HEALEY ALS Platform Trial - Regimen G for DNL343

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Refer to NCT04297683 for the HEALEY ALS Platform

Trial Master Protocol document

REGIMEN-SPECIFIC APPENDIX G

FOR DNL343

Regimen-Specific Appendix Date: 12/18/2023

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TABLE OF CONTENTS

Page

SIGNATURE PAGE 5
LIST OF ABBREVIATIONS 6
REGIMEN-SPECIFIC APPENDIX SUMMARY 8
SCHEDULE OF ACTIVITIES – Placebo-controlled Treatment period 10
1. INTRODUCTION 17
1.1 DNL343 Background Information 17
1.2 DNL343 Therapeutic Rationale 20
2. OBJECTIVES 21
2.1 Study Objectives and Endpoints 21
3. Regimen-specific Appendix DESIGN 23
3.1 Scientific Rationale for Regimen-Specific Appendix Design 23
3.2 End of Participation Definition 23
Placebo-Controlled Period 23
Active Treatment Extension Period 23
3.3 End of Regimen Definition 24
4. Regimen-Specific Appendix Enrollment 25
4.1 Number of Study Participants 25
4.2 Inclusion and Exclusion Criteria 25
4.2.1 Regimen-Specific Appendix Inclusion Criteria 25
4.2.2 Regimen-Specific Appendix Exclusion Criteria 25
4.3 Treatment Assignment Procedures 25
5. INVESTIGATIONAL PRODUCT 26
5.1 Investigational Product Manufacturer 26
5.2 Labeling, Packaging, and Resupply 26
5.3 Acquisition, Storage, and Preparation 26
5.4 Study Medication/Intervention, Administration, Escalation, and Duration 27
5.5 Justification for Dosage 27
5.6 Dosage Changes 29
5.6.1 Dose Modification for an Individual Participant 29
5.7 Participant Compliance 30
5.8 Overdose or Medication Administration Error 30
5.9 Prohibited Medications 30

TABLE OF CONTENTS (CONT'D)

Page

5.10 DNL343 Known Potential Risks and Benefits 31
5.10.1 Known Potential Benefits and Risks 31
5.10.2 Contraceptive Requirements for Participants in Regimen G 31
6. Regimen Schedule 34
6.1 Baseline Visit 35
6.2 Week 2 Telephone Visit 36
6.3 Week 4 and 8 Visits 36
6.4 Week 12 Telephone Visit 37
6.5 Week 16 Visit 37
6.6 Week 20 Telephone Visit 37
6.7 Week 24 Visit or Early Termination Visit 37
6.8 Follow-Up Safety Call 38
6.9 Process for Early Terminations 39
6.10 Active Treatment Extension 39
6.10.1 Week 2 ATE Telephone Visit 40
6.10.2 Week 4 ATE Visit 40
6.10.3 Week 8 ATE Visit 41
6.10.4 Week 12 ATE Telephone Visit 41
6.10.5 Week 16 ATE Visit 42
6.10.6 Week 20 ATE Telephone Visit 42
6.10.7 Week 24 ATE Telephone Visit 42
6.10.8 Week 28 ATE Visit 43
6.10.9 Week 40 ATE Visit 43
6.10.10 Week 52 ATE Visit 44
6.10.11 Visits after Week 52 45
6.10.12 Follow-Up Safety Call 45
6.10.13 Process for Early Terminations 45
7. OUTCOME MEASURES AND ASSESSMENTS 47
7.1 Amyotrophic Lateral Sclerosis Assessment Questionnaire-40 (ALSAQ-40) 47
7.2 Center for Neurologic Study Bulbar Function Scale (CNS-BFS) 47
7.3 Rasch-built Overall Amyotrophic Lateral Sclerosis Disability Scale (ROADS) 47
7.4 The Patient Global Impression of Change (PGI-C) 47
7.5 The Patient Global Impression of Severity (PGI-S) 48

TABLE OF CONTENTS (CONT'D)

Page

7.6 Clinician Global Impression of Change (CGI-C) 48
7.7 Vital Status Determination 48
8. BIOFLUID COLLECTION 49
9. DNL343-SPECIFIC STATISTICAL CONSIDERATIONS 50
9.1 Deviations from the Default Master Protocol Trial Design 50
9.2 Regimen Specific Operating Characteristics 50
9.3 Sharing of Controls from other Regimens 50
Appendix I: The ALSAQ-40 51
Appendix II: The Center for Neurologic Study Bulbar Function Scale (CNS-BFS) 60
Appendix III: Contraceptive Guidance for Female Participants of Childbearing Potential 63
Contraceptive Guidance for Male Participants with Female Partners of Childbearing Potential 65
Appendix IV: Concomitant Medication Restrictions 65
REFERENCES 68

List of Tables

Table 1: Summary of Preliminary PK Parameters in Participants with ALS 18
Table 2: Study Drug Administered 27
Table 3: Predicted Safety Margins for Proposed DNL343 Clinical Doses of 200 mg Once Daily in Relation to NOAEL and LOAEL Exposures in the Good Laboratory Practice Toxicity Studies 29
Table 4: Strong CYP3A4/5 Inducers with the Drug Half-Life and Washout Periods 65
Table 5: Sensitive CYP3A4/5 Substrates 66
Table 6: Substrates of BCRP or OAT3 Transporters 67

List of Figures

Figure 1: DNL343 Regimen-Specific Appendix Study Schema 23

SIGNATURE PAGE

I have read the attached Regimen-Specific Appendix (RSA) entitled, "REGIMEN-SPECIFIC APPENDIX G FOR DNL343" dated December 18, 2023 (Version 2.0) and agree to abide by all described RSA procedures. I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice, applicable FDA regulations and guidelines identified in 21 CFR Parts 11, 50, 54, and 312, central Institutional Review Board (IRB) guidelines and policies, and the Health Insurance Portability and Accountability Act (HIPAA).

By signing the RSA, I agree to keep all information provided in strict confidence and to request the same from my staff. Study documents will be stored appropriately to ensure their confidentiality. I will not disclose such information to others without authorization, except to the extent necessary to conduct the study.

Site Name: _____

Site Investigator: _____

Signed: _____ Date: _____

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACTH	adrenocorticotropic hormone
AE	adverse event
AESI	adverse event of special interest
ALS	amyotrophic lateral sclerosis
ALSAQ-40	Amyotrophic Lateral Sclerosis Assessment Questionnaire-40
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
ATF4/*ATF4*	activating transcription factor 4
ATE	active treatment extension
AUC_{∞}	area under the concentration-time curve from time zero to infinity
AUC_{24}	area under the concentration-time curve from time zero to 24 hours
BCRP	breast cancer resistance protein
CAFS	Combined Assessment of Function and Survival
CGI-C	Clinician Global Impression of Change
CHAC1	ChaC glutathione–specific gamma-glutamylcyclotransferase 1
C_{max}	maximum concentration
CNS	central nervous system
CNS-BFS	Center for Neurologic Study Bulbar Function Scale
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
EC_{75}	concentration producing 75% of maximum effect
EC_{90}	concentration producing 90% of maximum effect
ECG	electrocardiogram
eCRF	electronic case report form
eIF2B	eukaryotic translation initiation factor 2B
ET	early termination
fT4	free thyroxine
G-tube	gastrostomy tube
GLP	Good Laboratory Practice
IB	Investigator's Brochure
ISR	integrated stress response
J-tube	gastrostomy tube
LOAEL	lowest-observed-adverse-effect level
LPLV	last participant, last visit
MOP	Manual of Procedures
Nf-L	neurofilament light chain
NOAEL	no-observed-adverse-effect level
OAT	organic anion transporter

Abbreviation	Definition
OTC	over-the-counter
PAV	permanent assisted ventilation
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
p-eIF2α	phosphorylated eukaryotic translation initiation factor 2a
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PRO	patient reported outcome
QD	once daily
ROADS	Rasch-built Overall Amyotrophic Lateral Sclerosis Disability Scale
RSA	Regimen-Specific Appendix
SAE	serious adverse event
SOA	Schedule of Activities
SVC	slow vital capacity
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
WOCBP	women of childbearing potential

REGIMEN-SPECIFIC APPENDIX SUMMARY

Regimen-Specific Appendix G

For DNL343

Rationale and Regimen-Specific Appendix Design

DNL343 is a central nervous system (CNS)–penetrant eukaryotic translation initiation factor 2B (eIF2B) small molecule activator that is being developed by Denali Therapeutics Inc. (Denali) as a potential treatment for amyotrophic lateral sclerosis (ALS). The effect of DNL343 treatment is the inhibition of the integrated stress response (ISR) pathway. Inhibition of the ISR is a novel potential therapeutic opportunity for treatment of ALS.

Regimen G of the HEALEY ALS Platform Trial will evaluate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of DNL343 200 mg once daily (QD) to participants with ALS. The principal aim of Regimen G is to investigate the efficacy of DNL343 in slowing clinical progression of disease as compared to placebo; and the secondary aim is to investigate the safety and tolerability of DNL343. The study will also explore the PK and PD of DNL343 to determine whether DNL343 affects biomarkers related to ISR, neurodegeneration, and ALS pathophysiology at exposures predicted to provide clinical efficacy. Following completion of the 24-week placebo-controlled treatment period, all participants in Regimen G will enter an active treatment extension (ATE) where all participants will receive DNL343 200 mg QD for up to an additional 78 weeks.

Allocation to Treatment Regimens

Participants must first be screened under the Master Protocol and before they are randomly assigned to a regimen.

Assignment to the regimen will stop if pre-defined criteria for futility for the regimen are met or after the target number of randomized participants has been reached.

Number of Planned Participants and Treatment Groups

The number of planned participants for Regimen G is approximately 240.

There are two treatment groups for Regimen G: Active and Placebo. Participants will be randomized in a 3:1 ratio to active treatment or placebo (i.e., approximately 180 active:60 placebo).

Planned Number of Sites

Research participants will be enrolled from up to 80 centers in the United States (US).

Treatment Duration

The planned duration of the placebo-controlled treatment period of the study is 24 weeks. The duration of the ATE period is planned for a minimum of 52 weeks (i.e., 76 weeks total treatment duration). The ATE will continue until all active participants have completed a minimum of 52 weeks of the ATE; no participant will exceed 78 weeks of ATE (i.e., 102 weeks total from Baseline visit).

Follow-up Duration

At the conclusion of the 24-week placebo-controlled treatment period, all participants will continue in the ATE period and receive DNL343. Once a participant completes the final visit in the ATE and discontinues study drug, a 28-day follow-up safety phone call will be scheduled. Any participant who stops study drug early will be encouraged to remain in the study and follow the study protocol under the intent-to-treat principle. If the participant discontinues study medication and decides not to continue follow-up under the intent-to-treat principle, an Early Termination Visit and Follow-Up Safety Phone Call should be completed.

Total Planned Trial Duration

Including the placebo-controlled treatment and the ATE periods, the total planned amount of time for a participant in Regimen G is a minimum of approximately 86 weeks and a maximum of approximately 112 weeks. This duration assumes a 6-week screening window, 24-week placebo-controlled treatment period, 52- to 78-week ATE period, and 4-week safety follow-up period.

SCHEDULE OF ACTIVITIES – PLACEBO-CONTROLLED TREATMENT PERIOD

As per the Schedule of Activities (SOA) below, visits must occur every 4 weeks and will be clinic-, phone-, or telemedicine based, as applicable. There is a maximum 24-week duration of placebo-controlled treatment for a regimen.

Activity	Master Protocol or Regimen-Specific	Master Protocol Screening [1]	Regimen Specific Screening [1]	Baseline [1]	Week 2	Week 4 [12]	Week 8 [12]	Week 12	Week 16 [12]	Week 20	Week 24 or ET Visit [19]	Follow-Up Safety Call [10]
		Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone
		–42 to –1 Days [13]	–41 to 0 Day [13]	Day 0	Day 14 ± 3	Day 28 ± 7	Day 56 ± 7	Day 84 ± 3	Day 112 ± 7	Day 140 ± 3	Day 168 ± 7	28 days after last dose ± 3 days
Written Informed Consent [2]	Master	X	X									
Inclusion/Exclusion Review	Master	X	X [3]									
ALS & Medical History	Master	X										
Demographics	Master	X										
Physical Examination	Master	X										
Neurological Exam	Master	X										
Vital Signs [4]	Master	X		X		X	X		X		X	
Slow Vital Capacity	Master	X		X			X		X		X	
Muscle Strength Assessment	Master			X			X		X		X	
ALSFRS-R	Master	X		X		X	X	X	X	X	X	
ALSAQ-40	Regimen			X					X		X	
CNS-BFS	Regimen			X			X		X		X	
ROADS	Regimen			X					X		X	
PGI-C [17]	Regimen								X		X	
PGI-S [17]	Regimen			X					X		X	
CGI-C [18]	Regimen								X		X	
12-Lead ECG	Regimen	X		X		X	X		X		X	
Clinical Safety Laboratory Tests [5]	Master	X		X		X	X		X		X	
Coagulation Laboratory Tests (PT, PTT, INR)	Master	X							X			

Activity	Master Protocol or Regimen-Specific	Master Protocol Screening [1]	Regimen Specific Screening [1]	Baseline [1]	Week 2	Week 4 [12]	Week 8 [12]	Week 12	Week 16 [12]	Week 20	Week 24 or ET Visit [19]	Follow-Up Safety Call [10]
		Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone
		–42 to –1 Days [13]	–41 to 0 Day [13]	Day 0	Day 14 ± 3	Day 28 ± 7	Day 56 ± 7	Day 84 ± 3	Day 112 ± 7	Day 140 ± 3	Day 168 ± 7	28 days after last dose ± 3 days
Endocrinology Safety Laboratory Tests (blood ACTH, Cortisol, fT4) [14]	Regimen			X							X (for all participants prior to ATE)	
Biomarker Blood Collection	Master			X			X		X		X	
Pharmacokinetic Blood Collection [15]	Regimen					X (pre, post)	X (post)		X (post)		X (pre, post)	
Biomarker Urine Collection	Master			X			X		X		X	
DNA Collection [7] (optional)	Master			X								
CSF Collection[16] (optional)	Regimen			X							X	
Concomitant Medication Review	Master	X	X	X	X	X	X	X	X	X	X	
Adverse Event Review [6]	Master	X	X	X	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale	Master			X		X	X		X		X	
Assignment to the Regimen	Master	X										
Randomization within the Regimen	Master			X								
Administer/Dispense Study Drug	Master			X [8]		X	X		X		X [9]	
Study Drug Accountability/Compliance	Master				X[20]	X	X	X[20]	X	X[20]	X	
Review contraception method[21]	Regimen		X	X	X	X	X	X	X	X	X	X
Exit Questionnaire	Master										X	
Vital Status Determination [11]	Master										X	

Abbreviations: ACTH, adrenocorticotropic hormone; ALS, amyotrophic lateral sclerosis; ALSAQ-40, Amyotrophic Lateral Sclerosis Assessment Questionnaire-40; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; ATE, active treatment extension; CBC, complete blood cell count; CGI-C, Clinician Global Impression of Change; CNS, central nervous system; CNS-BFS, Center for Neurologic Study Bulbar Function Scale; CSF, cerebrospinal fluid; ECG, electrocardiogram; ET, early termination; fT4, free thyroxine; ICF, informed consent form; INR, international normalized ratio; PK, pharmacokinetic; ROADS, Rasch-built Overall Amyotrophic Lateral Sclerosis Disability Scale; PAV, permanent assisted ventilation; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PK, pharmacokinetic; PT, prothrombin time; PTT, partial thromboplastin time; TEAE, treatment-emergent adverse event; TSH, thyroid-stimulating hormone.

[1] Master Protocol Screening procedures must be completed within 42 days to 1 day prior to the Baseline Visit. The Regimen-Specific Screening visit and Baseline Visit should be combined, if possible.

[2] During the Master Protocol Screening Visit, participants will be consented via the Platform Trial ICF. After a participant is randomly assigned to a regimen, participants will be consented a second time via the regimen-specific ICF.

[3] At the Regimen-Specific Screening Visit, participants will have regimen-specific eligibility criteria assessed.

[4] Vital signs include weight, systolic and diastolic pressure, respiratory rate, heart rate, and temperature. Height will be measured at the Master Protocol Screening Visit only.

[5] Clinical safety laboratory tests include hematology (CBC with differential), complete chemistry panel, thyroid function, and urinalysis. Serum pregnancy testing will occur in participants of childbearing potential at the Master Protocol Screening Visit and as necessary during the study. Urine pregnancy testing will occur at every in clinic visit for women of childbearing potential.

[6] Adverse events that occur after signing the consent form will be recorded. If a TEAE is reported that results in dose modification or dose interruption or for severe TEAEs that require an in-clinic evaluation, an unscheduled PK sample should be obtained as needed.

[7] The DNA sample can be collected after the Baseline Visit if a baseline sample is not obtained or the sample is not usable.

[8] Administer the first dose of study drug only after the Baseline Visit procedures are completed.

[9] Study drug will only be dispensed at this visit if the participant continues in the ATE.

[10] Participants will only have a Follow-Up Safety Call at this time if they terminate early from the study. Otherwise, participants will have a Follow-Up Safety Call after their last dose of study drug during the ATE period. Refer to Section 6.9 for additional details regarding the process for early terminations.

[11] Vital status, defined as a determination of date of death or PAV status or date last known alive, will be determined for each randomized participant at the end of the placebo-controlled portion of their follow-up (generally the Week 24 Visit, as indicated). If at that time the participant is alive, his or her vital status should be determined again at the time of the last participant, last visit (LPLV) of the Regimen. We may also ascertain vital status (death or date last known alive only) at later time points by using publicly available data sources as described in Section 8.15 of the Master Protocol.

[12] Visit may be conducted via phone or telemedicine with remote services instead of in-person if this is needed to protect the safety of the participant due to a pandemic, disability, or a medically necessary reason. Refer to Section 6.9 for additional details regarding the process for early terminations.

[13] Master Protocol Screening and Regimen-Specific Screening Visit windows are relative to Baseline (Day 0).

[14] Endocrinology safety laboratory tests (blood ACTH, cortisol, fT4) may be performed additionally during the study as clinically indicated based on signs and symptoms. Collect blood sample for measurement of ACTH/cortisol at approximately the same time in the morning for each endocrinology laboratory assessment, if possible. It is not considered a protocol deviation if not taken at the same time in the morning as previous endocrinology laboratory assessments.

[15] For visits with a predose PK sample (Week 4 and Week 24), these visits should be scheduled for the morning and participants should take their dose in the clinic at approximately the same time in the morning as usual. The predose sample should be collected prior to dosing (ie, any time 0 to 2 hours before the dose) and approximately 24 hours after the most recent dose. The postdose sample can be collected anytime between 1 to 8 hours postdose. For the Week 4 Visit, if it is not possible to collect a predose PK sample, 2 postdose samples should be collected (at least 1 hour apart). The Week 24 Visit is the first day of the ATE and, therefore, the ATE dose would be provided in the clinic with a predose and postdose PK sample obtained. Additional unscheduled PK samples should be collected as needed as part of assessment for TEAEs leading to dose reduction or dose interruption or for severe TEAEs requiring an unscheduled visit for assessment.

[16] CSF collection is scheduled to occur for this Regimen during the placebo-controlled period. CSF collection may be performed on a separate date from the other assessments scheduled for the visits. For the Baseline visit, CSF may be collected at any time within one week prior to administration of the first dose of study medication after Regimen G eligibility is confirmed. Post treatment CSF collection will only be collected for participants with baseline CSF collected. For the Week 24 Visit, CSF may be collected at any time within the allowed visit window of the Week 24 Visit as defined in the protocol. For participants continuing into ATE, CSF collection must occur prior to taking the first dose of study medication from the ATE period. For the early termination (ET) visit, CSF collection is to be completed in participants with a Baseline CSF collection and only if the ET visit occurs at or after the Week 12 visit.

[17] PGI-C and PGI-S should be completed by the participant prior to other clinical assessments scheduled during the visit whenever possible.

[18] CGI-C should be completed after all clinical assessments are completed by the investigator whenever possible.

[19] The assessments listed must be completed for Early Termination Visit that occur prior to Week 24 in the placebo-controlled treatment period.

[20] Drug accountability will not be done at phone visits. A drug compliance check in should be held during phone visits to ensure participant is taking drug per dose regimen and to note any report of missed doses.

[21]For female participants of childbearing potential and for men with a female partner of childbearing potential, review and document current contraceptive method(s) and ensure they meet study requirements.

SCHEDULE OF ACTIVITIES – ACTIVE TREATMENT EXTENSION

Activity	Study Week in ATE [5]	Week 2	Week 4 [7]	Week 8 [7]	Week 12	Week 16 [7]	Week 20	Week 24	Week 28 [7]	Week 40 [7]	Week 52 or ET Visit [6,8]	All visits occurring after week 52 (every 13weeks) [7]	Follow-Up Safety Call [4,6]
	Study Week from Baseline Visit	Week 26	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	Week 64	Week 76	Week 89 and Week 102	
	Master Protocol or Regimen-Specific	Phone	Clinic	Clinic	Phone	Clinic	Phone	Phone	Clinic	Clinic	Clinic	Clinic	Phone
		Day 14 ± 3	Day 28 ± 7	Day 56 ± 7	Day 84 ± 3	Day 112 ± 7	Day 140 ± 3	Day168 ± 3	Day 196 ± 14	Day 280 ± 14	Day 364 ± 14	84 days (± 14 days) from last visit after 52 weeks	28 days after last dose ± 3 days
Vital Signs [1]	Master		X	X		X			X	X	X	X	
12-lead ECG	Regimen		X	X		X			X	X	X	X	
Slow Vital Capacity	Master		X	X		X			X	X	X	X	
ALSFRS-R	Master		X	X	X	X	X	X	X	X	X	X	
ALSAQ-40	Regimen								X		X [11]		
CNS-BFS	Regimen			X		X			X	X	X	X	
ROADS	Regimen								X		X [11]		
PGI-C	Regimen								X		X [11]		
PGI-S	Regimen								X		X [11]		
CGI-C	Regimen								X		X [11]		
Clinical Safety Laboratory Tests [2]	Master		X	X		X			X	X	X	X	
Biomarker Blood Collection	Master					X			X		X	X	
Biomarker Urine Collection	Master					X			X		X	X	

Activity	Study Week in ATE [5]	Week 2	Week 4 [7]	Week 8 [7]	Week 12	Week 16 [7]	Week 20	Week 24	Week 28 [7]	Week 40 [7]	Week 52 or ET Visit [6,8]	All visits occurring after week 52 (every 13weeks) [7]	Follow-Up Safety Call [4,6]
	Study Week from Baseline Visit	Week 26	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	Week 64	Week 76	Week 89 and Week 102	
	Master Protocol or Regimen-Specific	Phone	Clinic	Clinic	Phone	Clinic	Phone	Phone	Clinic	Clinic	Clinic	Clinic	Phone
		Day 14 ± 3	Day 28 ± 7	Day 56 ± 7	Day 84 ± 3	Day 112 ± 7	Day 140 ± 3	Day168 ± 3	Day 196 ± 14	Day 280 ± 14	Day 364 ± 14	84 days (± 14 days) from last visit after 52 weeks	28 days after last dose ± 3 days
Concomitant Medication Review	Master	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Review [3]	Master	X	X	X	X	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale	Master		X	X		X			X	X	X	X	
Administer/ Dispense Study Drug	Master			X		X			X	X	X [9]	X [9]	
Study Drug Accountability/ Compliance	Master	X[12]	X	X	X[12]	X	X[12]	X[12]	X	X	X	X	
Review contraception method[13]	Regimen	X	X	X	X	X	X	X	X	X	X	X	X
Vital Status Determination[10]	Regimen										X	X	

Abbreviations: ALSAQ-40, Amyotrophic Lateral Sclerosis Assessment Questionnaire-40; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; ATE, active treatment extension; CBC, complete blood cell count; CGI-C, Clinician Global Impression of Change; CNS, central nervous system; CNS-BFS, Center for Neurologic Study Bulbar Function Scale; ECG, electrocardiogram; ET, early termination; PAV, permanent assisted ventilation; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PK, pharmacokinetic; ROADS, Rasch-built Overall Amyotrophic Lateral Sclerosis Disability Scale; RSA, Regimen-Specific Appendix; TEAE, treatment-emergent adverse event.

[1] Vital signs include weight, systolic and diastolic pressure, respiratory rate, heart rate, and temperature. Height will be measured in cm at the Master Protocol Screening Visit only.

[2] Clinical safety laboratory tests include hematology (CBC with differential), complete chemistry panel, thyroid function, and urinalysis. Serum pregnancy testing will occur in participants of childbearing potential at the Master Protocol Screening Visit and as necessary during the study. Urine pregnancy testing will occur at every in clinic visit for women of childbearing potential.

[3] Adverse events that occur after signing the consent form will be recorded. If a TEAE is reported that results in dose modification or dose interruption or for a severe TEAE that requires an in-clinic evaluation, an unscheduled PK sample should be obtained.

[4] All participants will have a Follow-Up Safety Call (as described in the body of this RSA) after their last dose of study drug during the ATE period. Refer to Section 6.9 for additional details regarding the process for early terminations.

[5] The duration of the ATE is a minimum of 52 weeks with a maximum of 78 weeks per participant and will be completed when all active participants have completed the 52-week Visit in the ATE.

[6] Participants who withdraw consent or early terminate during the ATE will be asked to complete an Early Termination Visit and Follow-Up Safety Call as described in the body of this RSA. Refer to Section 6.9 for additional details regarding the process for early terminations.

[7] Visit may be conducted via phone or telemedicine with remote services instead of in-person if this is needed to protect the safety of the participant due to a pandemic, disability, or a medically necessary reason.

[8] All visits after the 52-week Visit in the ATE will be in-clinic visits that occur at 13-week (96 days ±14 days) intervals. Participants will continue in the ATE until all active participants have completed a minimum of 52 weeks of the ATE; no participant will exceed 78 weeks in the ATE.

[9] For participants returning for another visit only.

[10] Vital status, defined as a determination of date of death or PAV status or date last known alive, will be determined for each participant at the end of the ATE portion of their follow-up. If at that time the participant is alive, his or her vital status should be determined again at the time of the last participant, last visit (LPLV) of the Regimen ATE. We may also ascertain vital status (death or date last known alive only) at later time points by using publicly available data sources as described in Section 8.15 of the Master Protocol.

[11] Not required for early terminations that occur after Week 52 in the ATE.

[12] Drug accountability will not be done at phone visits. A drug compliance check in should be held during phone visits to ensure participant is taking drug per dose regimen and to note any report of missed doses.

[13] For female participants of childbearing potential and for men with a female partner of childbearing potential, review and document current contraceptive method(s) and ensure they meet study requirements.

1. INTRODUCTION

Regimen G: DNL343

DNL343 is a central nervous system (CNS)–penetrant eukaryotic translation initiation factor 2B (eIF2B) small molecule activator that is being developed by Denali Therapeutics Inc. (Denali) as a potential treatment for amyotrophic lateral sclerosis (ALS).

1.1 DNL343 Background Information

Description of DNL343

DNL343 is a selective, orally bioavailable, CNS–penetrant, activator of eIF2B that is being developed by Denali as a potential treatment for ALS. DNL343 is an activator of eIF2B that overcomes phosphorylated eukaryotic translation initiation factor 2a (p-eIF2α) mediated inhibition of protein translation. The effect of DNL343 treatment is the inhibition of the integrated stress response (ISR) pathway as observed by reduction in activating transcription factor 4 (ATF4) translation, re-initiation of normal protein synthesis, and decreased stress granule formation in otherwise stressed cells. See the DNL343 Investigator's Brochure (IB) for detailed information on relevant nonclinical and clinical studies, both completed and ongoing.

Comprehensive nonclinical safety pharmacology and toxicity studies with up to 9 months of daily dosing were conducted with DNL343 to characterize the safety profile, define no-observed-adverse-effect levels (NOAELs), establish a safe starting dose for the first-in-human study, support chronic daily dosing in humans, and inform the clinical monitoring strategy in human trials. Clinical signs consistent with possible CNS and/or peripheral nervous system disturbance were observed in rats and monkeys and included tremor, whole body twitching, excessive salivation, and ataxia in monkeys, and tremors, ataxia, and convulsion-like activity in rats at exposures exceeding those to be administered in the clinic (see Section 5.5, Justification for Dose). The toxicity studies indicate that the adrenal, pituitary, and thyroid glands are potential target organs for DNL343 based on microscopic evaluation. The findings showed evidence of recovery following a treatment free period and are considered nonadverse, based on their nature, mild severity, and lack of functional impact. In addition, the CNS and/or peripheral nervous system are considered possible target organ systems based on the nature of the clinical signs in rats and monkeys. Refer to the DNL343 IB for more information.

The safety, tolerability, and pharmacokinetics (PK) of orally administered DNL343 has been evaluated in multiple Phase 1 clinical studies. Three Phase 1 studies have been completed, a Phase 1 study in healthy volunteers (Study DNLI-F-0001), and two Phase 1 clinical pharmacology studies (Study DNLI-F-0002 and Study DNLI-F-0004); a description of the findings can be referenced in the DNL343 IB. Preliminary findings from two ongoing studies (Study DNLI-F-0003 and Study DNLI-F-0005) are summarized below. Collectively, DNL343 doses up to 260 mg once daily (QD) for up to 14 days in healthy participants and up to 200 mg for up to 10 months in participants with ALS have been generally well tolerated and support continued evaluation of DNL343 in participants with ALS.

Phase 1b Study (DNLI-F-0003): Interim Analysis for Multiple-Dose Safety and Tolerability in Participants with Amyotrophic Lateral Sclerosis (Preliminary Data)

Study DNLI-F-0003 is an ongoing randomized, placebo controlled, double blind 28-day Phase 1b study, followed by an 18-month open-label extension, designed to evaluate the safety, PK, and pharmacodynamics (PD) of DNL343 in participants with ALS. As of the interim analysis (n=20 completing the double-blind 28-day treatment period) cutoff date of 08 September 2022, ALS participants were randomized to DNL343 100 mg (n=7), 200 mg (n=7), or placebo (n=6). DNL343 was generally safe and well-tolerated in participants with ALS. At the interim analysis, there were no deaths, no serious adverse event (SAEs), and no adverse events of special interest (AESIs) reported during the double-blind period. All treatment-emergent adverse event (TEAEs) were Grade 1 or 2. There was one discontinuation for TEAE of Grade 2 rash, considered by the investigator to be related to study drug. There were two dose reductions during the double-blind period for TEAEs: one participant with "brain fog" (Grade 1) reduced from 200 mg to 100 mg, one TEAE of "shivers" (Grade 1) led to dose reduction from 100 mg to placebo. TEAEs in ≥2 participants and more common in DNL343 vs placebo were fatigue and headache, all Grade 1 in the DNL343 groups. There were no dose-dependent or clinically meaningful changes in safety laboratory tests, electrocardiogram (ECG), vital signs neurological exam, or Columbia-Suicide Severity Rating Scale (C-SSRS).

At the Phase 1b interim analysis, PK demonstrated low variability, slow absorption, long half-life, extensive blood-brain barrier penetration with predictable dose-related increases in exposure supporting QD dosing. PK results in ALS participants (Table 1) were generally consistent with results in healthy participants.

Table 1: Summary of Preliminary PK Parameters in Participants with ALS

Dose (mg QD)	Statistic	Day 1			Day 28			
		T_{max} (h)	C_{max} (μM)	AUC_{24} (μM·h)	$t_{max,ss}$ (h)	$C_{max,ss}$ (μM)	$AUC_{24,ss}$ (μM*h)	C_{trough} (μM)
100 (n = 6)	Mean	3	1.24	21.0	2.0	5.54	88.7	3.39
	SD	[2–24]	0.357	7.44	[1–4]	1.15	18.4	1.10
	%CV	–	28.8	35.4	–	20.7	20.7	32.4
200 (n = 5)	Mean	4	1.94	34.5	4	11.8	194	6.99
	SD	[2–24]	0.650	8.98	[1–4]	2.52	55.1	2.43
	%CV	–	33.5	26.0	–	21.4	28.5	34.7

Abbreviations: AUC_{24}, area under the concentration-time curve from time zero to 24 hours; $AUC_{24,ss}$, area under the concentration-time curve from time zero to 24 hours at steady state; C_{max}, maximum concentration; $C_{max,ss}$, maximum concentration at steady-state ; C_{trough}, trough concentration; CV, coefficient of variation; SD, standard deviation; t_{max}, time to reach maximum concentration; $t_{max,ss}$, time to reach maximum concentration at steady state. Note: t_{max} shown as median [range]. Some participants were excluded from the population included in this table due to down-dosing or discontinuation of treatment prior to the PK collection or issues with sample collection (such as thawing of samples) that made the PK unevaluable for a given participant on a given day.

Phase 1b (IA) PD analysis evaluated inhibition of two ISR biomarkers (ATF4 protein, [ChaC glutathione–specific gamma-glutamylcyclotransferase 1] *CHAC1* gene expression) in ex-vivo stimulated peripheral blood mononuclear cells (PBMCs). DNL343 achieved robust inhibition of

ATF4 protein levels (73%–79%) and *CHAC1* gene expression (56%–89%) at both the 100 mg and 200 mg QD doses studied in ALS participants.

Phase 1 Study (DNLI-F-0005): A Fixed-Sequence, Drug-Drug Interaction Study Evaluating the Effect of the Cytochrome P450 3A Inhibitor Itraconazole on DNL343 in Healthy Participants

Study DNLI-F-0005 is a Phase 1, single-center, open-label, fixed-sequence DDI study designed to evaluate the PK, safety, and tolerability of a single dose of DNL343 in the absence and presence of itraconazole (ITZ), a potent cytochrome P450 (CYP3A) inhibitor. The study conduct is complete and the clinical study report is complete. Twenty-four healthy participants were enrolled and received at least one dose of study drug (DNL343 or ITZ). No deaths, other SAEs, or AESIs were reported. All reported TEAEs were Grade 1 or 2, and no TEAEs were considered to be related to DNL343 by the investigator. There were no clinically meaningful trends in ECG results, vital sign measurements, or safety laboratory test results, and DNL343 was generally safe and well tolerated in the presence and absence of itraconazole. PK data was obtained after administration of DNL343 (40 mg) in the presence and absence of multiple doses of ITZ (200 mg). Coadministration of DNL343 with ITZ resulted in a slight increase in the overall exposure of DNL343 (area under the concentration-time curve from time zero to infinity [AUC_{∞}] increased 13%) and a slight decrease in peak exposure (maximum concentration [C_{max}] decreased 14%). The results indicate that DNL343 is not a sensitive substrate of CYP3A4 and that DNL343 can be coadministered with strong, moderate, or weak inhibitors of CYP3A4. Additionally, these preliminary results show a minor contribution of CYP3A4 to the metabolism of DNL343, indicating that coadministration with moderate CYP3A4 inducers are unlikely to affect the PK of DNL343 and can be coadministered with DNL343 freely in this trial.

Phase 1 Study (DNLI-F-0007): A Drug-Drug Interaction Study of the Effect of DNL343 on Midazolam Pharmacokinetics in Healthy Participants (Preliminary Data)

Study DNLI-F-0007 is a Phase 1, single-center, open-label, fixed-sequence DDI study to investigate the effect of DNL343 on the PK of oral MDZ (a sensitive index substrate of CYP3A). The study conduct is complete and the clinical study report is in progress. Based on preliminary study results, 16 healthy participants were enrolled and received at least one dose of study drug (DNL343 or MDZ). Preliminary review of safety and tolerability data demonstrate no deaths, or other SAEs. One participant had a laboratory abnormality meeting the AESI criteria (AST >= 3xULN). All TEAEs were Grade 1 and TEAEs occurring in more than one participant included abnormal dreams in 4 (25%) participants and fatigue in 3 (18.8%) participants. There were no clinically meaningful trends in ECG results, vital sign measurements, or safety laboratory test results. Preliminary PK data was obtained after administration of MDZ (1 mg) in the presence and absence of DNL343 (200 mg QD). Midazolam AUC_{∞} and C_{max} were reduced by 60% and 55% respectively in the presence of DNL343. The preliminary results indicate that DNL343 is moderate CYP3A inducer; medications that are CYP3A substrates may have increased hepatic clearance and decreased exposure when taken with DNL343.

1.2 DNL343 Therapeutic Rationale

Nonclinical studies have implicated dysregulation of the ISR in the pathogenesis of ALS. Chronic activation of the ISR can lead to cellular dysfunction (Pakos-Zebrucka et al 2016), including the loss of active eIF2B complex. ISR pathway activation is evident in multiple animal models of ALS (Nagata et al 2007; Cheng et al 2018; Sonobe et al 2018; Westergard et al 2019), and inhibition of the ISR has been shown to be neuroprotective and results in functional benefits in a range of neurodegenerative models (Kim et al 2013; Hetz and Saxena 2017; Larhammar et al 2017; Moreno et al 2013; Wong et al 2019). The ISR pathway appears to be similarly overactive in ALS, as several markers of the ISR pathway are elevated in tissues of patients with ALS, including p-eIF2α and ATF4 (Ilieva et al 2007; Hetz et al 2009).

DNL343 inhibits the ISR in stressed cells, restores normal protein synthesis, and inhibits stress granule formation. The nonclinical neuroprotective findings of ISR pathway inhibition, combined with the observation of increased ISR activity in patients with ALS, indicate that inhibition of the ISR pathway by DNL343 activation of eIF2B could be beneficial in the treatment of ALS. Additional information regarding the disease and target is provided in Section 2 of the DNL343 IB.

2. OBJECTIVES

2.1 Study Objectives and Endpoints

Primary Efficacy Objective:

- To evaluate the efficacy of DNL343 as compared to placebo on ALS disease progression

Secondary Efficacy Objective:

- To evaluate the effect of DNL343 on selected secondary measures of disease progression, including survival

Safety Objective:

- To evaluate the safety of DNL343 in participants with ALS

Exploratory Objectives:

- To evaluate the effect of DNL343 on selected biomarkers and endpoints
- To evaluate DNL343 concentrations in plasma and cerebrospinal fluid (CSF)

Primary Efficacy Endpoint:

- Change from baseline through Week 24 in disease severity as measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) total score and survival.

Secondary Efficacy Endpoints:

- Change in ALSFRS-R total score from baseline to Week 24
- Combined Assessment of Function and Survival (CAFS) to Week 24
- Change in respiratory function as assessed by slow vital capacity (SVC) from baseline to Week 24
- Change in muscle strength as measured isometrically using hand-held dynamometry and grip strength from baseline to Week 24
- Survival evaluated as time to death or permanent assisted ventilation (PAV)
- Survival evaluated as time to death
- Change in log-transformed serum neurofilament light protein (NfL) concentration from baseline to Week 24

Safety Endpoints:

- Treatment-emergent adverse events and serious adverse events
- Changes in laboratory values and treatment-emergent and clinically significant laboratory abnormalities
- Changes in ECG parameters and treatment-emergent and clinically significant ECG abnormalities
- Treatment-emergent suicidal ideation and suicidal behavior

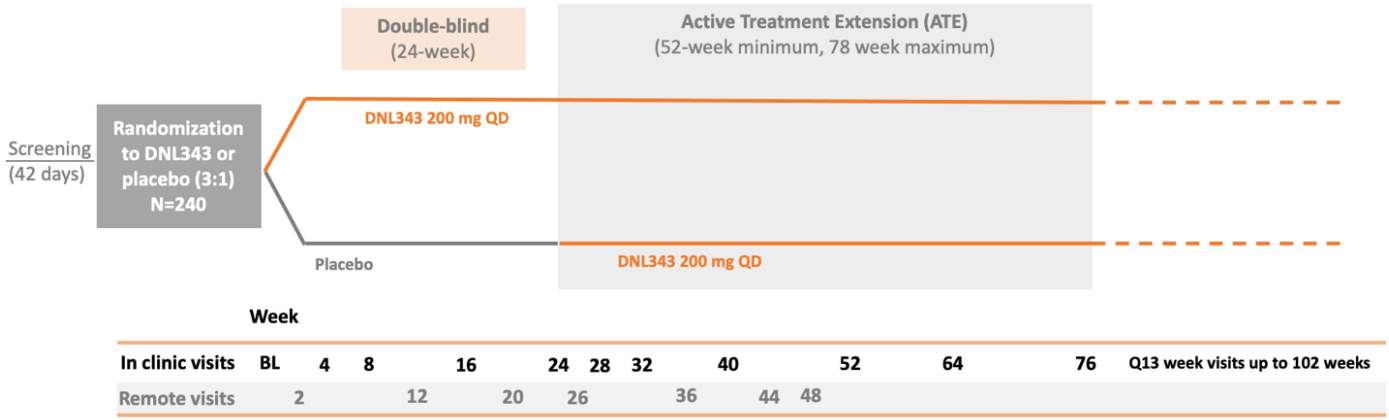
Exploratory Endpoints:

- Changes in patient reported outcomes (PROs) (Amyotrophic Lateral Sclerosis Assessment Questionnaire-40 [ALSAQ-40], Center for Neurologic Study Bulbar Function Scale [CNS-BFS], Rasch-built Overall Amyotrophic Lateral Sclerosis Disability Scale [ROADS], Patient Global Impression of Change [PGI-C], Patient Global Impression of Severity [PGI-S])
- Change in body weight
- Changes in biofluid biomarkers (urine, plasma, optional CSF)
- DNL343 plasma and optional CSF concentrations and CSF-to-plasma concentration ratios
- Changes in clinician reported outcome (Clinician Global Impression of Change [CGI-C])

3. REGIMEN-SPECIFIC APPENDIX DESIGN

Regimen G is a multi-center, randomized, placebo-controlled trial, testing active dose of DNL343 200 mg administered orally QD versus placebo. Participants will be randomized 3:1 active:placebo. Following 24 weeks of double-blinded treatment, all participants will enter the active treatment extension (ATE) period to receive DNL343 200 mg QD for a minimum of additional 52 weeks to a maximum of additional 78 weeks.

Figure 1: DNL343 Regimen-Specific Appendix Study Schema



Abbreviations: BL, baseline; QD, once daily.

3.1 Scientific Rationale for Regimen-Specific Appendix Design

This Regimen-Specific Appendix (RSA) is designed to correspond with the design of the Master Protocol and the goals of the Platform Trial.

In addition to the objectives in the Master Protocol, Regimen G includes a secondary objective evaluating a CAFS and exploratory objectives to characterize the PK of DNL343 in participants with ALS, additional exploratory measures to measure health-related quality of life in individuals with ALS (ALSAQ-40), functional changes (ROADS, CNS-BFS, PGI-C, PGI-S, and CGI-C), body weight, and exploratory biomarkers.

3.2 End of Participation Definition

Placebo-Controlled Period

A participant is considered to have completed the placebo-controlled period of the Regimen when they have completed Week 24 or the Early Termination (ET) Visit.

Active Treatment Extension Period

Participants are considered to have completed their participation in the ATE period of Regimen G if planned ATE period visits, including the last visit, ET Visit, or the last scheduled procedure shown in the Schedule of Activities (SOA), have been completed.

3.3 End of Regimen Definition

The end of the placebo-controlled period in Regimen G occurs when all randomized participants have completed their participation in the placebo-controlled period as defined in Section 3.2.

The end of the ATE period in Regimen G occurs when all participants who initiated study drug in the ATE period have completed their participation in that period as defined in Section 3.2.

4. REGIMEN-SPECIFIC APPENDIX ENROLLMENT

4.1 Number of Study Participants

Approximately two hundred-forty (n=240) participants will be randomized in Regimen G.

4.2 Inclusion and Exclusion Criteria

In order to be randomized to Regimen G, participants must meet the Master Protocol eligibility criteria. In addition, participants meeting all of the following inclusion and exclusion criteria will be allowed to enroll in Regimen G.

4.2.1 Regimen-Specific Appendix Inclusion Criteria

There are no additional RSA Inclusion Criteria beyond those described in the Master Protocol.

4.2.2 Regimen-Specific Appendix Exclusion Criteria

Participants who meet any of the following criteria will be excluded from study entry:

1. Diagnosis of epilepsy currently requiring antiepileptic therapy, or seizure of any cause within 6 months of randomization
2. Hypersensitivity to DNL343 or any of the excipients contained within the DNL343 drug product
3. Use of prescription or over-the-counter (OTC) medications (including herbal medicines such as St. John's wort) that are strong CYP3A4/5 inducers within 2 weeks or 5 half-lives (whichever is longer) of the first dose administration or anticipated use during the study treatment period (see Section 5.9)
4. Use of prescription or OTC medications that are sensitive CYP3A4/5 substrates with a narrow therapeutic index within 7 days or 5 half-lives (whichever is longer) of the first dose administration or anticipated use during the study treatment period (see Section 5.9)
5. Use of prescription or OTC medications that are substrates for breast cancer resistance protein (BCRP) or organic anion transporter (OAT)3 transporters and have a narrow therapeutic index within 7 days or 5 half-lives (whichever is longer) of the first dose administration or anticipated use during the study treatment period (see Section 5.9)

There are RSA-specific requirements that apply to Master Protocol Exclusion Criterion #6. For further details of contraceptive requirements for this RSA, please refer to Section 5.10.2.

4.3 Treatment Assignment Procedures

Each participant who meets all eligibility criteria for the Regimen will be randomized to receive either DNL343 200 mg or placebo for approximately 24 weeks of placebo-controlled treatment and will continue on to the ATE period for up to an additional 78 weeks.

5. INVESTIGATIONAL PRODUCT

5.1 Investigational Product Manufacturer

DNL343 drug product and placebo will be provided for this trial; both are comprised of granules filled into stick packs. DNL343 drug product and placebo are manufactured at the same site, Catalent Germany Schorndorf GmbH, located at Steinbeisstrasse 1-2, 73614 Schorndorf, Germany. Secondary packaging, labeling, and initial distribution of DNL343 drug product and placebo is performed at Fisher Clinical Services located at 7554 Schantz Rd, Allentown, PA 18106 USA.

5.2 Labeling, Packaging, and Resupply

Both DNL343 drug product and placebo are packaged into individual stick packs made from aluminum foil at Catalent. The aluminum foil is composed of three layers of polyester, aluminum, and low-density polyethylene. The granules are only in contact with low-density polyethylene, which is on the inside of the stick pack.

The individual stick packs, or packets, are packaged into secondary cartons at Fisher Clinical Services and each carton contains 14 packets segmented into 7 doses containing 2 packets each. Each packet contains DNL343 100 mg or placebo. Each packet and each carton are labeled at Fisher Clinical Services.

The final labeled cartons are shipped to the Central pharmacy for distribution to clinical sites. All shipments to clinical sites are controlled using an Integrated Response Technology solution.

5.3 Acquisition, Storage, and Preparation

DNL343 drug product and placebo should be stored at room temperature (store below 30°C). All drug supplies must be stored in a secure, temperature-controlled area with limited access. For batch-specific storage instructions, see the packaging.

All study drug will be transported, received, stored, and handled in accordance with the container or product label, the instructions supplied to the research site and its designated pharmacy, the site's standard operating procedures, and the applicable country regulations. Appropriate storage temperature and transportation conditions will be maintained for the study drug from the point of manufacture up to delivery of the study drug to each participating clinical site.

Upon receipt by the study site, the research pharmacy staff will transfer the shipment to the appropriate environmentally controlled storage area. The shipment and temperature monitoring devices (if applicable) will then be examined to verify that the study drug was received in acceptable condition. Once inspected and deemed acceptable, the study drug will then be stored in a restricted access, secured area with access limited to authorized research site staff, under physical conditions consistent with the study drug's specific requirements.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study drug received and that any discrepancies are reported and resolved before use of the study drug.

Refer to the Manual of Procedures (MOP) for additional instructions on handling and storage of study drug.

5.4 Study Medication/Intervention, Administration, Escalation, and Duration

DNL343 drug product and placebo will be administered reconstituted in water for oral or feeding tube administration (eg, gastrostomy tube [G-tube], jejunostomy tube [J-tube], or nasogastric tube) or coadministered with soft food (eg, applesauce or yogurt). Participants can take the drug with fluid thickener as needed.

Study drug administered are described in Table 2.

Table 2: Study Drug Administered

	Placebo-Controlled Period		ATE Period
Arm Name	DNL343	Placebo	DNL343 ATE
Intervention Name	DNL343	Placebo	DNL343
Type	Drug	Drug	Drug
Dose Formulation	Granules in stick pack	Granules in stick pack	Granules in stick pack
Unit Dose Strength(s)	100 mg	Placebo	100 mg
Dose Level(s)	200 mg QD	Placebo QD	200 mg QD
Route of Administration	Oral or feeding tube	Oral or feeding tube	Oral or feeding tube
Use	Experimental	Sham comparator	Experimental

Abbreviations: ATE, active treatment extension; QD, once daily.

Participants should take the study drug at approximately the same time each day in the morning without regard to food. All dosing should be completed within 15 minutes. On clinic visit days with predose PK assessments, participants will be administered their dose of study drug in the clinic.

Participants may take their missed dose as soon as they remember to take it in the same day. If the participant remembers the day after the dose was missed, only the next dose should be taken. Only one dose is to be taken per day.

5.5 Justification for Dosage

The DNL343 dose selected for this study (200 mg QD) is based on safety, PK, and PD data from the Phase 1 study in healthy participants (Study DNLI-F-0001) and interim data from the Phase 1b study in ALS participants (Study DNLI-F-0003) and is further supported by neuroprotection data from DNL343-treated mouse models of neurodegeneration.

In Study DNLI-F-0001, DNL343 oral doses ranging from 45 to 260 mg QD for 14 days were generally safe and well tolerated in healthy participants. In Study DNLI-F-0003, DNL343 was generally safe and well tolerated in ALS participants based on an interim analysis when 20 participants had completed 28-day double-blind treatment period. A summary of human exposure at a dose of 200 mg and associated safety margins to the NOAEL and lowest-observed-adverse-effect level (LOAEL) in nonclinical toxicity studies are provided in Table 3. A dose of 200 mg is estimated to provide a margin of safety of 7 to 8 × (C_{max}–area under the concentration-time curve from time zero to 24 hours [AUC_{24}] range) to total and 2 to 3 × (C_{max}–AUC_{24} range) to unbound AUC_{24} and C_{max} values associated with the male rat NOAEL in the 6-month Good Laboratory Practice (GLP) toxicity study (most sensitive sex and species, based on unbound exposure).

In nonclinical models, plasma and brain exposures achieving or exceeding the *in vitro* EC_{90} (22 nM) estimated from H4 human neuroglioma cells provided consistent and maximal efficacy. In the optic nerve crush mouse model, reduced retinal ganglion cell loss and axonal degeneration were observed with DNL343 doses that achieved coverage of the EC_{90}. In the $eIF2B^{R191H}$ mouse model, DNL343 exposures at the concentration producing 75% of maximum effect (EC_{75}) were associated with improvements in motor function as measured by the balance beam test and reductions in the plasma neurodegeneration biomarker neurofilament light chain (Nf-L) and exposures that exceeded the concentration producing 90% of maximum effect (EC_{90}) led to further improvement, resulting in normalization of these endpoints. These effects were associated with a 35% and 64% reduction in the expression of the brain ISR genes *ATF4* and *CHAC1*, respectively, compared with vehicle treated baseline.

PK/PD modeling of data from healthy participants and participants with ALS showed decreases in ISR pathway biomarkers (*CHAC1* gene expression and ATF4 protein levels) in stimulated PBMCs, with unbound EC_{90} values estimated to range from 55 to 69 nM, suggesting that concentrations higher than that required to see effects in animals may be needed for pharmacologic effects in humans. Based on the evidence above, a DNL343 dose of 200 mg QD is expected to provide (on average) trough coverage above the EC_{90} values from PK/PD modeling of data from clinical studies. The dose selected for the current study (200 mg QD) is estimated to result in approximately ≥ 60% reduction in *CHAC1* gene expression and ATF4 protein levels based on PK/PD modeling.

In summary, DNL343 200 mg QD administered orally is estimated to decrease relevant ISR pathway biomarkers and have exposures at or above concentrations required for potential clinical efficacy, based on PK/PD modeling of data from the clinical studies, Study DNLI-F-0001 and Study DNLI-F-0003, and also based on data from *in vivo* mouse models of neurodegeneration. The exposures achieved at DNL343 200 mg QD was shown to be safe and well tolerated in Study DNLI-F-0001 for 14 days and to have adequate safety margins to the rat and monkey NOAELs. In addition, interim analysis of safety and tolerability data from the ongoing Phase 1b study (Study DNLI-F-0003) in ALS patients supports a dose of 200 mg for a longer-term dosing in the late-stage studies in ALS patients.

Table 3: Predicted Safety Margins for Proposed DNL343 Clinical Doses of 200 mg Once Daily in Relation to NOAEL and LOAEL Exposures in the Good Laboratory Practice Toxicity Studies

Nonclinical Study Dose Level	Exposure Multiples to 200 mg QD [a]			
	Total		Unbound [b]	
	C_{max} (μM)	AUC_{24} (μM · h)	C_{max} (μM)	AUC_{24} (μM · h)
GLP 3-month rat toxicity study				
M, 50 mg/kg (LOAEL) [c]	8 ×	9 ×	3 ×	3 ×
GLP 6-month rat toxicity study				
F, 25 mg/kg/d (NOAEL)	8 ×	10 ×	3 ×	3 ×
M, 25 mg/kg/d (NOAEL)	7 ×	8 ×	2 ×	3 ×
GLP 3-month monkey toxicity study				
M + F, 25 mg/kg/d (NOAEL)	3 ×	3 ×	11 ×	11 ×
GLP 9-month monkey toxicity study				
M + F, 25 mg/kg/d (NOAEL)	3 ×	3 ×	11 ×	12 ×

Abbreviations: AUC_{24}, area under the concentration-time curve from time zero to 24 hours; C_{max}, maximum concentration; F, female; f_u, fraction unbound; GLP, Good Laboratory Practice; LOAEL, lowest-observed-adverse-effect level; M, male; NOAEL, no-observed-adverse-effect level; QD, once daily.

[a] Exposure multiples are calculated using total and unbound AUC_{24} and C_{max} from the nonclinical toxicity studies relative to observed steady-state total and unbound AUC_{24} and C_{max} in healthy participants at a dose of 200 mg QD (total AUC_{24} = 243 μM·h and total C_{max} = 16.2 μM; unbound AUC_{24} = 2.92 μM·h and unbound C_{max} = 0.194 μM).

[b] Unbound multiples derived from total plasma exposure using f_u in rats (0.004), cynomolgus monkeys (0.046), and humans (0.012).

[c] LOAEL is defined as the mean C_{max} and AUC exposure in male rats following a single dose of 50 mg/kg in the 3-month GLP toxicity study (mean total C_{max} = 129 μM and total AUC_{24} = 2130 μM·h).

5.6 Dosage Changes

5.6.1 Dose Modification for an Individual Participant

The DNL343 dose (200 mg QD) was selected given that it is considered to have the highest potential to demonstrate efficacy based on data from preclinical studies, clinical biomarker engagement, and clinical safety (see Section 5.5). To adequately evaluate the efficacy of DNL343 participants should be maintained on the randomized treatment. For situations of substantial intolerability (moderate or severe adverse events [AEs], clinically significant abnormal laboratory test results, or other safety parameter, as judged by the investigator or medical monitor), the site investigator, in consultation with the medical monitor, may withhold study drug (dose interruption), temporarily reduce the dose (administer one stick pack rather than two stick packs), or discontinue study drug for an individual participant. Investigators should consider resuming treatment at the randomized dose within 28 days from the dose reduction or dose interruption. The blind will be maintained throughout the dose modification procedure.

All participants in the ATE will be dosed with DNL343 200 mg QD regardless of whether they had a dose reduction during the placebo-controlled period. In situations that may necessitate initiation of DNL343 at the reduced dose (100 mg) in the ATE, the investigator should discuss with the medical monitor before entry into the ATE. As in the placebo-controlled period, the site investigator, in consultation with the medical monitor, may withhold study drug (dose interruption), temporarily reduce the dose (administer one stick pack rather than two stick packs), or discontinue study drug for an individual participant. Investigators should consider resuming treatment at the 200 mg dose level if possible.

5.7 Participant Compliance

When participants are dosed at the site, they will receive study drug directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and electronic case report form (eCRF). The dose of study drug and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug.

When participants self-administer study drug at home, compliance with study drug will be assessed at each study visit. Participants will be instructed to bring all their unused packets of study drug with them to all clinic visits. Compliance with home administration of study drug will be performed by the study staff by counting the number of unused packets and will be recorded. Deviation(s) from the prescribed dosage regimen should be recorded.

5.8 Overdose or Medication Administration Error

Certain safety events that occur in association with DNL343 may require reporting. These safety events include, but are not limited to, the following:

- Overdose of DNL343, where ‘overdose’ is defined as the accidental or intentional use of a drug in an amount higher than the dose being studied. No safety data related to overdosing of DNL343 are available.
- Suspected abuse/misuse of DNL343
- Inadvertent or accidental exposure to DNL343
- Medication error involving study drug (with or without participant exposure to DNL343)

These safety events should be reported to the Coordination Center whether they result in an AE/SAE or not. Safety events associated with an AE/SAE should also be reported in the electronic data capture. In the event of overdose, study staff should monitor the participant and provide supportive care as needed. The Site Investigator should also contact the Medical Monitor within 24 hours of the Site Investigator’s awareness.

5.9 Prohibited Medications

Participants may not take any prescription or OTC medications (including herbal medicines such as St. John’s wort) that are strong CYP3A4/5 inducers within 2 weeks or 5 half-lives (whichever is longer) of the first dose of study drug and must not anticipate needing to take any of these medications during the study treatment period (see Appendix IV Table 4).

Participants may not take any prescription or OTC medications that are sensitive CYP3A4/5 substrates with a narrow therapeutic index within 7 days or 5 half-lives (whichever is longer) of the first dose of study drug and must not anticipate needing to take any of these medications during the study treatment period (see Appendix IV, Table 5 for common examples of sensitive substrates). Medications that are sensitive CYP3A4/5 substrates with a wide therapeutic index are permitted; participants taking them are to be monitored for signs of loss of efficacy and/or may require dose increase based on the respective medication's prescribing information and discretion of the investigator and/or medical monitor.

Participants may not take any prescription or OTC medications that are substrates for BCRP or OAT3 and have a narrow therapeutic index within 7 days or 5 half-lives (whichever is longer) of the first dose of study drug, and must not anticipate needing to take any of these medications during the study treatment period (see Appendix IV, Table 6 for common examples of sensitive substrates).

The medical monitor may be consulted to assess whether any of the sensitive CYP3A4/5 substrates and BCRP and OAT3 substrates (See Appendix IV, Table 5 and 6 for common examples) would be considered to have narrow therapeutic index for the individual participant taking the medication.

For all excluded therapies described in this section, rescreening of participants is allowed after the defined window has passed.

5.10 DNL343 Known Potential Risks and Benefits

5.10.1 Known Potential Benefits and Risks

The benefit and risks of DNL343 treatment in participants with ALS have not been established. Based on the mechanism of action of DNL343, inhibition of the ISR is being investigated for its therapeutic potential in individuals with ALS. The risks of DNL343 treatment are based on extensive evaluation in nonclinical studies and evaluation in clinical studies in approximately 95 healthy participants for up to 14 days and 20 participants with ALS for up to 10 months to characterize the safety profile. DNL343 was generally safe and well-tolerated in participants with ALS. The potential risks of participation in the current study are primarily those associated with adverse reactions to the study drug and study procedures.

More detailed information regarding the known and expected benefits, risks, and reasonably anticipated adverse reactions associated with DNL343 are provided in the DNL343 IB.

5.10.2 Contraceptive Requirements for Participants in Regimen G

Participants will be asked to provide verbal confirmation of the contraceptive method that they are using at Screening and at each in clinic visit for the duration of the double-blind and ATE periods of the study. The contraceptive method(s) will be documented in the CRF at each clinic visit.

Participants must adhere to the following requirements for contraceptive use throughout the trial.

1. For female participants, one of the following must apply:

a. Postmenopausal (defined as no menses for ≥ 12 consecutive months before screening without an alternative medical cause, with a follicle-stimulating hormone level of > 40 IU/L or mIU/mL at screening)

b. Surgically sterilized (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) at least 6 months before dosing

OR

c. For participants of childbearing potential: both the participant and the male partner must use highly effective contraception at the start of dosing, throughout the study period, and for 90 days after the final administration of study drug. Highly effective contraception consists of two forms of birth control, one of which must be a male barrier method such as a latex or polyurethane condom. The other must be a highly effective method (as defined in Appendix III), which includes one of the following:

- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal ligation
- Abstinence, defined as **refraining from heterosexual intercourse during the entire study and for 90 days after last dose of study drug**. 'Periodic abstinence' (calendar, symptothermal, postovulation methods) is considered not reliable and would not be acceptable.

OR

d. For participants of childbearing potential with an azoospermic male partner, the male partner must use a male barrier method such as a latex or polyurethane condom. Azoospermia is a highly effective contraceptive method provided that **the partner is the sole sexual partner of the woman of childbearing potential.** Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. For male participants:

a. When engaging in sex with a female partner of childbearing potential, both the male participant and his female partner must use highly effective contraception consisting of two forms of birth control, one of which must be a male barrier method such as a latex or polyurethane condom, and the other of which must be a highly effective form of birth control (as defined in Appendix III) used by the female partner. This is required from the start of dosing, throughout the study period, and for 90 days after the final administration of study drug.

OR

b. For azoospermic male participants with a woman partner of childbearing potential the male partner must use a male barrier method such as a latex or polyurethane condom.

Male participants must not donate sperm at any time from the start of dosing, throughout the study period, and for 90 days after the final administration of study drug.

6. REGIMEN SCHEDULE

In addition to procedures in the Master Protocol, the following DNL343-specific procedures will be conducted during the study:

- ALSAQ-40
- CNS-BFS
- ROADS
- PGI-S, PGI-C
- CGI-C
- PK blood collection
- 12-lead ECG (to be done at all in-clinic visits)
- Endocrinology safety laboratory tests (blood adrenocorticotropic hormone [ACTH], cortisol, free thyroxine [fT4]) (Baseline and Week 24 Visits)
- Urine Pregnancy testing for women of childbearing potential
- Review contraceptive methods being used by participant and partner
- Optional CSF collection

Unscheduled visits for safety assessments that are deemed medically appropriate and necessary by the Investigator may be performed at any time, independent of scheduled in-clinic visits. Additional unscheduled PK samples should be collected as needed as part of assessment for TEAEs leading to dose reduction or dose interruption or any severe TEAE that requires an unscheduled visit for assessment.

Participants may be required to reconsent to the regimen if new procedures or information are added in the future. Should a participant need to reconsent, this should occur during the participant's next in-person visit. If the participant's next in-clinic visit is conducted remotely, reconsent may also be completed remotely using the following procedures:

1. The site staff sends copy of the informed consent form to the participant.

2. The participant reads through the consent form but does not sign.

3. The Site Investigator, or other study staff member approved and delegated to obtain informed consent, contacts the participant and reviews the informed consent form with the participant.

4. The participant signs the informed consent form and returns the original signed consent form back to the site.

5. Once received at the site, the individual who consented the participant signs the informed consent form.

Modifications to Regimen Schedule

Designated visits in the SOA (i.e., Week 4, Week 8, and Week 16) may be conducted via telemedicine (or phone if telemedicine is not available) with remote services instead of in-person if needed to protect the safety of the participant due to a pandemic, disability, or other medically necessary reason. If a planned in-clinic visit is conducted via telemedicine (or phone if telemedicine is not available) with remote services, only selected procedures will be performed. Instructions on how to document missed procedures are included in the MOP.

In addition to the procedures in the Master Protocol that should be conducted during the phone or telemedicine and remote visits, the following regimen-specific procedures should be completed:

- CNS-BFS (Weeks 8 and 16 only)
- ROADS (Week 16 and 24 only)
- PGI-C (Week 16 and 24 only)
- PGI-S (Week 16 and 24 only)

Details on collection of the CNS-BFS, ROADS, PGI-C, and PGI-S and dispensing of study drug during remote visits are described in the MOP.

6.1 Baseline Visit

This visit will take place on Day 0. The following procedures will be performed for the regimen schedule:

- ALSAQ-40
- CNS-BFS
- ROADS
- PGI-S
- 12-lead ECG
- Endocrinology safety laboratory tests (blood ACTH, cortisol, fT4)
- Urine pregnancy testing for women of childbearing potential
- Review contraceptive methods being used by participant and partner
- Optional lumbar puncture for CSF collection (biomarkers only; no CSF PK sample collected at baseline)
    - CSF collection may be performed on a separate date from the other assessments scheduled for the visit. For the Baseline visit, CSF may be collected at any time within one week prior to administration of the first dose of study medication after Regimen G eligibility is confirmed.
- Dispense study drug
- Administer first dose of study drug in clinic *after* all Baseline procedures have been completed
- Remind participant to bring in study drug, including unused study drug packets to the next visit

6.2 Week 2 Telephone Visit

This visit will take place 14 ± 3 days after the Baseline Visit via telephone. The following procedures will be performed for the regimen schedule:

- Perform drug compliance check-in (remind of the importance of compliance)
- Remind participant to bring any unused study drug to the next visit
- Review of Concomitant Medications and Adverse Events
- Review contraceptive methods being used by participant and partner

6.3 Week 4 and 8 Visits

The Week 4 visit should be scheduled in the morning to accommodate the pre/post dose PK collection. On the day of the Week 4 visit the participant should take their daily dose in-clinic. Study drug should not be taken until after study visit procedures are complete.

If the Week 4 Visit cannot occur in the morning, the participant should take their dose at home at their usual dosing time rather than receiving the dose in-clinic. Two post dose PK blood samples would be obtained if dosing has already occurred prior to arriving at the clinic. The two PK collections should occur at least one hour apart without a dose administered in between and a minor protocol deviation recorded.

For the Week 8 Visit, the participant may take their daily dose at home or in clinic, depending on the time of the visit and one postdose PK blood sample would be obtained.

These visits will take place on Days 28 ± 7 and 56 ± 7 days, respectively. The following procedures will be performed for the regimen schedule:

- CNS-BFS [Week 8 only]
- 12-lead ECG
- PK blood collection (predose and postdose on Week 4, postdose only on Week 8)
    - For visits with a predose PK sample collection, participants should take their dose in the clinic at approximately the same time in the morning as usual.
    - The predose sample should be collected prior to dosing (0 to 2 hours before the dose) and approximately 24 hours after the last dose.
    - The postdose sample can be collected anytime between 1 to 8 hours postdose.
- Urine pregnancy testing for women of childbearing potential
- Review contraceptive methods being used by participant and partner
- Dispense study drug
- Remind participant to bring in study drug, including unused study drug packets, to the next visit

6.4 Week 12 Telephone Visit

This visit will take place 84 ± 3 days after the Baseline visit via telephone. The following procedures will be performed for the regimen schedule:

- Perform drug compliance check-in (remind of the importance of compliance)
- Remind participant to bring any unused study drug to the next visit
- Review of Concomitant Medications and Adverse Events
- Review contraceptive methods being used by participant and partner

6.5 Week 16 Visit

This visit will take place on Day 112 ± 7 days. The following procedures will be performed for the regimen schedule:

- CNS-BFS
- ALSAQ-40
- ROADS
- PGI-C
- PGI-S
- CGI-C
- 12-lead ECG
- PK blood collection (postdose only on Week 16)
  - Postdose sample can be collected anytime between 1 to 8 hours postdose.
- Urine pregnancy testing for women of childbearing potential
- Review contraceptive methods being used by participant and partner
- Dispense study drug
- Remind participant to bring in study drug, including unused study drug packets, to the next visit

6.6 Week 20 Telephone Visit

This visit will take place 140 ± 3 days after the Baseline Visit via telephone. The following procedures will be performed for the regimen schedule:

- Perform drug compliance check-in (remind of the importance of compliance)
- Remind participant to bring any unused study drug to the next visit
- Review of concomitant medications and adverse events
- Review contraceptive methods being used by participant and partner

6.7 Week 24 Visit or Early Termination Visit

The Week 24 Visit should be scheduled in the morning to accommodate the pre/post dose PK collection. On the day of the Week 24 Visit, the participant should not take any dose from the

placebo-controlled period and take their ATE dose in-clinic. Study drug should not be taken until after study visit procedures are complete.

This visit will take place on Day 168 ± 7 days. The following procedures will be performed for the regimen schedule:

- ALSAQ-40
- CNS-BFS
- ROADS
- PGI-C
- PGI-S
- CGI-C
- 12-lead ECG
- PK blood collection (predose and postdose on Week 24)
    - For the predose PK sample collection, participants should take their ATE dose in the clinic at approximately the same time in the morning as usual.
    - The predose sample should be collected prior to dosing (0 to 2 hours before the dose) and approximately 24 hours after the last dose.
    - The postdose sample can be collected anytime between 1 to 8 hours postdose.
- Endocrinology safety laboratory tests (blood ACTH, cortisol, TSH, fT4) (for participants continuing in the ATE)
- Urine pregnancy testing for women of childbearing potential
- Review contraceptive methods being used by participant and partner
- Optional lumbar puncture for CSF collection (collect *both* biomarker and PK samples)
    - CSF collection may occur on a separate date from the other assessments scheduled at the Week 24 Visit, provided CSF collection occurs within the allowed window for the Week 24 Visit as defined in the protocol. For participants continuing into ATE, optional CSF collection must occur prior to taking the first dose from the ATE period. The date of the other assessments (ie, not the date of CSF collection) will be considered the date of the Week 24 Visit. CSF collection at Week 24 will only be performed on participants with baseline CSF collection.
    - CSF collection for the ET visit will be performed only if the participant has consented to the lumbar puncture with baseline CSF collection and the ET visit occurs at or after the Week 12 visit.
- Dispense study drug
- Remind participant to bring study drug, including unused study drug packets to the next visit

6.8 Follow-Up Safety Call

Participants will have a Follow-Up Safety Call 28 + 3 days after their last dose of study drug. Participants who continue into ATE will not complete the follow up safety call during placebo-controlled phase.

The following procedures will be performed:

- Assess and document AEs
- Review contraceptive methods being used by participant and partner

6.9 Process for Early Terminations

Participants who withdraw consent or early terminate from the study and do not complete the protocol will be asked to be seen for an in-person ET Visit and complete a Follow-Up Safety Call.

The in-person ET Visit should be scheduled as soon as possible after a participant early terminates. If the participant early terminates or withdraws consent during the placebo-controlled portion of the Regimen, all assessments that are collected at the Week 24 in-clinic visit should be conducted. The Follow-Up Safety Call should be completed approximately 28 days after the last dose of study drug.

If the ET Visit occurs approximately 28±3 days after the last dose of study drug, the information for the Follow-Up Safety Call can be collected during the ET visit, and a separate Follow-Up Safety Call does not need to be completed. If the in-person ET Visit does not occur within 28±3 days of the last dose of study drug, the Follow-Up Safety Call should occur approximately 28 days after the last dose of study drug and the ET Visit will be completed after the Follow-Up Safety Call.

If a participant has to discontinue study drug, but will complete the protocol, an in-person ET Visit and Follow-Up Safety Call is not necessary. Every effort should be made to retain participants in the study, including the ATE period, regardless of whether they have discontinued study drug.

For the ET Visit, optional CSF collection will be completed in participants with a Baseline CSF collection and only if the ET visit occurs at or after the Week 12 visit.

6.10 Active Treatment Extension

Following the placebo-controlled period, participants will continue in the ATE as outlined in the SOA.

The ATE will continue until all active participants have completed a minimum of 52 weeks in the ATE; no participant will exceed 78 weeks in the ATE (ie, 102 weeks total from the Baseline visit). The Industry Partner may consider extending or discontinuing the ATE period depending on the results from the primary analysis.

Unscheduled visits for safety assessments that are deemed medically appropriate and necessary by the Investigator may be performed at any time, independent of scheduled in-clinic visits. Additional unscheduled PK samples should be collected as needed as part of assessment for TEAEs leading to dose reduction or dose interruption or any severe TEAE that requires an unscheduled visit for assessment.

Modifications to Regimen Schedule

Designated visits in the SOA (i.e., Week 4, Week 8, Week 16, Week 28, Week 40 in ATE) may be conducted via telemedicine (or phone if telemedicine is not available) with remote services instead of in-person if needed to protect the safety of the participant due to a pandemic, disability, or other medically necessary reason. If a planned in-clinic visit is conducted via telemedicine (or phone if telemedicine is not available) with remote services, only selected procedures will be performed. Instructions on how to document missed procedures are included in the MOP.

During the phone or telemedicine and remote visits, the following regimen-specific procedures should be completed:

- ALSFRS-R (Week 16, 20, 24, and 78/ET)
- CNS-BFS (Week 8, 16, 28, 40, 52 only)
- ROADS (Week 16, Week 28 and Week 52/ET)
- PGI-C (Week 16, Week 28 and Week 52/ET)
- PGI-S (Week 16, Week 28 and Week 52/ET)

6.10.1 Week 2 ATE Telephone Visit

This visit will take place via telephone 14 ± 3 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see Section 10.3 of the Master Protocol*)
- Perform drug compliance check-in
- Remind participant to bring study drug, including unused study drug, containers, to the next visit
- Review contraceptive methods being used by participant and partner

6.10.2 Week 4 ATE Visit

This visit will take place in-person 28 ± 7 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Collect vital signs including weight
- Perform SVC
- Administer ALSFRS-R questionnaire
- Collect blood samples for clinical safety laboratory tests
- Urine pregnancy testing for women of childbearing potential
- Review contraceptive methods being used by participant and partner
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see Section 10.3 of the Master Protocol*)

- Administer the C-SSRS Since Last Visit questionnaire
- 12-lead ECG
- Perform study drug compliance
- Remind participant to bring study drug, including unused study drug packets, to the next visit

6.10.3 Week 8 ATE Visit

This visit will take place in-person at 56 ± 7 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Collect vital signs including weight
- Perform SVC
- Administer ALSFRS-R questionnaire
- CNS-BFS
- Collect blood samples for clinical safety laboratory tests
- Urine pregnancy testing for women of childbearing potential
- Review contraceptive methods being used by participant and partner
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see Section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- 12-lead ECG
- Dispense study drug to participant
- Perform study drug compliance
- Remind participant to bring study drug, including unused study drug packets to the next visit

6.10.4 Week 12 ATE Telephone Visit

This visit will take place via telephone at 84 ± 3 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Administer ALSFRS-R questionnaire
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see Section 10.3 of the Master Protocol*)
- Perform drug compliance check-in
- Remind participant to bring study drug, including unused study drug packets, to the next visit
- Review contraceptive methods being used by participant and partner

6.10.5 Week 16 ATE Visit

Participants should be instructed to hold study drug on the day of the study visit. Study drug should not be taken until after study visit procedures are complete.

This visit will take place in-person at 112 ± 7 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Collect vital signs including weight
- Perform SVC
- Administer ALSFRS-R questionnaire
- CNS-BFS
- Collect blood samples for clinical safety laboratory tests
- Urine pregnancy testing for women of childbearing potential
- Review contraceptive methods being used by participant and partner
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see Section 10.3 of the Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Collect urine sample for biomarker analyses
- Collect blood sample for biomarker analyses
- 12-lead ECG
- Dispense study drug to participant
- Perform study drug compliance
- Remind participant to bring study drug, including unused study drug, packets, to the next visit

6.10.6 Week 20 ATE Telephone Visit

This visit will take place via telephone at 140 ± 3 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Administer ALSFRS-R questionnaire
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see Section 10.3 of the Master Protocol*)
- Perform drug compliance check-in
- Remind participant to bring study drug, including unused study drug packets, to the next visit
- Review contraceptive methods being used by participant and partner

6.10.7 Week 24 ATE Telephone Visit

This visit will take place via telephone at 168 ± 3 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Administer ALSFRS-R questionnaire

- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see Section 10.3 of the Master Protocol*)
- Perform drug compliance check-in
- Remind participant to bring study drug, including unused study drug packets, to the next visit
- Review contraceptive methods being used by participant and partner

6.10.8 Week 28 ATE Visit

Participants should be instructed to hold study drug on the day of the study visit. study drug should not be taken until after study visit procedures are complete.

The Week 28 ATE visit will take place in-person 196 ± 14 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Collect vital signs, including weight
- Perform SVC
- Administer ALSFRS-R questionnaire
- ALSAQ-40
- CNS-BFS
- Collect blood samples for clinical safety laboratory tests
- Urine pregnancy testing for women of childbearing potential
- Review contraceptive methods being used by participant and partner
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see Section 10.3 of the Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Collect urine sample biomarker analyses
- Collect blood sample for biomarker analyses
- 12-lead ECG
- ROADS
- PGI-C
- PGI-S
- CGI-C
- Dispense study drug to participant
- Perform study drug compliance
- Remind participant to bring study drug, including unused study drug packets, to the next visit

6.10.9 Week 40 ATE Visit

The Week 40 ATE Visit will take place in-person 280 ± 14 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Collect vital signs including weight

- Perform SVC
- Administer ALSFRS-R questionnaire
- CNS-BFS
- Collect blood samples for clinical safety laboratory tests
- Urine pregnancy testing for women of childbearing potential
- Review contraceptive methods being used by participant and partner
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see Section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Dispense study drug to participant
- 12-lead ECG
- Perform study drug compliance
- Remind participant to bring study drug, including unused study drug packets, to the next visit

6.10.10 Week 52 ATE Visit

Participants should be instructed to hold study drug on the day of the study visit. Study drug should not be taken until after study visit procedures are complete.

The Week 52 ATE Visit will take place in-person 364 ± 14 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Collect vital signs including weight
- Perform SVC
- Administer ALSFRS-R questionnaire
- ALSAQ-40
- CNS-BFS
- Collect blood samples for clinical safety laboratory tests
- Urine pregnancy testing for women of childbearing potential
- Review contraceptive methods being used by participant and partner
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see Section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Dispense study drug to participant
- Collect urine sample biomarker analyses
- Collect blood sample for biomarker analyses
- 12-lead ECG
- ROADS
- PGI-C
- PGI-S
- CGI-C
- Perform study drug compliance

6.10.11 Visits after Week 52

Visits that occur after 52 weeks of enrollment in the ATE will occur every 13 weeks (91 days ± 14 days) until all active participants have completed a minimum of 52 weeks in the ATE; no participant will exceed 78 weeks in the ATE. Visits after the 52-week Visit will take place in-person. The following procedures will be performed:

- Collect vital signs including weight
- Perform SVC
- Administer ALSFRS-R questionnaire
- CNS-BFS
- Collect blood samples for clinical safety laboratory tests
- Urine pregnancy testing for women of childbearing potential
- Review contraceptive methods being used by participant and partner
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see Section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Dispense study drug to participant
- Collect urine sample for biomarker analyses
- Collect blood sample for biomarker analyses
- 12-lead ECG
- Perform study drug compliance
- Remind participant to bring study drug, including unused study drug packets, to the next visit

6.10.12 Follow-Up Safety Call

Participants will have a Follow-Up Safety Call 28 ± 3 days after their last dose of study drug. Participants will complete this visit who:

1. Have their last dose of study drug prior to completing the ATE (those who discontinue early)
2. Complete the ATE

The following procedures will be performed:

- Assess and document AEs
- Review contraceptive methods being used by participant and partner

6.10.13 Process for Early Terminations

Participants who withdraw consent or early terminate from the study and do not complete the protocol will be asked to be seen for an in-person ET Visit and complete a Follow-Up Safety Call.

The in-person ET Visit should be scheduled as soon as possible after a participant early terminates. If the participant early terminates or withdraws consent during the ATE period before reaching Week 52, all assessments that are collected at the ATE Week 52 in-clinic visit should

be conducted. For early discontinuations after Week 52 in ATE, assessments for ALSAQ-40, ROADS, PGI-C, PGI-S, and CGI-C are not required. The Follow-Up Safety Call should be completed approximately 28 days after the last dose of study drug.

If the ET Visit occurs approximately 28±3 days after the last dose of study drug, the information for the Follow-Up Safety Call can be collected during the ET visit, and a separate Follow-Up Safety Call does not need to be completed. If the in-person ET Visit does not occur within 28±3 days of the last dose of study drug, the Follow-Up Safety Call should occur approximately 28 days after the last dose of study drug and the ET Visit will be completed after the Follow-Up Safety Call.

7. OUTCOME MEASURES AND ASSESSMENTS

7.1 Amyotrophic Lateral Sclerosis Assessment Questionnaire-40 (ALSAQ-40)

The ALSAQ-40 is a patient self-report health status patient-reported outcome. The ALSAQ-40 consists of forty questions that are specifically used to measure the subjective well-being of patients with ALS and motor neuron disease.

Participants will be handed the questionnaire and asked to write their answers themselves. Caregivers or study staff can also help, if needed but should only assist in transferring the participant's responses to the form, and should not provide any assistance with determining answers.

7.2 Center for Neurologic Study Bulbar Function Scale (CNS-BFS)

The CNS-BFS is a patient self-report scale that has been developed for use as an endpoint in clinical trials and as a clinical measure for evaluating and following ALS patients. The CNS-BFS consists of three domains (swallowing, speech, and salivation), which are assessed with a 21-question, self-report questionnaire.

Participants will be handed the questionnaire and asked to write their answers themselves. Caregivers or study staff can also help, if needed, but should only assist in transferring the participant's responses to the form, and should not provide any assistance with determining answers.

7.3 Rasch-built Overall Amyotrophic Lateral Sclerosis Disability Scale (ROADS)

The ROADS is a PRO of function (Fournier et al 2020). It is a 28-question, validated, linear, self-report questionnaire created with Rasch modeling. Rasch modeling uses statistical principles to enhance scale validity (Vanhoutte et al 2015). Prior to analysis, ROADS raw scores are converted to normed whole numbers. The scale and conversion table are publicly available (https://med.emory.edu/departments/neurology/programs_centers/emory_als_center/_documents/roads.pdf).

Participants will be handed the questionnaire and asked to write their answers themselves. Caregivers or study staff can also help, if needed but should only assist in transferring the participant's responses to the form and should not provide any assistance with determining answers.

7.4 The Patient Global Impression of Change (PGI-C)

PGI-C is a PRO that reflects the respondent's belief about the efficacy of treatment. PGI-C is a 7-point scale that captures an individual's self-rating rating of overall improvement. Respondents rate their change relative to baseline as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse" (Hurst and Bolton 2004).

7.5 The Patient Global Impression of Severity (PGI-S)

PGI-S is a PRO scale that may be used to rate the severity of a specific condition. It is a simple, direct, easy to use 1-item questionnaire that asks an individual patient to rate the severity of a specific condition (single-state scales) at a given point in time. The PGI-S item asks the respondent to best describe the level of severity of their symptoms now on a 4-point scale scored as: “normal” (1), “mild” (2), “moderate” (3), or “severe” (4) (Viktrup et al 2012).

7.6 Clinician Global Impression of Change (CGI-C)

The CGI-C is a stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication (Busnar et al 2007). CGI-C asks the clinician one question, which is rated on a seven-point scale: “Compared to the patient’s condition at admission the project (prior to study drug initiation), this patient’s condition is 1=very much improved; 2=much improved; 3=minimally improved; 4=no change from baseline; 5=minimally worse; 6=much worse; 7=very much worse since the initiation of study drug treatment”.

7.7 Vital Status Determination

Vital status, including determination of dates of death and initiation of PAV or dates last known alive and last known PAV-free, will be recorded by site study staff for each randomized participant throughout the placebo-controlled portion of their follow-up (generally the Week 24 Visit, as indicated in the SOA) and at the conclusion of the ATE participation. At approximately the time of the last participant, last visit (LPLV) of the placebo-controlled portion of the regimen, a second vital status check will be completed by site study staff for each randomized participant. When prompted by the Coordination Center, sites will contact all randomized participants or their caregivers to assess vital status.

We may also ascertain vital status at later time points. An outside vendor will be used to ascertain death or date of last known alive for all randomized participants by using publicly available data sources. When prompted by the Coordination Center, sites will provide demographic information (e.g., participant name, date of birth, last known address) to the vendor using a secure method.

8. BIOFLUID COLLECTION

Biofluid samples (blood, urine, and CSF) that will be used for biomarker assessments for Regimen G are captured in the Master Protocol. It should be noted that the CSF biofluid collection is optional and collection for Regimen G occurs at Baseline and Week 24 (rather than Baseline and Week 16 as noted in the Master Protocol). Additional biofluid samples (blood) will be collected for Regimen G for evaluation of plasma PK at scheduled timepoints described in the SOA.

9. DNL343-SPECIFIC STATISTICAL CONSIDERATIONS

9.1 Deviations from the Default Master Protocol Trial Design

The statistical design for Regimen G will be in accordance with the statistical design described in Appendix I of the Master SAP, unless otherwise noted.

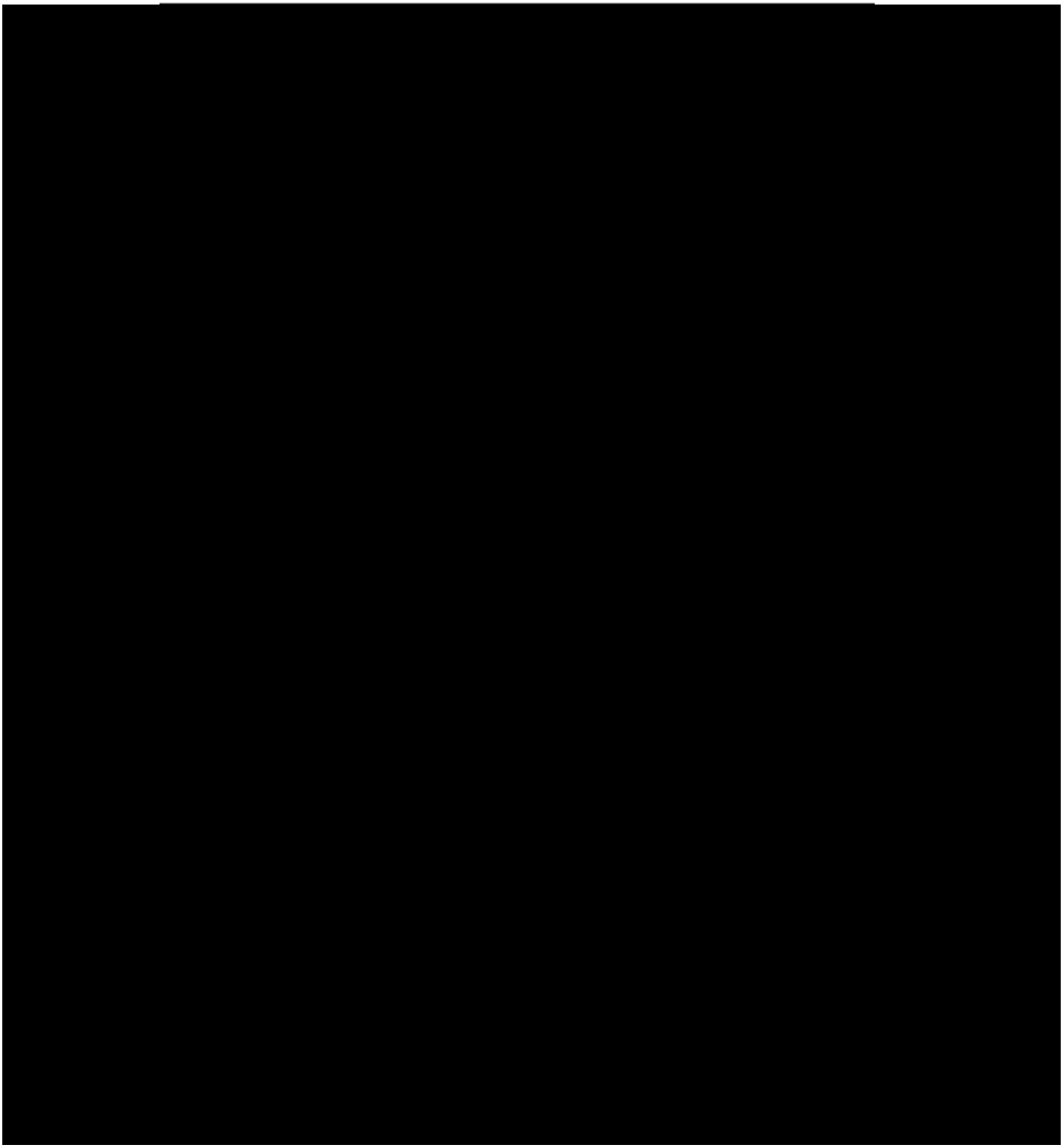
9.2 Regimen Specific Operating Characteristics

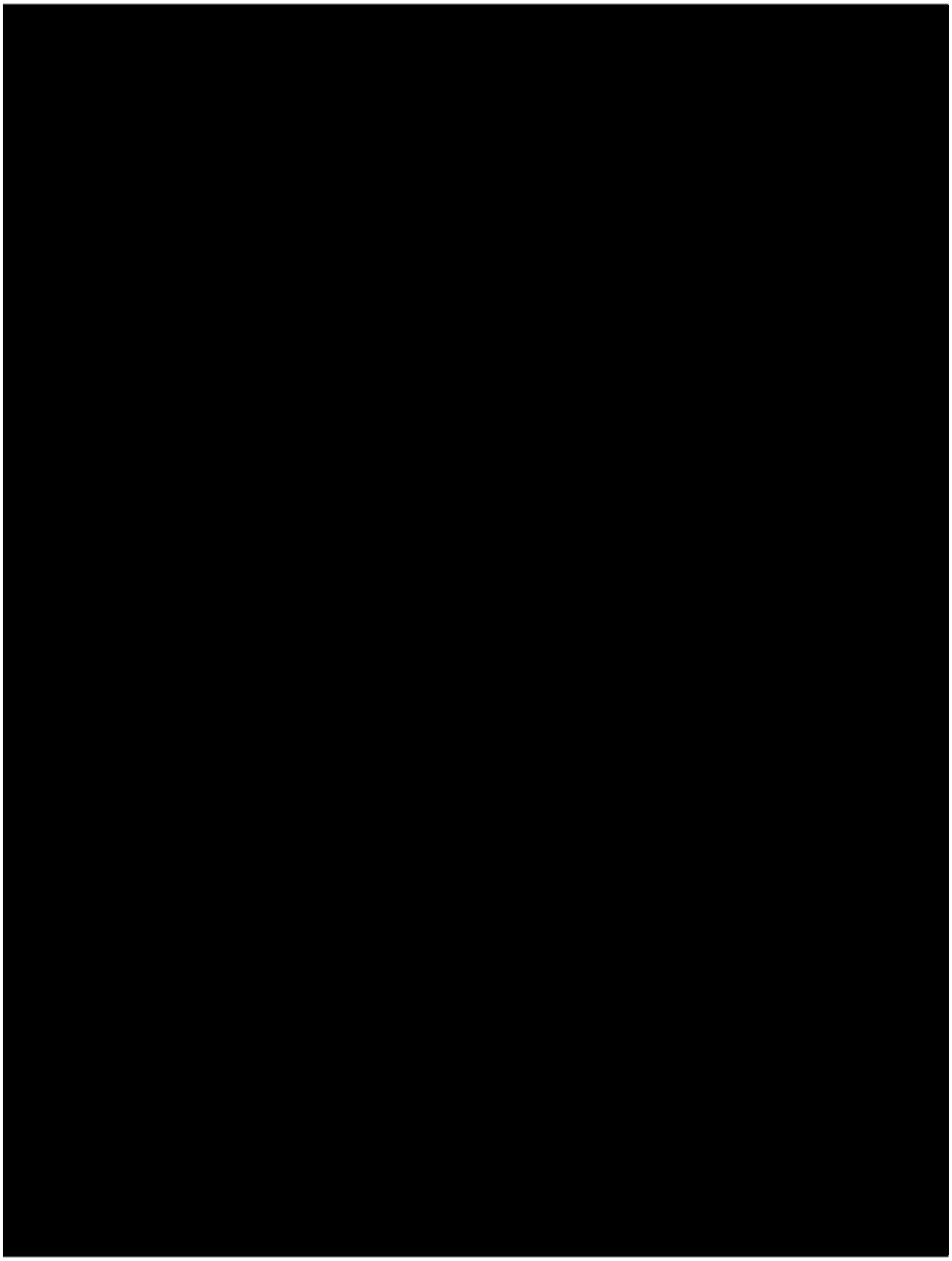
Clinical trial simulation was used to quantify operating characteristics for Regimen G (refer to the Regimen G statistical analysis plan for further details).

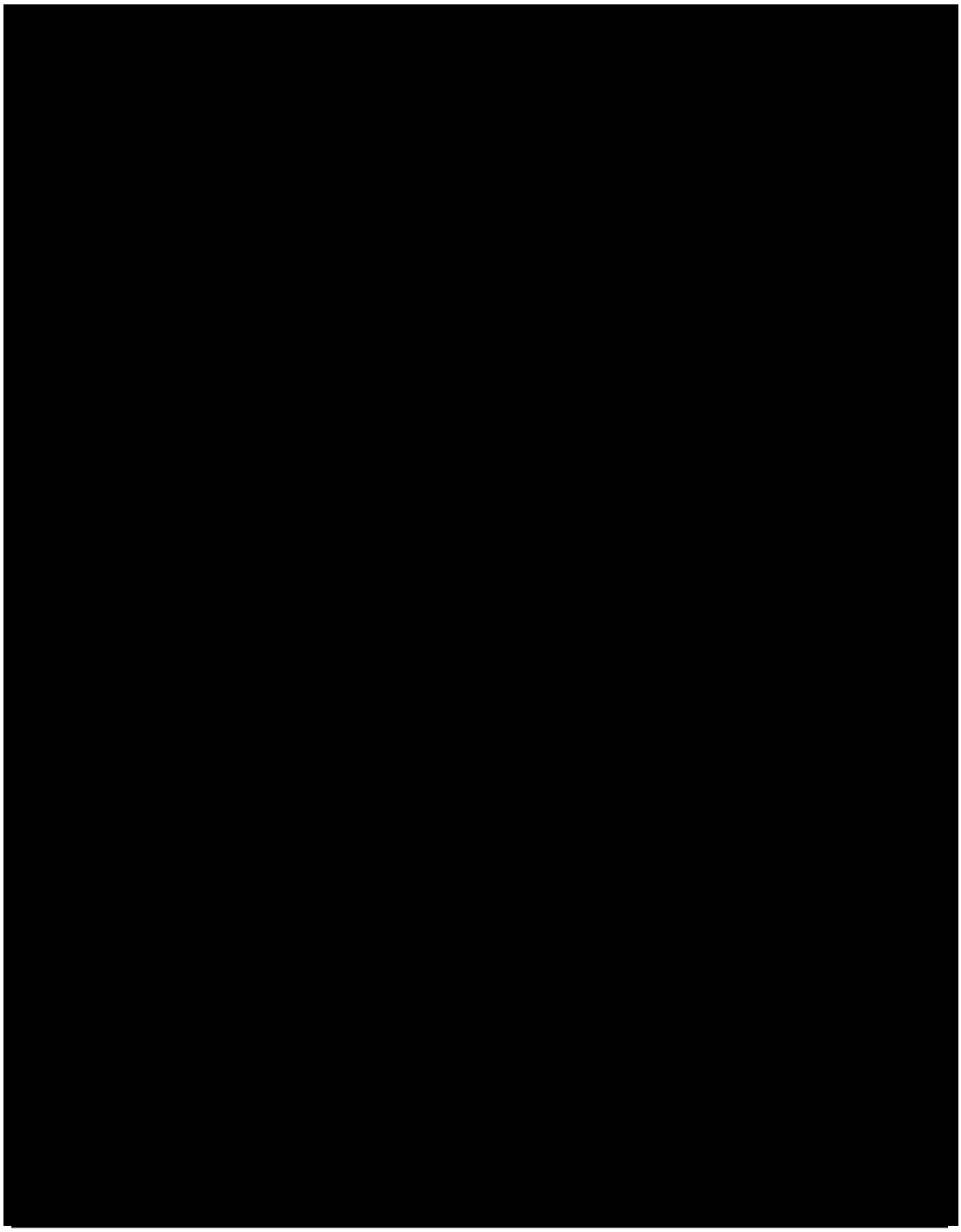
9.3 Sharing of Controls from other Regimens

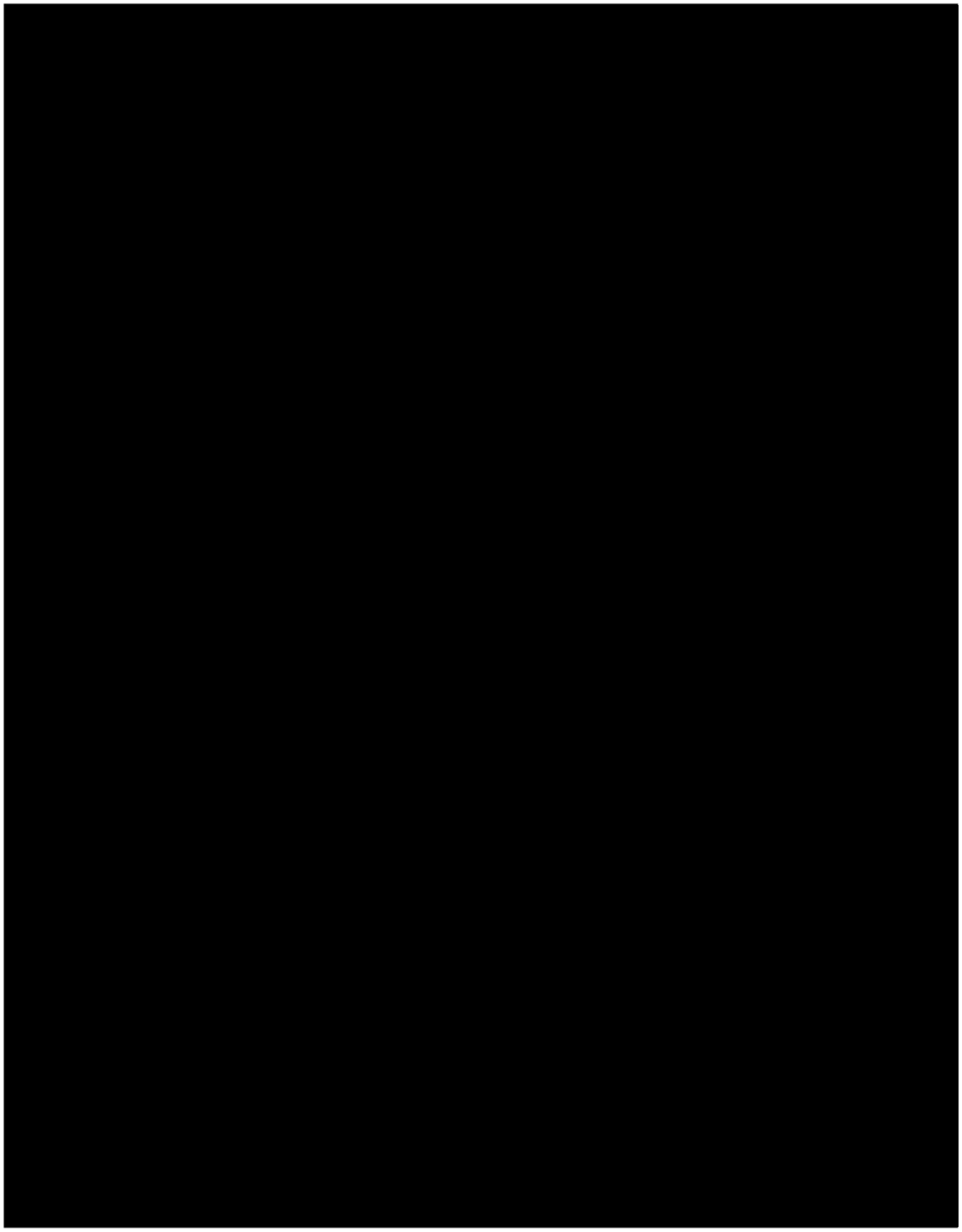
The primary or supportive analyses of Regimen G will include sharing of controls from other regimens. This is justified by the minor differences in inclusion/exclusion criteria of the RSAs, such that there are no expected systematic differences in the primary, secondary endpoints, or safety outcomes between the controls across regimens.

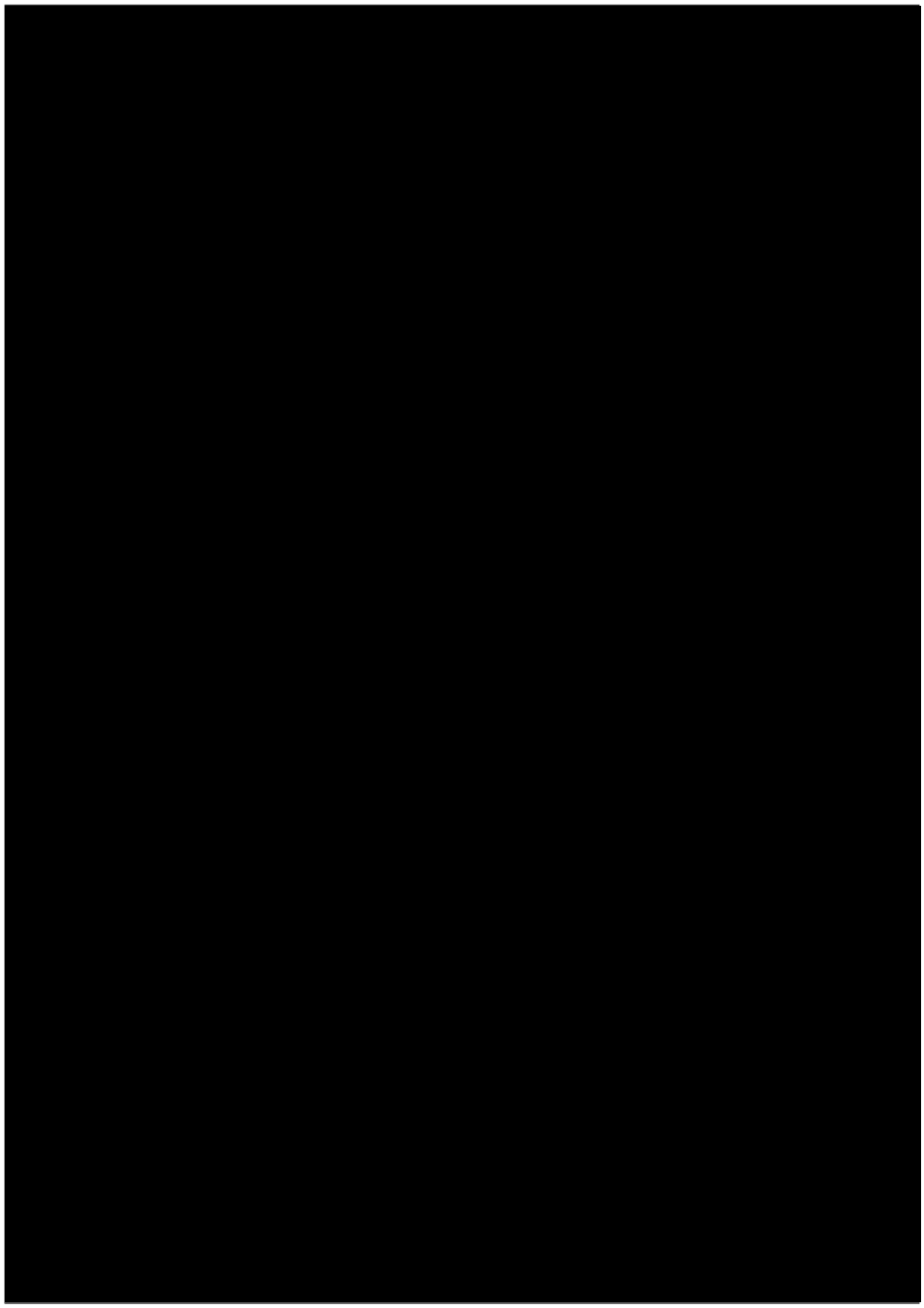
APPENDIX I: THE ALSAQ-40

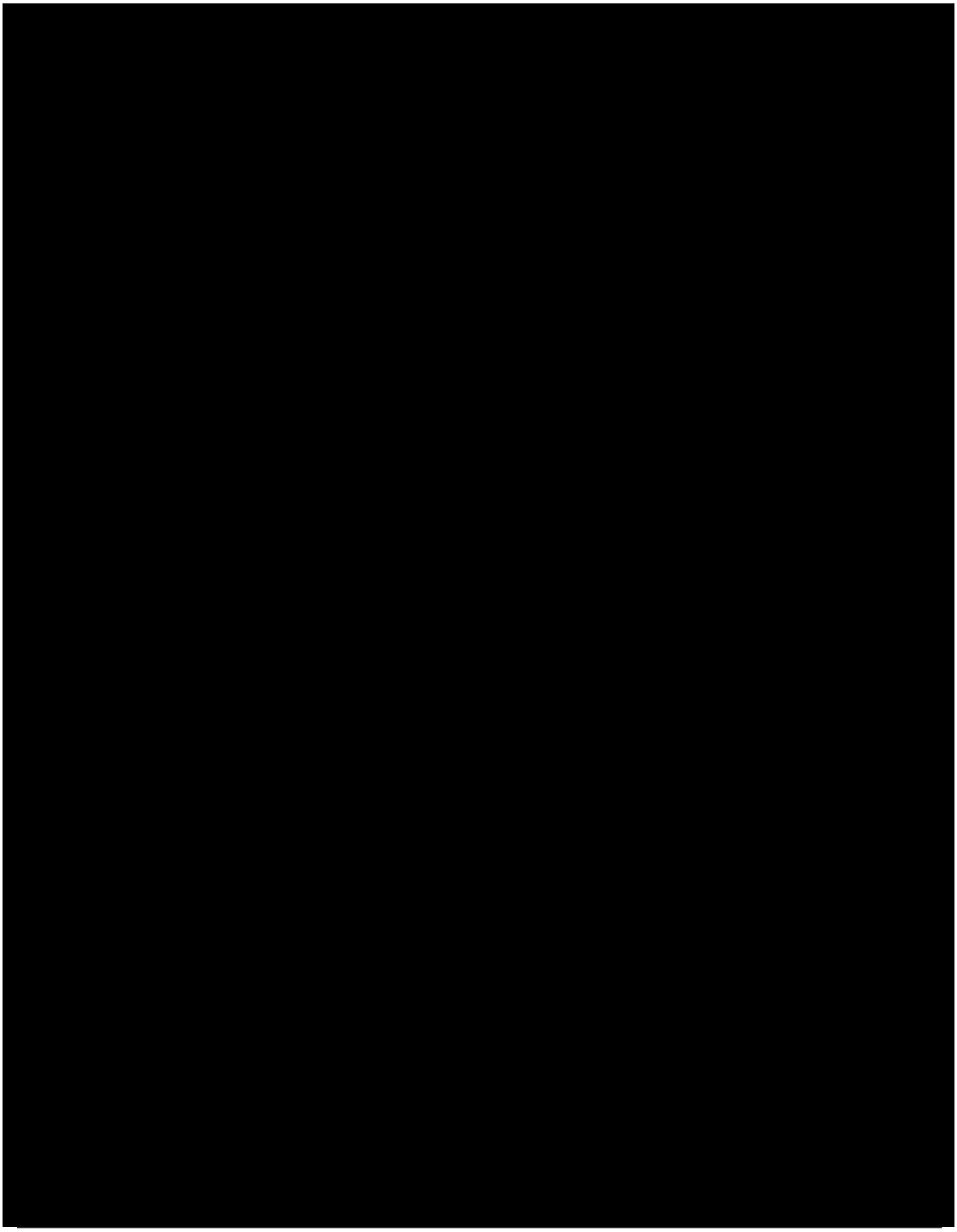


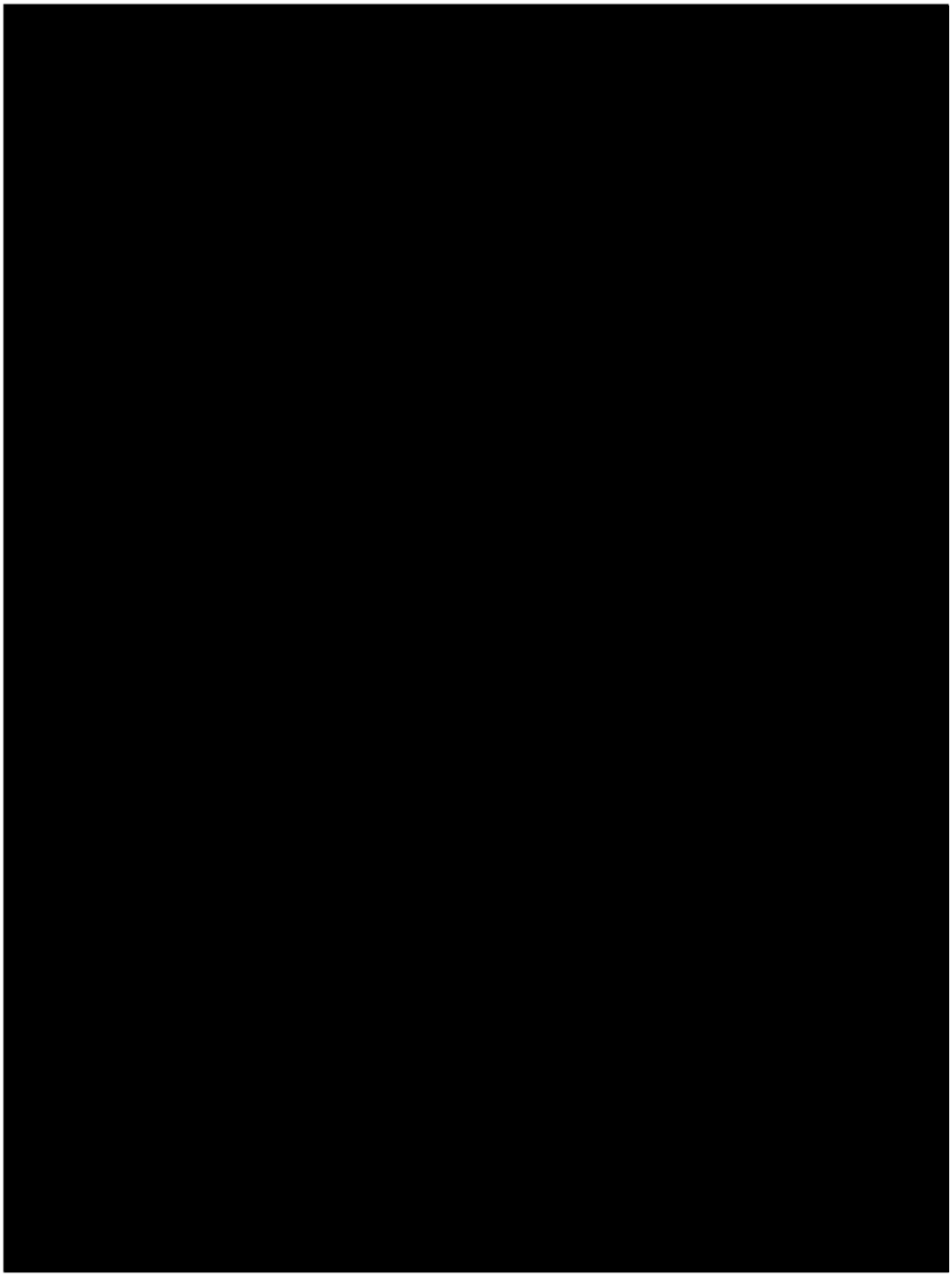


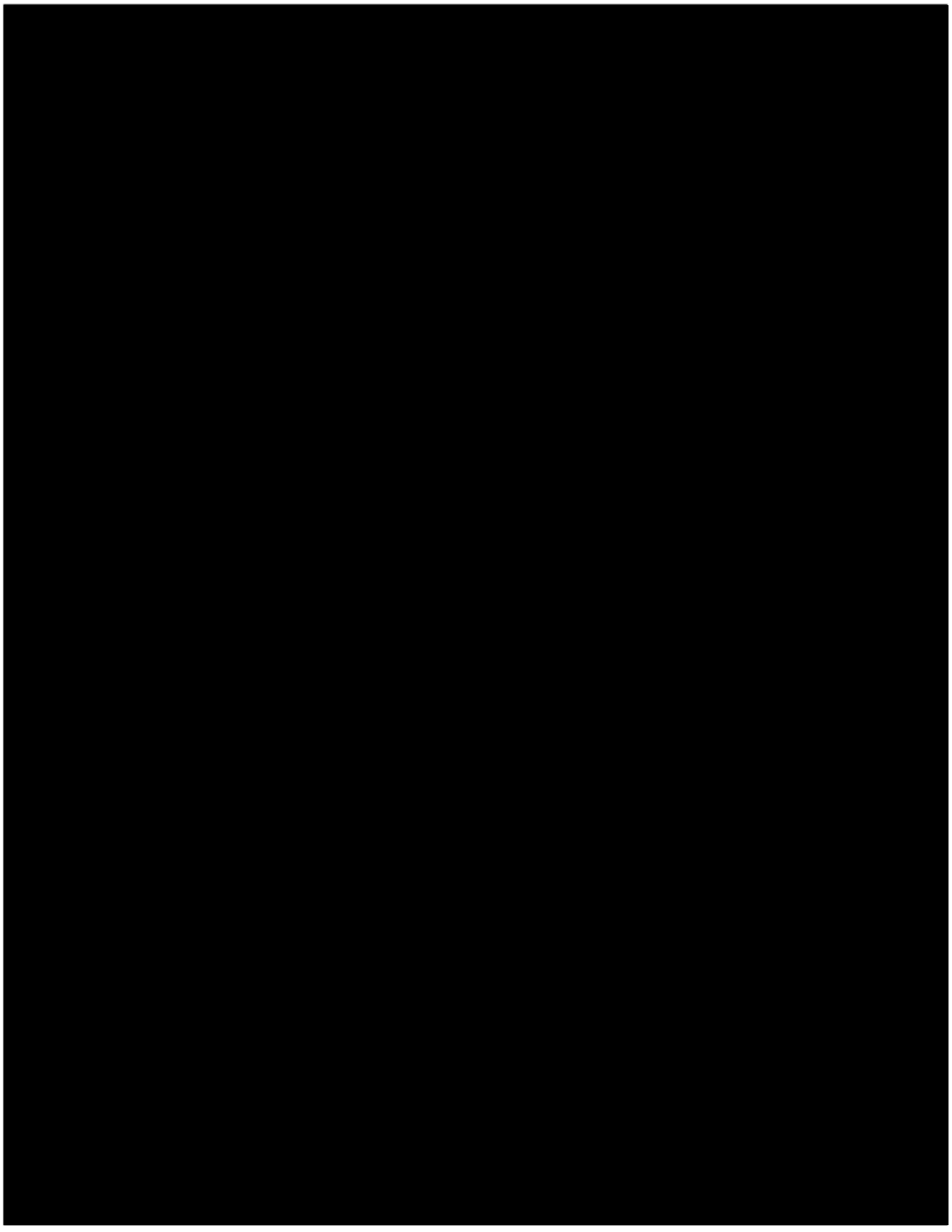


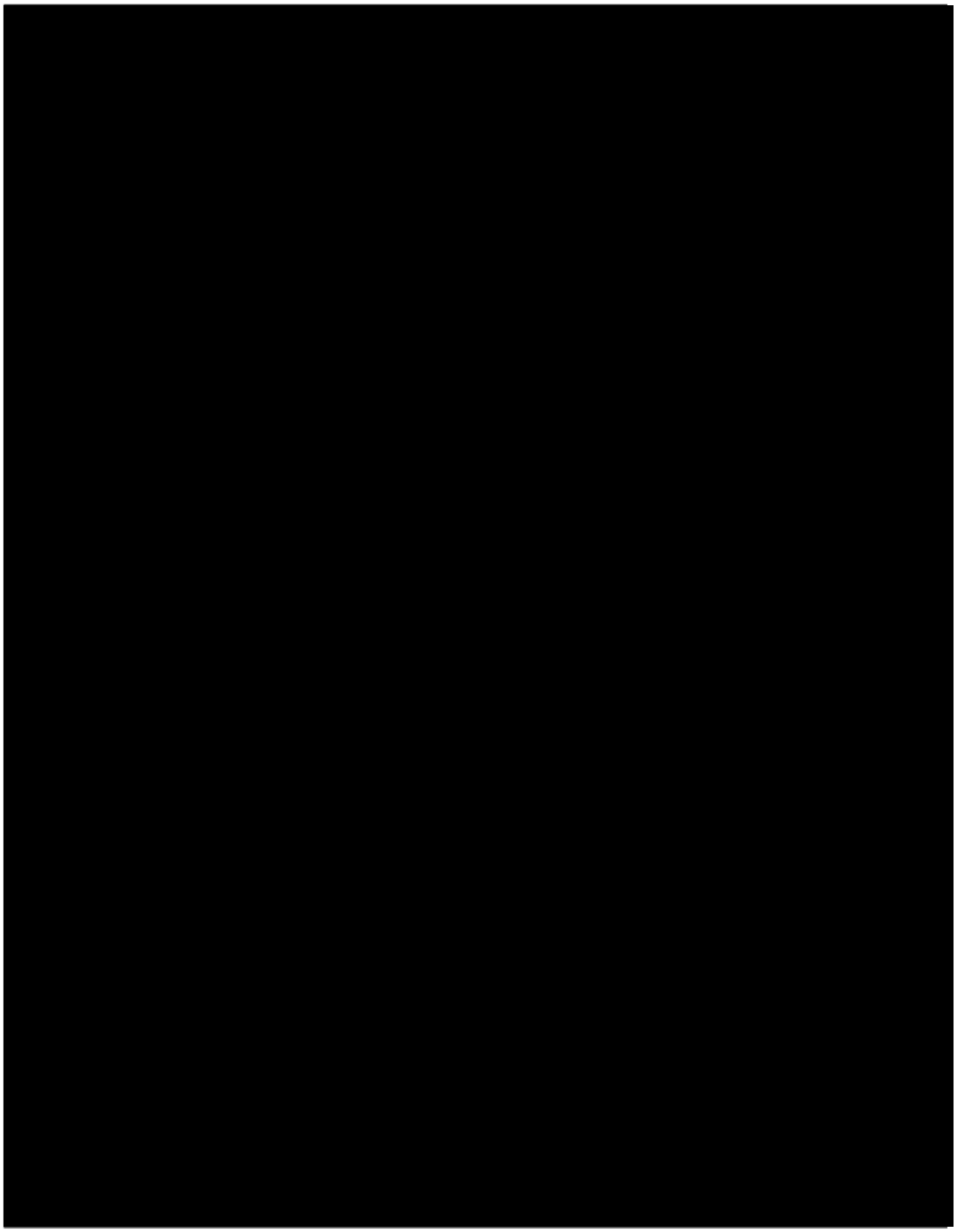




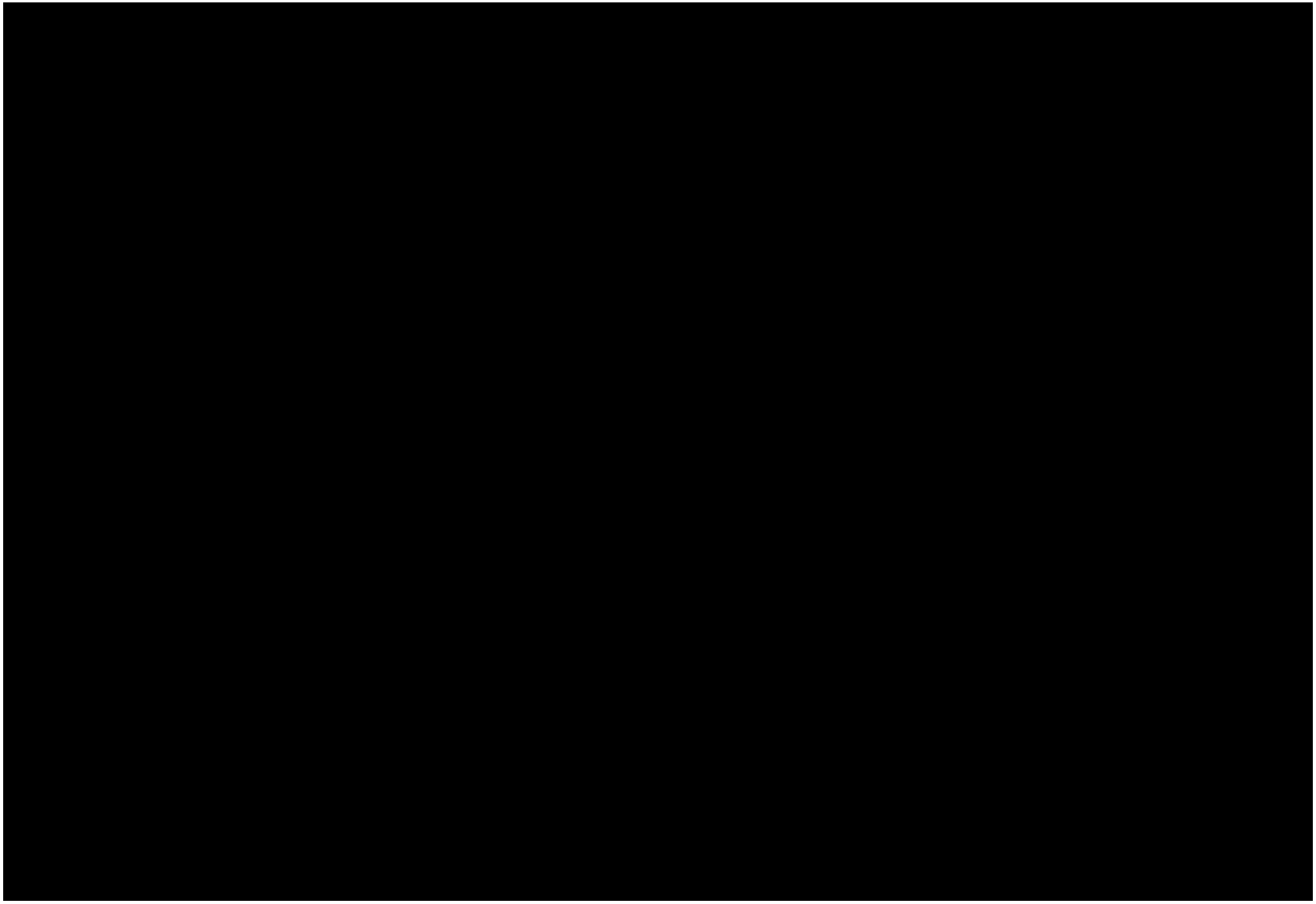








APPENDIX II: THE CENTER FOR NEUROLOGIC STUDY BULBAR FUNCTION SCALE (CNS-BFS)



APPENDIX III: CONTRACEPTIVE GUIDANCE FOR FEMALE PARTICIPANTS OF CHILDBEARING POTENTIAL

Highly Effective Methods [a] to be used in combination with a male barrier method (e.g. condom)
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [b]
• Bilateral tubal ligation [c]
• Azoospermic male partner of woman of childbearing potential participant[d]
Alternative Highly Effective Method
• Abstinence defined as **refraining from heterosexual intercourse during the entire duration of the study and for 90 days after last dose of study drug**. 'Periodic abstinence' is considered not reliable and would not be acceptable[e]

Notes: Male condom and female condom should not be used together (due to risk of failure with friction).

[a] Contraceptive use by participants should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b] Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] Essure® fallopian tube coil placement is not accepted, as the permanent contraception failure rate is likely greater than 1%.

[d] Azoospermia is a highly effective contraceptive method **provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed**. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

[e] Periodic abstinence (calendar, symptothermal, post ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are *NOT* acceptable methods of contraception.

APPENDIX III: CONTRACEPTIVE GUIDANCE FOR MALE PARTICIPANTS WITH FEMALE PARTNERS OF CHILDBEARING POTENTIAL

Highly Effective Methods [a] to be used in combination with a male barrier method (e.g. condom)
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [b]
• Bilateral tubal ligation [c]
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation −oral −intravaginal −transdermal −injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation**)** −Oral −injectable
• Azoospermic male participant[d]
Alternative Highly Effective Method
• Abstinence defined as **refraining from heterosexual intercourse during the entire duration of the study and for 90 days after last dose of study drug**. 'Periodic abstinence' is considered <u>not reliable</u> and would not be acceptable[e].

Notes: Male condom and female condom should not be used together (due to risk of failure with friction).

[a] Contraceptive use by participants should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b] Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] Essure® fallopian tube coil placement is not accepted, as the permanent contraception failure rate is likely greater than 1%.

[d] Azoospermia is a highly effective contraceptive method **provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed**. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

[e] Periodic abstinence (calendar, symptothermal, post ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are *NOT* acceptable methods of contraception.

APPENDIX IV: CONCOMITANT MEDICATION RESTRICTIONS

Excluded Medications

The medications indicated below are excluded during the study (unless otherwise specified) (See Section 5.9 for prohibited medications). **The lists below are not exhaustive**; the use of any concomitant medication is at the discretion of the investigator who knows the participant's medical history.

Strong CYP3A4/5 Inducers

DNL343 is a CYP3A4/5 substrate based on *in vitro* data; use of strong CYP3A4/5 inducers may decrease DNL343 plasma concentrations.

The medications in Table 4 are examples of strong CYP3A4/5 inducers and are excluded during the study. If needed, it is recommended that a tertiary source, such as the Drug Interactions Flockhart Table (found at *https://drug-interactions.medicine.iu.edu/MainTable.aspx*), be used for more information regarding other medications.

Table 4: Strong CYP3A4/5 Inducers with the Drug Half-Life and Washout Periods

Generic Drug Name	Drug Half-life	Recommended Washout
apalutamide	4.2 d	2 weeks
carbamazepine	15 h	2 weeks
phenytoin	24 h	2 weeks
rifampin	3.5 h	2 weeks
St. John's wort	36 h	2 weeks
bosentan	5 h	2 weeks

Abbreviations: CYP, cytochrome P450.
Source: US Food and Drug Administration (FDA). Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. FDA website. Published 2020. *https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers*.

Sensitive CYP3A4/5 Substrates

The clinical DDI study was conducted in healthy participants with midazolam, a sensitive substrate of CYP3A (DNLI-F-0007). The preliminary data showed DNL343 is a moderate inducer of CYP3A4 metabolism, indicating that sensitive CYP3A substrates may have reductions in exposure when coadministered with DNL343 which may lead to reduction in efficacy if the therapeutic index is narrow.

The medications in Table 5 are examples of sensitive CYP3A4/5 substrates. **The list below is not exhaustive** and if any of these medications are considered to have a narrow therapeutic index, they should be excluded during the study. Medications that are sensitive CYP3A4/5 substrates with a wide therapeutic index are permitted; participants taking them are to be

monitored for signs of loss of efficacy and/or may require dose increases based on the respective medication's prescribing information.

The medical monitor may be consulted to assess whether any of the medications listed in Table 5 would be considered to have narrow therapeutic index for the individual participant taking the medication.

Table 5: Sensitive CYP3A4/5 Substrates

Generic Drug Name	Drug Half-Life	Recommended Washout
buspirone	5.0 h	7 days
darunavir	3–5 h	7 days
dronedarone	1.6 ± 0.2 h	7 days
eplerenone	3–6 h	7 days
felodipine	4.8 min, 1.5 h, and 9.1 h (IV); 11–16 h (IR tablet)	7 days
indinavir	1.8 ± 0.4 h	7 days
lurasidone	18 h	7 days
maraviroc	13.2 (10.3–8.3) h	7 days
nisoldipine	3.2 h (young), 6.5 h (elderly)	7 days
quetiapine	6 h	7 days
Quinine	11 ± 2 h	7 days
saquinavir	7–12 h	7 days
sildenafil (when used for PAH)	2.4 ± 1.0 h	7 days
sirolimus	62.3 ± 16.2 h	13 days
tacrolimus	31.9 ± 10.5 h (based on radioactivity); 48.4 ± 12.3 h (based on tacrolimus concentrations)	10 days
ticagrelor	6.8 h (IV); 8.1 h (oral)	7 days
tipranavir	4.8 h (healthy volunteers); 5.5 h (female patients); 6.0 h (male patients)	7 days

Abbreviations: CYP, cytochrome P450; IM, intramuscular; IR, immediate release; IV, intravenous; PAH, pulmonary arterial hypertension.
Note: Sensitive substrates are drugs that demonstrate an increase in area under the concentration-time curve of ≥ 5-fold with strong inhibitors of a given metabolic pathway in clinical drug-drug interaction studies.
Source: US Food and Drug Administration (FDA). Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. FDA website. Published 2020. *https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers*.

Substrates of Major Transporters

DNL343 has a risk of inhibition of BCRP and OAT3 transporters at clinically relevant concentrations based on preliminary *in vitro* transporter inhibition studies. Medications that are substrates for these transporters may have increased exposure when taken with DNL343.

The medications in Table 6 are examples of substrates of BCRP or OAT3. **The list below is not exhaustive** and if any of these medications are considered to have a narrow therapeutic index, they should be excluded during the study. Medications that are considered to have a wide therapeutic index are permitted, and participants taking them are to be monitored for signs of AEs noted in the respective medication's prescribing information.

The medical monitor may be consulted to assess whether any of the medications listed in Table 6 would be considered to have narrow therapeutic index for the individual participant taking the medication.

Table 6: Substrates of BCRP or OAT3 Transporters

Substrate	Generic Drug Name	Drug Half-Life	Recommended Washout
BCRP Substrates	rosuvastatin	7.48 ± 1.65 h	7 days
	sulfasalazine	22.45 ± 6.366 h	7 days
OAT3 Substrates	adefovir	7.48 ± 1.65 h	7 days
	cefaclor	11 h	7 days
	ceftizoxime	1.8 ± 0.8 h	7 days
	famotidine	0.8 ± 0.2 h	7 days
	furosemide	20 ± 6 h	7 days
	methotrexate	15 h	7 days
	oseltamivir carboxylate	6 to 10 h	7 days
	penicillin G	7.6 ± 3.4 h	7 days

Abbreviations: BCRP, breast cancer resistance protein; OAT3, organic anion transporter 3Source: US Food and Drug Administration (FDA). Drug development and drug interactions: table of substrates, inhibitors and inducers. FDA website. Published 2020. *https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.*

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