TRIAL STATISTICAL ANALYSIS PLAN

C28709494-03

BI Trial No.:	1368-0010
Title:	Proof-of-concept study of BI 655130 add-on treatment in patients with mild-to-moderately active ulcerative colitis during TNF inhibitor therapy Including Protocol Amendment 3 [c11253289-04]
Investigational Product:	BI 655130
Responsible trial statisticians:	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	04 March 2020 REVISED
Version:	3.0

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADA	Anti-drug antibodies
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse event of special interest
ALQ	Above limit of quantification
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BM-SAP	Biomarker Statistical Analysis Plan
BMI	Body mass index
BRAVE	BI RAVE®
BRPM	Blinded Report Planning Meeting
CARE	Clinical data analysis and reporting environment
CHI3L1	Faecal chitinase 3-like-1
CR	Clinical remission
CRF	Case report form
CRP	C-reactive protein
CTC	Common Terminology Criteria
CTP	Clinical trial protocol
CTR	Clinical trial report
DBLM	Database lock meeting
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
EOT	End of treatment

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Term	Definition / description
ES	Enrolled set
EudraCT	European union drug regulating authorities clinical trials
FAS	Full analysis set
FLF	Faecal lactoferrin
F-NGAL	Faecal neutrophil gelatinase-associated lipocalin
HMGB1	High-mobility group box 1 protein
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IL	Interleukin
iPD	Important protocol deviation
IRT	Interactive response technology
KM	Kaplan-Meier
LD	Day of Last dose/infusion received
LLOQ	Lower limit of quantification
LOQ	Limit of quantification
MCS	Mayo Clinical Score
MedDRA	Medical Dictionary for Regulatory Activities
mESS	Modified Endoscopic Subscore
MPO	myeloperoxidase
MQRM	Medical quality review meeting
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
NRI	Non response imputation
NRI-IR	Non Response Imputation including rescue medication
OC	Observed cases
OC-IR	Observed cases including values after rescue medication
OR	Original results
pCR	Partial MCS remission
PD	Pharmacodynamic(s)
PG	Pharmacogenomic(s)

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Term	Definition / description
PGA	Physician Global Assessment
PK	Pharmacokinetic(s)
PPS	Per protocol set
PT	Preferred Term
PD	Protocol Deviation
Q1	1st quartile
Q3	3rd quartile
RAGe	Report appendix generator
RBS	Rectal Bleeding Subscore
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual effect period
RS	Randomized set
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SDL	Subject data listing
SFS	Stool Frequency Score
SMQ	Standardised MedDRA query
SOC	System Organ Class
tCR	Total clinical remission
TCM	Trial Clinical Monitor
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal range
ULOQ	Upper limit of quantification
VAS	Visual analogue scale

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3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 "Statistical Methods and Determination of Sample Size". Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

The screening of patients in the study was prematurely discontinued on February 4th, 2020. At that time, 22 patients had been randomized into the study and 15 patients had completed the trial. Five patients had completed through Week 12, but were still ongoing in the trial, and another two patients had not yet completed Week 12 and were still ongoing in the trial. There were no patients in the screening period. A decision was made that an early interim analysis of the Week 12 data would be done in order to discuss the results with both internal and external experts allowing for an early decision on the future of the project to be made.

The data cut-off for the interim snapshot of the database is February 4th, 2020. Of the five patients who have already completed Week 12 but are still ongoing, all five of them completed Week 12 prior to this cut-off date, leaving a total of 20 patients available for the interim analysis. The strategy for data cleaning in preparation for the interim snapshot of the database will be specified in a separate data cleaning plan.

The following data reporting strategy for safety and efficacy (along with any PK, ADA, and biomarker data which is available) is planned:

- A selection of data up to the Week 12 visit is to be summarized (including, at a minimum, the primary and secondary endpoints, as well as adverse event data). As a consequence of trial termination and of the need for a rapid decision on the future of the project, this analysis will be performed using the data of the 20 patients who have completed/discontinued through Week 12 prior to the cut-off date.

For further details on the subject sets thus defined, refer to Section 6.3. For further details on the data to be included into the Week 12 analysis, refer to Table 6.7: 1. Further specification on the safety summaries to be performed at the time of the interim database snapshot are specified in Section 7.8.1. A logistics and access plan, which will describe any measures used to protect the blind and integrity of the ongoing trial will be finalized prior to database snapshot and treatment unblinding.

In accordance with the CTP, a second interim database snapshot will be performed once all randomized patients complete/discontinue through Week 12. At this time, all displays as

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described in this TSAP will be produced. The results from this analysis will be used for potential authority interactions, if applicable.

A final analysis of the trial will be performed once all patients have completed the trial. For more details, please refer to Section 6.3.

Study data will be stored in a trial database within the BRAVE system.

The statistical analyses will be performed within the validated working environment CARE, including [redacted]), and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

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4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses stated in the CTP (latest version) will be performed as planned with the following adaptations.

For within-project consistency, the following efficacy endpoints were modified, added or re-named.

The further endpoint "Clinical response" and "Time to flare" were modified as follows:

- Clinical response (total MCS decrease from baseline ≥3 points, and by ≥30%; AND RBS decrease from baseline by ≥1 point, or abs. ≤1) at Week 8 and at Week 12
- Time to flare was modified as time to suspected flare (increase in partial MCS by ≥2 from nadir)

The following endpoints were added to the list of further endpoints:

- Partial MCS response (Partial MCS (i.e. excluding mESS) decrease from baseline ≥2 points; AND RBS decrease from baseline by ≥1 point, or absolute value ≤1) over time
- Complete remission (Robarts Histology Index ≤ 6 and mESS=0) at Weeks 8 and 12
- Endoscopic remission (mESS=0) at Week 8 and at Week 12
- Percent change in faecal lactoferrin (FLF) at all measured time points as compared to baseline
- Change from baseline in SFS by visit (calculated as the average of the last 3 SFS measurements used in the derivation of the partial Mayo score)
- Change from baseline in RBS by visit (calculated as the average of the last 3 RBS measurements used in the derivation of the partial Mayo score)

The following endpoints have been renamed as below (see also Table 9.2.5: 1):

Primary endpoint:
- "Mucosal healing" at Week 12 has been renamed "Endoscopic improvement" at Week 12

Secondary endpoints:
- "Clinical remission" at Week 12 has been renamed "Total clinical remission (tCR)" at Week 12
- "Modified clinical remission" at Week 12 has been renamed "Clinical remission (CR)" at Week 12

Further endpoints:
- "Clinical remission" at Week 8 has been renamed "Total clinical remission (tCR)" at Week 8
- "Modified clinical remission" at Week 8 has been renamed "Clinical remission (CR)" at Week 8

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- "Partial clinical remission" at Week 8 and at Week 12 has been renamed "Partial MCS remission (pCR)" at Week 8 and at Week 12

Subsets of the subject sets (see Section 6.3) are now defined which include only those patients who completed/discontinued through Week 12 prior to the cut-off date February 4th, 2020. These subsets will be used for the reporting of the outputs at the time of the first interim database snapshot.

The Reeve method for calculating confidence intervals was removed from the analysis plan in Section 7 due to low enrollment.

The subgroup analysis was expanded to include the concomitant use of steroids (yes/no) and prior TNFi failure (yes/no) (see Section 6.4).

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5. ENDPOINTS

For all endpoints and unless explicitly specified otherwise, Week 8 refers to visit V5 using extended time windows as defined in Table 6.7: 1.

For all endpoints and unless explicitly specified otherwise, Week 12 refers to EOT visit using extended time windows as defined in Table 6.7: 1.

For handling of missing data and corresponding sensitivity analyses, see Section 6.6.

5.1 PRIMARY ENDPOINT

Endoscopic improvement (MCS mESS ≤1) at Week 12 is the primary endpoint.

Derivation of the mESS is described in Section 9.2: 1.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable – there are no key secondary endpoints for this trial.

5.2.2 Secondary endpoints

The secondary endpoints are listed below.

- Treatment emerging adverse events
- Total Clinical remission (tCR) based on Mayo score (total MCS ≤2 points, and all subscores ≤1 point) at Week 12
- Histological remission (Robarts (RHI) score ≤6) at Week 12
- Clinical remission (CR) based on Mayo score (total modified MCS ≤2 and: RBS =0, SFS =0 or 1 and drop ≥1 from baseline, AND mESS ≤1) at Week 12

Derivation of tCR, CR, and Histological remission is described in Section 9.2.

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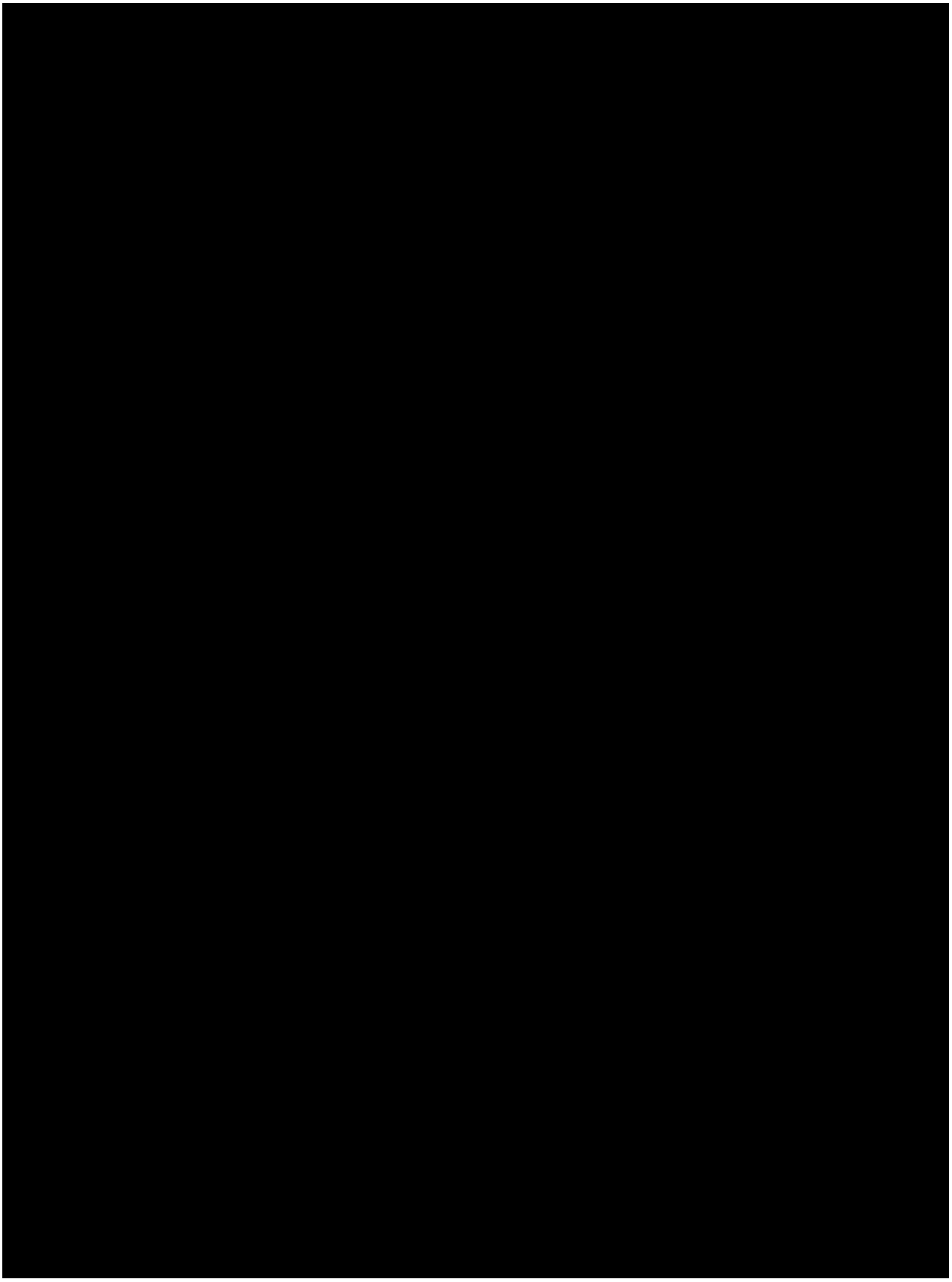

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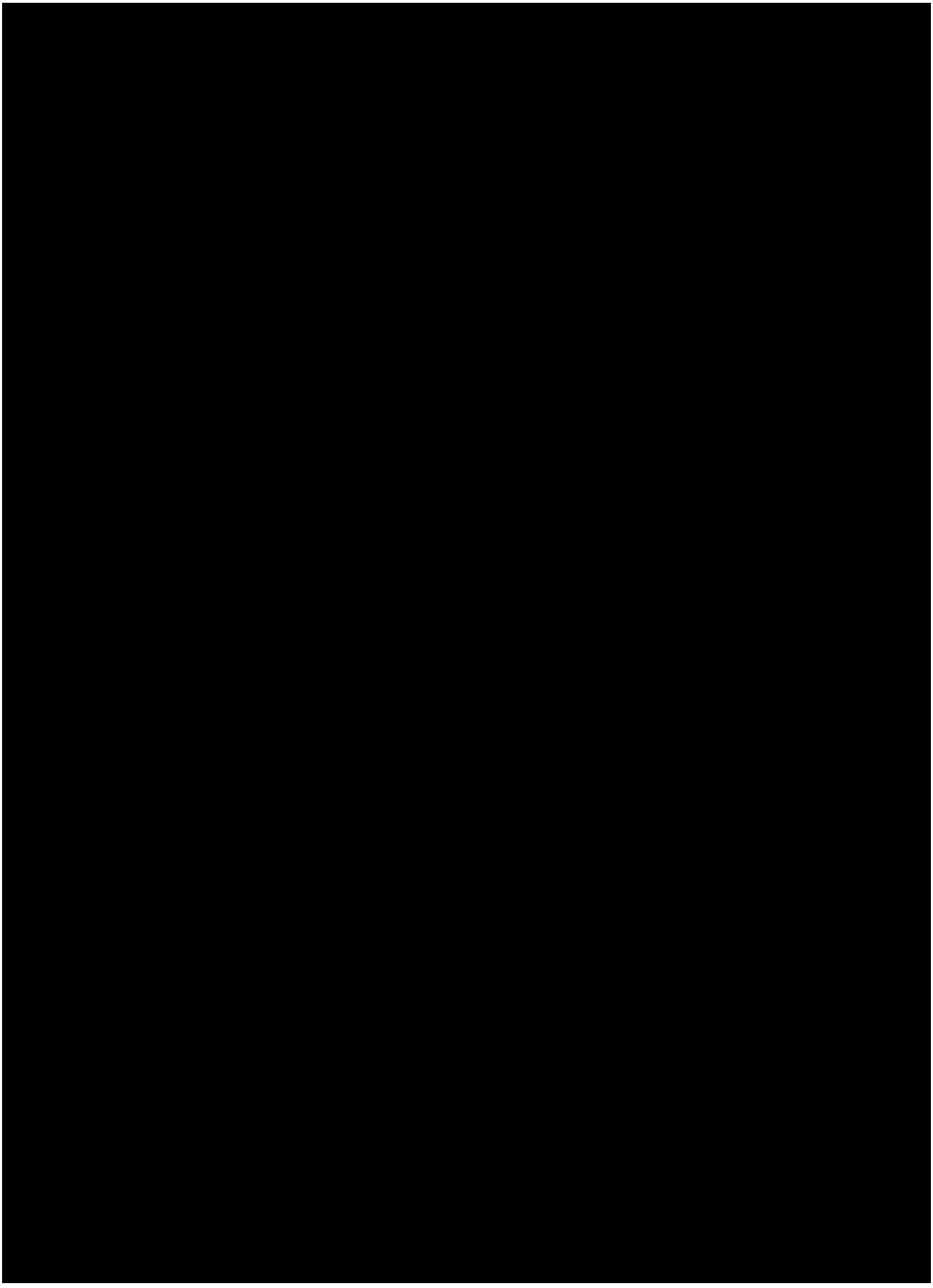

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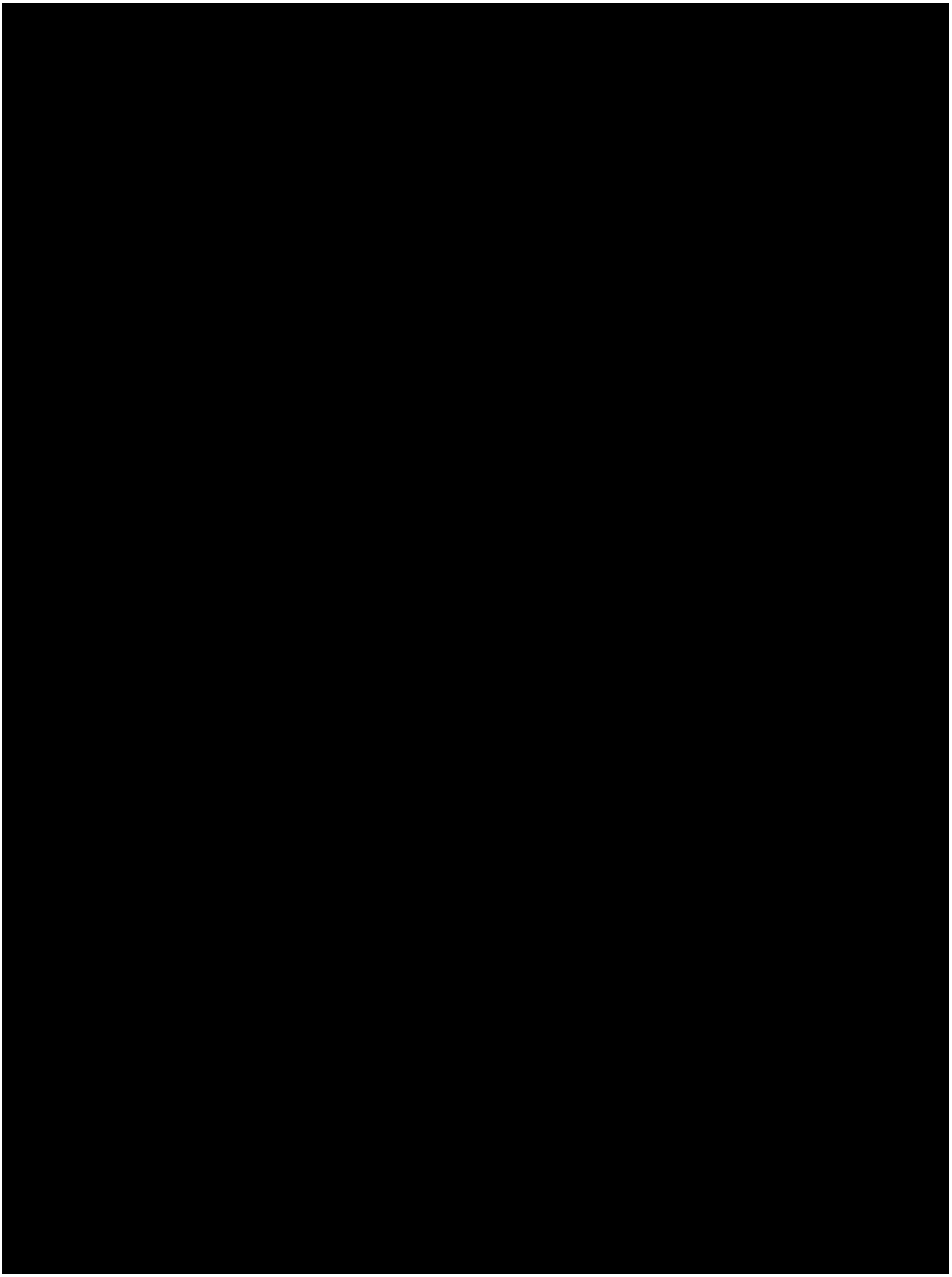

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6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on the treatment to be administered, assignment to treatment, and selection of dose, see Section 4 of the CTP.

All patients will receive either intravenous doses of 1200mg of BI 655130 solution for infusion (at Weeks 0, 4 and 8), or placebo.

The following study phases are defined:

Table 6.1: 1 Flow chart of analysis phases

Study analysis phase	Description	Start (included)	End (included)
Screening phase	Screening	Earliest of: i) Date of informed consent; ii) first screening procedure	Date/time of start of infusion of first study drug minus 1 minute.
Treatment phase & Residual effects period (REP)	On-treatment period	Date/time of start of infusion of first study drug (Day 1)	Date of end of infusion of last study drug + 140 days at 11:59 p.m.
Follow-up[1] phase	Off-treatment period	Date of end of infusion of last study drug + 141 days at 12:00 a.m.	Latest of: i) Date of EOS visit (Week 36 visit); ii) last contact date on End of Study page at 11:59 p.m.

Dates are defined individually per patient. If more than one date is associated with a specific visit, measurements associated with a specific date are assigned to a study analysis phase according to the rules specified in the table. An analysis phase will not extend beyond the start date of the following phase.
[1] The off-treatment period (i.e. Follow-up phase) only exists if the trial completion date is after the date of end of last infusion + 140 days.

The first interim database snapshot analysis will be performed based on the randomized patients who have completed/discontinued through the planned first 12 weeks of the trial up to the cut-off date, February 4th, 2020. For a description of the subject sets to be analysed, see Section 6.3. The following data will be used in this analysis:

- Selected summaries of the 12-week data will be performed up to the minimum of the (analysis-specific data cut-off; study day 99), unless otherwise specified.

The second interim database snapshot, to be performed once all randomized patients have completed/discontinued through the planned first 12 weeks of the trial (per CTP specification), will use the following data:

- All 12 weeks of data will be summarized up to the minimum of the (analysis-specific data cut-off; study day 99), unless otherwise specified.

The final analysis of the trial will be performed once all patients have completed the planned 36 weeks of trial; results will be summarized including all on-treatment data from the trial.

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The selection of data for presentation by visit in these analyses is described in Table 6.7: 1.

Treatment groups for the analysis will be labelled as follows:

- **"Placebo"**
- **"Speso 1200mg IV q4w"**
- **"Overall Total"** (across all arms), where appropriate.

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all patients in the database (i.e., enrolled patients). Consistency check listings (for identification of violations of time windows) and a list of protocol deviations will be provided to be discussed at the RPM/DBLM/MQRM. At this meeting, it will be decided whether a discrepant data value can be used in analyses or whether it must be queried in the clinical database. Each protocol deviation must be assessed to determine whether it is an important Protocol Deviation (iPD). For definition of iPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (2).

If any iPDs are identified, they are to be summarised into categories and will be captured in the RPM/DBLM/MQRM minutes via an accompanying Excel spreadsheet (3). The following table contains the categories which are considered to be iPDs in this trial. If the data show other iPDs, for example, based on monitor visits to the sites, then this table will be supplemented accordingly by the time of the RPM/DBLM/MQRM. Not all iPDs will lead to exclusion from analysis sets. IPDs leading to exclusion from analysis sets are indicated as such in Table 6.2: 1.

IPDs will be summarised and listed for the randomized set.

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Table 6.2: 1 Handling of iPDs

Category / Code		Description	Comments	Excluded from[1]
A		**Entrance criteria violated**		
A1		**Inclusion criteria not met**		
	A1.01	18-75 years, males or females (at Visit 1 and 2) LABEL: Age beyond 18-75.	IC01 Also check versus derived age for patient.	None
	A1.02	Body weight ≤120 kg (at Visit 1 and 2) LABEL: Weight beyond 120kg.	IC02 Also check versus reported body weight for patient	None
	A1.03	Diagnosis of ulcerative colitis ≥5 months prior to screening by clinical and endoscopic evidence and corroborated by a histopathology report. LABEL: Diagnosis too recent / insufficiently documented.	IC03 Also check derived time since diagnosis for patient	None
	A1.04	Receiving their TNFi treatment with infliximab (INF) with doses unchanged for ≥4 months prior to randomisation and detectable drug trough levels in blood; or adalimumab or golimumab with doses unchanged for ≥2 months prior to randomisation and detectable drug trough levels in blood LABEL: TNFi treatment changed / not detectable.	IC04	PPS
	A1.05	Mild or moderate disease activity, defined as: Total Mayo Score (MCS) (≤10), with - modified endoscopic subscore (mESS) ≥2, AND - disease extending 5 cm or more from anal verge LABEL: Disease activity not mild or moderate.	IC05 Also check derived total MCS and mESS at baseline, and distance from anal verge at baseline	PPS
	A1.06	If patients receive concurrent UC treatments, these need to be on stable doses. LABEL: UC treatment not on stable dose.	IC06 Also manually review concomitant medications as use of concurrent UC treatment. If patients receive unstable dose of probiotics, they will not be excluded from PPS	PPS

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Table 6.2: 1 (cont'd) Handling of iPDs

Category / Code		Description	Comments	Excluded from[1]
	A1.07	Patients with extensive colitis of >10 years duration or family history of colorectal cancer or personal history of increased colorectal cancer risk must have had an negative colorectal cancer screening within <1 year prior to screening (otherwise to be done during screening colonoscopy). LABEL: Increased risk for colorectal cancer	IC07	None
	A1.08	Women of childbearing potential (WOCBP) and men able to father a child must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. LABEL: Contraception methods not used.	IC08	None
A2		**Exclusion Criteria**		
	A2.01	Extensive colonic resection, subtotal or total colectomy LABEL: Extensive resection, or colectomy.	EC01	None
	A2.02	Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine LABEL: Ileostomy, colostomy, or stenosis.	EC02	None
	A2.03	Prior use of more than two different TNF inhibitor or vedolizumab LABEL: Use of more than two different TNF inhibitors or vedolizumab.	EC03 Also check the historical medication	PPS
	A2.04	Any treatment limiting safety or tolerability issue of the concurrent TNF inhibitor LABEL: Treatment limiting issue of TNFi.	EC04	PPS
	A2.05	Concurrent treatment with rectal 5-ASA compounds, parenteral or rectal corticosteroids (incl. budesonide) within 2 weeks, any investigational drug within 12 weeks or 5 half-lives, whatever is longer, or any prior dose of natalizumab or rituximab prior to screening LABEL: Co-treatment not as allowed.	EC05	PPS

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Table 6.2: 1 (cont'd) Handling of iPDs

Category / Code		Description	Comments	Excluded from[1]
	A2.06	Patients who must or wish to continue the intake of restricted medications (see CTP Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial LABEL: Use of restricted medication.	EC06	PPS
	A2.07	Evidence of infection with C. difficile or other intestinal pathogen <28 days prior to screening LABEL: Infection with intestinal pathogen.	EC07	PPS
	A2.08	Currently require or are anticipated to require surgical intervention for UC LABEL: Requires surgical intervention for UC.	EC08	PPS
	A2.09	Colonic moderate or severe mucosal dysplasia LABEL: Colonic mucosal dysplasia.	EC09	None
	A2.10	Colonic adenomas (unless properly removed) LABEL: Colonic adenomas.	EC10	None
	A2.11	Primary sclerosing cholangitis LABEL: Primary sclerosing cholangitis.	EC11	None
	A2.12	Faecal transplant ≤6 months before screening LABEL: Faecal transplant within 6 months.	EC12	None
A3		***Infectious Disease Exclusion Criteria***		
	A3.01	Increased risk of infectious complications (e.g. recent pyogenic infection, any congenital or acquired immunodeficiency (e.g. HIV), live vaccination within 6 weeks prior to screening, past organ or stem cell transplantation) LABEL: Increased risk of infectious complications.	EC13	None
	A3.02	Active or latent TB (Patients with positive QuantiFERON TB test are excluded. Patients with suspected false positive or undeterminable QuantiFERON TB result may be re-tested) LABEL: Active or latent TB.	EC14	None

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Table 6.2: 1 (cont'd) Handling of iPDs

Category / Code		Description	Comments	Excluded from[1]
	A3.03	Any severe infection <30 days prior to screening, including chronic or acute hepatitis B or C infection LABEL: Severe infection within 30 days.	EC15	None
A4		***General Exclusion Criteria***		
	A4.01	Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin LABEL: Malignancy within last 5 years.	EC16	None
	A4.02	Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomisation or planned during the study, e.g. hip replacement. LABEL: Recent or planned major surgery.	EC17	None
	A4.03	Pathological safety lab parameters: haemoglobin <8.5 g/dL, total white blood count (WBC) <3500 cells/µl, neutrophils <1000 cells/µl, thrombocytes <75.000/µl, albumin <30 g/l, creatinine ≥2 mg/dL, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 x ULN, total bilirubin >1.5 x ULN (patients with Gilbert's syndrome are not excluded). LABEL: Pathological safety lab parameters abnormal.	EC18 Also check corresponding safety lab parameters at baseline	None
	A4.04	Currently enrolled in another investigational device or drug study, or less than 12 weeks (or 5 half-lives, whichever is greater) since ending another investigational device or drug study(s), or receiving other investigational treatment(s) LABEL: Recent enrollment in other study.	EC19	None
	A4.05	Women who are pregnant, nursing, or who plan to become pregnant while in the trial LABEL: Pregnant or nursing.	EC20	None

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Table 6.2: 1 (cont'd) Handling of iPDs

Category / Code		Description	Comments	Excluded from[1]	
	A4.06	Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse) other than ulcerative colitis, surgical procedure, medical examination finding (including vital signs and electrocardiogram (ECG)), or laboratory value at the screening visit outside the reference range that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data LABEL: Unreliable protocol adherence or compromised safety.	EC21	None	
B		**Informed consent**			
	B.01	Informed consent not available LABEL: IC not available.	Based on direct assessment, not simply the tick box Date of informed consent missing or no signature on patient's "Declaration of Informed Consent" In this case: Patient's data will not be used at all.	All analyses	#
	B.02	Informed consent too late LABEL: IC too late.	Informed consent date was after Visit 1	None	
C		**Trial medication and randomisation**			
C1		**Incorrect trial medication**			
	C1.01	Incorrect medication received by patients in placebo arm	Placebo patient who received >= 1 vial (150mg) of BI 655130 verum overall /at any dosing visit Can only be finally judged after DBL since unblinding information is required	PPS	
	C1.02	Incorrect medication received by patients in BI arm	BI patient who received BI dose not matching treatment that was randomized would be considered an iPD. Patients randomized to BI 655130 1200mg q4w, but received any >=3 vials (450mg) of BI 655130 verum different from planned at any visit or overall Can only be finally judged after interim DBL since unblinding information is required	PPS	

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Table 6.2: 1 (cont'd) Handling of iPDs

Category / Code		Description	Comments	Excluded from[1]	
C2		**Non-compliance**			
	C2.01	Non-compliance with study drug intake- - administered dose too low	Administered overall infusion volume is less than 80% of the total planned volume. The total planned volume is • 60mL if discontinuation up to and including visit V2 • 120mL if discontinuation up to and including V4 • 180mL if discontinuation up to and including V5 The total planned volume overall is 180 mL.	PPS	
	C2.02	Non-compliance with study drug intake- - administered dose too high	Administered overall infusion volume is greater than 120% of the total planned volume The total planned volume is • 60mL if discontinuation up to and including visit V2 • 120mL if discontinuation up to and including V4 • 180mL if discontinuation up to and including V5 The total planned volume overall is 180 mL.	None	
C3		**Randomization not followed**			
	C3.01	Treated without randomisation LABEL: Treated without randomisation.	Patient treated according to eCRF, but not randomised according to IVRS.	RS(i), SAF(i), FAS(i), PPS	
C4		**Medication code broken**			
	C4.01	Medication code broken inappropriately LABEL: Medication code broken inappropriately	Medication code was broken prior to Week 12 for no valid reason. Final decision at the DBL meeting for the Week 12 analysis based on medical judgment.	PPS	#
D		**Concomitant medication**			
D1		**Previous medication**			
	D1.01	Washout of previous medication too short LABEL: Washout too short.		PPS	#
D2		**Prohibited medication use**			
	D2.01	Use of restricted medication as per CTP Table 4.2.2.1: 1 during the on-treatment period when not provided as a rescue treatment to stabilize a worsening disease condition – prior to or up to Week 12 LABEL: Restricted medication prior to Week 12		PPS	#

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Table 6.2: 1 (cont'd) Handling of iPDs

Category / Code		Description	Comments	Excluded from[1]	
	D2.02	Use of restricted medication as per CTP Table 4.2.2: 1 when not provided as a rescue treatment to stabilize a worsening disease condition - after Week 12 LABEL: Restricted medication after Week 12		None	#
D3		**Change in Background medication**			
			Note: Background medication is split into: • concurrent UC treatments • Background TNFi medication (e.g. infliximab)		
	D3.01	Concurrent UC treatments need to be on stable doses prior or up to Week 12: Oral 5-ASA compounds LABEL: Oral 5-ASA compounds not stable	Medical review, per investigator's judgement, any dose increase used as rescue treatment due to disease worsening or not improved, this will not be considered as iPD. Only dose increase not as rescue use will lead to exclusion from PPS	PPS	#
	D3.02	Concurrent UC treatments need to be on stable doses prior or up to Week 12: Oral corticosteroids LABEL: Oral corticosteroids not stable	Medical review, per investigator's judgement, any dose increase used as rescue treatment due to disease worsening or not improved, this will not be considered as iPD. Only dose increase not as rescue use will lead to exclusion from PPS	PPS	#
	D3.03	Concurrent UC treatments need to be on stable doses prior or up to Week 12: Azathioprine, 6-mercaptopurin or methotrexate LABEL: Azathioprine 6-mercaptopurin or methotrexate not stable	Medical review, per investigator's judgement, any dose increase used as rescue treatment due to disease worsening or not improved, this will not be considered as iPD. Only dose increase not as rescue use will lead to exclusion from PPS	PPS	#

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Table 6.2: 1 (cont'd) Handling of iPDs

Category / Code		Description	Comments	Excluded from[1]	
	D3.04	Concurrent UC treatments need to be on stable doses prior or up to Week 12: Probiotics (e.g. S. boulardii) LABEL: Probiotics not stable	Medical review	None	#
	D3.05	Any dose change in background TNF inhibitor medication when not provided as a rescue treatment to stabilize a worsening disease condition – prior to or up to Week 12 LABEL: Dose change in background TNFi prior Week 12	Dose change in background TNF inhibitor therapy is not allowed per CTP section 4.2.2 from Screening through End of Treatment.	PPS	#
	D3.06	Any dose change in background TNF inhibitor medication when not provided as a rescue treatment to stabilize a worsening disease condition – after Week 12 LABEL: Dose change in background TNFi after Week 12	Dose change in background TNF inhibitor therapy is not allowed per CTP section from Screening through End of Treatment.	None	#
E		**Missing data**	<not specified>		
F		**Study specific analysis**	<not specified>		
F1		**Other trial specific violation**	<not specified>		
	F1.01	Incomplete diagnosis of ulcerative colitis LABEL: Incomplete diagnosis of UC	Medical review	PPS	#
	F1.02	Primary endpoint assessment more than 2 weeks before planned day LABEL: Primary endpoint assessment > 2 weeks before planned.		PPS	
F2		**Certain violations of procedures used to measure primary or secondary efficacy data**	<not specified>		
G		**Other safety related violations**			
	G1	Pregnancy test not done for woman of child bearing potential or pregnant during study LABEL: Pregnancy test not done	Pregnancy test not done at any visit where such is scheduled	None	

PV will be detected manually
[1]For specification on definition of analysis sets, refer to Section 6.3. Analysis of efficacy data according to the PPS will not be done at the time of the 1st interim database snapshot.
Source: BI reference document: "Identify and Manage Important Protocol Deviations (iPD)" [001-MCS-40-413] (2).

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6.3 SUBJECT SETS ANALYSED

The following analysis sets will be defined for this trial:

- Enrolled set (ES):
  This patient set includes all patients who signed the informed consent form. It will be used for analyses of patient disposition.

- Randomized set (RS):
  This patient set includes all patients who were randomized into the trial.
  It will be used for analyses of patient disposition and patients with iPDs.

- Safety analysis set (SAF):
  This patient set includes all randomized patients who received at least one dose of study drug. It will be the main analysis set for presentation of safety. Treatment assignment will be analyzed according to the actual treatment.

For the primary analysis to be performed once all patients have completed through the Week 12 visit, and the final trial analysis, the following additional patient sets will be defined.

- Full analysis set (FAS):
  This patient set includes all patients in the SAF who had a baseline measurement available for the primary endpoint. Treatment assignment will be as randomized. This is the main analysis set for presentation of efficacy.

- Per protocol set (PPS):
  This patient set includes all patients in the FAS who adhered to the CTP without any iPDs which are flagged for exclusion from the PPS in the table above.
  This set will be used for sensitivity analysis on the primary efficacy endpoint.

For the first interim database snapshot, modified versions of the ES, RS, SAF, and FAS will be defined: the ESi, RSi, SAFi, and the FASi. Each of the modified patient sets will include those patients from the original set who completed/discontinued through the Week 12 visit on or prior to the cut-off date (see Section 3). Each of these modified patient sets will be handled according to the same procedures used to derive the full patient sets.

For the analyses to be performed at the time of the second interim database snapshot (when all randomized patients have completed/discontinued through Week 12), the ES, RS, SAF, FAS, and PPS will be used. Corresponding analyses performed at the time of the first interim database snapshot will use the ESi, RSi, SAFi, and FASi.

For the final analysis, the ES, RS, SAF, FAS, and PPS will be used.

The discussion of all exceptional cases and problems and the decisions on the allocation of patients to populations will be made at latest at the DBLM. A separate DBLM will be held prior to each database snapshot of this trial.

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Handling of Treatment Misallocations in Analysis Sets

If a subject is randomized but not treated, by definition such patients are excluded from FAS and PPS for efficacy analysis and excluded from SAF for safety analyses as no study medication was taken. However, they will be included in RS and reported under their randomized treatment group for sensitivity efficacy analysis. Please refer to Section 7.4 for more details.

If a subject is treated but not randomized, they will be excluded from both efficacy analysis and safety analysis by definition. However, subjects under such circumstances will be summarized in the final clinical trial report.

If a subject is randomized but took incorrect treatment during the study, then:

- For efficacy analyses according to FAS, PPS, and RS, they will be reported under their randomized treatment groups. But if the subject has an iPD as defined in Section 6.2, then they will be excluded from PPS for efficacy analysis.

- For safety analyses using the SAF,

    - if a subject is randomized with BI 655130 1200mg q4w treatment, then they will be reported under their randomized treatment group for safety analysis because the overall safety profile will be driven by the amount of drug received in totality over the entire treatment duration. It is not likely that the safety profile will deviate from the planned treatment regimen if the subject receives only one or two vials of the incorrect medication during only some dosing occasions. The subject will be assigned to the placebo treatment group only if they don't receive any BI 655130 during the entire treatment period.

    - if a subject is planned with placebo treatment group, then they will be reported under placebo if no treatment with BI 655130 is received at any visit. If the subject receives > = 1 vial (> = 150mg) of BI 655130 during the entire treatment duration, then they will be reported as BI 655130 1200mg treatment group.

Table 6.3: 1 (first interim database snapshot), and Table 6.3: 2 (second interim database snapshot and final trial snapshot) illustrate the data sets which will be used for each category class of endpoints, and the approaches used with regard to missing data. For explanation of the different methods of handling missing data see Section 6.6.

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Table 6.3: 1 Subject sets analysed (first interim database snapshot)

	Patient set			
Class of endpoint	**RSi**	**ESi**	**SAFi**	**FASi**
Disposition		OR		OR
Compliance				OR
Exposure			OR	
iPDs	OR			
Demographic/baseline characteristics				OR
Primary endpoint	NRI*, OC*			NRI, OC
Secondary efficacy endpoints	NRI*, OC*			NRI, OC
Further efficacy endpoints				All: OC Binary: NRI Continuous: MMRM
PK concentr.& ADA&DNA			OC (if available)	
Biomarker endpoints			OC (CRP, FLF, FCP. Others: if available)	
Safety parameters			OR, OC-IR	
Use of rescue medication				OR

For explanation of the different approaches with regard to missing data see Section 6.6.
OR = original results.
NRI = No Response Imputation excluding values after rescue medication taken
OC = observed cases excluding values after rescue medication taken
OC-IR = observed cases including also values after rescue medication taken
LOCF = Last observation carried forward
*only when RS are different from FAS

At the time of the first interim database snapshot, only the primary analysis on each efficacy endpoint will be done. All safety displays will be produced. No inferential subgroup analyses will be performed.

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Table 6.3: 2 Subject sets analysed (second interim database snapshot and final trial snapshot)

	Patient set				
Class of endpoint	**RS**	**ES**	**SAF**	**FAS**	**PPS**
Disposition		OR		OR	
Compliance				OR	
Exposure			OR		
iPDs*	OR				
Demographic/baseline characteristics				OR	
Primary endpoint	NRI**, OC**			NRI, OC	NRI, OC
Secondary efficacy endpoints	NRI**, OC**			NRI, OC	
Further efficacy endpoints				All: OC Binary: NRI Continuous: MMRM	
PK concentr.& ADA&DNA			OC		
Biomarker endpoints			OC		
Safety parameters			OR, OC-IR		
Use of rescue medication				OR	

For explanation of the different approaches with regard to missing data see Section 6.6.
OR = original results.
NRI = No Response Imputation excluding values after rescue medication taken
OC = observed cases excluding values after rescue medication taken
OC-IR = observed cases including also values after rescue medication taken
LOCF = Last observation carried forward
* any patient with the iPD of treated but not randomized (C3.02) will only be listed in the footnote of the iPD table.
**only when RS are different from FAS

At the time of the second interim and final trial database snapshots, all analyses per TSAP are scheduled to be performed.

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6.5 POOLING OF CENTRES

Given the low number of patients per centre and the primarily descriptive nature of the statistical analysis, separate analyses by centre are not meaningful and not desirable. All patients from all centres will be pooled for statistical analysis.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Section 7.5 of the CTP describes the handling of missing data.

The original results (OR) approach implies the presentation of data exactly as observed, i.e., not using time windows and not setting values to missing.

OR analysis will be performed on parameters and endpoints that are either not affected by patients' rescue medication use (e.g., plasma concentration level of BI 655130, or rescue medication use itself), or, if it is not meaningful to apply any imputation rule for the replacement of missing values.

6.6.1 Withdrawals

The reasons for withdrawal from treatment will be reported as indicated on the eCRF.

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6.6.2 Efficacy data

Based on the different reasons for a subject to have missing data, various approaches will be used to assess the impact of missing data on the different efficacy endpoints of this trial. The approaches to be applied are described below.

Missing data imputations at the primary analysis at Week 12, that is, once all patients have achieved the Week 12 visit, will be performed using all available on-treatment data observed up to the respective analysis cut-off date.

Binary efficacy endpoints

For all binary endpoints (i.e. endpoints that are either 1 (patient responded) or 0 (patient did not respond)), the following will be performed as the primary imputation approach (analysis type: Non Response Imputation [NRI]):

1. If there are data at visits both before and after the visit with a missing outcome, then impute as success only if both neighbouring visits also represent a success (independent of whether the preceding and following observations were selected for analysis based on time windows described in Section 6.7);

2. Otherwise, impute as a failure to achieve a response

If a patient takes a rescue medication as defined in Section 5.4.5 for the treatment of ulcerative colitis prior to observing the primary endpoint for this trial, then all data subsequent to rescue treatment will be considered to represent a failure to achieve a response.

Further approaches to the handling of missing data will be performed as follows:

- Observed cases (analysis type: OC) approach will be used as a sensitivity analysis and will include all collected data, with no imputation performed on the missing data. Such an OC approach will exclude all values measured after intake of a rescue medication (i.e. such values will be set to missing).
- Observed cases including rescue (analysis type: OC-IR) approach will be used as a further sensitivity analysis and is an extension of the OC approach which includes all values which were measured after rescue medication intake.

Missing data after premature discontinuation will not be imputed when following the OC and OC-IR approach.

Continuous further efficacy endpoints

For further efficacy endpoints which are continuous in nature, the use of a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach, if applicable, will ensure that missing data are handled implicitly, via a missing at random assumption, by the statistical model.

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The continuous further efficacy endpoints will also be summarized by visits descriptively via the OC approach (described above for the binary efficacy endpoints).

6.6.3 Safety data

From CTP Section 7.5: *With respect to safety evaluations, it is not planned to impute missing values.*

For safety data that are displayed by time point (or visit) of measurement, the OC-IR approach will be used.

The only exceptions where imputation might be necessary for safety evaluation are AE dates and start and stop dates for concomitant medications. Missing or incomplete AE dates are imputed according to BI standards (see *BI-KMED-BDS-HTG-0035*: "Handling of missing and incomplete AE dates" (4)).

Partial start and stop dates for concomitant medications and background, rescue, as well as historical medication for UC will be imputed to enable subsequent calculation (but not for display) by the following "worst case" approach:

- If the day of the end date is missing, then the end date is set to last day of the month (or to the patient's trial completion date, if it is earlier than the last day of the month).
- If the day and month of the end date are missing then the end date is set to 31st of December of that year (or to the patient's trial completion date, if it is earlier than the 31st of December of that year).
- If the day of the start date is missing the start date is set to the first day of the month (except for rescue medication, where the first dosing day will be used if first dosing happened in the same month).
- If the day and month of the start date are missing then the start date is set to the 1st of January of that year (except for rescue medication, where the first dosing day/month will be used if the first dosing happened in the same year).

All other cases need to be assessed by the trial team on an individual basis, using the above points as guidance.

6.6.4 PK data

Missing data and outliers of PK data are handled according to BI standards (see 001-MCS-36-472_RD-01) (5).

6.6.5 Biomarker data

Missing biomarker data (NOS - no sample, NOR - no valid result, NOA - not analysed) will not be imputed.

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For disease specific (protein) markers (from serum or stool samples) the following handling of data below or above the limit of quantification will be applied:

- BLQ data will be replaced by 0.5 · LLOQ. Hereby LLOQ will be the maximum used lower reference limit for classification of BLQs. All values lower than LLOQ will be imputed (regardless of whether they are classified as BLQ or not).

- ALQ data will be replaced by ULOQ, if ULOQs are available and are greater than observed study values (i.e. the highest solution was applied for the measurement). Otherwise, ALQ data will be excluded from the analysis.

The OC approach (see Section 6.6.2) will be used to present the data.

The handling of other biomarkers, e.g. RNA expression, will be specified in a separate document.

6.6.6 Time since first diagnosis

For incomplete information on the date of first diagnosis, time since first diagnosis will be calculated as follows:

- If the year of first diagnosis is unknown, then time since first diagnosis will be set to missing.
- If day and month of the first diagnosis are unknown, then time since first diagnosis will be calculated as if diagnosed on the 30th of June of that year.
- If only the day of the first diagnosis is unknown, then time since first diagnosis will be calculated as if diagnosed on the 15th of that month.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Measurements reported with the date and time and that were taken prior to start of administration of trial treatment will be considered pre-treatment values. Measurements reported with a date only (and no time) and that were taken on the day of first administration of trial treatment will also be considered pre-treatment values. These pre-treatment values will be assigned to visits according to the nominal visit number as recorded on the eCRF, or as provided by the laboratory.

Baseline, unless otherwise specified, is defined as the last measurement collected prior to the start of administration of the trial treatment.

Measurements taken after the start of administration of the trial treatment will be considered either on- or off-treatment values based on the definition in Section 6.1, and will be assigned to visits for statistical analysis, if applicable, as defined in Table 6.7: 1.

Neither analysis of AE data, concomitant medication, non-drug therapies, nor use of rescue medication will be based on visits. Therefore, no assignment to time windows will be necessary.

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Frequency tables for AE data will be using on-treatment data only up to the time of the planned trial analysis (Week 12, or Week 36). Frequency tables for concomitant medication, non-drug therapies, and rescue medication will be based on all available data up to the time of the planned trial analysis (Week 12, or Week 36).

For derivation of the last value on treatment, minimum value on treatment, and maximum value on treatment, all on-treatment values (whether or not selected in any time window; see Table 6.1: 1 for definition of the on-treatment period) will be considered; these will be derived for analysis of laboratory and vital signs data. For identification of potentially clinically significant abnormal laboratory values, all values (whether or not selected in any time window) before the off-treatment period will be considered.

A graphical analysis of the ALT and total bilirubin will be performed (so called eDISH plot) based on the available data obtained during the on-treatment period.

All other safety, efficacy, and biomarker measurements will be assigned to visits based on extended time windows around the planned visit dates defined relative to the day of first trial treatment (which is scheduled for Visit V2). These extended time windows are defined in Table 6.7: 1.

Table 6.7: 1 Time windows for assignment of efficacy, safety lab, vital signs and biomarker to visits for statistical analysis

Visit number /name	Visit label	Planned day	Time window (Days)				
			Window (per CTP)	Start (per CTP)	End (per CTP)	Start (extended)	End (extended)
V1a	Screening	-35 to -8	n/a				
V1b	Screening	- 28 to -6	n/a				
V2	Baseline	Day 1	+/- 0	1 [A]	1 [A]	≤1 [A]	1 [A]
On-treatment data only							
V3	Week 2	Day 15	+/- 2	13	17	2	22
V4	Week 4	Day 29	+/- 3	26	32	23	43
V5	Week 8	Day 57	+/- 3	54	60	44	71
EOT	Week 12/EoT	Day 85	+/- 4	81	89	72	99*
FU1	Week 16/FU1	Day 113	+/- 4	109	117	100	134
FU2	Week 22/FU2	Day 155	+/- 4	151	159	135	Min(175, LD+140)
All data (on- and off-treatment)							
FU3 [B]	Week 28/FU3	Day 197	+/- 4	193	201	176	225
EOS [B]	Week 36/EOS	Day 253	+/- 4	249	257	226	Day of last follow up value [B]

For primary analysis for efficacy (Week 12) – Data after minimum (cut-off [C] , Day 99) will not be used for analyses
For final analysis – Data after (LD [D] + 140) will not be used for any planned on-treatment analyses

Days are counted relative to the day of first treatment, which is defined as Day 1.
[A] Note that measurements made at Day 1 and assigned to the on-treatment period (because mistakenly made after start of infusion of trial treatment) via assessment on date and time (i.e. safety laboratory) will not be assigned to Day 1. Such data will be listed only.
[B] Note that measurements assigned to the Week 28/FU3 or Week 36/EOS visits but after LD+140 are intended to represent off-treatment (i.e., follow-up) measurements, as they are made after the end of the on-treatment

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period.
[C] The cut-off date is not applicable for the final trial analysis.
[D] LD = Day of Last dose/infusion received

Repeated and unscheduled efficacy, safety, and biomarker measurements will be handled similarly to scheduled measurements and will also be assigned to a time window depending upon the date of measurement.

Only one observation per time window will be selected for statistical analysis at a particular visit – the value which is closest to the protocol planned visit day will be selected. If there are two observations which have the same difference in days to the planned day, the later value will be selected. If there are two observations on the same day, then for vital signs the latest value (according to the date and time) will be selected, and for other endpoints the worst value will be selected.

Assignment of efficacy observations to visits based on time windows will be based on the non-imputed (observed) data after setting values after rescue medication intake to missing (if applicable, i.e. for the "NRI" and the "OC" approaches defined in Section 6.6).

For visits without an assigned value based on time windows, a value will thereafter be imputed as defined in Section 6.6. Imputation of efficacy endpoints, when applicable, will be performed based on all available observations obtained, irrespective of whether the observation was selected in any time window.

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7. PLANNED ANALYSIS

All efficacy analyses will be purely exploratory in nature. The following analyses are planned at different stages throughout the trial.

- **First Interim Database Snapshot – Week 12 Analysis**

The analysis will be performed using all randomized patients who completed/discontinued through the Week 12 visit on or prior to the cut-off date (see Section 3). A database snapshot will then be done. At this time, an interim analysis of the efficacy and safety data through Week 12 will be performed by the sponsor.

The individual patient cut-off date for inclusion of data into the analysis is the minimum of the analysis-specific cut-off date, or study day 99, as described in Table 6.7: 1.

The analyses for this snapshot will be performed using the subject sets of ESi, RSi, SAFi, and FASi (see Section 6.3).

- **Second Interim Database Snapshot – Week 12 Analysis (Primary Analysis for CTR)**

The analysis will be performed using all randomized patients who completed/discontinued through the Week 12 visit. A database snapshot will then be done. At this time, a complete analysis of all efficacy, safety, and PK/Biomarker data will be done through Week 12, and will be performed by the sponsor.

The individual patient cut-off date for inclusion of data into the analysis is the minimum of the analysis-specific data cut-off, or study day 99, as described in Table 6.7: 1.

The analyses as described in Section 6.3 of this TSAP will be performed using the subject sets of ES, RS, SAF, FAS, and PPS.

- **Final analysis (Week 36)**

The analyses of the entire efficacy, safety, and biomarker data collected through the full 36 weeks of follow-up will be performed once all entered patients have completed the trial (up to EOS Visit); at that time point, a final database lock will be done and all on treatment data through Week 36 will be reported.

General Remarks

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (001-MCG-159) (10).

The individual values of all patients will be listed, including those collected during the off-treatment period. Listings will generally be sorted by country, centre number, patient number, and visit (if visit is applicable in the respective listing). AE listings will be sorted by treatment (see Section 7.8.1 below for details).

The following standard descriptive statistical parameters will be displayed in summary tables for continuous variables:

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N	number of non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Q1	lower quartile
Median	median
Q3	upper quartile
Max	maximum

Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline "Reporting of Clinical Trials and Project Summaries" (10).

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group; unless otherwise specified, this includes all patients in the respective patient set whether they have non-missing values or not. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there are missing values.

For the final trial analysis up to Week 36, displays of certain safety endpoints, such as AE, will be produced only for the on-treatment period. Displays of endpoints presented by-visit, additional outputs, which include both on- and off-treatment data, will be produced at the time of update analysis after final DBL (see also Section 6.7).

Disposition of the patient population participating in the trial will be summarised by presentation of the frequency of patients screened, entered, screened but not entered, treated, entered but not treated, who completed all doses of trial medication as planned, who completed the EOT visit, who completed the EOS visit, and who were prematurely discontinued, by reason. Disposition will be listed by country.

The frequency of patients with iPDs will be presented for the RS by treatment. The iPDs will be listed per patient indicating whether or not the iPD led to exclusion from patient sets analysed.

The frequency of patients in each of the different analysis sets will also be presented by treatment.

All Section 7 analyses described below are presented for the second interim database snapshot (based on all randomized patients) and the final analysis using the subject sets of ES, RS, SAF, FAS, and PPS. A sub-selection of these analyses will be performed at the time of the first interim database snapshot using the subject sets of ESi, RSi, FASi, and SAFi.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the CTR.

Descriptive statistics will be presented by treatment for demographic parameters and baseline characteristics based on the FAS.

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For the continuous variables described below, the following categories will be defined and presented according to the number and percentage of patients in each category:

Table 7.1: 1 Categories for summary of continuous variables

Variable	Categories
Age	< 50 years 50 to < 65 years 65 to < 75 years ≥ 75 years < 65 years ≥ 65 years
Weight	≤70 kg >70 to ≤80 kg >80 to ≤ 90 kg >90 kg
BMI	< 25 kg/m^2 25 to < 30 kg/m^2 ≥ 30 kg/m^2
Time since first diagnosis	≤ 1 year > 1 to ≤ 5 years > 5 to ≤ 10 years > 10 years
Total MCS at baseline	< 4 4 to <6 6 to <8 8 to <=10

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7.2 CONCOMITANT DISEASES AND MEDICATION

Analyses of concomitant diseases and medication will be based on the FAS.

Concomitant diseases will be coded according to the most recent version of MedDRA.

Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary.

Concomitant non-drug therapy will be coded according to the most recent version of MedDRA.

Concomitant diseases which are present at start of the study, as well as characteristics of the trial disease, will be descriptively summarized by treatment.

Characteristics of the trial disease, such as the disease diagnosis and the type of extra-intestinal diagnoses which are present at start of the study, as well as the occurrence of any prior surgery for ulcerative colitis will be descriptively summarized by treatment. During the course of the study's on-treatment period, any changes in the pre-existing extra-intestinal diagnoses (improved or worsened) by visit (including as an overall on-treatment assessment), as well as the development of newly diagnosed extra-intestinal diagnoses will also be summarized.

A medication will be considered concomitant to treatment, if it

- is ongoing at the start of trial treatment or
- starts within the on-treatment period (see Section 6.1 for a definition of study analysis phases).

Concomitant medication use (excluding rescue medication, historical medication for UC and background medication) will be summarised by treatment with frequency and percentage of patients by preferred name. Summaries will be presented for

- concomitant medication started any time prior to the Week 12 visit (for any patient with a missing Week 12 visit, available data will be summarized up to the end of the Week 12 time window, see Table 6.7: 1).
- concomitant medication started any time on or after the Week 12 visit, and prior to EoS.

The frequency and percentage of patients with historical medication for UC will be displayed, and by reason for discontinuation. In addition, the reason for discontinuation will also be presented by type of medication.

The frequency and percentage of patients taking any background medication for UC will be tabulated by type of background therapy. Further displays regarding changes in background medication during the on-treatment period will be summarized in Section 7.6.4.

Use of rescue medication will be summarised separately (see Section 7.6.4).

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Concomitant use of non-drug therapies will be summarised with frequency and percentage. Summaries will be presented for:

- concomitant non-drug therapy started any time prior to the Week 12 visit (for any patient with a missing Week 12 visit, available data will be summarized up to the end of the Week 12 time window, see Table 6.7: 1).

- concomitant non-drug therapy started any time on or after the Week 12 visit, and prior to EoS.

7.3 TREATMENT COMPLIANCE

Treatment compliance will be summarised overall and by visit via total volume infused (as a % of planned) for the FAS using descriptive statistics (N, mean, SD, minimum, median, and maximum). The volume infused (as a % of planned) is defined as the volume infused at a visit (in ml as recorded in the eCRF), divided by 60 ml (the volume the patient should have received), times 100.

For the patients who discontinued the study treatment prematurely, only the visits on or before premature discontinuation will be used for the calculation of overall compliance.

The number and percentage of patients with the following overall compliance categories will be presented:

- "<50% of planned",
- "50 to <80% of planned"
- "80 to 100% of planned".

The number of patients who received a dose will be tabulated per visit.

7.4 PRIMARY ENDPOINT

The binary primary efficacy endpoint will be described using patient frequencies and percentages for the FAS (or its derivatives - see Section 6.3). The underlying mESS will be based on central reading - replacing missing values with results based on investigator assessment.

7.4.1 Primary analysis of the primary endpoint

The primary analysis of the primary endpoint will be based on Section 7.3.1 of the CTP.

From CTP Section 7.3.1: *The primary analysis of the unadjusted absolute risk difference versus placebo will be calculated simply as the difference in the observed proportion of patients with mucosal healing at Week 12, for the FAS. A 95% Newcombe confidence interval around this difference will also be provided.*

The method to provide confidence intervals for single proportions will be based on the Wilson method (14). The method to provide confidence intervals for the unadjusted risk

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differences is derived from the Newcombe method (15), and is constructed from the Wilson score confidence interval for each of the single proportions.

As described in Section 7.2 of the CTP, there will be no formal hypothesis testing performed in this trial.

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoint

The further analysis of the primary endpoint will be based on Section 7.3.1 of the CTP as below.

From CTP Section 7.3.1: *Exploratory analyses of the primary endpoint will include, in the absence of model convergence issues due to occurrence of low cell frequencies, the difference in the proportion of patients with mucosal healing at Week 12 between BI 655130 and placebo, for the FAS, using a logistic regression approach with a logit link. Fixed classification effects will include treatment and presence or absence of use of infliximab (yes/no). The estimates from the logistic regression are on the logit scale, and the difference in proportions will be calculated as the difference between the predicted probabilities in the treatment groups on the original scale, with the confidence interval calculated using the cumulative distribution function method of Reeve.*

Prior to the first interim database lock, it was decided that the Reeve confidence intervals will not be used due to low enrolment.

The subgroup analysis will create three logistic regression models for the primary endpoint for the covariates listed in Table 6.4: 1. The SAS code for the logistic regression model is as follows:

```
proc logistic data=indata;
  class trt (ref="&_j.") / param=GLM;
  model resp = trtseq &covar. / link=LOGIT CovB;
  lsmeans trt / cl ILINK;
run;
```

Other analyses of the primary endpoint will include:

- *Sensitivity analyses utilizing different patients sets (such as the PPS), as well as alternative methods for the handling of missing data as described in* CTP *Section 7.5;*

- *Exploration of the relationship between various demographic or baseline characteristics data and the primary endpoint will be performed via graphical methods as well as using a logit link with* [redacted]

A separate logistic regression model for the primary endpoint with each of the following baseline covariates and including treatment as well as treatment-by-covariate interaction as fixed effects will be fit:

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- Categorical:
  - Sex
  - Smoking status (previous/current or never)
- Continuous:
  - Age
  - BMI
  - Time to disease diagnosis

Parameter estimates from the logistic model will be presented. The estimated response rate for each treatment arm across the range of observed covariate values will be displayed graphically.

Note that exploratory and other analyses of the primary endpoint are planned to be performed at the time of the Week 12 primary analysis only, unless otherwise specified.

Table 7.4.2: 1 below summarizes the primary and further analyses as described above, together with the sensitivity analyses and subgroup analysis.

Table 7.4.2: 1 Summary of all analyses to be performed for the primary endpoint

		Summary of analysis	
Analysis	**Analysis set**	**Imputation Approach**	**Analysis model**
Primary analysis	FAS	NRI	Unadjusted absolute risk difference
Sensitivity (a) -1	RS*	NRI	Unadjusted absolute risk difference
Sensitivity (a) -2	FAS	OC	Unadjusted absolute risk difference
Sensitivity (a) -3	RS*	OC	Unadjusted absolute risk difference
Sensitivity (a) -4	PPS	NRI	Unadjusted absolute risk difference
Sensitivity (a) -5	PPS	OC	Unadjusted absolute risk difference
Further analysis	FAS	NRI	Adjusted risk difference via logistic regression
Subgroup analysis	FAS	NRI	Adjusted risk difference via logistic regression including different covariates

Note:

For explanation of the different approaches with regard to missing data see Section 6.6.
NRI = No Response Imputation excluding data after rescue treatment
OC = Observed Cases excluding data after rescue treatment
*Only when RS is different from FAS

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7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been specified.

7.5.1.1 Primary analysis of the key secondary endpoint(s)

This section is not applicable as no key secondary endpoints have been specified.

7.5.1.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the key secondary endpoint(s)

This section is not applicable as no key secondary endpoints have been specified.

7.5.2 (Other) Secondary endpoints

Analysis of secondary endpoints is described in Section 7.3.2 of the CTP.

From CTP Section 7.3.2:

For the secondary binary endpoints, for the FAS, the unadjusted absolute risk difference versus placebo will be calculated and a 95% Newcombe confidence interval around this difference will also be provided.

A logistic regression analysis on the binary secondary efficacy endpoints, per the approach described for the primary endpoint, will also be done on the FAS. As defined for the primary endpoint, the method to provide confidence intervals for single proportions will be based on Wilson (14), and for unadjusted risk differences is derived from the Wilson method by Newcombe (15).

Table 7.5.2: 1 below summarizes all of the analyses to be performed for the secondary endpoints.

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Table 7.5.2: 1 Summary of all analyses to be performed for the secondary endpoints

		Summary of analysis	
Analysis	**Analysis set**	**Imputation Approach**	**Analysis model**
Planned analysis in CTP	FAS	NRI	Unadjusted absolute risk difference
Sensitivity-1	FAS	OC	Unadjusted absolute risk difference
Sensitivity-2	FAS	NRI	Adjusted risk difference via logistic regression
Sensitivity-3*	FAS	NRI	Unadjusted absolute risk difference (worst case approach on SFS/RBS calculation)

Note:

Standard approach of SFS/RBS calculation is applied unless otherwise specified.

*only applicable to the secondary endpoints of clinical remission and total clinical remission and the further endpoint of clinical response.

For explanation of the different approaches with regard to missing data see Section 6.6.
NRI = No Response Imputation excluding data after rescue treatment
OC = Observed Cases excluding data after rescue treatment

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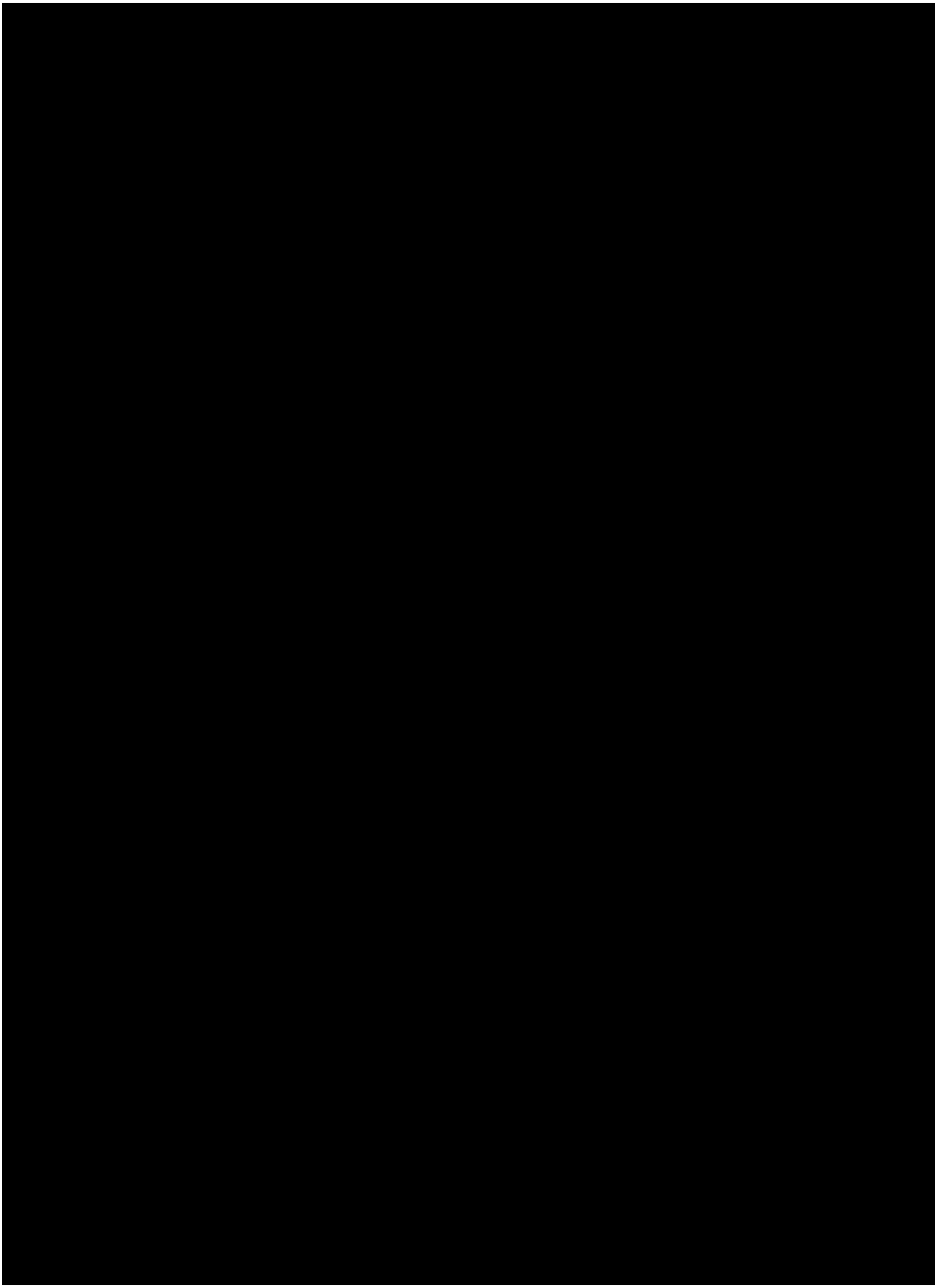

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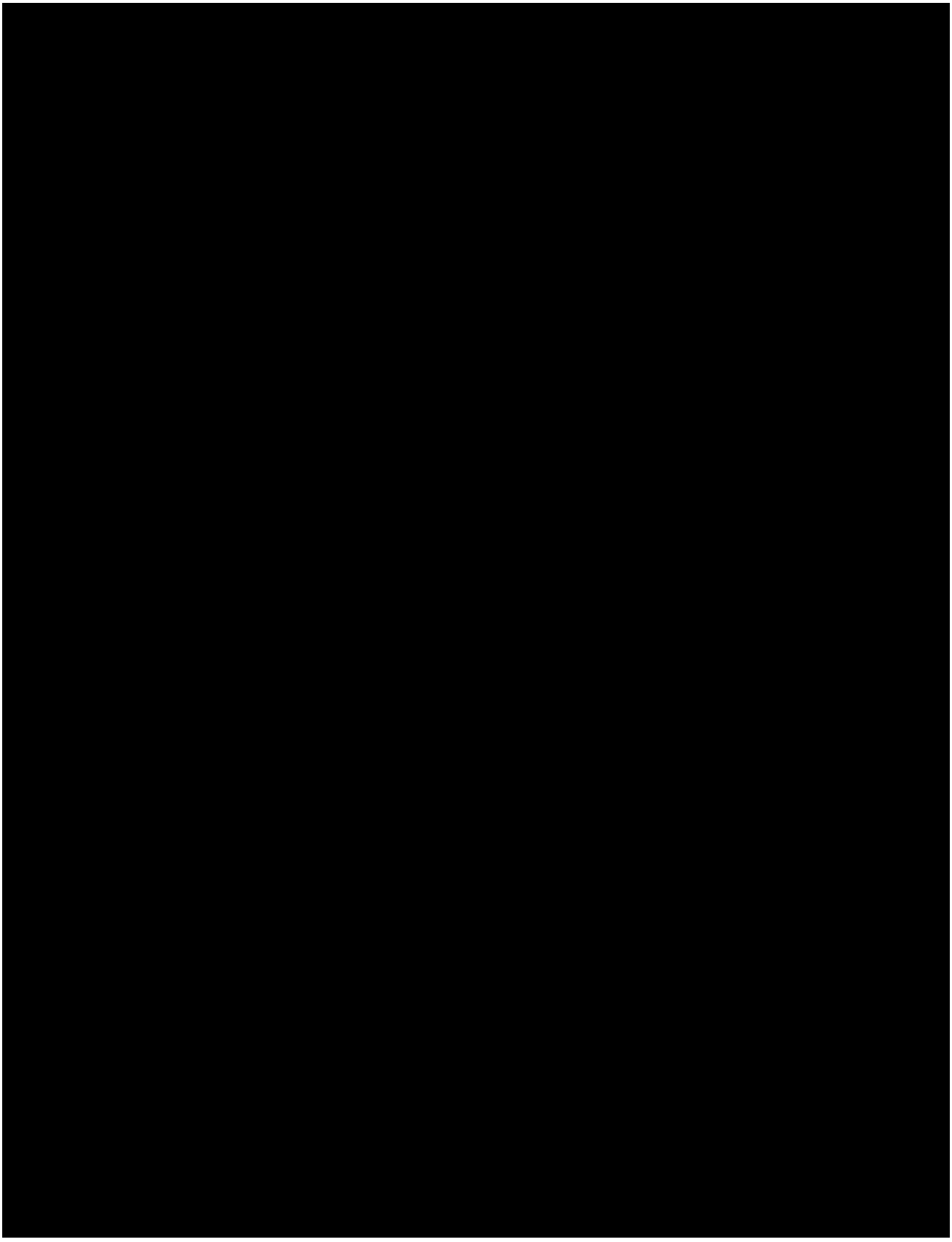

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[redacted]

7.7 EXTENT OF EXPOSURE

The number of subjects who received a dose of trial drug will be tabulated. The duration of infusion [minutes] and the amount of treatment received [mg] (actual and weight based) will be summarised by descriptive statistics (N, mean, SD, minimum, median, maximum) per visit and overall. The total duration of exposure [days), defined as the time from start of the first infusion to time of end of the last infusion plus one day, will also be displayed.

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7.8 SAFETY ANALYSIS

All safety analyses will be performed based on the SAF following BI standards. No hypothesis testing is planned.

For the first interim database snapshot analysis, selected safety data, such as AE listings and displays, beyond the Week 12 visit up to the earliest of the REP/cut-off date will be done for the SAFi (see Section 6.3).

For the second interim database snapshot analysis (the primary analysis for the CTR), a similar approach will be taken as above for the first snapshot. The final analysis will include all safety data up to the end of the trial.

7.8.1 Adverse events

AEs will be coded with the most recent version of MedDRA. Patients will be analysed according to the actual treatment received.

The exposure adjusted incidence rate (per 100 subject years) of a selected treatment emergent adverse event is defined as the number of subjects experiencing the adverse event per treatment group during time at risk divided by the total time of subjects at risk in that treatment group to contribute the event to the analysis multiplied by 100 (per 100 subject years), where:

> Time at risk [subject years] = (date of onset of TEAE – study drug start date + 1) /365.25

If, for a subject, the selected treatment emergent adverse event didn't occur then the time at risk, for the analysis phases according to randomized treatment, will be censored at the minimum of either date of death, last contact date per EoS page, or randomized drug stop date + 140 days. For each selected treatment emergent AE, the exposure adjusted incidence rate will be calculated as:

> Incidence rate [1/100 Subject years (pt-yrs)] = 100 * number of subjects with AE /Total AE-specific time at risk [subject years].

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the exposure adjusted incidence rates (per 100 subject years) as well as the number of patients with AEs, and not on the number of AEs. System organ classes (if applicable) will be sorted according to the standard sort order specified by the EMA. Preferred terms (if applicable) will be sorted by total frequency (within system organ class) across all treatment arms, or, if a total column across all arms is not foreseen in the table, by total frequency (within system organ class) within the BI arm.

For details on summarization of AE data, please refer to "Handling and summarization of adverse event data for clinical trial reports and integrated summaries" (7) [001-MCG-156] and *BI-KMED-BDS-HTG-0035*: "Handling of missing and incomplete AE dates" (4).

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The analysis of AEs will be based on the concept of treatment emergent AEs. Since only the start date of an AE is collected (without start time), any AE occurrence on the same day as the first BI 655130 administration will be assigned to the on-treatment period.

An overall summary of AEs will be presented by treatment. This overall summary will include summary statistics for the class of other significant AEs according to sponsor definition based on ICH E3 and for the class of AESIs.

The following are considered as AESIs (see CTP section 5.3.6.1):

- Infusion reactions including anaphylactic reaction
- Cytokine release syndrome
- Severe bacterial, fungal, and viral infections
- Infection with or reactivation of mycobacterium tuberculosis,
- Opportunistic infections
- Lymphoproliferative disorders
- Hepatic injury

  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

  - an elevation of AST and/or ALT $\geq$3 fold ULN combined with an elevation of total bilirubin $\geq$2 fold ULN measured in the same blood draw sample, and/or
  - marked peak aminotransferase (ALT, and/or AST) elevations $\geq$10 fold ULN.

The investigator identified AESI will be captured from the eCRF and reported in the "Investigator reported AESI" table. In addition, User-defined Adverse Event Concepts (UDAEC) identified through specific search criteria will be reported separately (see Table 7.8.1: 1). For these displays, separate tables will be created for each AESI category wherein frequencies by treatment group will be given.

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Table 7.8.1: 1 Project MEDDRA search criteria for User Defined Adverse Events Concepts

User Defined Adverse Event Concepts	**Categories**
Infusion/Systemic hypersensitivity reactions including anaphylactic reactions	Narrow SMQ "Anaphylactic reaction" Narrow SMQ "Angioedema" Narrow SMQ "Hypersensitivity"
Severe infections (according to RCTC grading)	SOC Infections and infestations of at least severe RCTC grade, by HLGT
Opportunistic and mycobacterium tuberculosis infections	BIcMQ "Infections": Narrow sub-search 8 "Opportunistic infections including Tuberculosis related terms"
Tuberculosis related terms	BIcMQ "Infections": Narrow sub-search 8.2 "Tuberculosis related terms" HLT "Tuberculosis infections"
Malignant tumours	(SMQ "Malignancies" – not for display) (Sub-SMQ "Malignant or unspecified tumours" – not for display) Narrow Sub-SMQ "Malignant tumours" Sub-SMQ "Haematological malignant tumours" Sub-SMQ "Non-Haematological malignant tumours"

Based on the specification provided in ICH E3 (9), the sponsor has defined AEs which are to be classified as 'other significant'. For the current trial, these will include those non-serious AEs which were reported with 'action taken = Drug Withdrawn' or 'action taken = Dose Reduced',

The exposure-adjusted incidence rate and frequency of patients with AEs will be summarised by treatment, primary system organ class, and preferred term. AEs which were considered by the investigator to be drug related will be summarised separately. Separate tables will also be provided for patients with SAEs, patients with AESIs, patients with AE leading to discontinuation of the trial, patients with other significant AEs and User-defined Adverse Event Concepts (UDAEC) (see Table 7.8.1: 1). AEs will also be summarized by maximum intensity based on the RCTC measure (see Section 5.4.1).

For disclosure of AE data on ClinicalTrials.gov, the frequency of patients with non-serious AEs occurring with an incidence of greater than 5% (in preferred terms) will be summarised by treatment, primary system organ class and preferred term. The frequency of patients with SAEs will also be summarised.

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For disclosure of AE data in the EudraCT register, the frequency of non-serious AEs with an incidence of greater than 5% (in preferred terms) and the frequency of SAEs will be summarised.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (8). Note that data from the central laboratory will be used for all displays described below, unless otherwise specified.

For continuous safety laboratory parameters, normalized values will be derived. Normalisation means transformation to a standard unit and to a standard reference range. The process of normalisation, handling of repeat values at the same visit for by-visit displays, as well as standard analyses for safety laboratory data are all described in the BI guidance for the Display and Analysis of Laboratory Data (8). All analyses considering multiple times of the ULN (as described below) will be based on standardized and not normalized values. For continuous safety laboratory parameters, differences to baseline will be calculated.

Only patients with at least one available post-baseline value will be included in the analysis of an individual laboratory parameter. All individual laboratory data will be listed. Values outside the reference range will be flagged.

Descriptive statistics of laboratory values over time (using on treatment data) and for the difference from baseline (see Section 6.7) will be based upon standardized values and provided by visit, including summaries of the last value on treatment, the minimum value on treatment, and the maximum value on treatment. Graphical displays via box plots will be produced for the change from baseline over time for each continuous laboratory endpoint.

Laboratory values will be compared to their reference ranges. Shift tables will be provided for the number of patients with a specific RCTC grade at baseline versus the grade at the last measurement on treatment, as well as the worst grade on treatment. These analyses will be based on standardized laboratory values.

Potentially clinically significant on-treatment abnormalities will be identified based on BI standard rules, which are based on normalized converted lab values, i.e., using the International System of Units. These rules will be listed in the SDL appendix of the CTR. Frequency tables will summarize the number of patients with potentially clinically significant abnormalities for patients without a possibly clinically significant abnormality at baseline. A separate listing will present potentially clinically significant abnormal lab values. If there exists at least one lab value with a clinically significant abnormality within a functional lab group, then for each functional lab group all patient's lab values will be listed.

The frequency of patients with AST or ALT elevations ≥ 3x ULN, ≥ 5x ULN, ≥ 10x ULN, and ≥ 20x ULN will be displayed based on standardized laboratory values. To support analyses of liver related adverse drug effects, the frequency of patients with AST and/or ALT ≥ 3xULN combined with a total bilirubin ≥ 2x ULN in a 30-day period after AST/ALT elevation will be displayed, stratified by alkaline phosphatase < 2x ULN and ≥ 2x ULN (a

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patient can potentially be in both alkaline phosphatase strata in case of multiple AST/ALT and bilirubin elevations). The start of the 30-day time span is triggered by each liver enzyme elevation above the defined thresholds. This analysis will be based on on-treatment standardized laboratory values.

A graphical analysis of the ALT and total bilirubin during the on-treatment period will also be performed; the so called eDISH plot. In the graph, for each subject, the peak total bilirubin is presented as a fold increase over the ULN against the peak ALT as a fold increase over the ULN, on a log10 scale. The measurements displayed or total bilirubin and ALT may, or may not, occur on the same date. Two reference lines, 2x ULN for total bilirubin and 3x ULN for ALT, are drawn onto the graph in order to divide the plane into four quadrants. Normal cases are in the lower left quadrant, potential DILI cases are in the upper right quadrant (Hy's Law quadrant), while the lower right quadrant is known as the Temple's corollary range (ALT ≥ 3x ULN and total bilirubin < 2x ULN).

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse rate, body temperature, and body weight) will be descriptive in nature.

Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided by treatment. At each on-treatment time-point, three assessments will be presented: the pre-dose measurement, the +5 minutes post-dose measurement, and the +2 hours post-dose measurement; change from baseline refers to the original baseline value. The summary will include additionally, the last value, the minimum value, and the maximum value during the on-treatment period presented for each of the three visit measurement times separately (see Table 6.1: 1 for the definition of the on-treatment period). Graphical displays via box plots will be produced for the change from baseline over time for each continuous vital sign endpoint.

Clinically relevant findings in vital signs data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.4 ECG

Abnormal findings in 12-lead ECG will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

No separate listing or analysis of ECG data will be prepared.

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7.8.5 **Others**

The frequency and percentage of patients with ADA to BI 655130 will be presented by visit. ADA will be analysed descriptively. A potential effect of ADA on PK and safety may be evaluated.

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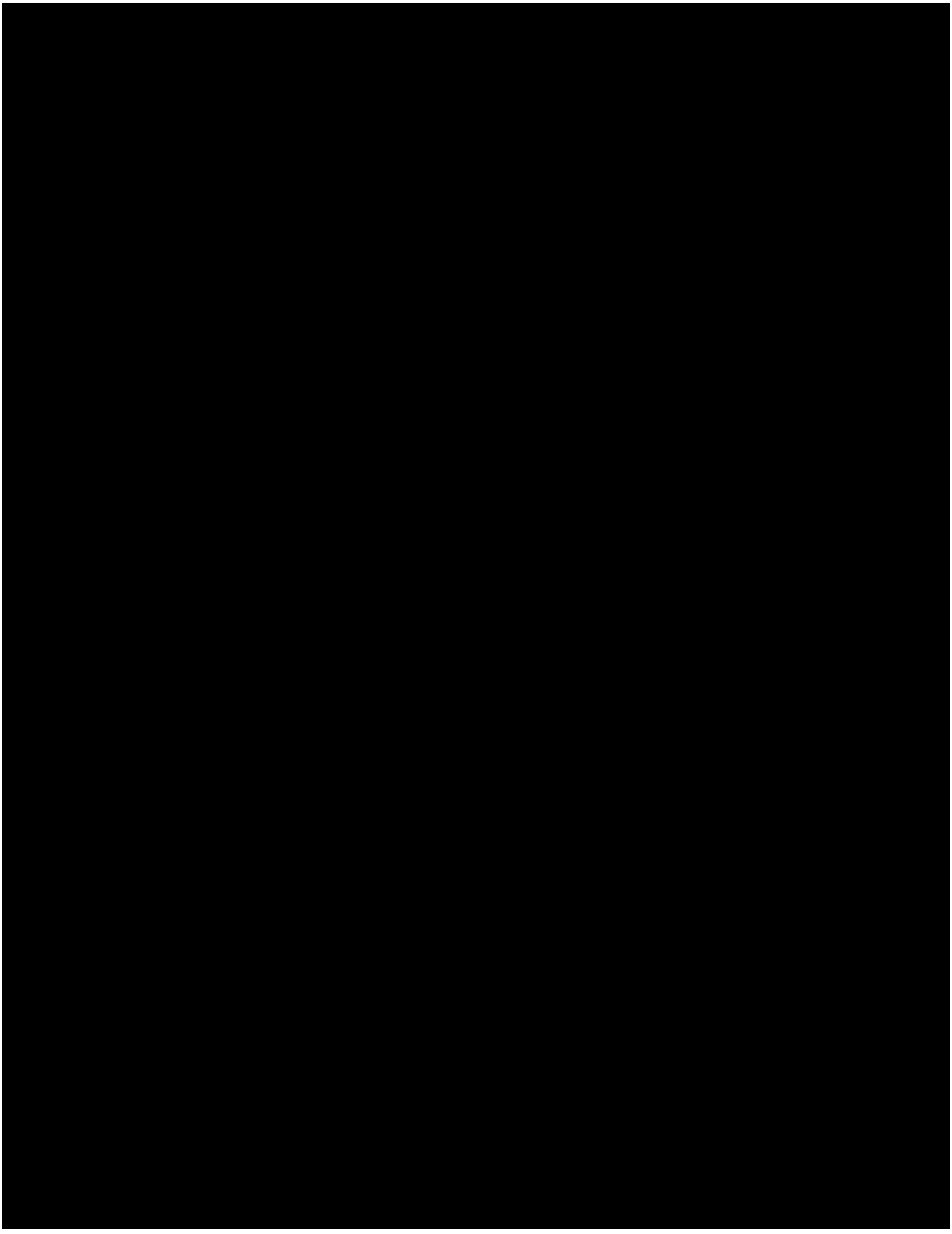

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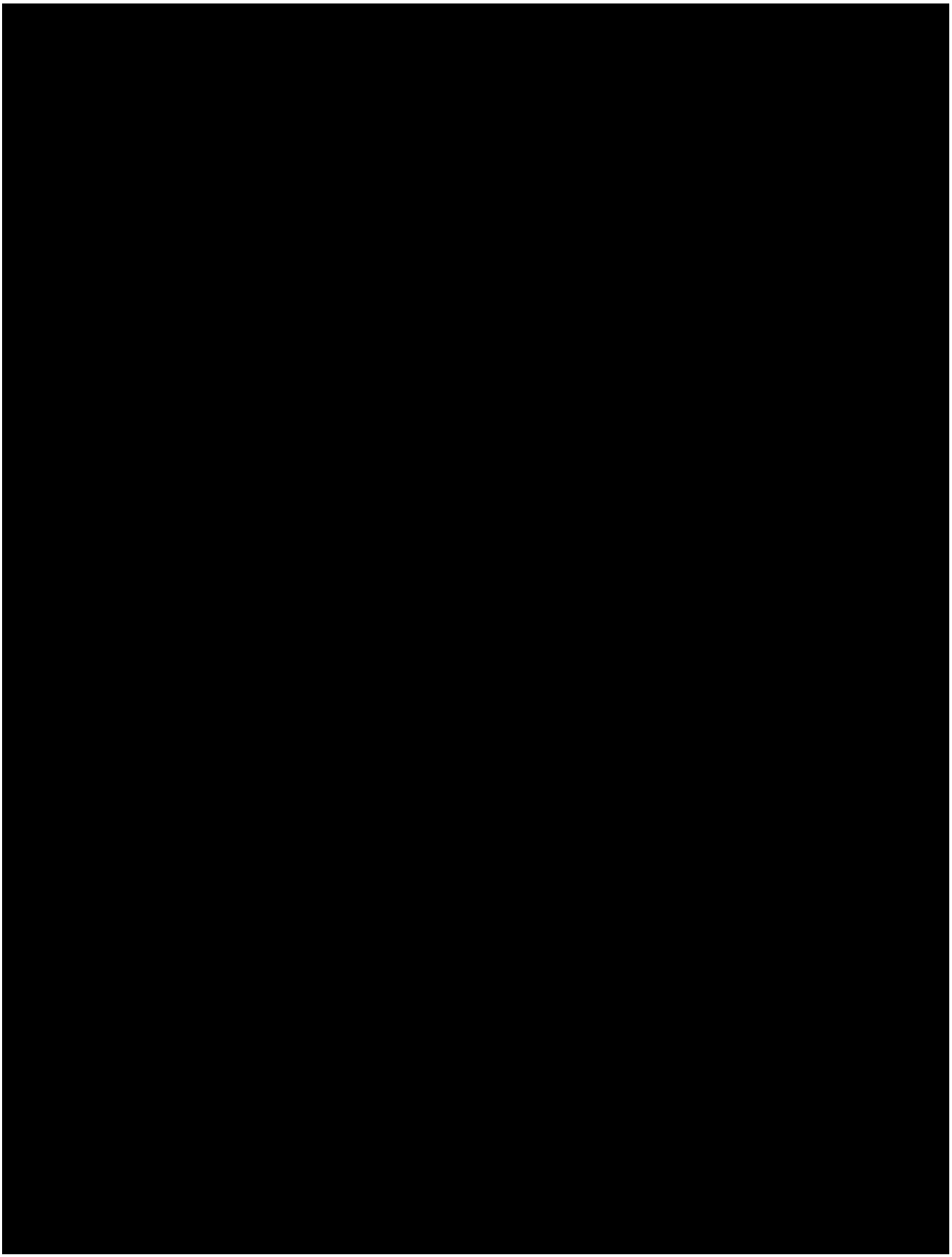

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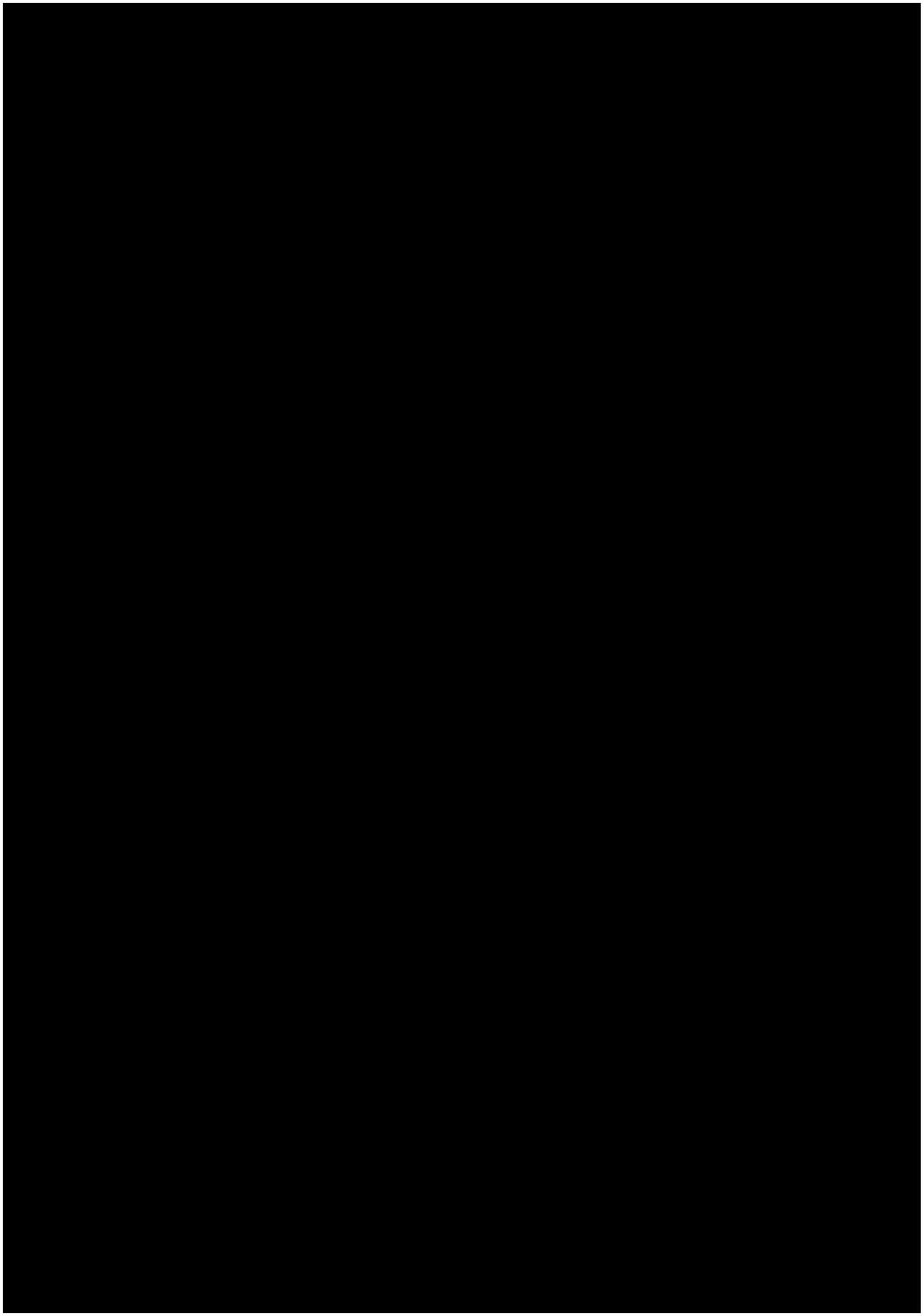

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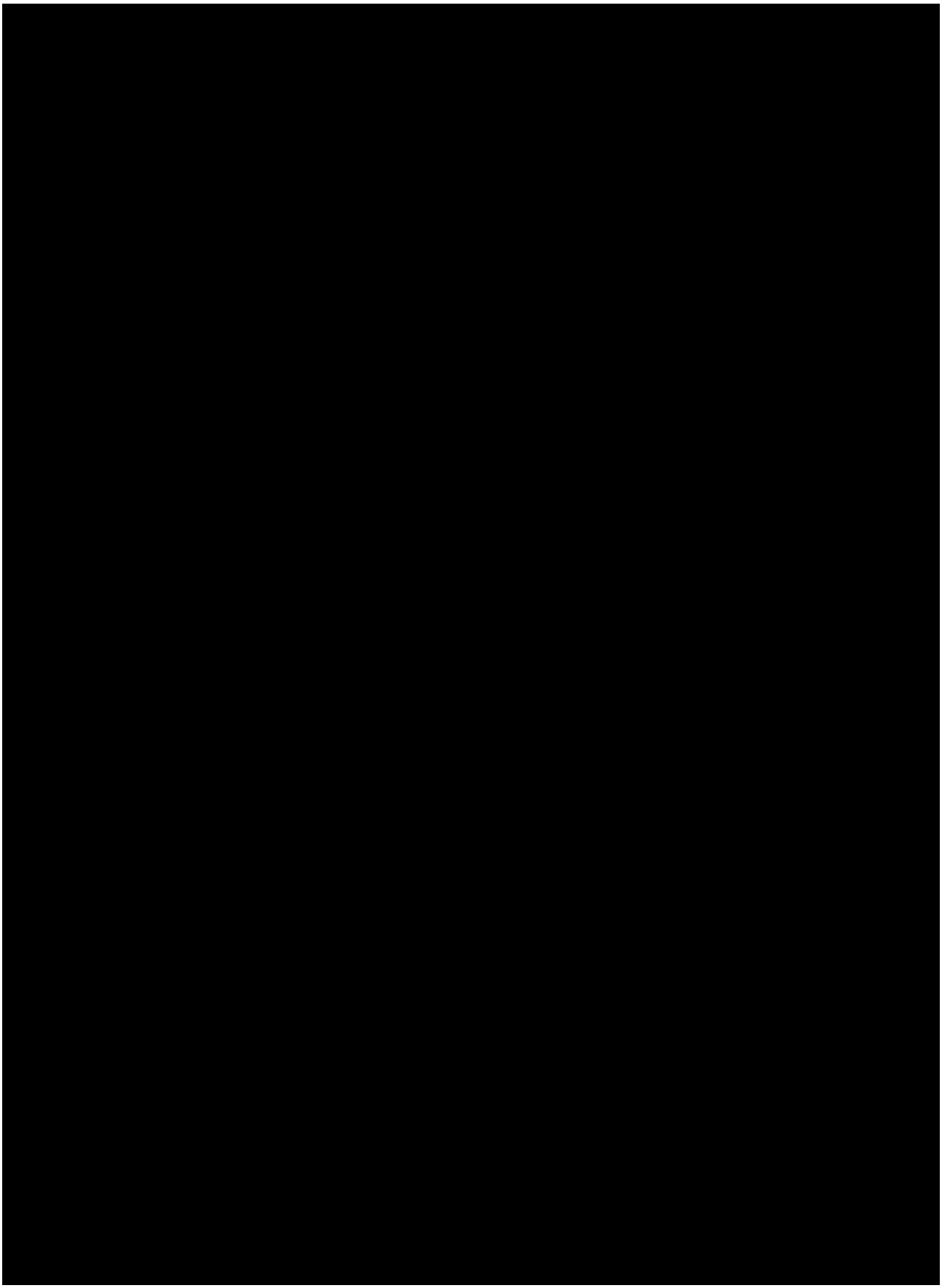

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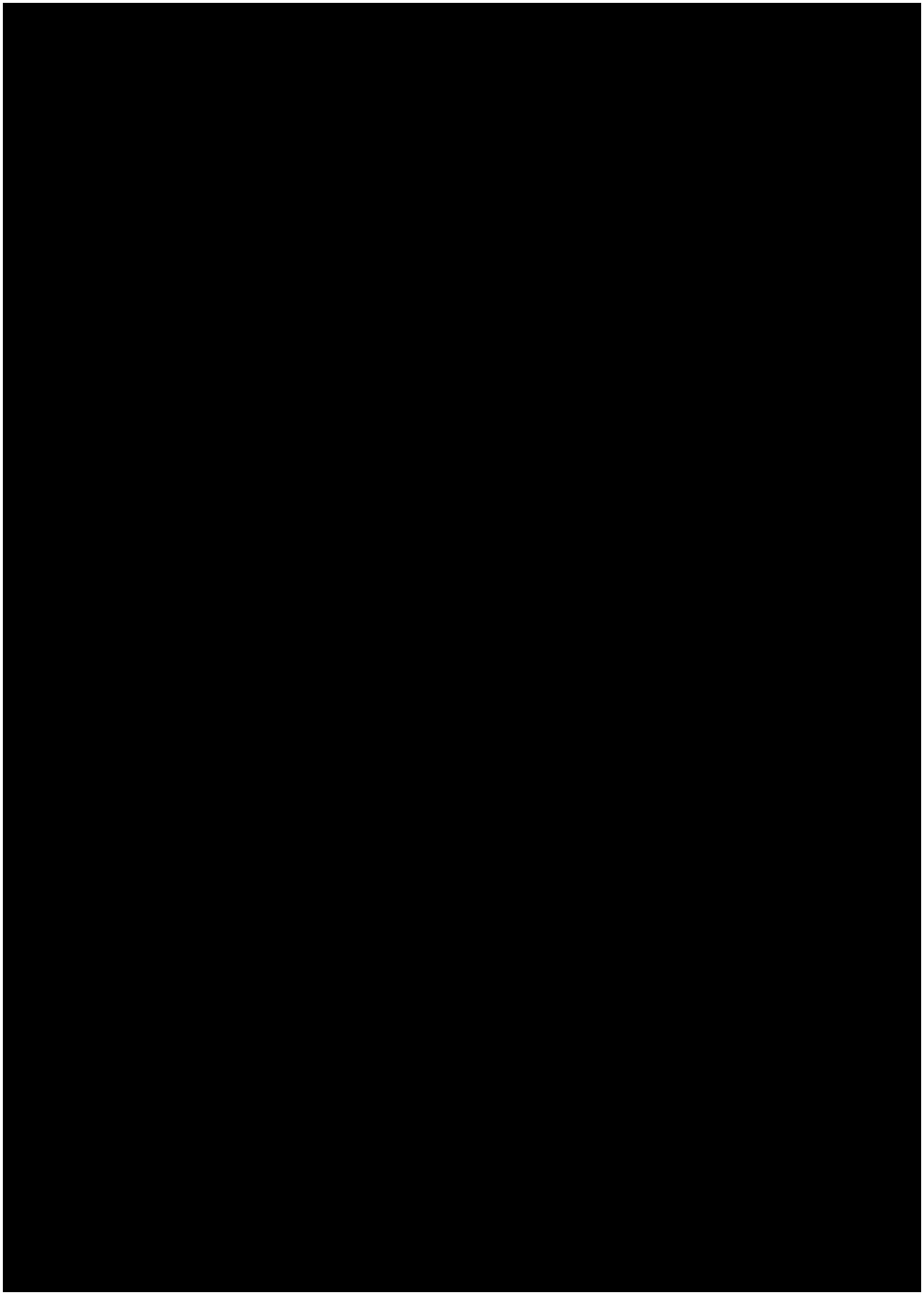

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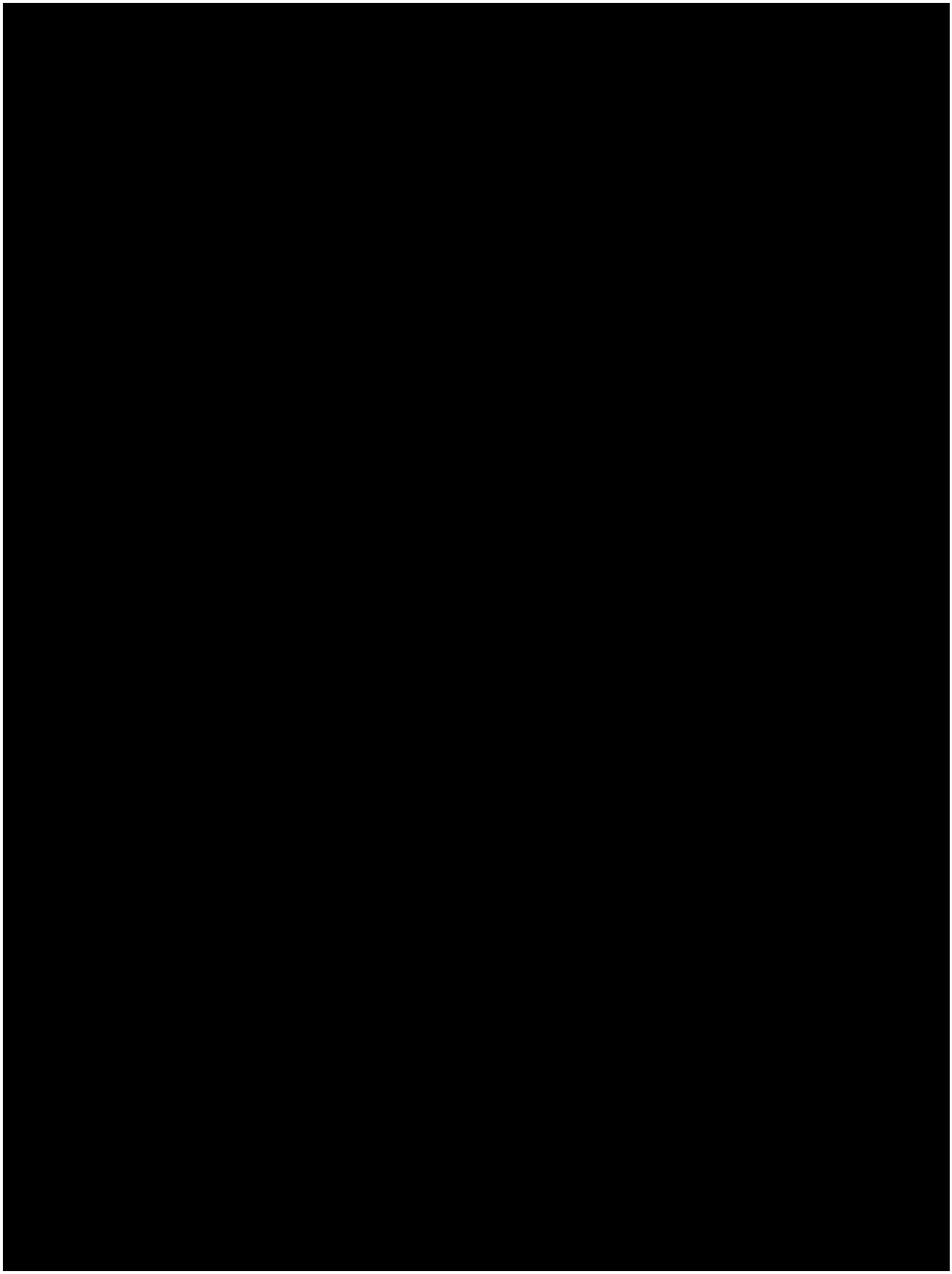

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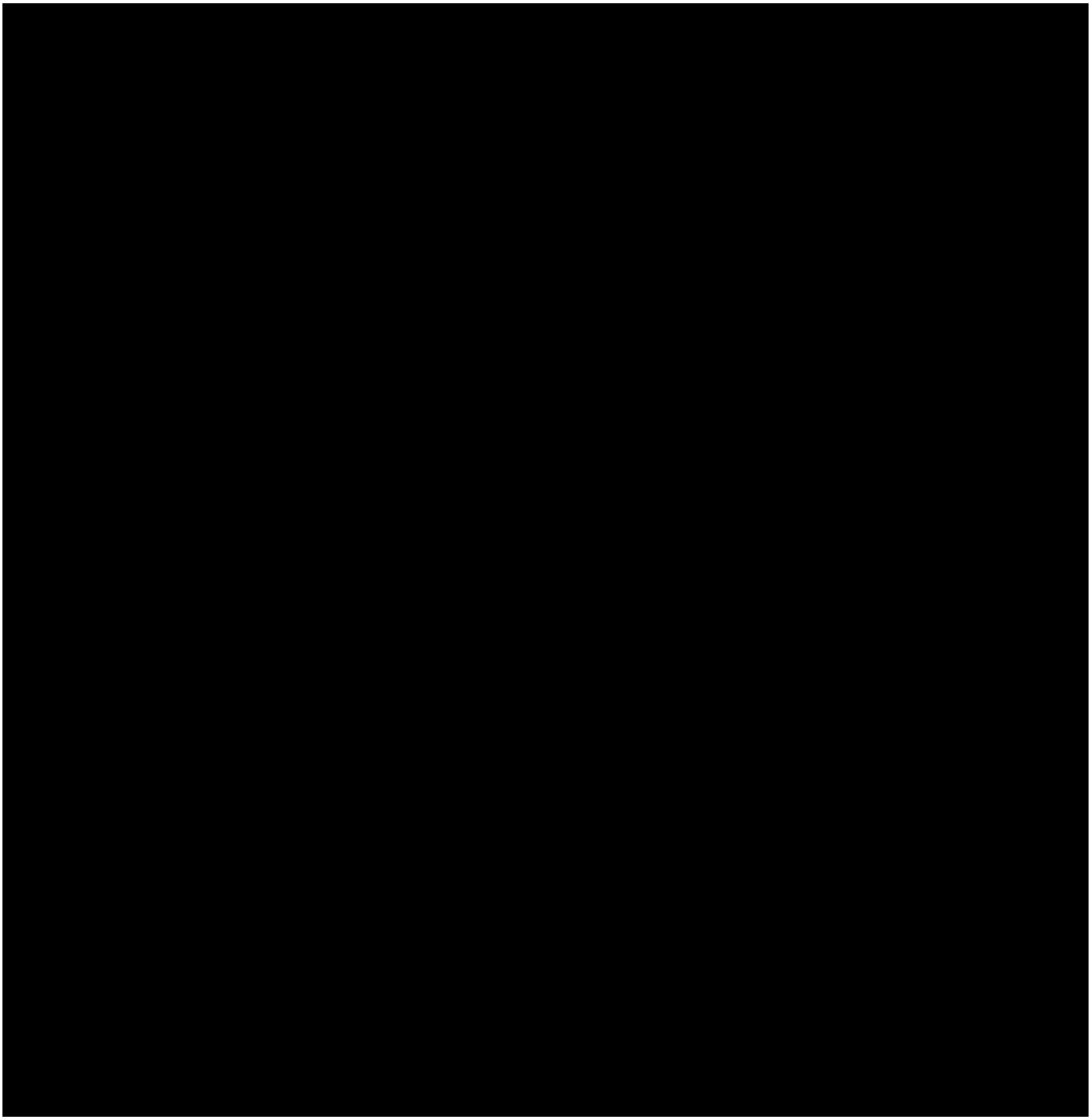

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10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial 1.0	**19-May-2017**	[redacted]	None	First approved version before first patient in.
1.1 (Stable TSAP)	**01-Aug-2017**	[redacted]	(multiple)	Stable TSAP after team comments at TSAP walkthrough, basis for initial programming. Various additions, including: Code for Reeve's method added; text for IBDQ and EQ-5D was amended. Analyses of biomarkers was removed to be shifted to a separate BM-SAP.
2.0	26-Aug-2019	[redacted]	(all)	This is the final version of core TSAP
3.0	04-Mar-2020	[redacted]	(all)	This is the revised TSAP due to early termination of the study.