AMENDED CLINICAL TRIAL PROTOCOL 04

Protocol title:	**A Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of tolebrutinib (SAR442168) in adults with generalized myasthenia gravis**
Protocol number:	**EFC17262**
Amendment number:	**04**
Compound number (INN/Trademark):	**SAR442168** **Tolebrutinib/NA**
Brief title:	**Efficacy and safety of tolebrutinib (SAR442168) tablets in adult participants with generalized myasthenia gravis** **URSA**
Study phase:	**Phase 3**
Sponsor name:	**SAR&D*** ***Sanofi corporation organized and existing under the laws of France is the ultimate parent of a worldwide group of affiliates including Sanofi US Services Inc., Sanofi Genzyme, and Genzyme Corporation**
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Monitoring team's representative name and contact information	**The study centers, the Investigators at each center are listed in a separate document**

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 04	All	14 September 2022, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 03	All	23 May 2022, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 02	All	03 November 2021, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All*	20 October 2021, version 1 (electronic 1.0)
Original Protocol		18 August 2021, version 1 (electronic 2.0)
*Submitted in UK only		

Amended protocol 04 (14 September 2022)

This amended protocol (amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The rationale for this protocol amendment is to further reduce the risk of drug-induced liver injury (DILI) [redacted]

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	[redacted]	To reduce the risk of DILI. Clarification.
[redacted]		
10.13 Appendix 13: Protocol amendment history	Updated.	Update.

Section # and Name	Description of Change	Brief Rationale
Throughout the document	Reformatting of existing content when necessary. Minor, editorial, stylistic changes as necessary. Updated table of contents, abbreviations, section numbers, references, as necessary.	Update in accordance with Sponsor's standards.

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[redacted]

[redacted]

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of tolebrutinib (SAR442168) in adults with generalized myasthenia gravis

Brief title:

Efficacy and safety of tolebrutinib (SAR442168) tablets in adult participants with generalized myasthenia gravis

Rationale:

There is an unmet need for people with generalized myasthenia gravis (gMG) for effective treatments with better long-term safety profiles and with more feasible modes of administration. Tolebrutinib (SAR442168), a covalent, irreversible inhibitor of Bruton's tyrosine kinase (BTK), is an immunomodulatory agent relevant to the pathophysiology of gMG that has the advantage of oral administration.

See Study Rationale, Section 2.1.

Objectives and endpoints

Objectives	Endpoints
Primary	
DB period	
To evaluate the efficacy of tolebrutinib 60 mg daily compared to placebo as measured by MG-ADL score in participants with gMG who are receiving SoC	Change from baseline in MG-ADL total score at Week 26
OLE	
To evaluate the long-term safety and tolerability of tolebrutinib 60 mg daily in participants with gMG who are receiving SoC	AEs, serious AEs, AEs leading to permanent study intervention discontinuation, AESIs, potentially clinically significant abnormalities in laboratory tests, ECG, and vital signs during the treatment period
Secondary	
DB period	
To evaluate the efficacy of tolebrutinib 60 mg daily compared to placebo on additional efficacy measurements: QMG, MGII, MG-QoL15, MG-ADL in participants with gMG who are receiving SoC	Change from baseline in QMG total score at Week 26 Change from baseline in QMG total score at Week 12 [redacted] Change from baseline in MGII total score at Week 26 Change from baseline in MG-QoL15 total score at Week 26 Proportion of participants with ≥2-point improvement (reduction) in MG-ADL total score at Week 26 Proportion of participants with ≥3-point improvement (reduction) in QMG total score at Week 26

Objectives	Endpoints
To evaluate the safety and tolerability of tolebrutinib 60 mg daily compared to placebo in participants with gMG who are receiving SoC	AEs, serious AEs, AEs leading to permanent study intervention discontinuation, AESIs, potentially clinically significant abnormalities in laboratory tests, ECG, and vital signs during the treatment period
OLE	
To evaluate the long-term efficacy of tolebrutinib 60 mg daily in participants with gMG who are receiving SoC	Change from baseline in MG-ADL total score over time Change from baseline in QMG total score over time Change from baseline in MGII total score over time Change from baseline in MG-QoL15 total score over time Proportion of participants with ≥2-point improvement (reduction) in MG-ADL total score at EOT (timeframe: baseline, up to Week 130) Proportion of participants with ≥3-point clinical improvement (reduction) in QMG total score at EOT (timeframe: baseline, up to Week 130) Proportion of participants achieving any reduction from baseline of daily dose of OCS over time

[redacted]; AE: adverse event; AESI: adverse event of special interest; DB: double-blind; ECG: electrocardiogram; EOS: end of study; EOT: end of treatment; gMG: generalized myasthenia gravis; [redacted]; MG-ADL: Myasthenia Gravis Activities of Daily Living; [redacted] MG-QoL15: Myasthenia Gravis Quality of Life 15-item scale; MGII: Myasthenia Gravis Impairment Index; MuSK: muscle-specific kinase; OCS: oral corticosteroid; OLE: open-label extension; PD: pharmacodynamic; PK: pharmacokinetic; QMG: Quantitative Myasthenia Gravis; QoL: quality of life; SoC: standard of care.

For China, please see Section 10.8 for details.

Overall design:

EFC17262 is a multicenter, randomized, double-blind (DB), placebo-controlled, Phase 3 study to evaluate the efficacy and safety of tolebrutinib 60 mg daily compared with placebo in participants aged 18 to 85 years with moderate-to-severe gMG who are receiving the standard of care (SoC). The DB period will be followed by an open-label extension (OLE) period to evaluate the safety and efficacy of tolebrutinib.

The DB period will include a screening period (up to 28 days) and a treatment period of 26 weeks. After screening, eligible participants will be randomly assigned (1:1 ratio) to receive 60 mg of a tolebrutinib oral, daily dose or matching placebo. Randomization will be stratified by the Myasthenia Gravis Foundation of America (MGFA) class (II, IIIa/ IVa, or IIIb/IVb) and region (United States [US], non-US). The primary endpoint will be change from baseline in the Myasthenia Gravis-Activities of Daily Living (MG-ADL) score at Week 26.

Participants will receive the investigational medicinal product (IMP) as an add-on therapy to their SoC, ie, their gMG treatment(s) prior to screening maintained at stable doses throughout the 26-week duration of the DB period. These treatments are required to be at a stable dose for a predefined duration prior to the entry in the study; see details in the inclusion criteria (Section 5.1). The SoC may consist of an acetylcholinesterase inhibitor (AChEI) (eg, pyridostigmine), oral corticosteroids (OCS) up to the maximal dose of 20 mg daily, and/or

a single immunosuppressive treatment (IST), such as azathioprine, mycophenolate mofetil, tacrolimus, or methotrexate.

However, the use of rescue therapy for gMG worsening will be allowed at the discretion of the Investigator if there is at least a 2-point increase of individual non-ocular MG-ADL items compared to the Day 1 MG-ADL score, or new or worsening of respiratory/ bulbar symptoms. Rescue therapy can include intravenous immunoglobulin (IVIg), plasma exchange, change in the SoC, OCS dose, or any use of new corticosteroids (CS). If rescue therapy is needed, the Sponsor should be informed, preferably prior to the administration of treatment, where possible, without compromising the participant's safety (see Section 6.8.3). In case of use of rescue therapy during the DB period, the study intervention will be permanently discontinued.

If a participant prematurely and permanently discontinues treatment with the IMP during the DB period, the participant will be asked to perform a premature end-of-treatment (pEOT) visit and to continue to perform DB period visits without IMP. If the participant is not willing to continue with DB study visits without IMP, there will be a safety follow-up (FU) period (4 to 8 weeks) after the pEOT visit.

All participants who complete the DB period on treatment will enter the OLE. During this study period, all participants will receive open-label tolebrutinib 60 mg daily while continuing to receive the same SoC treatment. However, during the OLE, SoC treatments may be adjusted (ie, dose change, discontinuation, or addition of other allowed SoC treatments) at the discretion of the Investigator based on the clinical presentation. Rescue therapy medications will also be allowed during the OLE, as described in Section 6.8.3, and participants using rescue therapy during the OLE will not be required to discontinue study intervention. Please refer to Section 6.8 for drugs that will continue to be prohibited during the OLE. The OLE will include a safety FU period (4 to 8 weeks) upon discontinuation of open-label IMP, prematurely or at the premature end of study (EOS).

An IDMC will review the safety data of participants in the study and advise the Sponsor on the conduct of the clinical study.

Brief summary:

This is a multicenter, randomized, DB, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of tolebrutinib 60 mg daily compared with placebo in adult participants aged 18 to 85 years with moderate-to-severe gMG who are receiving the SoC. The DB treatment period of 26 weeks will comprise 7 site visits followed by a 2-year OLE period with quarterly visits. The efficacy of tolebrutinib versus placebo during the DB period will be assessed by clinical evaluations, which include scales based on the physician's examination or direct participant feedback, ie, clinical outcome assessments. These evaluations will continue during the OLE in order to measure long-term efficacy and safety.

Number of participants:

Approximately [redacted] people will be screened to achieve [redacted] participants randomized to the study intervention at a randomization ratio of 1:1 (assuming a screen failure rate of 20%).

Intervention groups and duration:

The DB period will include a screening period (up to 28 days), after which eligible participants will be randomized to a treatment group, 60 mg oral, daily tolebrutinib or matching placebo. The duration of the treatment period will be 26 weeks.

The OLE will include all eligible participants who have completed the DB period on treatment. Participants will receive 60 mg of oral, daily tolebrutinib for a duration of up to 2 years.

Post-trial access may be considered, if required, and approved by local regulations.

Study intervention(s)

Investigational medicinal product

- Formulation: tolebrutinib film-coated tablet
- Route of administration: oral
- Dose regimen: 60 mg once daily taken with a meal

Investigational medicinal product

- Formulation: placebo to match tolebrutinib film-coated tablet
- Route of administration: oral
- Dose regimen: once daily taken with a meal

Noninvestigational medicinal products(s)

- Not applicable.

Devices

Not applicable.

Post-trial access to study medication

Post-trial access may be considered, if required, and approved by local regulations.

Statistical considerations:

The modified intention-to-treat (mITT) population will include all randomized and treated participants with a baseline value and at least 1 post-baseline value for any efficacy assessment. Participants will be analyzed as randomized. This will be the primary efficacy population.

- **Primary endpoint (DB period):**

A combination of treatment policy strategy and composite variable strategy will be used to handle intercurrent events (ICEs) for the analysis of the primary endpoint of change from baseline in MG-ADL total score at Week 26 in the mITT population (see Table 5).

Population level summary: Difference in mean change from baseline MG-ADL total score between tolebrutinib and placebo will be analyzed using an analysis of covariance (ANCOVA) with change from baseline MG-ADL total score at Week 26 as the response variable, accounting for ICEs as detailed in Table 5; and treatment, baseline MG-ADL total score, and all randomization stratification factors as covariates. For participants who prematurely discontinue study intervention due to a reason other than rescue therapy or lack of efficacy and then further withdraw from the study before Week 26, their MG-ADL total score will be missing at Week 26 and therefore will not be included in the ANCOVA model. Difference in least squares means, the corresponding 95% confidence intervals (CIs) and p-value will be provided for the comparison of tolebrutinib versus placebo.

- **Main secondary endpoints (DB period):**

The primary analysis of the main secondary efficacy endpoints, change from baseline in QMG total score at Week 26, and change from baseline in Myasthenia Gravis Impairment Index (MGII) total score at Week 26, will be based on a combination of treatment policy strategy and composite variable strategy in the mITT population.

These secondary endpoints will be analyzed in the same way as the primary endpoint, except that the respective baseline value corresponding to the endpoint will be included as the covariate in the ANCOVA model and the worst change from baseline value as stated in Section 9.3.2 for participants who permanently discontinue study intervention due to rescue therapy and/or lack of efficacy will be based on the corresponding assessment.

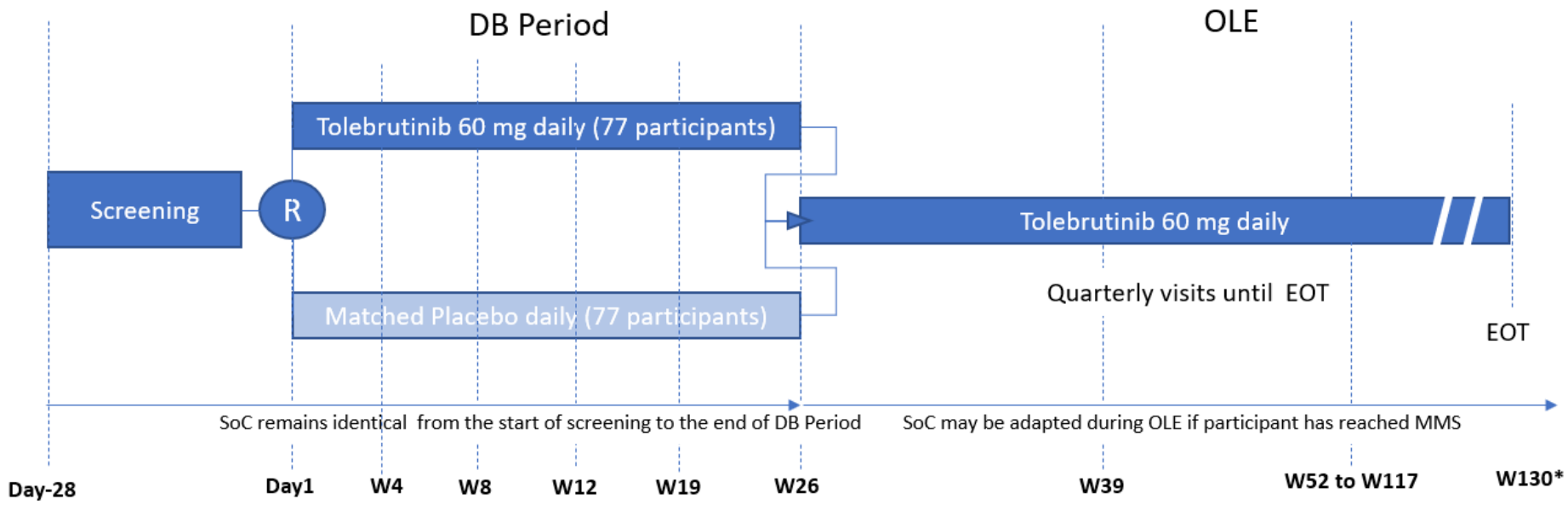
Data Monitoring Committee: Yes

Scientific Advisory Committee: Yes

Independent Hepatology Assessment Committee: Yes

1.2 SCHEMA

Figure 1 - Graphical study design



DB: double-blind; EOT: end of treatment; MMS: minimal manifestation status; OLE: open-label extension; R: randomization; SoC: standard of care; W: week.

*A follow-up visit will occur 4 to 8 weeks after EOT visit and will be considered as EOS for participant reaching this visit (see Section 4.4 for more details on EOS in other cases).

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening (up to 28 days before D1)[a]	DB period[b]											OLE[b]											
		D1	[redacted]	W4	[redacted]	W8	[redacted]	W12	[redacted]	W19[g]	[redacted]	W26[c]	[redacted]	W39	[redacted]	W52	[redacted]	W65	[redacted]	W78, W91, W104, W117	EOT[d] W130	pEOT[e]	Follow up[f, g] (4 to 8 weeks after pEOT/EOT)
Visit (a window of ±7 days is allowed for all visits after D1)	**V1**	**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11, 12, 13, 14**	**15**		
Informed consent	X																						
Inclusion and exclusion criteria	X	X																					
Demography	X																						
Medical and surgical history	X																						
Prior/ concomitant medications[h]	←==========→																						
Randomization		X																					
IRT contact	X	X						X				X		X		X		X		X	X	X	X
IMP dispensation		X						X				X[i]		X		X		X		X			
IMP compliance								X				X		X		X		X		X	X	X	

Procedure	Screening (up to 28 days before D1)[a]	DB period[b]										OLE[b]											
		D1	[redacted]	W4	[redacted]	W8	[redacted]	W12	[redacted]	W19[g]	[redacted]	W26[c]	[redacted]	W39	[redacted]	W52	[redacted]	W65	[redacted]	W78, W91, W104, W117	EOT[d] W130	pEOT[e]	Follow up[f, g] (4 to 8 weeks after pEOT/EOT)
Visit (a window of ±7 days is allowed for all visits after D1)	**V1**	**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11, 12, 13, 14**	**15**		
Diary dispensation and collection[j]		X						X				X		X		X		X		X	X	X	
Safety																							
Physical examination[k]	X	X						X				X		X		X		X		X	X	X	X
Vital signs[l]	X	X		X		X		X				X		X		X		X		X	X	X	X
Body height	X																						
Body weight	X	X						X				X		X		X		X		X	X	X	X
Pregnancy test (WOCBP only)[m]	X	X		X		X		X				X		X		X		X		X	X	X	X
Serum FSH[n]	X																						
HIV, hepatitis B and C screening	X																						

Procedure	Screening (up to 28 days before D1)[a]	DB period[b]							OLE[b]								
		D1	[redacted]	W4	[redacted]	W8	[redacted]	W12	[redacted]	W19[g]	[redacted]	W26[c]	[redacted]	W39	[redacted]	W52	[redacted]	W65	[redacted]	W78, W91, W104, W117	EOT[d] W130	pEOT[e]	Follow up[f, g] (4 to 8 weeks after pEOT/EOT)
Visit (a window of ±7 days is allowed for all visits after D1)	**V1**	**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11, 12, 13, 14**	**15**		
Tuberculosis testing[o]	X																						
Laboratory tests (include hematology and clinical chemistry)[p]	X	X		X		X		X		X		X		X		X		X		X	X	X	X
[redacted]																							
Iron panel (serum): iron, ferritin, transferrin saturation, TIBC; to be repeated during the study, if needed	X																						

Procedure	Screening (up to 28 days before D1)[a]	DB period[b]										OLE[b]											
		D1	[redacted]	W4	[redacted]	W8	[redacted]	W12	[redacted]	W19[g]	[redacted]	W26[c]	[redacted]	W39	[redacted]	W52	[redacted]	W65	[redacted]	W78, W91, W104, W117	EOT[d] W130	pEOT[e]	Follow up[f, g] (4 to 8 weeks after pEOT/EOT)
Visit (a window of ±7 days is allowed for all visits after D1)	**V1**	**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11, 12, 13, 14**	**15**		
Urinalysis	X											X		X[r]		X[r]		X[r]		X[r]	X	X	
Coagulation: PT/INR, aPTT (to be repeated during the study, if needed)	X																						
12-lead ECG	X			X				X				X		X[s]		X[s]		X[s]		X[s]	X	X	X
Suicidality assessment by C-SSRS	X	X						X				X		X		X		X		X	X	X	X
AE/SAE review	←==========→																						
Efficacy[t]																							
MG-ADL	X	X		X		X		X				X		X		X		X		X	X	X	
QMG		X		X		X		X				X		X		X		X		X	X	X	
MGII		X		X		X		X				X		X		X		X		X	X	X	

Procedure	Screening (up to 28 days before D1)[a]	DB period[b]										OLE[b]									
		D1	[redacted]	W4	[redacted]	W8	[redacted]	W12	[redacted]	W19[g]	[redacted]	W26[c]	[redacted]	W39	[redacted]	W52	[redacted]	W65	[redacted]	W78, W91, W104, W117	EOT[d] W130	pEOT[e]	Follow up[f, g] (4 to 8 weeks after pEOT/EOT)
Visit (a window of ±7 days is allowed for all visits after D1)	V1	2		3		4		5		6		7		8		9		10		11, 12, 13, 14	15		
MG-QoL15		X										X		X		X		X		X	X	X	
[redacted]																							

Procedure	Screening (up to 28 days before D1)[a]	DB period[b]										OLE[b]											
		D1	[redacted]	W4	[redacted]	W8	[redacted]	W12	[redacted]	W19[g]	[redacted]	W26[c]	[redacted]	W39	[redacted]	W52	[redacted]	W65	[redacted]	W78, W91, W104, W117	EOT[d] W130	pEOT[e]	Follow up[f, g] (4 to 8 weeks after pEOT/EOT)
Visit (a window of ±7 days is allowed for all visits after D1)	V1	2		3		4		5		6		7		8		9		10		11, 12, 13, 14	15		
[redacted]																							

[redacted] AE: adverse event; ALT: alanine aminotransferase; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; BUN: blood urea nitrogen; AChEI: acetylcholinesterase inhibitor; C-SSRS: Columbia-Suicide Severity Rating Scale; D: day; eCRF: electronic case report form; DB: double-blind; EOS: End of Study; [redacted]; EU: European Union; ECG: electrocardiogram; EOT: end of treatment; FU: follow-up; FSH: follicle-stimulating hormone; h: hour; [redacted] HIV: human immunodeficiency virus; ICF: informed consent form; [redacted]; IMP: investigational medicinal product; INR: international normalized ratio; IRT: interactive response technology; MG: myasthenia gravis; MG-ADL: Myasthenia Gravis-Activities of Daily Living; [redacted]; MGII: Myasthenia Gravis Impairment Index; MG-QoL15: Myasthenia Gravis Quality of Life 15-item Scale; [redacted]; OLE: open-label extension; pEOT: premature end of treatment; [redacted]; PK: pharmacokinetic(s); PT: prothrombin time; QMG: Quantitative Myasthenia Gravis; SAE: serious adverse event; TB: tuberculosis; TIBC: total iron-binding capacity; V: visit; W: week; WOCBP: woman of childbearing potential; β-HCG: β-human chorionic gonadotropin.

a The screening period can range from D -28 to D -1. The randomization visit can be performed only once IMPs are available onsite. The interval between screening and randomization visits can range from 11 days (minimum) to 28 days (maximum). However, if required, the randomization visit can be performed earlier than 11 days upon IMP receipt at the site, assuming the participant is eligible for randomization.

b From D1 to the EOT, unscheduled visits may be performed at any time by the Investigator (eg, for a suspected MG crisis or evaluation of an AE). Assessments may be performed as needed to evaluate the participant in accordance with the Investigator's best judgment and in line with the study protocol. At a minimum, a physical examination should be performed, and body temperature and vital signs should be measured. In case of a suspected MG crisis suspicion, at least the MG-ADL assessment should be performed (see Section 6.8.3 [rescue therapy]).

c The Week 26 Visit will also be Day 1 for the OLE. Participants will begin the OLE treatment (open label tolebrutinib once daily 60 mg) on the next day.

d The EOS visit will be the FU visit, 4 to 8 weeks after last dose of study intervention.

e During the DB period, if a participant prematurely and permanently discontinues treatment with the IMP, he/she will undergo a pEOT visit as soon as possible. Participants will then be asked to continue in the study with all study procedures/visits, except those associated with IMP administration. In the OLE period, participants with pEOT will be encouraged to attend the safety FU visit (4 to 8 weeks after pEOT), which will be considered as the EOS.

f A safety FU visit needs to be performed 4 to 8 weeks after pEOT for participants who discontinue the DB IMP prematurely and who do not wish to continue the study, or 4 to 8 weeks after EOT. This visit will be considered as the EOS. In the case the FU visit is conducted as a home visit and some assessments are not possible during the visit (eg, neurological examination part of the physical examination), these parts of the assessment may be skipped.

g Week 19 and Follow-up visits can be conducted as a home visit. Home visits can be replaced by site visits with the same assessments and procedures, depending on the Investigator's assessment and/or local regulatory requirement(s).

h Any MG medication taken at any time prior to signing the informed consent needs to be reported in the eCRF; other prior medications will be reported for the period of 6 months prior to signing the ICF.

i Investigational medicinal product dispensation for participants who will continue in the OLE period.

j Diaries will be collected at EOS for participants completing their study and at pEOT for participants who prematurely discontinue the study.

k Complete physical examination due at Screening, D1, Visit 7 (Week 26), Visit 11 (Week 78), and EOT. Brief physical examination is sufficient for the rest of the visits (complete and brief physical examination will include neurological examination).

l Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), and body temperature (°C) will be measured.

m Serum β-HCG at central laboratory at Screening and urine pregnancy tests within 24 hours before the first dose of IMP and at scheduled times during the study. In addition to scheduled visits, pregnancy tests will be performed monthly for all participants who are WOCBP. Additional serum or urine pregnancy tests may be performed, as deemed necessary by the Investigator or required by local regulations, to establish the absence of pregnancy at any time during the participant's participation in the study.

n Only in female participants, if needed to establish menopausal status.

o To be performed at Screening for all participants. To be repeated based on clinical judgment, borderline results, or clinical suspicion of TB infection. Refer to the exclusion criteria (Section 5.2).

p Clinical chemistry (blood urea nitrogen [BUN], creatinine, glucose, potassium, sodium, chloride, bicarbonate, calcium, liver function tests [AST, ALT, albumin, alkaline phosphatase, total and direct bilirubin, total protein; creatine phosphokinase], hematology (platelet count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, reticulocytes, white blood cell count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils). Lipase will be tested at the Screening Visit only. Week 19 will include hematology and full liver panel only (see Table 6).

[redacted]

r During OLE, urinalysis will be conducted at Visits 9, 11, and 13.

s During OLE, ECG will be performed at Visits 8, 9, and 13.

t For all visits with QMG or MGII assessments: to reduce fluctuations in performance on functional tests due to temporary symptomatic effects associated with AChEI use, AChEIs should not be taken for at least 12 hours prior to efficacy endpoint testing at each visit. It is important that participants complete the outcome assessments after the ICF is signed and prior to any treatment- or study-related activities including administration of study intervention, laboratory work, radiological assessments, discussion with participants regarding their treatment or health status, and similar activities. This ensures the objectivity of the data. Detailed site training on clinical outcome assessments will be provided. These clinical outcome assessments will be administered and documented electronically by both the Investigator and participants.

[redacted]

2 INTRODUCTION

Tolebrutinib is an inhibitor of BTK that is being developed for the treatment of multiple sclerosis (MS) and gMG.

2.1 STUDY RATIONALE

The purpose of Study EFC17262 is to evaluate the efficacy and safety of tolebrutinib 60 mg daily compared with placebo in adult participants with moderate-to-severe gMG receiving the SoC.

Current management of gMG is initially based on the use of symptomatic treatments and IST. Treatment goals have been defined in recent international consensus guidance (1, 2), such as reaching minimal or no symptoms or functional limitations from gMG, even with some residual muscle weakness, and with no more than Grade 1 Common Terminology Criteria for Adverse Events (CTCAE) adverse events (AEs). The treatment for gMG usually starts with symptomatic use of AChEIs to enhance synaptic function by increasing the reliability of neuromuscular transmission in affected individuals. However, AChEIs alone do not adequately control signs and symptoms, and immunomodulation with corticosteroids (CS) or non-steroid ISTs are often required to control disease activity (1). Corticosteroids have an unfavorable safety profile and best practices tend to recommend their use at minimally effective doses. Immunosuppressive drugs may be added to a course of CS to achieve minimal manifestation status. Therefore, the SoC for most people will often include AChEIs, CS, and/or immunosuppressive drugs. In general, such treatments have limited benefit, with slow onset accompanied by significant side effects. Their efficacy is also not predictable, and many people with gMG fail to respond to some of these treatments.

There is an unmet need for people with gMG for effective treatments with better long-term safety profiles and with more feasible modes of administration (2, 3).

Tolebrutinib, a covalent, irreversible inhibitor of BTK, is an immunomodulatory agent relevant to the pathophysiology of gMG that has the advantage of oral administration.

Bruton's tyrosine kinase is essential to integrating cellular signaling downstream of the B-cell receptor (BCR), Fc-gamma receptor (FcγR), Fc-epsilon receptor (FcεR), and other sensors tied to innate responses, such as toll-like receptors (TLRs) (4). Inhibition of BTK activity in B cells produces phenotypic changes consistent with blockade of the BCR, preventing activation, maturation, and antibody production, muting B-cell related pathology without depleting these cells. Inhibition of BTK also modulates the activation of other hematopoietic cells such as basophils, mast cells, macrophages, and neutrophils, primarily through FcγR and FcεR signaling, blocking the inflammatory cytokine cascade driven by antibody crosslinking to surface receptors (5, 6).

Deficiency or inhibition BTK has shown to reduce disease in several rodent models of autoimmune disease, including experimental autoimmune encephalomyelitis, arthritis (5, 6, 7, 8, 9, 10), systemic lupus erythematosus (8, 11), and antibody-mediated glomerulonephritis. Bruton's tyrosine kinase inhibitors also suppress antibody-mediated skin inflammation in Arthus and passive cutaneous anaphylaxis models in mice via the inhibition of FcγR and FcεR signaling, respectively (5).

The pathogenesis of gMG is linked to activated T, B, and plasma cells that produce autoantibodies and drive inflammation at the neuromuscular junction (12). Dysregulated production of proinflammatory cytokines and impaired B- and T-regulatory cells have also been implicated (13, 14). Innate immunity in the context of ectopic germinal centers and thymic hyperplasia are also encountered in gMG (15, 16). Certain pattern-recognition receptors, such as toll-like receptors (TLRs), are expressed in germinal center macrophages (17, 18) and may participate in persistent autoimmune dysfunction (19). Bruton's tyrosine kinase plays a key role in the signal transduction downstream of TLR signaling, offering a new way to target inflammatory mechanisms.

In summary, BTK signaling in multiple cell types implicated in gMG pathogenesis suggests that targeting this pathway can be an effective therapy.

2.2 BACKGROUND

Myasthenia gravis (MG) is a rare, chronic, autoimmune, inflammatory disease affecting the neuromuscular junction mediated by pathogenic antibodies targeting AchR and a component of its recycling machinery at the postsynaptic membrane. Generalized MG is clinically characterized by an abnormal muscular weakness and fatigability. The clinical picture fluctuates with a course of remissions and relapses, and all muscles can be affected over time (20, 21).

The prevalence of MG is estimated to be between 1.5 to 36.7 cases per 100 000 individuals depending on the geographic location (22). These data indicate an overall estimate of approximately 56 000 to 123 000 people with MG in Europe and 60 000 in the US (22). The incidence for the MG with anti-AChR antibodies is estimated to be between 0.43 and 1.80 new cases per 100 000 individuals annually, with larger variations (between 0.17 and 2.13) when considering all MG subgroups (23, 24).

Most people with gMG (ie, 80% to 90%) have detectable antibodies against the AChR. Anti-AChR antibodies are not detected in 10% to 15% of people with gMG, usually because the sensitivity of the assay used is too low (19, 20). A small number of people have antibodies against MuSK (approximately 4%), lipoprotein-receptor-related protein 4 (approximately 2%) (25) or are considered to be seronegative.

Most autoantibodies found in people with gMG are class switched and have been affinity maturated, implicating B- and T-cell interactions in their generation (13). These autoantibodies are involved in gMG pathogenesis through different mechanisms - increased internalization or direct functional blockage of the AChR and complement activation, both leading to synaptic dysfunction. Generalized MG pathophysiology also involves dysregulated production of proinflammatory cytokines and impaired B- and T-cell regulatory mechanisms (12, 13).

Generalized MG can be classified using autoantibody subtypes, but the classification may also be based on the age of onset with gMG occurrence as an early (before the age of 50 years) or late onset disease. Presence or absence of thymic anomalies, from thymic hyperplasia to thymoma, are also used to classify gMG. Thymic anomalies occur more frequently in anti-AChR autoantibody positive people (anti-AChR-MG) and are mostly absent in people with anti-MuSK autoantibodies (anti-MuSK-MG). An additional clinical classification is the MGFA classification, in which people with gMG are classified according to the muscle groups impacted by the disease and the severity of the muscle weakness (2).

Thymic involvement (thymic hyperplasia) with the presence of germinal centers showing B-cell activation reinforces the role of B cells (higher antibody concentration is associated to these germinal centers) (15).

The treatment for gMG usually starts with symptomatic use of AChEIs to enhance synaptic function by increasing reliability of neuromuscular transmission in affected individuals. However, AChEIs alone do not adequately control signs and symptoms, and immunomodulation with CS or ISTs is often required to control disease activity (1).

Due to the role of B cells in the pathogenesis of gMG, the anti-CD20, B-cell-depleting monoclonal antibody rituximab has been used off label for treatment-resistant gMG. In a recent international guidance (26), rituximab is recommended for anti-MuSK subtypes, but there is limited evidence for its use in anti-AChR subtypes. Eculizumab, a monoclonal antibody against complement factor C5, has been recently approved by the FDA for treatment of gMG in adults who are seropositive for anti-AChR; in the European Union (EU), its approval is restricted to the treatment of refractory gMG (27). It is also presently recommended by international experts as third-line therapy in refractory gMG (26).

For more severe disease, characterized by myasthenic crises involving respiratory muscles that can precipitate respiratory failure requiring urgent, faster-acting treatment, IVIgs, and plasma exchange have been used.

Despite available therapies, there remains a need for safer and more effective treatments. The mechanism of action of tolebrutinib may be relevant to treatment of gMG in that it modulates multiple functions of B cells and the innate immune system.

2.3 BENEFIT/RISK ASSESSMENT

A detailed description of the chemistry, pharmacology, efficacy, safety, known and expected benefits and risks, and reasonably expected AEs of tolebrutinib may be found in the Investigator's Brochure (IB).

2.3.1 Risk assessment

Tolebrutinib has been studied in healthy participants and participants with relapsing forms of MS. Oral administration of tolebrutinib was generally safe and well tolerated in the Phase 1 studies conducted with healthy participants to date.

The results from the Phase 2b trial (DRI15928) suggested that tolebrutinib was generally safe and well tolerated in people with relapsing multiple sclerosis (RMS). No new risks were identified in this study. The key safety results are summarized as follows:

- There were no deaths or treatment-emergent adverse events (TEAE) leading to permanent treatment discontinuation during the study. One treatment-emergent (TE) serious adverse event (SAE) (MS relapse) was reported in a participant treated with 60 mg tolebrutinib; the remainder of the reported TEAEs were of mild or moderate intensity.
- There was no direct correlation between the dose of tolebrutinib administered and number or intensity of TEAEs. The most common events reported in participants in the tolebrutinib treatment arms were headache, upper respiratory tract infection, and nasopharyngitis.
- Two participants had TE transient alanine aminotransferase (ALT) increase >3 × upper limit of normal (ULN): 1 in the 30 mg tolebrutinib treatment group (at Week 8, 105 U/L [normal range 6 to 34 U/L]) that returned to normal range within 4 days and 1 in the 60 mg tolebrutinib treatment group (at Week 4, 107 U/L [normal range 6 to 34 U/L]). The participant in the 60 mg group had slightly elevated ALT at screening (48 U/L) and at baseline (50 U/L); ALT levels returned to the normal range in 8 weeks. Both participants continued study treatment. All other liver enzyme levels for both participants were within normal ranges during the treatment period; 1 event was assessed as related and 1 as unrelated to the study drug by the Investigators. Both participants completed the DRI15928 study and successfully rolled over to the long-term safety FU study.
- One event of mild petechia in a female participant (at Week 8 in the tolebrutinib 30 mg group) and 2 events of mild microscopic hematuria in 2 male participants (1 event at Week 16 in the tolebrutinib 30 mg group and 1 event on Day 1 in the tolebrutinib 60 mg group, with occult blood noted in urine) were reported during the treatment period. The hematology results were clinically insignificant for all 3 participants from the onset of the events. The participant with mild petechia had benign pigmentary lesions noted during screening, and the event was assessed as related to the study drug by the Investigator. The 2 events of mild microscopic hematuria were assessed as unrelated to the study drug. All 3 events resolved spontaneously.
- No severe infections occurred. The most frequently reported (≥3 events total) in the tolebrutinib treatment group were upper respiratory tract infection, nasopharyngitis, gastroenteritis, and respiratory tract infection.
- No clinically significant cytopenia, including thrombocytopenia and neutropenia, was reported or detected based on hematologic laboratory results, and no clinically significant cardiac arrhythmia was observed via electrocardiogram (ECG) monitoring during the study.

Based on tolebrutinib nonclinical safety data, Phase 1 results in healthy participants, Phase 2b results in participants with RMS, and the published data of other marketed or investigational BTK inhibitors for various indications, the potential risks of tolebrutinib are as follows:

- Bleeding (hemorrhage)

- Infections
- Cytopenia including thrombocytopenia
- Atrial arrhythmias (atrial fibrillation and atrial flutter)

In the ongoing Phase 3 and long-term safety studies, tolebrutinib has been generally well tolerated to date. An identified risk for tolebrutinib has been identified as follows:

- Treatment-emergent SAEs of drug-induced liver injury (DILI) were reported in in the ongoing Phase 3 trials; [redacted]

Assessment of COVID-19 in study participants:

Antiviral responses are likely to be driven mainly by T cells, in particular, CD8+ cytotoxic T lymphocytes and natural killer cells, and less so, at least initially, by B cells (28). In vitro and cell-based assays indicate that tolebrutinib does not deplete B lymphocytes and does not exhibit significant cellular off-target activity in human T lymphocytes. In the completed Phase 2b study in participants with RMS (DRI15928), the mean counts of CD19+ B cells, CD4 and CD8 T cells, CD16+56 natural killer cells, and the levels of IgG and IgM remained stable at the end of 12 weeks of treatment with tolebrutinib.

Infections are an important potential risk for tolebrutinib, and severe infections are being monitored as an adverse event of special interest (AESI) in all ongoing studies and will be monitored in future clinical studies. In the completed Phase 2b trial in 130 people with RMS, 23.8% of participants reported only mild or moderate infections at the end of 12 weeks of treatment with tolebrutinib. No participant discontinued treatment due to infection or any other TEAE. At present, it is unknown if people with gMG are at increased risk for severe acute respiratory syndrome coronavirus 2 infection, acquiring coronavirus disease-2019 (COVID-19) or of developing severe COVID-19 (29, 30).

In the current study, eligibility criteria exclude people with some known risk factors for COVID-19 including comorbidities that may put the participants at higher risk for serious illness such as chronic cardiovascular disease, liver disease, kidney disease and malignancies. Among allowed comedications, the risk of a severe COVID-19 course association with CS use is discussed. These results suggest that in case of a MG crisis during COVID-19, IVIg therapy may be preferred to increasing CS dose. On the contrary, azathioprine or mycophenolate mofetil appears to have no impact on the course of COVID-19. COVID-19 treatments such as remdesivir, favipiravir and convalescent plasma appear not to be associated with MG exacerbation (31, 32, 33).

In addition, appropriate safety monitoring measures are in place including physical examination, monitoring of vital signs and clinical laboratory tests, ECG, and collection of AEs and AESIs. Every effort will be made to complete study visits and study assessments and to provide study drug for participants. If needed, temporary treatment discontinuation can be considered by the Investigator or by the participant for any reason, including due to any safety concerns because of

COVID-19 or another illness or if there is a need for a prohibited concomitant medication. Treatment can be resumed later when it is considered safe and appropriate.

In conclusion, considering the mechanism of action of tolebrutinib, the available data on the course of COVID-19 in people with MG receiving the SoC allowed in this study, the safety monitoring and mitigation measures already in place, and the favorable benefit-risk profile observed in the completed Phase 2b study in participants with RMS, the Sponsor maintains that the study can be initiated and conducted as planned.

2.3.2 Benefit assessment

Tolebrutinib modulates both adaptive and innate immunity and may provide the following benefits to participants with gMG in this study:

- Clinically meaningful improvements in MG-specific activities of daily living (ADL), muscle weakness, and MG impairment fatigability as measured by the MG-ADL, QMG test, and MGII, respectively. Improvements in the signs and symptoms of MG and MG-related quality of life (QoL) as measured by the Myasthenia Gravis-Quality of Life 15-item scale (MG-QoL15) measure;
- Reduced need for both rescue therapy and CS use.

2.3.3 Overall benefit: risk conclusion

No safety or tolerability concerns have been identified in the Phase 1 studies in healthy participants up to a single dose of [redacted] mg of tolebrutinib taken with food (ongoing study TDU16831 with study conduct recently completed) and up to repeated doses of [redacted] mg once daily taken with food for 2 weeks (completed study TDR16862), or in the completed Phase 2b study (DRI15928) in participants with RMS. The potential risks associated with tolebrutinib are well defined, and appropriate safety monitoring measures and risk mitigation strategies are in place.

Drug-induced liver injury has been identified in the ongoing Phase 3 trials. [redacted]

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with tolebrutinib are justified by the anticipated benefits that may be afforded to participants with gMG.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
DB period	
To evaluate the efficacy of tolebrutinib 60 mg daily compared to placebo as measured by MG-ADL score in participants with gMG who are receiving SoC	Change from baseline in MG-ADL total score at Week 26
OLE	
To evaluate the long-term safety and tolerability of tolebrutinib 60 mg daily in participants with gMG who are receiving SoC	AEs, serious AEs, AEs leading to permanent study intervention discontinuation, AESIs, potentially clinically significant abnormalities in laboratory tests, ECG, and vital signs during the treatment period
Secondary	
DB period	
To evaluate the efficacy of tolebrutinib 60 mg daily compared to placebo on additional efficacy measurements: QMG, MGII, MG-QoL15, MG-ADL in participants with gMG who are receiving SoC	Change from baseline in QMG total score at Week 26 Change from baseline in QMG total score at Week 12 (for the interim analysis only) Change from baseline in MGII total score at Week 26 Change from baseline in MG-QoL15 total score at Week 26 Proportion of participants with $\geq$2-point improvement (reduction) in MG-ADL total score at Week 26 Proportion of participants with $\geq$3-point improvement (reduction) in QMG total score at Week 26
To evaluate the safety and tolerability of tolebrutinib 60 mg daily compared to placebo in participants with gMG who are receiving SoC	AEs, serious AEs, AEs leading to permanent study intervention discontinuation, AESIs, potentially clinically significant abnormalities in laboratory tests, ECG, and vital signs during the treatment period
OLE	
To evaluate the long-term efficacy of tolebrutinib 60 mg daily in participants with gMG who are receiving SoC	Change from baseline in MG-ADL total score over time Change from baseline in QMG total score over time Change from baseline in MGII total score over time Change from baseline in MG-QoL15 total score over time Proportion of participants with ≥2-point improvement (reduction) in MG-ADL total score at EOT (timeframe: baseline, up to Week 130) Proportion of participants with ≥3-point clinical improvement (reduction) in QMG total score at EOT (timeframe: baseline, up to Week 130) Proportion of participants achieving any reduction from baseline of daily dose of OCS over time

Objectives	Endpoints
[redacted]	

[redacted] AE: adverse event; AESI: adverse event of special interest; DB: double-blind; ECG: electrocardiogram; EOS: end of study; EOT: end of treatment; [redacted]; gMG: generalized myasthenia gravis; [redacted] MG-ADL: Myasthenia Gravis-Activities of Daily Living; [redacted] MG-QoL15: Myasthenia Gravis Quality of Life 15-item Scale; MGII: Myasthenia Gravis Impairment Index; MuSK: muscle-specific kinase; OCS: oral corticosteroid; OLE: open-label extension; PD: pharmacodynamic; [redacted]; PK: pharmacokinetic(s); QMG: Quantitative Myasthenia Gravis; QoL: quality of life; SoC: standard of care.

For China, please see Section 10.8 for details.

3.1 APPROPRIATENESS OF MEASUREMENTS

The efficacy and safety assessments used in this study are standard for the evaluation of therapy in people with MG.

The primary and secondary endpoints of MG-ADL and QMG scores are consistent with previously approved and current gMG treatments (ie, eculizumab) and are considered relevant among the target population for this clinical study.

However, we have included a secondary endpoint that has not yet been included in MG registration clinical trials, the MGII. The MGII is a measure of MG impairment focused on the severity of the impairments and the concept of fatigability (ie, triggering or worsening of MG impairment with activity which results in signs and symptoms fluctuation) (34, 35). It consists of a 22-item patient-reported questionnaire with a 6 clinician-reported items. The MGII provides a total score for overall MG which is a summary score of the 2 sub-scores, ocular and generalized impairments.

The Myasthenia Gravis Impairment Index was developed to uniquely measure heterogeneity in MG fatigability, which is defined as triggering or worsening of an impairment with activity and MGII measures impact of MG on daily activities using triggers such as time of day. Other scales do not always capture the daily impact or the nuance of the impairments that people with MG face. As an example, the MGII distinguishes between tonal and speech articulation, which is considered to be more appropriate than combining these symptom features (34). Consequently, the MGII captures aspects of MG symptoms including fatigability that are not assessed by other measures. MGII has been validated in multiple studies and has also been assessed for reliability. Barnett et al (35) conducted a study with 200 participants (54 of whom contributed to the reliability assessments) to assess reliability and conduct validity for the MGII, which showed excellent test-retest as well as inter-rater reliability. The conduct validity showed very high correlation with MG-ADL ($r = 0.91$). The MGII also had high correlation with other MG measures, and the floor effect was also lower than for MG-ADL. Another study (36) of 99 people with MG showed that the MGII confirmed a lower floor effect (4%) than the QMG test (6%) and the MG-ADL (11%). This study also confirmed the validity of the MGII by showing good correlation with the MG-ADL and QMG scores. Overall, the MGII has a higher sensitivity for generalized muscle weakness. Barnett et al (37) conducted a study with 95 people with MG receiving one of IVIg, plasma exchange, and prednisone compared to 54 controls in which the people with MG were assessed with the MGII, MG-ADL, and QMG test. This study revealed that the MGII demonstrated responsiveness to IVIg, plasma exchange, and prednisone with a relative efficiency >1 favoring the MGII.

Therefore, the MGII is a well validated and reliable measure that has also shown responsiveness to various treatment modalities used in MG and is a viable option for clinical trials. It also provides some key advantages relative to the traditional measures used in MG clinical trials.

4 STUDY DESIGN

4.1 OVERALL DESIGN

EFC17262 is a multicenter, randomized, DB, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of tolebrutinib 60 mg daily compared with placebo in participants aged 18 to 85 years with moderate-to-severe gMG, who are receiving the SoC. The DB period will be followed by an OLE period to evaluate the safety and efficacy of tolebrutinib.

The DB period will include a screening period (up to 28 days) and a treatment period of 26 weeks. After screening, eligible participants will be randomly assigned (1:1 ratio) to receive 60 mg of a daily dose of oral tolebrutinib or matching placebo. Randomization will be stratified by MGFA class (II, IIIa/IVa, or IIIb/IVb) and region (US, non-US). The primary endpoint will be change from baseline in the MG-ADL score at Week 26.

Participants will receive the IMP as an add-on therapy to their SoC, ie, their gMG treatment(s) prior to screening maintained at stable doses throughout the 26-week duration of the DB period. These treatments are required to be at stable doses for a predefined duration prior to the entry in the study; see details in the inclusion criteria (Section 5.1). The SoC may consist of an AChEI (eg, pyridostigmine), an OCS up to the maximal dose of 20 mg daily, and/or a single IST, such as azathioprine, mycophenolate mofetil, tacrolimus, or methotrexate.

The use of rescue therapy for gMG worsening will be allowed at the discretion of the Investigator if there is at least a 2-point increase of individual non-ocular MG-ADL items compared to the Day 1 MG-ADL score or new or worsening of respiratory/bulbar symptoms. Rescue therapy can include IVIg, plasma exchange, change in the SoC OCS dose, and use of new CS. If rescue therapy is needed, the Sponsor should be informed, preferably prior to the administration of treatment, where possible, without compromising the participant's safety (see Section 6.8.3). In case of use of rescue therapy during the DB period, the study intervention will be permanently discontinued.

If a participant prematurely and permanently discontinues treatment with the IMP during the DB period, the participant will be asked to perform a pEOT visit and to continue to perform DB period visits without IMP. If the participant is not willing to continue with DB study visits without IMP, there will be a safety FU period (4 to 8 weeks) after the pEOT.

All participants who complete the DB period on treatment will enter the OLE. During this study period, all participants will receive open label tolebrutinib 60 mg daily while continuing to receive the same SoC treatment. However, during the OLE, SoC treatments may be adjusted (ie, dose change, discontinuation, or addition of other allowed SoC treatments) at the discretion of the Investigator based on the clinical presentation. Rescue therapy will also be allowed during the OLE, as described in Section 6.8.3, and participants using a rescue therapy during OLE will not be required to discontinue the study intervention. Please refer to Section 6.8 for drugs that will continue to be prohibited during the OLE. The OLE will include a safety FU visit 4 to 8 weeks after discontinuation of open-label IMP, prematurely or at the planned EOT.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A randomized, placebo-controlled study design where the effects of the IMP are assessed on top of SoC background therapy is considered to be the most appropriate design to examine the efficacy and safety of a novel therapy in gMG.

Standard of care background therapies allowed in the study include AChEI, given as symptomatic treatment, OCS, which are considered as one of the most effective immunosuppressive therapies for gMG, and/or one other immunosuppressive drug, used as CS-sparing agent and limited to azathioprine, mycophenolate mofetil, tacrolimus, or methotrexate. Some conditions for prior use and stability at the given dose at the time of Screening have been added to offset their variable onset of action in participants and differences in dose adjustment strategies (see Section 5.2). Immunosuppressive treatments are given in gMG based on clinical practice and have limited clinical trial data supporting their use.

During the DB part of the study, the dose of allowed SoC treatments, especially OCS, will be required to be maintained stable. Changes in SoC will be allowed during the OLE period. Participants will also have the option to receive rescue therapy (IVIgs or plasma exchange, change in the SoC OCS dose or any use of new CS) if there is an exacerbation of their symptoms. See Section 6.8.3 for details of rescue therapy.

Placebo has been selected as the comparator because there are no globally approved medications in the gMG indication.

Eculizumab has been approved recently in the US for gMG in adults who are seropositive for anti-AChR, but in the EU its approval is restricted to the treatment of refractory gMG (27). Moreover, a recent MG guidance issued by international experts also recommended to limit the use of eculizumab for the treatment of refractory gMG (26). Therefore, eculizumab is not an appropriate comparator for the study.

The primary endpoint of the study will be the change from baseline in the MG-ADL total score at Week 26, which is a validated endpoint used in Phase 3 clinical trials for MG and for routine MG clinical management (38). The MG-ADL score correlates well with the QMG (38, 39) and MG-QoL scores (38, 40).

4.2.1 Participant input into the study design

In order to evaluate the impact of gMG, 2 Patient Advisory Panels were conducted in which 5 people with gMG participated. During these panels, the Sponsor provided an overview of the clinical study design to obtain feedback from the perspective of potential participants in the study concerning the recruitment criteria, study visits, endpoints, and any additional relevant input. The patient advisors were enthusiastic about the possibility of a novel mechanism of action for people with gMG and highlighted that there remains an unmet need for efficacious treatments with improved safety profiles.

On the study design, the advisors commented on the need to include seronegative participants and, following this feedback, the recruitment criteria of the study were expanded to include such participants. The advisors also noted the need to allow rescue treatments and to ensure that this option is appropriately explained to improve participation in the study. Other input emphasized the symptoms of concern for people with gMG including but not limited to fatigability, energy levels, and fluctuations in symptoms.

The feedback from the Patient Advisory Panel has been factored into the current clinical study design.

4.3 JUSTIFICATION FOR DOSE

The rationale for targeting BTK-dependent mechanisms in gMG has been developed in Section 2.1. In this context, the anti-inflammatory effect demonstrated in a Phase 2b, proof-of-concept study (DRI15928) in adult participants with relapsing forms of MS is relevant to support the 60 mg dose used in this study. In DRI15928, this 60 mg dose was the only dose clearly effective in reducing the number of new gadolinium-enhancing T1 MRI lesions, the primary endpoint, as well as the number of new or enlarging T2 MRI lesions, a key secondary endpoint, demonstrating a strong anti-inflammatory effect mediated notably by peripheral mechanisms. Based on further PK/pharmacodynamic (PD) analysis of this study data, the 60 mg dose given daily with a meal was chosen for further development and is currently being tested in the 4 ongoing MS Phase 3 pivotal studies.

The dose regimen of 60 mg of tolebrutinib administered daily was also well tolerated when administered for 12 weeks in DRI15928. There were no TEAEs leading to study treatment discontinuation or study discontinuation. The most common events (preferred terms) observed in participants in the SAR442168 treatment arms were headache, upper respiratory tract infection, and nasopharyngitis. All TEAEs reported were of mild or moderate intensity except for 1 severe TEAE reported in the 60 mg SAR442168 group, a SAE of severe MS relapse. There were small numbers of AESIs and potentially clinically significant abnormalities (PCSAs) observed in multiple dose groups. No new risks were identified in this Phase 2b trial.

The exposures from the 60 mg daily dose given with a meal in humans have adequate safety factors to exposures in chronic rat and dog Good Laboratory Practices safety toxicology studies. Please refer to the IB for more details.

4.4 END OF STUDY DEFINITION

“End of study” for the overall study is defined as the point at which the last participant has completed the last visit of the study.

For the participants eligible for the OLE, the EOS is defined as the point at which participants have completed their FU visit (ie, 4 to 8 weeks after the participant’s last dose of tolebrutinib).

For participants completing the DB period who are not eligible for the OLE, the EOS is defined as the point at which participants have completed their FU visit (ie, 4 to 8 weeks after the participant’s last dose of tolebrutinib/placebo at Week 26 visit).

Participants who discontinue the IMP prematurely during DB period should have a pEOT visit as soon as possible with assessments as outlined in the Schedule of Activities (SoA) (Section 1.3). These participants will be asked to continue to perform scheduled DB period visits without IMP in order to minimize missing data. In case the participant does not wish to continue in the study, a safety FU visit (4 to 8 weeks after pEOT) will be performed, and it will be considered as the EOS.

Participants who are not able to complete the OLE period as planned and discontinue the IMP early during the OLE should also be encouraged to come back for a pEOT visit as soon as possible and complete the required assessments. The EOS will be the FU visit.

In the event that the pEOT visit occurs ≥3 weeks after their last dose of tolebrutinib/placebo in the DB period or tolebrutinib in the OLE, and only for participants who do not wish to complete all visit scheduled in the DB period, the pEOT visit will be recorded as the FU visit and as the EOS.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participants must be 18 years of age to 85 years of age, inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Participants with a diagnosis of gMG at Screening with generalized muscle weakness meeting the clinical criteria for diagnosis of MG, as defined by the MGFA Clinical Classification Class II, III, or IV, and likely not in need of a respirator for the duration of the study, as judged by the Investigator.

I 03. **a)** Positive serologic testing for anti-AChR or anti-MuSK autoantibody at Screening OR

b) Seronegative for both anti-AChR and anti-MuSK autoantibodies and with prior diagnosis supported by ≥1 of the following 3 tests:

- History of abnormal neuromuscular transmission demonstrated by single-fiber electromyography or repetitive nerve stimulation
- History of positive edrophonium chloride test
- Participant has demonstrated improvement in gMG signs on oral acetylcholinesterase inhibitors as assessed by the treating physician.

[redacted]

I 04. The participant must have a score ≥6 on MG-ADL scale at Screening and Day 1 visits with greater than half of the score attributed to non-ocular items.

I 05. Participants are allowed to use a stable dose of one or more of the following gMG treatments prior to randomization: AChEIs, OCS or IST as described thereafter. Allowed ISTs include azathioprine, mycophenolate mofetil, tacrolimus or methotrexate, and only one can be used at any time, during the study. Participants must be on a stable dose of their treatments prior to Screening visit, as applicable and according to the following requirements:

a) Stable dose of AChEIs for at least 2 weeks.

b) Stable dose of OCS ≤20 mg/daily for at least 1 month.

c) Azathioprine, mycophenolate mofetil, tacrolimus or methotrexate should have been initiated at least 6 months prior to the Screening visit and continued on a stable dose for at least 3 months.

Weight

I 06. Not applicable.

Sex, contraceptive/barrier method, and pregnancy testing requirements

I 07. All

The methods of contraception should be consistent with local regulations of participating sites.

a) Male participants

Not applicable.

b) Female participants

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP).

  OR

  - Is a WOCBP and agrees to use an acceptable contraceptive method as described in Appendix 4 (Section 10.4) during the intervention period.
  - A WOCBP must have a negative, highly sensitive pregnancy serum test at Screening and urine test within 24 hours before the first dose of study intervention.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2 (Section 10.2).
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy, if allowed by local regulation.
- For country-specific requirements see Section 10.8.

Informed Consent

I 08. The participant is capable of giving signed informed consent as described in Appendix 1 (Section 10.1) of the protocol, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. MGFA Class I (ocular MG) or Class V.

E 02. History of thymectomy within 6 months from Screening or planned for a thymectomy during the study period.

E 03. The participant has a history of infection or may be at risk for infection:

- A history or a current diagnosis of active or untreated latent tuberculosis (TB), or currently undergoing treatment for latent TB.

  In case of confirmed active or latent TB, the patient can be re-screened after full completion and written documentation of anti-tuberculosis treatment.

  In the cases where latent TB is suspected or being treated based on the screening TB testing and an infectious disease expert is starting TB treatment, this specialist can decide and provide written documentation that the patient has completed treatment for latent TB, even if it is shorter than standard treatment timelines.
- Participants with existing household contacts with active TB, with the exception of those for whom prophylaxis treatment has been completed for both the participant and household contact.
- A positive TB test at Screening or during the study, with the exception of patients for whom latent TB treatment has been completed per local guidelines. TB testing should be performed at Screening and again during the study, if clinically indicated, and may be repeated based on clinical judgment, borderline results, or clinical suspicion of TB infection. QuantiFERON-TB Gold blood test is preferred; tuberculin skin testing with ancillary testing is allowable if blood testing is not available. For an indeterminate QuantiFERON-TB Gold or blood test result, results may be repeated once and will be considered positive if retest results are positive.
- If repeat QuantiFERON-TB Gold continues to be indeterminate, T-SPOT.TB testing is preferred as the next appropriate test. Screening tests for TB are described in Appendix 2 (Section 10.2).

  The Investigator may also consult with an infectious disease expert if required, eg, test results are unclear or there is a suspicion of false positive test results. If the infectious disease expert considers the test results false positive and not clinically relevant and confirms that the participant does not have TB, the Investigator must document this in source data and may then randomize the participant provided other recruitment criteria are met.
- Participants at risk of developing or having reactivation of hepatitis, ie, results at Screening for serological markers for hepatitis B and C indicating acute or chronic infection. Serology tests will include hepatitis B virus surface antigen, anti-hepatitis B core antigen immunoglobulin M (IgM) and total immunoglobulins (Igs), anti-hepatitis B surface antigen Igs and anti-hepatitis C virus Igs; in case these results are inconclusive (eg, anti-hepatitis B surface antigen negative and anti-hepatitis B core

positive or anti-hepatitis C virus immunoglobulin G [IgG] positive), hepatitis B virus-DNA and/or hepatitis C virus-RNA testing, respectively, should be performed for confirmation.

- Persistent chronic or active recurring infection requiring treatment with antibiotics, antivirals, or antifungals.
- Fever within 4 weeks of the Screening visit (≥38°C; however, if due to brief and mild ear, nose, throat viral infection participant may be included based on the Investigator's judgment).
- A history of infection with human immunodeficiency virus (HIV) (eg, any known positive HIV test or information from participant interview).
- A history of T-lymphocyte or T-lymphocyte-receptor vaccination, transplantation (including solid organ, stem cell, and bone marrow transplantation) and/or antirejection therapy.
- The participant has a lymphocyte count less than the lower limit of normal at the Screening visit.
- Any other active infections that would adversely affect participation or IMP administration in this study, as judged by the Investigator.

E 04. Any malignancy within 5 years prior to the Screening Visit (except for effectively treated carcinoma in situ of the cervix, adequately treated non-metastatic squamous or basal cell carcinoma of the skin and malignant thymoma that have been resected or are considered as cured by any treatment with no evidence of metastatic disease for ≥3 years) will be exclusionary.

E 05. History of autoimmune disease other than gMG (eg, thyroiditis, rheumatoid arthritis, etc.) that would interfere with an accurate assessment of clinical symptoms and gMG diagnosis.

E 06. Conditions that may predispose the participant to excessive bleeding:

- A bleeding disorder or known platelet dysfunction at any time prior to the Screening Visit.
- A platelet count <150 000/μL at the Screening Visit.
- The participant has had major surgery within 4 weeks prior to the Screening Visit, which could affect the participant's safety or affect immune response (as judged by the Investigator) or has planned any elective major surgery during the study.
- A history of significant bleeding event within 6 months prior to the Screening Visit, according to the Investigator's judgment such as, but not limited to cerebral or gastrointestinal bleeding.

E 07. Confirmed screening ALT >1.5 × ULN OR AST >1.5 × ULN OR alkaline phosphatase >2 × ULN (unless caused by non-liver-related disorder or explained by a stable chronic liver disorder) OR total bilirubin >1.5 × ULN (unless due to Gilbert syndrome or non-liver-related disorder).

E 08. A history or presence of significant other concomitant illness according to the Investigator's judgment such as, but not limited to cardiovascular (including Stage III or IV cardiac failure according to New York Heart Association classification), or renal (ie, undergoing dialysis), neurological, endocrine, gastrointestinal, metabolic, pulmonary, or lymphatic disease that would adversely affect participation in this study.

E 09. A history or presence of psychiatric disturbance or substance abuse, as evidenced by:

a) A history of any psychiatric disease, behavioral condition, or depression requiring hospitalization within 2 years prior to the Screening Visit.

b) A documented history of attempted suicide or suicidal ideation of category 4 or 5 according to the Columbia-Suicide Severity Rating Scale (C-SSRS) baseline/screening version over the 6 months prior to the Screening Visit, OR if in the Investigator's judgment, the participant is at risk for a suicide attempt.

c) Active alcohol use disorder or a history of alcohol or drug abuse within 1 year prior to the Screening Visit.

d) Current alcohol intake >2 drinks per day for men and >1 drink per day for women (1 drink = approximately 14 grams of alcohol = 350 mL beer = 140 mL wine = 40 mL of spirits).

E 10. The following findings obtained during the Screening Visit considered in the Investigator's judgment to be clinically significant:

a) Any Screening laboratory values outside normal limits.

b) Abnormal ECG.

Note: a one-time retest at Screening may be performed if an abnormal laboratory test value is considered temporary.

Prior/concomitant therapy

E 11. The participant has received any live (attenuated) vaccine (including but not limited to varicella zoster, oral polio, and nasal influenza) within 2 months before the first treatment visit.

E 12. The participant is receiving potent and moderate inducers of cytochrome (CYP) P450 3A; or potent inhibitors of CYP2C8 hepatic enzymes as listed in Section 10.10.

E 13. The participant is receiving anticoagulant/antiplatelet therapies, including:

- Acetylsalicylic acid (aspirin) >81 mg/day
- Antiplatelet drugs (eg, clopidogrel)
- Warfarin (vitamin K antagonist)
- Heparin, including low molecular weight heparin (antithrombin agents)
- Dabigatran (direct thrombin inhibitor)
- Apixaban, edoxaban, rivaroxaban (direct factor Xa inhibitors)

Note: All the above-mentioned drugs must be stopped at least 5 half-lives before study intervention administration except for aspirin, which must be stopped at least 8 days

before. These washout periods are only applicable in the case that the Investigator deems it clinically appropriate to discontinue the listed medications or there is a recent history of use of these medications (as in the case when short term treatment with anticoagulants is clinically recommended for certain thrombotic events), and therefore these washout periods will need to be followed prior to enrollment.

If, however, the participant has a chronic underlying medical condition (stroke, coronary or carotid artery disease, heart valvular disease etc.) requiring continued use of these medications, the participant cannot be enrolled in the study.

E 14. Treatments prior to randomization:

a) Intravenous immunoglobulin (IVIg) or plasma exchange within 4 weeks.

b) Oral or IV cyclophosphamide or cyclosporine treatment within 3 months.

c) Intravenous CS bolus (dose higher than 1 mg/kg) within 1 month.

d) Rituximab and other B-cell-depleting therapies (anti-CD20 or anti-CD19) used within 6 months.

e) Eculizumab, and other complement pathway targeting drugs or anti-neonatal Fc receptor (FcRn) targeting drugs used within 3 months.

Prior/concurrent clinical study experience

E 15. The participant was previously exposed to any BTK inhibitor, including tolebrutinib.

E 16. Current enrollment or past participation within the last 3 months or 5 half-lives, whichever is longer, before signing of consent in this clinical study.

Other exclusions

E 17. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 18. Any country-related specific regulation that would prevent the participant from entering the study - see Section 10.8 of the protocol (country-specific requirements).

E 19. Participants not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance with study procedures, or participants unable to follow the schedule of protocol assessments due to other reasons.

E 20. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the International Council for Harmonisation-Good Clinical Practice [ICH-GCP] Ordinance E6).

E 21. Any specific situation during study implementation/course that may raise ethics considerations.

E 22. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

Other exclusion criteria added in protocol amendments

E 23. At screening, elevated transferrin saturation (>50% in males and >40% in females) and/or with elevated ferritin levels >500 µg/L.

E 24. Acute liver disease, cirrhosis, chronic liver disease (unless considered stable for >6 months).

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

Tolebrutinib shall be taken with a regular meal. When possible, the meal with which tolebrutinib is taken (eg, breakfast, lunch, or dinner) should be consistent throughout the study. The typical meal with which the study intervention is taken will be recorded at each visit. In case the mealtime for study intervention administration needs to be changed, a gap of a minimum of 12 hours between 2 doses should be maintained.

5.3.2 Caffeine, alcohol, and tobacco

For each visit with PK/PD assessment (refer to Section 1.3), participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 2 hours before the start of treatment until after collection of the final PK and/or PD sample later that day.

For each visit with PK/PD assessment (refer to Section 1.3), participants will abstain from alcohol for 24 hours before the start of treatment until after collection of the final PK and/or PD sample later that day.

During the entire study, participants should be warned not to consume substantial quantities of alcohol, defined as >14 grams (1 standard drink) per day in female participants or >28 grams (2 standard drinks) per day in male participants on a regular basis.

5.3.3 Activity

No special restrictions.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study may be rescreened up to 2 times. Rescreened participants should be assigned a new participant number. There is no requirement for a waiting period between the screen failure date and the rescreen.

If a participant does not meet the inclusion criteria for certain dynamic laboratory tests at Screening (Visit 1), these laboratory assessments may be repeated, at the discretion of the Investigator, if the parameter result is judged to be likely to return to acceptable range for study inclusion within the screening period prior to Baseline/Randomization (Visit 2). There is no need to screen fail such participants if the test finally meets the inclusion criteria.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION ADMINISTRATION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in (Section 10.9) Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency. These measures should be considered for temporarily delaying screening/randomization/administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo, intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 2 - Overview of study interventions administered

Intervention label	SAR442168 60 mg	Placebo
Intervention name	SAR442168 60 mg	Placebo
Type	Drug	Drug
Dose formulation	film-coated tablet	film-coated tablet
Unit dose strength(s)	60 mg	0 mg
Dosage level(s)	Once daily	Once daily
Route of administration	Oral taken with a meal	Oral taken with a meal
Use	Investigative	Placebo comparator
IMP and NIMP	IMP	IMP
Packaging and labeling	Study intervention will be provided in wallet blister packaging. The content of the labeling is in accordance with the local regulatory specifications and requirements.	Study intervention will be provided in wallet blister packaging. The content of the labeling is in accordance with the local regulatory specifications and requirements.
[Current/Former name(s) or alias(es)]	SAR442168-Tolebrutininb	Not applicable

Table 3 - Arms and associated interventions

Arm name	SAR442168	Placebo
Associated interventions (intervention label[s])	SAR442168-60 mg	Placebo

The SAR442168/placebo may be supplied at the site or from the Investigator/site/Sponsor to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in (Section 10.9) Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency.

6.1.1 Devices

Not applicable.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc.) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.8).

A potential defect in the quality of the IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for direct-to-patient [DTP] shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical study protocol, or dispose of IMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All participants will be centrally assigned to randomized study intervention using an interactive response technology (IRT).

A participant assigned to a specific arm at randomization may be allocated, by the IRT, to several (varying) intervention numbers (and corresponding intervention kit numbers) for multiple visits despite having the same intervention arm assignment from randomization. That is, in these cases, the intervention/kit number varies but the arm assignment at randomization does not change.

Before the study is initiated, the log-in information and instructions for the interactive web response system will be provided to each site.

Study intervention will be dispensed at the study visits summarized in the SoA (Section 1.3).

Returned study intervention should not be re-dispensed to the participants.

Methods of blinding

This study is blinded for assignment of SAR442168 and placebo. Tablets of SAR442168 and placebo will appear identical.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted.

Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, he/she may, at his/her discretion, contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of participant.

If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

If unblinded, information pertaining to the treatment allocation should not be shared with other members of the study team or Sponsor.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

6.4 STUDY INTERVENTION COMPLIANCE

- Measures taken to ensure study intervention accountability include the following:
  - Intervention units are returned by the participant at each visit. In case of DTP process, the intervention units can be returned by the carrier (if defined in the contract).

- The Investigator or his/her delegate counts the number of tablets remaining in the returned packs and fills in the Intervention Log Form.
- The Investigator or his/her delegate records the dosing information on the appropriate page(s) of the eCRF.
- The monitor in charge of the study then checks the eCRF data by comparing them with the IMP that has been retrieved and Intervention Log Forms.

- Participant compliance with study intervention will be assessed at each study site visit. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

6.5 DOSE MODIFICATION

Dose reduction is not foreseen in this study. Treatment may need to be interrupted or permanently discontinued if deemed necessary due to an AE. See Section 7.1 for discontinuation of the study intervention.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

No study intervention with tolebrutinib is currently planned after the end of the study.

6.7 TREATMENT OF OVERDOSE

Symptomatic overdose is an AESI (defined in Section 8.3.7). No antidote is available for tolebrutinib.

In the event of an overdose, the Investigator should:

1. Closely monitor the participant for any AE/SAE and laboratory abnormalities. Provide supportive and symptomatic treatment as needed.
2. Obtain a plasma sample for PK analysis within 24 hours from the last dose of study intervention.
3. Evaluate the participant to determine, based on the clinical evaluation of the participant, whether study intervention should be interrupted or whether the dose should be reduced.
4. Document the quantity of the excess dose as well as the duration of the overdose appropriately in the eCRF).
5. Inform the Sponsor as soon as possible.

6.8 CONCOMITANT THERAPY

6.8.1 Prohibited medications

Any medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements), vaccine or medical procedure that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription herbal medications containing Saint John's Wort extract within 14 days before the start of study intervention until completion of the last visit.

Live (attenuated) vaccines should not be administered during the study.

For some prohibited concomitant medications (eg, aspirin for headache), if use is not chronic, temporary discontinuation of IMP can be considered prior to a decision to permanently stop the IMP.

Prohibited treatments during the study will also include:

- IV CS and OCS >20 mg/daily except if used as rescue treatment
- Cyclosporine and cyclophosphamide.
- Rituximab and other B-cell-depleting therapies (anti-CD20 or anti-CD19), eculizumab and other complement pathway targeting drugs, anti-FcRn, or any monoclonal antibodies.

Anticoagulant/antiplatelet therapies are not permitted to be taken concomitantly with the IMP, including:

- Acetylsalicylic acid (aspirin) >81 mg/day
- Antiplatelet drugs (eg, clopidogrel)
- Warfarin (vitamin K antagonist)
- Heparin, including low molecular weight heparin (antithrombin agents)
- Dabigatran (direct thrombin inhibitor)
- Apixaban, edoxaban, rivaroxaban (direct factor Xa inhibitors)

CYP inhibitors/inducers:

Potent and moderate inducers of CYP3A or potent inhibitors of CYP2C8 hepatic enzymes are not permitted throughout the study (see Section 10.10).

Tolebrutinib is a substrate of the CYP3A4 and CYP2C8 isoenzymes. In healthy participants, potent CYP3A4 inhibitor (itraconazole 200 mg once daily for 4 days) increased tolebrutinib (area under the curve [AUC]) exposure by 1.8-fold (Study INT16385) and potent CYP2C8 inhibitor (gemfibrozil 600 mg twice daily for 6 days) increased tolebrutinib (AUC) exposures by 8.4-fold (Study INT16726). Based on a satisfactory safety and tolerability profile and on the observed exposure in healthy participants who received tolebrutinib at a dose of up to 240 mg once daily for 14 days under fed conditions (Study TDR16862), drugs that strongly inhibit CYP3A4 are allowed and drugs that strongly inhibit CYP2C8 are not permitted. In healthy participants, the potent CYP3A4 and moderate CYP2C8 induction by rifampicin (600 mg once daily for 8 days) decreased tolebrutinib exposure by 6-fold (Study INT16726). Therefore, potent and also moderate (based on prediction) CYP3A inducers are not permitted due to their potential to decrease tolebrutinib exposure and efficacy. See Section 10.10 for the list of drugs not to be used.

6.8.2 Particular permissible medications

Standard of care medications allowed in the study may include any combination of AChEI, (eg, pyridostigmine), OCS, and/or a single IST limited to azathioprine, mycophenolate mofetil, tacrolimus or methotrexate. The inclusion criteria (I 05) (Section 5.1) provides details on the duration of stability and start date prior to screening required for eligibility in this study.

During the DB period, all participants will continue with the SoC treatment used prior to screening maintained at stable doses throughout the 26-week duration. However, during the OLE, SoC treatments may be adjusted (ie, dose change, discontinuation, or addition of other allowed SoC treatments) at the discretion of the Investigator based on clinical presentation.

During the study, AChEIs will be held at least 12 hours prior to QMG test and MGII administration at each study visit when performed.

Other drugs permitted with some restrictions:

Anticoagulant/antiplatelet

- Acetylsalicylic acid (aspirin) ≤81 mg/day
- Paracetamol/acetaminophen, at doses of ≤3 grams/day, is permitted for use at any time during the study. Short courses (up to 5 days) of nonsteroidal anti-inflammatory drugs (NSAIDs) (other than acetylsalicylic acid) at the recommended dose may be given during the study if clinically necessary for the treatment of an existing medical condition or a new event. The Investigator must record the use of NSAIDs (and any other comedication) in the eCRF. The Investigator should assess for signs of bleeding events for a participant taking NSAIDs with IMP. Nonsteroidal anti-inflammatory drugs should be interrupted for Grade 2 and above bleeding events.

6.8.3 Rescue therapy

The use of rescue therapy for gMG worsening will be allowed at any time during both the DB and OLE parts of the study at discretion of the Investigator in case of at least a 2-point increase of individual non-ocular MG-ADL items compared to the Day 1 MG-ADL value or new or worsening of respiratory/ bulbar symptoms. Rescue therapy can include IVIg, plasma exchange, change in the SoC OCS dose or any use of new CS. If rescue therapy is required, the Sponsor should be informed, preferably prior to administration of treatment, where possible, without compromising the participant's safety. The date and time of rescue therapy administration as well as the name and dosage regimen must be recorded. In case of use of rescue therapy during the DB period, the study intervention should be permanently discontinued (see Section 7.1 for handling of participants after permanent intervention discontinuation).

The supply of rescue therapy will be specified at the country level.

Use of rescue therapy must be recorded in the eCRF.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

The study intervention should be continued whenever possible.

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

Permanent intervention discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the participant not to re-expose the participant to the study intervention at any time.

In rare instances, it may be necessary for a participant to permanently discontinue study intervention.

During the DB period, the use of rescue therapy will lead to permanent discontinuation of the study intervention.

The following may also be justifiable reasons for the Investigator or Sponsor to discontinue a participant from the study intervention:

- Adverse events that endanger the safety of the participant, or if discontinuation of study intervention is desired or considered necessary by the Investigator and/or participant.
- If IMP discontinuation criteria are met as per guidance for the FU of laboratory abnormalities in Appendix 6 (Section 10.6).
- At participant's request, ie, withdrawal of the consent for treatment.
- If a female participant becomes pregnant or wishes to become pregnant during the study.
- Any serious opportunistic infections.
- Continued need for/chronic use of a prohibited concomitant medication (see Section 6.8, Appendix 10 [Section 10.10]).

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation after 24 hours before making a decision of permanent discontinuation of the IMP for the concerned participant.

Handling of participants after permanent intervention discontinuation

Participants will be followed up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed up as specified in this protocol, whichever comes last.

During the DB period, if possible, and after the definitive discontinuation of study intervention, the participants should be encouraged to come back as soon as possible for the pEOT visit and will be assessed using the procedures planned for the visit. Participants will be asked to continue in the study, attending all scheduled visits as per SoA (Section 1.3) if possible until the end of the DB period. If the participant does not agree to the full visit schedule per SoA after a decision for permanent end of treatment (EOT), the FU visit (4 to 8 weeks after pEOT) will be performed.

During the OLE period, after the definitive discontinuation of study intervention, the participants will also be encouraged to come back for the pEOT visit and will be assessed using the procedures planned for the visit. The participant will be asked to perform a FU visit (4 to 8 weeks after pEOT).

In the event the pEOT visit occurs ≥3 weeks after their last dose of tolebrutinib/placebo in DB period, and only for participant who do not wish to complete all visit scheduled in this period, or after last dose of tolebrutinib in OLE, this pEOT visit will be recorded as the FU visit, and there will be no need for the 4- to 8-week safety FU visit.

All cases of definitive study intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

[redacted]

7.1.3 QTc stopping criteria

If a clinically significant finding is identified in the ECG (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the Investigator or qualified designee will determine if the participant can continue to receive study intervention and if any change in participant management is needed. Review of ECG findings by a cardiologist may be considered for a decision of a definitive discontinuation of study intervention because of ECG changes. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.4 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical study due to a regional or national emergency declared by a governmental agency ([Section 10.9] Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

If surgery is needed during the study, the benefit-risk of withholding the IMP for at least 3 to 7 days pre- and post-surgery and the risk of bleeding should be considered.

The following shall lead to temporary treatment discontinuation:

- Cytopenias: the Sponsor's algorithms for neutropenia and thrombocytopenia as per Appendix 6 (Section 10.6) should be followed.
- Serum creatinine, creatine phosphokinase (CPK) and liver enzyme increase: follow corresponding algorithms as per Appendix 6. (Section 10.6).
- Cardiac arrhythmia (atrial fibrillation): Any Grade 3 event (symptomatic, urgent intervention indicated, device [eg, pacemaker], ablation, new onset).
- Suicidal risk as per C-SSRS: if a participant scores "yes" on items 4 or 5 of the Suicidal Ideation Section, or "yes" on any item of the Suicidal Behavior Section.

If needed, temporary treatment discontinuation can be considered by the Investigator or by the participant for any other reason, including due to any safety concerns because of disruption of the study due to a regional or national emergency declared by a governmental agency such as COVID-19 (Appendix 9 [Section 10.9]), or another illness or if there is a need for a prohibited concomitant medication. Treatment can be resumed later when it is considered safe and appropriate.

7.1.5 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned AE was unlikely and if the selection criteria for the study are still met (refer to Section 5.1 and Section 5.2).

For a regional or national emergency declared by a governmental agency, contingency measures are included in (Section 10.9) Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency. Refer to Appendix 6 (Section 10.6) for details on restart/rechallenge process.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and FU and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

Investigators should discuss with participants key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the CRF or eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for FU visits and from withdrawal of consent for non-participant contact FU, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be rerandomized/reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to FU if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant, reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to FU, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

- If a participant continues to be unreachable and has been withdrawn from the study, the site should continue to try to obtain a vital status update (death) via available resources, if possible.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count, urine tests) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. This includes PK assessments and any post-baseline biomarker or PD assessments.
- Blood sampling details including volume for all laboratory assessments will be provided in the laboratory manual and the ICF. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- In exceptional cases, under regional or national emergencies (eg, natural disaster, epidemic disease, terrorist attack), onsite visits may be replaced with telephone/remote visits. For example, participant interviews for medical history/prior medications could be performed by phone, local safety labs and some efficacy assessments could be performed off-site/at the participant's home (eg, home nursing) if agreed by the participant and permissible per local regulations. In such circumstances, the visit window may be expanded, if needed (eg, ±14 days for quarterly visits).
- When needed for this protocol, training and certification of the evaluators will take place either at Investigator's meetings, or via the Sponsor's designated online training portal(s). Detail will be included in the provided manuals.

For a regional or national emergency declared by a governmental agency, contingency measures are included in (Section 10.9) Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency.

8.1 EFFICACY ASSESSMENTS

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

8.1.1 Clinical outcome assessments

Clinical outcome assessments will be performed in this study in line with the SoA (see Section 1.3). These outcome assessments are to be administered prior to treatment and prior to discussion of a participant's health status. It is important that participants complete the outcome assessments after ICF is signed and prior to any treatment- or study-related activities, including administration of study intervention, laboratory work, discussion with the participant regarding their treatment or health status, and similar activities. This ensures the objectivity of the data. Clinical outcome assessments will be completed electronically, with paper options available as backup. Refer to the electronic clinical outcome assessment manual for details about administration, assessment order through visits and necessary trainings or certifications.

8.1.1.1 Myasthenia gravis-activities of daily living (MG-ADL)

The MG-ADL is a categorical scale that assesses the impact on daily function of 8 signs or symptoms that are typically affected in MG. The MG-ADL is composed of items related to people with MG assessment of functional disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb impairment (2 items) (1-week recall time). Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function (total score 0 to 24). The MG-ADL correlated well with the QMG score (39). The MG-ADL had strong correlation with MG-QoL. A clinically meaningful (within-participant) change score of 2 points for the MG-ADL has been reported (40, 41). The MG-ADL will be interviewer-administered (see Appendix 11 [Section 10.11.1]).

8.1.1.2 Quantitative Myasthenia Gravis (QMG) Test

The Quantitative Myasthenia Gravis test is clinician-reported outcome/assessment to assess muscle weakness in people with MG. The QMG test consists of 13 items ranging from 0 to 3 with 3 being the most severe. A total QMG score ranges from 0 to 39, where higher scores indicate greater disease severity. The QMG score is composed of the following items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item). Clinically significant changes have been reported as follows: in mild (QMG score 0 to 9) to moderate (QMG score 10 to 16) MG, a 2-point change has been reported as clinically significant. For more severe (QMG score >16) MG, a 3-point change has been reported as clinically significant (42). Change from baseline in QMG score at Week 12 will be used for the IA based on its correlation to MG-ADL. Acetylcholinesterase inhibitors will be held at least 12 hours prior to QMG test administration at each study visit. The QMG test shall be administered at approximately the same time of day throughout the study at the protocol specified timepoints. See Appendix 11 (Section 10.11.2).

8.1.1.3 Myasthenia Gravis Impairment Index (MGII)

The Myasthenia Gravis Impairment Index (MGII) is a measure of MG impairment focused on the severity of MG impairment and the concept of fatigability (ie, triggering or worsening of MG impairment with activity) (34) of significant importance for people with MG. The MGII consists of a 22-item patient-reported questionnaire (2-week recall time) with 6 clinician-assessment items

that result in an MGII total score which includes 2 sub-scale-scores on ocular and generalized impairments. The ocular sub-scale-score is calculated by summing 8 items reflecting ocular impairments. These items are patient questionnaire items 1 to 6 and examination items 1 and 2. The generalized score is calculated by adding items 7 to 22 from the patient questionnaire and items 3 to 6 from the examination (37). Total scores range between 0 and 84, but the MGII can also be scored as an ocular (0 to 23) and generalized (0 to 61) score, where higher scores indicate greater disease severity. Acetylcholinesterase inhibitors will be held at least 12 hours prior to MGII administration at each study visit. See Appendix 11 (Section 10.11.3).

8.1.1.4 Myasthenia Gravis Quality of Life Questionnaire (MG-QoL15)

The MG-QoL15 is a 15-item measure QoL instrument for people with MG that will be self-reported by the participant and is derived from a comprehensive 60 item QoL instrument. The 15 items are meaningful to people with MG, and some of the items address meaningful consequences of MG that are not always consistently ascertained by a symptom-only appraisal. The instrument is developed and validated to evaluate general QoL of people with MG by a clinician in the practice setting. The domains covered by the questionnaire are mobility (9 items), symptoms (3 items), general contentment (1 item) and emotional well-being (2 items) (recall period of 4 weeks). It targets aspects of symptoms and well-being that are most worrisome to people with MG, including physical, social, and psychological components that are integral to QoL but not measured by the MG-ADL or QMG scores (43). See Appendix 11 (Section 10.11.4).

[redacted]

8.1.2 Other clinical outcome assessments

Not applicable.

8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than AEs which are presented in Section 8.3.

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

- Whenever possible, the same Investigator should perform the physical examination at all study visits.
- The complete physical examination will include, at a minimum, assessments of the general appearance, head and neck, abdomen, lymph nodes, skin (skin exams shall include inspection for signs of bleeding, bruises, petechiae and will involve questioning participant for signs of minor bleedings, eg, in nose or while teeth brushing), cardiovascular system, respiratory system, musculoskeletal system, and neurological examination by the Investigator.
- A brief physical examination will include, at a minimum, assessments of the skin (as described above), lungs, cardiovascular system, neurological examination, and abdomen (liver and spleen).
- The extent of the physical examination can be broadened at the discretion of the Investigator in order to evaluate AEs or abnormal clinical laboratory test values.
  - Investigators should pay special attention to clinical signs related to previous serious illnesses.
  - Any clinically significant new finding or worsening of a previous finding should be reported as an AE, per Investigator's judgment.

8.2.2 Vital signs

- Body temperature (degrees Celsius [°C]), heart rate (beats/minute), and blood pressure (mmHg) will be assessed. Body temperature will be collected using the same method/body part for a given participant.
- Blood pressure and pulse measurements will be assessed under standardized conditions using the same method for a given participant with a completely automated as well as calibrated device and with the participant in a supine or sitting position. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Blood pressure and heart rate measurements will be taken before blood collection for laboratory tests and will consist of 1 heart rate and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute and the average will be recorded in eCRF).

8.2.3 Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7.1.3 for QTcF withdrawal criteria. In case the ECG machine does not automatically calculate QTcF, manual calculation using the following formula: QTcF = QT/RR1/3, or an automatic website calculator (eg, https://reference.medscape.com/calculator/48/ecg-corrected-qt) is acceptable.
- ECGs and longer rhythm strips will be obtained locally.
- If a clinically significant finding is identified in the ECG (including, but not limited to changes from baseline in QTcF after enrollment), the Investigator or delegate will determine if the participant can continue in the study and if any change in participant management is needed including but not limited to referral to cardiology, and/or Holter monitor. The Investigator or delegate should perform the following tasks:
  - Review the ECG in a timely manner;
  - Document the interpretation, sign, and date it on ECG printout;
  - Record her or his (or appropriate qualified physician) medical opinion (“normal” or “abnormal”) on the study participant´s records and in the eCRF;
  - Assess for any symptoms of cardiac issues;
  - Each time when it is medically needed for clinical management of the study participant or/and in case of any safety concerns, additional ECG should be performed, and findings reported in the eCRF dedicated unscheduled visits ECG forms;
  - Clinically significant findings are to be checked with pre-existing medical history or/and, if appropriate, consider AE.

Please refer to (45) and (46) for definitions of heart failure classifications.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
  - If abnormal laboratory test values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified. In the event the laboratory assessments in Appendix 6 (Section 10.6) indicate discontinuation of study intervention, temporary discontinuation should be considered unless otherwise specified.
  - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3.)
  - If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.
  - Local testing can be used for safety test (hematology and biochemistry) at Week 19 Visit.
  - In exceptional situations where central laboratory cannot be used (reason should be well documented and local monitoring team informed as soon as possible when the issue is identified), a local laboratory can be used at Screening to determine eligibility. Use of a local laboratory would have to be limited to participants with autoantibody identification already available (see Section 8.6). In all cases the laboratory tests at Visit 2 (Randomization visit) must be done at the central laboratory and before administration of the first dose of study intervention.

8.2.5 Pregnancy testing

Refer to Section 5.1 and Section 10.2 for details on pregnancy testing.

8.2.6 Suicidal ideation and behavior risk monitoring

Tolebrutinib crosses the blood-brain barrier. Assessment of suicidal ideation and behavior/treatment-emergent suicidal ideation and behavior will be monitored during this study using the C-SSRS (Appendix 11 [Section 10.11.6]). For safety reasons, C-SSRS will be

administered throughout the study by the Investigator or delegated to an individual that is certified to administer the scale.

Study intervention administration must be interrupted if a participant scores "yes" on items 4 or 5 of the Suicidal Ideation Section of the C-SSRS, or "yes" on any item of the Suicidal Behavior Section. A mental health professional will be consulted and will decide whether the study intervention can be restarted and if any additional risk mitigation strategies are required (eg, increased monitoring, antidepressant administration).

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3). The definition of AESIs is provided in Section 8.3.7.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of the ICF until the participant's final study visit.

All SAEs and AESIs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end date, all SAEs and AESIs (as defined in Section 8.3.7), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to FU (as defined in Section 7.3). Further information on FU procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious AEs that are considered expected will be specified in the reference safety information (IB).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until the FU/EOS visit.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant pregnancy.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect FU information on the participant and the neonate, and the information will be forwarded to the Sponsor.

- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.3.6 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

In this study and given that the natural history of gMG includes possible variation of symptoms, these changes measured through the efficacy scales used as part of the study evaluation will not be reported as AE but considered as efficacy data, unless an exacerbation of gMG or myasthenic crisis requires hospitalization, in which case it will be reported as an SAE, or if the Investigator considers that there is a reasonable possibility that the event was related to the study intervention.

8.3.7 Adverse events of special interest

Adverse event of special interest

An AESI is a treatment-emergent AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified, or removed during a study by protocol amendment.

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP:
  - Pregnancy occurring in a female participant entered in the clinical study or in a female partner of a male participant entered in the clinical study. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, the IMP should be discontinued.
  - Follow up of pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (see Appendix 4 [Section 10.4]).
- Symptomatic overdose (serious or nonserious) with IMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval, (eg, ≥2 tablets of the IMP within a 12-hour interval).

- Increase in ALT
  - Any increase of ALT >3 × ULN confirmed by retest within 72 hours or in the absence of a retest within 72 hours.
  - In case of ALT AESI, the algorithm provided in Appendix 6. (Section 10.6) will be followed, especially for the assessment of the causality for which specific recommendations are provided in the appendix. See also Assessment of causality in Section 10.3.3.
- Other project-specific AESI(s)
  - ECG observation of atrial fibrillation or atrial flutter.
  - Severe infection (National Cancer Institute [NCI] CTCAE Grade 3 or above), that may or may not meet seriousness criteria (eg, a Grade 3 opportunistic infection).
  - Moderate or severe hemorrhagic events (NCI CTCAE Grade 2 or above), including, but not limited to, symptomatic bleeding, bleeding in a critical area or organ such as the central nervous system, or intraocular bleeding.
  - Thrombocytopenia, platelet count <75 × 10^9/L (see Appendix 6 [Section 10.6] for management flow chart).

8.3.8 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.3.8.1 Medical device deficiencies

Not applicable.

[redacted]

[redacted]

8.7 IMMUNOGENICITY ASSESSMENTS

Not applicable.

8.8 HEALTHCARE RESOURCE UTILIZATION

Healthcare resource utilization-myasthenia gravis will be assessed according to the SoA.

Healthcare resource utilization data, associated with medical encounters due to a participant's MG, will be collected using the eCRF. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number of medical care encounters due to MG, including outpatient visits (ie, general practitioner, specialists, nurse, etc.), number of emergency visits and hospitalizations.
- Duration of emergency visits and hospitalizations due to gMG (total days or length of stay).
- Number of sick day leave/day off (number of days missed from work due or usual activities due to participant's gMG condition).

Related objectives/endpoints are:

- Evaluate the efficacy of tolebrutinib compared with placebo on healthcare utilization in people with gMG.
- Annualized number of days of healthcare resource utilization over the 26-week placebo-controlled treatment period.

See Appendix 11 (Section 10.11.7).

9 STATISTICAL CONSIDERATIONS

The data from the placebo-controlled and the OLE treatment phases will be the focus of the clinical study report of the respective phase. The following statistical methods/considerations relate to the analysis of the data from the placebo-controlled period. The data from the open-label portion are non-controlled and supportive in nature; summary statistics will be provided for each of the efficacy variables and for safety data.

The null hypothesis for the primary efficacy endpoint of the change from baseline in MG-ADL score at Week 26 is that there is no treatment difference between tolebrutinib and placebo, and the alternative is that there is a between-treatment difference. To strongly control the type I error rate for the study, a procedure will be applied at a 2-sided 5% significance level. If tolebrutinib is significant for the primary endpoint, a selective set of secondary endpoints will be tested following a pre-specified procedure. The complete list of the secondary endpoints that will be adjusted for multiplicity will be detailed in the statistical analysis plan (SAP) prior to the interim database lock. The study will be declared positive at the final analysis if the null hypothesis for the change from baseline in MG-ADL score at Week 26 for tolebrutinib versus placebo is rejected.

9.1 SAMPLE SIZE DETERMINATION

A total sample size of [redacted] participants (randomization ratio 1:1, ie, [redacted]) is needed to have at least 80% power to demonstrate superiority of tolebrutinib versus placebo (0.05 2-sided significance level) based on the following assumptions on the primary endpoint (change from baseline in MG-ADL total score at Week 26):

- True mean difference of -2 between tolebrutinib and placebo.
- Common standard deviation (SD) of 4.
- 15% early discontinuation from the treatment/study.

Calculations were made using East® 6.5.

Randomization will be stratified by MGFA class (II, IIIa/IVa, or IIIb/IVb) and region (US, non-US).

[redacted]

9.2 POPULATIONS FOR ANALYSES

The following populations for analyses are defined:

Table 4 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Randomized	All participants from screened population who have been allocated to a randomized intervention by IRT regardless of whether the intervention was received.
ITT	All randomized participants. Participants will be analyzed according to the intervention allocated by randomization.
mITT	All randomized and treated participants with a baseline value and at least 1 post-baseline value for any efficacy assessment. Participants will be analyzed as randomized. This will be the primary efficacy population.
Safety	All randomized participants who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
[redacted]	
OLE	All participants who received at least one dose of intervention during the open-label extension phase.

ICF: informed consent form; ITT: intention-to-treat; IRT: Interactive Response Technology; mITT: modified intention-to-treat; PK: pharmacokinetic(s); OLE: open-label extension.

Participants exposed to the study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

For any participants randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

9.3 STATISTICAL ANALYSES

The SAP will be finalized prior to the database lock for the IA and will include more technical and detailed descriptions of the statistical analyses, including methods to assess the impact of missing data, subgroup analyses, etc. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.3.1 General considerations

The baseline value of efficacy parameters is defined as the last available value prior to the first dose of the study medication unless otherwise specified. The baseline value of safety parameters is defined as the last available value prior to the first dose of IMP. For participants randomized but not treated, the baseline value is defined as the last available value before randomization.

Unless otherwise specified, analyses will be performed by treatment group (and overall for baseline and demographic characteristics).

The observation period will be divided into 4 segments:

- The pre-treatment period is defined as the period from signed informed consent up to the first IMP administration.
- The on-treatment period (ie, TE period) for the DB period is defined as the period from the first IMP administration to the earliest of 1) last IMP administration plus 10 days, 2) first IMP in the OLE, 3) death date, or 4) last contact date.
- The on-treatment period for the OLE is defined as the first IMP administration in the OLE to the earliest of 1) last IMP administration plus10 days, 2) death date, or 3) last contact date.
- If applicable, the post-treatment period is defined as the period from the end of the on-treatment period to the last contact date.

9.3.2 Primary endpoints

A combination of treatment policy strategy and composite variable strategy will be used to handle ICEs for the analysis of the primary endpoint of change from baseline in MG-ADL total score at Week 26 in the mITT population (Table 5).

Table 5 - Intercurrent events

Intercurrent event	Strategy	Variable of interest
Permanent study intervention discontinuation before Week 26 due to a reason other than rescue therapy or lack of efficacy	Treatment policy strategy	Observed change from baseline MG-ADL total score at Week 26
Permanent study intervention discontinuation before Week 26 for rescue therapy and/or lack of efficacy	Composite variable strategy	Worst change from baseline MG-ADL total score during the 26 weeks DB treatment period before or after the intercurrent event

DB: double-blind; MG-ADL: Myasthenia Gravis-Activities of Daily Living.

Population level summary: Difference in mean change from baseline MG-ADL total score between tolebrutinib and placebo will be analyzed using an ANCOVA with change from baseline MG-ADL total score at Week 26 as the response variable, accounting for ICEs as detailed above; and treatment, baseline MG-ADL total score, and all randomization stratification factors as covariates. For participants who prematurely discontinue study intervention due to a reason other than rescue therapy or lack of efficacy and then further withdraw from the study before Week 26, their MG-ADL total score will be missing at Week 26 and therefore will not be included in the ANCOVA model. Difference in least squares means, the corresponding 95% CI and p-value will be provided for the comparison of tolebrutinib versus placebo.

Participants who prematurely discontinue study intervention, including those receiving rescue treatment, will be encouraged to continue study FU and have efficacy assessments performed at scheduled visits. These data will be included for supplementary analyses for the primary endpoint to assess the efficacy of tolebrutinib compared to placebo in an intention-to-treat (ITT) setting, ie, the assessment of the treatment policy or strategy. A mixed-effect model with repeated measures (MMRM) approach will be used with change from baseline in MG-ADL total scores at scheduled visits up through Week 26 as the response variable; and treatment, baseline MG-ADL total score, all randomization stratification factors, visit, treatment-by-visit interaction, and baseline MG-ADL total score-by-visit interaction as covariates. For participants who withdraw from the study before Week 26, MG-ADL total scores will be missing after the study discontinuation. No imputation will be performed for missing values in this supplementary analysis. An unstructured correlation matrix will be used to model the within-participant errors. Parameters will be estimated using the restricted maximum likelihood method. Statistical inference on the treatment comparison for the change from baseline in MG-ADL score at Week 26 will be derived from the mixed-effect model. Difference in least squares means, the corresponding 95% CI, and p-value will be provided for the comparison of tolebrutinib versus placebo.

Sensitivity analysis to assess the impact of missing data will be explored. Details will be included in the SAP. Additionally, subgroup analyses will be conducted to assess consistency of treatment effect. The subgroup factors will include at a minimum all stratification factors, age, gender, race and SoC. The detailed list of subgroups and additional details of the subgroup analyses will be provided in the SAP.

9.3.3 Secondary endpoints

The secondary efficacy endpoints are listed in the objectives and endpoints table (see Table 1). Primary analyses of secondary endpoints will be based on a combination of treatment policy strategy and composite variable strategy in the mITT population.

Secondary efficacy endpoints, defined as change from baseline score at Week 26, will be analyzed in the same way as the primary endpoint, except that the respective baseline value corresponding to the endpoint will be included as the covariate in the ANCOVA model and the worst change from baseline value as stated in Section 9.3.2 for participants who permanently discontinue study intervention due to rescue therapy and/or lack of efficacy will be based on the corresponding assessment.

The proportion of responders, defined as a ≥2-point reduction in MG-ADL score at Week 26, will be analyzed using a Cochran-Mantel-Haenszel test, stratified by at least the randomization stratification factors, in the mITT population. Participants not reaching at least a 2-point reduction at Week 26 or permanently discontinuing study intervention due to rescue therapy and/or lack of efficacy will be considered non-responders. The relative risk comparing tolebrutinib versus placebo will be provided along with the corresponding 95% CI. The same analysis approach will be used for the proportion of responders based on QMG score; a ≥3-point reduction in QMG score at Week 26.

Data collected after the premature discontinuation of study intervention will be included for supplementary analyses for the main secondary endpoints to assess the efficacy of tolebrutinib compared to placebo in an ITT setting, ie, the assessment of the treatment policy or strategy, using the same MMRM as stated for supplementary analysis of the primary endpoint in Section 9.3.2, except that the respective baseline value corresponding to the endpoint will be included as the covariate. Details, including any subgroup analyses, will be included in the SAP.

[redacted]

9.3.4 Tertiary/exploratory endpoints

[redacted]

9.3.5 Other/safety analysis

All safety analyses will be performed on the safety population.

Safety summaries will be descriptive, ie, no statistical significance tests will be performed on safety data. The summary of safety results will be presented by treatment group.

Safety analyses will be based on the reported AEs and other safety information, such as clinical laboratory data, vital signs, and ECG.

9.3.5.1 Adverse events

General common rules for adverse events

The AEs during the DB period will be analyzed in the following 3 categories (see Section 9.3.1):

- Pre-treatment AEs: AEs that developed, worsened, or became serious during the pre-treatment period.
- TEAEs: AEs that developed, worsened, or became serious during the DB on-treatment period
- Post-treatment AEs: AEs that developed, worsened, or became serious during the post-treatment period, if applicable.

Similarly, the deaths will be analyzed in the pre-treatment, DB on-treatment, and post-treatment periods.

Analysis of all adverse events

Adverse event incidence tables will be provided by treatment group for all types of TEAEs: all TEAEs, all TE AESIs (defined with a Preferred Term or a prespecified grouping), all TE SAEs, and all TEAEs leading to permanent treatment discontinuation.

The AE summaries will be generated with number (%) of participants experiencing at least one event.

Deaths will also be analyzed.

9.3.5.2 Laboratory variables, vital signs, and electrocardiograms (ECGs)

Quantitative analyses

For laboratory variables, vital signs, and ECG variables, descriptive statistics for results and changes from baseline will be provided for each analysis window during the on-treatment period. These analyses will be performed using central measurements only (when available) for laboratory variables and ECG variables.

Analyses according to PCSA

Potentially clinically significant abnormalities analyses will be performed based on the Sponsor's PCSA list currently in effect at the time of the database lock.

Analyses according to PCSA will be performed based on the worst value during the DB on-treatment period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables, vital signs, and ECG variables, the incidence of participants with at least one PCSA during the TE period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For ECG, the incidence of participants with at least one abnormal ECG during the TE period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal

9.3.6 Other analysis

[redacted]

For a regional or national emergency declared by a governmental agency, contingency measures are included in (Section 10.9) Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency.

[redacted]

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH-GCP Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - [GDPR]).
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.

- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participants or their legally authorized representative, and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the GDPR and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s). Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc.).
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative, where applicable.

Participants who are rescreened are required to sign a new ICF.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in (Section 10.9) Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency.

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR. The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant, and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

- Participant race and ethnicity will be collected in this study because they are expected to modify the drug response and are required by regulatory agencies (eg, on the African American population for the Food and Drug Administration, on the Chinese population for the National Medical Product Administration, China or on the Japanese population for the

Pharmaceuticals and Medical Devices Agency in Japan). They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study.
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering

an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:

- The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
- Sanofi's Binding Corporate Rules for intra-group transfers.

- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to 30 years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committee structures

10.1.5.1 Independent Data Monitoring Committee

An IDMC, operating independently of the Sponsor and clinical Investigators, will be responsible for overseeing the safety of participants throughout the study. This committee is composed of externally based individuals with expertise in the disease under study, biostatistics, or clinical research. The primary responsibilities of the IDMC are to review and evaluate the safety data and to make appropriate recommendations to the Sponsor regarding the conduct of the clinical study.

Details describing the IDMC processes and procedures are outlined in the IDMC charter.
To maintain continuous blinding and study integrity, the analysis, including the IA developed in Section 9.4, will be conducted by an independent statistical group who will directly transfer data to IDMC members, and measures will be taken to ensure the validity of the data.

The IDMC will review the unblinded results of the IA, provided by the independent statistical group, and recommend the Sponsor (therapeutic area head or development head only) of the next steps based on the pre-specified criteria.

10.1.5.2 Scientific Advisory Committee

A Scientific Advisory Committee will provide advice to the Sponsor regarding scientific issues and operational conduct of the study. This committee will be composed of a Chairperson, selected by the Sponsor, field experts, and Sponsor-based scientists with clinical and methodological expertise. The Scientific Advisory Committee will also review any amendments and provide input regarding interpretation of study results. The members will remain blinded until completion of the study. Among its responsibilities, the Scientific Advisory Committee will receive blinded study status reports from the Sponsor and will review the recommendations from the Data Monitoring Committee throughout the study.

The responsibilities of the Scientific Advisory Committee are provided in the Scientific Advisory Committee charter.

[redacted]

10.1.6 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

Professionals involved in the study or in the drug development program

Sanofi undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/ hospital's name and location on the China Trial Disclosure website as required by the National Medical Products Administration in its guidance "Implementation of Drug Clinical Trial Information Registration and Disclosure" ("Notification No. 28"), requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial.

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Completion Instructions document.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records such as hospital records, clinic and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, etc. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. If a certified copy is used, reason for this use must be documented in the "comments" part of the "list of documents to be archived by the Site." The list of source documents and location is to be provided in the investigator's study file (ISF). Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study/Site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio.
  - Discontinuation of further study intervention development.
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
  - Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or FU.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 6 will be performed by the central laboratory when feasible. Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations. Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 6 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	RBC indices:
	MCV
	MCH
	%Reticulocytes
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a]	
	Blood urea nitrogen (BUN)
	Creatinine[b]
	Glucose (nonfasting)
	Total and direct bilirubin
	Potassium
	Sodium
	Chloride
	Bicarbonate
	Calcium
	Albumin
	Creatine phosphokinase
	Alkaline phosphatase
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)
	Lipase
	Total protein
Routine urinalysis	Specific gravity
	pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
	Microscopic examination (if blood or protein is abnormal)

Laboratory tests	Parameters
Pregnancy testing	Serum (required at Screening [Visit 1]) or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c]
Other screening tests	Follicle-stimulating hormone (if needed, only in female participants to confirm postmenopausal state)
	Coagulation: PT/ INR, aPTT
	Iron panel (serum): iron, ferritin, transferrin saturation, TIBC.
	Serology tests for HIV and other infectious diseases, if locally required
	Hepatitis serologic testing at Screening (Visit 1): hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb IgM and Total), and hepatitis C virus antibodies (HCVAb). In case of results showing HBsAg (negative) and HBcAb Total (positive), HBV DNA testing will be performed prior to randomization to rule out a false positivity to clarify the serological status. In case of results showing HCV Ab (positive), HCV RNA testing will be performed to rule out a false positivity.[d]
	Tuberculosis test: Blood testing (eg, QuantiFERON® TB Gold test) is preferred; skin testing (eg, tuberculin skin test) will be allowed if blood testing is not available or blood test result is indeterminate[d]
	Serum autoantibodies (anti-AChR or anti-MuSK)

AChR: acetylcholine receptor; AESI: adverse event of special interest; aPTT: activated thromboplastin time; DNA: deoxyribonucleic acid; HBV: hepatitis B virus; HIV: human immunodeficiency virus; IEC: Institutional Ethics Committee; IgM: immunoglobulin M; INR: international normalized ratio; IRB: Institutional Review Board; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MuSK: muscle-specific kinase, PT: prothrombin time, RNA: ribonucleic acid; SAE: serious adverse event; TIBC: total iron-binding capacity; ULN: upper limit of normal.

NOTES:

a Details of liver chemistry stopping criteria and required actions and follow-up after observations of ALT >3 × ULN are given in Section 7.1.2, Liver chemistry stopping criteria) and Appendix 6 (Section 10.6, Liver and other safety). All events of ALT >3 x ULN which may indicate liver injury must be reported to the Sponsor in an expedited manner (refer to section on AESIs [Section 8.3.7]). Clinical laboratory findings of ALT >3 ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT >3 × ULN and INR >1.5, if INR measured, that may suggest severe liver injury (possible Hy's Law) must be reported as an SAE.

b Other renal function parameters, creatinine clearance (CrCl) will be calculated.

c With the mentioned exception of the Screening Visit when a serum test is required, local monthly urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

d See E 03 for further details.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

  NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm

- Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc.)
- Convulsions (seizures, epilepsy, epileptic fit, absence, etc.).
- Development of drug dependence or drug abuse.

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will assess the severity for each AE and SAE using the NCI CTCAE version 5.0, published on 27 November 2017. Listings of Medical Dictionary for Regulatory Activities (MedDRA) terms should be consulted first in NCI CTCAE to look for severity grade description for a particular AE. For AEs not listed in the NCI CTCAE, the Investigator will be required to assess the severity of the AE using general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental ADL*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Note: ADL

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor's representative. However, **it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor's representative.**
- The Investigator may change his/her opinion of causality in light of FU information and send an SAE FU report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized FU period, the Investigator will provide the Sponsor's representative with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the contact list in the Investigator Study File.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the contact list in the Investigator Study File.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy,
   - Documented bilateral salpingectomy,
   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female

   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

   - A high follicle-stimulating hormone (FSH) level (>30 IU/L) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal acceptable contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly*
Implantable progesterone-only hormone contraception associated with inhibition of ovulation
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)
Bilateral tubal occlusion
Vasectomized partner (Vasectomized partner 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.)
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] Oral Intravaginal Transdermal injectable
Progesterone-only hormone contraception associated with inhibition of ovulation[c] Oral Injectable
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
ACCEPTABLE METHODS[d]
Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
Male or female condom with or without spermicide[e]
Cervical cap, diaphragm, or sponge with spermicide
A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

a Contraceptive use by men or women 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 If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

d Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

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

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor.
- Generally, the FU will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 1 day of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect FU information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, FU will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4 of the protocol. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.
- The participant will be invited to remain in the study in any case. The pregnancy outcome and data of the newborn will be reported to the Sponsor as per usual pharmacovigilance reporting practice.

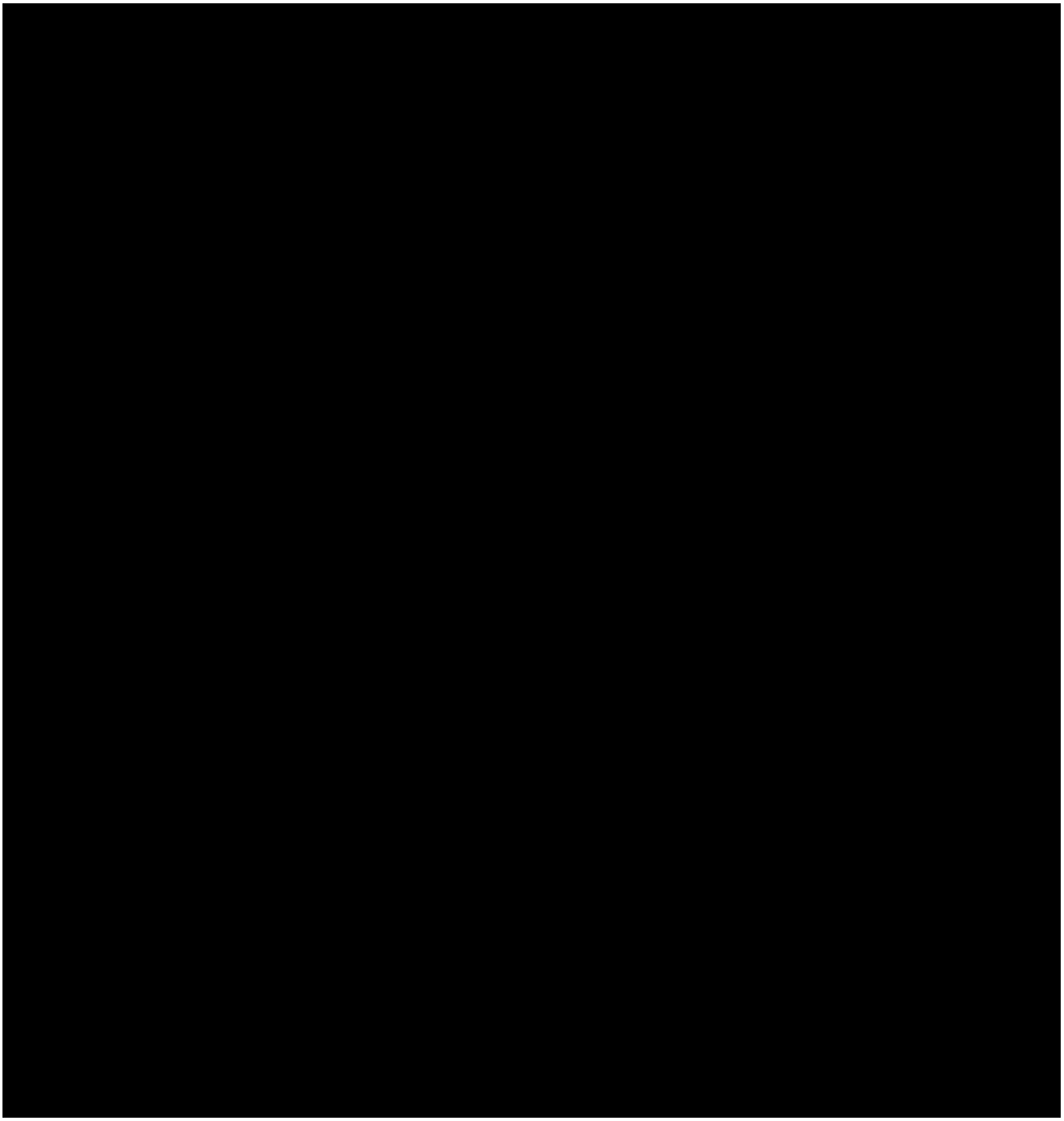
10.5 APPENDIX 5: GENETICS

Use/Analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated.

Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

- DNA samples will be used for research related to MG and related diseases. They may also be used to develop tests/assays including diagnostic tests related to MG. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on this indication but no longer than 25 years or other period as per local requirements. For China, see Section 10.8.2 for details.



10.7 APPENDIX 7: AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

10.8.1 Inclusion criteria

Contraceptive/barrier method requirements

For United Kingdom and Germany Only: Acceptable forms of effective contraception include:

- Established use of oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation;
- Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS);
- Bilateral tubal occlusion;
- Male sterilization (provided that the partner is the sole sexual partner of the WOCBP study participant and that the sterilized partner has received medical assessment of the surgical success);
- True abstinence: When this is in line with the preferred and usual lifestyle of the participant. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

[redacted]

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Continuation of the study in the event of a regional or national emergency declared by a governmental agency (including related to COVID-19):

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical study site. The continuity of clinical study conduct, and oversight may require implementation of temporary or alternative mechanisms, eg, phone contact, virtual visits, online meetings, use of local clinic or laboratory locations, and home visits by skilled staff (see hereafter). Implementation of such mechanisms may differ from country to country, depending on country regulations and local business continuity plans. Additionally, no waivers to deviate from protocol enrollment criteria due to regional or national emergency declared by a governmental agency will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to regional or national emergency and will remain in effect only for the duration of the public health emergency.

Contingency procedures are suggested below for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect the integrity of the study, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency; this agreement must be provided in writing by the Sponsor and will be kept in the Investigator file.

During the emergency, if the site is unable to adequately follow protocol-mandated procedures, screening and enrollment may be temporarily delayed/halted.

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

Section 7.1.4: Temporary discontinuation

A temporary study intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical study due to a regional or national emergency declared by a governmental agency.

Reinitiation of study intervention can only occur once the Investigator has determined, according to his/her best judgment, that the study intervention did not contribute to the occurrence of the epidemic event (eg, COVID-19).

For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the CRF or eCRF.

Section 8: Study Assessments and Procedures

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

1. New screenings during a regional or national emergency declared by a governmental agency can be performed only if allowed by local competent authorities and after Sponsor’s agreement is obtained. Rescreening will be permitted when the situation normalizes and only if allowed by local competent authorities and after Sponsor’s agreement is obtained.
2. If onsite visits or alternative location (out of participant’s home) are not possible, all visits from Week 1 (including those planned to be done onsite) will be performed at home by a trained healthcare professional and if allowed by local competent authorities for:
   - Treatment administration.
   - Blood sampling for safety (at least hematology, hepatic function panel, coagulation panel), other safety assessment (at least serum creatinine), and pregnancy test (if applicable).
   - Measuring vital signs.
   - Monitoring of injection site reactions, AEs and SAEs.

The use of a local laboratory may be allowed for safety FU in case the central laboratory cannot be used.

The Investigator or delegate will perform a phone-call visit at each onsite planned visit to collect safety data and concomitant treatment. All data collected remotely will be properly documented in the participant's medical record and the study CRF.

For all assessments that will not be performed remotely, the assessment windows will be extended until participants may access the site.

If onsite visit and home visit are not possible, a temporary treatment discontinuation may be considered. The Investigator or delegate will perform a phone-call visit at each onsite planned visit to collect safety data and concomitant treatment.

Contingencies implemented due to emergency will be documented in the participant's medical record.

Section 9: Statistical analysis

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

Section 10.1.3: Informed consent

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local laboratories), and the verbal information given to the participant should be documented in the participant's medical record.

10.10 APPENDIX 10: EXAMPLES OF DRUGS WITH A POTENTIAL TO CHANGE TOLEBRUTINIB METABOLSIM

The following drugs should not be taken during the study concomitantly with the IMP due to their potential to change tolebrutinib kinetics due to interaction with P450-mediated metabolism, being potent/moderate inducers of CYP3A or potent inhibitors of CYP2C8 liver enzymes (per the lists of the Drug Interaction Database Program of the University of Washington).

Please note that the lists provided are not exhaustive and that the product information of drugs intended for concomitant use should be consulted.

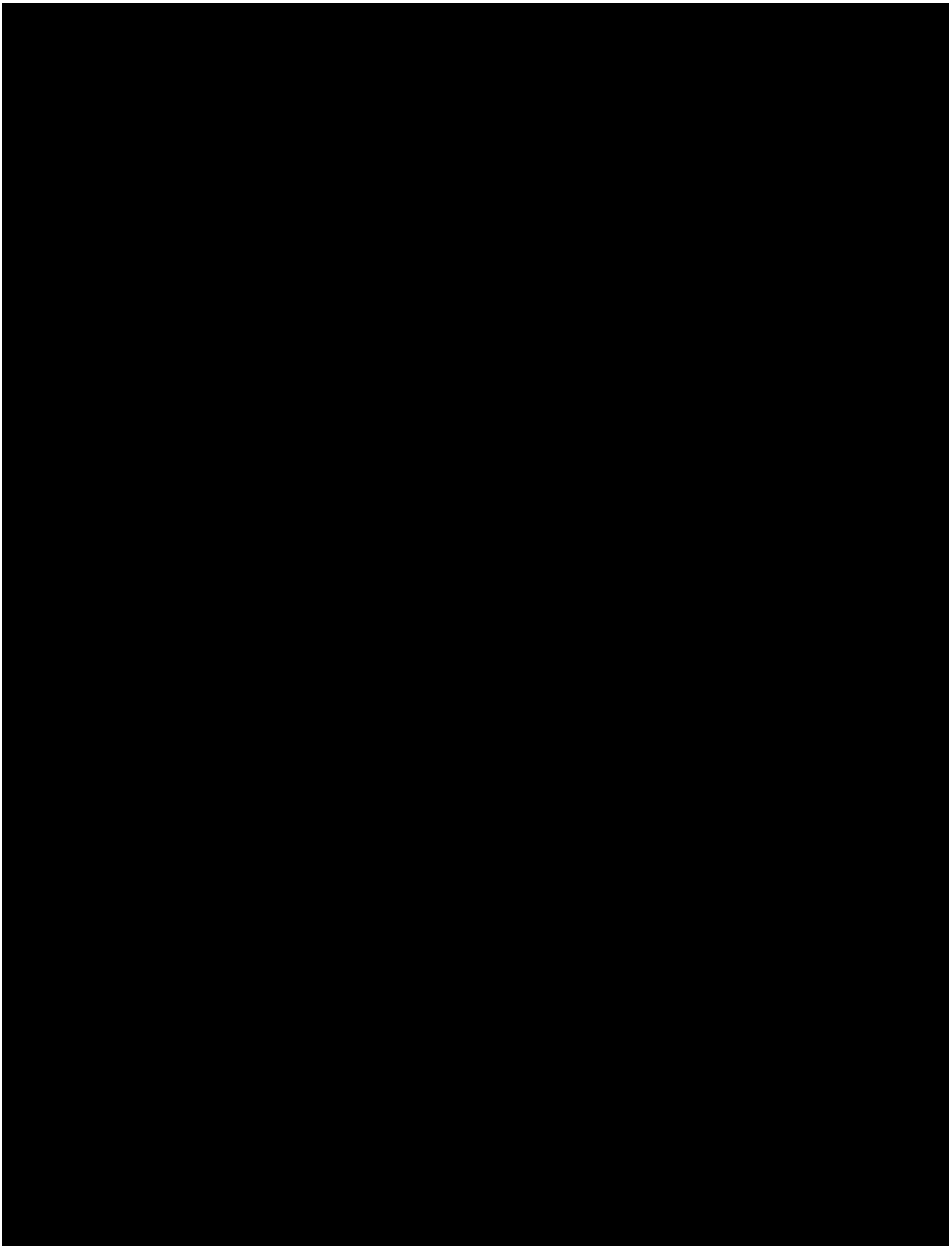
Potent CYP3A Inducers:	
rifampin	carbamazepine
phenobarbital	St John's wort extract
avasimibe	lumacaftor
rifapentine	rifabutin
phenytoin	

Potent CYP2C8 Inhibitors:
gemfibrozil
clopidogrel

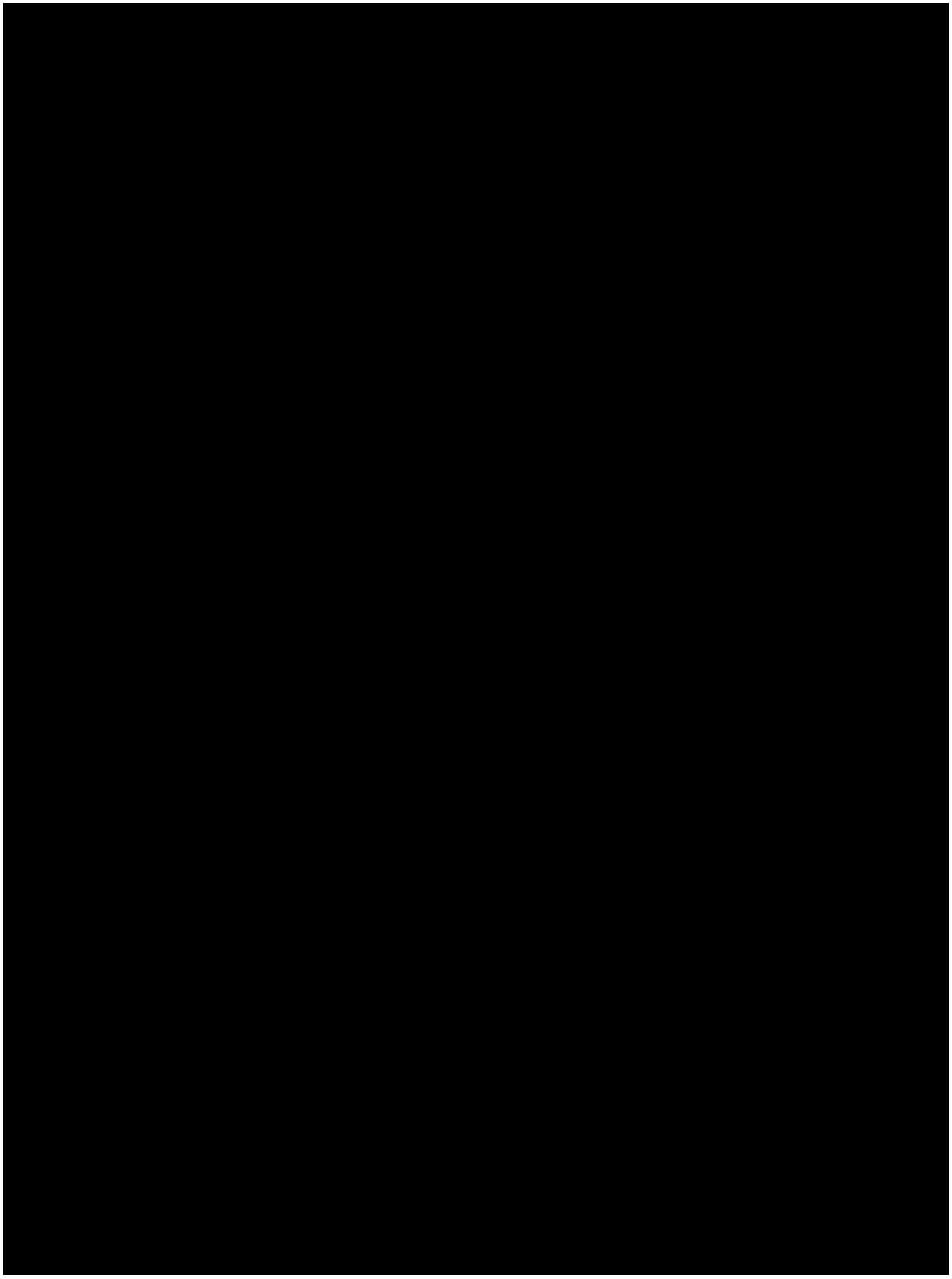
Moderate CYP3A Inducers:	
semagacestat	rifabutin
cenobamate	nafcillin
lesinurad	asunaprevir / beclabuvir / daclatasvir
bosentan	modafinil
thioridazine	telotristat ethyl
	elagolix

10.11 APPENDIX 11: CLINICAL OUTCOME QUESTIONNAIRES

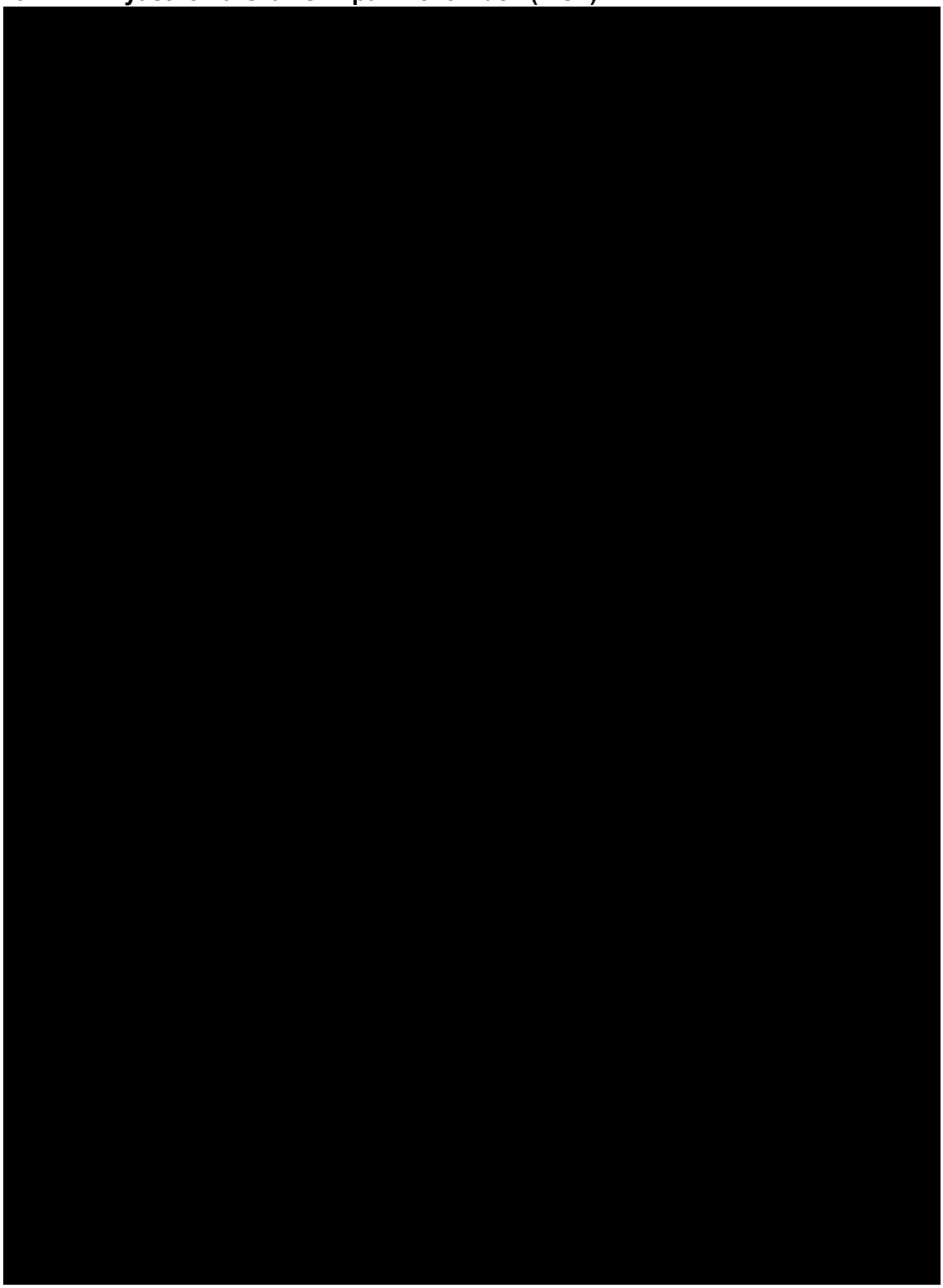
10.11.1 Myasthenia gravis activities of daily living (MG-ADL)

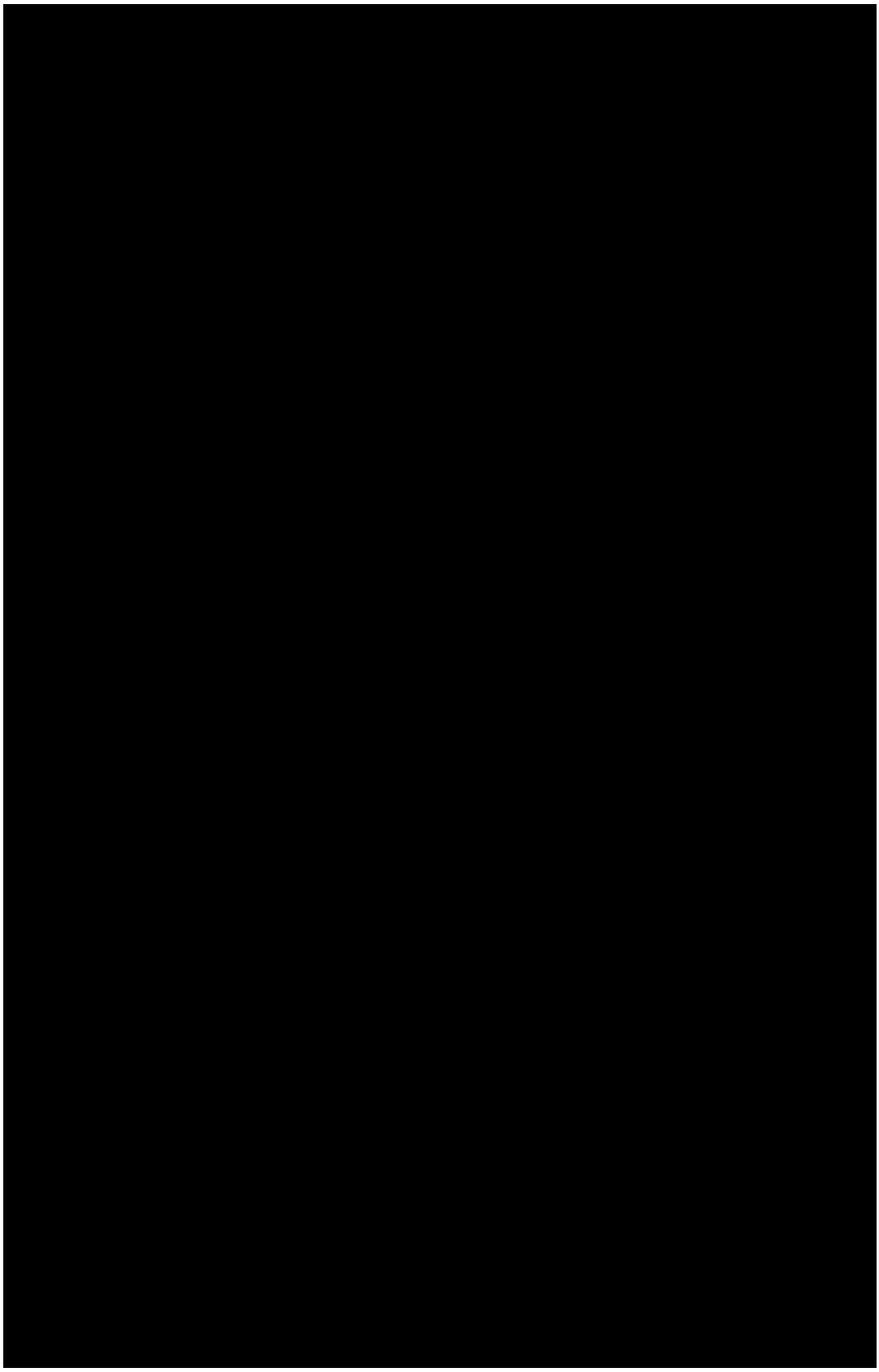


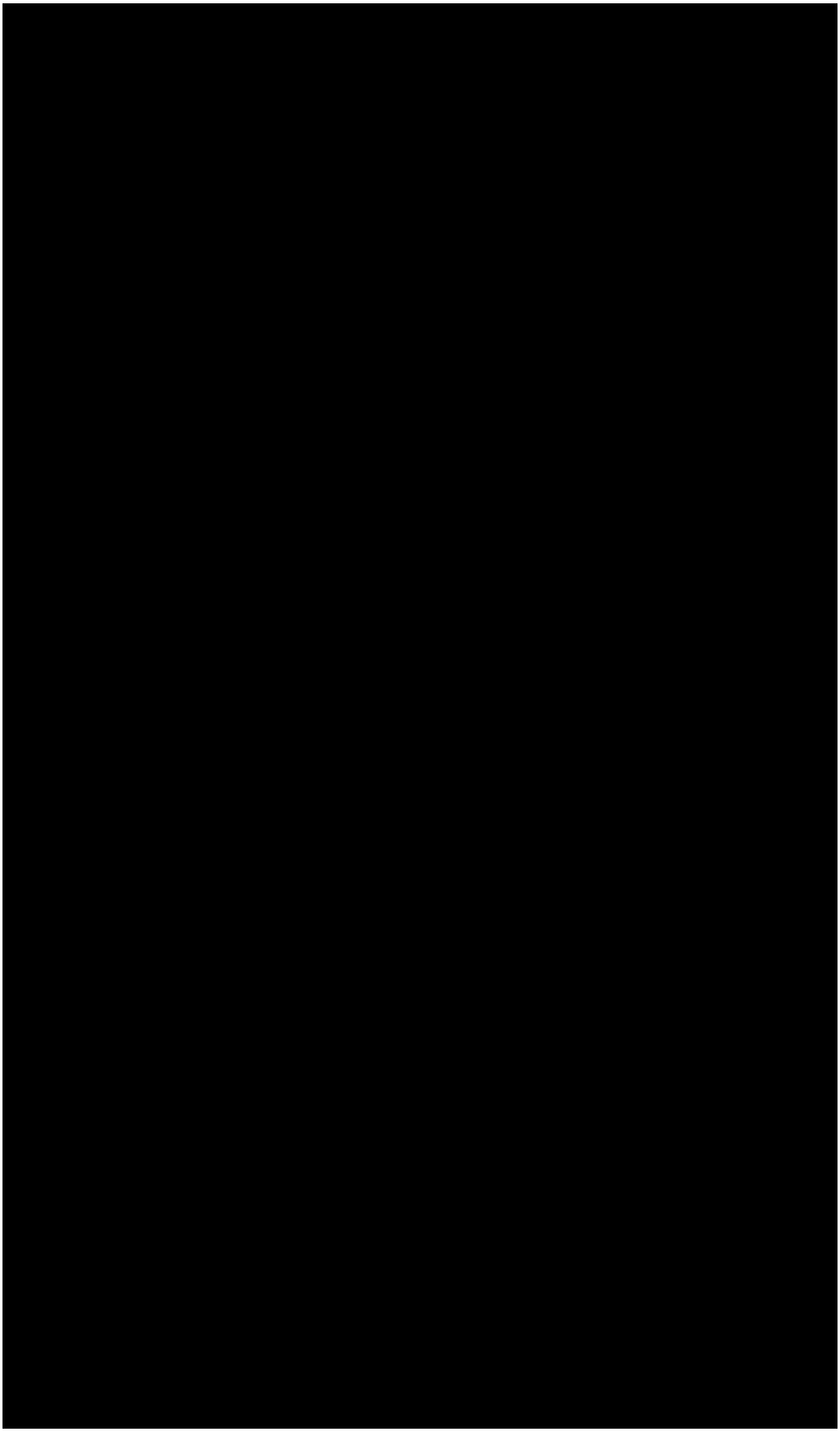
10.11.2 Quantitative Myasthenia Gravis (QMG)

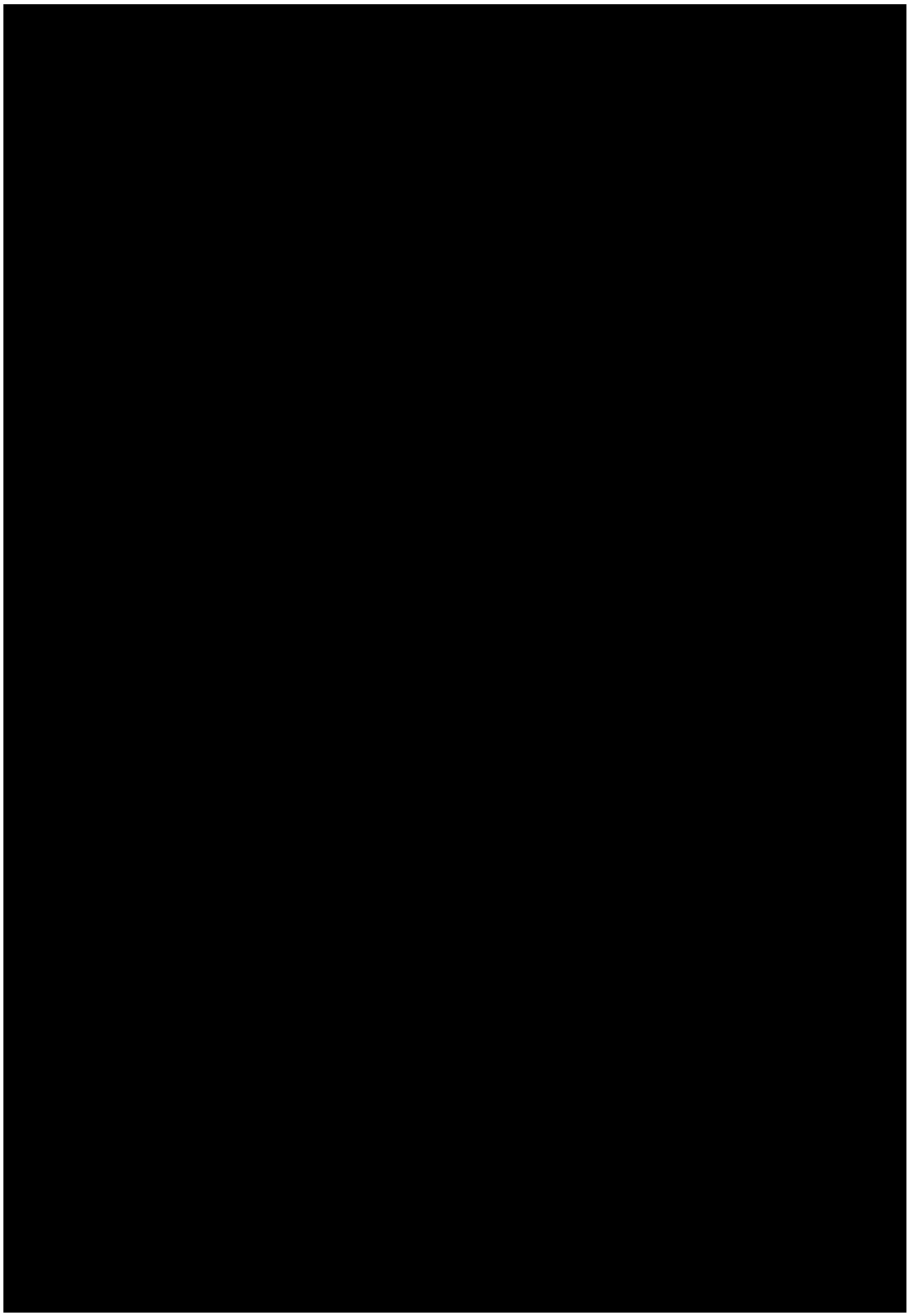


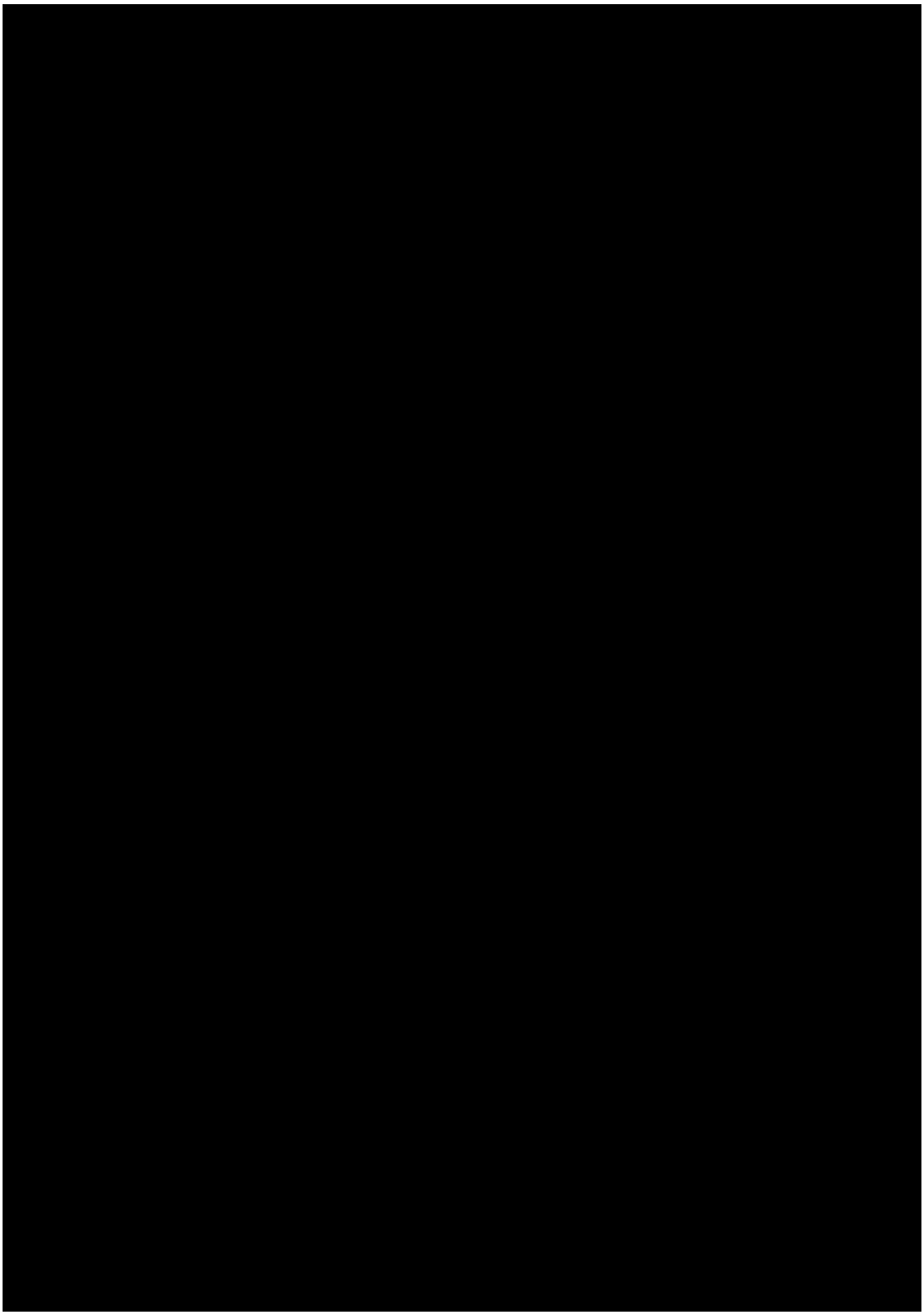
10.11.3 Myasthenia Gravis Impairment Index (MGII)



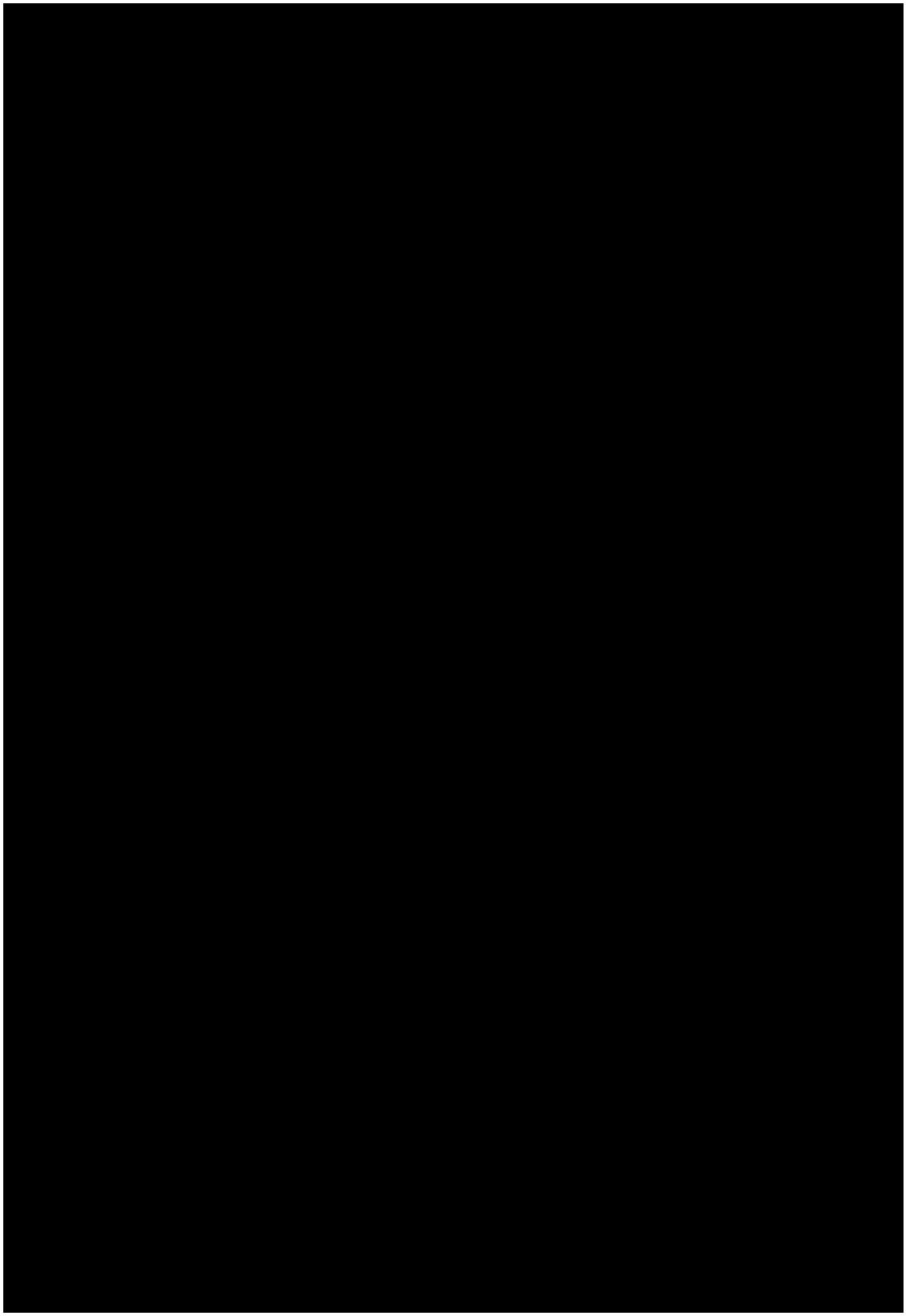




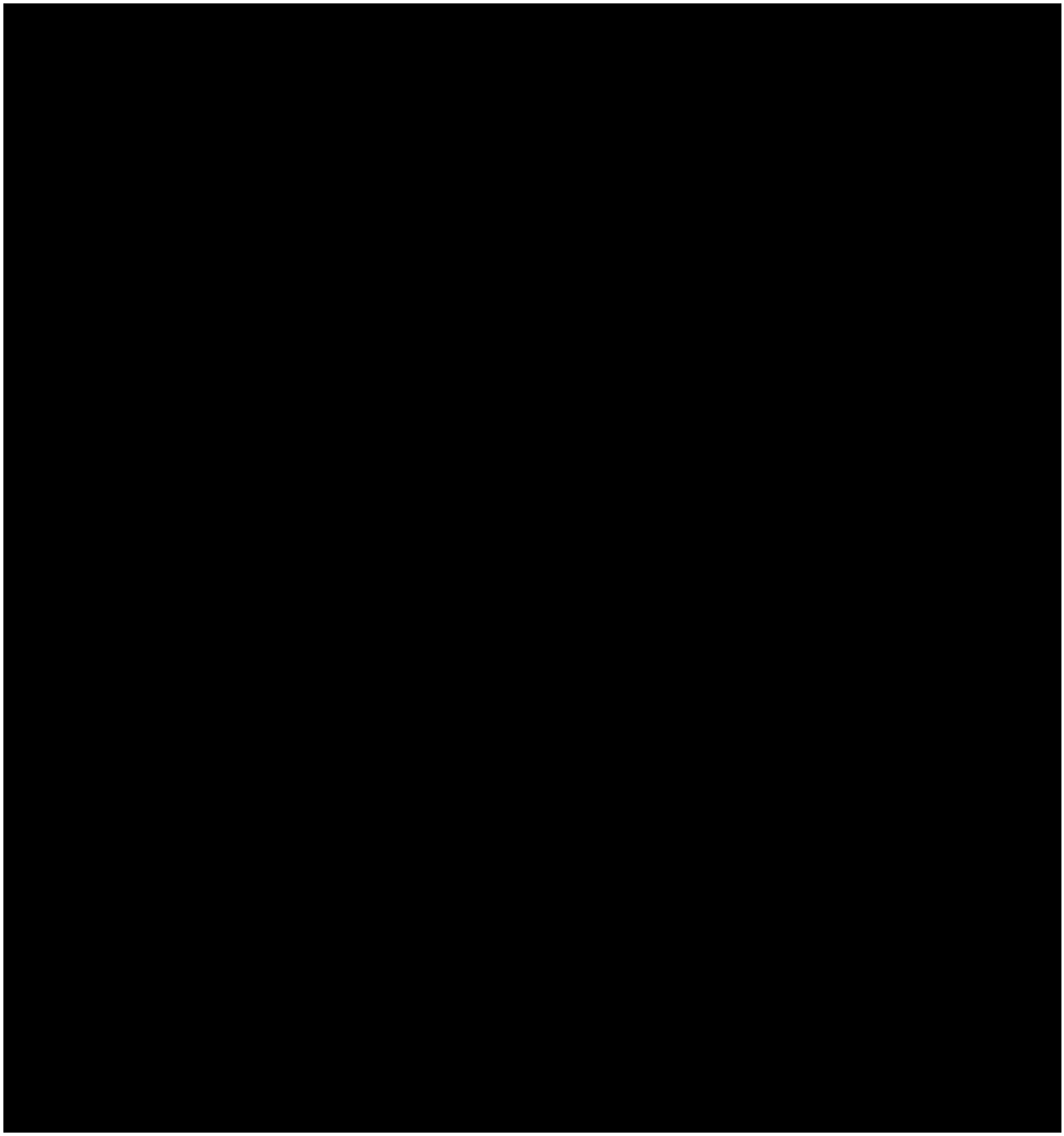


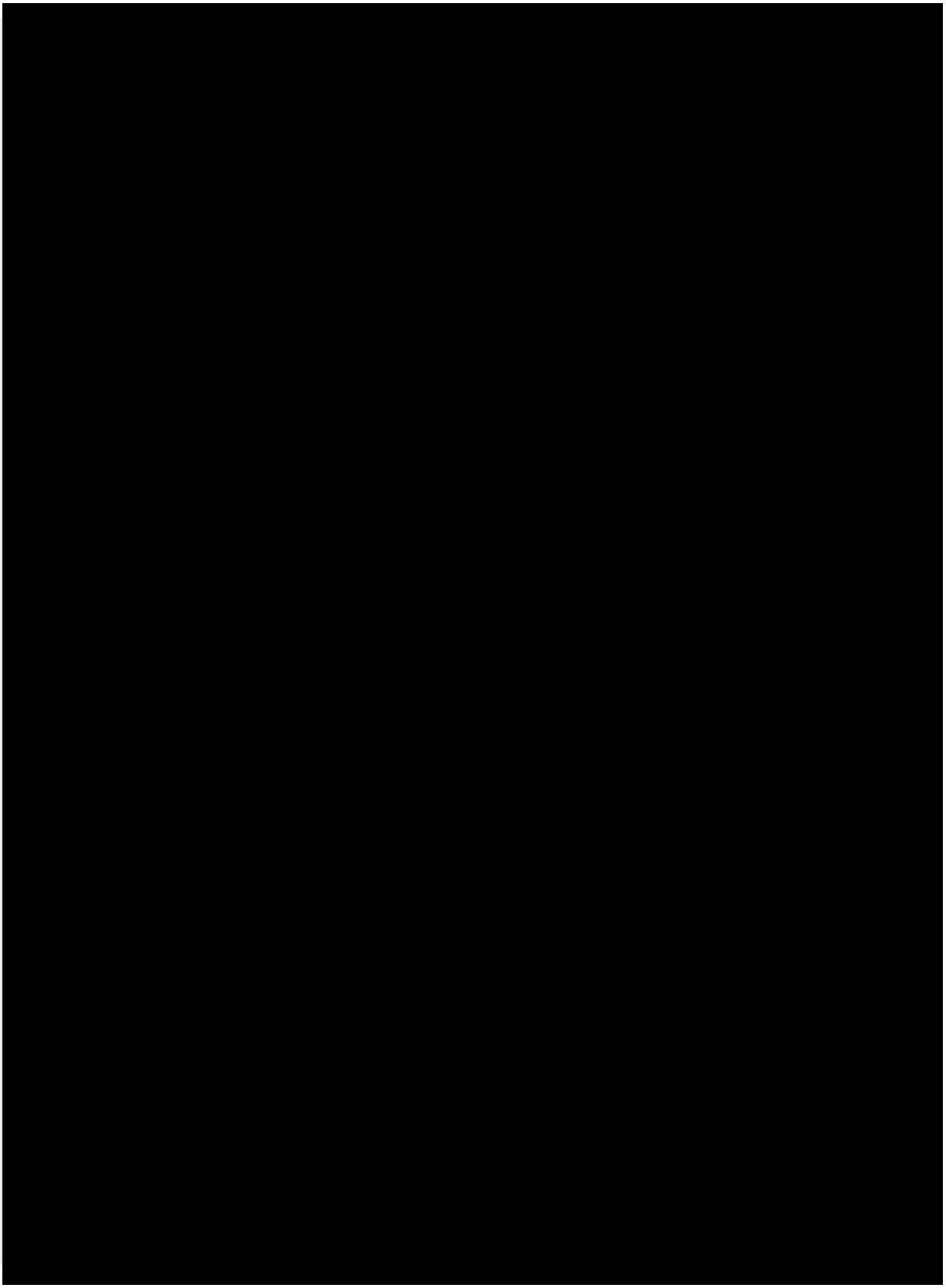


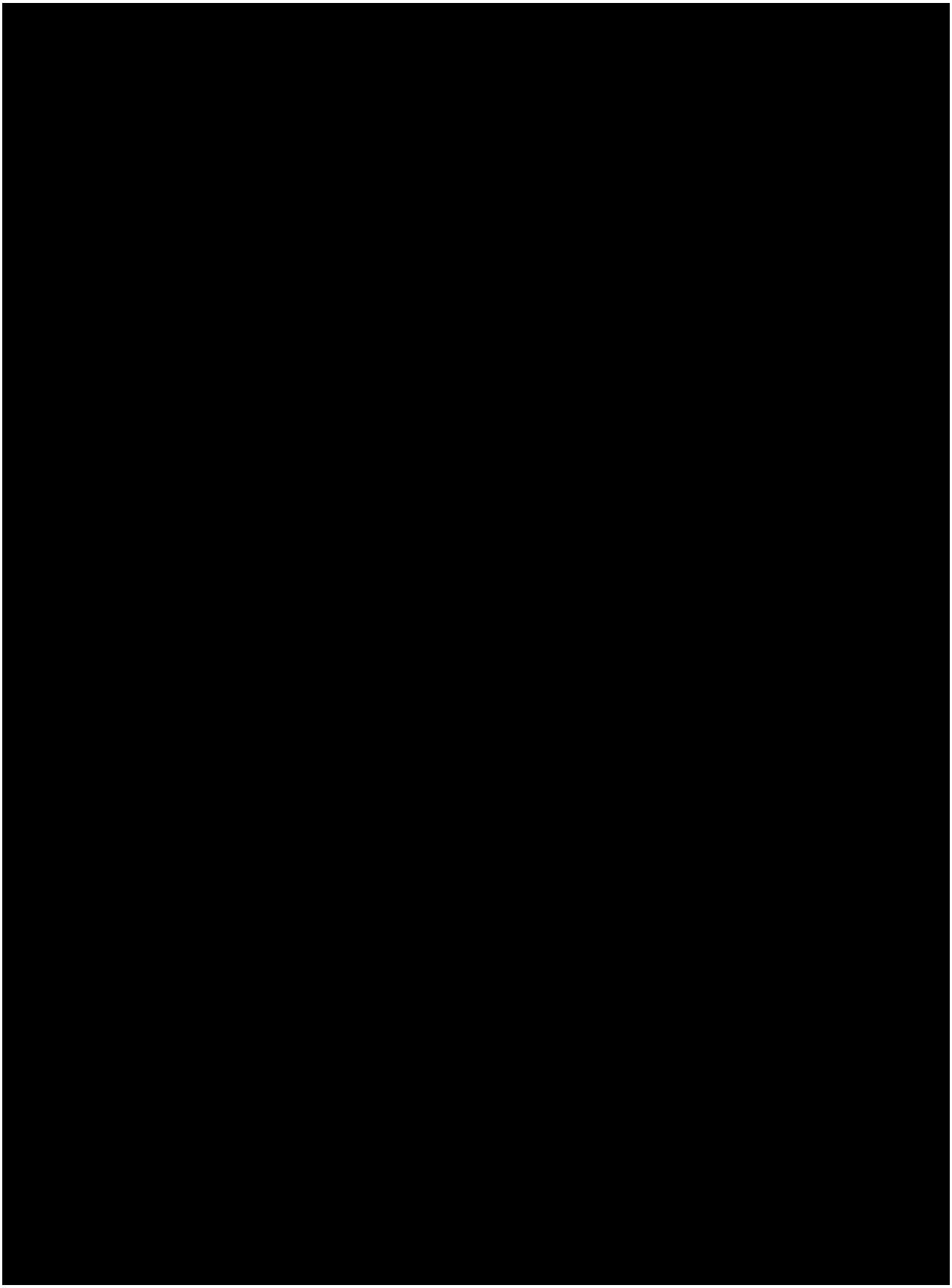
10.11.4 Myasthenia Gravis Quality of Life Questionnaire (MG-QoL15)

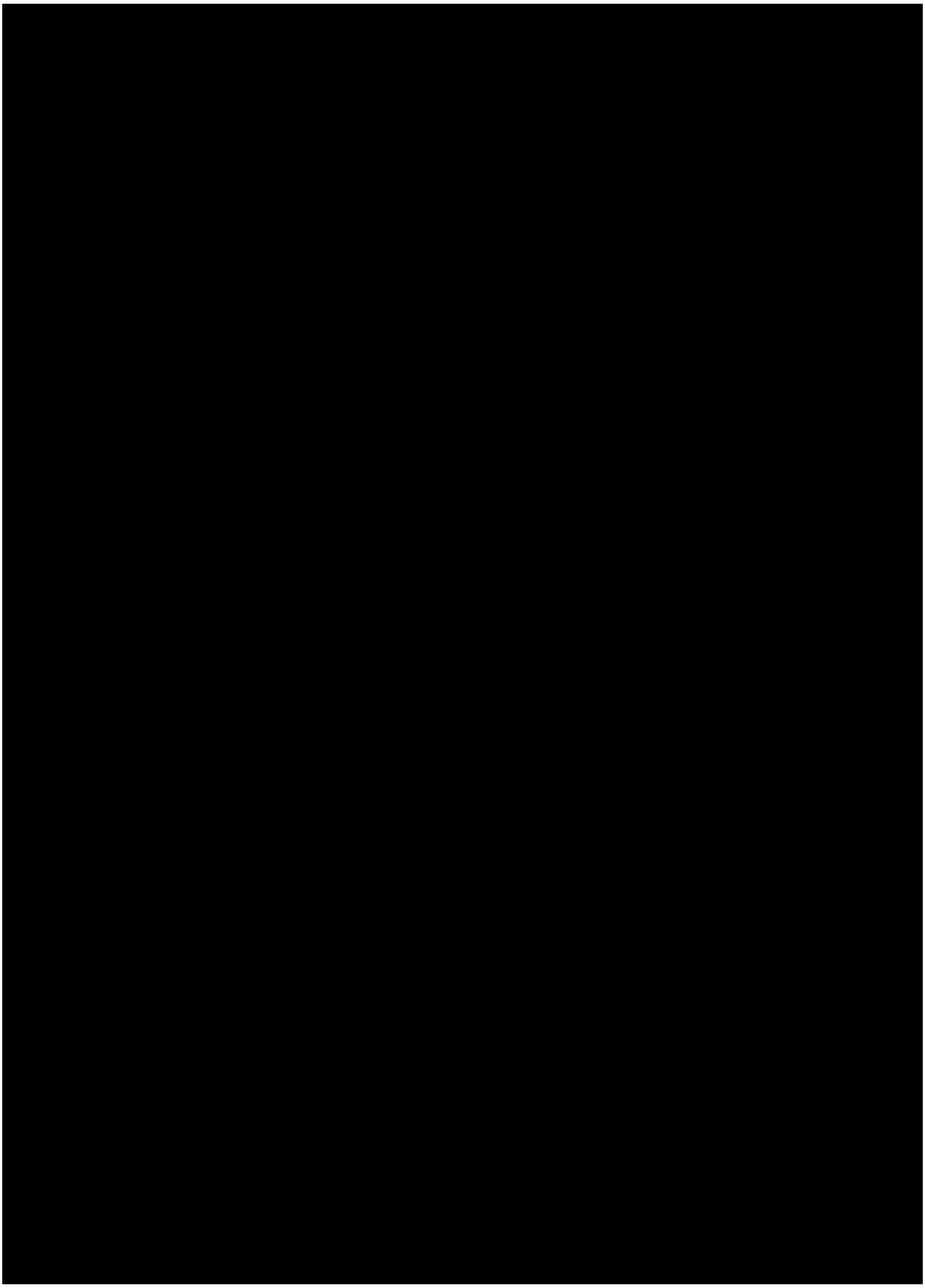


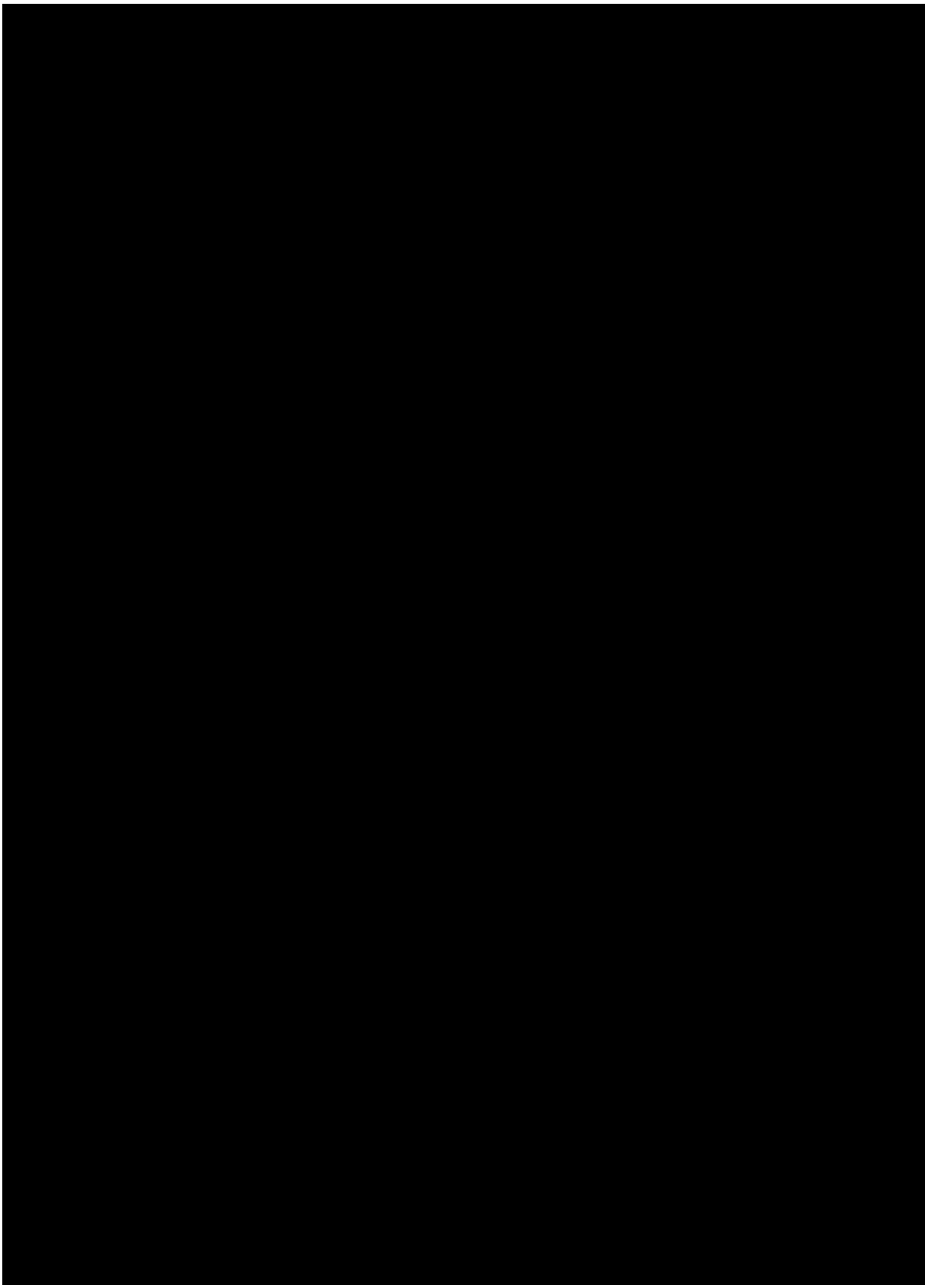
10.11.6 Columbia-Suicide Severity Rating Scale (C-SSRS)

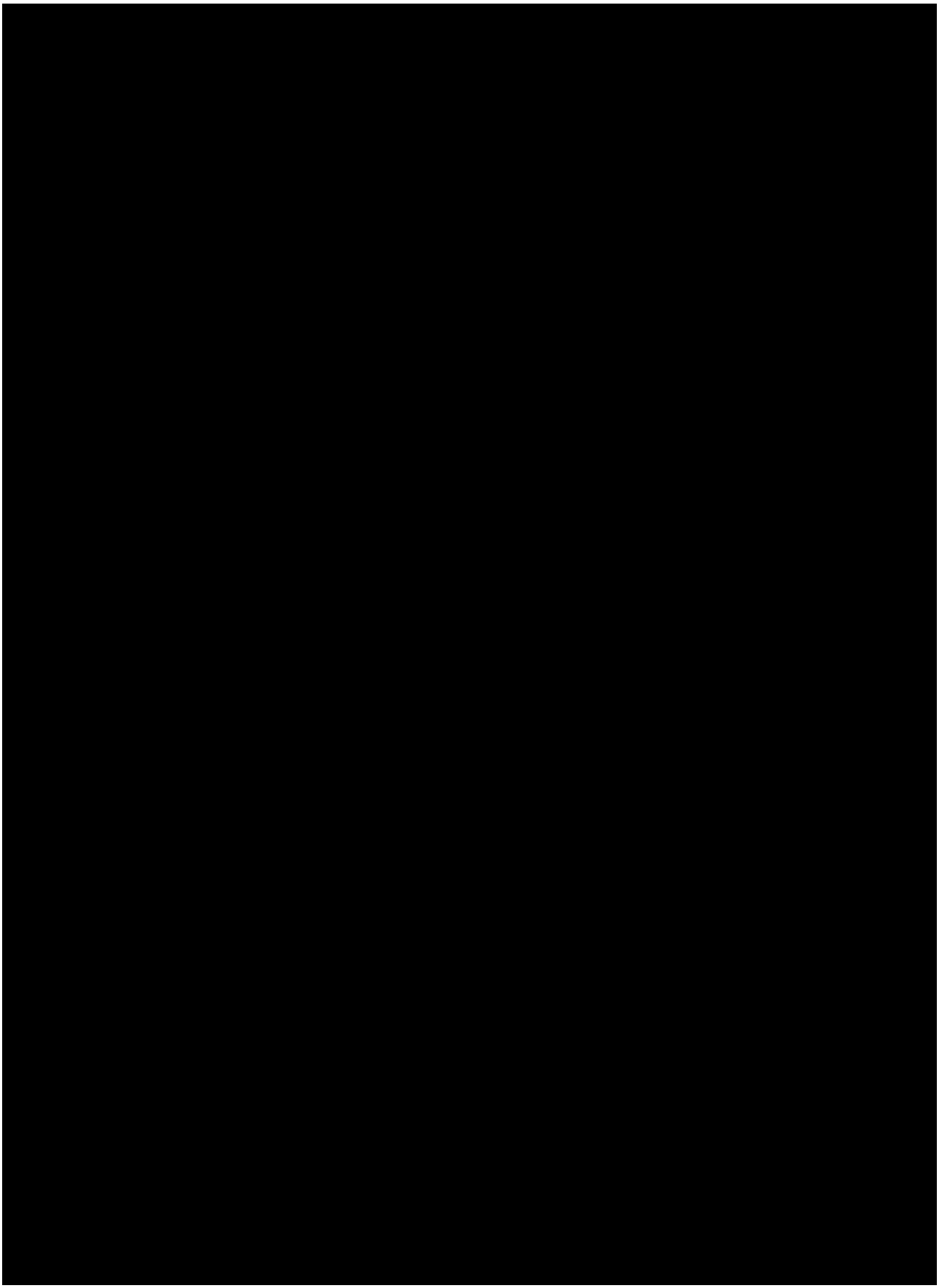




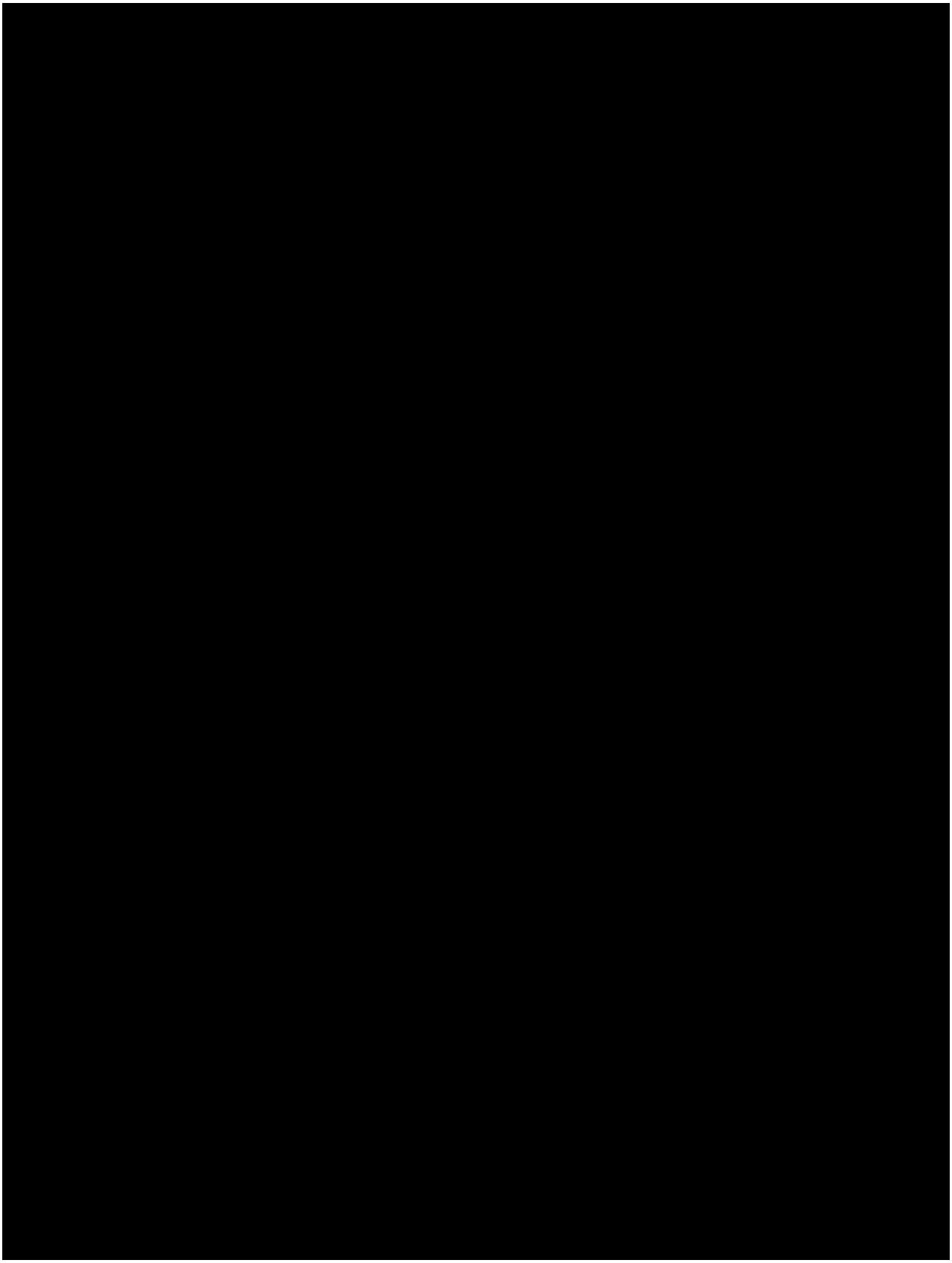


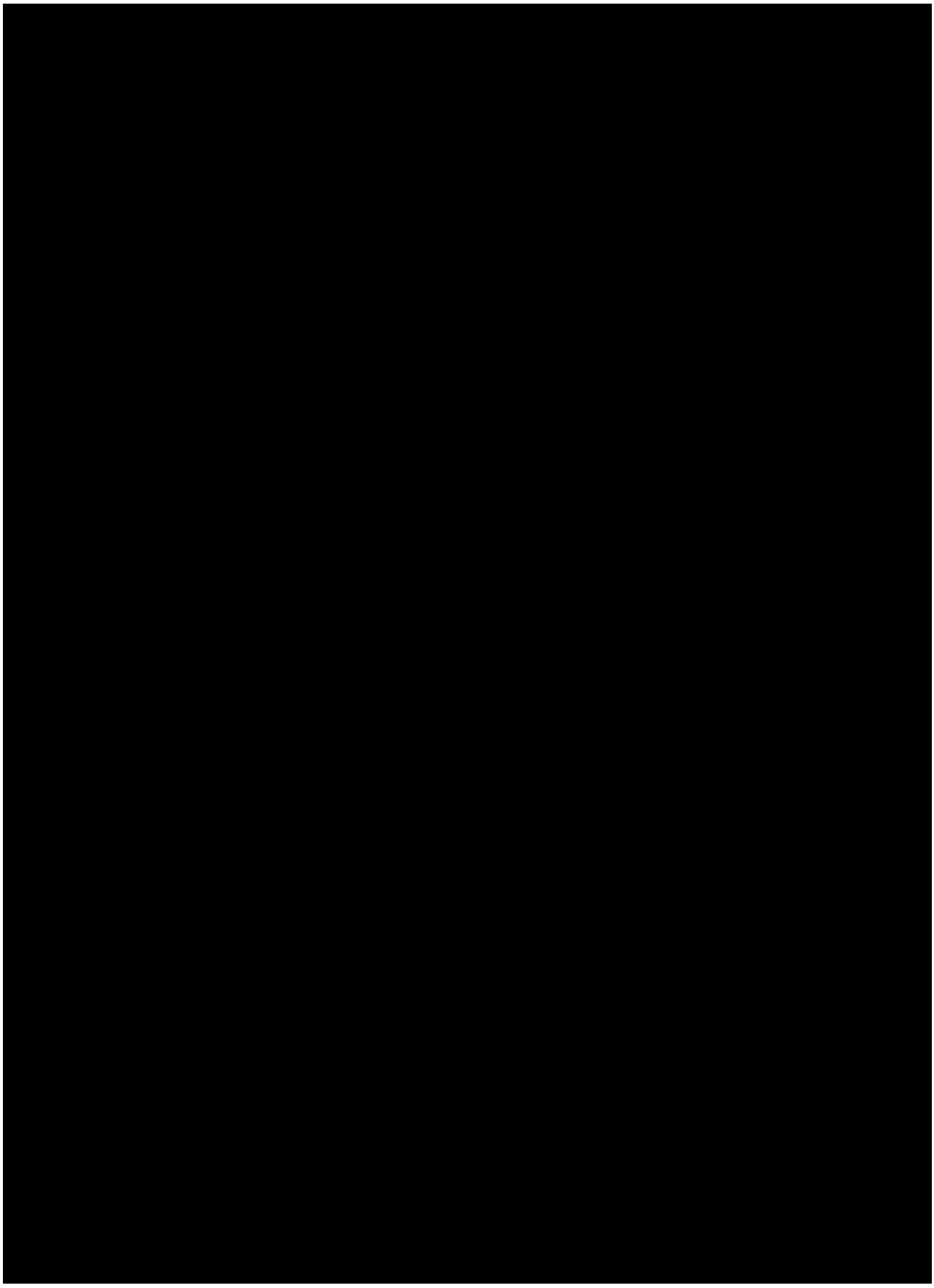






10.11.7 Health Care Resource Utilization





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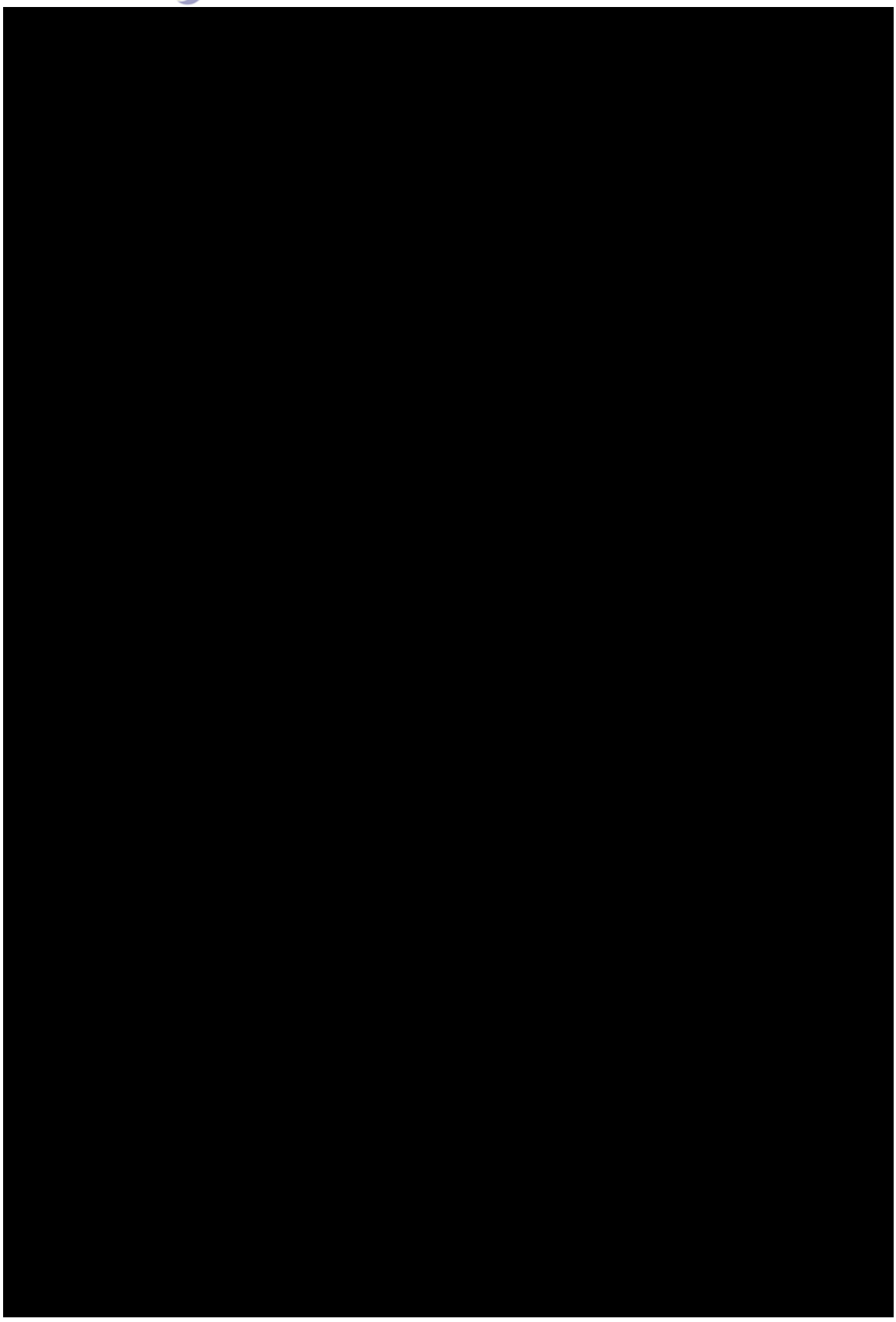

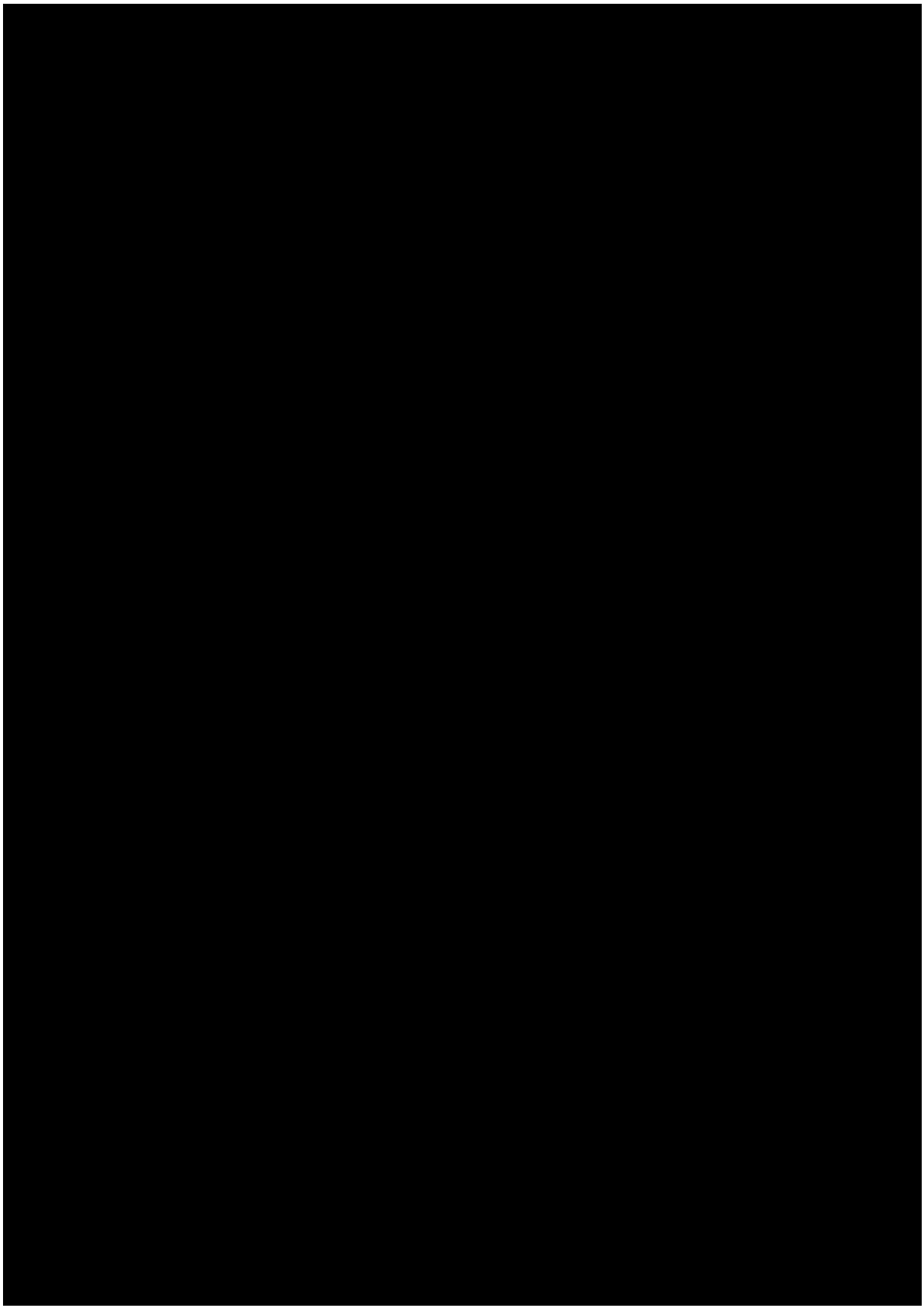

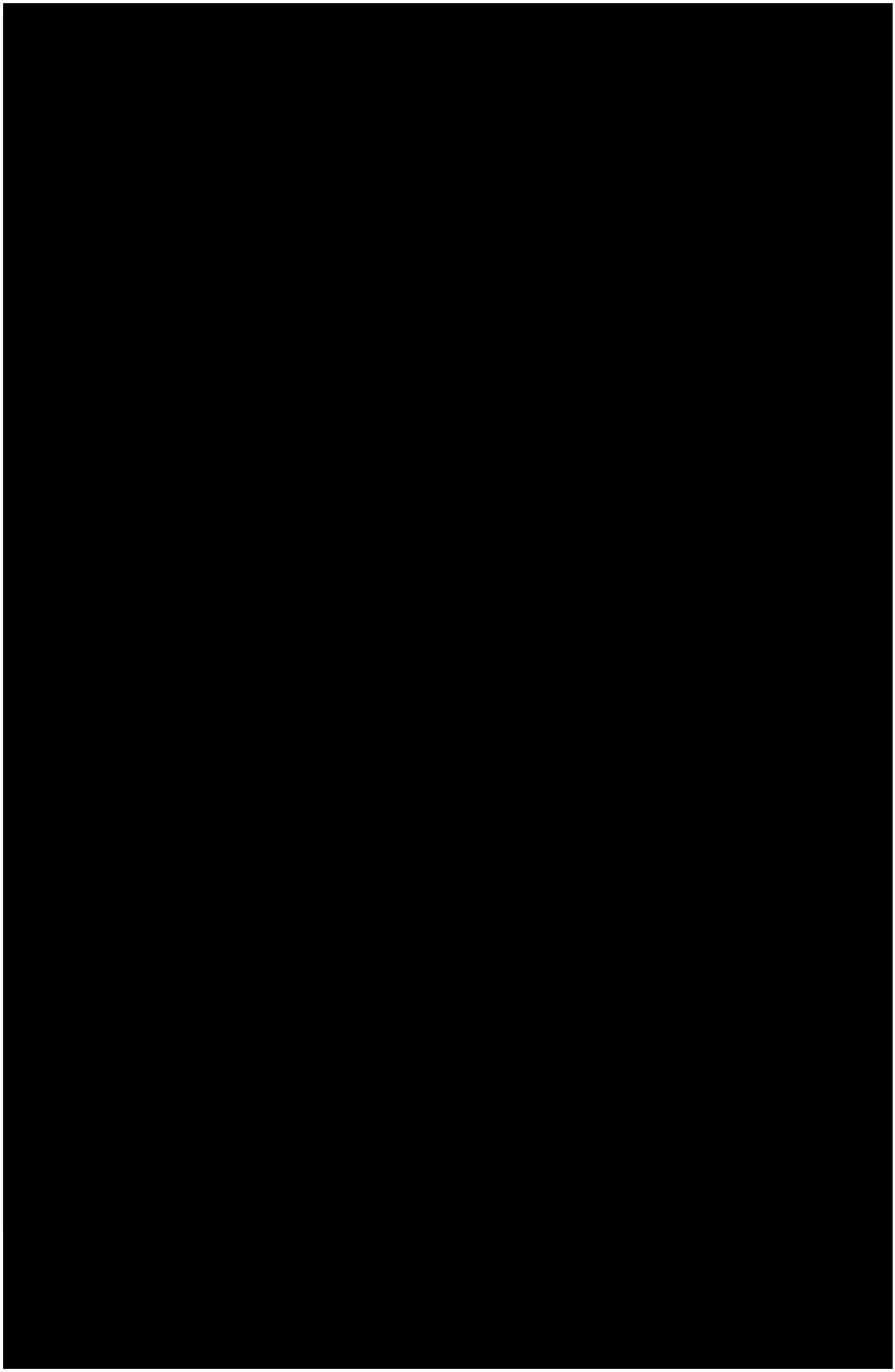

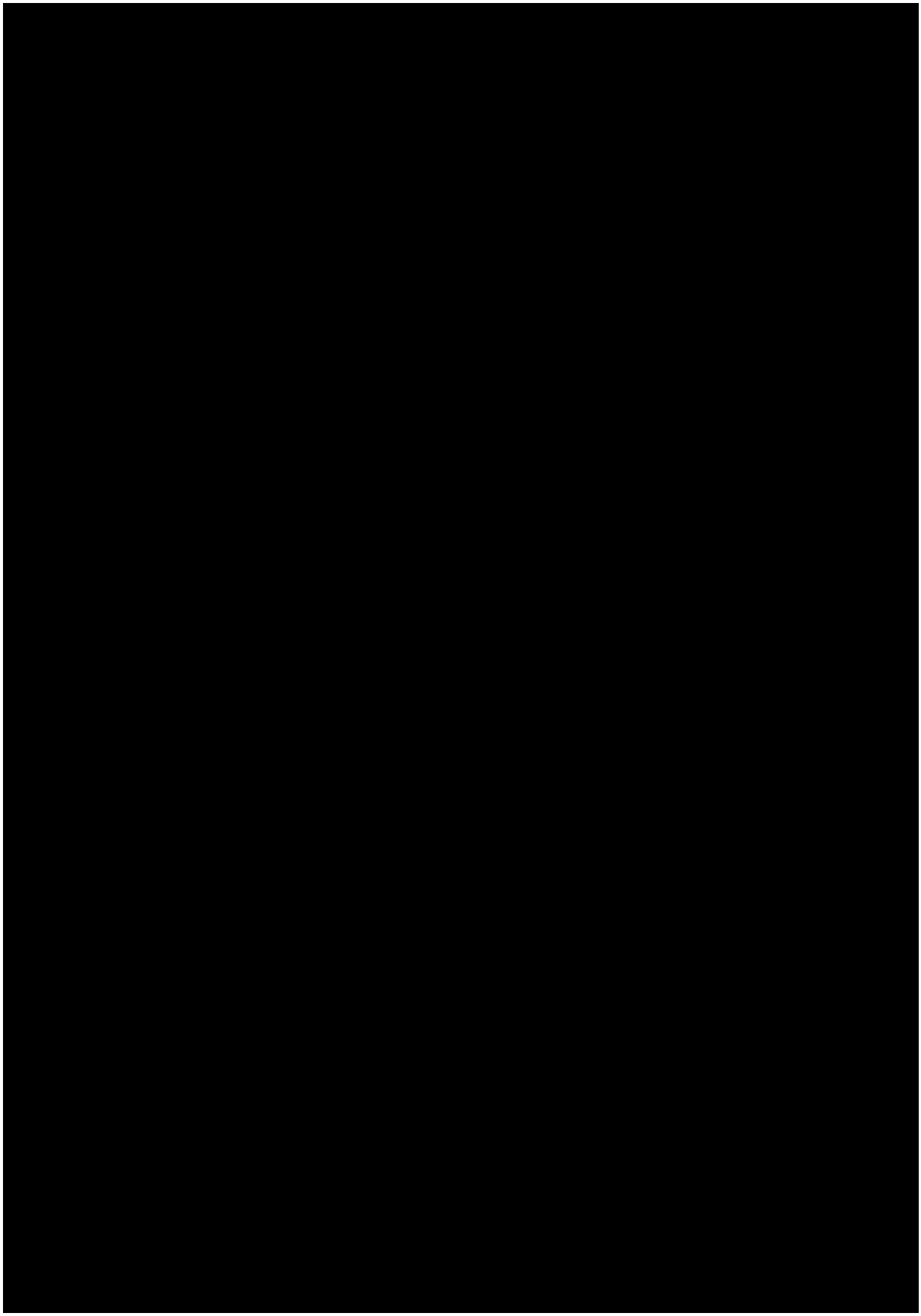

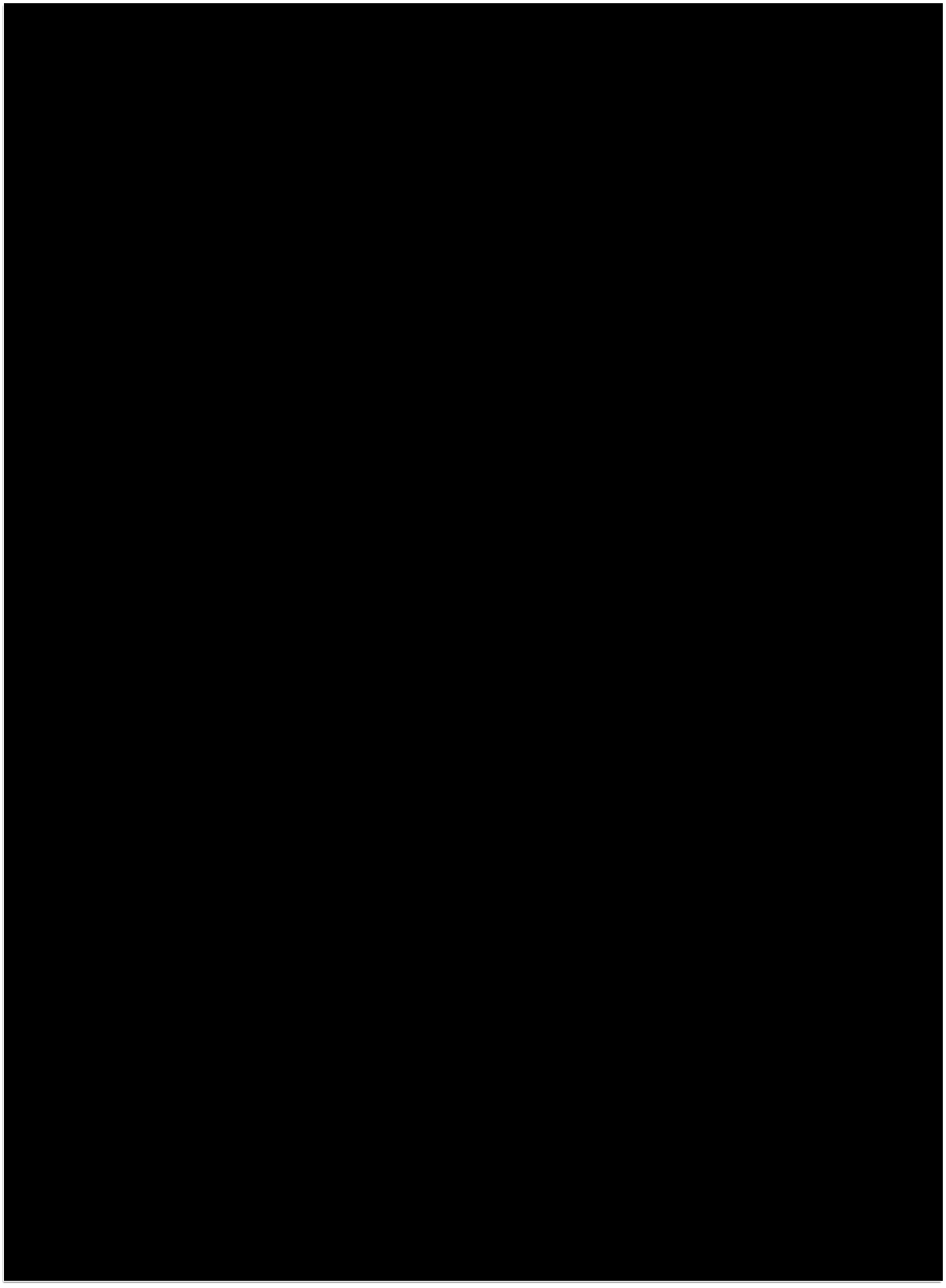

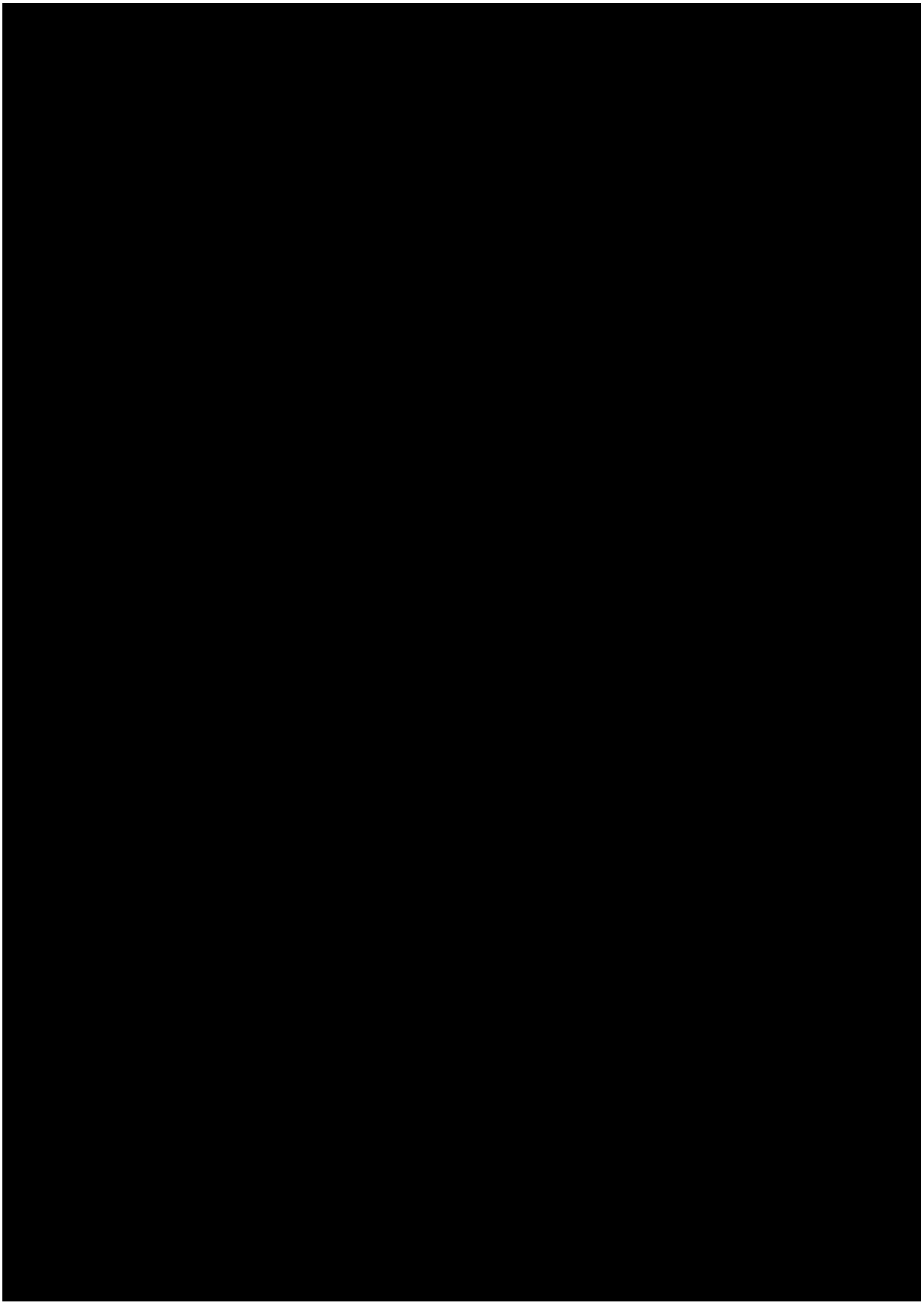

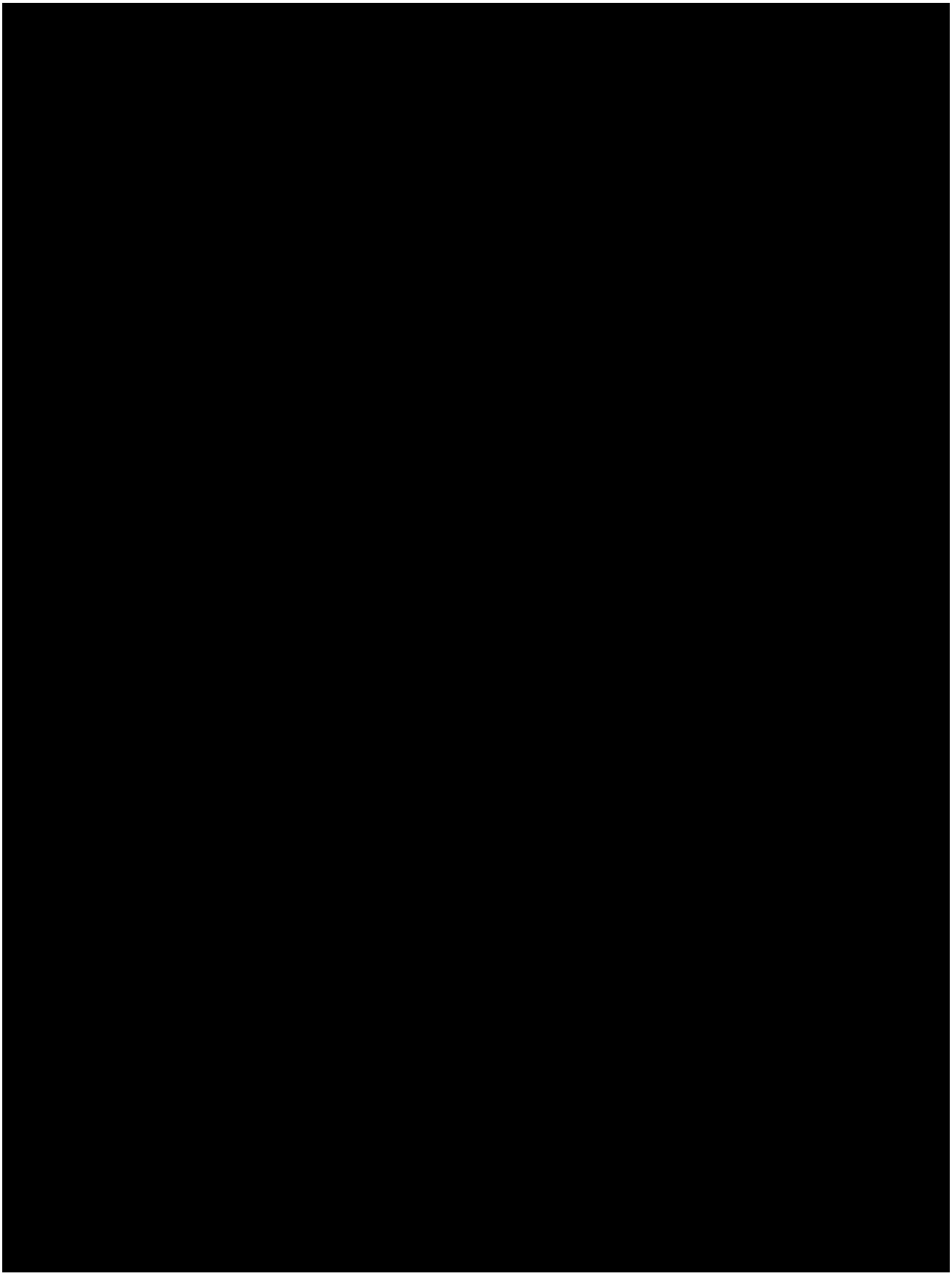

10.12 APPENDIX 12: ABBREVIATIONS

AChEI:	acetylcholinesterase inhibitor
AChR:	acetylcholine receptor
ADL:	activities of daily living
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AUC:	area under the curve
BCR:	B-cell receptor
BTK:	Bruton's tyrosine kinase
BUN:	blood urea nitrogen
CFR:	Code of Federal Regulations
CI:	confidence interval
CIOMS:	Council for International Organizations of Medical Sciences
COVID-19:	coronavirus disease 2019
CPK:	creatine phosphokinase
CRF:	case report form
CS:	corticosteroid(s)
CSICF:	core study informed consent form
C-SSRS:	Columbia Suicide Severity Rating Scale
CTCAE:	common terminology criteria for adverse event(s)
CYP:	cytochrome
DB:	double-blind
DILI:	drug-induced liver injury
DTP:	direct-to-patient
ECG:	electrocardiogram
eCRF:	electronic case report form
EOS:	end of study
EOT:	end of treatment
[redacted]	
EU:	European Union
FcRn:	neonatal Fc receptor
FcγR:	Fc-gamma receptor
FcεR:	Fc-epsilon receptor
FSH:	follicle-stimulating hormone
FU:	follow-up
GCP:	good clinical practice
GDPR:	General Data Protection Regulation
gMG:	generalized myasthenia gravis
[redacted]	

HIV:	human immunodeficiency virus
HRT:	hormone replacement therapy
IA:	interim analysis
IB:	Investigator's Brochure
ICE:	intercurrent event
ICF:	informed consent form
ICH:	International Council for Harmonisation
IDMC:	Independent Data Monitoring Committee
IEC:	Independent Ethics Committee
Ig:	immunoglobulin
IgG:	immunoglobulin G
IgM:	immunoglobulin M
IMP:	investigational medicinal product
IMP:	investigational medicinal product
IRB:	Institutional Review Board
IST:	immunosuppressive treatment
ITT:	intention-to-treat
IUD:	intrauterine device
IUS:	intrauterine hormone-releasing system
IVIg:	intravenous immunoglobulin
MG:	myasthenia gravis
MG-ADL:	myasthenia gravis-activities of daily living
MGFA:	myasthenia gravis foundation of America
[redacted]	
MGII:	myasthenia gravis impairment index
MG-QoL15:	myasthenia gravis-quality of life 15-item scale
mITT:	modified intention-to-treat
MMRM:	mixed-effect model with repeated measures
MS:	multiple sclerosis
MuSK:	muscle-specific kinase
NCI:	National Cancer Institute
NSAIDs:	nonsteroidal anti-inflammatory drugs
OCS:	oral corticosteroid(s)
OLE:	open-label extension
PCSA:	potentially clinically significant abnormalities
PD:	pharmacodynamic(s)
pEOT:	premature end of treatment
[redacted]	
PK:	pharmacokinetic(s)
QMG:	quantitative myasthenia gravis
QoL:	quality of life
QTcF:	QT interval corrected using Fridericia's formula
RMS:	relapsing multiple sclerosis
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	standard deviation

SoA:	schedule of activities
SoC:	standard of care
SUSAR:	suspected unexpected serious adverse reaction
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
TLR:	toll-like receptor
ULN:	upper limit of normal
US:	United States
[redacted]	
WOCBP:	woman of childbearing potential

10.13 APPENDIX 13: PROTOCOL AMENDMENT HISTORY

10.13.1 Amended protocol 03 (23 May 2022)

This amended protocol (amendment 03) was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary driver for this amended protocol is to update liver related exclusion criteria and monitoring to mitigate risk of drug-induced liver injury.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Document history	Date of original protocol corrected.	Correction of error.
1.1 Synopsis (Objectives and endpoints) 3 Objectives and endpoints (Secondary)	MG-QoL 15 endpoint wording corrected. Homogenization of wording: 'reduction' changed to 'improvement (reduction)'. "Over time" replaced by "at EOT (timeframe: baseline, up to Week 130)" in secondary OLE endpoints of clinical improvement. Daily dose of OCS over time (secondary endpoint in the OLE) wording updated.	Correction of error. Update. Clarification.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis (Statistical considerations) 9.3.2 Primary endpoint	Analysis method for primary endpoint updated based on the FDA feedback on the handling of participants using rescue therapy. 'Sensitivity analyses' replaced for 'supplementary analyses'.	To optimize analysis methodology. Correction of error.
1.1 Synopsis (Statistical considerations) 9.3.3 Secondary endpoints	Analysis of secondary endpoints updated based on changes to the analysis of primary endpoints. 'Sensitivity analyses' replaced for 'supplementary analyses'.	Update. Correction of error.
[redacted]		
1.1 Synopsis	Scientific Advisory Committee added.	Correction of error.
1.3 Schedule of activities (SoA)	'Medical/surgical history' & 'Past and current medical conditions' rows combined as "Medical and surgical history".	Clarification.
	[redacted]	Correction of error.
	Check mark for 12-lead ECG added in the last column since this visit may serve as the EOS visit.	Correction of error.
[redacted]		

Section # and Name	Description of Change	Brief Rationale
[redacted]		
2.3 Benefit/Risk Assessment	Text related to drug-induced liver injury identified in an ongoing Phase 3 trial added.	Update.
[redacted]		
4.1 Overall Design	Wording related to FU safety visits in the OLE period updated.	Correction of error.
5.1 Inclusion criteria	I 07: Deletion of the following text for WOCBP female participants: “at a minimum after the last study intervention”.	Clarification.
5.2 Exclusion criteria	E 03 TB related wording updated.	Clarification.
[redacted]		
8.1.1.3 Myasthenia Gravis Impairment Index (MGII)	Definition updated.	Correction of error.
9.2 Populations for analyses Table 4	Description of mITT population updated.	Clarification.
9.3.1 General considerations	Definitions of baseline values for efficacy parameters and the on-treatment period for the DB and OLE periods clarified.	Clarification.

Section # and Name	Description of Change	Brief Rationale
[redacted]		
10.13 Appendix 13: Protocol amendment history	Updated.	Update.
Throughout the document	Reformatting of existing content when necessary. Minor, editorial, stylistic changes as necessary. Updated table of contents, abbreviations, section numbers, references as necessary.	Update in accordance with Sponsor's standards.

10.13.2 Amended protocol 02 (03 November 2021)

In Europe, this amended protocol (amendment 02) was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reason for this amendment was response to a HA request.

Section # and Name	Description of Change	Brief Rationale
Document history	"UK" changed to "All" for Countries impacted by amended protocol 01. Footnote added to table.	Correction of error.
1.1 Synopsis	"Principal Investigator" changed to "Investigator" for permission for rescue therapy.	Correction of error.

Section # and Name	Description of Change	Brief Rationale
1.0 Synopsis 4.1 Overall design 4.2 Scientific rationale for study design 6.8.3 Rescue therapy 7.1.1 Permanent discontinuation	Use of rescue therapy during DB and OLE periods clarified.	Clarification.
1.2 Schema	Clarification of follow-up visit.	Clarification
1.3 Schedule of activities (SoA)	Monthly pregnancy testing to be performed in all countries.	HA request.
	IRT contact added to EOT/pEOT visit. MGFA-PIS added to pEOT visit. ECG added to pEOT visit. EOT changed to EOS in footnote d. “Some assessments are possible” corrected to “some assessments are not possible” in footnote f. Week 74 physical exam corrected to Week 78 in footnote k. Monthly pregnancy testing limited to WOCBP in footnote m.	Correction of errors.
2.3.1 Risk assessment	Reworded statement about tolebrutinib being generally safe and well tolerated.	Clarification.
[redacted]		
8.1.1 Clinical outcome assessments	Use of electronic versus paper assessments clarified.	Clarification.
8.3.7 Adverse events of special interest	Removed mention of NIMPs because this study has no NIMPs.	Clarification.
[redacted]		
10.2 Appendix 2: Clinical laboratory tests	Alkaline phosphatase and total added to Table 5, Protocol required laboratory tests. E 04 was corrected to E 03 in footnote d.	Correction of errors.
	Monthly urine testing for pregnancy added to footnote c of Table 5.	HA request.

Section # and Name	Description of Change	Brief Rationale
[redacted]		
10.8.2 Pregnancy test in EU countries	Section deleted because monthly testing will be required in all countries.	HA request.
10.13 Protocol amendment history	Updated.	Update.
11 References	New reference added and citation numbering updated accordingly.	Update.
Throughout the document	Reformatting of existing content when necessary. Minor, editorial, stylistic changes as necessary. Update table of contents, section numbers, footnote numbers, references as necessary.	Update in accordance with Sponsor's standards.

10.13.3 Amended protocol 01 (20 October 2021)

In Europe, this amended protocol (amendment 01) was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reason for this amendment was response to a Health Authority (HA) request.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Clinical laboratory tests	Direct and total bilirubin were added to Table 5, Protocol required laboratory tests.	Correction of error.

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