weight [time frame: baseline to day 28]



4. STUDY DESIGN

4.1. Overview

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/m^2.

This study has a planned enrollment of approximately 18 subjects and will be conducted in a two centers in the United States

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.

ARD-101 will be administered orally twice a day approximately 60 minutes **before** a meal (not shorter than 60 min after the last meal to avoid food-effects). Both daily doses must be at least 6h apart. (For example, 60 min before breakfast and dinner; or before lunch and dinner etc).

Under the current 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, or end of the study.

A total of approximately 18 subjects will be enrolled in the clinical study. This includes about 6 subjects receiving the escalated dose regimen under this amendment, in addition to the 12 subjects previously enrolled and dosed at 200 mg BID.

4.2. Justification for Dose

The dose s of 200, 400, 600, and 800 mg BID were chosen based on the available nonclinical studies and accumulated clinical data..

4.3. Study Duration

The duration of participation for each subject will be up to approximately 84 days (12 weeks).

- Screening Period: Up to 28 days (4 weeks)

- Treatment Period: 28 days on ARD-101 (Patients 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.)
- Follow-up Period: 14 days (2 weeks). The EOS Visit will occur within 14 days after receiving the dose of ARD-101

4.4. Study Completion

For the entire study, study completion is defined as the last visit of the last subject for any protocol-related activity (last subject, last visit). For individual subjects, study completion is defined as the time of the subject's last data collection.

4.5. Early Termination

If a subject withdraws prematurely after dosing, all data normally collected should be collected at the time of premature discontinuation. If deemed necessary by the Principal Investigator, the subject will be asked to return at the regularly scheduled EOS Visit.

5. STUDY POPULATION

The study population will consist of male and female subjects with PWS age 17-65.

5.1. Number of Subjects

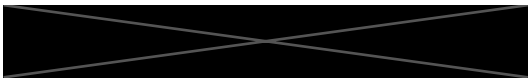
Up to 18 subjects will be enrolled in the clinical study.

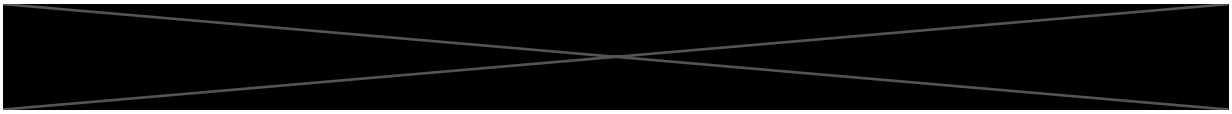
If any assessments for inclusion or exclusion criteria are out of permissible ranges during the Screening Period, repeat assessments may be allowed for those subjects at Principal Investigator's discretion.

5.2. Inclusion Criteria

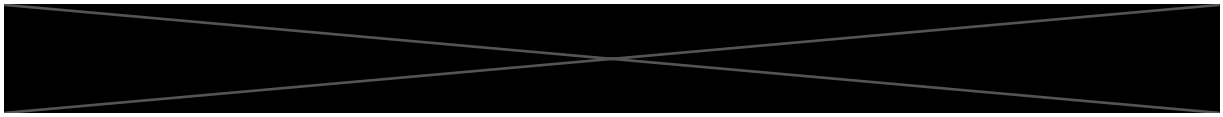
Subjects must meet all the following criteria to be eligible for participation in this study:

1. Male and female subjects, 17-65 years of age
2. Provide voluntary, written informed consent (parent(s) / legal guardian(s) of participant); provide voluntary, written assent (participants, as appropriate)
3. PWS due to chromosome 15 micro-deletion, maternal uniparental disomy, or imprinting defect, confirmed by fluorescent in situ hybridization, chromosomal microarray, and/or methylation studies
4. A BMI ≥ 18.5 kg/m²
5. [redacted]
6. [redacted]
7. Stable or well-controlled blood pressure (BP) and vital signs. [redacted]



8. 

9. Standard 12-lead ECG parameters after 10 minutes resting in supine position in the following ranges; 120 ms <PR <220 ms, QRS <120 ms, QTc ≤430 ms if male, ≤450 ms if female and normal ECG tracing unless the Investigator considers an ECG abnormality to be not clinically relevant.
10. Parent or guardian is able to communicate well with the investigator, to understand and comply with the requirements of the study, and be able to understand and sign the written informed consent. Assent is to be provided for the patient who cannot consent for himself or herself
11. Results of screening clinical laboratory tests [complete blood count (CBC) with differential and platelets and chemistry profile] and vital signs must be within normal range or, if outside of the normal range, must be accepted by the investigator and sponsor as not clinically significant
12. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months (and confirmed with a screening FSH level in the post-menopausal lab range), do not require contraception during the study. This may also apply to subjects with documented hypogonadism with and without estrogen replacement therapy as per investigator judgement. All other females of child-bearing potential must agree to use contraception as outlined in the protocol
13. Males with female partners of childbearing potential must agree to a double barrier method if they become sexually active during the study and for 90 days following the study.
14. 14. Patients previously treated on this trial may be re-enrolled based on investigator preference and if at least 3 months have passed since the last dose.
15. Patients must be on a stable dose of any allowed chronic concomitant medications while participating in the study, as described in protocol. This is defined as no changes in medication or dose for at least 30 days prior to Day 1



16. Men should refrain from sperm donation for the duration of the study and for 90 days after the last dose of study intervention

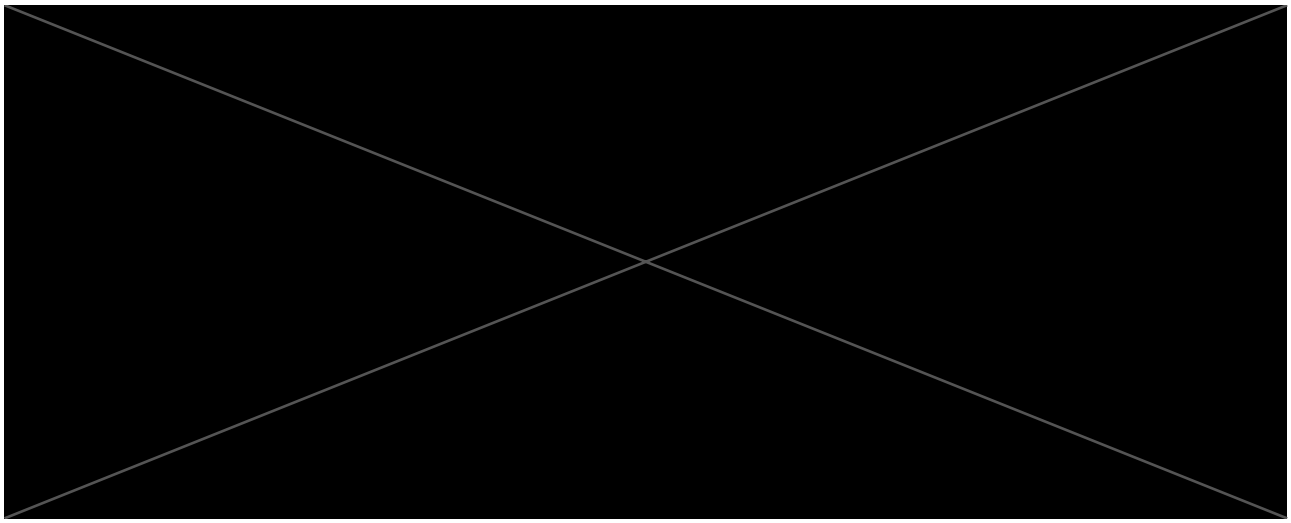
5.3. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from study participation:

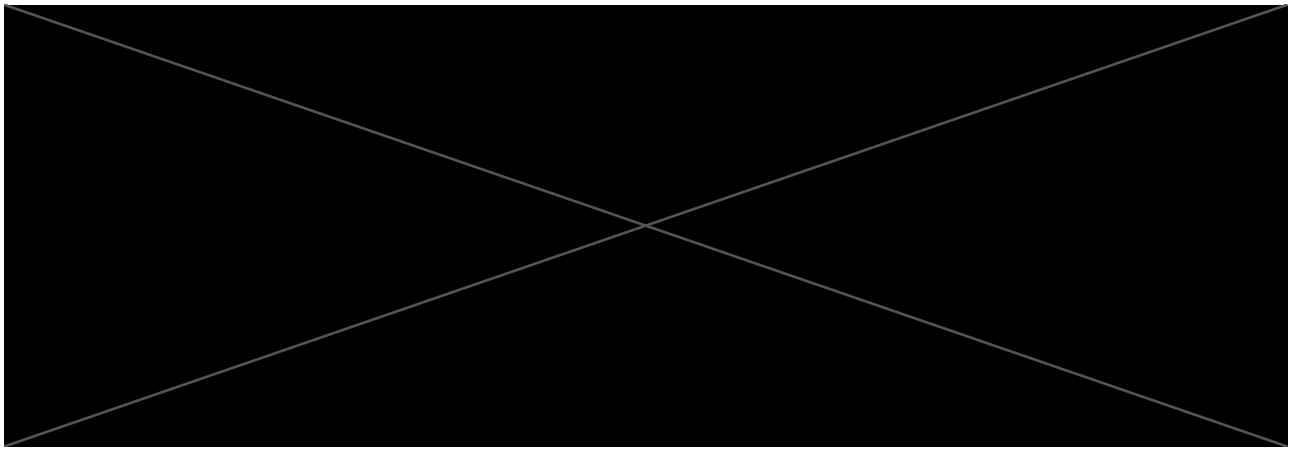
1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. [redacted]
8. [redacted]
9. [redacted]
10. Significant history of abuse of drugs within 1 year prior to enrollment or a positive DOA test at screening
11. History of alcohol abuse within 1 year prior to enrollment or currently drinks in excess of 21 units per week (3 servings or units/day)
12. Caffeine consumption exceeding 6 cups of caffeinated tea/coffee (or equivalent) per day
13. Participation in any clinical study with an investigational drug/device within 1 month prior to enrollment
14. [redacted]
15. [redacted]
16. [redacted]

17. History of significant drug hypersensitivity or anaphylaxis
18. Any condition that the investigator or primary physician believes may not be appropriate for participating the study

5.4. Restrictions



5.4.2. Lifestyle Considerations



6. INVESTIGATIONAL MEDICINAL PRODUCT

[redacted]

6.2. Identity of the Investigational Medicinal Products

ARD-101 drug product [redacted]
The ARD-101 and placebo drug product will be supplied as [redacted] The ARD-101 drug product [redacted] together with [redacted] s inactive ingredients. The inner content of the lacebo has the same weight as the inner content of ARD-101 drug product, but only contains [redacted] (no active ingredient).

6.3. Supply, Packaging, Labeling and Storage

Study drug will be supplied by Sponsor. The study medication will be packaged and labeled according to applicable local and regulatory requirements.

[redacted]

Further details will be provided in the Pharmacy Manual.

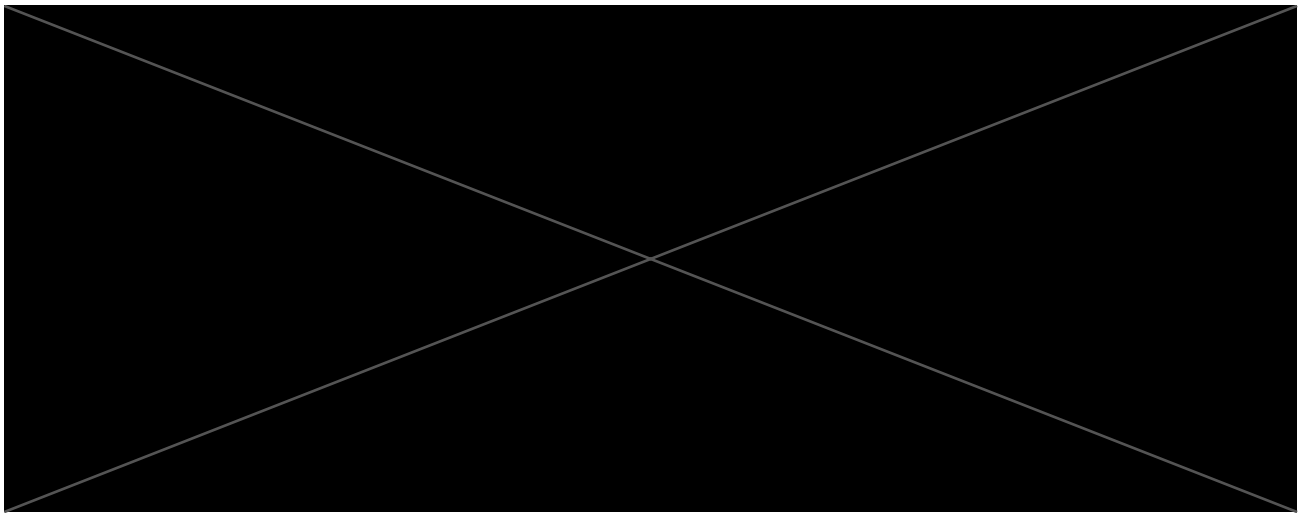
6.4. Drug Accountability, Dispensing and Destruction

The Principal Investigator or designee is responsible for maintaining accurate accountability records of the study drug throughout the clinical study. Products returned will be stored under the same conditions as products not yet dispensed.

All dispensing and accountability records will be available for Sponsor review. The Study Monitor will perform drug accountability at regular intervals.

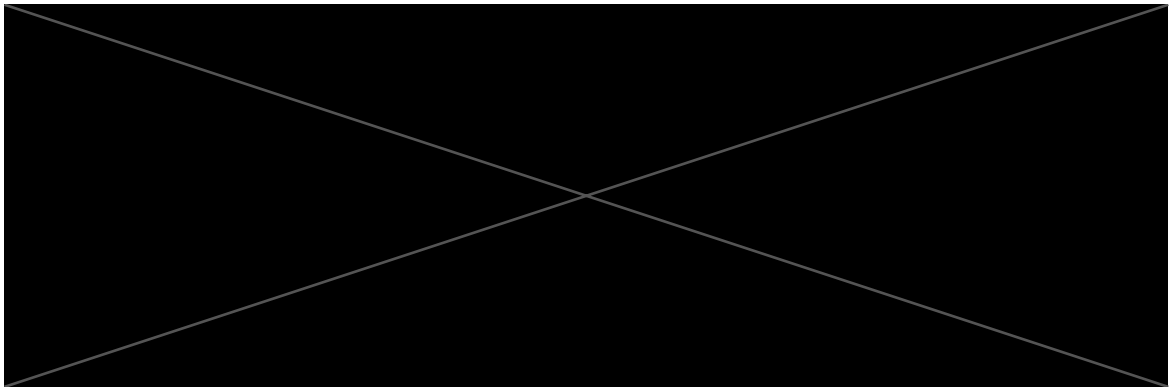
Study medication will be dispensed for each subject according to the protocol and Pharmacy Manual.

After receiving Sponsor approval in writing, all unused or partially used study medication will be returned to the Sponsor or designated third party or for preparing the study medication for destruction via incineration.



6.6. Stopping Rules

At any time during the study, the subject must discontinue study drug treatment, if one of the following events occur:



If any of the above stopping rules are met the following action(s) should be taken:

1. Stop dosing and convene a Safety Review Committee meeting

2. Review AE for evidence of relationship to treatment

3. May resume enrollment and continue the study if recommended by the Safety Review Committee.

6.7. Subject Identification

6.7.1. Screening Numbers

All screened subjects are assigned a unique screening number. The screening numbers are numbers that identify subjects from time of screening until time of enrollment.

6.7.2. Enrollment Numbers

Eligible subjects will be assigned an enrollment number. The enrollment number will include 6-digit site number and subject numbers starting with 101 as below.

- Subject 100-101

Once an enrollment number has been allocated to one subject, it may not be assigned to another subject.

6.8. Compliance

Dosing will be performed by trained, qualified personnel designated by the Principal Investigator.

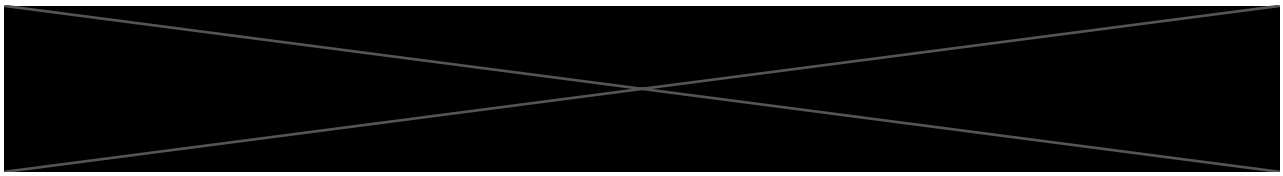
6.9. Special Precautions and Management of AEs

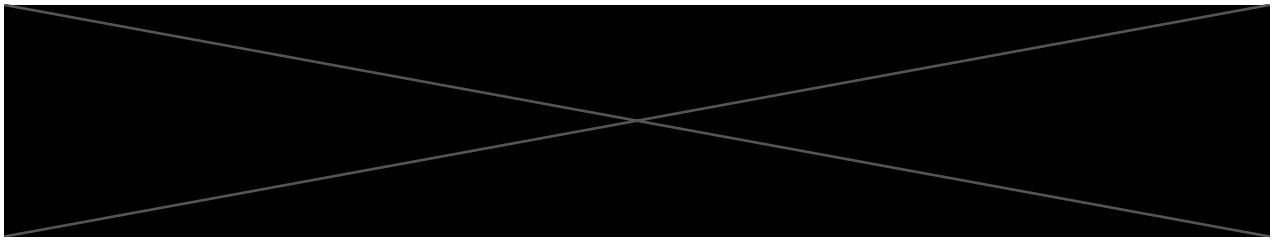
6.9.1. Eating disorders

ARD-101 may decrease appetite and subsequently change a subject's eating behavio [redacted]

Subjects who develop any eating disorders during study treatment should be permanently discontinued from study drug.

[redacted]





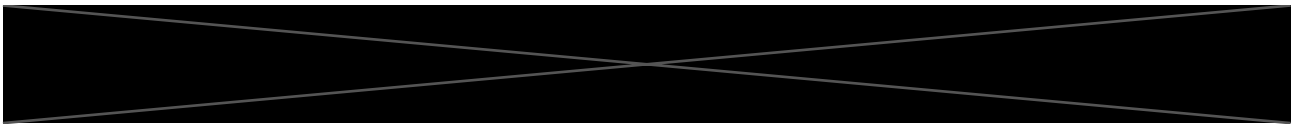
6.10. Concomitant Therapy

Any medicinal product, prescribed or OTC, including vitamins, natural, and herbal remedies, taken by a subject other than the study medication, is considered concomitant medication.

Any concomitant treatment will be given only if deemed strictly necessary by the Principal Investigator or designee. Use of concomitant medication will be recorded and reported. Particularly, as described in Section 2.3.2,   ransporters. Coadministration of these transporter inhibitors have the potential to alter the pharmacokinetics of ARD-101. Therefore, before placing a subject on a specific medication/therapy, it is the responsibility of the investigator to check on potential drug-drug interactions between that medication/therapy and ARD-101 based on the Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers), and Drug-Drug Interaction Database (https://www.fda.gov/drugs/drug-interactions-labeling/databases) of FDA.

6.10.1. Permitted Medications/Procedures

Subjects are permitted to use medications consistent with those permitted include the use of contraceptive medications and hydrocortisone cream. All concomitant medications are subject to approval by the principal investigator.



7. DISCONTINUATION

7.1. Subject Withdrawal and Replacement

Subject participation may be terminated prior to completing the study and the reason recorded as follows:

1. Adverse event
2. Protocol violation
3. Lost to follow-up
4. Subject withdrew consent at own request
5. Other

A genuine effort must be made to determine the reason(s) why a subject fails to return for the necessary visits or is discontinued from the study. If the subject is unreachable by telephone, a registered letter, at the minimum, should be sent to the subject requesting him/her to contact the clinic.

Withdrawn subjects may be replaced until the full cohort has completed the study.

8. STUDY ASSESSMENTS AND PROCEDURES

For timing of assessments, refer to the Scheduled Assessment

Please note: All screening assessments may be performed at day 1 (predose).

8.1. Eligibility Screening

All subjects must sign an informed consent form (ICF) prior to the conduct of any screening procedures. Screening assessments will occur within 28 days prior to the first dose of study medication. The subject's relevant medical history and demographic data will be obtained. Retesting of abnormal screening values that lead to exclusion are allowed during the Screening Period (to reassess eligibility). The last result obtained prior to the first dose of study medication will be used to determine eligibility.

8.2. Safety Variables

8.2.1. Adverse Events

Adverse event reporting will begin for each subject from the date the ICF is signed and will continue until the EOS Visit.

8.2.1.1. Definitions

8.2.1.1.1. Definition of Adverse Event

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.

Other untoward events occurring in the framework of a clinical study will be recorded as AEs, e.g. those occurring during treatment-free periods (including screening or post-treatment follow-up periods), in association with study-related procedures and assessments, or under placebo. For study medication, lack of efficacy may be an expected potential outcome and should not be reported as an AE unless the event is unusual in some way, e.g., greater in severity.

Concomitant illnesses, which existed prior to entry into the clinical study, will not be considered AEs unless they worsen during the Treatment Period. Pre-existing conditions will be recorded as part of the subject's medical history.

8.2.1.1.2. Definition of Serious Adverse Event

An 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.

A distinction should be drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but would not be considered an SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

8.2.1.2. Recording of Adverse Events

Adverse events should be collected and recorded for each subject from the date the ICF is signed until the end of their participation in the study, i.e., the subject has discontinued or completed the study.

Adverse events may be volunteered spontaneously by the subject, or discovered by study staff during physical examinations or by asking an open, non-leading question such as 'How have you been feeling since you were last asked?' All AEs and any required remedial action will be recorded. The nature of AE, date (and time, if known) of AE onset, date (and time, if known) of AE outcome to date, severity and action taken of the AE will be documented together with the Principal Investigator's assessment of the seriousness of the AE and causal relationship to study drug and/or study procedure.

All AEs should be recorded individually in the subject's own words (verbatim) unless, in the opinion of the Principal Investigator, the AEs constitute components of a recognized condition, disease or syndrome. In the latter case, the condition, disease or syndrome should be named rather than each individual symptom. The AEs will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September, 2007).

8.2.1.3. Assessment of Adverse Events

Each AE will be assessed by the Principal Investigator as per the categories discussed in the following sections.

8.2.1.3.1. Intensity

The Principal Investigator 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 (ER) visit or hospitalization.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted for that day. Any change in severity of signs and symptoms

over a number of days will be captured by recording a new AE, with the amended severity grade, and the date (and time, if known) of the change.

8.2.1.3.2. Causality

The Principal Investigator will assess the causality/relationship between the study medication and the AE. The Principal Investigator is responsible for assessing the relationship to study medication using clinical judgment and the following considerations:

- No: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, concomitant medication)
- Yes: There is reasonable possibility that the event may have been caused by the study medication.

8.2.1.4. Reporting of Serious Adverse Events

The Principal Investigator will review each SAE and evaluate the intensity and the causal relationship of the event to study drug. All SAEs will be recorded from signing of the ICF until the EOS Visit. Serious AEs occurring after the EOS Visit and coming to the attention of the Principal Investigator must be reported only if there is (in the opinion of the Principal Investigator) reasonable causal relationship with the study drug.

The Principal Investigator is responsible for providing notification to Sponsor of any SAE, whether deemed study medication-related or not, that a subject experiences during their participation in study within 24 h of becoming aware of the event.

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (e.g., hospital reports, consultant reports, autopsy reports), with the subject's personal identifiers removed.

Information on SUSARs will be collected and reported to the regulatory authority and the IEC as required per guidelines.

If the SUSAR is fatal or life-threatening, associated with the use of the study medication, and unexpected, the regulatory authority and the IEC will be notified per guidelines after being made aware of the case. Additional follow-up (cause of death, autopsy report, hospital report) information should be reported per guidelines. SUSARs which are not fatal and not life-threatening are to be reported per guidelines.

The Sponsor will notify the Investigators of relevant information about SUSARs that could adversely affect the safety of subjects in a timely fashion. Follow-up information may be submitted if necessary. The Sponsor will also provide annual safety reports for submission to the regulatory authority and the IEC responsible for the clinical study. These updates will include information on SUSARs and other relevant safety findings.

8.2.1.5. Follow-up of Adverse Events

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the event has resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Principal Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed or until the subject is lost to follow-up.

8.2.1.6. Pregnancy

The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical study.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

Each pregnancy must be reported by the Principal Investigator to the Sponsor within **2 days** after becoming aware of the pregnancy. The Principal Investigator must follow-up and document the course and the outcome of all pregnancies even if the subject was withdrawn from the clinical study or if the clinical study has finished.

All outcomes of pregnancy must be reported by the Principal Investigator to the Sponsor on the pregnancy outcome report form within **2 days** after he/she has gained knowledge of the normal delivery or elective abortion.

Any SAE that occurs during pregnancy must be recorded on the SAE Report Form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 h in accordance with the procedure for reporting SAEs.

8.2.2. Clinical Laboratory Assessments

Samples for clinical laboratory assessments will be collected at the time points detailed in the Scheduled Assessment. Samples will be collected in appropriate tubes and handled according to standard procedures of the applicable laboratory.

Any value outside the normal range will be flagged for the attention of the Principal Investigator or designee at the site. The Principal Investigator or designee will indicate whether the value is of clinical significance. Additional testing during the study may be done if medically indicated. If a clinically significant abnormality is found in the samples taken after dosing, during the study, and/or at the EOS Visit, it should be recorded as an AE and the subject will be followed until the test(s) has (have) normalized or stabilized, at the discretion of the Principal Investigator.

8.2.3. Vital Signs

Vital signs will be assessed at the time points detailed in the Scheduled Assessment. The following vital signs will be measured:

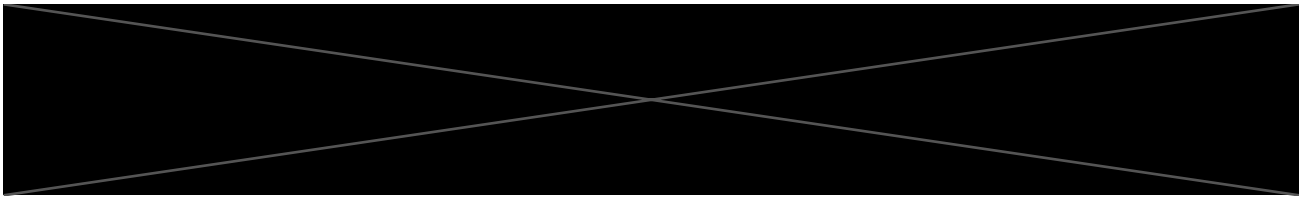
- Blood pressure (systolic and diastolic [mmHg])
- Pulse (bpm)
- Body temperature (°C)
- Respiratory rate (breaths per minute)

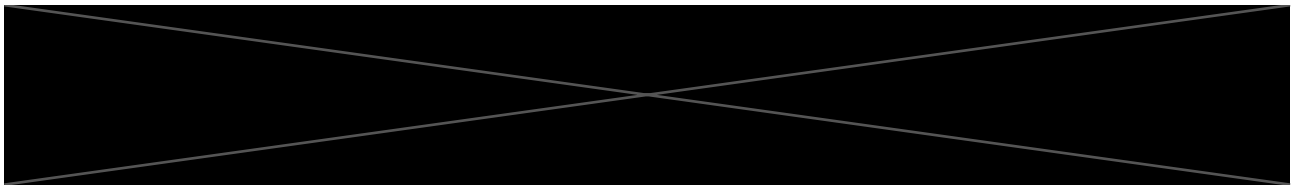
8.2.4. Standard 12-lead Electrocardiograms

Standard safety 12-lead ECGs will be performed at the time points detailed in the Scheduled Assessment.

The ECG will include all 12 standard leads.

All ECGs must be evaluated by a qualified physician for the presence of abnormalities. If a clinically significant abnormality is found, it should be recorded as an AE and the subject will be followed until the test(s) has (have) normalized or stabilized, at the discretion of the Principal Investigator.





8.2.7. Physical Examinations

Physical examinations will be performed at the time points detailed in the Scheduled Assessment.

Full physical examination:

An assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic and psychiatric systems).

Brief physical examination:

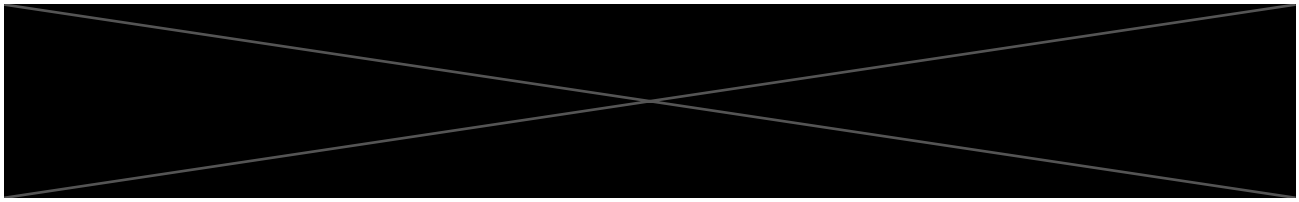
An assessment of the general appearance, skin, cardiovascular system, respiratory system and abdomen.

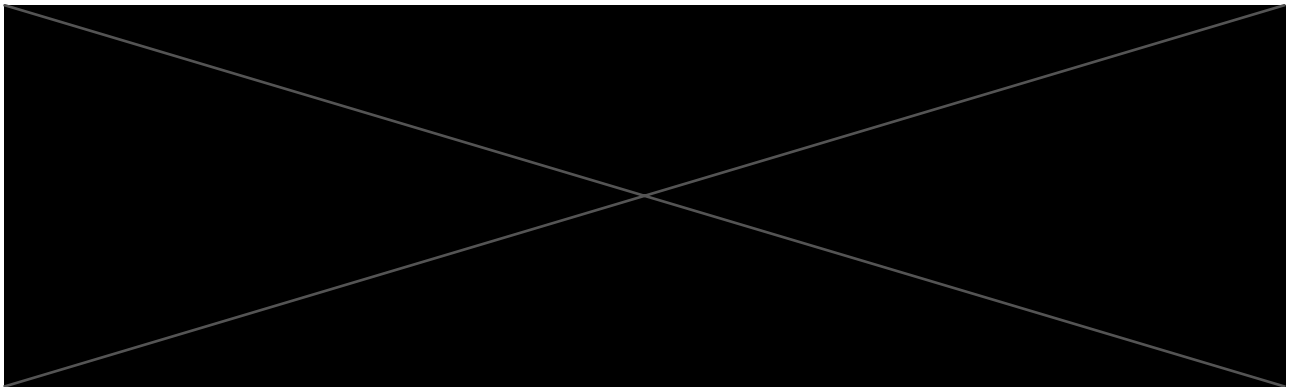
The brief physical examination may be extended to a full physical examination if considered necessary by the Principal Investigator. Other evaluations may be performed as deemed necessary by the Principal Investigator.

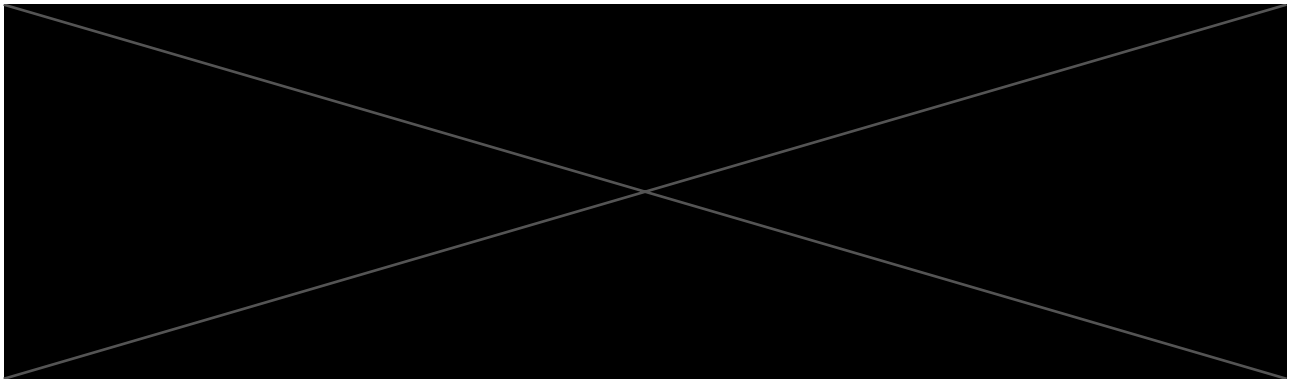
8.3. Questionnaires

8.3.1. HQ-CT questionnaire

The Hyperphagia Questionnaire (HQ) is a well-established, caregiver-reported questionnaire that focuses on food-seeking behaviors common among individuals with Prader-Willi syndrome (PWS). Qualitative and quantitative evidence provide support for use of the 9-item HQ-CT total score for the assessment of food-seeking behaviors in PWS clinical trials. The HQ-CT is a validated questionnaire to measure hyperphagia, the secondary outcome being change in score from baseline. The range of scores is 0-36, with scores above 13 typically considered to be moderate to severe hyperphagia. While the questionnaire typically refers to a child, it is not restricted for use in children. (Example in Appendix 12.1)







9. STATISTICAL CONSIDERATIONS

9.1. Study Population

9.1.1. Protocol Deviations

Important protocol deviations will be listed by subject.

9.2. General Considerations

Continuous data per treatment arm will be summarized using descriptive statistics (number, mean, standard deviation [SD], minimum, median and maximum). Categorical data will be summarized using frequency tables (number and percentage).

9.3. Subject Disposition

Subjects excluded from the safety analysis sets will be listed including the reason for exclusion. Subject disposition will be summarized and will include the following information: Number of subjects dosed, number and percentage of subjects completing the study and the number and percentage of subjects who were withdrawn (including reasons for withdrawal). Disposition data will be presented based on all.

Subject discontinuations will be listed including the date of study exit, duration of treatment and reason for discontinuation. A listing of informed consent response will also be presented.

9.4. Demographic and Anthropometric Information and Baseline Characteristics

Demographic and anthropometric variables (age, sex, ethnicity, race, height, body weight and BMI) will be listed by subject. Demographic characteristics (age, sex, ethnicity and race) and anthropometric characteristics (height, body weight, and BMI) will be summarized for all subjects in the safety analysis set. The denominator for percentages will be the number of subjects in the safety analysis set for each treatment or for all subjects as applicable.

Medical history data will be listed by subject including visit, description of the disease/procedure, MedDRA system organ class (SOC), MedDRA preferred term (PT), start date, and stop date (or ongoing if applicable).

9.5. 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 listed by subject and will include the following information: reported name, PT, the route of administration, dose, frequency, start date/time, duration and indication.

Prior and concomitant medication will be coded according to the World Health Organization Drug Dictionary (WHO-DD) latest version.

Drug administration dates and times will be listed for each subject.

9.6. Exposure

A listing of drug administration will be created and will include the date and time of administration.

9.7. Safety Analyses

Where applicable, pre-dose measurements on Day 1 are considered baseline values for safety variables.

9.7.1. Adverse Events

All AEs will be listed and summarized per treatment arm. The number and percent of subjects experiencing an event will be tabulated for each SOC and PT. The AEs will also be tabulated according to intensity and causality. 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. For purposes of data analysis, the end of the TEAE period will be the last time point when a subject was evaluated for AEs.

The AEs (TEAEs) will be tabulated according to intensity and causality, as applicable.

Non-TEAEs will be listed, as applicable.

Serious AEs will be listed separately.

9.7.2. Clinical Laboratory Tests

Individual data listings of laboratory results will be presented for each subject. Flags will be attached to values outside of the laboratory's reference limits along with the Principal Investigator's assessment or designee. Clinically significant laboratory test abnormalities that were considered AEs by the Principal Investigator will be presented in the AE listings.

Clinical laboratory tests (observed values) will be summarized descriptively in tabular format. Shift tables will be presented for select laboratory parameters.

9.7.3. Vital Signs

Individual data listings of vital signs (observed and change from baseline) will be presented for each subject. Individual clinically significant vital signs findings that were considered AEs by the Principal Investigator will be presented in the AE listings.

Observed values as well as change from baseline data will be summarized descriptively in tabular format.

9.7.4. Standard 12-lead Electrocardiogram

Standard 12-lead ECG data (observed and change from baseline) will be listed for each subject and time point. Observed values will be summarized descriptively in tabular format. Change from baseline will be summarized descriptively for QTc data. A categorical QTc analysis will also be performed.

9.7.5. Physical Examination

Abnormal physical examination findings will be listed.

9.8. Exploratory analysis

Exploratory analysis may be presented separately from the main clinical study report (CSR). Further details on exploratory analyses will be provided in the SAP.

10. ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

10.1. Data Quality Assurance

The Sponsor or designee will conduct a study initiation visit to verify the qualifications of the Principal Investigator, inspect the facilities and inform the Principal Investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The Principal Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Principal Investigator will make all appropriate safety assessments on an ongoing basis. The Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to Good Clinical Practice (GCP) and SOPs for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Principal Investigator.

10.2. Data Collection and Access to Source Data/Documents

The Principal Investigator will ensure the accuracy, completeness and timeliness of the data reported to the Sponsor. The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data at each scheduled monitoring visit. Data clarification requests will be provided to the study team by means of electronic or manual queries.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors and the IEC to have direct access to all electronic records pertaining to the study.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

10.3. Archiving Study Documents

All source documents generated in connection with the study will be retained in the limited access file storage area, respecting the privacy and confidentiality of all records that could identify the

subjects. Direct access is allowed only for authorized people for monitoring and auditing purposes. Source documents will be handled, stored and archived according to in-house procedures.

The Investigator's Site File will be archived by the CRO for at least 2 years after completion of the study or longer if agreed upon by the Sponsor.

10.4. Good Clinical Practice

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the Principal Investigator abide by the principles of the ICH guidelines on GCP. The clinical study also will be carried out in keeping with national and local legal requirements (in accordance with United States investigational new drug [IND] regulations [21 CFR 56]).

10.5. Informed Consent

Eligible subjects may only be included in the study after providing IRB/IEC approved informed consent.

Informed consent must be obtained from the subject before conducting any study-specific procedure.

As part of the informed consent procedure, the Principal Investigator or designee must explain orally and in writing the nature, duration and purpose of the study and the action of the drug in such a manner that the subject is aware of the potential risks, inconveniences or AEs that may occur. The subject should be informed that he/she is free to withdraw from the study at any time. Subjects will receive all information that is required by federal regulations and ICH guidelines. The ICF must be signed and dated; one copy will be handed to the subject, and the Principal Investigator will retain a copy as part of the clinical study records. The Principal Investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must be documented in the subject source documents.

The Sponsor will review the Investigator-proposed ICF to ensure it complies with the ICH GCP guideline (including the ethical principles that have their origins in the Declaration of Helsinki) and regulatory requirements and is considered appropriate for this study. The Principal Investigator or designee will provide the Sponsor with a copy of the IRB/IEC approved ICF prior to the start of the study.

If a protocol amendment is required, then the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the responsible IRB/IEC and signed by all subjects subsequently enrolled in the clinical study, as well as those currently enrolled in the clinical study as applicable.

10.6. Insurance and Compensation for Injury

The Sponsor has covered this clinical study by means of an insurance of the clinical study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's Site File.

10.7. Protocol Approval and Amendment(s)

Before the start of the clinical study, the clinical study protocol and other relevant documents will be approved by the IRB/IEC, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the clinical study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, which must be released by the responsible staff and receive IRB/IEC approval prior to implementation (as appropriate).

Administrative changes may be made without the need for a formal amendment but will also be mentioned in the integrated CSR. All amendments will be distributed to all study protocol recipients, with appropriate instructions.

10.8. Confidentiality Data Protection

All clinical study findings and documents will be regarded as confidential. Study documents (protocols, IBs and other material) will be stored appropriately to ensure their confidentiality. The Principal Investigator and members of his/her research team (including the IRB/IEC) must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study or to comply with regulatory requirements.

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number, initial or birth date, not by name. Documents that identify the subject (e.g., the signed ICF) must be maintained in confidence by the Principal Investigator.

10.9. Publication Policy

By signing the clinical study protocol, the Principal Investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the regulatory authorities will be notified of the Principal Investigator's name, address, qualifications and extent of involvement.

A Principal Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance.

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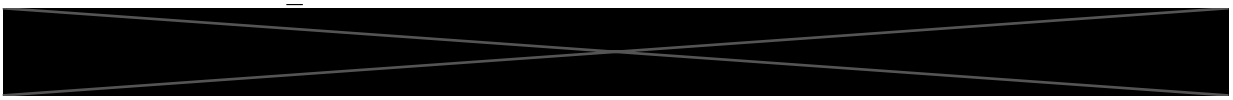
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12. APPENDIX

12.1. Hyperphagia Questionnaire HQ-CT

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

Hyperphagia Questionnaire for Clinical Trials (HQ-CT)

Evaluating food-related problem behaviors is an important part of this study. Please take your time to think carefully and in some detail about the last 2 weeks of hyperphagic (intense, incessant sensation of hunger) and food-related behaviors shown by the person with PWS in your care. Be sure to consider the full 2-week period including nights and weekends, seeking input from other caregivers as necessary. Please be as accurate and as honest as you can, without minimizing or over-inflating the person's behaviors

Instructions:
The following items refer to the person in your care and assessment of his/her food-related behavior during the past 2 weeks.

(1) During the past 2 weeks, how upset did the person generally become when denied a desired food?
- ☐ Not at all upset
- ☐ A little upset
- ☐ Moderately upset
- ☐ Very upset
- ☐ Extremely upset

(2) During the past 2 weeks, how often did the person try to bargain or manipulate to get more food at meals?
- ☐ Never
- ☐ Up to 2 times a week
- ☐ 3 to 6 times a week
- ☐ Every day
- ☐ Several times a day

(3) During the past 2 weeks, how often did the person forage through trash for food?
- ☐ Never
- ☐ 1 time
- ☐ 2 times
- ☐ 3 times
- ☐ 4 or more times

(4) During the past 2 weeks, how often did the person get up at night to food seek?
- ☐ Never
- ☐ 1 time
- ☐ 2 times
- ☐ 3 times
- ☐ 4 or more times

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

(5) During the past 2 weeks, how persistent was the person in asking or looking for food after being told "no" or "no more"?

☐ Not at all persistent
☐ A little persistent
☐ Moderately persistent
☐ Very persistent
☐ Extremely persistent

(6) During the past 2 weeks, outside of normal meal times, how much time did the person generally spend asking or talking about food?

☐ Less than 5 minutes a day
☐ 5 to 15 minutes a day
☐ 15 to 30 minutes a day
☐ 30 minutes to 1 hour a day
☐ More than 1 hour a day

(7) During the past 2 weeks, how often did the person try to sneak or steal food (that you are aware of)?

☐ Never
☐ 1 time
☐ 2 times
☐ 3 times
☐ 4 or more times

(8) During the past 2 weeks, when others tried to stop the person from asking about food, how distressed did he or she generally appear?

☐ Not at all distressed
☐ A little distressed
☐ Moderately distressed
☐ Very distressed
☐ Extremely distressed

(9) During the past 2 weeks, how often did food-related behavior interfere with the person's normal daily activities, such as self-care, recreation, school, or work?

☐ Never
☐ Up to 2 times a week
☐ 3 to 6 times a week
☐ Every day
☐ Several times a day

Contact information and permission to use: Foundation for Prader-Willi Research (www.fpwr.org)

