Official Title:	**A Phase 2, Multicenter, Open-Label, Extension Study to Evaluate the Long-Term Safety, Clinical Activity, and Pharmacokinetics of ALN-TTR02 in Patients With Familial Amyloidotic Polyneuropathy Who Have Previously Received ALN-TTR02**
NCT Number:	**NCT01961921**
Document Date:	**Statistical Analysis Plan Version 2.0, 14 September 2016**

STATISTICAL ANALYSIS PLAN

A Phase 2, Multicenter, Open-Label, Extension Study to Evaluate the Long-Term Safety, Clinical Activity, and Pharmacokinetics of Patisiran in Patients with Familial Amyloidotic Polyneuropathy Who Have Previously Received Patisiran

Protocol Number:	ALN-TTR02-003
Protocol Version and Date:	Global Amendment 1: 15 June 2015 Original: 26 April 2013
Name of Test Drug:	Patisiran
Phase:	Phase 2
Methodology:	Multi-center, open-label, extension study
Sponsor:	Alnylam Pharmaceuticals, Inc 300 Third Street Cambridge, MA 02142 Tel: (617) 551-8200 Fax: (617) 551-8101
Sponsor Representative:	[redacted]
Analysis Plan Date:	Amendment 1: 14 September 2016 Original: 29 December 2014
Analysis Plan Version:	Version 2.0

APPROVAL SIGNATURE PAGE

Protocol Title: A Phase 2, Multicenter, Open-Label, Extension Study to Evaluate the Long-Term Safety, Clinical Activity, and Pharmacokinetics of Patisiran in Patients With Familial Amyloidotic Polyneuropathy Who Have Previously Received Patisiran

Sponsor: Alnylam Pharmaceuticals, Inc.
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Protocol Number: ALN-TTR02-003

Document Date / Version: 14 September 2016/ Version 2.0

Veristat, Inc. Author:

[redacted]

Signature: [redacted]

Date: 14 September 2016

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

[redacted]

Signature: [redacted]

Date: 14 SEP 2016

[redacted]

Signature: [redacted]

Date: 14 Sep 2016

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
ATC	Anatomic therapeutic class
ATTR	Transthyretin-mediated amyloidosis
AUC	Area under the plasma concentration-time curve
COMPASS 31	Composite Autonomic Symptom Score
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme linked immunosorbent assay
EOI	End of infusion
ET	Early termination
EU	European Union
FAC	Familial amyloidotic cardiomyopathy
FAP	Familial amyloidotic polyneuropathy
H1/H2 blocker	Histamine H1/H2 receptor antagonist
HRdb	Heart rate response to deep breathing
ICH	International Conference on Harmonisation
IENFD	Intraepidermal nerve fiber density
IRR	Infusion-related reaction
IV	Intravenous(ly)
LNP	Lipid nanoparticles
mBMI	Modified body mass index
MedDRA®	Medical Dictionary for Regulatory Activities
mNIS	Modified Neuropathy Impairment Score
mRNA	Messenger ribonucleic acid
NCS	Nerve conduction studies
NIS	Neuropathy Impairment Score
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
PD	Pharmacodynamic
PK	Pharmacokinetic
PND	Polyneuropathy disability
PO	By mouth
QST	Quantitative sensory testing
QTc	QT interval corrected for heart rate
RBP	Retinol binding protein

Abbreviation	Definition
Rel Day	Relative study day
RNAi	Ribonucleic interference
R-ODS	Rasch-built Overall Disability Scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SGNFD	Sweat gland nerve fiber density
SI	International system of units
siRNA	Small interfering ribonucleic acid
SOC	System organ class
T4	Thyroxine
TP	Touch pressure
TTR	Transthyretin
VAS	Visual analogue scale
VDT	Vibration detection threshold
WHO	World Health Organization
WT	Wild type

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

Transthyretin (TTR), also known as prealbumin, is a tetramer protein produced predominantly by hepatocytes (>95% of TTR is liver-derived), with a small fraction produced in the choroid plexus and retina [1]. The primary physiological role of TTR is to serve as a carrier of retinol (also known as vitamin A); it also plays a minor role as a carrier for thyroxine (T4).

Mutations in the TTR gene can lead to destabilization of the tetrameric protein and disassociation of the TTR subunits into dimers and individual monomers. These misfolded TTR monomers (both mutant and wild type [WT]) can then self-assemble into amyloid fibrils [1]. The amyloid fibrils are deposited into the extracellular space of various tissues where they form amyloid plaques, with the peripheral nervous system, gastrointestinal tract, and heart being the major sites of deposition.

There are over 100 reported TTR genetic mutations. These mutations are phenotypically expressed as a spectrum of disease which is collectively referred to as TTR-mediated amyloidosis (ATTR) [2]. There is a range of clinical manifestations of ATTR; the most common manifestations include some form of cardiac and/or neurologic involvement (e.g., cardiomyopathy, autonomic neuropathy, and sensory and motor neuropathy) that depends, in part, upon the particular TTR mutation and the site of amyloid deposition. Transthyretin amyloidosis is associated with severe morbidity and mortality, with a life expectancy limited to approximately 5 to 15 years from symptom onset [2].

Two significant clinical syndromes of ATTR have been described: familial amyloidotic polyneuropathy (FAP) and familial amyloidotic cardiomyopathy (FAC), both of which are characterized by amyloid deposits of both mutant and WT TTR [1].

Familial amyloidotic polyneuropathy, caused predominantly by the V30M mutation, occurs primarily in families with heritage from Portugal, Sweden and Japan, has an earlier onset (age 30 to 50 years), and is characterized initially by peripheral neuropathy leading to sensory and motor deficits, as well as profound autonomic dysfunction that produces disabling gastrointestinal pathology, orthostatic hypotension, and bladder dysfunction [1, 2]. Amyloid infiltration of the sinus node and atrioventricular conduction system in the heart is also common in FAP. Sudden death is not uncommon in FAP, and is believed to result from heart block or tachyarrhythmias [8, 9].

It is estimated that 45,000 to 50,000 individuals have FAP or FAC. In both FAP and FAC, quality of life is severely impacted following the onset of symptoms, and the disease proceeds inexorably to death [10, 11].

Because the liver is the primary source of mutant TTR, liver transplantation has been used over the past 20 years in an attempt to treat ATTR [1]. However, the procedure is only effective in halting or slowing the progression of disease in patients with an early age of onset [1], especially for those with the V30M mutation and short disease duration prior to transplant; consequently almost two-thirds of ATTR patients are not transplant-eligible. When performed early in the course of the disease, liver transplantation can stabilize and slow progression of neuropathy in patients with FAP due to V30M. However, in FAC patients and FAP patients with evidence of cardiac involvement, liver transplantation is contraindicated since it does not

halt the progression of cardiac disease in these patients [13, 14, 15, 16] and may actually accelerate the course of cardiomyopathy due to further deposition of WT TTR (originating from the transplanted liver) in the heart [1].

Tafamidis, a TTR tetramer stabilizer, was approved in November 2011 in the European Union (EU) for the treatment of ATTR in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment [1]; it has not been approved in the US. Diflunisal, is another TTR tetramer stabilizer available in generic form. A US government sponsored multicenter, placebo-controlled Phase 3 study in FAP patients was completed in 2012; data suggest an effect of diflunisal on NIS+7, the primary endpoint of the study [1].

However, the large majority of ATTR patients do not qualify for either liver transplantation or tafamidis, and therefore, the disease is primarily managed with palliative care.

Ribonucleic acid interference (RNAi) is a naturally occurring cellular mechanism for regulating gene expression that is mediated by "small interfering ribonucleic acids" (siRNAs) [1]. Typically, synthetic siRNAs are 19 to 23 base pair double-stranded oligonucleotides in a staggered duplex with a 2-nucleotide overhang at one or both of the 3' ends. Such siRNAs can be designed to target an endogenous or virally-expressed gene. When introduced into cells, the net effect of an RNAi-based pharmacological approach is the binding of the siRNA to its complementary messenger ribonucleic acid (mRNA) sequence, cleavage of this target mRNA, and suppression of the target protein [1]. The ability to selectively and potently degrade the mRNA encoding the TTR protein using an siRNA offers a potent and specific approach for the treatment of ATTR.

Patisiran Solution for Injection (hereafter referred to as patisiran), is a novel drug to treat ATTR and consists of a single LNP-formulated TTR siRNA targeting both WT and all known mutant forms of TTR. Since TTR amyloid deposits consist of both mutant and WT TTR, it is desirable to be able to lower the production of both WT and mutant TTR with a single drug in order to treat the different variants of ATTR. Patisiran is intended for administration as an intravenous (IV) infusion over 70 minutes.

1.1.2. Study Objectives

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial. This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.1.2.1. Primary Objective

The primary objective of this study is to evaluate the safety of long-term (approximately 2 years) dosing with patisiran.

1.1.2.2. Secondary Objectives

Secondary objectives include:

- Assessing the pharmacodynamic (PD) effect of long-term dosing of patisiran on serum TTR.
- Assessing changes from baseline in:
  - Neurologic impairment using the modified Neuropathy Impairment Score (mNIS) +7 composite score.
  - Quality of life (EQ5D) and disability (Rasch-built Overall Disability Scale [R-ODS]).
  - Motor function impacting activities of daily living, including a 10-meter walk test and test of grip strength.
  - Nutritional status (modified body mass index [mBMI]).

1.1.2.3. Tertiary Objectives

Tertiary objectives include:

- Further characterization of the plasma and urine pharmacokinetics (PK) of patisiran.
- Assessing changes from baseline in:
  - Secondary PD biomarkers, including RBP, and vitamin A.
  - Sensory and autonomic innervation (skin punch biopsies for intraepidermal nerve fiber density [IENFD] and sweat gland nerve fiber density [SGNFD]).
  - Neuropathy Impairment Score (NIS)
  - Vibration detection threshold (VDT).
  - Heart rate variability with deep breathing (HRdb).
  - NIS+7 composite score
  - Ambulation, using FAP stage and polyneuropathy disability (PND) score.
  - Patient reported autonomic neuropathy symptoms using the Composite Autonomic Symptom Score (COMPASS 31) questionnaire.
  - Healthcare utilization using a pharmacoeconomics questionnaire.
  - Cardiac structure/function through echocardiograms and serum levels of troponin I and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) in patients with evidence of pre-existing cardiac amyloid involvement.

1.2. Study Design

1.2.1. Synopsis of Study Design

This study is a multicenter, multinational, Phase 2, open-label, extension study designed to evaluate the safety and tolerability of long term patisiran administered to patients with FAP. Additional information to be evaluated includes PK, PD, and clinical activity.

Patients eligible for inclusion in this study had to have previously received and tolerated patisiran in the Phase 2 Study ALN-TTR02-002. In addition, they must have an adequate performance status (Karnofsky performance status of 60% or greater), and adequate hepatic and renal function.

Patients will be screened within 28 days prior to administration of study medication. Consented eligible patients will be enrolled and receive 0.3 mg/kg patisiran infusion over 70 min once every 3 weeks for approximately 2 years. The infusion time may be extended up to 3 hours in the event of a mild or moderate infusion-related reaction (IRR) (study drug administration will not be resumed for any patient following a severe IRR). Patients will remain at the clinic from 2 to 6 hours after the end of the study drug infusion. PK, PD, and clinical activity (see Table 1-1 and Table 1-2 for details) will be evaluated every 6 months in addition to continued safety monitoring throughout the study and during study drug administration visits every 3 weeks.

The duration of patient participation in this study is approximately 2 years and 4 months.

1.2.2. Randomization Methodology

Not applicable as this is a single arm non-randomized study.

1.2.3. Stopping Rules and Unblinding

No unblinding procedures or stopping rules are required, as this is an open-label, single-arm study and all patients will receive 0.3 mg/kg patisiran.

1.2.4. Study Procedures

The schedules of assessments for Years 1 and 2, as outlined in the study protocol, are presented in Table 1-1 and Table 1-2, respectively.

Table 1-1: Schedule of Assessments for Year 1 — ALN-TTR02 Administered Once Every 3 Weeks

Procedure	Visit Type	Screening/ Baseline[a]	Dosing									Mid-year/Annual Efficacy Assessment
	Study Week	NA	1 & 28	4 & 31	7 & 34	10 & 37	13 & 40	16 & 43	19 & 46	22 & 49	25 & 52	27 & 54
	Study Day	Day -28 to -0	D0 & D189	D21 & D210	D42 & D231	D63 & D252	D84 & D273	D105 & D294	D126 & D315	D147 & D336	D168 & D357	D182 & D371
	Window	NA	±3D[b]	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±5D
Informed Consent		X										
Demographics		X										
Medical History[c]		X										
Inclusion/Exclusion Criteria		X	X[d]									
Physical Examination		X										X
Weight[e]		X	X	X	X	X	X	X	X	X	X	X
Height		X										
Vital Signs[f]		X	X	X	X	X	X	X	X	X	X	X
Echocardiogram		X										
12-Lead ECG[g]		X										X
Urine Pregnancy Test (females only)[h]		X										
Hematology[i]		X	X[d]								X	
Serum Chemistry and Urinalysis[i]		X	X[d]				X				X	
Thyroid Function Tests and Coagulation Studies[i]		X	X[d]								X	
Ophthalmology Exam		X										X
PD Assessments:												
TTR protein (ELISA and turbidimetric)[j]		X	X[d]				X				X	X
RBP and Vitamin A[j]		X	X[d]				X				X	X

Procedure	Visit Type	Screening/ Baseline[a]	Dosing									Mid-year/Annual Efficacy Assessment
	Study Week	**NA**	**1 & 28**	**4 & 31**	**7 & 34**	**10 & 37**	**13 & 40**	**16 & 43**	**19 & 46**	**22 & 49**	**25 & 52**	**27 & 54**
	Study Day	**Day -28 to -0**	**D0 & D189**	**D21 & D210**	**D42 & D231**	**D63 & D252**	**D84 & D273**	**D105 & D294**	**D126 & D315**	**D147 & D336**	**D168 & D357**	**D182 & D371**
	Window	**NA**	**±3D[b]**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±5D**
Other Assessments:												
Exploratory Biomarkers[k]		X	X[d]				X				X	
Anti-drug Antibodies[k]		X	X[d]	X[l]			X[l]				X	
Pharmacoeconomics Questionnaire		X										X
Clinical Activity Assessments:												
mNIS + 7[m,n]		X										X
VDT[n]		X										X
HRdb[n]		X										X
Grip Strength[n,o]		X										X
10-Meter Walk Test[n,p]		X										X
NIS[n]		X										X
Skin Punch Biopsy (IENFD & SGNFD)[q]		X										X
mBMI		X										X
FAP Stage and PND Score		X										X
COMPASS 31		X										X
QOL and Disability Questionnaires[r]		X										X
Premedication Administration[s]			X	X	X	X	X	X	X	X	X	
Study Drug Administration[t]			X	X	X	X	X	X	X	X	X	
Plasma PK Sampling[u]			X[v]	X[v]	X[v]	X[v]	X				X	X[w]
Urine PK Sampling[x]			X[v]	X[v]	X[v]	X[v]	X				X	X[w]

Procedure	Visit Type	Screening/ Baseline[a]	Dosing									Mid-year/Annual Efficacy Assessment
	Study Week	**NA**	**1 & 28**	**4 & 31**	**7 & 34**	**10 & 37**	**13 & 40**	**16 & 43**	**19 & 46**	**22 & 49**	**25 & 52**	**27 & 54**
	Study Day	**Day -28 to -0**	**D0 & D189**	**D21 & D210**	**D42 & D231**	**D63 & D252**	**D84 & D273**	**D105 & D294**	**D126 & D315**	**D147 & D336**	**D168 & D357**	**D182 & D371**
	Window	**NA**	**±3D[b]**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±5D**
PK/PD Subgroup Only												
TTR (ELISA and turbidimetric)[y]			X		X							
RBP and Vitamin A[y]			X		X							
Plasma PK Sampling			X[z]		X[z]							
Urine PK Sampling			X[aa]		X[aa]							
Cardiac Subgroup Only:												
Echocardiogram												X
Troponin I and NT-proBNP			X[d]				X				X	
Concomitant Medications		X	X									
Adverse Events			X[bb]									

Note: The schedule of assessments for patients administered ALN-TTR02 once every 4 weeks is provided in Appendix 2.

a Assessments performed during the ALN-TTR02-002 study that occur within the Screening/Baseline timeframe will not need to be repeated at the Screening/Baseline visit.
b Window does not apply to Day 0.
c Any AEs from the previous study (ALN-TTR02-002) that are ongoing on Day 0 are to be recorded on the Medical History case report form for the current study (ALN-TTR02-003) and followed until resolution.
d To be performed only on Day 0, not on Day 189.
e On dosing days, weight will be measured predose.
f On dosing days, vital signs will be measured predose. Vital signs to include: blood pressure, pulse rate, oral body temperature, and respiratory rate. Parameters are to be measured in the supine position using an automated instrument after the patient has rested comfortably for 10 minutes.
g Triplicate recordings will be obtained.
h A pregnancy test will be performed on all females of child-bearing potential at Screening/Baseline and any time pregnancy is suspected.
i To be performed before dosing with ALN-TTR02.
j Blood samples for TTR, RBP, and vitamin A will be collected on Day 0 at 2 separate time points: 1) prior (within 10 minutes) to administration of premedications and 2) after administration of premedications but immediately prior (within 10 minutes) to dosing of ALN-TTR02. At all other dosing visits, a blood sample will be collected only once; prior to administration of premedications. At the Mid-year and Annual visits, one sample should be collected on each day. Additionally, aliquots of serum samples will be taken and frozen, to permit testing of additional proteins related to FAP.
k Blood samples for exploratory biomarkers and ADA will be collected prior to dosing with ALN-TTR02.
l To be collected only on Days 21 and 84, not on Days 210 and 273.
m The mNIS + 7 consists of the modified NIS tool (or aspects of the tool; weakness and reflexes only), nerve conduction studies (NCS), quantitative sensory testing (QST) by body surface area including touch pressure (TP) and heat pain (HP), and postural blood pressure. Every effort will be made to use the same devices for a patient throughout the duration of the study.
n Two independent assessments will be performed on separate days at Screening/Baseline and then approximately every 6 months. The Screening/Baseline assessments must be performed within 14 days prior to the first dose of study drug (Day 0). The second (repeat) assessment must be conducted at least 24 hours (approximately) after the first assessment, but not more than 7 days apart.
o Hand grip strength will be measured using a dynamometer held in the dominant hand. Every effort will be made to use the same device for a patient throughout the duration of the study. At each time point, 2 independent assessments (each assessment performed in triplicate) will be performed.
p Patient will walk without assistance for 10 meters in order to complete the 10-meter walk test. The time required for the patient to complete 2, 8, and 10 meters will be recorded.
q Two 3-mm skin punch biopsies are to be obtained. One will be obtained from the distal lower leg, when a patient's clinical status allows, and one from the distal thigh.
r Quality of life and disability assessments will include the EQ5D and R-ODS questionnaires.
s The following premedications will be administered at least 60 minutes prior to the start of the infusion of ALN-TTR02: dexamethasone (10 mg IV, or equivalent), paracetamol (PO 500 mg; or equivalent), IV H2 blocker (e.g., ranitidine 50 mg, famotidine 20 mg, or equivalent other H2 blocker dose), and IV H1 blocker (e.g., diphenhydramine 50 mg or equivalent; hydroxyzine or fexofenadine 25 mg PO or cetirizine 10 mg PO may be substituted for any patient who does not tolerate IV diphenhydramine or other IV H1 blockers).
t The infusion site will be assessed for any localized reaction pre-dose, during the infusion, at the end of the infusion (EOI), and for 30 minutes after the infusion.
u Plasma PK samples will be collected pre-dose (within 1 hour of planned dosing start; -5 minutes), EOI (+5 minutes), and 1 hour post-dose (±5 min), except on Days 0 and 231 for subjects in the PK/PD Subgroup. The EOI will usually occur at 70 minutes after the start of the infusion, except in patients where the infusion has been prolonged. All post-infusion times are relative to the EOI, regardless of the duration of the infusion. In addition, if the infusion is stopped and the site is considering restarting the infusion, a PK blood sample will be taken while the infusion is stopped.
v Samples to be collected on Day 0, 21, 42 and 63 only.
w Samples will be collected once on each day of the 2-day study visit.
x For each dose, urine PK samples will be collected pre-dose (within 1 hour of planned dosing start; -5 minutes) and 1 hour (±5 minutes) after dosing with ALN-TTR02.

y For patients in the PK/PD subgroup, blood samples for TTR, RBP, and vitamin A will be collected on Days 0 and 231 immediately prior (within 10 minutes) to administration of premedications. In addition, a TTR, RBP, and vitamin A sample will also be collected 24 hours (±120 minutes) post-dose, and 3, 7, and 17 days (±1 day) after dosing with ALN-TTR02 for the study visits noted (blood samples for TTR will not be collected on Days 42 and 189).

z On Days 0 and 231, patients in the PK/PD subgroup will have PK samples taken pre-dose (within 1 hour of planned dosing start; -5 minutes), EOI (+5 minutes), and 1, 2, 4, 6, and 24 hours postinfusion. In addition, a plasma PK sample will also be collected 3, 7, and 17 days (±1 day) after dosing with ALN-TTR02 for the study visits noted. The windows for sampling are ±5 minutes for the 1, 2, 4, and 6 hour sampling periods; and ±120 minutes for the 24 hour sampling period.

aa On Days 0 and 231, patients in the PK/PD subgroup will have a urine sample for PK analysis taken pre-dose (within 1 hour of planned dosing start; -5 minutes), EOI (+5 minutes), and 6 and 24 hours postinfusion. In addition, a urine PK sample will also be collected 3, 7, and 17 days (±1 day) after dosing with ALN-TTR02 for the study visits noted. The windows for sampling are ±5 minutes for the 1, 2, 4, and 6 hour sampling periods; and ±120 minutes for the 24-hour sampling period.

bb Adverse events are to be documented beginning with the initiation of the first infusion.

Table 1-2: Schedule of Assessments for Year 2 — ALN-TTR02 Administered Once Every 3 Weeks

Procedure	Visit Type	Dosing									Mid-year/ Annual Efficacy Assess-ment	21- and 56-day Follow-up[a]		Early Termi-nation
	Study Week	55 & 82	58 & 85	61 & 88	64 & 91	67 & 94	70 & 97	73 & 100	76 & 103	79 & 106	81 & 108	109	114	ET
	Study Day	D378 & D567	D399 & D588	D420 & D609	D441 & D630	D462 & D651	D483 & D672	D504 & D693	D525 & D714	D546 & D735	D560 & D749	D756	D791	N/A
	Window	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±5D	±5D	±5D	2D to 7D
Physical Examination											X	X		X
Weight[b]		X	X	X	X	X	X	X	X	X	X	X		X
Vital Signs[c]		X	X	X	X	X	X	X	X	X	X	X		X
12-lead ECG[d]											X	X		X
Hematology[e]										X		X		X
Serum Chemistry and Urinalysis[e]						X				X		X		X
Thyroid Function Tests and Coagulation Studies[e]										X		X		X
Ophthalmology Exam											X			X
PD Assessments:														
TTR protein (ELISA and turbidimetric)[f]		X	X	X	X	X	X	X	X	X	X	X	X	X
RBP and Vitamin A[f]						X				X	X	X	X	X
Other Assessments:														
Exploratory Biomarkers[g]						X				X				
Anti-drug Antibodies										X[h]				
Pharmacoeconomics Questionnaire											X			X[i]
Clinical Activity Assessments:														
mNIS + 7[j,k]											X			X[i]

Procedure	Visit Type	Dosing									Mid-year/ Annual Efficacy Assess-ment	21- and 56-day Follow-up[a]		Early Termi-nation
	Study Week	**55 & 82**	**58 & 85**	**61 & 88**	**64 & 91**	**67 & 94**	**70 & 97**	**73 & 100**	**76 & 103**	**79 & 106**	**81 & 108**	**109**	**114**	**ET**
	Study Day	**D378 & D567**	**D399 & D588**	**D420 & D609**	**D441 & D630**	**D462 & D651**	**D483 & D672**	**D504 & D693**	**D525 & D714**	**D546 & D735**	**D560 & D749**	**D756**	**D791**	**N/A**
	Window	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±5D**	**±5D**	**±5D**	**2D to 7D**
VDT[k]											X			X[i]
HRdb[k]											X			X[i]
Grip Strength[k,l]											X			X[i]
10-Meter Walk Test[k,m]											X			X[i]
NIS[k]											X			X[i]
Skin Punch Biopsy (IENFD & SGFND)[n]											X			X[i]
mBMI											X			X[i]
FAP Stage and PND Score											X			X[i]
COMPASS 31											X			X[i]
QOL and Disability Questionnaires[o]											X			X[i]
Premedication Administration[p]		X	X	X	X	X	X	X	X	X				
Study Drug Administration[q]		X	X	X	X	X	X	X	X	X				
Plasma PK Sampling[r]						X				X	X	X	X	X
Urine PK Sampling[s]						X				X	X			X

Procedure	Visit Type	Dosing									Mid-year/ Annual Efficacy Assess-ment	21- and 56-day Follow-up[a]		Early Termi-nation
	Study Week	**55 & 82**	**58 & 85**	**61 & 88**	**64 & 91**	**67 & 94**	**70 & 97**	**73 & 100**	**76 & 103**	**79 & 106**	**81 & 108**	**109**	**114**	**ET**
	Study Day	**D378 & D567**	**D399 & D588**	**D420 & D609**	**D441 & D630**	**D462 & D651**	**D483 & D672**	**D504 & D693**	**D525 & D714**	**D546 & D735**	**D560 & D749**	**D756**	**D791**	**N/A**
	Window	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±5D**	**±5D**	**±5D**	**2D to 7D**
PK/PD Subgroup Only:														
TTR (ELISA and turbidimetric)										X[t]				
RBP and Vitamin A										X[t]				
Plasma PK Sampling										X[u]				
Urine PK Sampling										X[v]				
Cardiac Subgroup Only:														
Echocardiogram											X			X
Troponin I and NT-proBNP						X				X				X
Concomitant Medications		X[w]												
Adverse Events		X[x]												

Note: The schedule of assessments for patients administered ALN-TTR02 once every 4 weeks is provided in Appendix 2.

a If a patient enrolls in the global extension study, the patient will only have to complete the 21-day follow-up assessments (Day 756) and not the 56-day follow-up assessments (Day 791). Patients who do not enroll in the extension study will need to complete both Follow-up visits (Days 756 and 791).

b On dosing days, weight will be measured predose.

c On dosing days, vital signs will be measured predose. Vital signs to include: blood pressure, pulse rate, oral body temperature, and respiratory rate. Parameters are to be measured in the supine position using an automated instrument after the patient has rested comfortably for 10 minutes.

d Triplicate recordings will be obtained.

e On dosing days, to be performed before dosing with ALN-TTR02.

f Blood samples for TTR, RBP, and vitamin A will be collected on Day 0 at 2 separate time points: 1) prior to administration of premedications and 2) after administration of premedications but before dosing with ALN-TTR02. At all other dosing visits, a blood sample will be collected only once; prior to administration of premedications. At the Mid-year and Annual visits, one sample should be collected on each day. Additionally, aliquots of serum samples will be taken and frozen, to permit testing of additional proteins related to FAP.

g Blood samples for exploratory biomarkers will be collected prior to dosing with ALN-TTR02.

h Blood samples for ADA will be collected only at the Day 735 visit (approximately 24 months), prior to dosing with ALN-TTR02.

i To be performed only in patients who have received at least 4 doses of study drug and who withdraw >3 months after the last clinical activity assessments were performed. These tests will not be repeated.

j The mNIS + 7 consists of the modified NIS tool (or aspects of the tool; weakness and reflexes only), NCS, QST by body surface area including TP and HP, and postural blood pressure. Every effort will be made to use the same devices for a patient throughout the duration of the study.

k Two independent assessments will be performed at Screening/Baseline and at the Mid-year and Annual visits. The second (repeat) assessment must be conducted at least 24 hours (approximately) after the first assessment, but not more than 7 days apart.

l Hand grip strength will be measured using a dynamometer held in the dominant hand. Every effort will be made to use the same device for a patient throughout the duration of the study. At each time point, 2 independent assessments (each assessment performed in triplicate) will be performed.

m Patient will walk without assistance for 10 meters in order to complete the 10-meter walk test. The time required for the patient to complete 2, 8, and 10 meters will be recorded.

n Two 3-mm skin punch biopsies are to be obtained. One will be obtained from the distal lower leg, when a patient's clinical status allows, and one from the distal thigh.

o Quality of life and disability assessments will include the EQ5D and R-ODS questionnaires.

p The following premedications will be administered at least 60 minutes prior to the start of the infusion of ALN-TTR02: dexamethasone (10 mg IV, or equivalent), paracetamol (PO 500 mg; or equivalent), IV H2 blocker (e.g., ranitidine 50 mg, famotidine 20 mg, or equivalent other H2 blocker dose), and IV H1 blocker (e.g., diphenhydramine 50 mg or equivalent; hydroxyzine or fexofenadine 25 mg PO or cetirizine 10 mg PO may be substituted for any patient who does not tolerate IV diphenhydramine or other IV H1 blockers).

q The infusion site will be assessed for any localized reaction pre-dose, during the infusion, at the end of the infusion and for 30 minutes after the infusion.

r Plasma PK samples will be collected pre-dose (within 1 hour of planned dosing start; -5 minutes) and at EOI (+5 minutes). In addition, if the infusion is stopped and the site is considering restarting the infusion, a PK blood sample will be taken while the infusion is stopped. In addition, plasma samples will be collected once on each day of the Mid-year and Annual visits.

s For each dose, urine PK samples will be collected 1 hour postdose (±5 minutes).

t For patients in the PK/PD subgroup, blood samples for TTR, RBP, and vitamin A will be collected on Day 735 immediately prior (within 10 minutes) to administration of premedications. In addition, a TTR, RBP, and vitamin A sample will also be collected 24 hours (±120 minutes) post-dose, and 3, 7, and 17 days (±1 day) after dosing with ALN-TTR02 for the study visit noted.

u On Day 735, patients in the PK/PD subgroup will have PK samples taken pre-dose (within 1 hour of planned dosing start; -5 minutes), EOI (+5 minutes), and 1, 2, 4, 6, and 24 hours post-infusion. In addition, a plasma PK sample will also be collected 3, 7, and 17 days (±1 day) after dosing with ALN-TTR02 for the study visit noted. The windows for sampling are ±5 minutes for the 1, 2, 4, and 6 hour sampling periods; and ±120 minutes for the 24 hour sampling period.

v On Day 735, patients in the PK/PD subgroup will have a urine sample for PK analysis taken pre-dose (within 1 hour of planned dosing start; -5 minutes), EOI (+5 minutes), and 6 and 24 hours post-infusion. In addition, a urine PK sample will also be collected 3, 7, and 17 days (±1 day) after dosing with ALN-TTR02 for the study visit noted. The windows for sampling are ±5 minutes for the 1, 2, 4, and 6 hour sampling periods; and ±120 minutes for the 24-hour sampling period.

w Use of all concomitant medications during Screening/Baseline, predose, and postdose will be recorded on the patient's CRF up to the 21-day or 56-day Follow-up visit (depending on whether or not the patient plans to roll over to the open-label global extension study).

x Adverse events are to be documented beginning with the initiation of the first infusion through the 21-day or 56-day Follow-up visit (depending on whether or not the patient plans to roll over to the open-label global extension study).

1.2.5. Pharmacokinetic, Pharmacodynamic, Clinical Activity, and Safety Parameters

1.2.5.1. Pharmacokinetic, Pharmacodynamics, and Pharmacology Parameters

Blood samples for determination of patisiran PK are to be collected as outlined in the schedule of events.

Pharmacodynamics associated with long-term dosing of patisiran in patients with FAP will be evaluated by serial measurement of serum levels of TTR from collected blood samples. Secondary PD biomarkers to be assessed include RBP and vitamin A.

A subset of the FAP patients will undergo additional blood draws for assessment of PK/PD (PK/PD subgroup).

Blood will also be collected to evaluate exploratory biomarkers and anti-drug antibodies (ADA).

1.2.5.2. Clinical Activity Parameters

Clinical activity will be assessed at baseline, 6, 12, 18, and 24 months through clinical examinations and electrophysiologic testing of neurologic impairment, patient reported outcomes for quality of life and disability, evaluation of motor functions with impact on activities of daily living, assessment of nutritional status, autonomic symptom assessment, and pathologic evaluation of sensory and autonomic innervation. Specifically, activity assessments will include:

- Neurologic impairment will be assessed using the mNIS+7 composite score. The mNIS+7 includes the modified NIS (weakness and reflexes), Σ5 NCS, QST, as well as autonomic assessment through postural blood pressure. Parameters include the mNIS+7 composite score and each component. A scoring algorithm, including methods for handling missing components of the mNIS+7, is included in Section 7.1.
- Patient reported QOL will be evaluated using the EQ-5D index value. Categorical summaries of each EQ-5D domain will be provided. Overall health will be assessed by the EQ visual analogue scale (EQ-VAS). Disability will be reported by patients using the R-ODS. Scoring algorithms for these instruments are included in Section 7.2 and Section 7.3.
- Autonomic symptoms will be assessed using the COMPASS-31 total score and domain scores. A scoring algorithm for the COMPASS-31 total score and domain scores is included in Section 7.4.
- Motor function assessments include NIS-W, timed 10-meter walk test, and grip strength test.
- Assessment of ambulation through PND score and FAP stage.
- Nutritional status will be assessed using mBMI.
- Pathologic evaluation of sensory and autonomic innervation will be evaluated by IENFD analysis and quantitation of SGNFD via tandem 3 mm skin punch biopsies taken from the leg.

- Neurologic impairment will also be assessed by NIS+7 (including full NIS, Σ5 NCS [distinct from the 5 NCS calculated for mNIS+7], VDT, and HRdb). A scoring algorithm for the NIS+7 is included in Section 7.1.

Magnetic resonance neurography (MRN) of peripheral nerves in the lower extremity and lumbar plexus will be performed for consenting patients. In addition, any patients with pre-existing cardiac amyloid involvement (Cardiac subgroup) will undergo additional testing including echocardiograms, troponin I, and NT-proBNP assessments to evaluate cardiac structure and function.

Disease burden and healthcare utilization will be assessed using a patient reported pharmacoeconomics questionnaire.

1.2.5.3. Safety Parameters

Safety evaluations will include assessment of adverse events (AEs) including serious AEs (SAEs) and IRRs, ECGs, vital signs (blood pressure, pulse rate, oral body temperature, and respiration rate), clinical laboratory tests (hematology, serum chemistry, thyroid function parameters, coagulation parameters, and urinalysis), and ophthalmology and physical examinations. Patients will be closely monitored for both acute and delayed IRRs. All IRRs will be recorded as AEs.

Mental status as it relates to suicidal ideation and behavior will be assessed using the Columbia–Suicide Severity Rating Scale (C-SSRS) questionnaire.

2. SUBJECT POPULATION

2.1. Population Definitions

The following subject populations (i.e., analysis sets) will be evaluated and used for presentation and analysis of the data:

- Full Analysis Set: All patients who were enrolled will be included in the full analysis set. The full analysis set will be the primary set for the analysis of PD data and clinical activity assessments.
- Safety Analysis Set: All patients in the full analysis set who received at least one dose of study drug. The safety analysis set will be used for the analysis of safety assessments.
- Pharmacokinetic (PK) Analysis Set: All patients in the Safety Analysis Set who have adequate PK data to determine at least one key PK parameter.

2.2. Protocol Deviations

A deviation is considered any departure from the procedures set forth in the protocol. Protocol deviations will be classified into major and minor by medical review prior to database lock. A major deviation is a deviation that may impact patient safety or efficacy interpretation (for example, failure to meet key inclusion and exclusion criteria, error in premedication or investigational product dosing with potential for safety implications). GCP deviations will be classified under major deviations as well. Deviations not designated as major will be considered minor.

All protocol deviations and major protocol deviations will be presented in separate data listings.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

Based on the number of patients enrolled in Study ALN-TTR02-002, up to 28 patients are expected to be enrolled in this extension study. Of these patients, up to 19 are expected to be included in the PK/PD subgroup. Any patient with pre-existing cardiac amyloid involvement will be included in the Cardiac subgroup for analysis (see Section 3.7).

The sample size was chosen based on the study ALN-TTR02-002 enrollment and was not based on power calculations.

3.2. General Methods

All data listings that contain an evaluation date will contain a study day (Rel Day) relative to the first date of study medication, which is designated as Day 1. On-treatment study days will be calculated as evaluation date – first dose date +1 and pre-treatment days will be calculated as evaluation date – first dose date. For example, the day prior to study medication will be Day -1 and the second day after the first dose of study medication will be Day 2, etc.

Tabulations will be produced for appropriate demographic, baseline, clinical activity, PD, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented.

Laboratory data (including vitamin A and RBP) collected and recorded as below the limit of detection will be set equal to the lower limit of detection for the calculation of summary statistics.

As this is a Phase 2 extension study, formal statistical hypothesis testing will not be performed. Ninety-five percent confidence intervals (CIs) will be produced where indicated, and are intended to be descriptive in nature.

All data will be presented in by-subject data listings.

3.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.3 or higher, unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 16.0 (or later). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version Q12013 (or later).

3.4. Baseline Definitions

Unless otherwise noted, baseline will be defined as the study ALN-TTR02-003 Day 1 pre-dose value when non-missing, otherwise the latest value from amongst any screening or unscheduled assessments prior to dosing on Day 1 will be used (i.e., the measurement closest to and prior to dosing will be considered baseline). For PD parameters (TTR, RBP, vitamin A), baseline will be defined as the average of all records, including those from any unscheduled visits, prior to the date and time of first dose. For the mNIS+7/NIS+7 total score and individual components, grip test and 10m walk test, baseline is defined as the average of the Screening/Baseline assessments.

3.5. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned.

3.6. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study with a descriptive interpretation.

3.7. Subpopulations

Patients who have pre-existing cardiac amyloid involvement will be eligible for inclusion in the cardiac subgroup for analysis. The inclusion criteria are the following:

1) Have a left ventricular wall thickness of ≥13 mm on transthoracic echocardiogram;
2) Be normotensive or have hypertension that is well-controlled;
3) No aortic valve disease.

Patients enrolled in the cardiac subgroup will complete additional clinical activity assessments to evaluate cardiac structure/function. This will be achieved through echocardiograms and monitoring of NT-proBNP and troponin I.

Patients will be eligible for inclusion in the PK/PD subgroup if their last dose of patisiran was administered at least 6 months prior to the first dose in this study. Patients enrolled in the PK/PD subgroup will have additional samples taken for evaluation of PK and PD (TTR and secondary PD biomarkers [RBP and vitamin A]).

3.8. Withdrawals, Dropouts, Loss to Follow-up

Patients are free to withdraw from the study at any time and for any reason, without penalty to their continuing medical care. A patient will be considered to have completed the study if the patient completes Year 2 efficacy assessments and either the 21-day or the 56-day follow-up visit. Every effort should be made to also complete the Early Termination (ET) visit, if applicable.

In the event a patient withdraws early from the study, the contract research organization (CRO) Medical Monitor must be informed immediately. If there is a medical reason for withdrawal, the patient will remain under the supervision of the Investigator for protocol-specified safety follow up procedures.

Patients who voluntarily withdraw are termed dropouts. Dropouts will not be replaced.

If a patient is withdrawn/withdraws every effort should be made to conduct the ET visit. Patients who fail to return for final evaluations will be contacted by the site in an attempt to have them comply with the protocol. The site will follow up by telephone at least twice and send a registered letter to any patient who fails to return for the final evaluation.

When a patient withdraws from the study, the primary reason for discontinuation must be recorded in the appropriate section of the electronic case report form (eCRF) and all efforts will be made to complete and report the observations as thoroughly as possible.

3.9. Missing, Unused, and Spurious Data

Specific algorithms will be used impute values and/or subcomponents of particular clinical activity assessments when subcomponents are missing (mNIS+7, NIS+7, EQ-5D, R-ODS, and

COMPASS; see Sections 7.1-7.4). In general, there will be no imputation for missing data for other endpoints unless specified otherwise. All data recorded on the CRF will be included in data listings that will accompany the CSR.

3.10. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated and analyzed per the evaluation visit as recorded on the electronic case report form (eCRF) even if the assessment is outside of the visit window. In data listings, the relative day of all dates will be presented.

Data collected at unscheduled visits will be included in by-subject data listings and figures, but no assignment to a study visit will be made for the purpose of by-visit summary tabulations. However, unscheduled visits will be considered for baseline values, as discussed in Section 3.4, and for inclusion in any categorical shift summaries (e.g., shift from baseline to "worst" post-baseline value). In addition, summaries of PD parameters (serum TTR, vitamin A, and RBP) will include separate tables and figures using All Data and Scheduled Visits Only.

Note that in the protocol Schedule of Assessments, the first dose day is designated as Day 0. In the SAP, the first dose day will be defined as Day 1 as specified in Section 3.2. In all tables, figures, and listings, on-treatment study days will equal to reported visit days + 1.

3.11. Interim Analyses

There is no formal interim analysis planned for this study. Interim data examinations may be performed, but these will be of a descriptive nature and will not involve any formal hypothesis testing. In particular, summaries of changes from baseline for clinical activity parameters will be conducted on the 6, 12, 18, and 24 month data.

4. STUDY ANALYSES

4.1. Subject Disposition

Subject disposition will be tabulated and include the number enrolled, the number dosed with patisiran, the number who completed the study, the number in each subject population for analysis, the number who withdrew prior to completing the study and reason(s) for withdrawal.

A by-subject data listing of study completion information including the reason for premature study withdrawal will be presented.

4.2. Demographics and Baseline Characteristics

Demographics, baseline characteristics, and medical history information will be summarized for the Full Analysis Set and Cardiac Subgroup.

Age, height, weight, BMI, albumin, and mBMI will be summarized using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Sex, race, ethnicity, and country will be summarized by presenting the numbers and percentages of subjects in each category. The numbers of subjects included in the PK/PD and cardiac subgroup will also be summarized.

Baseline disease characteristics will be summarized, including the time since diagnosis with ATTR, and the numbers and percentages of subjects

- V30M or other mutation
- FAP stage (0, I, II, III)
- PND score (0, I, II, IIIA, IIIB, IV)
- Karnofsky Performance Status (≤60, 70-80, 90-100)
- New York Heart Association class (I, II, III, IV)
- Concomitant TTR stabilizer (yes or no)

Baseline clinical activity parameters including NIS, mNIS+7, NIS+7, EQ-5D, R-ODS, COMPASS-31, 10-meter walk test, and grip strength test scores will also be summarized.

Baseline data will be also be summarized for Cardiac Subgroup separately.

All demographic and baseline data for each subject will be provided in data listings.

Medical history will be summarized by system organ class (SOC), high level terms (HLT), and preferred terms. Medical history and prior surgeries will be presented in a data listing. Pregnancy test results will be presented in data listings.

Any data from former neurological test scores will be presented in a data listing.

4.3. Pharmacodynamic Analysis

The following biomarkers will be evaluated for assessment of the PD effect of patisiran:

- TTR protein
- Retinol binding protein (RBP)
- Vitamin A

PD analyses will use the Full Analysis Set. Summary statistics for each PD parameter will be presented. Serial measurements, changes and percentage changes from baseline will be summarized for each scheduled time point using descriptive statistics. Maximum and mean TTR % reduction from baseline over 24 months will be summarized. Mean TTR % reduction from baseline will be calculated using all TTR values on or after Day 8. Mean TTR % reduction will also be calculated for all pre-dose (within 1 hour of planned dosing start) visits.

In addition, serial TTR will be summarized by genotype (V30M versus non-V30M), stabilizer use (yes versus no), gender (female versus male), and age (<65 versus ≥ 65 years old).

TTR levels over time will be plotted. Each subject's TTR levels will be joined by a line. Group means (with standard error bars) for observed values and percent change from baseline will be plotted over time. Similar plots will be produced for RBP and Vitamin A.

The post-hoc non-native TTR analysis will also be summarized.

4.4. Summary of Clinical Activity Assessments

The following clinical activity assessments will be collected:

- Neurologic impairment will be assessed using the mNIS + 7 composite score, consisting of the NIS weakness and reflex domains, 5 nerve conduction studies (Σ5 NCS), quantitative sensory testing (QST) by body surface area including touch pressure (TP) and heat pain (HP), as well as autonomic assessment through postural blood pressure. A scoring algorithm, including methods for handling missing components of the mNIS+7, is included in Section 7.1.
- The NIS score (i.e., the sum of cranial nerve, muscle weakness, reflex and sensation scores) will also be assessed.
- Neurologic impairment will also be assessed by NIS+7 [19]. The NIS+7 includes the full NIS, sum of five NCS (overlapping but not identical to the Σ5 NCS calculated for mNIS+7 above, vibration detection threshold [VDT], and heart rate response to deep breathing [HRdb]). A scoring algorithm for the NIS+7 is included in Section 7.1.
- Patient reported QOL will be evaluated using the EQ-5D index value (using U.S. references to calculate the index). Categorical summaries of each EQ-5D domain will be provided. Overall health will be assessed by the EQ-VAS. Disability will be reported by patients using the R-ODS. Scoring algorithms for the EQ-5D and R-ODS are included in Section 7.2 and Section 7.3.
- Motor function assessments will include a timed 10-meter walk test and test of grip strength in dominant arm, as well as an evaluation of ambulation using PND score and FAP stage.
- Pathologic evaluation of sensory and autonomic innervation will be evaluated by IENFD analysis and quantitation of SGNFD via tandem 3 mm skin punch biopsies taken from the leg and thigh.
- Nutritional status of patients will be evaluated using the mBMI, calculated as BMI (kg/m^2) multiplied by albumin (g/L).

- To evaluate patient reported autonomic neuropathy symptoms, patients will complete the COMPASS 31 questionnaire, consisting of 31 clinically selected questions which evaluate 6 autonomic domains [1]. A scoring algorithm for the COMPASS-31 total score and domain scores is included in Section 7.4.
- Magnetic resonance neurography (MRN) of peripheral nerves in the lower extremity and lumbar plexus will be performed for consenting patients.

Analyses of clinical activity assessments will use the Full Analysis Set. Summary statistics of observed values and changes from baseline will be provided for the mNIS+7 composite score. Summaries will also be provided for the components of the composite score (i.e., the NIS weakness and reflex scores, the Σ5 NCS, QST values, and postural blood pressure). The full NIS (i.e., the sum of cranial nerve, muscle weakness, reflex and sensation scores) and NIS+7 will also be summarized overall and by component as above.

Patient reported autonomic neuropathy symptoms will be assessed by descriptive statistics for the COMPASS 31 (including overall and domain scores).

Descriptive statistics will also be provided for observed values and changes from baseline in motor function (10-meter walk test speed and grip strength), nutritional status (mBMI), sensory and autonomic innervation (IENFD and SGNFD), and ambulation (FAP stage and PND score).

The above clinical activity parameters will be summarized overall, by stabilizer use (any versus none), and by Cardiac Subgroup versus all others. The mNIS+7 composite score and component scores will also be summarized by baseline age (<65 vs ≥65) and gender.

4.4.1. Association between TTR Reduction and Clinical Activity

The therapeutic hypothesis for patisiran is that TTR reduction will result in clinical benefit in hATTR-PN patients. The inter-patient variability in the degree of TTR reduction at 0.3 mg/kg provides an opportunity to examine the relationship of TTR reduction to change in neuropathy progression as measured by mNIS+7. TTR reduction 17 days after the first dose of patisiran (Day 18 %TTR Reduction) was chosen for analysis of the correlation between TTR reduction and change in mNIS+7 because it reduces the impact of missed doses or missed TTR assessments over 24 months of dosing.

Pearson correlation coefficients will be calculated for Day 18 TTR % reduction and mNIS+7 change from baseline (including total score and component scores) at each of the 6, 12, 18, and 24 month time points. Scatterplots will be provided to visualize the data.

4.4.2. Associations among Baseline Clinical Activity Parameters

Associations among baseline clinical activity parameters will also be explored. Pearson correlation coefficients will be calculated to evaluate the linear relationship among continuous variables (*e.g.* mNIS+7 versus NIS+7, mNIS+7 versus EQ-5D index score, etc.). Spearman correlation coefficients will be calculated for a continuous variable versus a nominal variable or for two nominal variables (*e.g.* FAP stage and mNIS+7, PND score and NIS). Scatterplots will be provided to visualize the data.

4.5. Pharmacokinetic Analysis

PK analysis will be conducted in the PK analysis set.

4.5.1. Study Variables

4.5.1.1. Concentration Data

Urinary concentrations of ALN-18328 (siRNA) and 4-dimethylaminobutyric acid, as well as plasma concentrations of ALN-18328, DLin-MC3-DMA and PEG_{2000}-C-DMG will be obtained. Concentration values that are below the limit of quantification (LLOQ or BLQ) will be set to zero for analysis.

4.5.1.2. Plasma ALN-TTR02 Pharmacokinetic Parameters

Pharmacokinetic parameters to be calculated include:

- Observed trough concentration (Ctrough)
- Observed maximum concentration (Cmax)
- Time of observed maximum concentration (Tmax)
- Area under the plasma concentration-time curve within a dosing interval (AUC(tau))
- Elimination half-life (t(1/2 beta) and t(1/2 alpha))
- Systemic clearance (CL)
- Volume of distribution at steady state (V_{ss})
- Volume of distribution based on the terminal phase (V_z)

4.5.2. Statistical Methods

Descriptive statistics for plasma and urine concentration and plasma PK parameters will include the number of subjects, mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum.

The plasma concentrations of ALN-18328 (siRNA), DLin-MC3-DMA and PEG_{2000}-C-DMG as well as urinary ALN-18328 and 4-dimethylaminobutyric acid concentrations data will be summarized at each nominal time point. Mean concentrations (+SD) as well as individual concentrations will be plotted versus nominal sampling time on a log-linear scale.

The PK parameters will be summarized for ALN-18328 (siRNA), DLin-MC3-DMA and PEG_{2000}-C-DMG. Ctrough and Cmax will be summarized for Days 22, 43, 64, 85, 169, 274, 358, 463, 547, 673, and 736. The following parameters will be summarized for Day 1: Cmax, Ctrough, Tmax, and AUC(tau); for Day 232: Cmax, Ctrough, and Tmax; for Day 726: Cmax, Ctrough, Tmax, t(1/2 alpha), t(1/2 beta), CL, Vss, and Vz.

Plasma concentration data and PK parameters will be presented in by-subject listings.

The relationship between exposure to ALN-18328 (C_{max}) and the extent of reduction of TTR protein, vitamin A and RBP will be explored graphically. Mixed-effects models may be used to assess the relationship between exposure to ALN-18328 and the reduction of TTR protein, vitamin A, and RBP.

4.6. Safety Analyses

Safety analyses will be conducted using the Safety Analysis Set. Baseline values for all safety analyses will be defined as the last observation prior to dosing.

4.6.1. Study Drug Exposure

Duration of drug exposure will be defined as (the last dose of study drug – the first dose of study drug + 21)/30.44 months. Duration of drug exposure and duration of infusion will be summarized using descriptive statistics. Summaries of the numbers and percentages of subjects with a dose reduction, any missing dose, and the numbers of missed doses per subject, will be provided. Duration of interruption will be summarized using descriptive statistics. Summary statistics will also be provided for the total volume infused.

All data related to study drug administration will be presented in a data listing.

4.6.2. Adverse Events

All AEs will be coded using the MedDRA coding system and displayed in tables and data listings using system organ class (SOC) and preferred term.

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined per protocol as any AE with onset during or after the administration of study medication through 28 days following the last dose of study drug. In addition, any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study will be considered treatment-emergent. Events with a fully or partially missing onset date will be assumed to be treatment emergent unless it can be unequivocally determined (from the partial onset date and/or a partial or complete stop date) that the event occurred prior to the first administration of study medication.

AEs are summarized by the numbers and percentages of subjects reporting a given AE. Therefore, in any tabulation, a subject contributes only once to the count for a given AE (overall, by SOC, by preferred term).

Tabulations by SOC and preferred term will be produced for all AEs, for all AEs related to study medication, for all severe AEs, for all AEs leading to study discontinuation, and for all serious AEs. Separate summary tables will be provided characterizing signs and symptoms of IRRs and AEs related to pre-medications. The incidence and frequency of IRRs over time will also be provided. AEs and serious AEs will be also summarized for Cardiac Subgroup. AEs will be tabulated by preferred term in decreasing order in frequency.

Separate tables will present AE incidence by maximum relationship to study drug and by maximum severity. Subjects who report multiple occurrences of the same AE (preferred term) will be classified according to the most related or most severe occurrence, respectively.

No formal hypothesis-testing analysis of AE incidence will be performed.

All AEs occurring on-study will be listed in subject data listings. A separate listing will be provided for IRRs. Listings will be provided for any AEs caused by pre-medications or any study procedure.

By-subject listings will also be provided for the following: subject deaths, SAEs, and AEs leading to discontinuation.

4.6.3. Laboratory Data

Clinical laboratory values will be expressed in SI units.

Summary data for each laboratory parameter will be presented for each continuous clinical laboratory parameter (including hematology, serum chemistry, coagulation studies and thyroid and liver function tests). Descriptive statistics will be presented for the actual values, change, and percentage change from baseline by visit.

For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Shift tables will be employed to summarize the baseline category versus the post-baseline category, where the post-baseline category will be based on the maximum difference (in absolute value) from the upper or lower limit of the normal range. All out-of-range and clinically significant laboratory results will be identified in subject data listings.

A listing will be produced for all subjects with abnormal liver function tests defined as an ALT >3xULN, AST >3xULN, and/or total bilirubin >2xULN at any time point.
A table will be produced to summarize the number and percentage of subjects in each of below category at any post-baseline time point. ALT >1 & <=3, >3 & <=5, >5 & <=10, >10 & <=20, >20 x ULN,

- AST >1 & <=3, >3 & <=5, >5 & <=10, >10 & <=20, >20 x ULN,
- ALT or AST >1 & <=3, >3 & <=5, >5 & <=10, >10 & <=20, >20 x ULN,
- ALP > 1.5 x ULN,
- Total Bilirubin >1.5 & <=2, >2 & <=3, >3 & <=5 and >5 x ULN,
- Total Bilirubin > 2 x ULN concurrent with ALT or AST > 3 x ULN.

A shift table from baseline to worst post-baseline for ALT, AST, and total bilirubin will also be provided.

For hematology and blood chemistry, summary tables of potentially clinically significant abnormalities will be provided. The results may also be graded according to the NCI CTCAE Version 4.0 or above. A shift summary of baseline to maximum post-baseline CTCAE grade may be presented, as appropriate.

The estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) will be categorized as below: ≥ 90; 60-89; 30-59; 15-29 and <15. A shift summary of baseline to worst post-baseline eGFR category will be presented.

All laboratory data will be provided in data listings. Laboratory values outside of the normal ranges will be listed separately, together with comments as to their clinical significance.

4.6.4. Vital Signs and Physical Examination

Descriptive statistics will be provided for vital signs, including blood pressure, pulse rate, oral body temperature and respiration rate. Summaries will also include change from baseline at each scheduled visit.

Vital sign measurements will be presented for each subject in a data listing.

Abnormal physical examination findings will be presented in by-subject data listing.

4.6.5. Electrocardiogram

Electrocardiogram (ECG) findings will include rhythm, ventricular rate, PR interval, QRS duration, QT interval, and QTc interval. Descriptive statistics will be provided for each measure over time. Change from pre-dose to each post-dose assessment will also be summarized.

Corrected QT interval (QTc) will be calculated using both Fridericia's and Bazett's correction formula. Categorical analyses of the QTcF/QTcB data will be conducted and summarized as follows:

- The number and percentage of subjects with maximum increase from baseline in QTcF/QTcB (<30, 30-60, >60ms)
- The number and percentage of subjects with maximum post-baseline QTcF/QTcB (<450, 450-< 480, 480-500, >500ms)

A listing will be provided for subjects with any post-baseline value > 500ms or an increase > 60ms.

All ECG data for each subject will be provided in a data listing.

4.6.6. Premedication

All patients received premedication in order to reduce the potential of an IRR. The original premedication regimen as outlined below was used at the start of the study. A subset of patients experienced AEs suspected to be related to steroids (eg, flushing) and were transitioned to a modified premedication regimen, with a reduced dose of corticosteriod to mitigate these events, as sanctioned in the protocol. After observing that the subset of patients tolerated the lower corticosteroid dose with no increase in IRRs, the protocol was amended (Global Amendment 1) to transition the rest of the patients to the modified premedication regimen (see below).

The following original premedication regimen was used prior to Global Amendment 1:

- Dexamethasone 8 mg PO or equivalent administered the evening before dosing and 20 mg PO at least 60 minutes prior to the start of the infusion of patisiran;
- Paracetamol 500 mg PO or equivalent administered the evening before dosing and at least 60 minutes prior to the start of the infusion of patisiran;
- H2 blocker PO (e.g., ranitidine 150 mg or famotidine 20 mg or equivalent other H2 blocker dose) administered the evening before dosing and at least 60 minutes prior to start of the infusion of patisiran; and
- H1 blocker PO, 10 mg cetirizine or equivalent (hydroxyzine 25 mg or fexofenadine could be substituted if patient did not tolerate cetirizine) administered the evening before dosing and at least 60 minutes prior to start of the infusion of patisiran.

The following modified premedication regimen was instituted with Global Amendment 1:

- Dexamethasone 10 mg IV or equivalent, administered at least 60 minutes prior to the start of the infusion of patisiran;
- Paracetamol 500 mg PO or equivalent at least 60 minutes prior to the start of the infusion of patisiran;
- H2 blocker IV (e.g., ranitidine 50 mg, famotidine 20 mg, or equivalent other H2 blocker dose) at least 60 minutes prior to the start of the infusion of patisiran; and
- H1 blocker IV, diphenhydramine 50 mg (or equivalent other IV H1 blocker available at the study site) at least 60 minutes prior to the start of the infusion of patisiran. Hydroxyzine

25 mg PO or fexofenadine 30 or 60 mg PO or cetirizine 10 mg PO could be substituted for any patient who did not tolerate IV diphenhydramine or other IV H1 blocker.

A drug exposure table summarizing the treatment duration under "original" and "modified" regimens will be provided. A patient who switches from "original" to "modified" regimen during treatment will be counted in both categories. TTR percentage reduction, AE/IRR incidence rates will also be summarized by original and modified regimens of premedication.

Premedication data will be listed. In addition, a listing for patients with premedication regimen change during treatment will be provided to display the study day of regimen change and durations of study drug exposure under original and modified regimens.

4.6.7. Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary. Results will be tabulated by anatomic therapeutic class (ATC) and preferred term. Medications taken as protocol specified pre-medications will be summarized separately.

For concomitant medications, any medications that did not end prior to first dose will be included. If an end date is missing or the medication is ongoing, the medication will be included.

The use of concomitant medications will be included in a by-subject data listing.

4.6.8. Ophthalmology Examinations

Ophthalmology examinations include Visual Acuity, Slit Lamp Biomicroscopy, Intraocular Pressure, Dilated Indirect Ophthalmoscopy, and Fundus Photography.

Visual Acuity Exam and Intraocular Pressure Results: The actual value and change from baseline results will be summarized.

Biomicroscopy (Slit Lamp) and Dilated Indirect Ophthalmoscopy Exam Results: For the baseline results, the number and percentage of patients falling into each category of the examination status (normal, abnormal/not clinically significant, abnormal/clinically significant) will be summarized for each eye structure. For post-baseline results, the number and percentage of patients falling into each category of the examination status (new findings/worsening of finding, no change, improvement of finding etc) will be summarized for each eye structure.

Abnormal fundus findings at baseline will be recorded in the medical history log. Treatment-emergent abnormal fundus findings that are considered clinically significant will be recorded in the adverse event log.

Data for each of these assessments will be provided in a data listing.

4.6.9. Suicide Questionnaire

Data from the C-SSRS questionnaire will be provided in a data listing.

4.7. Measures of Cardiac Structure and Function

For those patients in the Cardiac subgroup, cardiac structure and function will be assessed through echocardiograms as well as measurement of serum levels of the cardiac biomarkers NT-proBNP and troponin I. Quantification of these biomarkers will be performed at a central

laboratory. The assessments will be conducted prior to the first dose of study drug and approximately once every 3 months.

Descriptive statistics will be provided for actual values, changes, and percentage changes from baseline in echocardiogram parameters (including wall thickness, LV strain and other Echo parameters), serum levels of troponin I and NT-proBNP.

All echocardiogram and cardiac function biomarkers data will be presented in patient data listings.

4.8. Anti-Drug Antibody

Anti-drug antibody data will be presented in a patient data listing.

5. CHANGES TO PLANNED ANALYSES

The changes to planned analyses include the following:

6. REFERENCES

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7. QUESTIONNAIRE/SCORING APPENDICES

In questionnaires, if multiple responses are provided to a single-response question, the question is deemed as missing.

7.1. Modified Neuropathy Impairment Score (mNIS+7) and Original Neuropathy Impairment Score + 7 Nerve Tests (NIS+7)

Note: the mNIS+7 and NIS+7 measurements are conducted in duplicate per timepoint. The average of two complete duplicate values will be reported, except in cases of missing or partially missing data as described below.

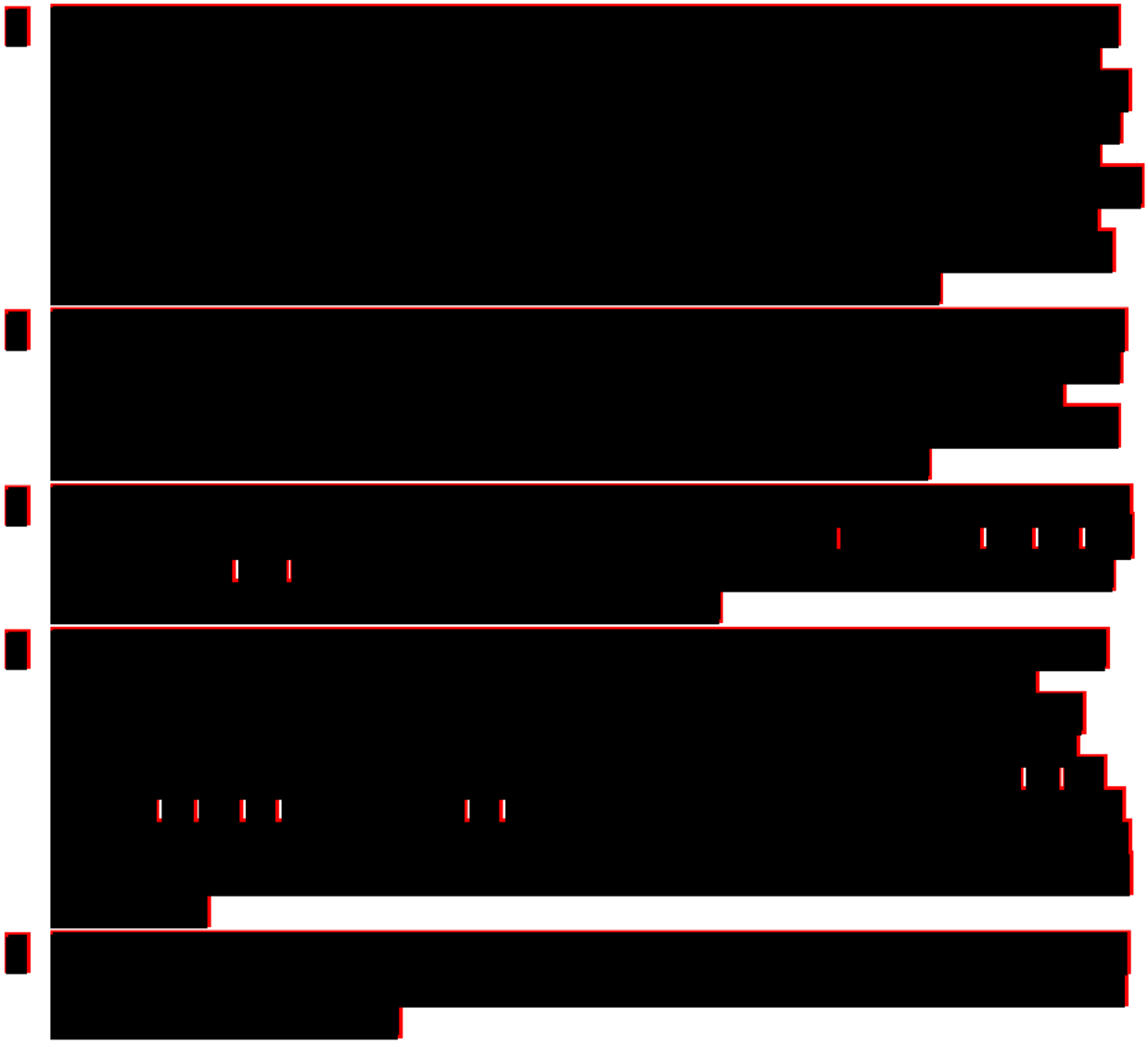
Assessment Tool	Total Points	Components (maximum points)

Modified NIS+7	304	• NIS-W: Weakness (192)
		• NIS-R: Reflexes (20)
		• Quantitative sensory testing by body surface area including touch pressure (TP) and heat as pain (HP): QST-BSA$_{TP+HP5}$ (80)
		• ∑5 nerve conductions (10)
		  ◦ Ulnar compound muscle action potential (ulnar CMAP)
		  ◦ Ulnar sensory nerve action potential (ulnar SNAP)
		  ◦ Sural sensory nerve action potential (sural SNAP)
		  ◦ Tibial compound muscle action potential (tibial CMAP)
		  ◦ Peroneal compound muscle action potential (peroneal CMAP)
		• Postural blood pressure (BP) (2)

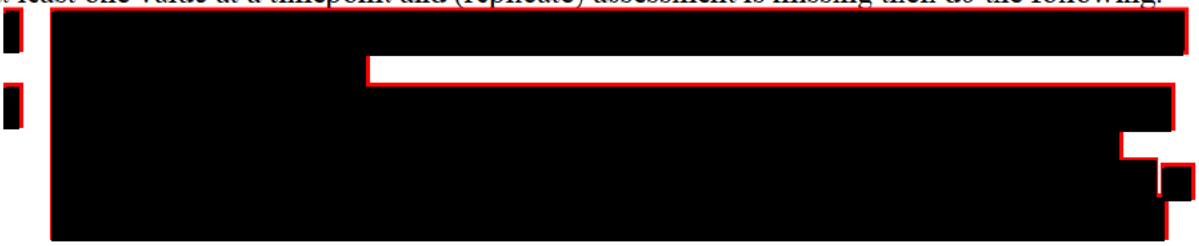
NIS+7	270	• NIS-W: Weakness (192)
		• NIS-R: Reflexes (20)
		• NIS-S: Sensation (32)
		• ∑7 Nerve tests
		  • 5 Nerve conduction studies ∑5 (18.6)
		  ◦ Peroneal compound muscle action potential (peroneal CMAP)
		  ◦ Peroneal motor nerve conduction velocity (peroneal MNCV)
		  ◦ Peroneal motor nerve distal latency (peroneal MNDL)
		  ◦ Tibial motor DL
		  ◦ Sural sensory nerve action potential (sural SNAP)
		  • Vibration detection threshold (VDT) (3.72)
		  • Heart rate response to deep breathing (HRdb) (3.72)

7.1.1. Modified Neuropathy Impairment Score (mNIS+7)

There are five components within mNIS+7 total score including NIS-W, NIS-R, QST, ∑5 NC, and postural BP, as described in details below:



If at least one value at a timepoint and (replicate) assessment is missing then do the following:



[redacted]

7.1.2. Original Neuropathy Impairment Score (NIS+7)

[redacted]

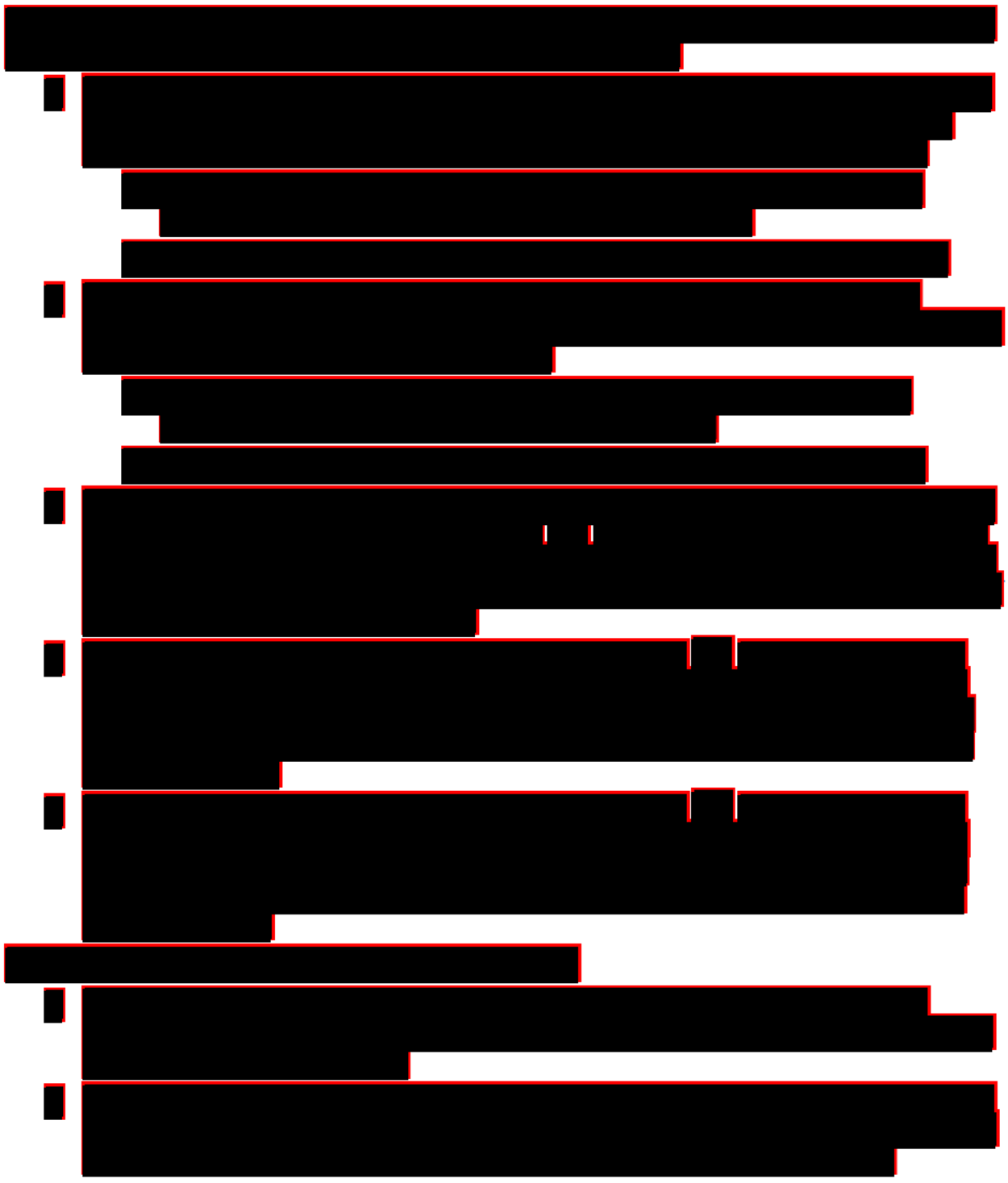
[redacted]

7.1.3. NIS Total Score

[redacted]

7.1.4. Algorithms for Setting Normal Deviates and Points

[redacted]



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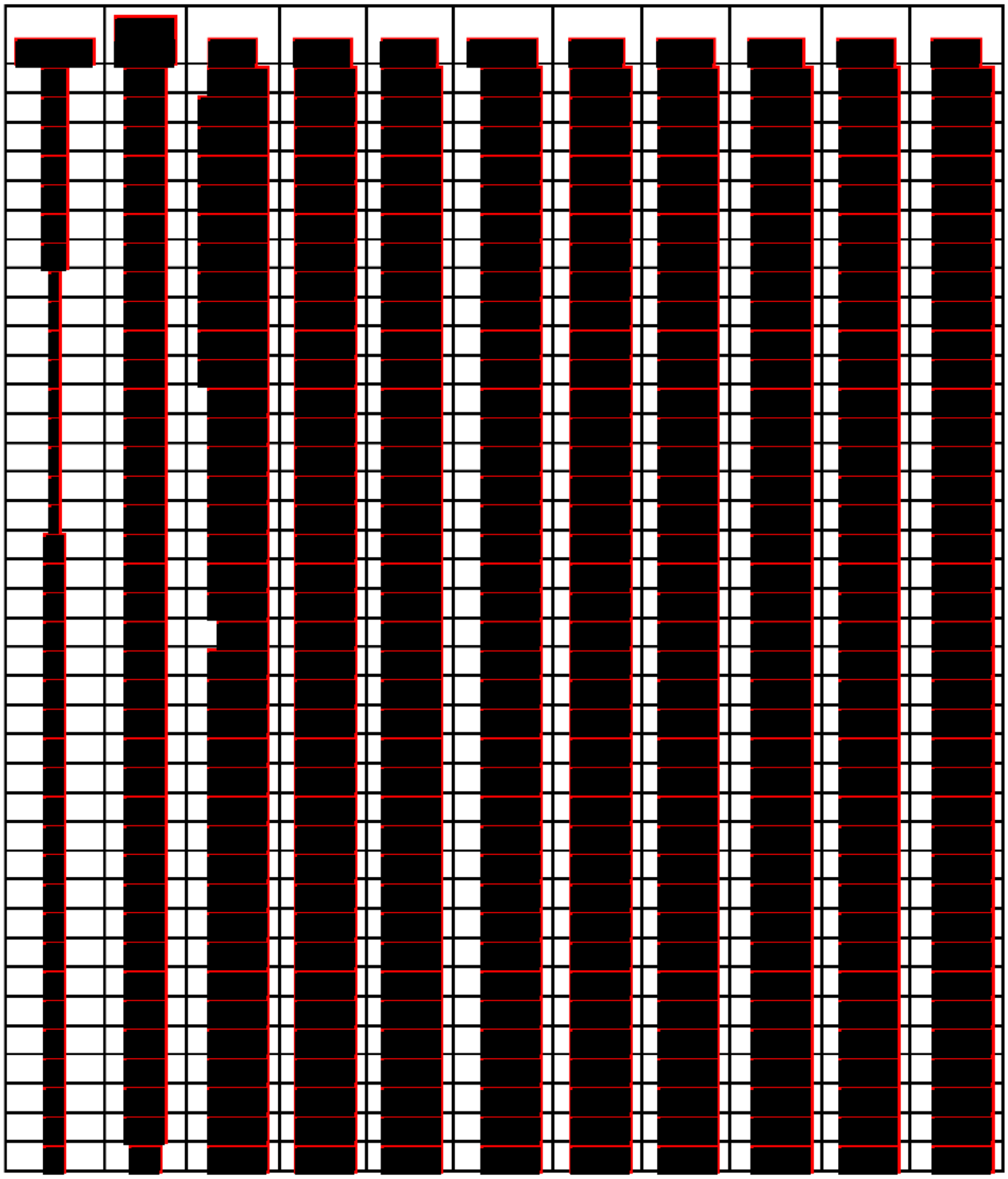

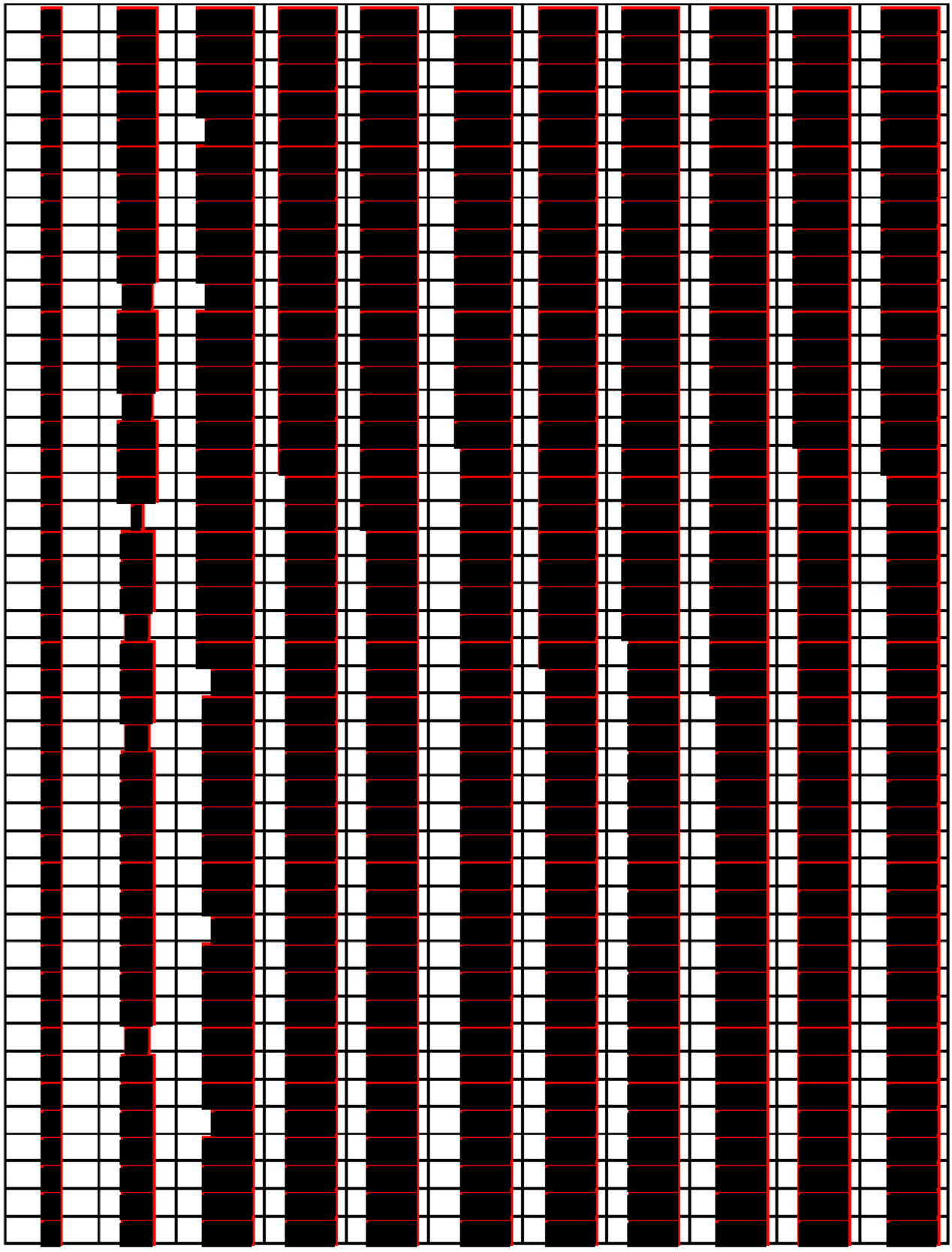

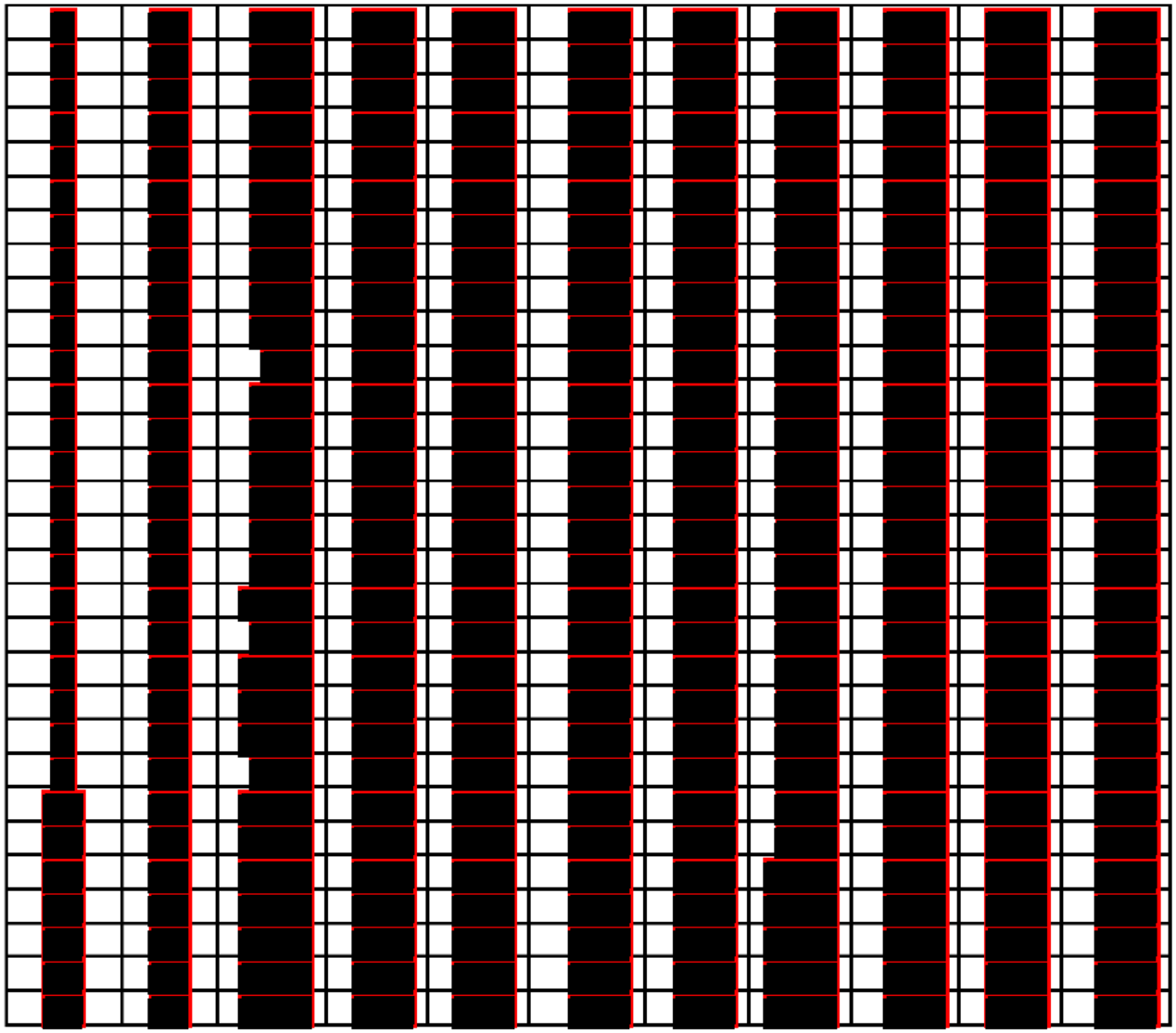

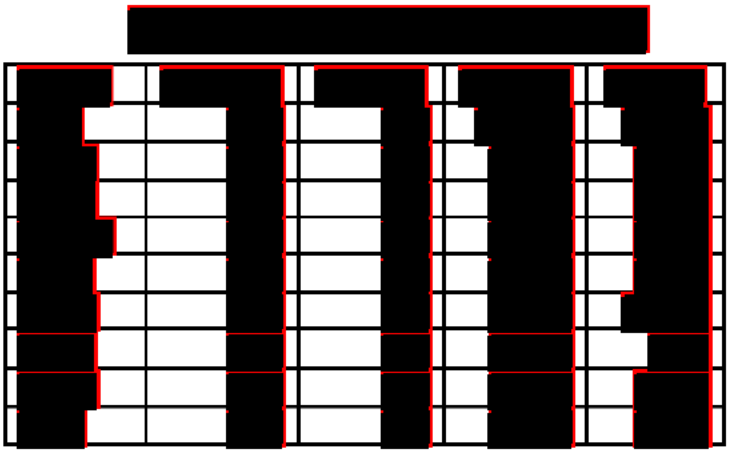

7.2. Euro Quality of Life-5-Dimension 5-Level (EQ-5D-5L)

Each of the 5 dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) is scored on a 5-point Likert scale from 1 ("I have no problems/pain/anxiety") to 5 ("I am unable to…", "I have extreme anxiety/depression").

The five scores are concatenated together (in the order of Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) to create an EQ-5D-5L profile (e.g., 11111, 55555). The profile is then used to obtain an index value using the United States value set. The index values range from –0.109, associated with a profile of 55555, to 1.0, associated with a profile of 11111. Smaller index values indicate greater impairment.

Missing values are handled as follows:

- Missing items are coded as "9" in creating patient profiles.
- The index value is deemed as missing when responses are missing for 1 or more of the five dimensions.

If the entire instrument is missing, the EQ-5D-5L index value is considered as missing.

7.3. Rasch-Built Overall Disability Scale (R-ODS)

The R-ODS consists of 24 items scored on a scale of 0 (unable to perform), 1 (able to perform, but with difficulty) or 2 (able to perform without difficulty). A total score will be calculated as the average of all non-missing items multiplied by 24 if at least 90% of the items are non-missing. The total score will be deemed as missing if more than 10% of the items (3 or more items) are missing.

7.4. Composite Autonomic Symptom Score (COMPASS-31)

The COMPASS-31 questionnaire comprises 6 domains: Orthostatic intolerance, Vasomotor, Secretomotor, Gastrointestinal, Bladder, and Pupillomotor. Within each domain, individual questions are scored as follows: Simple yes or no questions are scored as 0 points for no and 1 point for yes. Questions about a specific site of symptoms or symptoms under specific circumstances are scored as 0 if not present and as 1 if present for each site or circumstance. All questions regarding the frequency of symptoms are scored as 0 points for rarely or never, 1 point for occasionally or sometimes, 2 points for frequently or "a lot of the time," and 3 points for almost always or constantly. All questions regarding the severity of symptoms are scored as 1 point for mild, 2 points for moderate, and 3 points for severe. Questions assessing the time course of a symptom are scored 0 points for responses such as "gotten somewhat better," "gotten much better," "completely gone," and "I have not had any of these symptoms," 1 point for "stayed about the same," 2 points for "gotten somewhat worse," and 3 points for "gotten much worse." The scores for changes in bodily functions depend on the individual question asked. For example, "I get full a lot more quickly than I used to when eating a meal" is scored 2 points and "I get full a lot less quickly than I used to" is scored 0 points, while the answer "I sweat much more than I used to" is given 1 point and "I sweat much less than I used to" is scored 2 points.