CLINICAL STUDY PROTOCOL

Project Number:	GLPG3970
Study Number:	GLPG3970-CL-210
Study Title	A randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of GLPG3970, administered orally for 6 weeks in adult subjects with moderately to severely active ulcerative colitis
Short Study Title	A study evaluating the effects of GLPG3970 given as an oral treatment for 6 weeks in adults with ulcerative colitis
Clinical Study Phase:	2
Protocol Version:	1.0
Date:	2-Jul-2020
Status	Final
EudraCT No:	2020-000659-11 CT.gov No: to be confirmed
IND No:	not applicable
Sponsor:	Galapagos NV, Generaal De Wittelaan L11 A3, 2800 Mechelen, Belgium
Medical Leader:	[redacted]
General Protocol	

Confidentiality Statement

EMERGENCY CONTACT INFORMATION

In case of a **serious adverse event (SAE)**, a special situation (see Section 11.1.6) or in case of **pregnancy** during the clinical study the investigator must report this immediately, and under no circumstances later than 24 hours following the knowledge of the event as follows:

E-mail: [redacted]

or

SGS Medical Affairs SAE Fax [redacted]

In case of medical questions during the course of the study, the investigator must contact the contract research organization (CRO) medical monitor or, if unavailable, his/her back-up and the sponsor scientific leader for all scientific, protocol and IP related questions:

CRO medical monitor:

[redacted] Medical Emergency Contact Center

Phone: [redacted]

[redacted] (alternative number)

Sponsor medical leader:

[redacted]

Sponsor contact number:

[redacted]

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CLINICAL STUDY PROTOCOL HISTORY

Clinical Study Protocol (CSP)/Amendment #	**Date**	**Main Rationale** **General/Country-Specific**
CSP Version 1.0	2 July 2020	Initial CSP Version General

SUMMARY OF CHANGES

Not applicable because this is the initial clinical study protocol (CSP).

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

AE	adverse event
ALT	alanine aminotransferase
5-ASA	5-aminosalicylate
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BCRP	breast cancer resistance protein
BMI	body mass index
CI	confidence interval
Cl	clearance
ClCr	creatinine clearance
C_{max}	maximum observed plasma concentration
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CSP	clinical study protocol
CTCAE	Common Terminology Criteria for Adverse Events
$C_{through}$	plasma trough concentration
CYP	cytochrome P450
DTP	Direct to Patient
[redacted]	[redacted]
[redacted]	[redacted]
ECG	electrocardiogram

ED	early discontinuation
ES	endoscopy subscore
ESP	European Society of Pathology
EU	European Union
F	absolute oral bioavailability
FIH	first-in-human
FSH	follicle stimulating hormone
GALT	gut-associated lymphoid tissue
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HbA1c	glycosylated hemoglobin
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
IB	investigator's brochure
IBD	inflammatory bowel disease
[redacted]	[redacted]
[redacted]	[redacted]
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

IL	interleukin
IP	investigational product
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
ISF	investigator site file
IXRS	interactive voice/web response system
JAK	Janus kinase
LFT	liver function test
LPS	lipopolysaccharide
LRV	lower reference value
MCS	Mayo Clinic Score
MMRM	Mixed Models for Repeated Measure
NAG	N-acetyl-β-D-glucosaminidase
NOAEL	no-observed-adverse-effect level
OATP	organic anion transporter
OCT	organic cation transporter
PBMC	peripheral blood mononuclear cells
[redacted]	[redacted]
PGA	physician's global assessment
P-gp	permeability-glycoprotein
PK	pharmacokinetic(s)
q.d.	once daily
QMP	Quality Management Plan

RB	rectal bleeding
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SF	stool frequency
SI	international system of units
SIK	salt-inducible kinase
SoC	standard-of-care
spp	species
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
Th	helper T cell
TMF	Trial Master File
TNFα	tumor necrosis factor alpha
T_{reg}	regulatory T cell
TV	target value
UC	ulcerative colitis
[redacted]	[redacted]
ULN	upper limit of normal range
[redacted]	[redacted]
V_{ss}	volume of distribution at steady state
WBC	white blood cell

WOCBP	women of childbearing potential

Definition of Terms

BMI	body mass index Weight (kg) / (height [m])^2
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted] [redacted]
[redacted]	[redacted] [redacted]
[redacted]	[redacted] OR [redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted] [redacted]

QTcF	QT interval corrected for heart rate using Fridericia's formula: $QTcF = QT/RR^{1/3\ QT}$ RR = the interval from the onset of one QRS complex to the onset of the next QRS complex
QTv	QT interval corrected by heart rate using the van de Water formula

1. CLINICAL STUDY PROTOCOL SYNOPSIS

Title of Study

A randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of GLPG3970 administered orally for 6 weeks, in adult subjects with moderately to severely active ulcerative colitis

Short Title of Study

A study evaluating the effects of GLPG3970 given as an oral treatment for 6 weeks in adults with ulcerative colitis

Phase of Development: 2

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of GLPG3970 compared to placebo on the signs and symptoms of ulcerative colitis (UC) in subjects with moderately to severely active UC.	Change from baseline in total Mayo Clinic Score (MCS) at Week 6.
Secondary	
To evaluate the safety and tolerability of GLPG3970 compared to placebo in subjects with moderately to severely active UC.	Number, incidence, and severity of treatment-emergent adverse events (TEAEs).
To characterize the pharmacokinetics (PK) of GLPG3970 in subjects with moderately to severely active UC.	Observed GLPG3970 plasma trough concentrations (C_{trough}).

[redacted]

[redacted]

Planned Number of Subjects

The study is planned to randomize 30 subjects in a 2:1 ration (20 subjects planned to receive GLPG3970 and 10 subjects planned to receive placebo).

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multi-center parallel-group study evaluating GLPG3970 in adult subjects with moderately to severely active UC. In this study, subjects will receive 1 dose level of GLPG3970 (400 mg once daily [q.d.]).

A schematic diagram of clinical study design, procedures and stages is provided below.

Study Duration

The subjects will be in the study for a duration of 13 weeks (screening to follow-up): up to 5 weeks of screening, 6 weeks of treatment, and 2 weeks of follow-up.

Main Criteria for Inclusion and Exclusion

Main Inclusion Criteria

1. Subject must be able and willing to comply with the clinical study protocol (CSP) requirements and must sign and date the informed consent form (ICF) as approved by the Independent Ethics Committee (IEC) / Institutional Review Board (IRB), prior to any screening evaluations.
2. Subjects must be ≥18 and <65 years of age, on the date of signing the ICF.
3. Documented diagnosis of UC of ≥3 months. The criteria for documentation of UC diagnosis based on endoscopy will be medical record documentation, and/or a colonoscopy report dated ≥3 months before screening, which shows features consistent with UC.
4. Treatment-experienced subjects with moderately to severely active disease, who have either previously demonstrated inadequate clinical response, loss of response, or intolerance to at least 1 course of standard-of-care (SoC) therapy for UC (i.e. steroids [oral or parenteral, including but not limited to prednisone, prednisolone, budesonide], 5-aminosalicylate [5-ASA] derivatives [including but not limited to mesalamine, sulfasalazine], anti-metabolites [including but not limited to azathioprine, 6 mercaptopurine, methotrexate], anti-TNF agents, anti-integrins, Janus kinase [JAK] inhibitors), as confirmed by the investigator.
5. Moderately to severely active UC as determined at screening by:
   a. Centrally-read endoscopic evidence of disease activity (MCS-ES ≥2 OR UCEIS ≥4) with a minimum disease extent of 15 cm from anal verge; AND
   b. MCS SF subscore ≥1; AND
   c. MCS RB subscore ≥1.
6. Subjects currently receiving the following SoC therapies for UC are eligible providing they have been on a stable dose for the designated period of time and are anticipated to be stable throughout the study:
   a. oral corticosteroids (prednisone ≤20 mg/day or equivalent or budesonide ≤3 mg/day) stable dose for at least 2 weeks prior to first IP dosing.
   b. oral 5-ASA compounds (mesalamine ≤4 g/day or sulfasalazine ≤4 g/day) stable dose for at least 4 weeks prior to first IP dosing.
   c. oral thiopurines (azathioprine ≤2.5 mg/kg/day and 6-mercaptopurine 1.5 mg/kg/day) stable dose for at least 12 weeks prior to first IP dosing, or methotrexate ≤20 mg/week, stable dose for at least 12 weeks prior to first investigational product (IP) dosing.

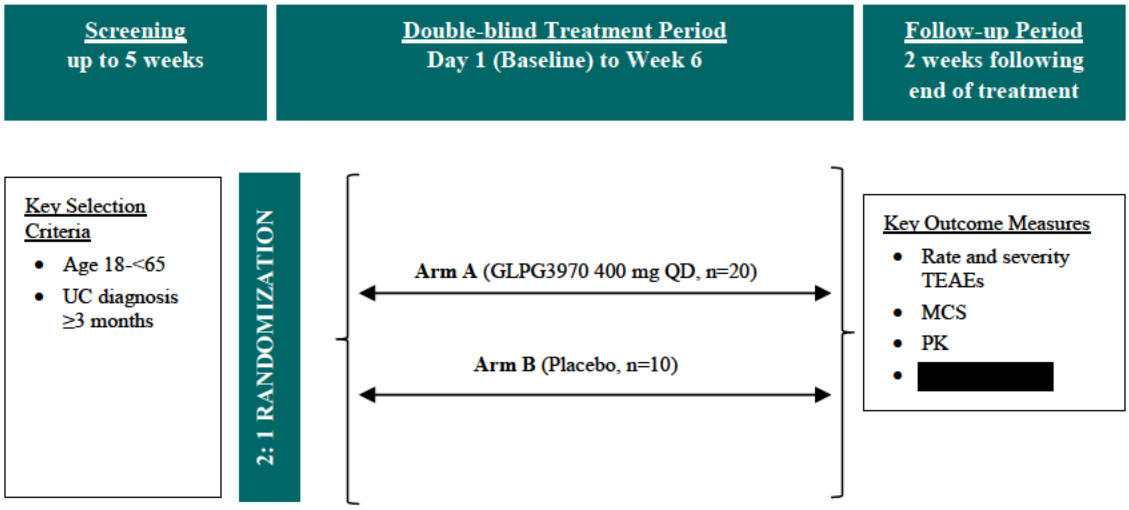
Main Exclusion Criteria

1. Diagnosis of Crohn's disease, indeterminate colitis, ischemic colitis, fulminant colitis, or toxic megacolon.
2. Prior surgical intervention for UC (e.g. colectomy, partial colectomy, ileostomy or colostomy) or likely requirement for surgery for UC, during the study.
3. History or evidence of incompletely resected colonic mucosal dysplasia.
4. Exhibit acute severe UC per the following criteria:
   a. bloody diarrhea ≥6/day
      AND

b. any of the following signs of systemic toxicity:
Body temperature (oral or tympanic) ≥37.8°C
OR
Resting pulse (after 5 min seated position) >90 beats per min
OR
hemoglobin <105 g/L,
OR
erythrocyte sedimentation rate >30 mm/h
OR
C-reactive protein (CRP) >30 mg/L.

5. Screening stool sample positive for ova and/or parasites, Clostridium difficile toxin, Escherichia coli, Salmonella species (spp), Shigella spp, Campylobacer spp or Yersinia spp.
6. Subject testing positive at screening for SARS-CoV-2 infection as detected by real time polymerase chain reaction (RT-PCR), subjects presenting any signs or symptoms as detected at baseline following careful physical examination (e.g. cough, fever, headaches, fatigue, dyspnea, myalgia, anosmia, dysgeusia, anorexia, sore throat, others) or reporting any signs and symptoms for the preceding 2 weeks, or subjects who have been exposed to individuals with confirmed or suspected diagnosis of SARS-CoV-2 within 2 weeks prior to baseline. In addition, any other locally applicable standard diagnostic criteria may also apply to rule out SARS-CoV-2 infection.

Treatment and Treatment Schedule



Investigational Medicinal Product, Dosage, and Mode of Administration

GLPG3970 will be provided as a powder and solvent for oral solution, to be reconstituted prior to use. The final dosage form for administration is an oral solution containing 400 mg of the active pharmaceutical ingredient G1567970 (G1567970 is the compound code for GLPG3970).

A placebo powder and solvent for oral solution, to be reconstituted prior to use, will also be provided.

Statistical Analysis

Safety Analysis

All safety analyses will be performed using the Safety Analysis Set, consisting of all screened subjects who received at least 1 dose of IP. All safety data collected on or after the first dose of IP administration up to the last contact after the last dose of IP, unless specified otherwise, will be summarized by treatment group according to the IP received. Clinical safety will be addressed by assessing adverse events (AEs), laboratory assessments, physical examinations, vital signs, and 12-lead electrocardiograms (ECGs).

Efficacy Analysis

All efficacy analyses will be performed using the Full Analysis Set, consisting of all randomized subjects who received at least 1 dose of IP. Continuous efficacy endpoints, including the primary endpoint: mixed model for repeated measures to compare treatment groups, with a 90% confidence interval (CI) of the treatment difference at each time point. Binary efficacy endpoints: Binary efficacy endpoints will be presented with a 90% exact CI of the treatment difference at each time point. For the primary efficacy endpoint: go/consider/stop methodology will be used additionally to provide further insight in the treatment effect.

PK Analysis

GLPG3970 plasma concentrations will be listed and predose concentrations (C_{trough}) will be summarized descriptively.

All observed GLPG3970 plasma concentrations will be analyzed using a population PK approach to characterize the PK profile of GLPG3970 and determine the PK parameters (e.g. clearance and volume of distribution) and their associated variability. The influence of covariates may be investigated.

[redacted]

2. INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease affecting the mucosal lining of the large intestine. Characteristic signs and symptoms include bloody diarrhea, frequent bowel movements, and may include abdominal pain and weight loss. The highest prevalence (per 100000 persons) of UC is reported in Europe (43 to 412 in Western European countries, 91 to 505 in Northern European countries), in North America (140 to 286) and in Oceania (145 to 196). Currently available therapies for the treatment of moderate to severe disease result in fewer than 50% of subjects achieving remission in either induction or maintenance (Feagan, et al., 2013; Sands, et al., 2019; Rutgeerts, et al., 2005; [redacted]. Hence, there is a need for novel efficacious therapies with a different mechanism of action for the treatment of UC. Oral, small-molecule inhibitors of intracellular kinases might bring therapeutic benefit in a wide range of inflammatory diseases and could address this need.

GLPG3970 has a dual mechanism of action, with the potential to improve upon the currently available treatments, via the induction of immunoregulatory mechanisms in addition to its anti-inflammatory properties. GLPG3970 is an oral, selective, small-molecule serine/threonine salt-inducible kinase (SIK) 2 and 3 inhibitor. These kinases provide a molecular switch in the control of pro- and anti-inflammatory cytokine production. Inhibition of these target blocks the production of pro-inflammatory cytokines (tumor necrosis factor [TNF]α, interleukin [IL] 12) and increases IL-10 levels, which has a tolerogenic effect, by activated macrophages and dendritic cells, thereby, converting the inflammatory state of these cells toward regulatory and tolerogenic phenotypes. In three different mouse models of inflammatory bowel disease, treatment with GLPG3970 reduced disease activity.

For more details refer to the latest version of the investigator's brochure (IB) and its relevant updates/addenda.

This clinical study will be conducted in compliance with this CSP, the current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (ICH-GCP) Guideline E6, and applicable local ethical and legal requirements (see also Section 12).

2.1. Background - Non-clinical Studies

2.1.1. Nonclinical Pharmacokinetics

[redacted]

[redacted]

2.1.2. Safety pharmacology

[redacted]

2.1.3. General toxicology

[redacted]

2.1.4. Genotoxicity

[redacted]

2.1.5. Embryo-fetal Development Toxicity

The safety of GLPG3970 for use during pregnancy has not been established. [redacted]

[redacted]

[redacted]

2.1.6. Phototoxicity

[redacted]

2.2. Background - Clinical Studies

[redacted]

[redacted]

[redacted]

[redacted]

3. CLINICAL STUDY OBJECTIVES

3.1. Primary Objective

- To evaluate the effect of GLPG3970 compared to placebo on the signs and symptoms of UC in subjects with moderately to severely active UC.

3.2. Secondary Objective

- To evaluate the safety and tolerability of GLPG3970 compared to placebo in subjects with moderately to severely active UC.
- To characterize the PK of GLPG3970 in subjects with moderately to severely active UC.

3.3. Other Objective

[redacted]

4. ENDPOINTS

4.1. Primary Endpoint

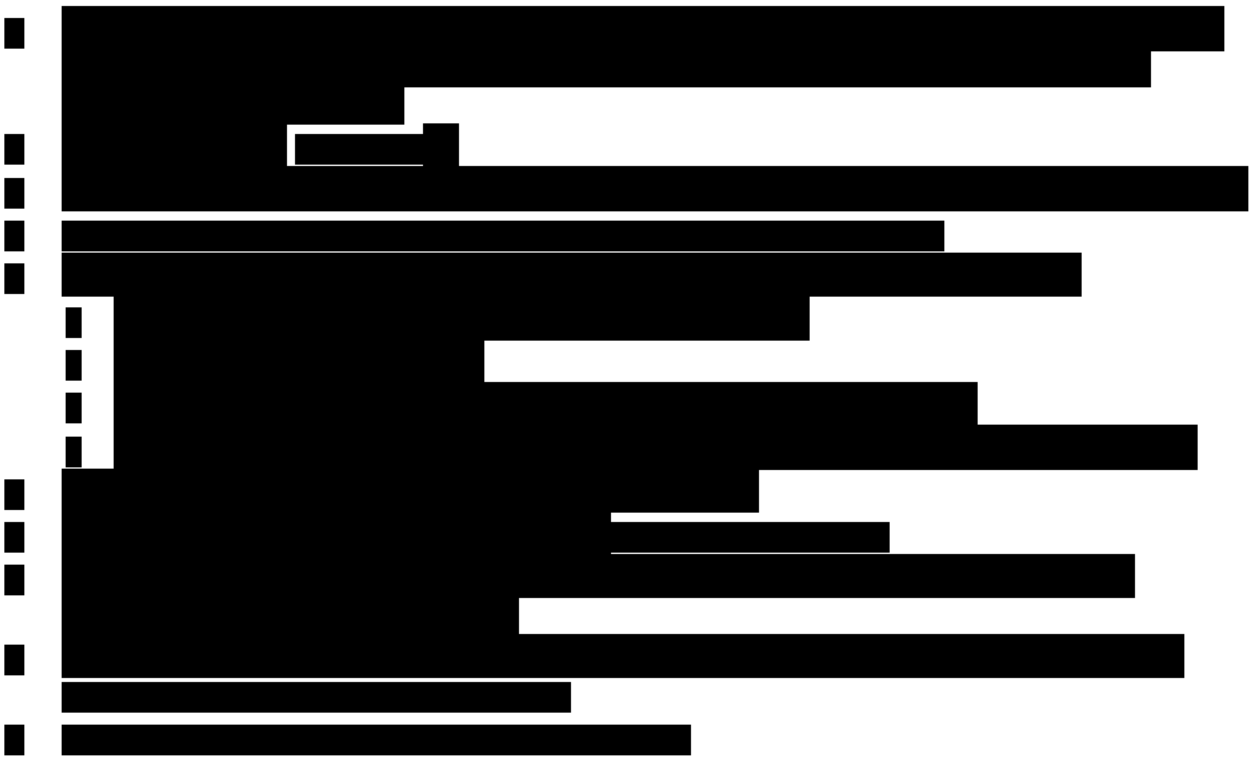
- Change from baseline in total Mayo Clinical Score (MCS) at Week 6.

4.2. Secondary Endpoints

- Number, incidence, and severity of treatment-emergent adverse events (TEAEs).
- Observed GLPG3970 plasma trough concentrations (C_{trough}).

4.3. Other Endpoints

[redacted]



5. INVESTIGATIONAL PLAN

5.1. Clinical Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multi-center parallel-group study to evaluating GLPG3970 in adult subjects with moderately to severely active UC. In this study, subjects will receive 1 dose level of GLPG3970 (400 mg once daily [q.d.])

The study is planned to randomize 30 subjects in a 2:1 ratio (20 subjects planned to receive GLPG3970 and 10 subjects planned to receive placebo).

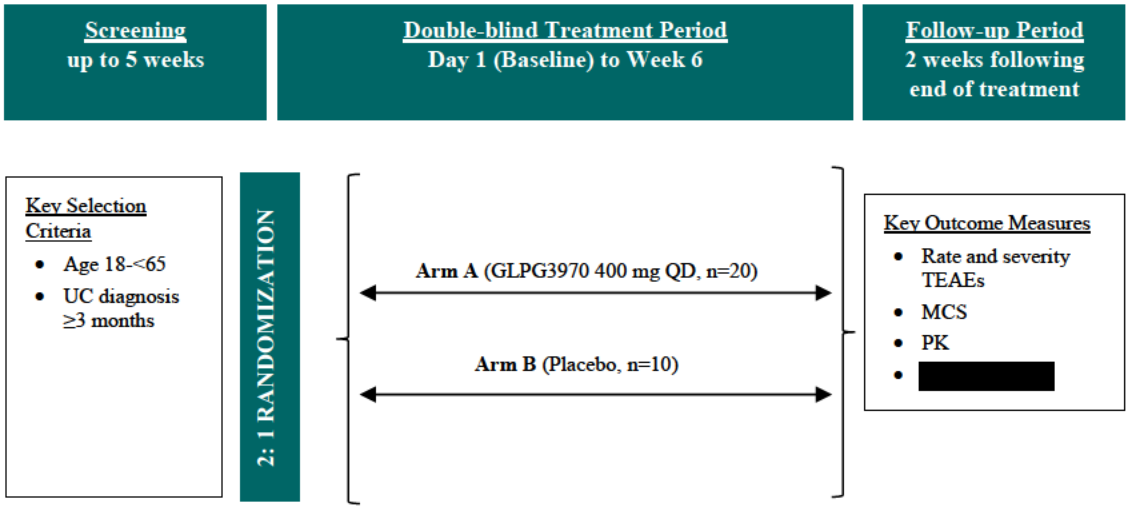
The study will consist of 3 study periods:

- Screening period: up to 5 weeks with 2 study visits, with a maximum of 2 weeks from screening visit 2 until randomization.
- Double-blind treatment period: 6 weeks with 4 study site visits (Days 1, 15, 29, and 43 or early discontinuation [ED]) and 1 telephone call (Day 8).
- Follow-up period: 2 weeks with 1 study visit.

The subjects will be in the study for a duration of a maximum of 13 weeks (screening to FU) and will receive oral GLPG3970 or placebo, as a reconstituted oral solution, once daily (q.d.) for 6 weeks.

A schematic diagram of clinical study design, procedures and stages is provided in Figure 1.

Figure 1: Schematic Diagram



For detailed information regarding dosage form, packaging, and labeling of the investigational medicinal product (IP) refer to Section 7.2, "Dosage and Administration" and Section 7.3, "Packaging, Labeling and Distribution".

5.2. Start and End of Study Definitions

The study start is defined when the first informed consent form (ICF) is signed. The end of the study is reached when the last FU visit, as planned according to the Schedule of Activities (Section 8.11), for the last subject is performed.

5.3. Clinical Study Design Rationale

UC is a chronic inflammatory disease affecting the mucosal lining of the large intestine. GLPG3970 may decrease disease activity through induction of immunoregulatory mechanisms in addition to its anti-inflammatory properties. GLPG3970 demonstrated strong effects on disease activity in 3 different types of preclinical inflammatory bowel disease (IBD) models. Prophylactic treatment with GLPG3970 showed a strong and significant dose-dependent protective effect in a murine dextran sodium sulfate-induced colitis model. Treatment with GLPG3970 showed a strong and significant protective effect in a T-cell transfer model. In addition, GLPG3970 induced a significant decrease of TNFα levels coupled with an increase of IL-10 protein levels; the relative ratio of regulatory T cells (T_{reg})/ helper T cells (Th)17 was significantly increased compared to the vehicle control in this model. The efficacy with GLPG3970 was also demonstrated in an Mdr1a-deficient model.

Additional information on experimental IBD models can be found in the latest version of the IB.

The use of a placebo arm in this type of design has an important value, as "placebo-response" is known to occur during clinical studies. Although the reported magnitude of this response varies from study to study, it can be substantial. Hence, the addition of a placebo arm enables a control for potential influences derived from the natural course of UC and other effects that are inherent

to overall medical care. The use of placebo for 6 weeks in a 2:1 ratio is deemed acceptable and justified given the limited treatment duration. Low stable, doses of prednisone and MTX are allowed as background therapy to avoid high placebo-response and side effects due to higher doses of steroids.

The currently registered therapeutic options have shown improvement in the clinical symptomatology early in the treatment (Week 2-4) with statistical significance of the clinical effect demonstrated at about 6-8 weeks (Vedolizumab. Summary of Product Characteristics.; Golimumab. Summary of Product Characteristics.). Keeping in mind the early stage of development and the limited safety data, it is therefore considered that the proposed 6-week study duration, is sufficient to assess if the compound is well tolerated and if there is any signal of efficacy.

5.4. Dosing Rationale

The dose of 400 mg q.d. GLPG3970 will be used in this study. [redacted]

5.5. Potential Risks and Benefits

GLPG3970 has been studied in a nonclinical setting (Section 2.1) and is being studied in a FIH study (Section 2.2) where the single and multiple ascending dose parts of the study are completed up to the dose of 400 mg q.d. GLPG3970 was well tolerated at all dose levels studied in the FIH study. Study GLPG3970-CL-210 is the first study where GLPG3970 is being administered to subjects with moderately to severely active UC.

[redacted]

GLPG3970 has a novel dual mechanism of action, which is intended to restore the balance of the immune system by reducing several mediators of inflammation and by improving immune-regulatory mechanisms that may be impaired in autoimmune diseases such as, for example, RA, psoriasis and inflammatory bowel disease. Thus, this may weaken the immune response and can potentially increase subject's risk to developing infections (opportunistic infections, SARS-CoV-2, etc). Careful monitoring and reporting of signs and symptoms is therefore required, to enable prompt medical evaluation and pharmacological or clinical intervention.

Based on the mechanism of action of GLPG3970 and its potential to control pro-inflammatory and immunomodulating cytokines, such as TFNα and IL-10, an improvement of clinical symptoms of UC may be derived. As additional safety measure, a generally stable population of patients (from the perspective of the disease, associated medical conditions, and previous use [dose and time] of the current standard of care medication) are allowed to participate in the study. Treated subjects in the study may or may not derive benefit from administration of the IP.

Risk Mitigation

Mitigation measures have been taken to ensure safety of the subjects targeting population selection, dose, concomitant medications, and safety surveillance on certain laboratory parameters and biomarkers. Information on important safety risks is included in the latest version of the IB and ICF.

In the forthcoming study subjects' risk will be minimized by implementing conservative eligibility criteria, including RT-PCR testing to exclude subjects with SARS-CoV-2, by standard laboratory tests, by collecting TEAEs throughout the study, and monitoring of subjects for infection symptoms. Any potential negative effects of GLPG3970 will be carefully assessed through regular physical assessments and laboratory monitoring that will happen at every visit. Laboratory alerts will be set up for the study in order to early inform the study investigator and the Sponsor on highly abnormal laboratory values (severity Grade 3 and above). A data safety monitoring committee will monitor unblinded data.

- [redacted]
- The selection of the dose proposed for this study lies within the exposure safety limits defined based on nonclinical safety studies, and exposures previously shown to be safe and well tolerated in healthy subjects.
- [redacted]

For more details refer to the latest version of the IB and its relevant updates/addenda.

Subjects at risk of tuberculosis, HIV positive subjects, subjects testing positive for hepatitis B or C and subjects tested positive for SARS-CoV-2 are excluded from the study. Given this study may be performed during a SARS-CoV-2 pandemic, the age limit of participants was set to 65 years of age and appropriate measures should be taken to minimize the risk of SARS-CoV-2 infection for subjects participating in the study as well as study site personnel. Local guidelines to prevent SARS-CoV-2 infection should be adhered to and a leaflet should be made available for all subjects detailing the SARS-CoV-2 safety measures to be taken.

In case a randomized subject is not available to attend a scheduled study visit on site due to SARS-CoV-2 travel restrictions, a phone call or a televisit may be conducted instead. It is strongly recommended to conduct planned study assessments for the applicable visit as per protocol as much as possible. If possible and if local regulations allow and the subject agrees, trained study staff or trained personnel are encouraged to collect study assessments at the study subjects' home or local facility if social distancing and hygiene rules can be applied.
Only staff trained in conducting the protocol planned assessments are authorized to perform home or local facility visits assessments and the alternative arrangements need to be adequately documented. Direct to Patient (DTP) shipments are possible if needed. Subjects presenting with signs and symptoms of infection, including SARS-CoV-2 infection should immediately contact the site investigator, who should inform the sponsor's medical responsible as soon as possible, and SARS-CoV-2 testing should be performed.

6. CLINICAL STUDY POPULATION

6.1. Inclusion Criteria

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

1. Subject must be able and willing to comply with the CSP requirements and must sign and date the ICF as approved by the Independent Ethics Committee (IEC) / Institutional Review Board (IRB), prior to any screening evaluations.

2. Subjects must be ≥18 and <65 years of age, on the date of signing the ICF.

3. Documented diagnosis of UC of ≥3 months. The criteria for documentation of UC diagnosis based on endoscopy will be medical record documentation, and/or a colonoscopy report dated ≥3 months before screening, which shows features consistent with UC.

4. Treatment-experienced subjects with moderately to severely active disease, who have either previously demonstrated inadequate clinical response, loss of response, or intolerance to at least 1 course of standard-of-care (SoC) therapy for UC (i.e., steroids [oral or parenteral, including but not limited to prednisone, prednisolone, budesonide], 5-aminosalicylate [5-ASA] derivatives [including but not limited to mesalamine, sulfasalazine], anti-metabolites [including but not limited to azathioprine, 6 mercaptopurine, methotrexate], anti-TNF agents, anti-integrins, Janus kinase [JAK] inhibitors), as confirmed by the investigator.

5. Moderately to severely active UC as determined at screening by:
   a. Centrally-read endoscopic evidence of disease activity (MCS-ES ≥2 OR UCEIS ≥4) with a minimum disease extent of 15 cm from anal verge; AND
   b. MCS SF subscore ≥1; AND
   c. MCS RB subscore ≥1.

6. Subject must be otherwise healthy on the basis of physical examination, medical history, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory tests performed during

screening. If there are abnormalities, they should be consistent with the underlying illness in the study population or considered not to be clinically significant in the opinion of the investigator.

7. Female subject of child bearing potential must have a negative highly sensitive (serum beta human chorionic gonadotropin) pregnancy test at screening and a negative pregnancy test prior to the first dose of IP.

8. Female subject of child bearing potential or male subject must agree to use highly effective contraception/preventive exposure measures (as described in Section 6.3.1).

9. Female subjects of nonchildbearing potential (as defined in Section 6.3.1) must also have a negative blood pregnancy test at screening. For surgical sterilization, documented confirmation will be requested.

10. Subject must have a body mass index (BMI) between 17-30 kg/m^2, inclusive.

11. Subject must be able and willing to comply with restrictions on prior and concomitant medication (as described in Section 6.3.2).

12. Subjects currently receiving the following standard of care therapies for UC are eligible providing they have been on a stable dose for the designated period of time and are anticipated to be stable throughout the study:
    a. oral corticosteroids (prednisone ≤20 mg/day or equivalent (see conversion table in Appendix 1) or budesonide ≤3 mg/day) stable dose for at least 2 weeks prior to first IP dosing.
    b. oral 5-ASA compounds (mesalamine ≤4 g/day or sulfasalazine ≤4 g/day) stable dose for at least 4 weeks prior to first IP dosing.
    c. oral thiopurines (azathioprine ≤2.5 mg/kg/day and 6-mercaptopurine 1.5 mg/kg/day) stable dose for at least 12 weeks prior to first IP dosing, or methotrexate ≤20 mg/week, stable dose for at least 12 weeks prior to first IP dosing.

13. The results of the following laboratory tests at screening must be as specified below:
    a. Hemoglobin International System of Units (SI): ≥90 g/L
    b. White blood cells (WBCs) ≥3.0 x 10^9 cells/L
    c. Neutrophils ≥2.0 x 10^9 cells/L
    d. Lymphocytes ≥1.0 x 10^9 cells/L
    e. Platelets ≥100 x 10^9 cells/L
    f. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤1.5 x upper limit of normal range (ULN)
    g. Total bilirubin level ≤1.5 x ULN unless the subject has been diagnosed with Gilbert's disease and this is clearly documented
    h. Alkaline phosphatase ≤1.5 x ULN
    i. Creatinine clearance >60 mL/min. Creatinine clearance will be calculated using the Cockroft-Gault formula.

6.2. Exclusion Criteria

Subjects meeting one or more of the following criteria cannot be selected for this clinical study:

1. Diagnosis of Crohn's disease, indeterminate colitis, ischemic colitis, fulminant colitis, or toxic megacolon.

2. Prior surgical intervention for UC (e.g. colectomy, partial colectomy, ileostomy or colostomy) or likely requirement for surgery for UC, during the study.

3. History or evidence of incompletely resected colonic mucosal dysplasia.

4. Subject has a known hypersensitivity to IP ingredients or history of a significant allergic reaction to IP ingredients as determined by the investigator, such as anaphylaxis requiring hospitalization.

5. Currently on any chronic systemic (oral or intravenous) anti-infective therapy for chronic infection (such as pneumocystis, cytomegalovirus, herpes zoster, atypical mycobacteria).

6. Active clinically significant infection OR any infection requiring oral or systemic anti-infective therapy within 2 weeks prior to screening (including use of oral anti-infective therapy for UC).

7. History of tuberculosis (TB) diagnosis or evidence of active or latent infection with *Mycobacterium tuberculosis* as defined by one of the following assessments:
   a. Positive QuantiFERON-TB Gold test result,
      OR
   b. Chest radiograph (posterior anterior view) taken within 12 weeks prior to screening, read by a qualified radiologist or pulmonologist, with evidence of current active TB or old inactive TB.

8. Subject has a known or suspected history of or a current immunosuppressive condition, or a history of invasive opportunistic infections (e.g. human immunodeficiency virus [HIV] infection, histoplasmosis, listeriosis, coccidiodmycosis, pneumocystosis, aspergillosis).

9. Subject has a history of malignancy within the past 5 years prior to screening with the exception of excised and curatively treated non-metastatic basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of cervix which is considered cured with minimal risk of recurrence.

10. Subject has a history or presence of clinically significant abnormalities detected on 12-lead ECG of either rhythm or conduction e.g. known long QT syndrome or a QT interval corrected for heart rate using Fridericia's formula [QTcF] >450 ms (male), >460 ms (female) detected on the 12-lead ECG. A first-degree atrioventricular block will not be considered as a significant abnormality.

11. Female subject is pregnant or breast feeding or intending to become pregnant or breastfeed during the study.

12. Dependence on parenteral nutrition.

13. History of major surgery (requiring regional block or general anesthesia) within the last 12 weeks prior to screening, including bowel surgery.

14. Investigator or other study staff or relative thereof who is directly involved in the conduct of the study.

15. Subject has any condition or circumstances that, in the opinion of the investigator, may make a subject unlikely or unable to complete the study or comply with study procedures and requirements (e.g., active alcohol or drug abuse).

16. Subject has taken any disallowed therapies before the planned first dose of IP.

17. Subject has any condition (including but not limited to chronic cardiac or pulmonary disease, chronic renal failure) for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

18. Exhibit acute severe UC per the following criteria:
    a. bloody diarrhea ≥6/day
       AND
    b. any of the following signs of systemic toxicity:
       Body temperature (oral or tympanic) ≥37.8°C
       OR
       Resting pulse (after 5 min seated position) >90 beats per min
       OR
       hemoglobin <105 g/L,
       OR
       erythrocyte sedimentation rate >30 mm/h
       OR
       C-reactive protein (CRP) >30 mg/L.

19. Screening stool sample positive for ova and/or parasites, *Clostridium difficile* toxin, *Escherichia coli*, *Salmonella species* (*spp*), *Shigella spp*, *Campylobacer spp* or *Yersinia spp*.

20. Subject has a chronic hepatitis B virus (HBV) infection, as defined by persistent HBV surface antigen (HBsAg) positivity. Subject has hepatitis C virus infection, as defined by positive hepatitis C virus (HCV) antibody (Ab) at screening and detectable HCV viremia. Subjects with positive HCV Ab must undergo reflex HCV RNA testing, and subjects with HCV RNA positivity will be excluded. Subjects with positive HCV Ab and negative HCV RNA are eligible.

21. Subject testing positive at screening for SARS-CoV-2 infection as detected by real time polymerase chain reaction (RT-PCR), subjects presenting any signs or symptoms as detected at baseline following careful physical examination (e.g. cough, fever, headaches, fatigue, dyspnea, myalgia, anosmia, dysgeusia, anorexia, sore throat, others) or reporting any signs and symptoms for the 2 preceding weeks, or subjects who have been exposed to individuals with confirmed or suspected diagnosis of SARS-CoV-2 within 2 weeks prior to baseline (BMJ, 2020). In addition, any other locally applicable standard diagnostic criteria may also apply to rule out SARS-CoV-2 infection.

22. Subject has presence or sequelae of gastrointestinal, liver, kidney (creatinine clearance ≤90 mL/minute, for elderly ≤60 mL/minute, using the Cockcroft-Gault formula: if calculated result is ≤90 mL/minute, for elderly ≤60 mL/minute, if applicable, a 24-hour urine collection can be done) or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs.

23. Subject concurrently participates or participated in a drug, drug/device or biologic investigational research study within 12 weeks or 5 half-lives of the IP, whichever is longer, prior to the first dose.

6.3. Prohibition and Restrictions

6.3.1. Precautions for Sexual Intercourse

Highly effective contraceptive measures for both males and females of childbearing potential must be documented in the source documents.

6.3.1.1. Female Subjects

Female subjects are considered of non-childbearing potential if they meet one of the following criteria:

- No menses for 12 or more months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Permanently surgically sterile (bilateral oophorectomy, i.e., surgical removal of ovaries, bilateral salpingectomy or hysterectomy, i.e., surgical removal of uterus).

All other female subjects are considered to be of childbearing potential (WOCBP) and must use one of the following highly effective methods of birth control prior to the first dose of IP, during the clinical study and for at least 35 days after the last dose of IP:

- Combined (estrogen and progesterone containing) (oral, intravaginal, transdermal) hormonal contraception associated with inhibition of ovulation plus a barrier method.
- Progesterone-only hormonal (oral, injectable, implantable) contraception associated with inhibition of ovulation plus a barrier method.

- Intrauterine device.
- Intrauterine hormone-releasing system plus a barrier method.
- Bilateral tubal occlusion.
- Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

Periodic abstinence (e.g., calendar, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a clinical study, withdrawal, spermicides only, and lactational amenorrhea method are not acceptable as methods of contraception.

In case a WOCBP has a vasectomized partner, provided that partner is the sole sexual partner of the WOCBP clinical study participant and that the vasectomized partner has received medical assessment of the surgical success, then she is not required to use an additional form of contraception.

Within these limits, the specific forms of contraception employed are left to the discretion of the subject, the investigator, and/or the subject's physician.

The safety of GLPG3970 during breastfeeding is unknown. Nursing women are not allowed to take part in this clinical study.

6.3.1.2. Male Subjects

Non-vasectomized male subjects with female partners of childbearing potential must be willing to use a condom from the time of the first dose of IP, during the clinical study, and for at least 7 days after the last dose of IP, in addition to having their female partner use one of the following forms of contraception:

- Intrauterine device.
- Intrauterine hormone-releasing system.
- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal).
- Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable).

Sexual abstinence defined as refraining from heterosexual intercourse is considered a highly effective contraceptive measure only if it is the preferred and usual lifestyle of the subject. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study.

Periodic abstinence (e.g. calendar, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a clinical study, withdrawal, spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.

In a case where the female partner of a male subject, provided that this partner is the sole sexual partner of the subject, has undergone documented surgical sterilization that was performed more than 1 year before screening, then the subject is not required to use an additional form of contraception.

Vasectomized male subjects with female partners of childbearing potential are not required to use an additional form of contraception providing that surgical sterilization has been successful (documented azoospermia by semen analysis).

No sperm donation is allowed from the first dose of IP during the clinical study until 7 days after the last dose of IP.

6.3.2. Prior and Concomitant Medications

Prior and concomitant therapies taken for long-term treatment of pre-existing conditions are allowed, provided they are in accordance with the inclusion and exclusion criteria (see Sections 6.1 and 6.2, respectively) and with the prohibitions and restrictions listed below.

All medications used for UC within 2 years prior to screening should be recorded with approximate dates of use (year, duration in months). In case of multiple courses of steroids, only the most recent course needs to be recorded. Information on previous failed courses of UC therapy should be reported, indicating the class/product(s).

In case additional concomitant medications need to be administered or dose adjustments for pre-existing conditions (except for UC) are needed during the study, the risk/benefit to the subject should be carefully assessed by the study physician and consideration given to the timing of any necessary introduction of new medications.

If during the study, the subject's condition necessitates the use of prohibited medication, the use of IP may be interrupted, preferably after consultation with the sponsor's medical leader. Re-introduction of IP can be considered after the treatment course with the prohibited medication has been stopped and after consultation with the sponsor's medical leader.

During the study, subjects will be instructed to record any change in concomitant medication in a diary (see Section 8.8.1).

Permitted Medications:

All other medications are permitted as long as they are not listed in the section on prohibited/restricted medications below.

Prohibited/Restricted Medications:

The following rules should apply:

Medication	Restriction
Antibiotics/ anti-infectives	Oral antibiotics/ anti-infectives: not allowed within 2 weeks prior to screening. Intravenous antibiotics/ anti-infectives: not allowed within 8 weeks prior to screening. During the study: not allowed for the treatment of bowel related infections up to the follow-up visit (allowed for treatment of other infections). Allowed for the treatment of infections (other than bowel related infections).
Corticosteroids (intramuscular or intravenous)	Not allowed within 4 weeks prior to screening and up to the follow-up visit.
Corticosteroids (oral) [2]	Oral corticosteroids (prednisone ≤20 mg/day or equivalent (see conversion table in Appendix 1) or budesonide ≤3 mg/day) allowed at stable dose for at least 2 weeks prior to first IP dosing. (see inclusion criterion 12)
Oral 5-ASA compounds	Mesalamine ≤4 g/day or sulfasalazine ≤4 g/day allowed at stable dose for at least 4 weeks prior to first IP dosing. Please also refer to the dosing instructions for sulfasalazine below under 'further guidance for the use of concomitant medications'.
Rectal formulation therapies (5-ASA compounds or corticosteroids)	Not allowed within 2 weeks prior to screening endoscopy and up to the last IP dose.
Oral thiopurines and methotrexate	Azathioprine ≤2.5 mg/kg/day and 6-mercaptopurine 1.5 mg/kg/day, allowed at stable dose for at least 12 weeks prior to first IMP dosing. Methotrexate ≤20 mg/week, allowed at stable dose for at least 12 weeks prior to first IP dosing.
Lymphocyte depleting therapies (including, but not limited to, alemtuzumab, cyclophosphamide, tacrolimus, cyclosporine, leukocyte apheresis, total lymphoid radiation or rituximab)	Rituximab is not allowed 6 months prior to screening and up to the follow-up visit. Cyclophosphamide and lymphocyte apheresis are not allowed 3 months prior to screening and up to the follow-up visit. Cyclosporine and tacrolimus are not allowed 30 days prior to screening and up to the follow-up visit. Alemtuzumab treatment and total lymphocyte radiation are not prior to the study or at any time during the study up to follow-up.
Anti-TNF Anti-integrin monoclonal antibodies Tofacitinib	Not allowed during screening period and for 5 half-lives prior to first MP dosing and up until the follow up visit.
Vaccines [a]	Live or attenuated vaccines not allowed within 60 days prior screening. Live or attenuated vaccines: not allowed throughout the study and up to the follow-up visit Inactivated vaccines should be administered according to local vaccination standards whenever medically appropriate.

[a] Refer to Appendix 2 for further vaccination-related recommendations

Other prohibited medications and dietary/herbal products:

The following medications should be discontinued at least 2 weeks or 5 half-lives of the drug, whichever is longer, prior to the first dose of IP administration and throughout the study:

- [redacted]

Additional guidance for the use of concomitant medications:

- [redacted]

The list provided in Appendix 3 through Appendix 8 are non-exhaustive.

In case of questions on concomitant medications, the sponsor's medical monitor (as per study contact list) and sponsor's medical leader can be contacted.

6.3.3. Food and Beverage Restrictions

Subjects must come for the study visits, during the treatment and FU period, in the morning. At baseline (Visit 1), Day 15 (Visit 3), and Day 43 (Visit 5) and if applicable the ED visit, subjects need to come for the study visits in a fasting state (no food intake for at least 8 hours).

Subjects will refrain from the consumption of grapefruit juice, grapefruit or Seville oranges beginning 48 hours prior to administration of the initial dose of IP, throughout the study until 7 days after the last IP administration.

6.4. Treatment Discontinuation (Temporarily and Permanently), Subject Withdrawal and Study Termination

A subject may be withdrawn from the clinical study at any time without the subject's consent if the investigator or sponsor determines that it is not in the best interest of the subject to continue participation. In such case, the reason for withdrawal will be documented in the source documents, and the subject will be asked to complete the ED visit and FU visit for safety assessments.

Treatment with IP should be discontinued by the investigator (who may consult the sponsor's medical leader) for any of the following conditions:

- Life-threatening adverse event (AE) or an SAE that places the subject at immediate risk.
- Serious infections deemed related to study treatment by the investigator, and requiring parenteral antimicrobial therapy and/or hospitalization.
- Confirmed pregnancy or lactation.
- Arrhythmia or conduction abnormality, including but not limited to prolonged QTcF, where the severity is categorized as Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher (QTc >500 ms on at least 2 separate ECGs), or clinically significant arrhythmia from any grade.
- Liver enzyme increase (see also Appendix 9)
  - AST and/or ALT ≥8x the ULN.
  - AST and/or ALT elevations ≥3x ULN with signs of liver damage (i.e., with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia [>5%], and/or total bilirubin ≥2.0x ULN or international normalized ratio [INR] >1.5)
  - In addition, a dose interruption or reduction (if applicable) should be considered if AST and/or ALT ≥3x ULN and <5x ULN and dosing with IP should be interrupted if AST and/or ALT ≥5 and <8x ULN.

- Subjects presenting with signs and symptoms of SARS-CoV-2 infection should immediately contact the site investigator, who should inform the sponsor's medical responsible as soon as possible, and report an AE/SAE as applicable. In case of suspected SARS-CoV-2 infection RT-PCR and serology tests should be performed to confirm the infection. The investigator, preferably after consultation with the sponsor's medical responsible, must discontinue the subject from the study. The subject could be tested for SARS-CoV-2 in facilities outside the study site and if so, the subject should be instructed to immediately inform the study investigator if the test is positive and test results should be shared with the investigator as soon as possible.

  For subjects having:

  - AST or ALT ≥8xULN
  - AST or ALT ≥3xULN with signs of liver damage (i.e. with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia [>5%], and/or total bilirubin ≥1.5xULN or INR >1.5)

  The following steps will need to be performed by the investigator:

  - The site should immediately contact the subject and require the subject to discontinue IP immediately. The subject should be asked to return to the site within a 48-hour window from awareness of the result.
  - A full evaluation of various causes of hepatitis should be conducted (i.e., infectious, alcohol, medications, anatomical).

- An assessment of other concomitant medications and SoC should be made. The investigator should consider whether it is in the best interest of the subject to stop/interrupt concomitant medications and SoC treatment.
- A detailed history including relevant information on alcohol use, recreational drug use, supplement consumption, any herbal remedies, family history, sexual history, travel history, history of contact with a jaundiced subject, surgery, occupational history, blood transfusion, history of liver or allergic disease, and any other potential causes of attributable to a liver insult should be collected.
- A detailed assessment of the subject's clinical condition and repeat laboratory tests for liver function tests (LFTs), including albumin, creatine kinase, total bilirubin (direct and indirect), gamma glutamyl transferase (GGT), INR and alkaline phosphatase should be done.
- Further testing for hepatitis A, B, and C, and for autoimmune hepatitis should be done. Other causes of viral hepatitis (cytomegalovirus or Eppstein Barr virus etc) should be excluded. Liver imaging should be considered.
- Referral to a hepatologist or gastroenterologist should be requested.
- All these cases should be reported as SAEs.

Every effort should be made to keep subjects in the study and on treatment. However, the investigator, who may consult the sponsor's medical leader, can consider stopping the study treatment in case of concerns about the subject's safety, serious or severe AEs or worsening of the disease condition, which in the investigator's opinion needs an alternative treatment approach not being covered in the clinical study (e.g., rescue medication). If IP treatment is interrupted due to an SAE, IP could be restarted, as per the investigator's judgement and after consultation with the sponsor medical leader.

When study treatment is discontinued, the subject will be requested to complete the assessments for the ED visit and return for the FU visit. Reason for discontinuation must be documented in the case report form (CRF).

Subjects will be informed prior to clinical study entry that they are allowed to withdraw from the clinical study. At any time and for any reason, a subject's participation in the clinical study may terminate at their request, without prejudice to their future medical care. The subject will be encouraged to share the reason(s) for withdrawal so this can be documented in the source documents, and to complete the ED Visit and follow-up visit for safety assessments, but will not be obliged to do so.

Subjects who withdraw from the clinical study without contact with the site (lost-to-follow-up) should be contacted by the site so that their health status can be assessed and documented in the source documents. The site should make every effort to understand whether the subject is alive, including checking the medical records and contacting general practitioner or relatives, if necessary. All attempts must be documented in the source documents.

The sponsor has the right to terminate the clinical study at any time and for any reason. In this event, the investigator(s) and relevant authorities will be informed of the reason for clinical study termination.

6.5. Measures to Minimize Bias

6.5.1. Randomization

At screening, subjects will be assigned a subject identification number. When a subject is confirmed to be eligible for the clinical study, the subject will be randomized. Allocation of each subject to a given treatment will be done using a centralized electronic system (interactive voice/web response system [IXRS]). IP will be randomized in a 2:1 ratio to GLPG3970 or placebo.

6.5.2. Blinding and Unblinding

This is a randomized, double-blind clinical study. The subjects and the entire clinical study team, including the investigators, clinical study coordinators, and sponsor personnel are blinded to treatment assignment.

Blinded and packaged medication will be provided to the site. All IP formulations will be identical in appearance, shape, smell and taste and will be packaged in the proper proportion to assure desired dosages and maintenance of the blinding.

The blind can be broken by the investigator for the safety of a subject. The investigator is encouraged to discuss considerations to break the blind with the medical leader, whenever possible and where the situation allows. However, the responsibility to break the treatment code in emergency situations resides solely with the investigator. The investigator is not required to discuss unblinding beforehand if he or she feels rapid emergency unblinding is necessary, but is required to inform the sponsor in within 24 hours after unblinded has occurred.

The blind can be broken by the investigator via IXRS by the investigator.

If the blind is broken for any reason during the course of the clinical study, the moment on which the blind was broken and all other relevant information will be documented by the study site. The reason for breaking the blind will be indicated and justified in the source documentation.

If an AE leads to unblinding, the AE will be given as the reason for unblinding. All subjects who are unblinded should, where possible, complete the follow-up visit assessments 14±3 days after unblinding. Any AEs will be followed until resolution.

The code-break information (via IXRS vendor) will be provided to the bioanalytical laboratory responsible for PK sample analysis, the person responsible for providing unblinded data to the data safety monitoring committee, to the pharmacovigilance vendor for SAE reporting purposes, and, if applicable, to the contract research organization (CRO) performing population PK/PD analyses.

7. INVESTIGATIONAL MEDICINAL PRODUCT

7.1. Identity of the Investigational Medicinal Product

IP will be supplied to the pharmacist of the site, by and under the responsibility of the sponsor, who will also provide the investigator and pharmacist (or appropriate qualified member of the clinical study staff) with appropriate certificates of analytical conformity and European Union (EU) Qualified Person release documents.

For more details on the composition of the IP, refer to the latest version of the IB and its relevant updates/addenda.

Detailed instructions on preparing and storing the IP will be provided to both the study site and the subjects.

7.2. Dosage and Administration

GLPG3970 will be provided as a powder and solvent for oral solution, to be reconstituted prior to use. The final dosage form for administration is an oral solution containing 400 mg of the active pharmaceutical ingredient G1567970 (G1567970 is the compound code for GLPG3970). A placebo powder and solvent for oral solution, to be reconstituted prior to use, will also be provided.

The IP needs to be taken once daily at approximately the same time every morning and on an empty stomach (i.e. IP intake should be at least 1 hour prior and at least 2 hours after food intake). At baseline (Visit 1), Day 15 (Visit 3), and Day 43 (Visit 5), and if applicable the ED visit, subjects need to come for the study visits in a fasting state (no food intake for at least 8 hours).

Subjects will receive powder and solvent to take home. The total content of the oral solution, reconstituted from the whole amount of powder and solvent, will need to be drunk. Detailed instructions for preparing and storing the applicable doses will be provided to the subject via on-site training on dummy kits and via a patient leaflet.

If a subject misses a dose (e.g. because he/she forgot to take the medication), he/she should take the missed dose within 12 hours after the planned intake time. If IP is not taken within 12 hours after the planned time, the missed dose should be skipped. For each dose taken at home, the time and date should be recorded in the subject's diary card.

7.3. Packaging, Labeling and Distribution

IP packages will be labeled with clinical study-specific details, including storage conditions.

All manufacturing, packaging, and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Each medication kit will be identified with a unique kit number. Multiple kits can be provided to a subject at each visit, providing the subject with sufficient IP to cover the period until the next scheduled visit.

The distribution of IP to the site will only occur after the required local documentation is obtained, including clinical study approval by regulatory authorities and the IECs/IRBs, documentation on which the assessment of the investigator's qualifications was based (e.g. curriculum vitae), and the signed and dated study agreement and financial agreement.

To ensure study subjects maintain dosing per protocol requirements during this study special delivery services through DTP shipments of IP from the investigational site to the subject can be implemented in case of SARS-CoV-2 restrictions. DTP should only be used in case of emergency where on-site IP dispensation is not possible, and if allowed per local regulations. Local guidelines must be followed and regulatory approval or notification of authorities may be required. Agreement of the subject to receive IP at home is required prior to the shipment of IP from the investigational site to the subject's home. The DTP process used will be reviewed and approved by the sponsor, but the DTP shipments will be coordinated by the investigational site(s) in collaboration with the local CRO without the involvement of the sponsor to ensure clinical study integrity in case of SARS-CoV-2 restrictions.

7.4. Storage

Sites are to store IP supplies in a secure area until dispensed. Powder and solvent for oral solution are to be stored at room temperature (below 30 °C), should not be refrigerated or frozen and protected from light. Both the study sites and subjects will receive additional information on preparation and storage of the IP.

Sites will be required to monitor the storage temperature by using at least a min-max temperature-recording device and to keep a minimum to maximum temperature log, which must be completed each working day in order to establish a record of compliance with these storage conditions.

The investigator will instruct subjects on how the IP should be stored at home. Storage conditions to be taken into account by the subject when taking IP home, are described in the patient leaflet.

7.5. Treatment Compliance and Drug Accountability

The investigator should discuss treatment compliance with the subject prior to the start of the study. Missed doses should be discussed to try to ascertain the reason(s). Every effort should be made to ensure the proper subject dose. Subjects with poor compliance will be retrained by the

site. Subjects will record IP administration (amount administered, date and time of IP administration) done at home in a subject diary. On Visit Day 1, Day 15±2, Day 29±2 and Day 43±2 administration of IP must occur at the site and will be captured in the eCRF.

The pharmacist or designated clinical study staff will maintain a log (paper or electronic) of the total amount of IP received at site, amount dispensed to the subject, and number of empty and full bottles returned to the site. IP supplies for each subject will be inventoried and accounted for throughout the clinical study. At the end of the treatment period, these records will be checked against the inventory by the study monitor. All clinical supplies will be stored in locked facilities.

Subjects will return any unused IP and empty IP packages at each study visit and/or ED Visit. Upon sponsor approval, all used and unused IP are to be returned from the sites and/or any vendor involved in the clinical study supplies management activities to the agreed location (depot), if possible. All returns and destructions must be properly documented.

8. CLINICAL STUDY ASSESSMENTS

Every effort should be made to ensure that CSP-required tests and procedures are completed as described in the Schedule of Activities (see Section 8.11). To avoid inter-observer variability, every effort should be made to ensure that all safety and efficacy evaluations are completed by the same individual who made the initial baseline determinations. In case study assessments are not performed for reasons related to SARS-CoV-2 pandemic restrictions, this should be documented in the medical records and subject's e-CRF.

In case a randomized subject is not available to attend a scheduled study visit on site due to SARS-CoV-2 travel restrictions, a phone call or a televisit may be conducted instead. It is strongly recommended to conduct planned study assessments for the applicable visit as per protocol as much as possible. If possible and if local regulations allow and the subject agrees, trained study staff or trained personnel are encouraged to collect study assessments at the study subjects' home or a local facility if social distancing and hygiene rules can be applied.

Only staff trained in conducting the protocol planned assessments are authorized to perform home or local facility visit assessments and the alternative arrangements need to be adequately documented. Direct to patient shipments are possible if needed. Subjects presenting with signs and symptoms of infection, including SARS-CoV-2 infection should immediately contact the site investigator, who should inform the sponsor's medical responsible as soon as possible, and SARS-CoV-2 testing should be performed.

8.1. Timing of Assessments

The study assessments described below will be performed at time points as specified in the Schedule of Activities in Section 8.11. A window of ±2 days is allowed for Visits 2, 3, 4, and 5; and a window of ±3 days is allowed for the Follow-up Visit.

ICF needs to be signed before any study procedure, including screening procedure, is carried out.

The sequence of study assessments during the treatment period(s) will be as follows when planned at the same time point:

1. [redacted]
2. 12-Lead ECG and vital signs.
3. Blood sampling for clinical laboratory assessments and PK.
4. [redacted]

Note 1: In case of blood sampling via catheter, the order of predose assessments versus vital signs/ECG is less important when there is at least 30 minutes between the placement of the catheter/blood sampling via catheter and vital signs/ECG.

Note 2: Predose assessments, including vital signs, ECG, physical examinations, and laboratory safety tests: within 3 hours predose.

The following collection time windows apply:

- Vital signs, ECG, and physical examinations: within 3 hours predose.
- Urine sampling: any time predose, on the same visit day.
- Blood sampling for clinical laboratory safety: within 3 hours predose.
- Blood sampling for PK:
  - Visit 1: predose (within 30 minutes prior to dosing) and at 0.5-1.5 hour, 2-2.5 hours, and 3-4 hours postdose.
  - Visit 3 and 4: predose (within 30 minutes prior to dosing)
  - Visit 5: predose (within 30 minutes prior to dosing) and 4-6 hours postdose
- [redacted]
- [redacted]
- Endoscopy and colon biopsy sampling:
  - At screening visit 2 (either surveillance colonoscopy or flexible sigmoidoscopy, see Section 8.7.2): once other in- and exclusion criteria have been confirmed at screening visit 1). The screening endoscopy should be completed prior to Day -8 (to allow results availability for Day 1), and between the endoscopy day (screening visit 2) and Day 1, there should be maximum 2 weeks.
  - At Visit 5 and ED visit, if applicable: can be on the day prior to, or on the day of the final IP dose.

When multiple assessments are listed on 1 line, the sequence can be determined by the site. Additional safety assessments should be performed if clinically indicated (see also Section 6.4).

8.1.1. Retesting During Screening

During the screening period, one retest of the following assessments is allowed:

- For resting pulse (after 5 min seated position) outside range for defining acute severe UC (as defined in exclusion criterion #18).
- For QuantiFERON –TB Gold test with indeterminate result (the subject is not eligible if retest result is indeterminate or positive).
- During screening or later during the study, retesting (resampling) of clinical laboratory safety tests or SARS-CoV-2 RT-PCR test is allowed once, only for technical or transport reasons (e.g., sample hemolyzed, out of stability, late arrival at laboratory impacting sample quality, loss, or destruction of the sample before analysis).

8.1.2. Rescreening of Subjects

If a subject is a screening failure, it is allowed to rescreen the subject once, if the reason for failure is temporary and expected to resolve, as judged by the investigator. When a subject is rescreened, the subject needs to be reconsented and all screening assessments need to be repeated. The subject will be assigned a new subject identification number. The time in between 2 screening attempts could vary depending on the screen failure reason.

The following data will be collected for screening failure subjects: ICF signed data, demographics, failed inclusion or exclusion criteria, and AEs.

8.2. Unscheduled Visits

Additional visits can be performed at other time points for any safety assessments, if clinically indicated. These unscheduled visits and outcomes of additional assessments need to be recorded in the source and, if it is a CSP-specified assessment performed before the subject's last visit per CSP, also in the eCRF.

8.3. Subject and Disease Characteristics

Subjects will be asked to attend the site for a screening assessment. After giving written informed consent, demographic data (year of birth, age, sex , ethnicity and race), medical, and smoking history will be taken, including UC history. UC classification and/or extent will be provided per [redacted] (see Appendix 10) based on the screening colonoscopy or endoscopy examination (where applicable, as per Section 8.7.2) or based on the last available colonoscopy performed before screening. Questions regarding prior and concomitant medication intake will be asked. A physical examination will be performed, including measurement of weight and height.

Vital signs (systolic and diastolic blood pressure, pulse, tympanic body temperature) will be measured and a triplicate 12-lead ECG will be recorded. Subjects should rest for at least

5 minutes, in the supine position before the ECG recording and in a seated position before blood pressure and pulse measurement. Blood and urine samples will be collected for clinical laboratory safety tests. A stool sample will be collected for microbiology and PD assessments. If not possible to collect a stool sample during the visit, the subjects will receive a stool sample collection kit to collect the stool sample at home within 24 hours after screening visit 1. A serum pregnancy test will be done for all WOCBP as well as an FSH test for nonsurgical postmenopausal female subjects.

UC history will capture the duration of disease, clinical symptoms, number of stools per day under normal (healthy/remission) conditions, medication used to treat the disease, and clinical response to current and prior UC therapies.

Flexible sigmoidoscopy or surveillance colonoscopy videos will be centrally reviewed using [redacted] and MCS-ES indices to confirm active UC. The endoscopy procedure will be done at a second screening visit after the other in- and exclusion criteria have been confirmed.

The inclusion and exclusion criteria (Sections 6.1 and 6.2) will be checked to assess eligibility for the study. All screening tests will be reviewed to confirm eligibility before randomization and the first dose.

8.4. Efficacy Assessments

8.4.1. Endoscopy

An endoscopy (either a surveillance colonoscopy or flexible sigmoidoscopy, see below) will be performed on the visits specified in the Schedule of Activities in Section 8.11 (see also Section 8.1, "Timing of Assessments").

At screening visit 2:

a. In subjects with a history of UC ≥8 years:
   i) With a colonoscopy performed more than 24 months prior to screening, a surveillance colonoscopy will be performed.
   ii) With a colonoscopy performed less than 24 months prior to screening, a flexible sigmoidoscopy will be performed.

b. In subjects with a history of UC <8 years:
   i) A flexible sigmoidoscopy will be performed, irrespective of the time of the last colonoscopy.

At Visit 5 (or at the ED visit, if applicable):

a. A flexible sigmoidoscopy will be performed for all subjects in the study.

Videos of the flexible sigmoidoscopy or of the screening surveillance colonoscopy, will be recorded. These will be reviewed and scored by blinded central reviewer(s) using the MCS-ES and [redacted] indices (refer to Appendix 10 and Appendix 11). The MCS-ES (Schroeder,

Tremaine, & Ilstrup, 1987) [redacted] screening scores will be reported to the clinical site.

Details of the endoscopy, including bowel preparation before endoscopy, as well as the collection and processing of video films will be provided in a separate imaging charter.

8.4.2. Biopsy Sample Collection

During the endoscopy (either flexible sigmoidoscopy or surveillance colonoscopy) on the visits specified in the Schedule of Activities in Section 8.11 (see also Section 8.1, "Timing of Assessments"), 8 colonic biopsies will be collected per visit: 4 biopsies from the distal sigmoid colon (the area representative of UC disease activity) at approximately 25 cm proximal to the anal verge, and 4 biopsies from the rectum.

Colon biopsies will be stored at the site until shipment to a central lab for further processing, allowing:

– [redacted]

Biopsy sample collection, handling, and processing will be outlined in the laboratory manual provided by the central laboratory.

8.4.3. Mayo Clinical Score

The MCS is composed of 4 subscores (see Appendix 10):

1. MCS-SF subscore

2. MCS-RB subscore

3. MCS-ES subscore

4. Physician's global assessment (PGA)

For calculation of the MCS subscores MCS-RB and MCS-SF (Lewis J. , et al., 2008), subjects will be instructed to record symptoms of RB and SF daily in a diary (see Section 8.8.1).

The information on the UC symptomatology of the last 3 consecutive available days in the diary collected from the last week, will be used to score the MCS-RB and MCS-SF subscores, excluding the day before the endoscopy (with bowel preparation), the day of the endoscopy and the day after the endoscopy.

The PGA will be scored by the investigator or trained sub-investigator at visits specified in the Schedule of Activities (Section 8.11 [see also Section 8.1, "Timing of Assessments"]). To avoid inter-observer variability, every effort should be made to ensure that, per subject, PGA assessments are performed by the same assessor throughout the study.

[redacted]

8.5. Safety Assessments

This section describes methods and timing for all safety assessments and recording. Additional assessments (e.g. unscheduled clinical laboratory tests or extra vital signs recordings) are allowed to ensure appropriate collection of safety data and to assess any perceived safety concerns.

8.5.1. Adverse Events

Detailed definitions, reporting period, ratings and reporting requirements for AEs and SAEs are found in Section 11.

8.5.2. Clinical Laboratory Evaluations

The following clinical laboratory tests will be performed:

- **Hematology:**
  hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), hemoglobin, red blood cell count, red blood cell distribution width, white blood cell count, white blood cell differential count (absolute and relative), platelets, and erythrocyte sedimentation rate (erythrocyte sedimentation rate at screening only).

- **Coagulation:**
  INR (only when increase in LFTs, see Section 6.4), activated partial thromboplastin time, and prothrombin time.
- **Clinical chemistry:**
  fasting glucose (at baseline [Visit 1], Day 15 [Visit 3], and Day 43 [Visit 5] and the ED visit, if applicable), glycosylated hemoglobin (HbA1c), fasting insulin (at baseline [Visit 1], Day 15 [Visit 3], and Day 43 [Visit 5] and the ED visit, if applicable), homeostatic model assessment of insulin resistance (HOMA IR) (at baseline [Visit 1], Day 15 [Visit 3], and Day 43 [Visit 5] and the ED visit, if applicable), urea, creatinine, creatinine clearance (ClCr), uric acid, sodium, potassium, calcium (total), reflex calcium (free/ionized; only if serum calcium total is elevated), chloride, phosphorus/phosphate, AST, ALT, GGT, total bilirubin, alkaline phosphatase (alkaline phosphatase bone fractions only if alkaline phosphatase is elevated), lactate dehydrogenase, creatine phosphokinase (CK), albumin, total proteins, triglycerides, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, lipase, amylase, high sensitivity CRP, high sensitivity Troponin I and Troponin T (Troponin I on Day 1, later during the study only when troponin T is elevated).
  Homeostatic model assessment of insulin resistance (HOMA-IR, see Definition of Terms) and HDL/LDL ratio will be derived from clinical chemistry parameters. An estimate of the creatinine clearance (ClCr) based on the serum creatinine level will be calculated by the central laboratory using the Cockroft-Gault formula (see Definition of Terms).
- **Urinalysis:**
  Dipstick: pH, glucose, proteins (qualitative), blood, leukocytes, ketones.
  Microscopic examination of the sediment for cellular elements (cylinders, erythrocytes, leukocytes), if indicated (when the test strip was positive for blood and/or proteins).
  Quantitative urine proteins, only when the test strip was positive for proteins.
  Calcium, phosphate, creatinine and N-acetyl-β-D-glucosaminidase (NAG). The urine protein to creatinine ratio will be derived.
- **Serology/blood:**
  HBs Ag, (if positive, confirmed by HBV DNA PCR), HCV (Ab and/or PCR) and HIV 1 and 2 antibodies (at screening). Positive hepatitis and HIV results should be reported by the investigator as required by local law.
  FSH test for females of (nonsurgical) nonchildbearing potential at screening to confirm menopause, if applicable.
- **Pregnancy test for females:**
  Serum beta human chorionic gonadotropin at screening, baseline (Visit 1), Day 29 (Visit 4), and Day 43 (Visit 5) or ED, if applicable (all female subjects).
- **QuantiFERON-TB Gold test** to check for latent or active TB (at screening). TB results should be reported by the investigator as required by local law.
- **Stool culture/ Stool sample for microbiology/microbiome evaluation:**
  For enteric pathogens, *Clostridium difficile* cytotoxin assay and microscopic examination for intestinal parasites/ova in stool sample; *Escherichia coli*, *Salmonella* species (spp), *Shigella* spp, *Campylobacer* spp and *Yersinia* spp assay in stool culture (at screening).
  Note: Details of microbiome assessment are provided in Section 8.7.3.2.

– **SARS-CoV-2:**
RT-PCR from a nasal swab sample to check for SARS-CoV-2 infection at screening and RT-PCR from a nasal swab sample and serology testing at baseline, and throughout the study as needed (when SARS-CoV-2 symptoms present)

The clinical laboratory evaluations will be performed at visits specified in the Schedule of Activities in Section 8.11 (see also Section 8.1, "Timing of Assessments"). Reference ranges will be supplied by the local and central laboratory, as needed.

Clinical laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. Only laboratory test abnormalities judged as clinically significant by the principal investigator should be recorded as AEs. At the discretion of the investigator, when following up AEs, additional laboratory parameters may be tested, and additional samples taken.

In case of safety issues, as per decision of the investigator, the local laboratory at site could be used to verify some parameters.

An estimate of the ClCr based on the serum creatinine level will be calculated by the central laboratory using the Cockroft-Gault formula (see Definition of Terms).

Blood, urine, and stool sample handling and shipment instructions will be provided in a separate laboratory manual.

8.5.3. Physical Examination

Physical examinations, including weight and height (at screening), will be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation at visits specified in the Schedule of Activities in Section 8.11 (see also Section 8.1, "Timing of Assessments"). The person conducting the physical examination will document this in the subject's medical source records. Clinically significant abnormal findings should be recorded as AEs.

Particular attention should go to physical examination at all visits, to identify any potential SARS-CoV-2 related signs and symptoms, indicating potential infection (e.g. cough, fever, headaches, fatigue, dyspnea, myalgia, anosmia, dysgeusia, anorexia, sore throat, others). Subjects presenting such symptoms at screening/baseline should not be included/randomized in the study (see Section 6.2). Developing such symptoms during the study, should be managed as per Section 8.5.6.

8.5.4. Vital Signs

Vital signs (systolic and diastolic blood pressure taken at the same arm for each measurement, pulse, and oral/tympanic body temperature, the same method for measuring body temperate to be used throughout the study) will be recorded in a standardized manner (i.e. after the subject has rested in a seated position for at least 5 minutes) at visits specified in the Schedule of Activities in Section 8.11 (see also Section 8.1, "Timing of Assessments"). Clinically significant abnormal values should be recorded as AEs.

8.5.5. 12-lead Electrocardiogram

At the time points specified in the Schedule of Activities (see Section 8.11 and also Section 8.1, "Timing of Assessments"), a triplicate 12-lead ECG will be recorded and results will be sent for central reading.

12-lead ECG recordings will be performed before blood sampling and after subjects rested for at least 5 minutes in supine position. In case an indwelling catheter is used, ECGs may be recorded after blood sampling, provided that there is at least 30 minutes between catheter insertion and the ECG recording. When catheter insertion would fail, the 12-lead ECG needs to be taken before the venipuncture and at least 30 minutes after the failed attempt. Triplicate ECGs will be performed at the time points specified in the Schedule of Activities (see Section 8.11 and also Section 8.1, "Timing of Assessments") preferably within a time span of 10 minutes, with an approximate 3-minute interval between ECGs.

The following parameters need to be recorded: heart rate, PR interval, RR interval, QRS interval, uncorrected QT interval, morphology and rhythm analysis. QTcF will be derived. QTcF will be considered as normal if ≤450 ms (male) and ≤460 ms (female), while a prolongation of QTcF to >500 ms or an increase from baseline >60 ms will be considered a threshold of concern.

The ECG will be reviewed centrally to detect clinically significant abnormalities. This review during the visit needs to be documented in the subject's source. After receipt of the central report, also all flagged ECG abnormalities need to be assessed by the investigator on clinical relevance. Clinically significant abnormal values should be recorded as AEs.

8.5.6. Other Safety Assessments

SARS-CoV-2 infection will be assessed at screening by RT-PCR and at baseline through careful physical examination to exclude any potential signs and symptoms of infection, e.g. cough, fever, headaches, fatigue, dyspnea, myalgia, anosmia, dysgeusia, anorexia, sore throat, etc.

Additional RT-PCR and serology testing will be repeated at baseline for documentation and throughout the study as needed. The subject could be tested for SARS-CoV-2 in facilities outside the study site and if so, the subject should be instructed to immediately inform the study investigator if the test is positive and test results should be shared with the investigator as soon as possible.

In addition, on Day 8, the subjects should be contacted by the site via a telephone call. The site should remotely check the overall status of the subject and obtain safety related information, if applicable (both in the context of the clinical study and linked to the SARS-CoV-2 pandemic).

8.6. Pharmacokinetic Assessments

Blood samples for the PK assessment of GLPG3970 should be collected on the visits specified in the Schedule of Activities in Section 8.11 (see also Section 8.1, "Timing of Assessments"). In total 8 blood samples will be used for analysis of GLPG3970 in plasma.

Samples will be obtained by venipuncture (or indwelling cannula), preferably in the forearm into tubes containing K2EDTA and will be immediately chilled (ice bath). Within 30 min after blood collection, the plasma will be separated in a refrigerated centrifuge at 4 °C for 10 min at circa 1,500 g and transferred into tubes as described in the laboratory manual. The plasma samples will be stored at -60 °C or below at the site until shipment to the bioanalytical laboratory.

[redacted]

[redacted]

8.8. Other Assessments

[redacted]

8.8.1. Subject Diary and Questionnaires

At visits specified in the Schedule of Activities (Section 8.11) a diary and instructions for completion will be provided. The subjects will record on a daily basis symptoms, including, but not limited to, rectal bleeding, symptoms of urgency, and abdominal pain, bowel accidents, need to wake up due to bowel movements, daily stool frequency, AEs, exposure to individuals with confirmed or suspected diagnosis of SARS-CoV-2 infection, any change in concomitant medication, and IP intake throughout the study. An automated alert system will notify the investigator and sponsor of any signs or symptoms or information possibly related to SARS-CoV-2 that is entered by the subject in the diary.

Subjects will be trained on how to complete the subject diary.

[redacted]

8.9. Sample Management

Total Blood Volume

The total amount of blood to be taken during the clinical study for scheduled laboratory parameters will not exceed approximately [redacted] This includes sampling for PK [redacted] assessments.

Blood, Urine, and Stool Samples for Routine Safety Tests, Serology, Microbiology, Microbiome, FSH and Pregnancy Tests

All blood, urine, and stool samples for routine safety tests, serology, FSH and pregnancy tests will be analyzed in a central laboratory and will be destroyed after completion of analysis.

Blood, Stool and Colon Biopsy Samples for PK and [redacted]

After the end of the study (defined in Section 5.2), all biological samples obtained during the clinical study may be stored for a maximum period of 5 years, after which the samples will be destroyed. The sample storage period will be in accordance with the IRB/EC-approved ICF and applicable regulations (e.g. Regulatory Authority requirements).

The stored samples shall only be used by the sponsor, sponsor partners and/or other companies contracted by the sponsor, for research related to this clinical study. Any research outside the context described in this CSP may only be conducted after approval by the IRB/IEC and Regulatory Authority and after obtaining informed consent from the subject.

[redacted]

8.11. Schedule of Activities

For detailed instructions on the clinical study procedures, please see referred sections and Section 8.1, "Timing of Assessments".

EVENT	SCREENING PERIOD		TREATMENT PERIOD [1], [2]						FOLLOW-UP PERIOD[3]
Study Visit	**S1**	**S2[4]**	**1**	**2**	**3**	**4**	**5**	**ED[3]**	**Follow-up Visit**
Study Day (D) ± Days	**-35 to 0**		**1**	**8 ± 2**	**15 ± 2**	**29 ± 2**	**43 ± 2**		**14± 3 after last IP dosing**
On-site visit	✓	✓	✓		✓	✓	✓	✓	✓
Telephone call				✓					
Informed consent (Section 8.3)	✓								
Inclusion/exclusion criteria (Sections 6.1 and 6.2)	✓	✓	✓						
Demographics (Section 8.3)	✓								
Medical and smoking history including UC history (Section 8.3)	✓								
Physical examination (Section 8.5.3)	✓		✓				✓	✓	✓
Body weight and height[5] (Section 8.5.3)	✓		✓		✓	✓	✓	✓	✓
Vital signs (Section 8.5.4)	✓		✓		✓	✓	✓	✓	✓

[1] On dosing days, all assessments are to be performed within 3 hours predose, unless otherwise specified.
[2] Subjects must come for the study visits at baseline (Visit 1), Day 15 (Visit 3), and Day 43 (Visit 5) and the early discontinuation (ED) visit, if applicable in the morning in a fasting state (no food intake for at least 8 hours).
[3] Subjects who discontinue treatment early will be requested to return for an ED visit to complete all Visit 5 assessments and to return for a follow-up (FU) visit 14±3 days after last IP administration.
[4] The endoscopy procedure will be done at Screening Visit 2 once the other in- and exclusion criteria have been confirmed at Screening Visit 1.
[5] Height only to be measured at Screening Visit 1.

EVENT	SCREENING PERIOD		TREATMENT PERIOD [1], [2]						FOLLOW-UP PERIOD[3]
Study Visit	**S1**	**S2[4]**	**1**	**2**	**3**	**4**	**5**	**ED[3]**	**Follow-up Visit**
Study Day (D) ± Days	**-35 to 0**		**1**	**8 ± 2**	**15 ± 2**	**29 ± 2**	**43 ± 2**		**14± 3 after last IP dosing**
12-Lead triplicate ECG (Section 8.5.5)	✓		✓		✓	✓	✓	✓	✓
QuantiFERON TB Gold test (Section 8.5.2)	✓								
SARS-CoV-2 RT-PCR test[6]	✓		✓	As needed					
SARS-CoV-2 serology test			✓	As needed					
Randomization (Section 6.5.1)			✓						
Blood collection									
• Safety (hematology, coagulation, chemistry) (Section 8.5.2)	✓		✓[7]		✓[7]	✓	✓[7]	✓[7]	✓
• Serology (HBV, HCV, HIV) (Section 8.5.2)	✓								
• Pregnancy test serum (all WOCBP females) (Section 8.5.2)	✓		✓			✓	✓	✓	
• FSH test (WOnonCBP, non-surgical postmenopausal women) (Section 8.5.2)	✓								

[6] RT-PCR from a nasal swab sample at screening may be done at an earlier screening visit on a different day than the other screening assessments (after signature of the study informed consent form) and RT-PCR from a nasal swab sample and serology testing at a visit on Day -3, and throughout the study as needed when subject presents signs and symptoms of SARS-CoV-2 infection.
[7] Fasted glucose, fasted insulin, and HOMA-IR only at baseline (Visit 1), Day 15 (Visit 3), and Day 43 (Visit 5) and the ED visit, if applicable.

EVENT	SCREENING PERIOD		TREATMENT PERIOD [1], [2]						FOLLOW-UP PERIOD[3]
Study Visit	**S1**	**S2[4]**	**1**	**2**	**3**	**4**	**5**	**ED[3]**	**Follow-up Visit**
Study Day (D) ± Days	**-35 to 0**		**1**	**8 ± 2**	**15 ± 2**	**29 ± 2**	**43 ± 2**		**14± 3 after last IP dosing**
• PK (Section 8.6)			✓[8]		✓[9]	✓[9]	✓[10]	✓	
[redacted]									
Urine collection									
• Safety[12] (Section 8.5.2)	✓		✓		✓	✓	✓	✓	✓
Stool sample collection[13]	✓		✓		✓	✓	✓	✓	
• Microbiology	✓								

[8] Visit 1: predose (within 30 minutes prior to dosing), 1 sample within [0.5-1.5 hours postdose]; 1 sample within [2–2.5 hours postdose] and 1 sample within [3-4 hours postdose].
[9] Visit 3 and 4: predose (within 30 minutes prior to dosing).
[10] Visit 5: 1 sample predose (within 30 minutes prior to dosing) and 1 sample within [4-6 hours postdose].
[11] [redacted]
[12] On dosing days, safety urine samples will be taken predose, on the same visit day. Visit 1 and 5: predose and 2 hours postdose. Calcium and phosphate should only be evaluated at Visits 1 and 5.
[13] At Screening Visit 1, a stool sample should be collected during the visit. If not possible, the subject can collect the sample at home within 24 hours after start of Screening. For Visits 1, 3, and 4, stool samples can be collected within 24 hours prior to the visit or during the visit. At Visit 5 (Day 43) and ED visit, if applicable, when the stool sample must be taken before the bowel preparation for endoscopy, stool can be collected more than 24 hours before the visit. One sample can be used for different assessments.

EVENT	SCREENING PERIOD		TREATMENT PERIOD [1], [2]						FOLLOW-UP PERIOD[3]
Study Visit	**S1**	**S2[4]**	**1**	**2**	**3**	**4**	**5**	**ED[3]**	**Follow-up Visit**
Study Day (D) ± Days	**-35 to 0**		**1**	**8 ± 2**	**15 ± 2**	**29 ± 2**	**43 ± 2**		**14± 3 after last IP dosing**
• Microbiome (sampling before IP administration) (Section 8.7.3.2)			✓				✓	✓	
[redacted]									
Endoscopy + [redacted]									
Mayo Clinical Score subscores (MCS-SF, MCS-RB, PGA) (Section 8.4.3)		✓	✓		✓	✓	✓	✓	
[redacted]									
Subject diary evaluation (Section 8.8.1)		✓	✓	✓	✓	✓	✓	✓	✓
Allocation and dispensing of IP supplies (Section 7.2)			✓		✓	✓			
IP administration (Section 7.2)			Once daily throughout the treatment period[16]						
Prior and concomitant medication (Section 6.3.2)	Throughout the study								
Adverse events (Section 8.5.1)	Throughout the study								

[14] Central endoscopy reading, [redacted]
[15] Screening endoscopic assessment (either surveillance colonoscopy or flexible sigmoidoscopy) should be completed prior to Day -8.
[16] On Visit 1, 3, 4, and 5, administration of IP must occur at the site.

9. STATISTICAL METHODS

All statistical methods shall be detailed in a statistical analysis plan (SAP) that will be finalized prior to the database lock and unblinding. All relevant data collected in this clinical study will be documented using summary tables, figures, and subject data listings.

Any deviations from the CSP are to be justified in the SAP.

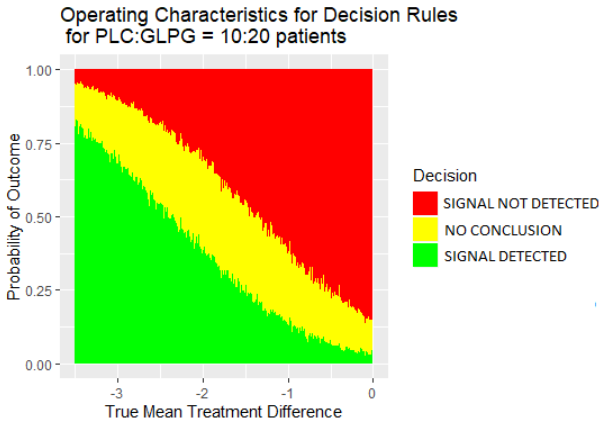
9.1. Determination of Sample Size

A sufficient number of subjects with UC will be screened in order to have 30 subjects randomized (20 planned subjects on GLPG3970 and 10 planned subjects on placebo).

The 30 subjects randomized in the study, are expected to be sufficient to provide preliminary insight in the safety, tolerability and PK of GLPG3970 in UC patients. In case of drop-outs due to SARS-CoV-2 infection, additional subjects may be randomized on top of the planned sample size. The number of additional subjects randomized will not exceed the number of subjects dropping out of the study in relation to SARS-CoV-2. Randomization of additional subjects will ultimately be decided by the sponsor before any study lock or related unblinding has occurred.

For the efficacy objective, the operating characteristics of the chosen decision framework for the most important endpoint (MCS change from baseline at Week 6) at a sample size of 30 subjects (10 on placebo and 20 on GLPG3970) are represented in the following graph and table, and were deemed acceptable. A common standard deviation of 3.3 was assumed in this small study. Lower Reference Value and Target Value for the decision framework were determined based on the published studies and the therapies in development or on the market. They were identified by the project team as the lowest delta of possible interest and the best case scenario for efficacy outcome respectively.

True Treatment Difference In MCS Change From Baseline At Week 6	Signal Score	Probability Of Outcome
-3.0	Signal detected	0.673
	No conclusion	0.220
	No signal detected	0.107
-1.3	Signal detected	0.205
	No conclusion	0.289
	No signal detected	0.506



PLC: placebo; GLPG: GLPG3970

9.2. Population for Analyses

9.2.1. All Screened Subjects

All subjects who signed and dated an ICF.

9.2.2. All Randomized Subjects

All screened subjects who were randomized into the clinical study.

9.2.3. Full Analysis Set

All randomized subjects who have received at least 1 dose of IP.

9.2.4. Safety Analysis Set

All subjects who used at least 1 dose of IP.

9.2.5. Pharmacokinetic Analysis Set

Subset of the Safety Analysis Set for which plasma concentration data are available to facilitate development of the population PK model as described in the pharmacometric analysis plan and excluding CSP deviations which have an impact on the PK analyses.

[redacted]

9.2.7. Pharmacokinetic/[redacted]

Intersection of the PK and [redacted]

9.3. Statistical Analyses

9.3.1. General Statistical Considerations

Summary tabulations will be presented and will display the number of observations, mean, standard deviations and/or standard error (as appropriate), median, minimum and maximum (for continuous variables), and the number and percentage per category (for categorical data). In addition to tabulated descriptive statistics, graphical data displays may be used to summarize the data.

Baseline is defined as the last available assessment prior to the first intake of IP. For ECG, the baseline ECG result is the mean of the last available triplicate prior to the first intake of IP.

Unless otherwise noted, inferential statistics will be interpreted at the 2-sided 10% significance level.

9.3.2. Interim Analysis

No interim analysis is planned for this clinical study.

9.3.3. Analyses of Demographics and Baseline Characteristics

Subject disposition (including reasons for ED), CSP deviations, demographics, baseline characteristics, medical history, and concomitant therapies will be analyzed descriptively. Unless otherwise noted, all analyses will be performed using the Safety Analysis Set

9.3.4. Analyses of Efficacy Parameters

Efficacy analyses will be performed on the FAS.

9.3.4.1. Analysis for Primary Efficacy Endpoint

The analysis of the MCS change from baseline will be descriptive by group. As some early dropouts or missing data can be expected, the analysis will run a mixed-effects model on continuous data. From this model, 90% confidence intervals (CIs) of the treatment differences (GLPG3970 versus placebo) will be estimated.

The signal detection methodology described by Frewer et al. (Frewer, Mitchell, Watkins, & Matcham, 2016) will be used to provide further insight into the treatment effect of GLPG3970 over placebo, and will support scenario analyses. The posterior distribution of this treatment effect will be estimated, and from this distribution probabilities of reaching at least a certain effect (delta) will be derived, e.g. a range of plausible effect size values going from as high as P (delta ≤ -3.0) to as low as P (delta ≤ -1.3).

The chosen framework is as follows:

- Target value (TV) – 3.0 and lower reference value (LRV) – 1.3
- False stop risk 20% and false go risk 10%
- Framework rules:
  - Signal detected if P10 <TV and P80 <LRV
  - No signal detected if P10 ≥TV
  - No conclusion if P10 < TV

9.3.4.2. Analyses for Secondary Efficacy Endpoints

Continuous efficacy endpoints, including the primary endpoint: mixed models for repeated measures (MMRM) to compare treatment groups, with a 90% CI of the treatment difference at each time point.

[redacted]

9.3.5. Analyses of Safety Data

All safety analyses will be performed using the Safety Analysis Set (Section 9.2.4). All safety data collected on or after the first dose of IP administration up to the last contact after the last dose of IP, unless specified otherwise, will be summarized by treatment group according to the IP received. Clinical safety will be addressed by assessing AEs, laboratory assessments, physical examinations, vital signs, and 12-lead ECGs.

9.3.5.1. Extent of Exposure

A subject's extent of exposure to the IP will be generated from the IP administration page of the CRF. Exposure data will be summarized by treatment group. Duration of exposure to the IP will be expressed as the number of days between the first and last dose of IP, inclusive, regardless of temporary interruptions in IP administration and summarized by treatment group.

9.3.5.2. Adverse Events

Clinical and laboratory AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities. System Organ Class, High-Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term will be attached to the clinical database.

The following AEs will be considered as TEAEs:

Any AE with an onset date on or after the IP start date and no later than 14 days after last dose of IP, or any worsening of any AE on or after the IP start date. Investigators are not obliged to actively seek SAEs after the CSP defined follow-up period. However, if the investigator is informed about SEA that occurs at any time after the subjects post-treatment follow-up visit and the event is deemed relevant to the use of IP, they should promptly document and report the event to the sponsor by using the SAE form.

Summaries (number and percentage of subjects) of TEAEs per subject by System Organ Class and Preferred Term will be provided by treatment group. TEAEs will also be summarized by causal relationship to the IP and severity. In addition, TEAEs leading to ED of the IP will be summarized and listed. Also, all SAEs, including the non-treatment-emergent SAEs, will be listed.

9.3.5.3. Clinical Laboratory Evaluations

Laboratory assessments will be analyzed descriptively. Changes from baseline and treatment-emergent shifts according to normal ranges and/or a laboratory abnormality grading scale

(CTCAE version current at the time of the assessment) will be presented as well. Analyses will be done per treatment group.

9.3.5.4. Physical examination

Only abnormal postbaseline physical examination results will be listed, when available.

9.3.5.5. Vital Signs

Vital signs will be analyzed descriptively. Changes from baseline will be presented as well. Analyses will be done per treatment group.

9.3.5.6. 12-Lead Electrocardiogram

A descriptive analysis will be done for the 12-lead ECG. Changes from baseline will be presented as well. Frequency analyses of abnormalities based on actual values and on changes from baseline will be presented as well. Analyses will be done per treatment group.

9.3.6. Pharmacokinetic Analyses

GLPG3970 plasma concentrations will be listed and predose concentrations (C_{trough}) will be summarized descriptively.

All observed GLPG3970 plasma concentrations will be analyzed using a population PK approach to characterize the PK profile of GLPG3970 and determine the PK parameters (e.g. clearance and volume of distribution) and their associated variability. The influence of covariates may be investigated.

[redacted]

9.3.7. [redacted]

[redacted]

9.3.8. Additional Statistical Considerations

Not applicable.

10. DATA MONITORING

10.1. Data Safety Monitoring Committee

An Internal Data Safety Monitoring Committee independent from the study will review unblinded data during the course of the study. This Committee may involve external medical experts (such as an expert in the field of UC and an infectious diseases expert) to support data interpretation. The Committee will review unblinded safety data and assess any potential safety issues arising during the conduct of the clinical study, including (but not limited to) any potential issues in the context of the SARS-CoV-2 pandemic. The process is described in a separate 'Internal Safety Monitoring Committee Charter'.

11. SAFETY REPORTING

11.1. Definitions of Adverse Events, Serious Adverse Events, and Special Situations

11.1.1. Adverse Events

An AE is any untoward medical occurrence, new or worsening of any preexisting condition, in a clinical study subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related. AEs may also include pre- or post-treatment complications that occur as a result of CSP-specified procedures, worsening of the targeted disease, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting conditions that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

11.1.2. Serious Adverse Events

An SAE is defined as an AE that:

- Results in death.
- Is life-threatening (Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly / birth defect.
- Is medically significant (medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might

jeopardize the subject or might require intervention to prevent one of the other outcomes listed in the definition above).

11.1.3. Unlisted (Unexpected) Adverse Events/ Reference Safety Information

An AE is considered unlisted if the nature or intensity is not consistent with the applicable product reference safety information. For an IP, the expectedness of an AE will be determined by whether or not it is listed in the reference safety information part of the IB.

11.1.4. Adverse Events of Special Interest

Not applicable.

11.1.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance based on the investigator's judgment are not considered AEs or SAEs. However, laboratory abnormalities (e.g. clinical chemistry, hematology, and urinalysis) or other abnormal (clinical study-specific) assessments (e.g. ECG, radiography, vital signs) that require medical or surgical intervention, are associated with signs and/or symptoms, and/or lead to IP interruption, modification or discontinuation must be recorded as an AE or SAE if they meet the definition as described in Sections 11.1.1 and 11.1.2, respectively. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis is to be reported (e.g. anemia instead of decreased hemoglobin).

The following liver enzyme elevations should be reported as SAEs:

- AST or ALT ≥8xULN.
- AST or ALT ≥3xULN with signs of liver damage (total bilirubin >2xULN OR international normalized ratio >1.5, and/or with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia [>5%]).

11.1.6. Special Situations

Special situations are situations that have a possible impact on the safe use of the IP. These situations might be or might not be associated with AEs.

- Pregnancy.
- Overdose with IP.
  An overdose of IP is defined as the administration of a quantity of the IP given per administration or cumulatively, which is above the recommended dose in the protocol.
- Medication error with IP.
  A medication error with IP is defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the subject.
- Product complaint or quality defect of IP.

Product complaint or quality defect of IP is defined as complaints or defects of the IP arising from potential deviations in the manufacture, packaging, or distribution of the IP.

- Drug interaction or food interaction with IP.
  A drug interaction with IP is defined as a situation in which there is evidence or a suspicion that the IP interacts with another drug when both are administered together.
  A food interaction with IP is defined as a situation in which there is evidence or a suspicion that the IP interacts with a food when taken together.
- Occupational exposure to IP.
  Occupational exposure to IP is defined as an exposure to the IP as a result of one's professional or non-professional occupation.

11.2. Assessment of Adverse Events and Serious Adverse Events

The investigator is responsible for assessing AEs and SAEs for causality and severity. This is the basis for the sponsor's final review and confirmation of accuracy and completeness of event information and causality assessments.

11.2.1. Action Taken Regarding Investigational Product

The action taken must be described by choosing from:

- Dose not changed: In case no action is taken regarding the IP.
- IP permanently discontinued: In case a subject is permanently discontinued from treatment or withdrawn from the study by the investigator (who may consult the sponsor's medical monitor).
- IP temporarily discontinued: In case the IP is temporarily discontinued by the investigator (who may consult the sponsor's medical monitor).
- Not applicable: Other situations (e.g. in case an AE started after the last IP administration).

11.2.2. Assessment of Causality

The investigator is responsible for assessing the causal relationship to IP(s) administration or study procedures (e.g. invasive procedures such as venipuncture) based on her/his clinical judgment. The following decision choice will be used by the investigator to describe the causality assessment between the reported event or laboratory test abnormality and the IP.

- **Unrelated:**
  Time relationship to IP intake is improbable. Related to other etiologies such as concomitant medications or subject's clinical state.
- **Unlikely:**
  Time relationship to IP intake is improbable (but not impossible). Concomitant disease or other drugs provide plausible explanations.

- **Possible:**
  Time relationship to IP intake is reasonable. Event or laboratory test abnormality could also be explained by disease or other drugs. Information on IP withdrawal may be lacking or unclear.
- **Probable:**
  Time relationship to IP intake is reasonable. Unlikely to be attributed to concurrent disease or other drugs. Response to withdrawal is clinically reasonable and rechallenge not required.
- **Certain:**
  Time relationship to IP intake is plausible. Cannot be explained by concomitant disease or other drugs. Response to withdrawal is plausible (pharmacologically, pathologically). Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon). Rechallenge satisfactory, if ethical and necessary.

It should be emphasized that ineffective treatment (worsening of the disease) should not be considered as causally related in the context of AE reporting.

11.2.3. Assessment of Severity

The severity of AEs should be graded using the CTCAE version current at the time of assessment. If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 1.

Table 1: Grading of AE Severity

Grade	Adjective	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening	Urgent intervention indicated
Grade 5	Death	Death-related AE

* Instrumental Activities of Daily Living (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.

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality. This is upon the investigator's assessment.

If there is a change in intensity (worsening or improvement) of an AE, it must be recorded.

11.2.4. Outcome

Each AE must be rated by choosing among:

- Recovered/resolved;
- Recovered/resolved with sequelae;
- Recovering/resolving;
- Not recovered/not resolved;
- Fatal;
- Unknown.

11.3. Instructions for Reporting Adverse Events, Serious Adverse Events, Pregnancies, and Other Special Situations

11.3.1. Adverse Events

The AE reporting period for safety surveillance begins when the subject signs the ICF and ends at the subject's last follow-up visit (the last follow-up visit after the last dose of IP). In this period, all new AEs, regardless of cause or relationship, derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questioning (such as "How do you feel?") need to be recorded in the source and in the CRF.

In case an AE is ongoing at the time of the last follow-up visit, the investigator needs to follow-up on the subject until AE resolution or reasonable stabilization and to document in the subject's source documentation. No related updates or additional data on the AE should be reported in the CRF.

If a subject is documented as lost-to-follow-up, ongoing/unknown outcome AEs will not be followed-up.

If the AE meets the criteria for seriousness, the SAE form must be completed and sent to the sponsor within 24 hours (see Section 11.3.2).

11.3.2. Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The subject will remain under observation as long as medically indicated. Appropriate laboratory tests will be performed until all parameters return to normal or are otherwise explained or stable.

All SAEs, whether or not deemed IP-related, must be recorded on the SAE form and in the CRF. The investigator must report each SAE immediately, and under no circumstances should this exceed 24 hours following the knowledge of the SAE, as is indicated on page 2 under "Emergency Contact Information".

The SAE form should at least contain identifiers of the subject and the reporter, SAE term and statement of relatedness to the IP, and at a later stage if not yet available within 24 hours, the form needs to be completed with a clearly written narrative describing signs, symptoms, and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae.

Follow-up and outcomes should be reported and documented in the source documents for all subjects that experience an SAE. It is important that the information provided on the SAE form matches the information recorded on the CRF for the same event.

Copies of additional laboratory tests, consultation reports, post-mortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and available. Only subject identifiers (subject number) should appear on the copies, and all names and initials should be blackened and rendered illegible. Follow-up reports relative to the subject's subsequent course must be submitted until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

Any SAEs that occur after the post-treatment follow-up visit but within 30 days of the last dose of IP(s), regardless of causality, should also be reported (Emergency Contact Information on page 2) but not entered in the CRF. Investigators are not obligated to actively seek SAEs after the CSP-defined follow-up period. However, if the investigator is informed about an SAE that occurs at any time after the subjects' post-treatment follow-up visit and the event is deemed relevant to the use of IP(s), he/she should promptly document and report the event to the sponsor by using the SAE form.

11.3.3. Pregnancy

All initial reports of pregnancy in female subjects and pregnancies in partners of male subjects included in the clinical study must be recorded and documented in the source documents and on the pregnancy form. The investigator must report each pregnancy immediately, and under no circumstances should this exceed 24 hours following the knowledge of the pregnancy, as is indicated on page 2 under "Emergency Contact Information".

All pregnancies should be followed-up until delivery or pregnancy interruption. The investigator will contact the subject or partner of the subject after giving consent, at the expected time of delivery for follow-up and for information regarding the outcome of the newborn. Abnormal pregnancy and/or abnormal newborn outcomes are considered SAEs and must be reported using the SAE form.

11.3.4. Reporting of Special Situations (Other Than Pregnancy) With or Without Associated Adverse Events

In case a special situation is not associated with an AE, the special situation should be reported within 24 hours by using the Special Situations form as is indicated on page 2 under "Emergency Contact Information".

In case a special situation is associated with an AE, the special situation should be reported within 24 hours by using the Special Situations form and the associated AE should be reported as specified in Section 11.3.1.

In case a special situation is associated with an SAE, the special situation should be reported within 24 hours by using the SAE form (and not the Special Situations form) and the associated SAE should be reported as specified in Section 11.3.2.

11.4. Sponsor Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable United States Federal Drug Administration Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, the sponsor may be required to expedite reports of SAEs and serious adverse drug reactions or suspected unexpected serious adverse reactions (SUSARs) to worldwide regulatory authorities. The sponsor or a specified designee will notify worldwide regulatory authorities and the relevant IEC/IRB in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined using the reference safety information section in the IB or relevant local label as applicable.

All concerned investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any IP(s). The investigator should notify the IEC/IRB of SUSAR reports as soon as is practical, where this is required by local regulatory authorities, and in accordance with the local institutional policy.

12. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This clinical study will be conducted in compliance with this CSP, the current ICH-GCP Guideline E6, and applicable local ethical and legal requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of clinical study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki (1996 and successive amendments), and that the clinical study data are credible.

The name and address of each third party vendor (e.g. CRO) used in this study and the sponsor's study team members will be maintained in the investigator's and sponsor's files as appropriate.

12.1. Sponsor's Responsibilities

12.1.1. Regulatory Authority Approval

Prior to clinical study start, this CSP together with all relevant documentation needs to be submitted to the respective regulatory authorities for review and approval in compliance with current regulations before the study can start.

12.1.2. Clinical Study Closure Considerations

The sponsor reserves the right to close the site or end the clinical study at any time for any reason. In case of an early termination of the clinical study or temporary halt by the sponsor, the IEC/IRB, and regulatory authorities should be notified according to local requirements, unless otherwise specified by the sponsor, the IEC/IRB or health authority, and/or the regulatory authorities including a detailed written explanation of the reasons for the termination/halt.

Reasons for the closure of a site may include, but are not limited to:

- Successful completion of the clinical study at the center.
- The overall required number of subjects for the clinical study has been recruited.
- Failure of the investigator to comply with the CSP, ICH-GCP guidelines or local requirements.
- Inadequate recruitment of subjects by the investigator, as decided by the sponsor.

Reasons for early termination of a clinical study by the sponsor may include, but are not limited to:

- Safety concerns.
- Sufficient data suggesting lack of efficacy.

The end of clinical study declaration will be submitted to the regulatory authorities and IEC/IRB after the complete clinical study has ended in all participating centers, in all countries. This notification will also be submitted according to local requirements of the end of the clinical study in a given country/member state.

12.1.3. Indemnification

Under the conditions of a contract concluded between investigator, site, and sponsor or designee, which shall prevail, the sponsor shall, except in case of gross negligence or willful misconduct, indemnify and hold harmless the investigator and his/her medical staff from any claim arising from the clinical study activities carried out in compliance with the CSP, sponsor's instructions, and applicable local regulations.

The investigator must notify the sponsor immediately upon notice of any claims or lawsuits.

12.1.4. Insurance

The sponsor shall maintain insurance coverage that is sufficient to cover its obligations and that is consistent with human clinical study local regulations. Provided that the subject has been treated according to the CSP and sponsor's instructions, any injury caused to a subject which is the direct result of his/her participation to the clinical study shall be covered by the sponsor's insurance, except in case of gross negligence or willful misconduct by the investigator.

12.1.5. Archiving

The sponsor will archive the content of the Trial Master File (TMF) for at least 25 years after the end of the clinical study.

12.2. Reporting

Where required by IEC/IRB per local requirements, at least once a year the investigator will provide the IEC/IRB with a progress report to allow review of the clinical study (see Section 12.6.1). At the end of the clinical study, the results of the clinical study will be reported in a clinical study report by the sponsor. The population-PK analysis data, exploratory PD microbiome, exploratory RNA, and other exploratory disease and/or drug-related biomarker data may be reported separately from the main clinical study report. A summary or full report, depending on the requirements, will be provided by the sponsor to the investigators, to the relevant regulatory authorities, and IECs/IRBs (if required by the applicable regulatory requirements) within one year, or 6 months for pediatric studies, after the end of the clinical study.

12.3. Publication

It is understood by the investigator that the sponsor shall be free to use the compound-related information, which is generated during the clinical study and may disclose it to other clinical investigators and to regulatory agencies. As a consequence, the investigator agrees to provide all clinical study results and data generated during this clinical study to the sponsor.

The investigator shall not be authorized to submit the results of this clinical study and any data for public disclosure (e.g. publication or presentation) without the prior written approval of the sponsor, which shall not be unreasonably withheld.

However, it is understood and agreed by the investigators that their results and/or findings shall not be authorized for publication prior to sponsor's publication of the overall clinical study results. The investigator agrees that prior to the publication of any results, he/she shall provide the sponsor with a draft copy of the intended publication, at least 2 weeks prior to the submission for publication. The sponsor shall have the right to review it and to make any comments. In accordance with generally accepted scientific collaboration principles, co-authorship with any staff member sponsor involved in the clinical study, will be discussed and mutually agreed upon before submission of any manuscript to a publisher.

12.4. Investigator's Responsibilities

12.4.1. Source Data and Data Capture

The nature and location of all source documents need to be identified and documented to ensure that all sources of original data required to complete the CRF are known and are accessible for verification by the monitor.

Source data may be directly captured from devices transferred from third partners (e.g. laboratory data) or entered manually into the CRF. The CRF completion guidelines will be provided to each site.

It is recommended that the author of an entry in the source documents should be identifiable. Following ICH-GCP guidelines, direct access to sponsor's representatives to source documents must be granted for the purpose of verifying that the data recorded on the CRF are consistent with the original source data.

12.4.2. Archiving

Unless local legislation requires archiving for a longer period, the investigator shall archive the content of the clinical investigator site file (ISF) for at least 25 years after the end of the clinical study. However, the medical files of subjects shall be archived in accordance with national law.

The investigator should take measures to prevent accidental or premature destruction of these documents.

Under no circumstance shall the investigator relocate or dispose any clinical study documents before having obtained a written approval of the sponsor.

If it becomes necessary for the sponsor or the appropriate Regulatory Authority to review any documentation relating to this clinical study, the investigator must permit access to such reports. The subject is granting access to his/her source data by signing the ICF.

Any difficulty in storing original documents must be discussed with the monitor prior to the initiation of the clinical study.

12.4.3. Participation Cards

If the subjects are not under 24-hour supervision of the investigator or site staff, they must be provided with a subject participation card indicating the name of the IP, the clinical study number, the investigator's name, and the site's 24-hour emergency contact number. The subject should be advised to keep the participation card in his/her wallet at all times.

12.5. Confidentiality

The subject will receive all information as required by the EU General Data Protection Regulation, namely the identity and contact details of the controller, the contact details of the data protection officer, the clinical research purposes, the legal basis for the processing, the recipients

of the personal data, the transfer of the personal data to third countries and respective safeguards, the retention periods, the fair processing of his data, and all his/her data subject's rights. All details are listed in the ICF.

All information concerning the product and the sponsor's operations (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the investigator by the sponsor and not previously published) is considered confidential and should not be disclosed by the investigator to any third party without the sponsor's prior written approval. The investigator agrees to use this information only in accomplishing the clinical study and will not use it for other purposes.

In order to permit easy identification of the individual subject during and after the clinical study, the investigator is responsible for keeping an updated Subject Identification Code List. The monitor will review this document for completeness. However, the investigator must guarantee the subject's anonymity will be maintained. Therefore, in order to ensure subject confidentiality, the Subject Identification Code List must remain at the center and no copy will be made.

12.6. Ethical Considerations

12.6.1. Independent Ethics Committee / Institutional Review Board

This clinical study can only be undertaken after IEC/IRB approval of this CSP together with all relevant documentation. This approval document must be dated and clearly identify the clinical study and the related clinical study documents being approved, including the subject compensation programs, if applicable.

During the course of the clinical study, at least the following documents have to be submitted to the IEC/IRB, per local requirements:

- Changes to the IB
- Reports of AEs that are serious, unlisted, and associated with the IP (in compliance with IEC/IRB, per local requirements)
- CSP amendments
- ICF amendments

After the subject has completed the study, the subject will receive a financial compensation, or depending on the country, the study investigator may offer the option of a course of post-study medication approved for the treatment of UC, at no cost and for a duration of up to 6 months. Subjects will be eligible for compensation in case a subject received at least 1 dose of study drug and completed the study, or discontinued early for e.g. safety reasons. In case a subject withdraws from the study early, compensation will be pro rata, unless the reason for withdrawal from the study is noncompliance, then no compensation will be provided. If the reason for withdrawal is noncompliance, there will be no compensation. Any form of compensation and conditions for compensation will require approval by an IEC and documented in the ICF.

The IEC/IRB is responsible for continuous review of the clinical study. Where required by IEC/IRB, per local requirements, at least once a year the investigator will provide the IEC/IRB with a progress report to allow review of the clinical study. Additional progress reports should be provided according to local legal requirements. These requests and (re-)approvals, if applicable, should be documented in writing.

12.6.2. Informed Consent

The investigator or designated personnel must explain the clinical study and the implications of participation (e.g. objectives, methods, anticipated benefits, possible risks) to potential subjects according to applicable regulations prior to any clinical study-related activity. Subjects will be informed that their participation is voluntary and that they may withdraw from the clinical study at any time. They will be informed that choosing not to participate or to withdraw from the clinical study will not have an impact on the care the subject will receive for the treatment of his/her disease.

The subject will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry in the clinical study, the subject's consent should be appropriately recorded by means of the subject's personally dated signature and by the investigator's dated signature. In case the subject is unable to read and/or write, oral consent in the presence of at least one impartial witness who was also included when the affected person was being informed, may be given. The witness may not be anyone working at the site nor a member of the investigating team. The orally given consent shall be documented in writing, dated and signed by the witness. After having obtained the consent, a copy of the signed and dated ICF must be given to the subject.

If new information becomes available relevant to the subject's willingness to participate in the clinical study, the subject will be informed in a timely manner by means of an amended ICF. This amended ICF will be signed and dated by the subject (or, if applicable, by an independent witness) and the investigator to document the willingness of the subject to continue with the clinical study.

This signed and dated amended version will be filed together with the initial signed and dated ICF.

A pregnant partner, who agrees that information will be gathered about her pregnancy and the birth, will be asked to sign a specific ICF to participate in the data collection. Data about the health of the baby will be collected if the parent(s)/legal guardian(s) agree with the data collection and sign a specific ICF.

Subjects who agree to participate in the study and who have signed informed consent, will be given the option to provide additional (and optional) informed consent for the long-term storage of left over samples and associated data, collected during the study, for future scientific research.

12.7. Data Quality Control/Assurance

12.7.1. Monitoring

Data quality will be assured through Risk-Based Monitoring, medical monitoring, and other relevant activities as described in the Data Management Plan or Medical Review Plan and monitoring plans available in the TMF. This clinical study will be monitored by sponsor representatives according to their current standard operating procedures.

To guarantee adequate protection of the subjects and to guarantee the quality of the data, the sponsor will ensure oversight of any clinical study-related duties and functions carried out on its behalf, including clinical study-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

A risk-based Quality Management Plan (QMP) is prepared for the study that evaluates potential risks in relation to rights, safety, and well-being of the study subjects as well as the data integrity. The QMP describes and evaluates all involved stakeholder interfaces having potential critical impact on the above. Risks are considered at both the system level (e.g. standard operating procedures, computerized systems, personnel, and vendors) and study level (e.g. IP, study design, data collection, informed consent process and recording).

12.7.2. Audit and Inspection

To ensure compliance with relevant regulations, an independent quality assurance representative, regulatory authorities and/or IECs/IRBs may review this clinical study. This implies that auditors/inspectors will have the right to inspect the clinical study center(s) at any time during and/or after completion of the clinical study and will have access to the data generated during the clinical study, source documents, and subject's files. By participating in this clinical study, investigators agree to this requirement.

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14. APPENDICES

Appendix 1: Prednisolone Conversion Table

Glucocorticoid Name	Dose Equivalent to 5 mg Prednisolone
Prednisone	5 mg
Betamethasone	0.6 mg
Cortisol (hydrocortisone)	20 mg
Cortisone	25 mg
Deflazacort	7.5 mg
Dexamethasone	0.75 mg
Methylprednisolone	4 mg
Methylprednisolone Acetate	4 mg
Methylprednisolone Sodium Succinate	4 mg
Paramethasone	2 mg
Prednisolone	5 mg
Triamcinolone	4 mg
Beclometasone Dipropionate	1.25 mg
Budesonide	1.5 mg
Hydrocortisone Sodium Succinate	20 mg

(Steriod Conversion Calculator)

Appendix 2: Vaccinations

Prior to study participation, it is recommended that the subject's vaccinations be brought up to date according to local vaccination standards.

Live or attenuated vaccines (including, but not limited to varicella and inhaled flu vaccine) are prohibited within 30 days prior screening, throughout the study and up to the follow-up visit (Lamb CA, et al., 2019).

Subjects should be advised to avoid routine household contact with persons vaccinated with live/attenuated vaccine components. General guidelines suggest that a study subject's exposure to household contacts should be avoided for the below stated time periods:

- Varicella or attenuated typhoid fever vaccination – avoid contact for 4 weeks following vaccination (GI Society, 2020)
- Oral polio vaccination - avoid contact for 6 weeks following vaccination (Troy, et al., 2013)
- Attenuated rotavirus vaccine - avoid contact for 15 days following vaccination (National Center for Immunization and Respiratory Diseases, Hamborski, Roger, & Wolfe , 2017)
- Inhaled flu vaccine - avoid contact for 1 week following vaccination (Fluenz Tetra nasal spray suspension Influenza vaccine (life attenuated, nasal). Summary of Product Characteristics., 2020)

Inactivated vaccines (such as inactivated flu vaccines) should be administered according to local vaccination standards whenever medically appropriate; however, there are no available data on the concurrent use of GLPG3970 and its impact on immune responses following vaccination.

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Appendix 9: Algorithm for Elevated Liver Function Tests

<table>
<tr><td></td><td colspan="5">AST or ALT increase to</td></tr>
<tr><td>Value Range</td><td>≥1.5x to 3xULN</td><td>≥3x to <5xULN</td><td>≥5x to <8xULN</td><td>≥3xULN with signs of liver damage[1]</td><td>≥8xULN</td></tr>
<tr><td rowspan="2">IP Action</td><td>Continue as planned</td><td>Reduce or interrupt IP for at least 2 weeks

Close observation[2]</td><td>Interrupt IP for at least 2 weeks

Close observation[2]</td><td>Discontinue IP[2]</td><td>Discontinue IP[2]</td></tr>
<tr><td colspan="5">↙ ↘</td></tr>
<tr><td>After at least 2 weeks</td><td colspan="2">AST and ALT <3xULN</td><td colspan="3">AST or ALT ≥3xULN</td></tr>
<tr><td></td><td colspan="2">Weekly LFTs for the first 2 weeks (biweekly for the following weeks, or more frequently at investigator's discretion)</td><td colspan="3">Discontinue IP

Report SAE and complete liver event page for any of abnormalities listed below[3]:

- AST/ALT increase ≥8xULN

- AST/ALT increase ≥3xULN with signs of liver damage[1]</td></tr>
</table>

[1] Signs of liver damage:

– total bilirubin ≥2.0xULN OR international normalized ratio >1.5, and/or

– symptoms: appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)

[2] Close observation recommendations:

– Monitor 2 to 3 times per week all of the following parameters: ALT, AST, alkaline phosphatase, total bilirubin, eosinophils, INR. If local regulations allow, home visits can be performed if subjects cannot come to the clinical study center.

– Frequency of retesting can be reduced to once a week or less if abnormalities stabilize or the IP has been discontinued; however, monitoring might still be needed more frequently taking into consideration the standard of care and/or changes to this.

– Based upon investigator's discretion gastroenterology or hepatology consultations, additional serology testing, imaging and pathology assessments may be required.

– Re-query history of symptoms, prior and concurrent diseases, concomitant medication and non-prescription medicines, herbal, dietary supplements, alcohol use, recreational drug use, special diets.

– Rule out all of the following: acute viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, non-alcoholic fatty hepatitis, hypoxic/ischemic hepatitis, biliary tract disease, and cholestasis.

– Re-query exposure to environmental chemical agents.

[3] The following steps should be followed:

– The site should immediately contact the subject and require the subject to discontinue IP immediately. The subject should be asked to return to the site within a 48-hour window from awareness of the result.

– A full evaluation of various causes of hepatitis should be conducted (i.e., infectious, alcohol, medications, anatomical).

- An assessment of other concomitant medications and standard of care should be made. The investigator should consider to whether is in the best interest of the subject to stop/interrupt concomitant medications and SoC treatment.
- A detailed history including relevant information on (alcohol use, recreational drug use, supplement consumption, any herbal remedies, family history, sexual history, travel history, history of contact with a jaundiced subject, surgery, occupational history, blood transfusion, history of liver or allergic disease, and any other potential causes of attributable to a liver insult should be collected.
- A detailed assessment of the subject's clinical condition and repeat laboratory tests for LFT, including albumin, creatine kinase, total bilirubin (direct and indirect), GGT, INR and alkaline phosphatase should be done.
- Further testing for Hepatitis A, B, and C, and for autoimmune hepatitis should be done. Other causes of viral hepatitis (cytomegalovirus [CMV] or Epstein-Barr virus [EBV] etc) should be excluded. Liver imaging should be considered.
- Referral to a hepatologist or gastroenterologist should be requested.
- All these cases should be reported as SAEs.

Appendix 10: Mayo Scoring System [redacted]

A. Mayo Scoring System

	0	1	2	3
Stool frequency [MCS-SF] [a]	Normal	1 -2 stools above normal	3 -4 stools above normal	>4 stools above normal
Rectal bleeding [MCS-RB] [a]	No blood seen	Streaks of blood less than half the time	Obvious blood with stool most of the time	Blood alone passed
Flexible sigmoidoscopy [MCS-ES] [b]	Normal or inactive disease	Mild disease (Erythema, decreased vascular pattern, no friability)	Moderate disease (Marked erythema, absent vascular pattern, friability, erosions)	Severe disease (Spontaneous bleeding, ulceration)
Physician's global assessment [PGA] [a]	Normal	Mild disease	Moderate disease	Severe disease

a (Lewis J. , et al., 2008)
b (Schroeder, Tremaine, & Ilstrup, 1987)

The total MCS equals the sum of all 4 subscores.
The [redacted] equals the sum of the MCS-SF, MCS-RB and PGA subscores.
The [redacted] (FDA CDER, 2016) equals the sum of the MCS-SF, MCS-RB and MCS-ES subscores.

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Appendix 11: [redacted]

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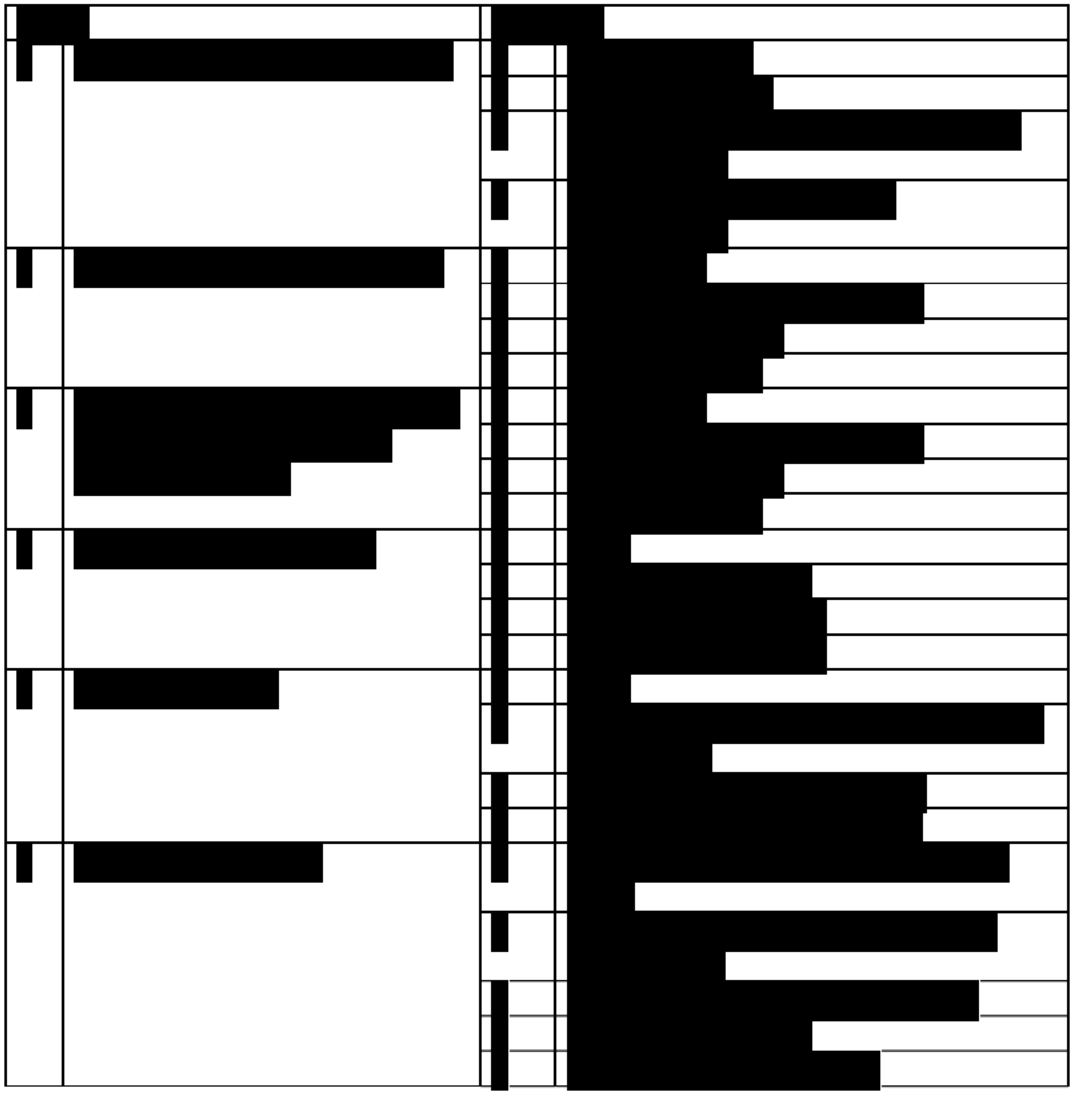

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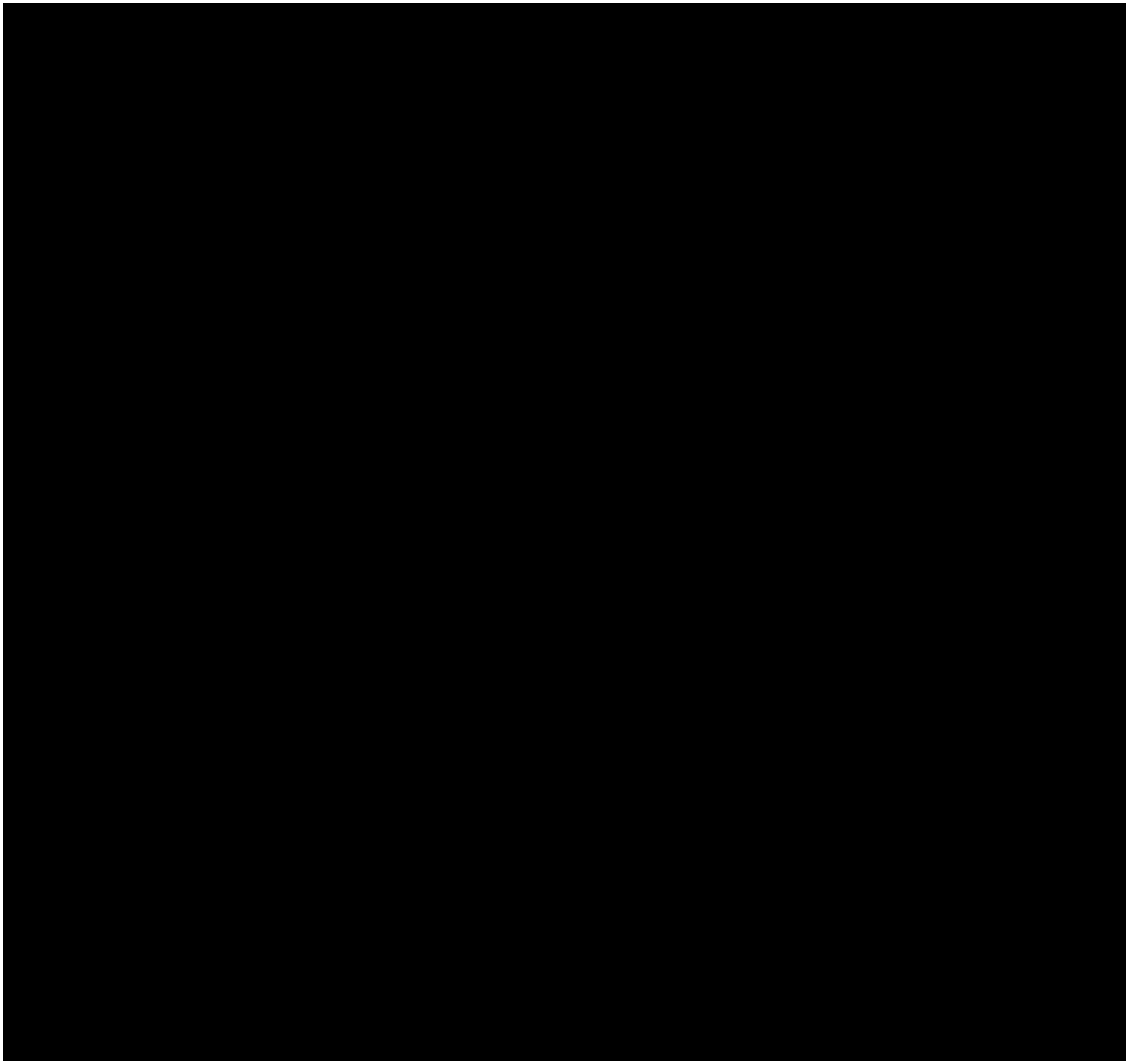

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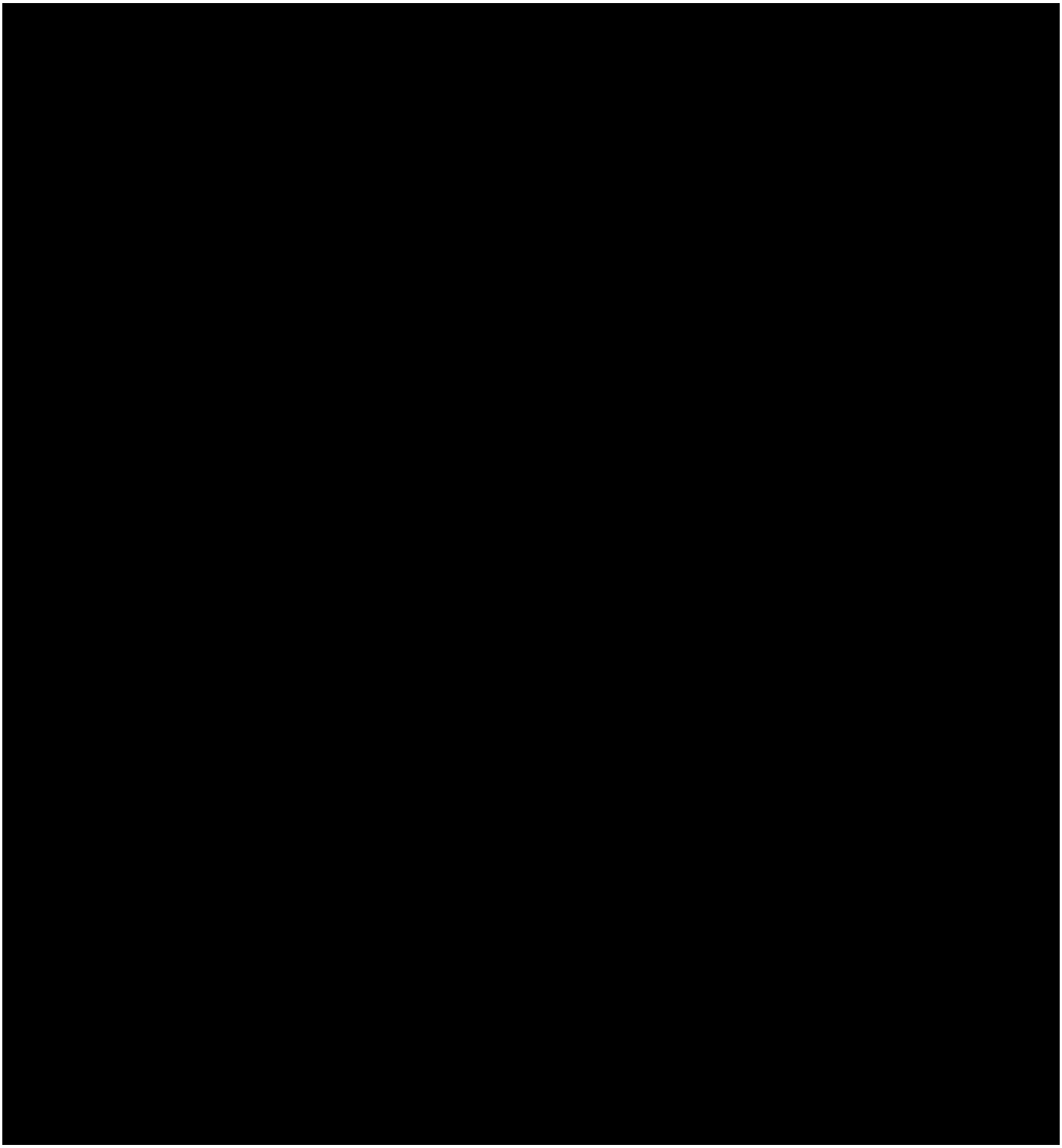

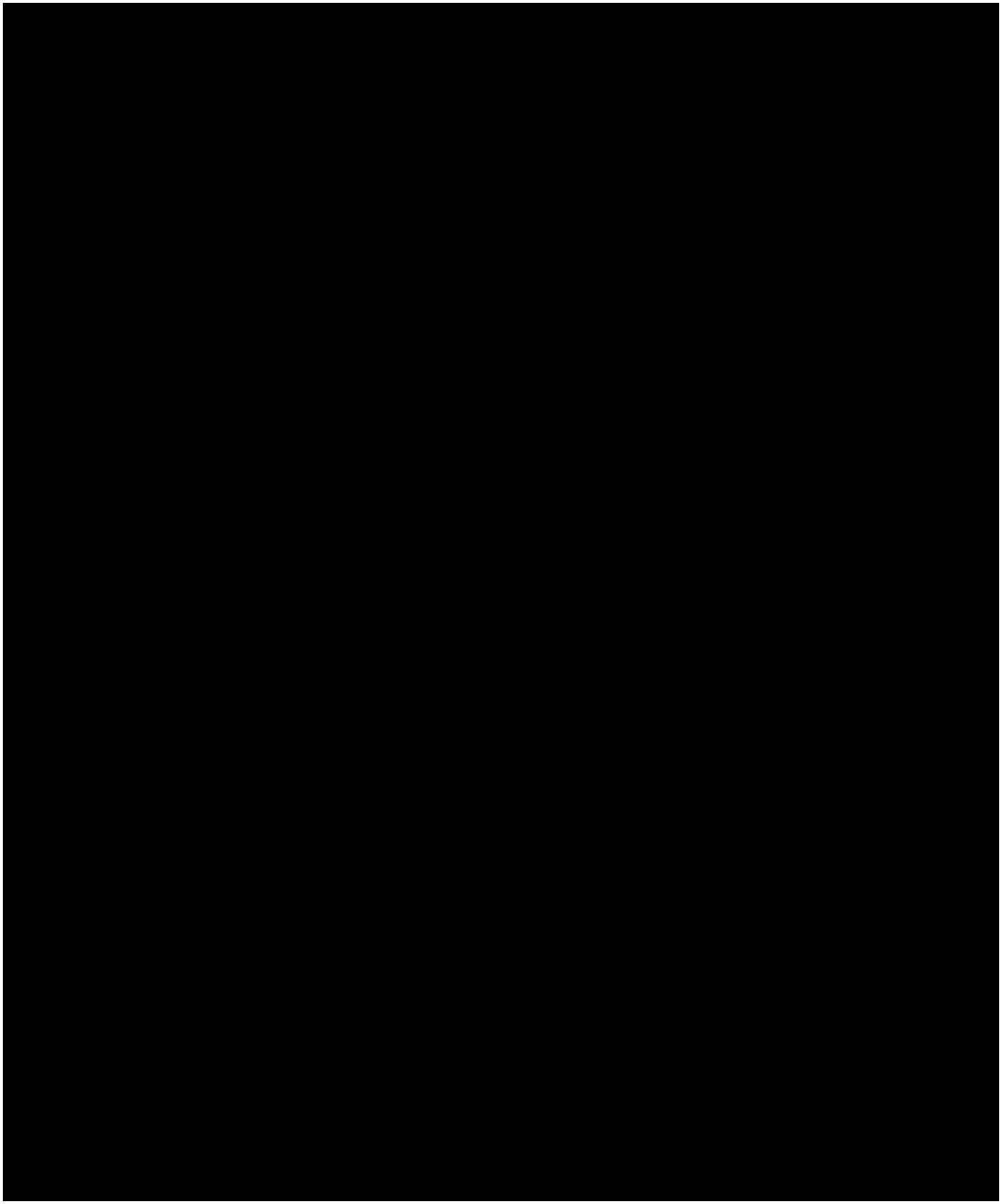

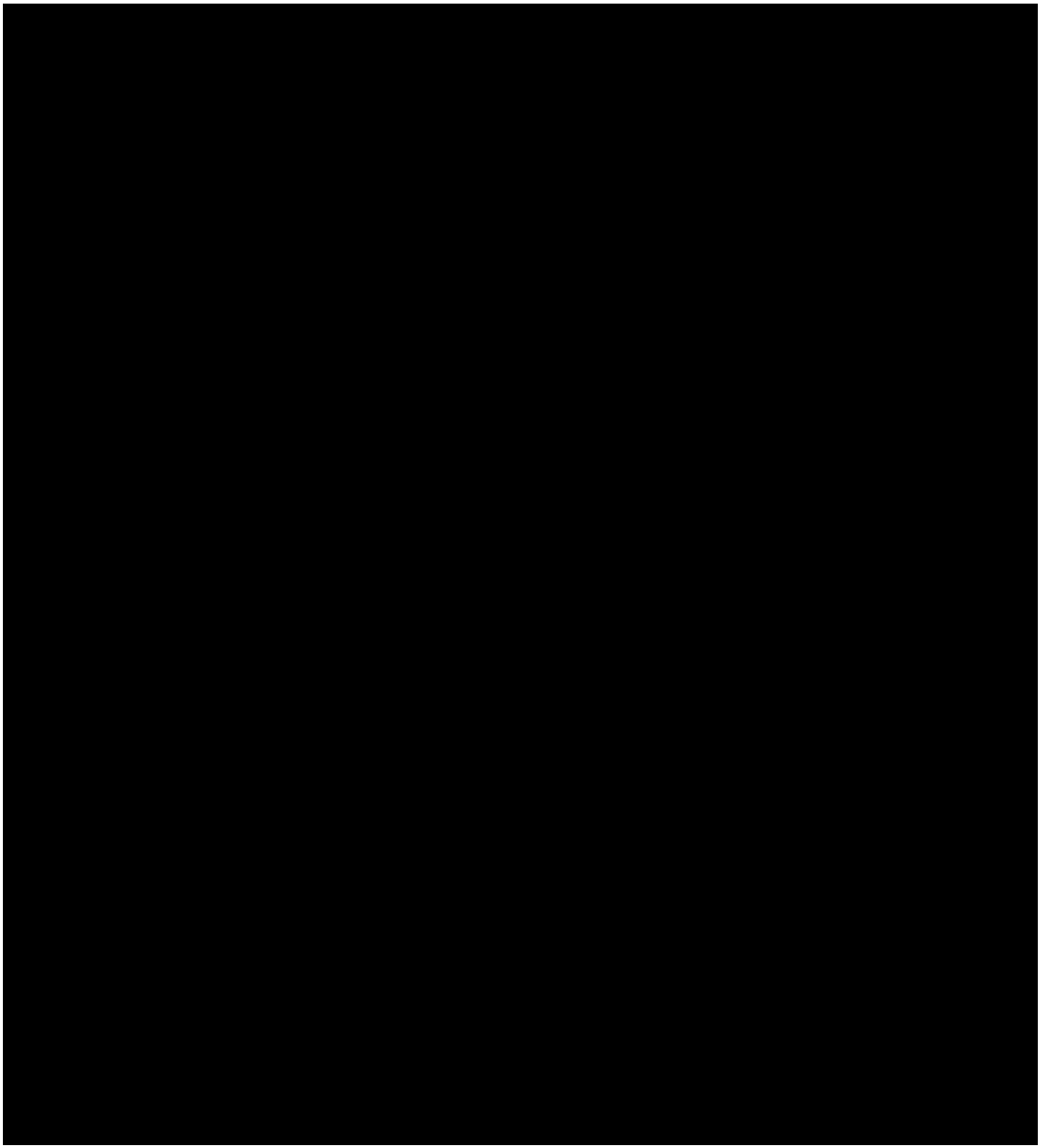

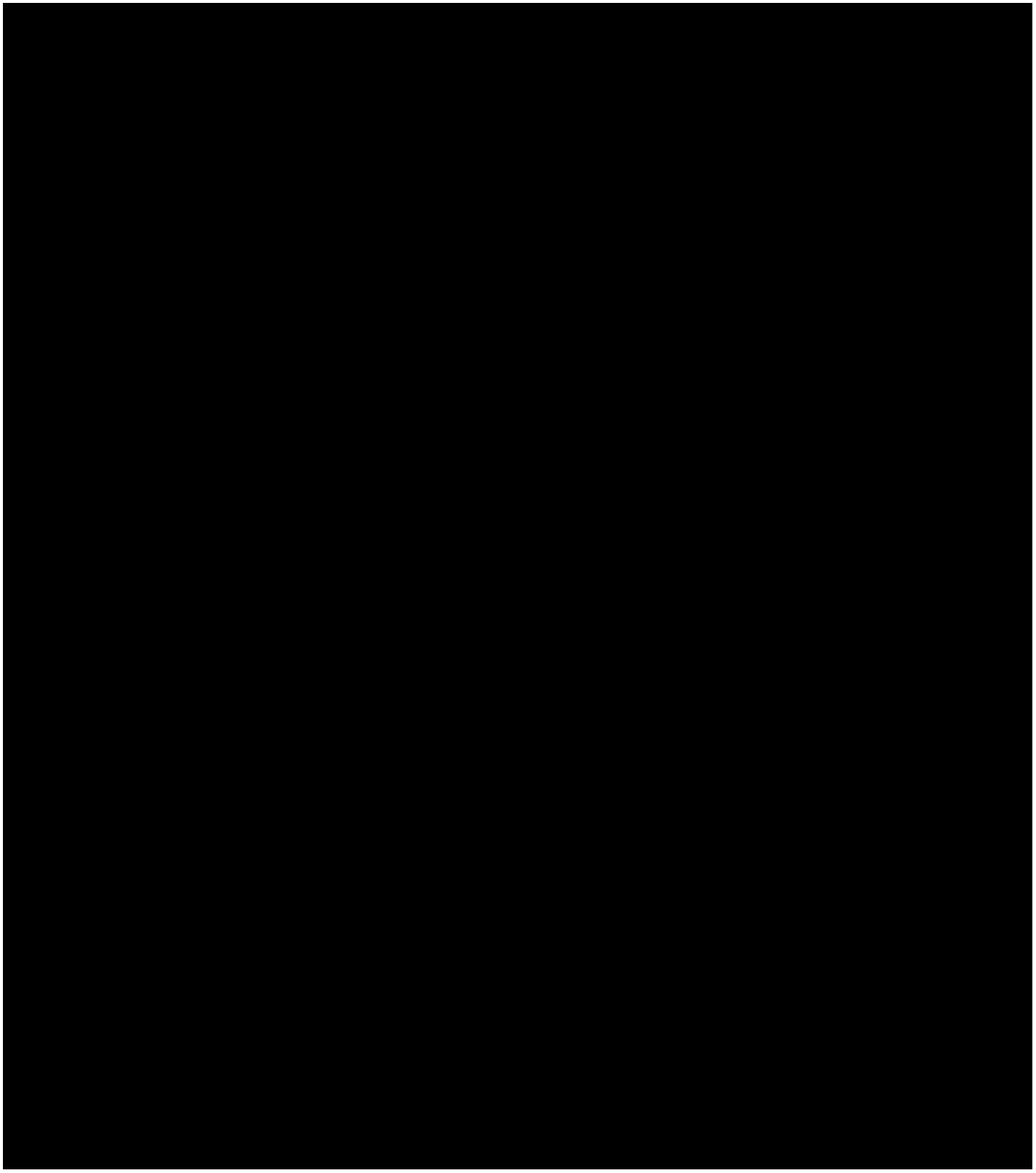

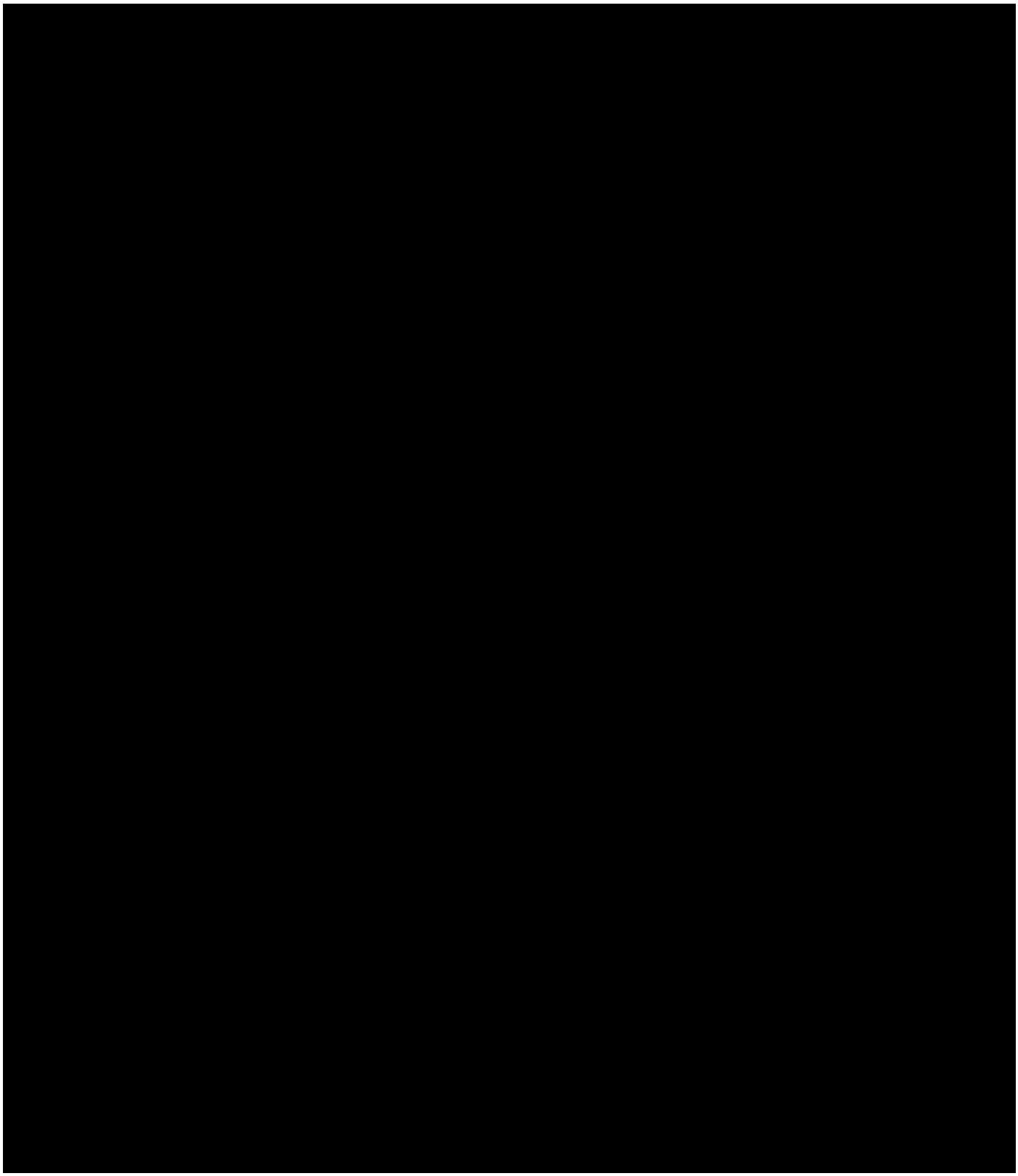

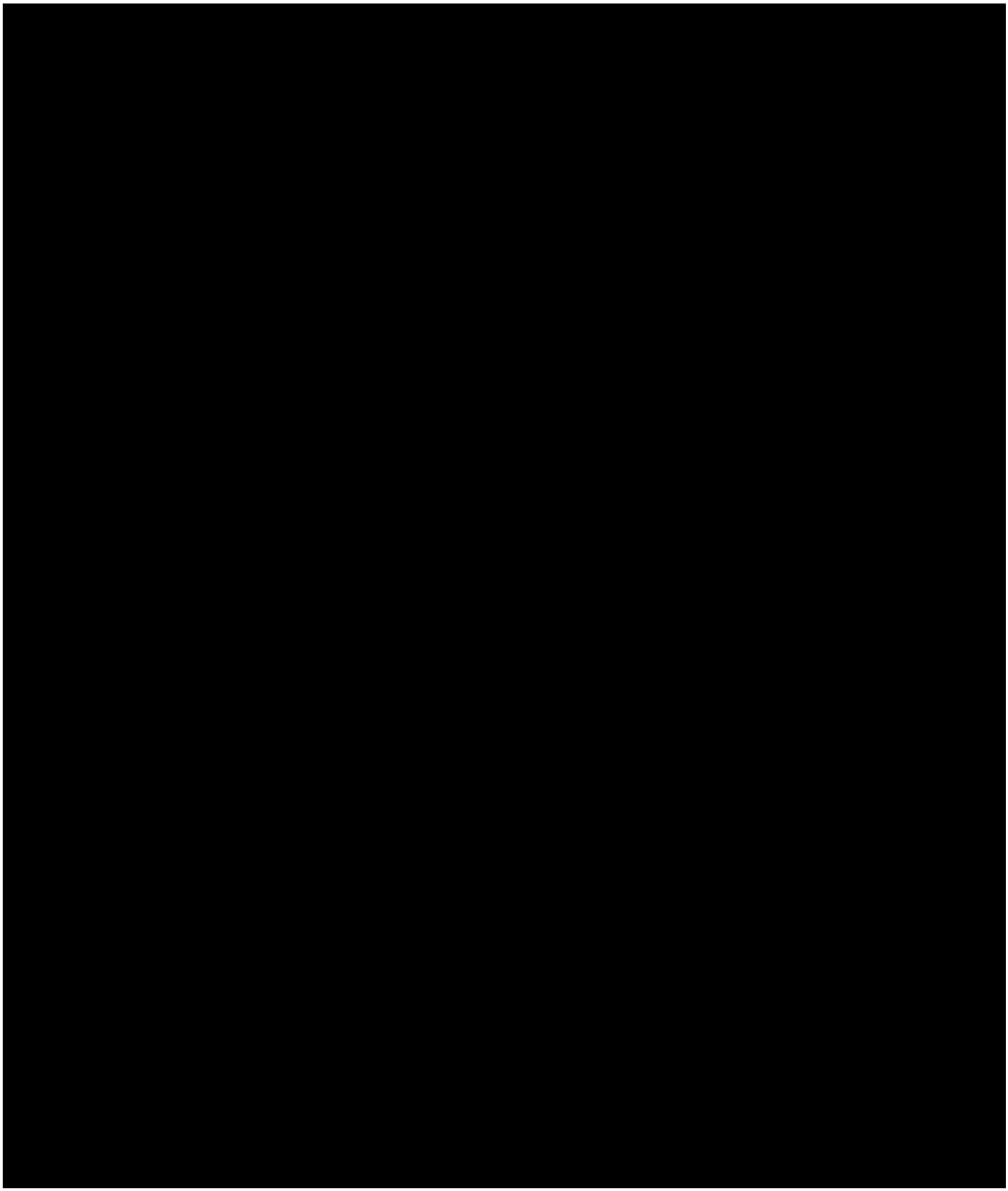

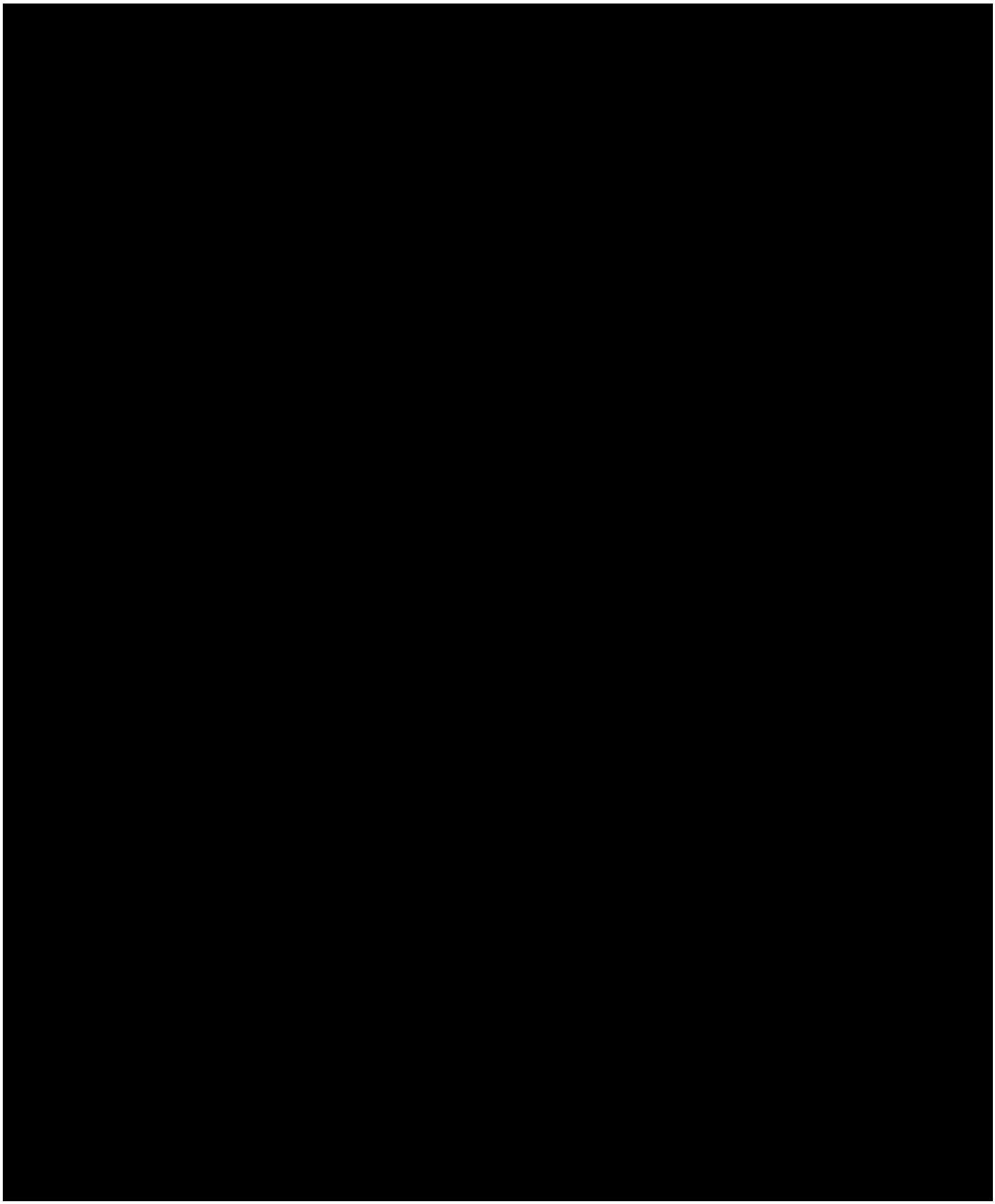

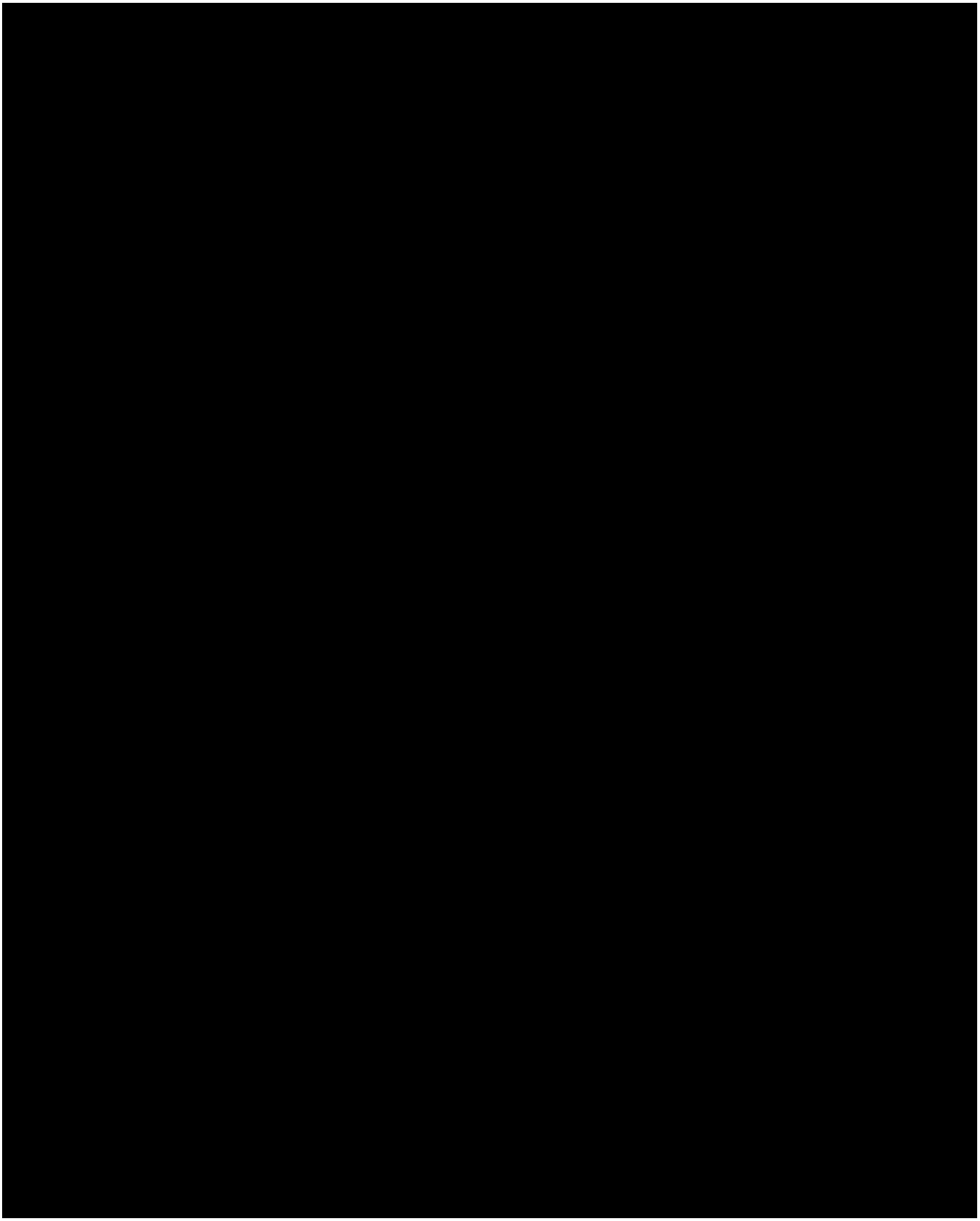

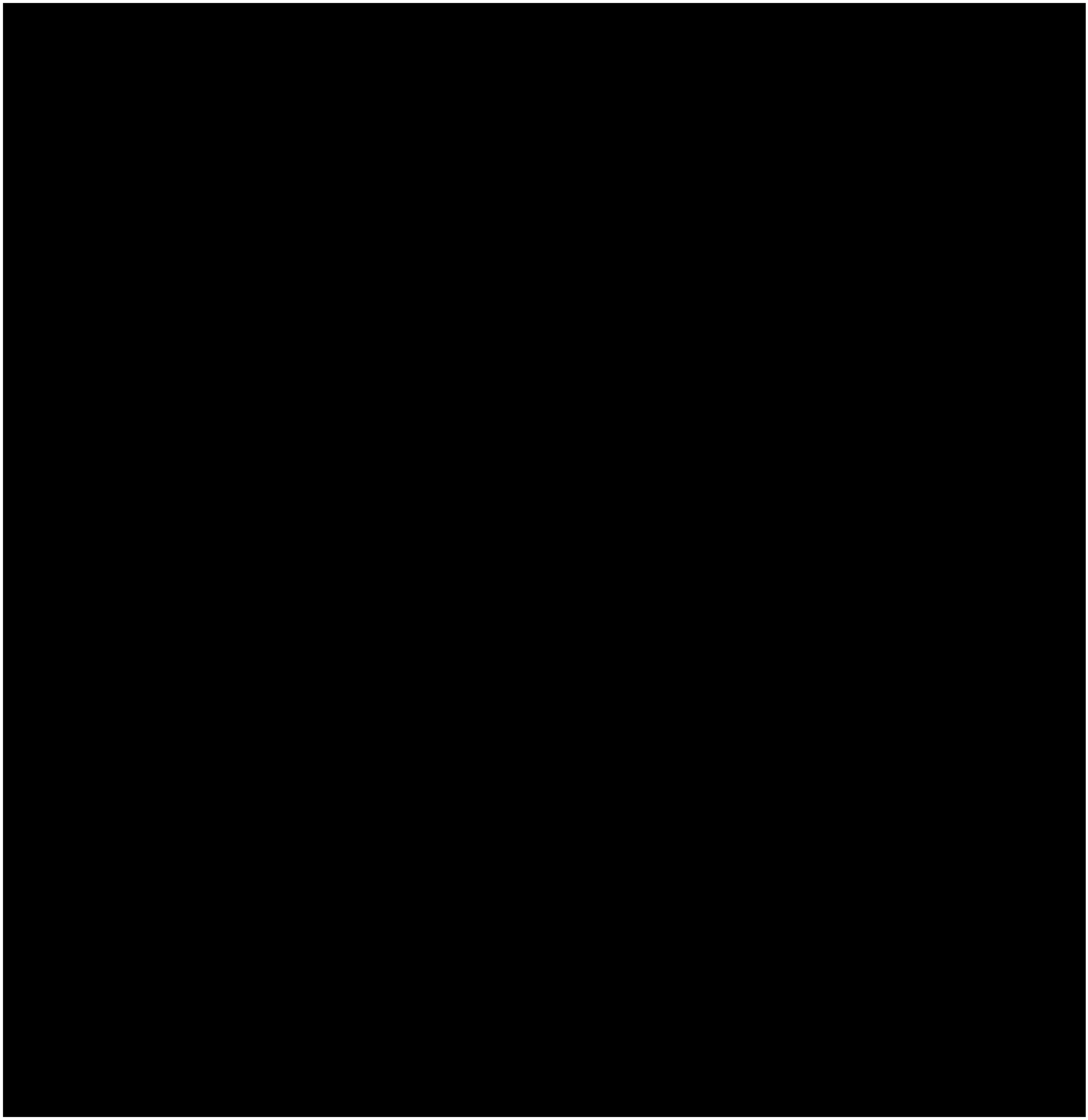

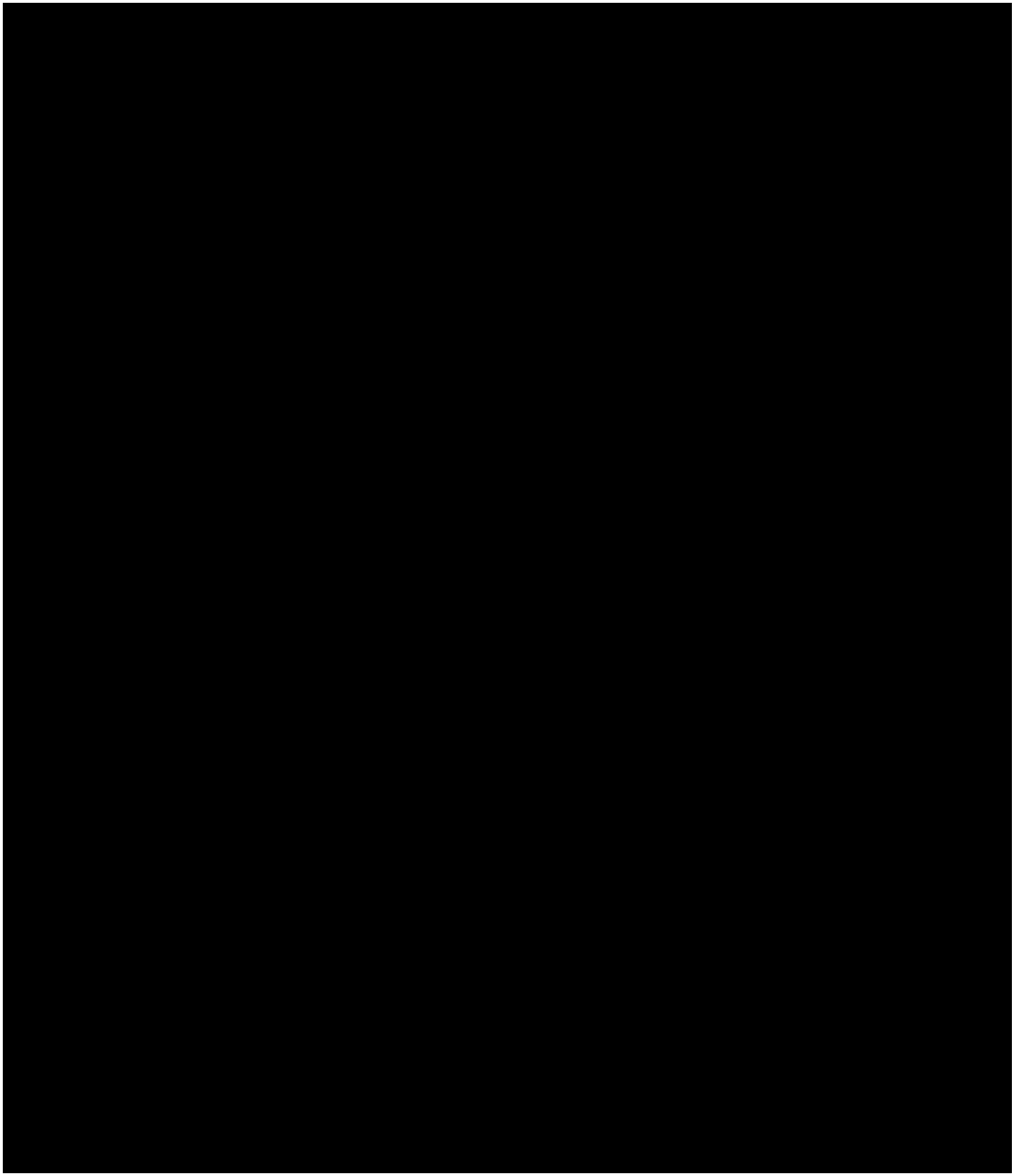

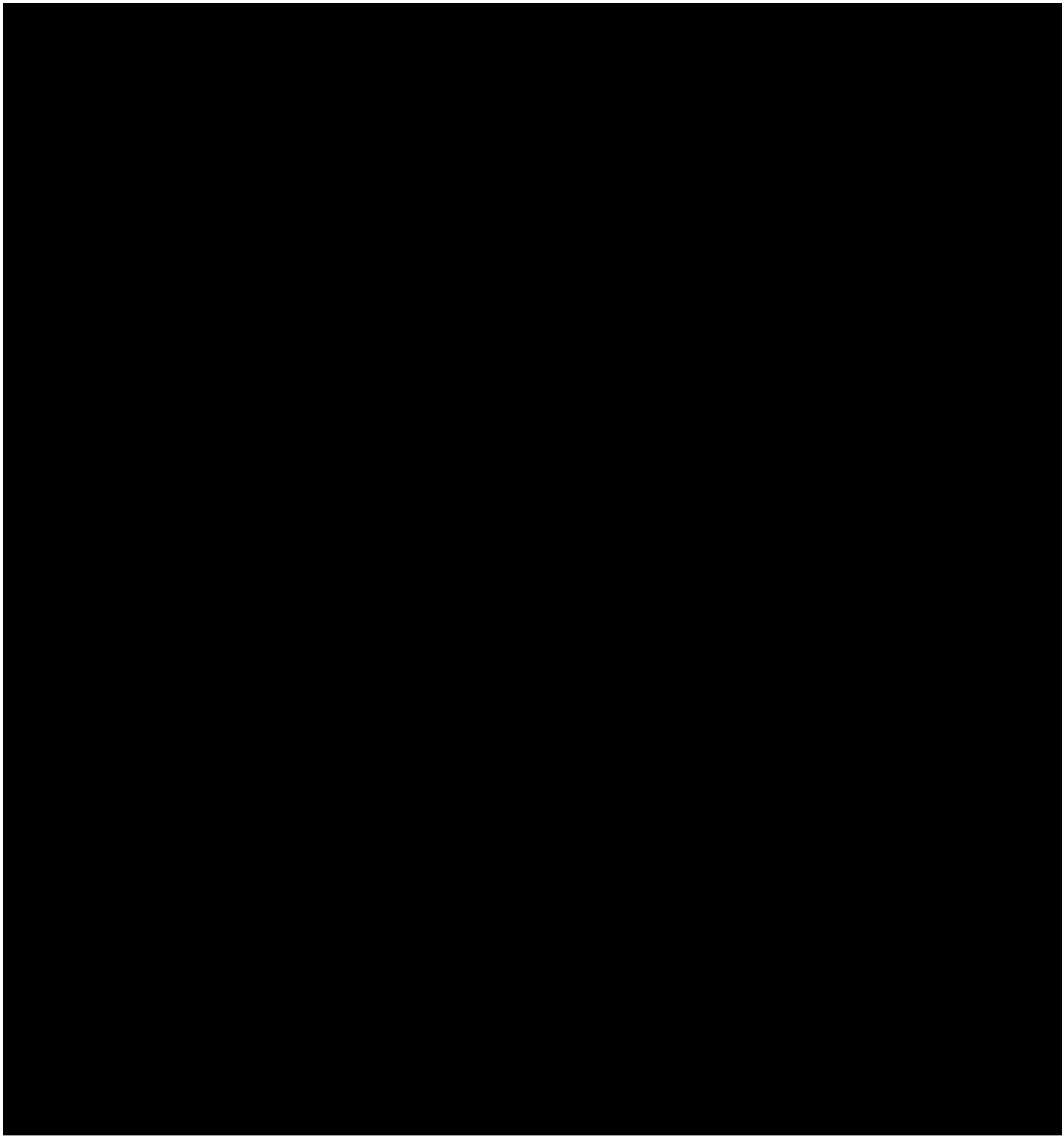

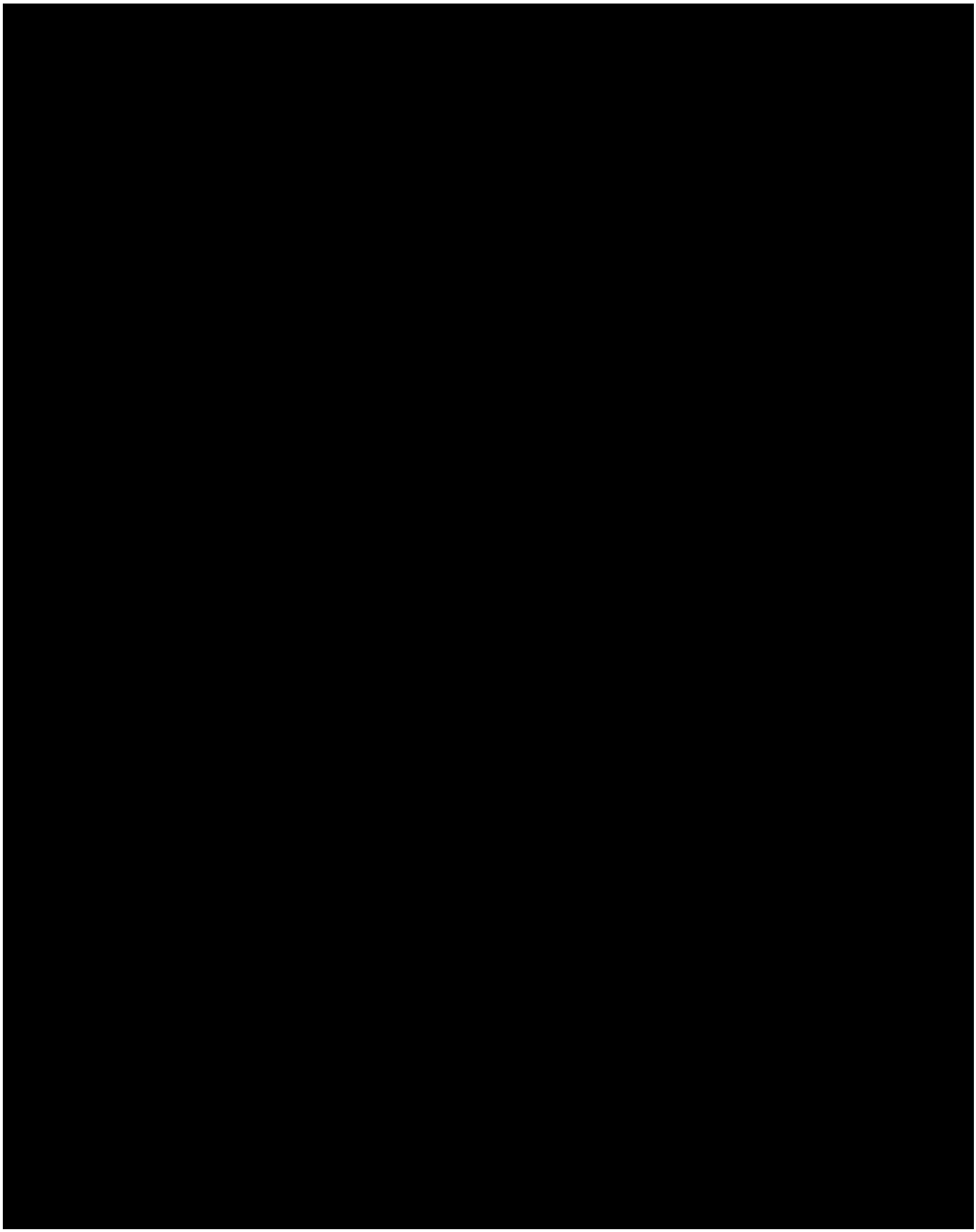

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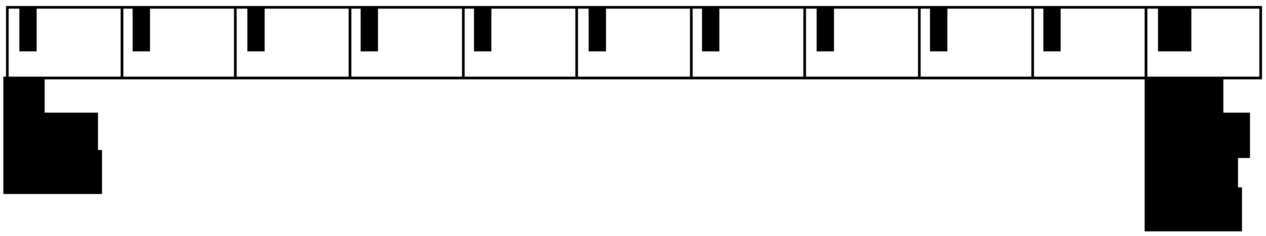

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SIGNATURE PAGE – SPONSOR

Study Title:	A randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of GLPG3970, administered orally for 6 weeks, in adult subjects with moderately to severely active ulcerative colitis
CSP Version:	1.0 Date: 29 May 2020

This CSP has been reviewed and approved by the sponsor to ensure compliance with this CSP, the current ICH-GCP Guideline E6, and applicable local ethical and legal requirements.

Medical Leader	Signature	Date

SIGNATURE PAGE – INVESTIGATOR

Study Title:	A randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of GLPG3970, administered orally for 6 weeks, in adult subjects with moderately to severely active ulcerative colitis
CSP Version:	1.0 Date: 29 May 2020

I, the undersigned, have read this CSP and will conduct the study as described in compliance with this CSP, the current ICH-GCP Guideline E6, and applicable local ethical and legal requirements.

Investigator Name	Signature	Date

Signature Page for glpg3970-cl-210-protocol 13822

Approval	[redacted] 02-Jul-2020 14:10:58 GMT+0000

Signature Page for glpg3970-cl-210-protocol 13822