STATISTICAL ANALYSIS PLAN

Project Number:	GLPG3970		
Study Number:	GLPG3970-CL-209		
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 rheumatoid arthritis and an inadequate response to methotrexate		
Development Phase:	2		
Status:	Final		
Version:	2.0	Date:	7-May-2021
EudraCT:	2020-000658-83	IND:	Not applicable
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VERSION HISTORY

SAP Amendment #	Date	Description of changes
SAP Version 1.0 Final	13-Nov-2020	Original Version
SAP Version 2.0 Final	07-May-2021	Derivation of duration of RA incorrect (dates need to be switched). Updated to [(date of first study drug administration) – (date of initial diagnosis)] / 365.25.
		SAP Section 6.2.2.2: Removal of waterfall plots. *Rationale: Waterfall plots were not previously removed from the SAP text.*
		SAP Section 6.3.2.6: Addition of a specification for the treatment-emergent definition for the toxicity grade, we went from this: *'A post-baseline toxicity grade 1, 2, 3 or 4 is defined as treatment-emergent when higher than the toxicity grade of the baseline result. If the baseline result is missing, a post-baseline toxicity grade 1, 2, 3 or 4 will be considered as treatment-emergent.'* To this: *'A post-baseline toxicity grade 1, 2, 3 or 4 is defined as treatment-emergent when higher than the toxicity grade of the baseline result* ***or when there is a change in direction (from H to L or from L to H)****. If the baseline result is missing, a post-baseline toxicity grade 1, 2, 3 or 4 will be considered as treatment-emergent*
		SAP Section 6.3.3.3 / Treatment-Emergent Abnormalities for ECG: Addition of a specification for the treatment-emergent definition for the Abnormalities, we went from this: *'Actual value: An abnormal post-baseline abnormality is defined as treatment-emergent when the abnormality is worse compared to the abnormality at baseline. When the baseline value is missing, post-baseline abnormalities are considered as treatment-emergent.'* To this:

		'Actual value: An abnormal post-baseline abnormality is defined as treatment-emergent when the abnormality is worse compared to the abnormality at baseline ***or when there is a change in direction (from H to L or from L to H)****. When the baseline value is missing, post-baseline abnormalities are considered as treatment-emergent.'*
		SAP Section 6.3.2.7: Specification of the definition of worst-case post-baseline toxicity grade, from: *'The worst-case toxicity grade is the highest toxicity grade scored for the laboratory test (and direction, increases and decreases).'* To: *'The worst-case toxicity grade is the highest toxicity grade* ***corresponding to the highest*** *laboratory test* ***value*** *(****by*** *direction, increases and decreases).* ***In case of several equal highest post-baseline actual values, the earliest occurrence will be taken for the analyses and will be flagged in the listings.****'*
		SAP Section 6.3.3.3 / Worst-Case Abnormality: Addition of a specification for the Worst-Case Abnormality definition, as here under in bold and underline: *'The worst-case categorized actual analysis value is the category corresponding to the highest post-baseline actual value.* ***In case of several equal highest post-baseline actual values, the earliest occurrence will be taken for the analyses and will be flagged in the listings.*** *The worst-case change from baseline is the category corresponding to the largest increase (positive change) from baseline.* ***In case of several equal largest increase from baseline, the earliest occurrence will be taken for the analyses and will be flagged in the listings.****'*
		SAP Section 6.3.4.5:

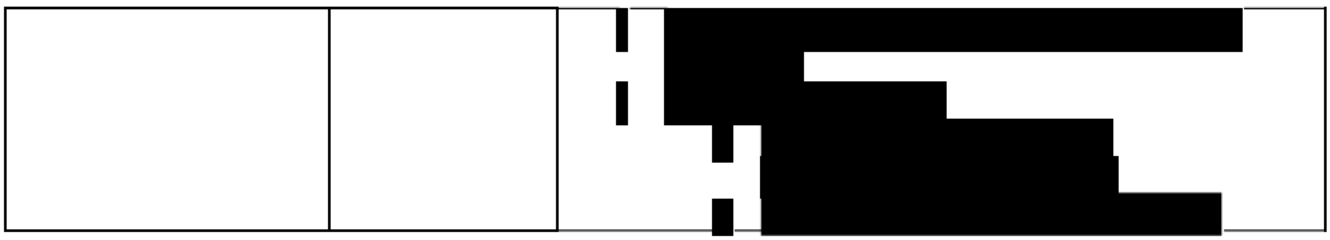
		Change of the entire section to be aligned with ECG for Worst-Case Abnormality definition. Changed in : *'The worst-case post-baseline categorized actual analysis value will be determined per subject, per parameter and for each analysis period, using all non-missing post-baseline records (including unscheduled and FU visits).* *The worst-case categorized actual analysis value is the category corresponding to the highest post-baseline actual value. In case of several equal highest post-baseline actual values, the earliest occurrence will be taken for the analyses and will be flagged in the listings.'*
		SAP Section 6.1.8.2. and Mock table MTSIEX04 - Summary of MTX Drug Administration: Specification that the dose, the route and the dose from to be summarized are the ones measured at baseline. Addition of the 'Dose form at baseline' in the Mock table. Removal of 'Dose adjusted from planned' in the mock table as it is not measure at baseline.
		SAP Section 4.4.1.2 Handling of Missing Result Data, change in the last paragraph here under in bold and underlined to specify the definition of the non-responder imputation (NRI): '*For some binary endpoints, missing data will be handled using both an OC approach and non-responder imputation* ***(NRI)*** *as specified in Section 6.2.* ***NRI being the imputation of missing values by a non-response/non-remission.***'
		SAP Section 4.3.4, baseline definition, addition of the sentence in bold and underlined, for the parameter for which the time was planned to be collected: *Baseline is defined as the last available assessment prior to the first intake of IP.* ***For the parameters for which the time of assessment was planned to be collected, if for their assessment on the day of first intake the time is missing, their assessment at time point "PRE-DOSE" (when applicable) will be considered as baseline, otherwise, previous days last available assessment will***

		<u>be selected.</u> *For the parameters for which the time of assessment was not planned to be collected, their assessment on the day of first intake of IP will be considered as baseline. If multiple values on the same day qualify as last available assessment, the average of these values will be used in the analysis.*
		SAP section 4.3.5. *Selection and Use of Analysis Visits*, proposition to remove the mention that the pre-baseline data will be provided in the profile line plot as these plots will be provide only on CHG and %CHG from baseline, as per change here under in bold: *Before first administration of IP, only Baseline will be used for the entire statistical analysis. Pre-baseline assessments will only be listed* ***~~and presented in individual subject profile plots~~***.
		SAP Section: 6.5.1: Updated the unit for fasting insulin as "mU/L". Updated derivation for HOMA-IR is HOMA-IR = (fasting insulin [mU/L] x fasting glucose [mg/dL]) / 405 Rationale: protocol contains a typo error
		[redacted]
		SAP Section 6.3.2.1:

		"Only data provided by the central laboratory will be used in tables and figures" has been replaced by "Only data provided by the central laboratory **along with corrected calcium (mmol/L)** will be used in tables and figures"
		SAP Section 6.3.2.2: Below derivation rule added: "The calcium level should be corrected in patients with low serum albumin levels, using the following formula: Adjusted total calcium(mmol/L) =Total calcium (mmol/L) + 0.02 [40−Albumin(g/L)]
		SAP section 6.3.2.9 Added additional profile plot in the log scale. "Also, profile line plots of the ratio to baseline will be provided by treatment group for the selected parameters."
		SAP section 6.2.2.2: Removal of the covariates 'baseline DAS28 (CRP), treatment, visit' from the definition of the covariates to be used in the MMRM to be compliant with the SAS code provided in appendix. TLF Mock: Removal of 'treatment, baseline value, visit (as categorical)' from the footnotes for MMRM, for all the endpoints for which a MMRM is used to be compliant with the SAS code provided in the SAP text appendix, and the MMRM actually used.
		
		SAP: Section numbering corrected for efficacy sections.
		SAP: Section 4.5.2: Inserted below texts "Some parameters namely hsCRP, cytokines (IL-10 and TNFα) and metabolic parameters (fasted insulin, HOMA-IR and

		HbA1c) are known to deviate heavily from the normal distribution but follow the log-normal distribution well. For these parameters, the geometric mean (GeoMean), geometric standard deviation (GeoSD), and geometric standard error (GeoSE) will be also reported for the summaries by treatment group and visit. GeoMean, GeoSD and GeoSE are not applicable for the summaries of the changes from baseline, however GeoMean, GeoSD and GeoSE will be reported for the summaries of percent changes from baseline. This will be done by obtaining the mean, SD and SE of log(value) - log(baseline) and then transforming these statistics back to the 'percent change scale' as 100 X {exponential(statistic) - 1}." Section 6.1.8: section added for additional listing "Procedure" SAP: Section 6.2.3.11.2: the paragraph starting from "The analysis of percent change from baseline…" updated as below "The analysis of percent change from baseline will be performed by analyzing the log(value) - log (baseline) and transforming statistics back to the 'percent change scale' as 100X{exponential(statistic)-1}. The analysis of percent change from baseline up to week 6 will use the same method as for analysis of the primary efficacy endpoint as detailed in section 6.2.2.2. The GeoMean (./÷ GeoSE) of the actual values and percent changes from baseline will be presented graphically over time." SAP section 6.3.2.9: updated this section to include "Profile line plots by subject of all actual observed values using relative day (ADY) will be presented by treatment group" TLF Mock: MGSFLB01: Figure for lab parameters of actual values over time added' SAP section 6.3.3.4: updated this section to include "Profile line plots by subject of all actual observed values using relative day (ADY) will be presented by treatment group"

		TLF Mock: MGSFEG01: Figure for ECG parameters of actual values over time added'
		SAP Section 6.5.2: [redacted]
		SAP Section 6.3.3.4: Section updated to include the following text: "A line plot by subject of the change from baseline will also be provided by treatment group."
		[redacted]



LIST OF ABBREVIATIONS

[redacted]	[redacted]
ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the plasma concentration-time curve
BLOQ	below lower limit of quantification
BMI	body mass index
[redacted]	[redacted]
CI	confidence interval
CL	clearance
CLCr	creatinine clearance
CRF	case report form
CRO	contract research organization
CRP	c-reactive protein
CSP	clinical study protocol
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
CTx	serum C terminal telopeptide type I collagen
DAS28	disease activity score based on 28 joints
ECG	electrocardiogram
eCRF	electronic case report form
EULAR	European League Against Rheumatism
FAS	full analysis set
FU	follow-up
H	high, above the upper limit of the normal range
[redacted]	[redacted]
HDL	high-density lipoprotein
High	high specificity test
HOMA-IR	homeostatic model assessment of insulin resistance
HR	heart rate
hsCRP	high sensitivity C-reactive protein

ICF	informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IP	investigational product
INF	infinity
IXRS	interactive voice/web response system
L	low, below the lower limit of the normal range
LDL	low-density lipoprotein
LLN	lower limit of the normal range
LLOQ	lower limit of quantification
LRV	lower reference value
LS	least squares
LSM	least square mean
MedDRA	medical dictionary for regulatory activities
MMRM	mixed models for repeated measures
MTX	methotrexate
n	number of non-missing data points
N	normal, with the limits of the normal range
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NRI	non-responder imputation
OC	observed cases
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic(s)
pop-PK	population PK
PR	pulse rate
QTc	corrected QT interval
QTcF	QT interval corrected for the heart rate using Fridericia's formula
RA	rheumatoid arthritis
Reg	regular test
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation

SDTM	study data tabulation model
SE	standard error
SJC66	swollen joint count evaluated in 66 joints
SI	standard international
SMC	Safety Monitoring Committee
TE	Treatment-emergent
TEAE	treatment-emergent adverse event
TJC68	tender joint count evaluated in 68 joints
TLF	tables, listings and figures
TV	target value
ULN	upper limit of the normal range
ULOQ	upper limit of quantification
VAS	visual analog scale
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the final statistical analysis of study GLPG3970-CL-209. The results of the analysis will be described in the clinical study report (CSR).

Technical details on derivations and mock tables, listings and figures (TLFs) will be presented in a separate document.

The statistical analysis will process and present the results following the International Council for Harmonization (ICH) standards, particularly the ICH-E3, ICH-E6, ICH-E9, ICH-R9 (R1) and ICH-E14 guidelines.

2. STUDY DESIGN AND OBJECTIVES

2.1. Study Objectives

2.1.1. Primary Objective

- To evaluate the effect of GLPG3970 compared to placebo on the signs and symptoms of rheumatoid arthritis (RA) in subjects with moderately to severely active RA and an inadequate response to methotrexate (MTX).

2.1.2. Secondary Objectives

- To evaluate the safety and tolerability of GLPG3970 compared to placebo in subjects with moderately to severely active RA and an inadequate response to MTX.
- To characterize the pharmacokinetic (PK) of GLPG3970 in subjects with moderately to severely active RA and an inadequate response to MTX.

2.1.3. Other Objectives

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Change from baseline in disease activity score based on 28 joints (C-reactive protein) [DAS28 (CRP)] at Week 6.

2.2.2. Secondary Endpoints

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

2.2.3. Other Endpoints

[redacted]

2.3. Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter parallel-group study evaluating GLPG3970 in adult subjects with moderately to severely active RA and an inadequate response to MTX. In this study, subjects will receive 1 dose level of GLPG3970 (400 mg once daily [q.d.]) or placebo on top of their stable dose and dosing regimen of MTX.

The study is planned to randomize 25 subjects in a 3:2 ratio (15 subjects planned to receive GLPG3970 and 10 subjects planned to receive placebo).

The study will consist of 3 study periods:

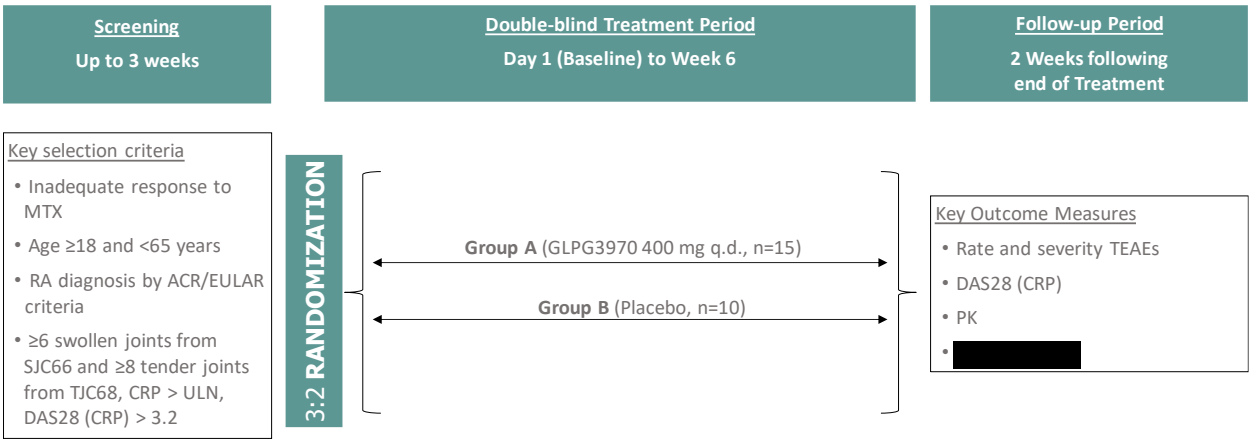
- Screening period: up to 3 weeks with 1 study visit.
- Double-blind treatment period: 6 weeks with 4 study site visits (Days 1, 15, 29, and 43) and 1 telephone call (Day 8).
- Follow-up (FU) period: 2 weeks with 1 study visit.

Subjects will participate in the study for a maximum of 11 weeks (screening to FU) and will receive oral GLPG3970 or placebo, as a reconstituted oral solution, q.d. for 6 weeks.

Refer to the Schedule of Assessments (Section 2.5) for further details.

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

Figure 1 Schematic Diagram



2.4. Clinical Study Protocol (CSP) and CSP Amendments

This SAP is based on the protocol version 1.0, dated 29-May-2020.

2.5. Scheduled of Assessments

The study assessments will be undertaken at time points as specified in the Schedule of Assessments (Table 1). For detailed instructions on the clinical study procedures, please see the relevant CSP sections and CSP Section 8.1, “Timing of Assessments”.

Table 1 Schedule of Assessments

EVENT	SCREENING PERIOD	TREATMENT PERIOD[1],[2]						FOLLOW-UP PERIOD[2]
Study visit	**S**	**1**	**2**	**3**	**4**	**5**	**ED[3]**	**FU Visit**
Study Weeks		**Baseline**	**1**	**2**	**4**	**6**		
Study Day (D) ± Days	**-21 to -1**	**1**	**8 ± 2**	**15 ± 2**	**29 ± 2**	**43 ± 2**	**Early treatment discontinuation**	**57 ± 3**
On site visit	✓	✓		✓	✓	✓	✓	✓
Telephone call			✓					
Informed consent	✓							
Inclusion/exclusion criteria	✓	✓						
Demographics	✓							
Medical history	✓							
FSH test (postmenopausal women)	✓							
Pregnancy test[4]	✓	✓			✓	✓	✓	
Physical examination	✓	✓				✓	✓	✓

[1] On dosing days, all assessments are to be performed within 3 hours pre-dose, unless otherwise specified.
[2] Subjects must come for the study visits 1, 3 and 5 in the morning in a fasting state (no food intake for at least 8 hours). For Visit 1 (predose measurements) and for 2 post dose visits (Visit 3, 4 or 5) all attempts should be made to plan the visit within 2 days following MTX intake.
[3] Subjects who discontinue treatment early will be requested to return for an early discontinuation (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] Serum beta human chorionic gonadotropin at screening, baseline (Visit 1), Visit 4 and Visit 5, or at the ED visit, if applicable (all female subjects).

EVENT	SCREENING PERIOD	TREATMENT PERIOD[1],[2]						FOLLOW-UP PERIOD[2]
Study visit	**S**	**1**	**2**	**3**	**4**	**5**	**ED[3]**	**FU Visit**
Study Weeks		**Baseline**	**1**	**2**	**4**	**6**		
Study Day (D) ± Days	**-21 to -1**	**1**	**8 ± 2**	**15 ± 2**	**29 ± 2**	**43 ± 2**	**Early treatment discontinuation**	**57 ± 3**
Vital signs	✓	✓		✓	✓	✓	✓	✓
Body weight and height [5]	✓	✓		✓	✓	✓	✓	✓
12-lead triplicate ECG	✓	✓		✓	✓	✓	✓	✓
Serology	✓							
QuantiFERON-TB Gold test	✓							
SARS-CoV-2 RT-PCR test[6]	✓	✓	As needed					
SARS-CoV-2 serology test[6]		✓	As needed					
Randomization		✓						
Clinical safety blood samples	✓	✓[7]		✓[7]	✓	✓[7]	✓	✓
Clinical safety urine samples [8]	✓	✓[9]		✓	✓	✓[9]	✓	✓

[5] Height only to be measured at screening.
[6] RT-PCR from a nasal swab sample at screening and RT-PCR from a nasal swab sample and serology testing at baseline (Visit 1), and as needed when subject presents signs and symptoms of SARS-CoV-2 infection.
[7] Fasted glucose, fasted insuline and HOMA-IR only at Visit 1, 3 and 5 and the ED visit, if applicable.
[8] On dosing days, clinical safety urine samples will be taken predose, on the same visit day.
[9] Visit 1 and 5: predose and 2 hours postdose. Calcium and phosphate should only be evaluated at Visits 1 and 5.

EVENT	SCREENING PERIOD	TREATMENT PERIOD[1],[2]						FOLLOW-UP PERIOD[2]
Study visit	**S**	**1**	**2**	**3**	**4**	**5**	**ED[3]**	**FU Visit**
Study Weeks		**Baseline**	**1**	**2**	**4**	**6**		
Study Day (D) ± Days	**-21 to -1**	**1**	**8 ± 2**	**15 ± 2**	**29 ± 2**	**43 ± 2**	**Early treatment discontinuation**	**57 ± 3**
PK blood samples for GLPG3970		✓[10]		✓[11]	✓[11]	✓[11,12]	✓	
[redacted]		✓		✓	✓			
[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	
[redacted]		[redacted]				[redacted]	[redacted]	
Subject diary evaluation		✓	✓	✓	✓	✓	✓	✓
SJC66/TJC68	✓	✓		✓	✓	✓	✓	
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	

[10] Visit 1: predose (within 30 minutes prior to dosing), 1 sample within [0.5-1.5 hours postdose] and 1 sample within [2 – 2.5 hours post dose].
[11] Visit 3, 4 and 5: predose (within 30 minutes prior to dosing).
[12] Visit 5: 1 sample within [4-6 hours postdose].
[13] [redacted]

EVENT	SCREENING PERIOD	TREATMENT PERIOD[1],[2]						FOLLOW-UP PERIOD[2]
Study visit	**S**	**1**	**2**	**3**	**4**	**5**	**ED[3]**	**FU Visit**
Study Weeks		**Baseline**	**1**	**2**	**4**	**6**		
Study Day (D) ± Days	**-21 to -1**	**1**	**8 ± 2**	**15 ± 2**	**29 ± 2**	**43 ± 2**	**Early treatment discontinuation**	**57 ± 3**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dispense IP		✓[15]		✓[15]	✓[15]			
IP administration [15]		Once daily throughout the treatment period						
AE and concomitant medication	throughout the study							

[15] On Visit 1, 3, 4 and 5 administration of IP must occur at site.

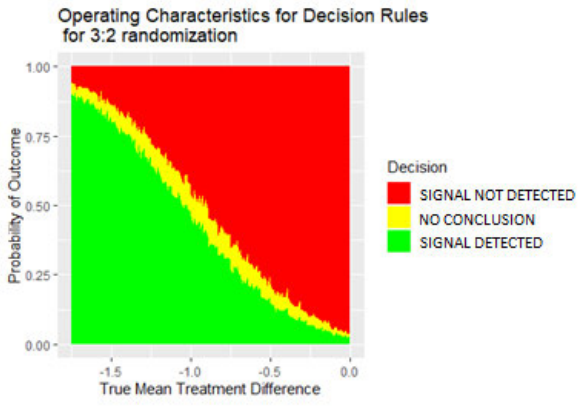
2.6. Sample Size Justification

The operating characteristics of the chosen decision framework at a sample size of 15 subjects (GLPG3970) + 10 subjects (placebo) are represented in the following graphical output and table, and were deemed acceptable. A common standard deviation (SD) of 1.3 for placebo and GLPG3970 was assumed based on previous experience with RA studies.

Lower Reference Value (LRV) and Target Value (TV) 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.

A dropout rate of 20% was taken into account to allow a minimum of 20 subjects to complete the study. 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.

Probability	Reference value	Outcome
0.852	-1.6	Signal detected
0.043	-1.6	No conclusion
0.105	-1.6	No signal detected
0.192	-0.6	Signal detected
0.091	-0.6	No conclusion
0.717	-0.6	No signal detected



2.7. Randomization and Blinding

2.7.1. 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 at visit 1. Allocation of each subject to a given treatment will be done using a centralized electronic system (interactive voice/web response system [IXRS]). Subjects will be randomized in a 3:2 ratio to GLPG3970 or placebo.

2.7.2. 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 sponsor's medical responsible, 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 within 24 hours after unblinding has occurred.

The blind can be broken 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 site. The reason for breaking the blind will be indicated and justified in the source documentation.

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

Code-breaking information (via IXRS vendor) will be provided to the bioanalytical laboratory responsible for plasma drug determination sample analysis, the person responsible for providing unblinded data to the internal Safety Monitoring Committee (SMC), the contract research organization (CRO) responsible for the population PK modeling, and to the sponsor pharmacovigilance vendor for serious adverse event (SAE) reporting purposes.

3. STUDY ESTIMANDS

Hypothetical and treatment policy estimand for primary efficacy endpoint:

Attribute	**Details**
Treatments	GLPG3970 (400 mg q.d.) vs. Placebo
Population	• Population target defined through the inclusion/exclusion criteria (see CSP). • Analysis Set: Full Analysis Set (FAS), defined as all randomized subjects

	who have received at least 1 dose of IP.
Endpoint	Change from baseline in DAS28 (CRP) at Week 6.
Population-level summary	Difference (GLPG3970-Placebo) in least square mean (LSM).For further details see study SAP section 6.2.2.2.
Intercurrent events and strategies to handle those	• Early treatment discontinuation (for any reason) is handled using the hypothetical strategy • Other intercurrent events (e.g. major protocol violations, intake of prohibited medication, lack of compliance) are handled using the treatment policy strategy (i.e. they are ignored)

Estimand for the secondary objective (safety)

Attribute	**Details**
Treatments	GLPG3970 (400 mg qd) vs. Placebo
Population	• Population target defined through the inclusion/exclusion criteria (see CSP). • Analysis Set: Safety Analysis Set, defined as all subjects who were administered IP at least once.
Endpoint	Presence of TEAE
Population-level summary	Percentage of subjects with TEAEs.
Intercurrent events and strategies to handle these	Intercurrent event: early treatment discontinuation (for any reason): handled using the while-on-treatment strategy. It is expected that no further data collection happens after treatment discontinuation, except of course the normal FU visit. All collected data up to (and including) the last contact FU visit is regarded as possibly

	influenced by the drug exposure and thus will be used in the analysis. Intercurrent event: major protocol deviations, intake of prohibited/rescue medication, lack of compliance: handled using the treatment policy strategy. All collected data will be used in the analysis.

4. GENERAL METHODOLOGY

4.1. Analysis Sets

The analysis set will always be indicated in a subtitle in the table, listing or figure.

4.1.1. All Screened Analysis Set

All subjects who signed and dated an informed consent form (ICF).

4.1.2. All Randomized Analysis Set

All screened subjects who were randomized into the clinical study.

4.1.3. Safety Analysis Set

All subjects who have been administered at least 1 dose of IP.

4.1.4. Full Analysis Set

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

4.1.5. 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 analysis.

For population PK modeling, besides the plasma concentration, the corresponding PK sampling time and the time of last drug intake prior to taking the sample should be available. The results from the population PK analysis will be presented in a separate document.

4.1.6. [redacted]

[redacted]

4.1.7. [redacted]

4.2. Randomized Versus Actual Treatment Group

For subject information and efficacy parameters, the treatment group as assigned by the randomization will be used in the analysis (i.e. as-randomized analysis).

The actual treatment groups will be used for the analysis of safety, PK and PD parameters. The "actual" rather than "randomized" treatment will be used only in case the "wrong" drug had been taken during the entire study duration.

Differences between the randomized and actual treatment group will be listed in the disposition/randomization section of the analysis.

4.3. Analysis Periods and Analysis Time Points

4.3.1. Relative Day

The timing of an assessment or an event relative to a reference date will be calculated as follows:

When the concerned date is before the reference date:

Relative day (days) = concerned date-reference date

When the concerned date is the equal to or later than the reference date:

Relative day (days) = concerned date-reference date +1 day

where:

- The *concerned date* could be the measurement date of the assessment, or the start or end date of the event.
- The *reference date* default is the date of the first dose of IP administration, unless specified otherwise.
- *Date* implies a complete date having day, month and year available. Unless otherwise specified, the *relative day* will remain missing when it cannot be calculated due to absence or incompleteness of the concerned and/or reference dates.

The general terms of this formula also apply when similar relative timings are required in other time units, for example in minutes.

4.3.2. Analysis Periods

For treated subjects, adverse events and assessments will be allocated to analysis periods according to

Table 1.

Table 1 Analysis Periods

Analysis Period	Start Analysis Period	End Analysis Period
Screening	Date of signing the ICF, with 00:00 added as time part	Date (time) of first IP administration - 1 minute
Treatment	Date (time) of first IP administration.	Study termination date (i.e. date of last contact), with 23:59 added as time part

The last analysis period will always end on the date of last contact.

For every subject, all assessments performed and all events occurring during the study are expected to have a (start) date (/time) between the date of informed consent (IC) signature and the last contact date. Obvious exemptions are historical records like medical history or concomitant therapies having started before the study.

Assessments and events will be allocated to one of these analysis periods by incidence, meaning placing the record (start) date and time between the matching start and end dates and times of the subject's own analysis periods, assuming completeness of all dates and times, or further determined by the presence of timing indicators such as tick boxes flagging AEs starting before/after first IP administration, or by worst-case considerations for AEs if needed. For the parameters for which the time of assessment was not planned to be collected, their assessment on the day of first IP administration will be considered as baseline and will be reported under the 'Screening' analysis period with the exception of AEs.

4.3.3. Analysis Windows

For the efficacy, PK, [redacted] and safety assessments, all data (including data obtained at unscheduled visits) will be placed into time windows based on the relative day (ADY) of the assessment (relative to the first dose of IP), according to the following allocation tables:

For endpoints with multiple components, analysis windows will be derived separately for each component/parameter.

Table 2: Analysis Visit Window for non-PK data

Visit date and time	Relative day (ADY)	Assessment visit (VISIT)	Time window (in ADY)	Target day	Analysis visit (AVISIT)
On or before first study drug administration	≤1	Last assessment at any point in time before first study drug administration	≤1	1	Baseline
After first study drug administration	>1	Any scheduled (non follow-up), unscheduled, or early discontinuation visit	2 to 12	8	Week 1
			13 to 22	15	Week 2
			23 to 36	29	Week 4
			37 to 49	43	Week 6
		Follow-up	CRF collected follow-up visit		Follow-up

Table 3: Analysis Visit Window for PK data

Visit date and time	Relative day (ADY)	Assessment visit (VISIT)	Time window (in ADY)	Target day	Analysis visit (AVISIT)	Analysis time point (ATPT)
Before first study drug administration	<1 or pre-dose at ADY=1	Last assessment at any point in time before first study drug administration	<1 or pre-dose at ADY=1	1	Baseline	Pre-dose (within 30 minutes prior to dosing)
Same as or after first study drug administration	≥ 1	Any scheduled (non follow-up), unscheduled, or early discontinuation visit	1	1	Day 1	As indicated in the database: 0.5-1.5, 2-2.5 hours post-dose
			13 to 22	15	Week 2	As indicated in the database: Pre-dose (within 30 minutes prior to dosing)
			23 to 36	29	Week 4	As indicated in the database: Pre-dose (within 30 minutes prior to dosing)
			37 to 49	43	Week 6	As indicated in the database: Pre-dose (within 30 minutes prior to dosing) and within [4-6 hours post dose].

Visit date and time	Relative day (ADY)	Assessment visit (VISIT)	Time window (in ADY)	Target day	Analysis visit (AVISIT)	Analysis time point (ATPT)
		Follow-up	CRF collected follow-up visit		Follow-up	

4.3.4. Definition of Baseline

Baseline is defined as the last available assessment prior to the first intake of IP. For the parameters for which the time of assessment was planned to be collected, if for their assessment on the day of first intake the time is missing, their assessment at time point "PRE-DOSE" (when applicable) will be considered as baseline, otherwise, previous days last available assessment will be selected. For the parameters for which the time of assessment was not planned to be collected, their assessment on the day of first intake of IP will be considered as baseline. If multiple values on the same day qualify as last available assessment, the average of these values will be used in the analysis.

For ECG data assessed in triplicate, baseline is defined as the average (stored without rounding) of the combination of the most complete replicated ECG parameter before first intake of IP and at the same time the closest to it, selecting in the following order:

First consider Day 1, pre-dose:

- Select the average of the last available triplicate ECG parameter on that day;
- If there is no triplicate, select the average of the last available duplicate ECG parameter;
- In the absence of triplicates and duplicates the last available single ECG parameter will become baseline.

If baseline is not yet determined, consider the previous day and repeat the above selection (average of last triplicate, average of last duplicate, last single ECG on that day). Repeat the whole process successively for each previous day(s) as needed until baseline is determined.

4.3.5. Selection and Use of Analysis Visits

Before first administration of IP, only Baseline will be used for the entire statistical analysis. Pre-baseline assessments will only be listed. After first administration of IP, if multiple valid, non-missing assessments exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- The record closest to the nominal day for that visit will be selected, or
- If there are 2 records that are equidistant from the nominal day, or more than 1 record (with time known) on the selected day, the latest record will be taken
- If chronological order cannot be determined (e.g., more than 1 record on the same day with time missing), the average of the records will be computed and reported in the analysisFor the composite endpoints including DAS28 (CRP), [redacted], the following steps will be used to derive [redacted], unless otherwise specified:
- Step 1: Put [redacted] component value into an analysis visit window.

- Step 2: Within each visit window, select the data points for analysis.
- Step 3: Combine these selected data points within each analysis visit window across the components

4.3.6. Handling of Missing Data

4.3.6.1. Handling of Missing Date-Time Data

No imputations will be done in case of missing date (time) fields, nor for the missing parts of partially known date (time) fields.

Assessments with missing date (time) will be omitted from the summaries by visit.

Event-type data (e.g. AEs, concomitant medications) with missing date (time) will be allocated to analysis periods using a worst-case approach as explained in the respective sections.

4.3.6.2. Handling of Missing Result Data

No imputation will be done of missing result data unless otherwise specified. That is, an observed case (OC) analysis will be performed unless otherwise specified. Endpoints analyzed via mixed models for repeated measures (MMRM) handle missing data via the maximum-likelihood function.

For some binary endpoints, missing data will be handled using both an OC approach and non-responder imputation (NRI) as specified in Section 6.2. NRI being the imputation of missing values by a non-response/non-remission.

4.3.6.3. Censoring of Time to Event Data

Not applicable.

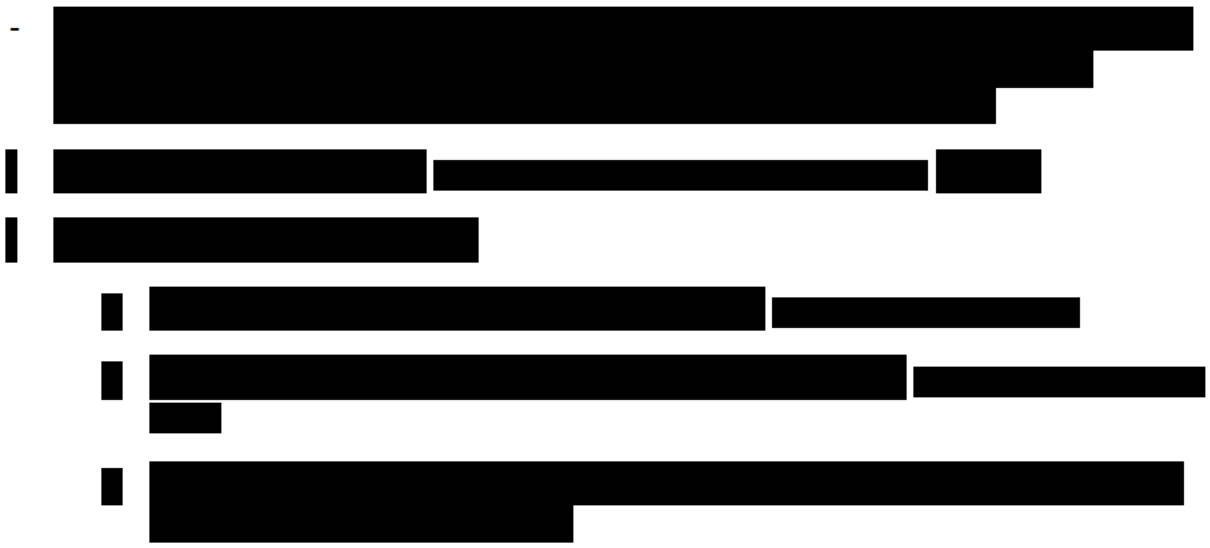
4.3.7. Handling of Values Below or Above a Threshold

Results of continuous parameters, as well as normal limits of these reported as below (or above) the detection limit will be imputed by the value one precision unit smaller (or larger) than the detection limit itself. In listings, the original value will be presented.

Example: if the database contains the value “<0.04”, then for the descriptive statistics the value “0.03” will be used. The value “>1000” will be imputed by “1001”.

For PK data, values below the limit of quantification will be imputed by 0 for the calculation of descriptive statistics presentation; except for the geometric mean and the geometric CV%, where it will be imputed as LLOQ/2. These values will be listed as “below lower limit of quantification (BLOQ)”.

[redacted]



4.3.8. Handling of Outliers

There will be no exclusion of outliers, all measured values will be included in the analyses.

4.3.9. Stratification Factors

Not applicable.

4.4. Presentation of Results

4.4.1. Presentation of Treatment Groups

Results will be presented by treatment group:

- GLPG3970 400 mg qd
- Placebo

In the Subject Information, a grand total "All Subjects" will be added to summarize all subjects over all treatment groups in tables.

4.4.2. Calculation of Descriptive Statistics

For continuous parameters, descriptive statistics will be presented when $N \geq 2$. When $N = 1$, the observation will not be shown in tables nor in figures of summary statistics but will only be listed.

Descriptive statistics will include:

- the number of non-missing data points (n);
- the arithmetic mean;
- the standard error (SE) and standard deviation (SD);

- the median, minimum and maximum;
- 90% confidence interval (CI) of the mean (if indicated in the relevant section).
- Some parameters namely hsCRP, cytokines (IL-10 and TNFα) and metabolic parameters (fasted insulin, HOMA-IR and HbA1c) are known to deviate heavily from the normal distribution but follow the log-normal distribution well. For these parameters, the geometric mean (GeoMean), geometric standard deviation (GeoSD), and geometric standard error (GeoSE) will be also reported for the summaries by treatment group and visit. GeoMean, GeoSD and GeoSE are not applicable for the summaries of the changes from baseline, however GeoM, GeoSD and GeoSE will be reported for the summaries of percent changes from baseline. This will be done by obtaining the mean, GeoSD and GeoSE of log(value) - log(baseline) and then transforming these statistics back to the 'percent change scale' as 100 X {exponential(statistic) - 1}.

For PK data, descriptive statistics will include:

- the number of non-missing observations (n);
- the number of data points above the LLOQ;
- the arithmetic mean;
- SE and SD;
- the median, minimum and maximum;
- the coefficient of variation (CV%);
- the geometric mean and geometric CV%.

If less than 50% of the subjects have quantifiable values, only the number of subjects with data, number of data points above the LLOQ, the arithmetic mean, median, minimum, and maximum will be presented with the original calculated value. The other descriptive statistics will be listed as “NC” (not calculated).

If the calculated descriptive statistic is BLOQ, then it will be presented as “BLOQ”.

Individual values and descriptive statistics of concentrations and PK parameters will be presented with 3 significant digits.

4.4.3. Calculation of Percentages

Frequencies and percentages will be generated for categorical parameters.

For event-type data (e.g. AEs), the denominator will be all subjects in the analysis set and analysis period. For other data (e.g. worst-case analysis of assessments), the denominator will be all subjects with (post-baseline) data for the parameter, in the analysis set and analysis window/period.

5. INTERIM ANALYSES AND INTERNAL DATA SAFETY MONITORING COMMITTEE

No formal interim analysis is planned for this clinical study.

An internal SMC independent from the study will review unblinded safety data during the course of the study. This Committee may involve external medical experts (such as an expert in the field of RA 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 clinical study team will remain blinded to the allocation of subjects to treatments during the course of the study. The process is described in a separate 'SMC Charter'.

6. STATISTICAL ANALYSES

6.1. Subject Information

Subject information will be tabulated using the Safety Analysis Set, unless specified otherwise. No inferential testing will be performed, nor will p-values be provided.

Subject information will be tabulated with descriptive statistics per planned treatment group, as well as overall.

6.1.1. Demographic and Baseline Disease Characteristics

The following parameters will be summarized:

- date of ICF signature (listed);
- sex;
- age at signing the ICF (years);
- age, categorized (years): 18 ≤ age < 65; 65 ≤ age < 85; age ≥85;
- race and ethnicity;
- height at baseline (cm);
- weight at baseline (kg);
- body mass index (BMI) at baseline (kg/m²) $= \frac{weight\ (kg)}{height^2\ (m^2)}$
  (BMI will not be recalculated if already available in the database);
- duration of RA (years)
  $= \frac{(date\ of\ first\ study\ drug\ administration) - (date\ of\ initial\ diagnosis) + 1}{365.25}$
  If missing day: use 1st day of the month
  If missing both day and month: use 1st of January;
- Duration of RA, categorized (years): < 1; 1 ≤ duration < 5; 5 ≤ duration < 10; 10 ≤ duration < 15; 15 ≤ duration < 20; duration ≥ 20;
- hsCRP (mg/L) at baseline;

- DAS28 (CRP) at baseline;
- [redacted]
- TJC68 and SJC66 joint counts;
- [redacted]

Demographic and baseline disease characteristics will be listed.

6.1.2. Allocation and Randomization

The number of subjects (and percent) per treatment group and overall will be tabulated per country and site.

The following listings will be provided:

- Listing per subject of the IP kit numbers, IP lot numbers dispensed/returned.
- Randomization schemes and codes, with the treatment assigned to each subject. This listing includes a flag in case of discrepancies or errors between the assigned and the actual treatment taken, and should also include flags declaring any (potential) unblinding.

6.1.3. Disposition Information

The following tabulations will be provided, by treatment group and overall:

- The number of subjects screened, not-randomized (including reasons), randomized (treated and not treated), and treated with GLPG3970 and Placebo.
- Number (percent) of subjects randomized per country and site.
- The number (percent) of subjects in each analysis set as defined in Section 4.1.
- The number (percent) of subjects per analysis window as defined in Section 4.3.3.
- The number (percent) of subjects who completed/discontinued the IP administration schedule and the reasons for discontinuation.
- The number (percent) of subjects who completed/discontinued the study and the reasons for discontinuation.

Discontinuation related to SARS-CoV-2 will be flagged in the listing.

Additionally, the following information will be provided in listings:

- Subject identification and randomization (country, site number, investigator, subject number).

- Randomization number and date, planned and actual randomization group, with flags for any discrepancies.
- Subjects excluded from the safety and full analysis sets, including reasons.
- First and Last Key Dates in the Study will be listed

6.1.4. Protocol Deviations and Eligibility

Major protocol deviations are determined and recorded while the study is ongoing, and the list is finalized prior to database lock (and unblinding). For more details, please refer to the Protocol Deviations Plan.

The number (percent) of subjects with major protocol deviations will be tabulated, overall and per class of deviation, by treatment group and overall.

All available information concerning major protocol deviations, including COVID-19 related verbatim, violations on eligibility criteria and subjects not treated will be listed. Protocol deviations leading to the exclusion of subjects from any analysis set, as applicable, will be flagged.

Minor protocol deviations will not be tabulated and will not be listed.

6.1.5. Medical History and Concomitant Diseases

Frequency tabulations, per treatment group and overall, per system organ class and preferred term will be provided for the medical history findings (i.e., conditions no longer present at the start of the study) as well as for the concomitant diseases (i.e. conditions present at the start of the study) using Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

All medical history findings and concurrent diseases will be listed separately.

6.1.6. Rheumatoid Arthritis Disease History (RA)

Frequency tabulations, per treatment group and overall, per system organ class and preferred term will be provided for the RA disease history using MedDRA coding dictionary.

All RA disease history will be listed.

6.1.7. Prior and Concomitant Medications

6.1.7.1. Coding of Reported Terms

All prior and concomitant medication terms will be coded in the database using the World Health Organization (WHO) drug coding dictionary.

6.1.7.2. Classification of Medications

All prior and concomitant medication records will be categorized as follows, considering their date and flags indicating the relative timing versus study (drug) start or end (before, after, ongoing):

- Prior only: when the record ended before the first IP administration date.
- Concomitant only: when the record started on or after the first IP administration date.
- Prior and concomitant: when the record started before the date of first IP administration, and ended on or after this point, or continued.

When the start or end date of the prior and concomitant medication records are incomplete (and no flags indicating relative timing are available), the date of first IP administration will be considered to the same level of information provided by these incomplete dates to categorize the timing of these records. This means that a record only having month and year will be categorized comparing only to the month and the year of the date of first IP administration.

6.1.7.3. Calculation of Relative Days

For both the start and the end dates of the concomitant medication records, their day relative to the day of first IP administration will be calculated as described in Section 4.3.1.

6.1.7.4. Presentation of Results

A frequency tabulation per planned treatment group and overall of the Anatomical Therapeutic Chemical (ATC) classification classes level 4 by therapeutic subgroup (ATC level 2) and generic term of the prior medication (defined as ‘prior only’ and ‘prior and concomitant’) will be provided as well as of the concomitant medication (defined as ‘concomitant only’ and ‘prior and concomitant’).

A listings of prior and concomitant medications will be provided. Also, prior and concomitant corticosterioid listing will be provided separately (the list of the ATC codes to be selected in this listing will be provided by the Galapagos medical services).

6.1.8. Procedures

Procedures results will only be listed.

6.1.9. Exposure to IP and Compliance

6.1.9.1. Derivation Rules

Derived Parameters: Extent of Exposure to IP

- *Total treatment duration* (days) = last IP administration date – first IP administration date + 1 day.

- *Total treatment duration, excluding days off IP*: Sum of the number of days with any IP administration.
- *Total treatment duration, full compliance* (days): Number of days where the complete volume of IP has been administered.

Derived Parameters: Compliance

- Overall compliance (%) $= 100 \times \frac{number\ of\ doses\ actually\ taken}{number\ of\ doses\ that\ should\ have\ been\ taken}$
- Percent days with any intake (%) $= 100 \times \frac{total\ treatment\ duration,excluding\ days\ off\ drug}{total\ treatment\ duration}$
- Percent days full compliance (%) $= 100 \times \frac{total\ treatment\ duration,fully\ compliant}{total\ treatment\ duration}$

Derived Parameters: Extent of Exposure to MTX Drug

- *Total treatment duration* (days) = last MTX administration date – first MTX administration date + 1 day.
- *Total treatment duration, excluding days off MTX*: Sum of the number of days with any MTX administration.

6.1.9.2. Presentation of Results

Summary statistics per planned treatment group and overall will be provided for each compliance and extent of exposure parameter for IP administration. Frequency tables will be provided for the compliance parameters, using the following categories: <80%; 80% ≤ x < 100%; 100%; 100% < x ≤ 120%; > 120%.

All original IP administration records will be listed per subject. The listing will include all deviations from IP schedules such as missed or reduced doses and GLPG3970/placebo switches and will also include food intake status at the time of IP administration. IP exposure and compliance data will be listed.

For MTX administration, a table summarizing the number and percent of subjects taking MTX by planned treatment group and overall will be provided. In addition, the following parameters will be summarized:

- Dose at baseline (mg);
- Route at baseline;
- Dose form at baseline;
- *Total treatment duration* (days);
- *Total treatment duration, excluding days off MTX*

6.2. Efficacy Analyses

Efficacy analyses will be performed on the FAS.

Tabulations will be shown per planned treatment group.

6.2.1. Level of Significance

Statistical tests for efficacy analysis will be done at a 2-sided significance level of 10%.

6.2.2. Primary Efficacy Parameter

The primary endpoint for this study is the change from baseline in DAS28 (CRP) at Week 6. The DAS28 (CRP) is a derived measurement with differential weighting given to each component such as TJC28, SJC28, patient's global assessment of disease activity (0–100-mm VAS), and serum CRP level. A DAS28-CRP below the value of 2.6 is interpreted as Remission.

6.2.2.1. Derivation Rules

The DAS assessment is a derived measurement with differential weighting given to each component. The DAS28 (CRP) will be calculated at each assessment time point.

The components of the DAS28 arthritis assessment include:

- Tender Joint Count 28 (TJC28) ranges from 0-28
- Swollen Joint Count 28 (SJC28) ranges from 0-28
- High sensitivity C-reactive protein (hsCRP) (in mg/L)
- Patient's disease activity VAS (in mm) (ranges from 0 = best to 100 = worst)

The DAS28 (CRP) score will be calculated using the below formula:

DAS28 (CRP) = 0.56 x $\sqrt{\text{TJC28}}$ + 0.28 x $\sqrt{\text{SJC28}}$ + 0.36 x Ln[1+CRP(in mg/L)] + 0.014 x patient's disease activity VAS (in mm) + 0.96 (Mack, Hsia, & Aletaha, 2017)

where Ln is the natural logarithm

A lower score is considered as better disease activity. If one of the component is missing at a specific analysis visit, DAS28 (CRP) will not be calculated for that assessment and will be set to missing.

6.2.2.2. Analyses Methods

DAS28 (CRP) data will be analyzed descriptively as actual (observed) values and changes from baseline. Percent change from baseline will not be calculated for the primary endpoint.

A MMRM will be used on the DAS28 (CRP) changes from baseline to compare treatment groups, with a 90% CI of the treatment difference at Week 6.

The following covariates will be used: treatment by visit interaction and baseline DAS28 by visit interaction. An unstructured variance-covariance matrix will be used to model the residuals. If the default Newton–Raphson algorithm used by SAS PROC MIXED fails to converge, the following will be tried to avoid lack of convergence while maintaining an unstructured variance:

A. The Fisher scoring algorithm (via the SCORING=5 option of the PROC MIXED statement) will be used to obtain the initial values of covariance parameters.

B. If the above fails, the no-diagonal factor analytic structure will be used which effectively performs the Cholesky decomposition via the TYPE=FA0(V) option of the REPEATED statement, where V is the total number of visits in the response vector (V = 3).

C. If all the above fails, the variance-and-correlations parameterization will be attempted using TYPE =UNR

In the rare case where all the above fails, the Toeplitz structure with the sandwich variance estimator (EMPIRICAL option) will be used. If this option also fails, the AR(1) + random intercept model will be tried with the sandwich variance estimator.

The LSM, LSM difference between GLPG3970 and the placebo group (reference category), standard error, two-sided 90% CIs for the LSM and difference between treatment groups and p-value for treatment differences will be presented. The number of subjects in the analysis population and number of subjects in the analysis will be provided by treatment group.

Graphs of the mean (+- SE) actual values over time and of the mean (+- SE) change from baseline. In addition, profile line plots of the change from baseline will be provided by treatment group.

6.2.2.3. Decision Making Methodology

The decision making 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 $\leq$ -1.6) to as low as P (delta $\leq$ -0.6).

The chosen framework parameters are as follows:

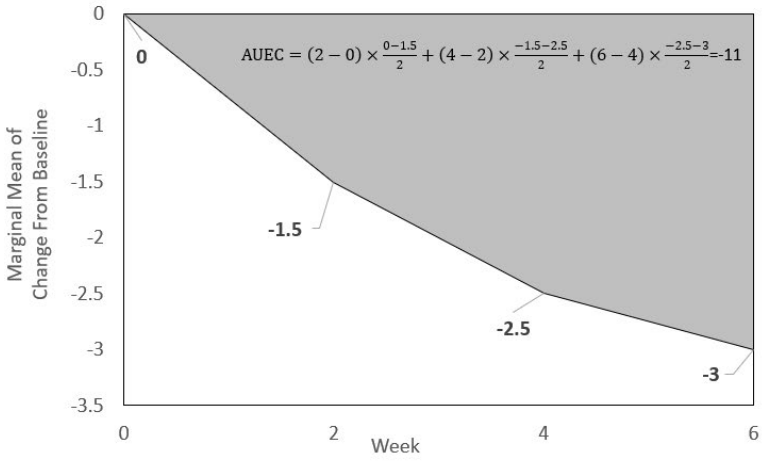
- TV: -1.6 and LRV: -0.6
- False stop risk: 10% and false go risk: 20%
- Framework rules:
    - Signal detected if P10 < TV and P80 < LRV
    - No signal detected if P10 ≥ TV
    - No conclusion if P10 < TV

More details about this analysis will be provided in a separate document. This output will be generated for decision making purposes and will not be part of the CSR.

6.2.2.4. Area Under the Efficacy Curve (AUEC)

To further explore the data in a slightly different fashion, the area under the efficacy curve (AUEC) based on the MMRM-derived LS-means will be derived for GLPG3970 and placebo. The AUEC will be calculated using the trapezoidal rule as illustrated in Figure 2. A 90% confidence interval and between-group p-value will be derived as well. All will be based on the MMRM model for the DAS28(CRP) change from baseline.

Figure 2: Graphical illustration calculation AUEC



	Week	Mean
V1	0	0.0
V2	2	-1.5
V3	4	-2.5
V4	6	-3.0

Period	Mean AUC
0-2	-1.5
2-4	-4.0
4-6	-5.5
0-6	**-11.0**

6.2.3. Secondary Efficacy Parameters

6.2.3.1. Disease Activity Score Based on 28 Joints (C-reactive Protein) [DAS28 (CRP)]: Binary/Ordinal Categorization

6.2.3.1.1 Derivation Rules

The binary categorizations of the DAS28 actual values calculated at each available time point are defined as follows:

- DAS28 remission: DAS28 < 2.6
- [redacted]

The ordinal categorization of the DAS28 actual values are defined as follows for each timepoint:

- High disease activity: > 5.1
- Moderate disease activity:] 3.2 , 5.1]
- Low disease activity: [2.6 , 3.2]
- Remission: < 2.6

If DAS28 values are missing at any time point, then corresponding binary and ordinal categories are also set to missing.

[redacted]

[redacted]

Actual DAS28(CRP)	Improvement (Reduction) in DAS28(CRP) from baseline:		
	> 1.2	] 0.6, 1.2]	≤ 0.6
≤ 3.2	Good	Moderate	None
]3.2, 5.1]	Moderate	Moderate	None
> 5.1	Moderate	None	None

6.2.3.1.2 Analysis Methods

The DAS28 remission will be summarized for the observed-case and non-responder imputation (NRI) using number and percentages by treatment group. Fisher's exact method will be used to compare the GLPG3970 and placebo based on NRI rates. Fisher's exact p-value and 90% CI of the difference between GLPG3970 and placebo will be presented.

Ordinal categorization of the DAS28 will be summarized using the descriptive table of the observed results with cumulative percentages by treatment group. A shift table from baseline to post-baseline visits will be provided.

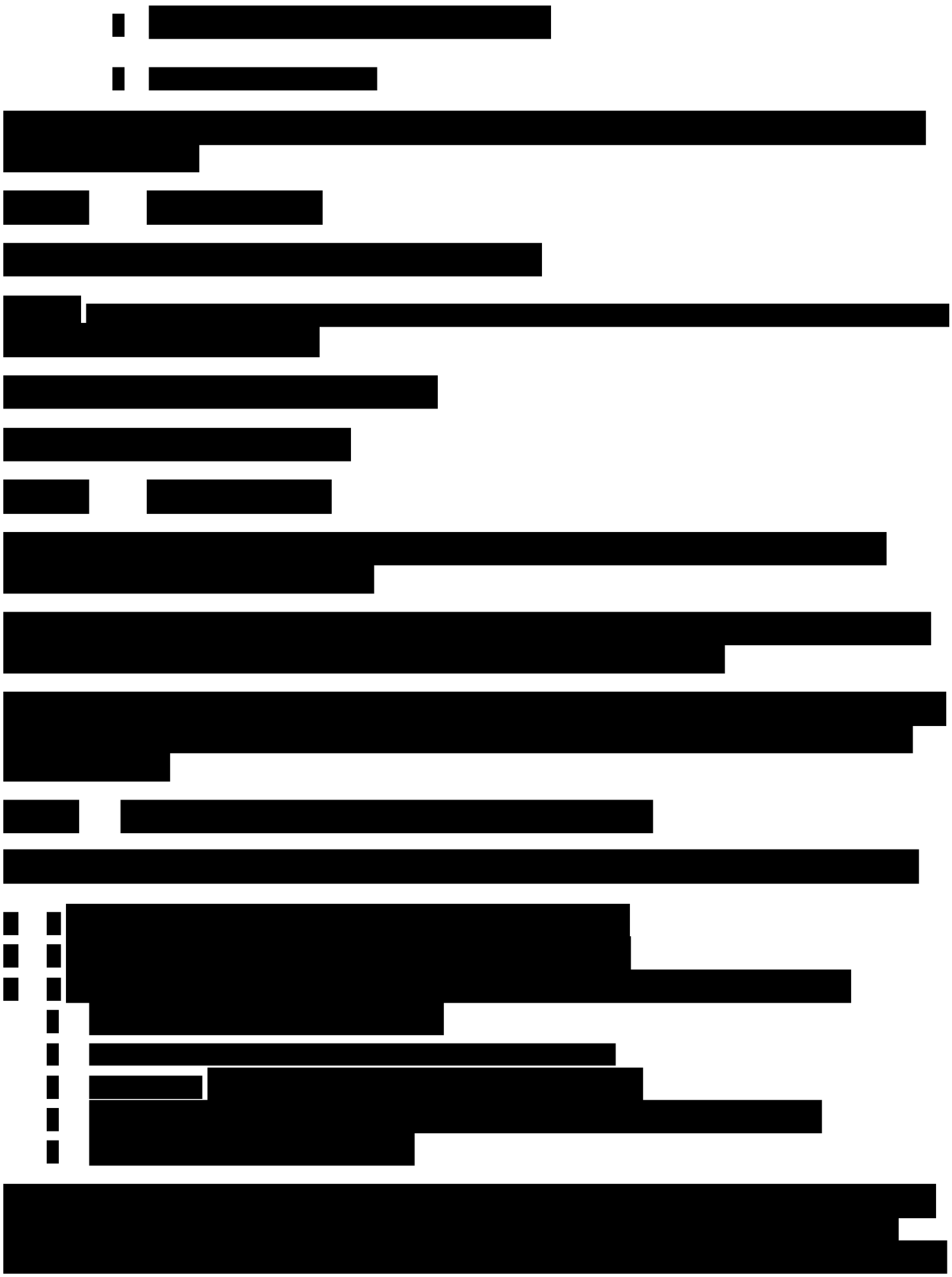
A line plot over time and bar chart will be provided for the binary categorization of DAS28 (CRP) based on NRI cases.

[redacted]

6.2.3.2.2 Analysis Methods

Observed and change from baseline over time will be summarized using descriptive statistics by treatment group and visit.

[redacted]



[redacted]

[redacted]

[redacted]

6.2.3.7. Joint Counts (TJC68/SJC66)

The joint counts (TJC68 and SJC66) will be evaluated on the visits specified in the Schedule of Assessments (See Section 2.5). Each of 68 joints will be evaluated for tenderness (tender joint count, TJC68), and each of 66 joints will be evaluated for swelling (swollen joint count, SJC66).

6.2.3.7.1 Derivation Rules

The assessment for swelling is the total number of joints with a present swelling and ranges from 0 to 66 for SJC66. The assessment for tenderness is the total number of joints with a present tenderness and 0 to 68 for TJC68.

In case not all 68 (66) joints are scored in the investigator "66/68 Swollen and Tender Joint Count" electronic diary (eCOA), then it is assumed that the joints that are not scored are not tender (swollen). In case there are permanently or temporarily unassessable joints (assessment 'Not applicable'), then no action is taken (so actually these are counted as not tender and not swollen).

If the overall 68 (66) joints count assessment is not performed at all ("Was the assessment performed?' ticked 'No' in the electronic case report form (eCRF), TJC68 and SJC66 will be set to missing.

6.2.3.7.2 Analysis Methods

Observed, change from baseline and % change from baseline values over time will be summarized using descriptive statistics by treatment group and visit for the TJC68 and SJC66 separately.

An MMRM model will be used on the percent change from baseline to compare the treatment groups (GLP3970 vs Placebo). For the presentation of results refer section 6.2.2.2.Listing will include all individual TJC68 and SJC66 joints along with total score.

6.2.3.8. [redacted]

[redacted]

6.2.3.9.1 Derivation Rules

Not applicable.

6.2.3.9.2 [redacted]

[redacted]

[redacted]

6.3. Safety Analyses

Safety analyses will be performed on the Safety Analysis Set.

Safety tables will be presented by treatment group and overall.

Safety parameters will be analyzed descriptively (see Section 4.4.2 and Section 4.4.3). No formal testing will be performed to compare the treatment groups.

6.3.1. Adverse Events

All AEs and changes in attributes (worsening and improvement) of AEs are reported in the database. An identification number serves to link the records considered by the investigator as describing the evolution of one and the same event.

6.3.1.1. Definition of Treatment-Emergent Adverse Events

The analysis of AEs will be based on treatment-emergent events (TEAE).
TEAEs are defined as

- 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.
- Improvement or no change of any ongoing AEs on or after the IP start date are not considered treatment-emergent. If an AE is ongoing at the time of first IP intake, if there is no change or an improvement in its toxicity grade or its seriousness status (reported in the 'Change in Adverse event details Entry' CRF page), this AE will not be considered as treatment-emergent.

6.3.1.2. Coding of Reported Terms

All AE terms will be coded in the database using the latest version of MedDRA coding dictionary. AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

All tables will show the AE preferred terms grouped into system organ class. Subject listings will also show the reported terms (verbatim). Any other coding levels will only be shown in a listing summarizing coding unless explicitly mentioned otherwise.

6.3.1.3. Allocation of Adverse Events to Analysis Periods

All AEs will be placed into analysis periods considering their start date, aiming to report the incidence of these events only in the analysis period during which they started.

The general rule for allocation of AEs to analysis periods follows:

$$\text{Analysis period start date} \leq \text{AE start date} \leq \text{analysis period end date}$$

If the start date of an AE is missing or incomplete to a level preventing a clear allocation of the AE to one single analysis period and no flag indicating timing relative to study medication is available, a worst-case consideration (see below) will be done aiming to allocate the AE to one single analysis period, if possible. When a worst-case consideration is needed, the end date of the AE, if and as available, should also be considered; if such AEs clearly end on a given point, this will exclude the possibility to allocate the AE to an analysis period after that point.

- An AE which according to the available information of its start date could belong to the screening as well as to the treatment analysis period will only be placed in the treatment period.
- An AE with a missing start date will be allocated to the treatment period unless the "Prior to First GLPG3970/Placebo Treatment= "Yes".

6.3.1.4. Treatment Relatedness

Following the guideline ICH-E3 Structure and Content of Clinical Study Reports (Step 4 Version), the originally reported relatedness to IP of an AE will be dichotomized as follows:

- *Not IP related*: all non-missing weaker levels of relatedness than 'possibly drug related'.
- *IP related*: 'possibly drug related' and all stronger levels of relatedness (this class also includes any missing drug relatedness, as a worst-case consideration).

Only this dichotomized relatedness will be used in tables and can apply to different IPs when relatedness has been collected separately per IP; relatedness as originally reported will only be listed.

6.3.1.5. Worst-Case Selections

When cross-tabulating AE preferred terms versus an AE attribute (like intensity), only the worst-case within each same preferred term, same subject and same analysis period will be considered, i.e. when the same subject has more than once the same AE preferred term reported in the same treatment group, the subject will be counted only once and will be shown under the worst outcome (like the worst intensity for that AE in the concerned treatment period).

The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be presented last in summary presentation.

6.3.1.6. Calculation of Relative Days and Duration

For each newly reported event, and reported worsening or improvement of an existing event, the start day in the study (the day of the AE start date relative to the date of first IP administration), the start day in the analysis period, and the duration (in days) will be calculated. In addition, the relative day and duration will be derived for the entire event; that is, the full evolution of the event, including the initial reporting and all subsequent worsening and/or improvement.

Relative days and durations will only be listed.

See Section 4.3.1 for the calculation of relative days.

6.3.1.7. Events of Special Interest

Not applicable.

6.3.1.8. Presentation of Results

The analysis will focus on AEs reported during the treatment period. AEs reported during the screening period will only be listed.

All AEs tables will show the number of subjects with TEAEs.

AEs which are not treatment-emergent will only be listed.

A summary table will be provided, showing the number (percent) of subjects with at least one:

- TEAE,
- IP-related TEAE,
- Serious TEAE,
- TEAE leading to death,
- TEAEs by worst intensity (CTCAE Toxicity Grade),
- TEAE leading to IP discontinuation.

The AE terms will be presented sorted in descending order of frequency, prioritizing the GLPG3970 treatment group and then for placebo, first by system organ class, then by preferred term, and then alphabetically.

Frequency tabulations, by system organ class and preferred term, of the number (percent) of subjects with a TEAE will be presented. Similar tables will be provided by worst intensity, and for IP-related TEAEs, grade 3-4-5 TEAEs, serious TEAEs and TEAEs leading to IP discontinuation of IP.

All AE data will also be listed, including separate lists for SAEs, AEs leading to death, and AEs leading to IP discontinuation. Listings will clearly indicate AEs to be treatment-emergent or not.

In addition, AEs related to SARS-Cov-2 will be listed separately.

6.3.1.9. EudraCT Adverse Events Reporting

For the purpose of EudraCT reporting, the following tabulations will be created:

Frequency tabulations, by system organ class and preferred term, of the number (percent) of subjects with non-serious TEAE will be presented. A similar table will be provided for all serious TEAEs, as well as a table for non-serious TEAEs reported in at least 2 subjects in any treatment group.

6.3.2. Laboratory Safety

6.3.2.1. Available Data

Laboratory tests scheduled are described in the protocol section 8.5.2. In addition, the derived laboratory tests described in Section 6.3.2.2 will be added.

The statistical analyses will only present results in Standard International (SI) standardized units. Other units will not be presented.

Only data provided by the central laboratory along with corrected calcium (mmol/L) will be used in tables and figures. Results from local labs will be listed only.

The parameter (hs)CRP will not be presented in this laboratory section of the analysis, but presented in the efficacy part.

[redacted]

6.3.2.2. Derivation Rules

Derived Laboratory Tests

The calcium level should be corrected in patients with low serum albumin levels, using the following formula:

Adjusted total calcium (mmol/L) =Total calcium (mmol/L) + 0.02 [40−Albumin(g/L)]

Fasted and Non-Fasted Results

Laboratory tests that are sensitive to the fasting status: glucose, triglycerides.

For these laboratory tests, only results from blood samples drawn in a fasted state will be included in the analysis. Results from blood samples taken in a non-fasted (not fasting and fasting not declared) state will be listed only and no toxicities or abnormalities will be calculated. Laboratory results for which the fasting status is missing will be considered as taken non-fasted.

6.3.2.3. Definition of Toxicity Grades

Toxicity grades will only be derived for laboratory tests for which toxicity grades are available.

Toxicity grades will be determined as implemented in the attached table (Appendix I).

For elevations (H1 to H4), values under the threshold of H1 are reported as 'Grade 0'.

For elevations (L1 to L4), values above the threshold of L1 are reported as 'Grade 0'.

6.3.2.4. Definition of Non-Graded Abnormalities

For all laboratory tests provided by the laboratory, the position of the actual analysis values versus their normal ranges will be determined directly by using the position indicator provided in the database as provided by the lab, expressing the classes for these analysis values as low (L), normal (N) or high (H). L, N and H are further referred to as non-graded abnormalities.

6.3.2.5. Urinalysis Tests with Categorical Results

Results of urinalysis with qualitative results will be tabulated by time point. No toxicity grading or non-graded abnormalities will be derived for these tests.

6.3.2.6. Treatment-Emergent Principle

Toxicity Grades

A post-baseline toxicity grade 1, 2, 3 or 4 is defined as treatment-emergent when higher than the toxicity grade of the baseline result or when there is a change in direction (from H to L or from L to H). If the baseline result is missing, a post-baseline toxicity grade 1, 2, 3 or 4 will be considered as treatment-emergent.

Non-graded Abnormalities

A post-baseline non-graded abnormality class L or H is defined as treatment-emergent when it differs from the abnormality class of the baseline result. If the baseline result is missing, a post-baseline abnormality L or H will be considered as treatment-emergent.

6.3.2.7. Worst-Case Principle

Toxicity Grading

The worst-case post-baseline toxicity grade 0, 1, 2, 3 or 4 will be determined per subject, per laboratory test (and direction, increases and decreases) and for each analysis period, using all non-missing post-baseline records (including unscheduled and FU visits).

The worst-case toxicity grade is the highest toxicity grade corresponding to the highest laboratory test value (by direction, increases and decreases). In case of several equal highest post-baseline actual values, the earliest occurrence will be taken for the analyses and will be flagged in the listings.

- Grade 0: all post-baseline toxicity grades are classified as 0
- Grade 1: all post-baseline toxicity grades are classified as ≤1
- Grade 2: all post-baseline toxicity grades are classified as ≤2
- Grade 3: all post-baseline toxicity grades are classified as ≤3
- Grade 4: all post-baseline toxicity grades are classified as ≤4

If any record is missing, then the toxicity grade is considered as ‘missing’.

Non-graded Abnormalities

The following worst-case post-baseline abnormalities L, N or H will be determined per subject, per laboratory test and for each analysis period, using all non-missing post-baseline records (including unscheduled and FU visits):

– L = low: at least one post-baseline result is classified as L.
– N = normal: all post-baseline results are classified as N.
– H = high: at least one post-baseline result is classified as H.

If, for a subject, both L and H are reported, the subject will be counted twice in the table: once with a worst-case L and once with a worst-case H.

6.3.2.8. Hepatotoxicity

Hepatotoxicity will be investigated by tabulating the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values categorized as >3, >5, >10 and >20 times their upper limit of normal (per analyte and over both analytes combined), ALP categorized as > 1.5 times the upper limit and total bilirubin as > 2 times the upper limit of normal. Elevations of AT (AST or ALT) > 3 times their upper limits accompanied by elevated total bilirubin (>1.5×ULN, >2×ULN) on the same day will also be tabulated.

To assess the potential of the drug to cause severe liver damage, possible Hy's Law cases will be identified. These subjects are defined as having any elevated AT (AST or ALT) of >3×ULN, ALP <2×ULN, and associated with an increase in total bilirubin >2×ULN on the same day.

6.3.2.9. Presentation of Results

No formal inferential statistics (p-values) will be derived.

Continuous laboratory tests[16] including glucose, cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and fasted glucose, will be summarized by means of descriptive statistics (including 90% CI of the mean change) by laboratory test, treatment group and analysis window. Actual values, changes from baseline and percent change from baseline will be tabulated separately. Continuous values for metabolic markers will be summarized in the pharmacodynamic analysis section.

Profile line plots by subject of all actual observed values using relative day (ADY) will be presented by treatment group. Graphs of the mean (+- SE) actual values over time and of the mean (+- SE) change from baseline, and percent changes from baseline will be presented for all continuous laboratory parameters, with the exception of the metabolic markers. Also, line plots for subjects will be provided by treatment group.

The analysis of abnormalities will focus on assessments reported during the treatment period. Results reported before baseline will only be listed.

Non-graded abnormalities and toxicities grades of the actual values will be presented as shift tables of the worst-case abnormality/toxicity grade versus the baseline abnormality/toxicity

[16] With the exception of the metabolic markers [fasted insulin, homeostatic model assessment of insulin resistance (HOMA-IR) and HbA1c] and inflammation marker hsCRP.

grade. The table will be created per laboratory test, treatment group and analysis period. The results of non-graded abnormalities and toxicities grades will be shown separately.

A frequency table of the number (percent) of subjects with treatment-emergent worst-case abnormalities/toxicity grade per laboratory test, treatment group and analysis period will be presented. The results of non-graded abnormalities and toxicities grades will be shown separately.

A frequency table of the number (percent) of subjects will be also provided for hepatotoxicity flags defined before. These abnormalities will be also flagged in the individual data laboratory listing.

Listing will be provided for the laboratory test along with flag for abnormality results. In addition, pregnancy result will be listed separately.

6.3.3. Electrocardiogram

6.3.3.1. Available Data

The following ECG parameters will be analysed: heart rate (HR), RR interval, PR interval, QRS interval, uncorrected QT interval, QTcF (derived).

6.3.3.2. Derivation Rules

Derived Parameters

The Fridericia's cube-root corrected QT (QTcF) will be calculated using the following formula.

Fridericia's cube-root corrected QT (Fridericia, 1920): $$QTcF\ (ms) = QT\ (ms) \times \sqrt[3]{\frac{1000}{RR\ (ms)}}$$

If RR is missing, then it will be derived from HR using the formula $RR(ms) = 60 \times HR(bpm)$.

Handling of ECGs Measured in Triplicate

If ECG is collected in triplicates, the following approach will be taken.

First, any derivation of ECG parameters will be done before handling ECG triplicates. Next, the mean of the triplicate ECG values will be calculated for each individual ECG parameter, without rounding the result. These calculated means will constitute the analysis values; any derivation (e.g. change from baseline, assignment of abnormalities) and statistic will be based on the mean value of the triplicates.

The values of the original members of a triplicate will be listed.

6.3.3.3. Abnormalities

The actual analysis values and changes from baseline of the QT and QTcF parameters will be categorized into the abnormality classes as defined in the SAP Appendix II.

Worst-Case Abnormality

The worst-case post-baseline categorized actual analysis value and the worst-case categorized change from baseline for QT and QTcF will be determined per subject, per parameter, and for each analysis period, using all non-missing post-baseline records (including unscheduled and FU visits).

The worst-case categorized actual analysis value is the category corresponding to the highest post-baseline actual value. In case of several equal highest post-baseline actual values, the earliest occurrence will be taken for the analyses and will be flagged in the listings.

The worst-case change from baseline is the category corresponding to the largest increase (positive change) from baseline. In case of several equal largest increase from baseline, the earliest occurrence will be taken for the analyses and will be flagged in the listings.

Treatment-Emergent Abnormalities

Actual value: An abnormal post-baseline abnormality is defined as treatment-emergent when the abnormality is worse compared to the abnormality at baseline or when there is a change in direction (from H to L or from L to H). When the baseline value is missing, post-baseline abnormalities are considered as treatment-emergent.

An abnormal category for change from baseline is always treatment-emergent.

6.3.3.4. Presentation of Results

No formal inferential statistics (p-values) will be derived.

Continuous parameters will be summarized by means of descriptive statistics (including 90% CI of the mean change) by parameter, treatment group and analysis window. Actual values, change from baseline and percent changes from baseline will be tabulated separately.

Profile line plots by subject of all actual observed values using relative day (ADY) will be presented by treatment group. Graphs of the mean (+- SE) actual values over time and of the mean (+- SE) change from baseline and percent change from baseline will be presented. A line plot by subject of the change from baseline will also be provided by treatment group.

The analysis of abnormalities will focus on assessments reported during the treatment period. Results reported during the screening or post-treatment (if defined) period will only be listed.

Abnormalities of the actual values will be presented as shift tables of the worst-case abnormality versus the baseline abnormality. The table will be created per parameter, treatment group and analysis period.

A frequency table of the number (percent) of subjects with treatment-emergent worst-case abnormalities and the worst change per parameter, treatment group and analysis period will be presented.

A frequency table per treatment group and time point of the ECG interpretations as recorded in the case report form (CRF) will be provided.

A Listing will be provided along with abnormality.

6.3.4. Vital Signs

6.3.4.1. Available Data

The following vital signs parameters will be analyzed: weight (kg), BMI (kg/m^2), diastolic and systolic blood pressure (mmHG), pulse rate (beats/min) and body temperature (C).

6.3.4.2. Derivation Rules

Not applicable.

6.3.4.3. Abnormalities

Vital signs data will be categorized according to the cutoffs provided in the SAP Appendix II.

6.3.4.4. Treatment-Emergent Principle

A post-baseline abnormality class L or H is defined as treatment-emergent when it differs from the abnormality class at baseline. If the baseline result is missing, a post-baseline abnormality L or H will be considered as treatment-emergent.

An abnormal category for change from baseline is always treatment-emergent.

6.3.4.5. Worst-Case Abnormality

The worst-case post-baseline categorized actual analysis value will be determined per subject, per parameter and for each analysis period, using all non-missing post-baseline records (including unscheduled and FU visits).

The worst-case categorized actual analysis value is the category corresponding to the highest post-baseline actual value. In case of several equal highest post-baseline actual values, the earliest occurrence will be taken for the analyses and will be flagged in the listings.

6.3.4.6. Presentation of Results

No formal inferential statistics (p-values) will be derived.

Continuous parameters will be summarized by means of descriptive statistics (including 90% CI of the mean change) by parameter, treatment group and analysis window. Actual values, change from baseline and percent change from baseline will be tabulated separately.

Graphs of the mean (+- SE) actual values over time and of the mean (+- SE) change from baseline, and percent changes from baseline will be presented.

The analysis of abnormalities will focus on assessments reported during the treatment period. Results reported during the screening or post-treatment (if defined) period will only be listed.

Abnormalities of the actual values will be presented as shift tables of the worst-case abnormality versus the baseline abnormality. The table will be created per parameter (and position if applicable), treatment group and analysis period.

A frequency table of the number (percent) of subjects with treatment-emergent worst-case abnormalities per parameter, treatment group and analysis period will be presented.

A listing will be provided along with abnormality.

6.3.5. Physical Examinations

Physical examination results will only be listed.

6.3.6. SARS-CoV-2 Infection

Results of the SARS-CoV-2 infection test will be listed for the subjects who have at least one positive test.

6.3.7. Subgroup Analyses

No subgroup analysis is planned for this clinical study as the study sample size is too small. Thus, any subgroup of this would have small sample size to be relevant or even uninterpretable.

6.4. Pharmacokinetic Analysis

6.4.1. Available Data

Blood samples for the PK assessment of GLPG3970 [redacted] should be collected on the visits specified in the Schedule of Assessments in Section 2.5

6.4.2. Presentation of Results

Descriptive statistics will be provided for GLPG3970, [redacted] at each assessment time point. Observed plasma C_{trough} for GLPG3970 [redacted] will be reported in the CSR.

For calculation of descriptive statistics of GLPG3970 C_{trough} (= pre-dose concentration), the following will apply:

- for pre-dose samples not collected within 21-27 hours after the last intake prior to the visit, or collected after the intake at the visit, the corresponding concentration will be excluded from descriptive statistics and flagged in the listing with appropriate footnoting.
- pre-dose samples collected within 3 days after a missed dose will also be excluded from descriptive statistics.

6.5. [redacted]

[redacted]

[redacted]

6.5.2. Presentation of Results

All continuous parameters mentioned in section 6.5.1 will be summarized by means of descriptive statistics (including 90% CI of the mean change from baseline) by treatment group and analysis window. Actual values, changes from baseline and percent change from baseline will be tabulated separately.

Between-group comparisons will be based on the percent change from baseline, and will present a p-value and 90% CI of the delta between GLPG3970 and placebo. The same MMRM approach as for the efficacy endpoints will be applied.

Graphs of the mean (+- SE) actual values over time and of the mean (+- SE) change from baseline, and percent changes from baseline will be presented for all continuous parameters. Also, linear-linear plots for actual values will be provided by treatment group. In addition, profile line plots of the percent change from baseline will be provided by treatment group.

For cytokines and metabolic markers mentioned under section 6.5.1, the analysis of percent change from baseline will be performed as described in section 4.5.2. The same MMRM approach as detailed in section 6.5.1.2 will be applied. The GeoLSM and GeoSE and corresponding 90 % CI will be presented (the same back transformation to the 'percentage scale' as for the geometric descriptive statistics will be applied to the LS-mean, SE and corresponding 90% CI bounds). The GeoMean (·/÷ GeoSE) of the actual values and percent changes from baseline will be presented graphically over time on a log-linear scale. Error band will be calculated as follows:

- Error bands: 100 x [exponential {mean (Z) +- SE (Z)} -1]. Where Z = log (value) - log (baseline).

Listings will be provided for all cytokines, bone markers and metabolic markers separtely. Column includes the actual values, change from baseline and percent change from baseline, and also a flag for high/low values in case a normal range exists.

Note: HOMA-IR values will be excluded from analysis if samples are not taken fasted (i.e. "fasted" is explicitly mentioned in the database),

[redacted]

6.6. [redacted]

[redacted]

6.7. Changes to the Planned Analyses, Not Covered by Protocol Amendments

Not applicable.

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APPENDIX

APPENDIX I: LABORATORY: TOXICITY GRADING

The following tables contain a list of safety tests with associated gradings. There may be tests in this table that are not measured in this particular study.

Table 1 Gradings for Hematology Parameters

Parameter	L1	L2	L3	L4	H1	H2	H3	H4
Hemoglobin	<LLN	<10 g/dL; <6.2 mmol/L	<8 g/dL; <4.9 mmol/L	NA	>ULN	Increase in >2 g/dL above ULN	Increase in >4 g/dL above ULN	NA
Hematocrit	<LLN	NA	NA	NA	>ULN	NA	NA	NA
Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC)	<LLN	NA	NA	NA	>ULN	NA	NA	NA
Platelet count - *(assuming no platelet cluster)*	<LLN	<75 x 10^9/L	<50 x 10^9/L	<25 x 10^9/L	>ULN	>600 x 10^9/L	>1000 x 10^9/L	NA

Parameter	L1	L2	L3	L4	H1	H2	H3	H4
Leukocytes	<LLN	<3.0 x 10^9/L	<2.0 x 10^9/L	<1.0 x 10^9/L	>ULN	>20.0 x 10^9/L	>100.0 x 10^9/L	NA
% Polymorphonuclear Leukocytes + Band Cells	NA	NA	NA	NA	>ULN	≥90%	>95%	NA
Neutrophils	<LLN	<1.5 x 10^9/L	<1.0 x 10^9/L	<0.5 x 10^9/L	NA	NA	NA	NA
Eosinophils	NA	NA	NA	NA	>ULN	>5.0 x 10^9 or eosinophils >5%	NA	NA
Lymphocytes	<LLN	<0.8 x 10^9/L	<0.5 x 10^9/L	<0.2 x 10^9/L	>ULN	>4.0 x 10^9/L	>20.0 x 10^9/L	NA

Parameter	L1	L2	L3	L4	H1	H2	H3	H4
Red blood cells	<LLN	NA	NA	NA	>ULN	NA	NA	NA

Table 3 Gradings for Blood Chemistry Parameters

Parameter	L1	L2	L3	L4	H1	H2	H3	H4
Alanine aminotransferase (ALT)	NA	NA	NA	NA	>ULN	>3.0 x ULN	>5.0 x ULN	>8.0 x ULN
Aspartate aminotransferase (AST)	NA	NA	NA	NA	>ULN	>3.0 x ULN	>5.0 x ULN	>8.0 x ULN
Gamma-glutamyl transferase (GGT)	NA	NA	NA	NA	>ULN	>2.5 x ULN	>5.0 x ULN	>20.0 x ULN
Alkaline Phosphatase (total)	NA	NA	NA	NA	>ULN	>2.5 x ULN	>5.0x ULN	>20.0 x ULN
Lactate dehydrogenase (LDH)	NA	NA	NA	NA	>ULN	NA	NA	NA
Total bilirubin	NA	NA	NA	NA	>ULN	>1.5 x ULN	>3.0 x ULN	>10.0 x ULN
Amylase	NA	NA	NA	NA	>ULN	>1.5x ULN	>2.0 x ULN	>5.0 x ULN
Lipase	NA	NA	NA	NA	>ULN	>1.5x ULN	>2.0 x ULN	>5.0 x ULN
Total protein	<LLN	<5.5 g/dL	<5.0 g/dL	NA	NA	NA	NA	NA
Activated partial thromboplastin time (APTT)	NA	NA	NA	NA	>ULN	>1.5 x ULN	>2.5 x ULN	NA

Parameter	L1	L2	L3	L4	H1	H2	H3	H4
Prothrombin time (PT)	NA	NA	NA	NA	≥1.10 x ULN	≥1.25 x ULN	≥1.50 x ULN	≥3.00 x ULN
International normalized ratio (INR)	NA	NA	NA	NA	>1.2 x Baseline	>1.5 x Baseline	>2.5 x Baseline	NA
Creatinine	NA	NA	NA	NA	>ULN	>1.5 x ULN	>3.0 x ULN	>6.0 x ULN
Glucose *(fasting)*	<LLN	<55 mg/dL; <3.0 mmol/L	<40 mg/dL; <2.2 mmol/L	<30 mg/dL; <1.7 mmol/L	>ULN	>125 mg/dL; ≥6.95 mmol/L	>250 mg/dL; ≥13.89 mmol/L	≥500 mg/dL; ≥27.75 mmol/L
Glucose *(non-fasting)*	<LLN	<55 mg/dL; <3.0 mmol/L	<40 mg/dL; <2.2 mmol/L	<30 mg/dL; <1.7 mmol/L	>ULN	>160 mg/dL; ≥8.89 mmol/L	>250 mg/dL; ≥13.89 mmol/L	≥500 mg/dL; ≥27.75 mmol/L
HbA1c	NA	NA	NA	NA	>6.0	> 6.5 %	NA	NA
Fasting insulin	<2.6 µU/mL or 18.1 pmol/L	NA	NA	NA	>24.9 µU/m or 172.9 pmol/L	NA	NA	NA
Cholesterol	NA	NA	NA	NA	>ULN	>300 mg/dL; >7.75 mmol/L	>400 mg/dL; >10.34 mmol/L	>500 mg/dL; >12.92 mmol/L
Low-density lipoprotein (LDL)	NA	NA	NA	NA	NA	≥160 mg/dL; ≥4.12 mmol/L	≥190 mg/dL; ≥4.90 mmol/L	NA

Parameter	L1	L2	L3	L4	H1	H2	H3	H4
High-density lipoprotein (HDL)	NA	<40 mg/dL; <1 mmol/L	NA	NA	NA	NA	NA	NA
Triglycerides	NA	NA	NA	NA	>ULN	>300 mg/dL; >3.42 mmol/ L	>500 mg/dL; >5.7 mmol/ L	>1,000 mg/d L; >11.4 mmol/L
Calcium *(corrected for albumin)*	<LLN	<8.0 mg/dL; <2.0 mmol/L	<7.0 mg/dL; <1.75 mmol/L	<6.0 mg/dL; <1.5 mmol/L	>ULN	>11.5 mg/dL ; >2.9 mmol/L	>12.5 mg/dL ; >3.1 mmol/L	>13.5 mg/dL ; >3.4 mmol/L
Ionized calcium	<LLN	<1.0 mmol/L	<0.9 mmol/L	<0.8 mmol/L	>ULN	>1.5 mmol/L	>1.6 mmol/L	>1.8 mmol/L
Sodium	<LLN	<130 mEq/L; <130 mmol/L	<125 mEq/L; <125 mmol/L	<120 mEq/L; <120 mmol/L	>ULN	>150 mEq/L; >150 mmol/L	>155 mEq/L; >155 mmol/L	>160 mEq/L; >160 mmol/L
Chloride	<LLN	NA	NA	NA	>ULN	NA	NA	NA
Potassium	<LLN	NA	<3.0 mmol/L	<2.5 mmol/L	>ULN	>5.5 mmol/L	>6.0 mmol/L	>7.0 mmol/L
Phosphate	<LLN	<2.0 mg/dL; <0.65 mmol/L	<1.4 mg/dL; <0.45 mmol/L	<1.0 mg/dL; <0.32 mmol/L	>ULN	NA	NA	NA
Creatine phosphokinase (CPK)	NA	NA	NA	NA	> ULN	>2.5 x ULN	>5 x ULN	>10 x ULN
Uric acid	NA	NA	NA	NA	>ULN	≥10 mg/dL; ≥0.59 mmol/L	≥12 mg/dL; ≥0.71 mmol/L	≥15 mg/dL; ≥0.89 mmol/L
Albumin	<LLN	<30 g/L	<20 g/L	NA	NA	NA	NA	NA

Parameter	L1	L2	L3	L4	H1	H2	H3	H4
eGFR (or Cr/Cl)	<LLN	<60 ml/min/ 1.73 m^2	<30 ml/min/ 1.73 m^2	<15 ml/min/ 1.73 m^2	NA	NA	NA	NA
Blood urea nitrogen (BUN)	NA	NA	NA	NA	>ULN	>2.5 ULN	>5 ULN	>10 ULN

Table 3 Gradings for Urine Analysis Parameters

Parameter	L1	L2	L3	L4	H1	H2	H3	H4
Urine erythrocytes	NA	NA	NA	NA	≥ULN	≥10 cells/HPF	NA	NA
Urine protein	NA	NA	NA	NA	1+ proteinuria	2+ and 3+ proteinuria; urinary protein <3.5 g/24 hrs	urinary protein ≥3.5 g/24 hrs; 4+ proteinuria	NA
Urine glucose	NA	NA	NA	NA	>ULN (presence of glucose)	NA	NA	NA

LLN: lower limit of normal, ULN: upper limit of normal, NA: not applicable.

Any laboratory parameter with treatment-emergent (i.e., worsening from baseline) abnormalities of grade 2 or above (ie, H2/L2 or higher/lower) should be considered a 'marked laboratory abnormality'. Marked laboratory abnormalities should be described in a corresponding section of the CSR as per ICH E3 guidance, section 12.4.2.3.

APPENDIX II: Vital Signs and Electrocardiogram grading

Table 4 Gradings for Vital Signs and Electrocardiogram Parameters

Parameter	L1	L2	L3	L4	H1	H2	H3	H4
Systolic blood pressure (mmHg)	<90	<60	NA	NA	NA	≥140	≥160	≥180
Diastolic blood pressure (mmHg)	<60	<45	NA	NA	NA	≥90	≥100	≥120
Heart rate (bpm)	<60	<50	<40	NA	>100	>115	>130	NA
Body temperature (°C)	NA	<35	NA	NA	>38	NA	NA	NA
Respiratory rate (breaths per minute)	<12	NA	NA	NA	>20	NA	NA	NA
O_2 saturation (%)	<95	<90	NA	NA	NA	NA	NA	NA
Weight	≥7% decrease from baseline	NA	NA	NA	≥7% increase from baseline	NA	NA	NA
QTc interval on ECG (ms)	NA	NA	NA	NA	>450	>480	>500	NA
QTc change from baseline (ms)	NA	NA	NA	NA	NA	>30	>60	NA
PR interval on ECG (ms)	<110	NA	NA	NA	>200	NA	NA	NA

Parameter	L1	L2	L3	L4	H1	H2	H3	H4
QRS complex on ECG (ms)	<60	NA	NA	NA	>120	NA	NA	NA

Source: FRM-MED-005/006, valid on 08JUL2020.

APPENDIX III: 66/68 Joint Count

Joints Assessed (left and right) for Swelling (66 Joints) and/or Tenderness (68 joints)

Temporomandibular
Sternoclavicular
Acromioclavicular
Shoulder*
Elbow*
Wrist*
Metacarpophalangeal*
- First
- Second
- Third
- Fourth
- Fifth

Proximal interphalangeal*
- First
- Second
- Third
- Fourth
- Fifth

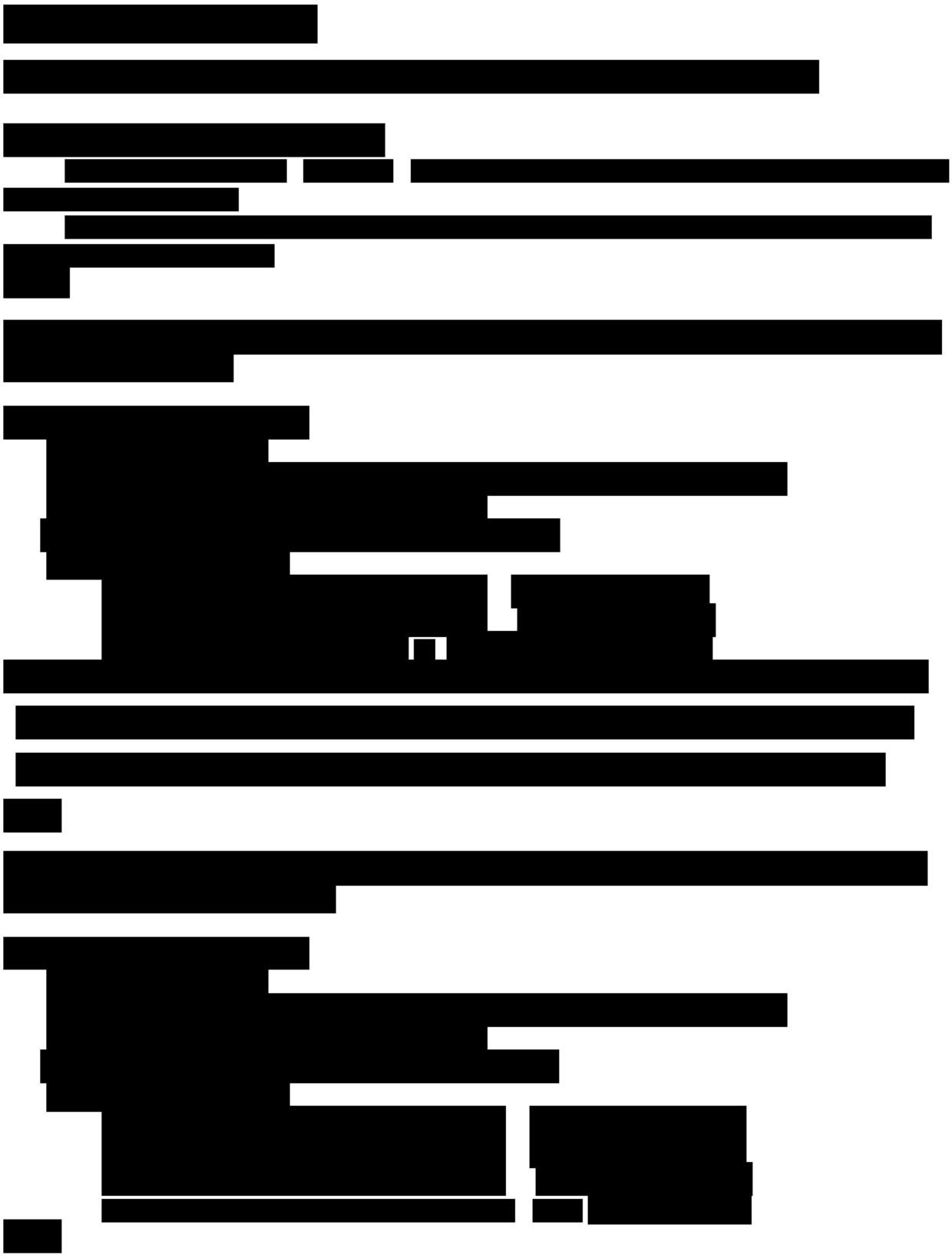
Distal interphalangeal
- Second
- Third
- Fourth
- Fifth

Hip #
Knee*
Ankle
Tarsus
Metatarsophalangeal
- First
- Second
- Third
- Fourth
- Fifth

Proximal interphalangeal (toe)
- First
- Second
- Third
- Fourth
- Fifth

#Assessed for tenderness only

*28 Joints (TJC28/SJC28) that are part of DAS (28)



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