Clinical Trial Protocol

	Document Number:	**c18863881-01**
EudraCT No. **EU Trial No.**	2018-003078-28	
BI Trial No.	1368-0016	
BI Investigational Medicinal Product(s)	BI 655130	
Title	Multi-center, double-blind, randomised, placebo-controlled, phase IIb dose-finding study to evaluate efficacy and safety of different subcutaneous doses of BI 655130 in patients with moderate to severe Palmoplantar Pustulosis (PPP)	
Lay Title	A study to test how effective and safe different doses of BI 655130 are in patients with a moderate to severe form of the skin disease Palmoplantar Pustulosis	
Clinical Phase	Phase IIb	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]	
Status	Final Protocol	
Version and Date	**Version: 1.0**	**Date: 03 Apr 2019**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	03 Apr 2019
Revision date	
BI trial number	1368-0016
Title of trial	Multi-center, double-blind, randomised, placebo-controlled, phase IIb dose-finding study to evaluate efficacy and safety of different subcutaneous doses of BI 655130 in patients with moderate to severe Palmoplantar Pustulosis (PPP)
Coordinating Investigator	[redacted]
Trial site(s)	Multi-center trial
Clinical phase	IIb
Trial rationale	The trial rationale is to demonstrate proof-of-concept with respect to a non-flat dose response curve and to define a suitable dose range for BI 655130 regarding efficacy and safety for further pivotal testing in Phase III in patients with PPP.
Trial objective(s)	The primary objective is to provide dose-ranging data for 4 dose regimens of BI 655130 (with each regimen consisting of a loading and a separate maintenance subcutaneous dose) compared to placebo. The target dose(s) will be estimated from the model by incorporating information on the minimum clinically relevant effect and accounting for safety. The additional objectives are to explore long-term efficacy, safety and tolerability of multiple dose regimens of BI 655130 in patients with PPP.
Trial endpoints	The primary endpoint to assess efficacy of BI 655130 is % change in PPP ASI (Palmoplantar Pustulosis Area and Severity Index) from baseline at Week 16. Secondary endpoints: • Change from baseline in Pain Visual Analogue Scale (VAS) score at Week 4 and 16 • PPP SI change from baseline at Week 16 • PPP ASI50 at Week 16 • PPP ASI75 at Week 16 • PPP PGA clear/almost clear at Week 16 • PPP PGA pustules clear/almost clear at Week 16 • Percent change in PPP ASI from baseline at Week 52

Trial design	Placebo-controlled, double-blind, randomised, parallel-design comparison of 5 arms over 52 weeks
Total number of patients randomised	140
Number of patients on each treatment	40/20/20/20/40 per arm
Diagnosis	Palmoplantar Pustulosis defined as primary, persistent (>3months duration), sterile, macroscopically visible pustules on the palms and/or soles, without or with plaque psoriasis elsewhere on the body
Main in- and exclusion criteria	• Male or female patients, 18 to 75 years of legal age (according to local legislation) at screening • Diagnosed with Palmoplantar Pustulosis with a minimum PPP ASI score of 12 and PPP PGA of at least moderate severity (≥3), both at screening and baseline • Presence of white or yellow pustules on palms and/or soles at screening and baseline • Pustular severity score ≥2 in at least one region and ≥10 well-demarcated pustules (white or yellow pustules) across all regions at screening and baseline • Patients with a reduction in PPP ASI total score ≥ 5 from screening (Visit 1) to baseline (Visit 2) are excluded
Test product(s)	BI 655130
dose	Arm 1: [redacted] Arm 2: Arm 3: Arm 4:
mode of administration	Subcutaneous (s.c.)
Comparator product(s)	Placebo
dose	Arm 5: [redacted]
mode of administration	Subcutaneous (s.c.)

Duration of treatment	52 weeks
Statistical methods	The primary analysis consists of a combination of MCPMod-based testing (with respect to a non-flat dose response curve) and an evaluation of the dose-wise benefit at Week 16. As a basis for the MCPMod analysis a mixed effect model for repeated measurements (MMRM) is used. The MCPMod procedure allows for simultaneous evaluation of different potential dose response patterns, whilst protecting the overall probability of Type I error. The pre-specified models and their parameters used for this test are outlined in Section 7.2.2.

FLOW CHART

Trial Periods	Screen-ing[1]	Randomised Treatment Period																	Post Treatment FU	
		Loading					Maintenance													
Visit	**1**	**2[2]**	**3**	**4**	**5**	**6**	**7**	**8**	**9 PE[3]**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18 EOT[4]**	**19**	**20 EOS[4]**
Week	-4 to -2		1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52	60	68
Day	-28 to -14	1	8 ±2	15 ±2	22 ±2	29 ±2	57 ±7	85 ±7	113 ±7	141 ±7	169 ±7	197 ±7	225 ±7	253 ±7	281 ±7	309 ±7	337 ±7	365 ±7	421 ±7	477 ±7
Informed Consent	x																			
In/exclusion criteria	x	x																		
Demographics, BC /Medical History[5]	x	x																		
Physical Examination[6]	x^C	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^C	x^T	x^C
Height and weight	x																	x		
Vital Signs[7]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Smoking Status / History		x							x									x		
12-lead ECG	x	x				x			x			x			x			x		x
Pregnancy Testing[8]	x_s	x u,(s)	x u,(s)	x u,(s)	x u,(s)	x u,(s)	x u,(s)	x u,(s)	x u,(s)	x u,(s)	x u,(s)	x u,(s)	x u,(s)	x u,(s)	x u,(s)	x u,(s)	x u,(s)	x u,(s)	x u,(s)	x u,(s)
Safety Laboratory	x	x		x		x	x	x	x	x	x		x		x		x	x	x	x
Infections Testing[9]	x																	x		
[redacted]																				
ADA / Nab[11]		x		x		x	x	x	x		x		x		x		x	x	x	x
DNA banking (optional)[12]		x																		

Trial Periods	**Screen-ing[1]**	**Randomised Treatment Period**																	**Post Treatment FU**	
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[redacted]																				
PPP ASI / PPP SI[14]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PPP PGA, [redacted]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
[redacted]	x	x				x		x				x						x		
Photos of skin lesions	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pain VAS, [redacted]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
[redacted]	x	x				x			x		x							x		
[redacted]		x							x									x		
Skin biopsy (optional)[18]		x							x											
IRT call[19]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Administer study drug[20]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Local tolerability		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant therapy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study completion																				x[4]

[1] The time window for Visit 1 may be extended at the discretion of the Clinical Trial Manager (CT Manager) in conjunction with the Clinical Trial Leader (CT Leader) on a case by case basis.

[2] Day of Randomisation / Day of first administration of randomised trial medication.

[3] PE = Primary Endpoint Visit.

[4] EOT = End of Treatment; EOS = End of Study. If the patient withdraws from the trial prematurely following randomisation, instructions in Sections 3.3.4 and 6.2.3 should be followed.

[5] Demographics, BC = Baseline Conditions and Medical History. For details please see Section 6.2.1.

[6] Physical examination; C = complete; T = targeted (focus on evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities). For details please see Section 5.2.1.

[7] Vital signs will be assessed predose and at dosing visits additionally 10 mins postdose and 1 hour after the end of study drug administration. For details please see Section 5.2.2.

[8] Pregnancy testing is applicable only for women of childbearing potential (WOCBP; for the definition please refer to Section 3.3.3). S = serum pregnancy test (performed at screening). U = urine pregnancy tests will be performed at all other visits. Urine pregnancy testing should be done prior to administration of study drug. Study drug should only be administered in case of a negative test result. (S) - in case of a positive urine pregnancy test, a serum pregnancy test will be done.

[9] For details on infections testing at baseline and EOT visit (or early discontinuation visit, if applicable) please refer to Table 5.2.3: 1.

[10] Al[redacted] samples will be collected within approximately 2 hour period prior to the study drug administration. For details please see Section 5.3.

[11] ADA / Nab = Anti-Drug Antibody / Neutralizing Antibody

[12] Desoxyribo Nucleid Acid (DNA) banking sample is optional. This sampling is only possible if the patient agreed by signing a separate informed consent. For details please see Section 5.5.

[13] If not possible at Visit 2, the whole blood sampling for DNA re-sequencing may also be collected during a later visit. For details please see Section 5.4.

[14] PPP ASI = Palmoplantar Pustulosis Area and Severity Index. Additionally, Palmoplantar Pustulosis Severity Index (PPP SI) will be calculated based on PPP ASI components. For details please see Sections 5.1.1 and 5.1.10, and Appendices 10.1.1 and 10.1.10.

[redacted]

[18] Skin biopsy is an optional procedure and not a prerequisite for the participation in this trial. Skin biopsy is only allowed for patients who have consented for this procedure. For details please refer to Section 5.4.1 and the skin biopsy manual.

[19] Interactive Response Technology (IRT) call at the screening visit indicates that a patient is in screening. IRT calls at dosing visits assign medication numbers.

[20] Administration of the study drug must be performed by a healthcare professional. Drug will be administered after PPP assessments. For the sequence of procedures please see Section 6.2. For details on the 4 subcutaneous injections (prefilled syringes) per dosing visit please refer to Section 4.1.5.1.

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ABBREVIATIONS

ADA	Anti-Drug Antibody
ADCC	antibody-dependent cellular cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AS	Ankylosing Spondylitis
AST	Aspartate Aminotransferase
AUC	Area under the Curve
[redacted]	
BI	Boehringer Ingelheim
CDC	complement-dependent cytotoxicity
C_{max}	Maximum Concentration
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
[redacted]	
DMC	Data Monitoring Committee
DNA	Desoxyribo Nucleid Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
EOS	End of Study
[redacted]	
EudraCT	European Clinical Trials Database
FAS	full analysis set
FC	Flow Chart

FU	Follow-up
GCP	Good Clinical Practice
GPP	Generalized Pustular Psoriasis
HIV	human immunodeficiency virus
i.v.	intravenous
IB	Investigator's Brochure
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITE	indirect target engagement
LPLT	Last Patient Last Treatment
LOCF	Last observation carried forward
MCID	Minimal clinically important difference
MCPMod	multiple comparison procedure with modelling techniques
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	mixed effect model for repeated measurements
MRD	Multiple Rising Dose
Nab	Neutralizing Antibodies
PAO	Pustulotic arthro-osteitis
[redacted]	
PBO	Placebo
PCS	Physical Component Summary
PD	Pharmacodynamics
[redacted]	
PoC	Proof of Concept
PoCC	Proof of Clinical Concept
PPP	Palmoplantar Pustulosis
PPP ASI	Palmoplantar Pustulosis Area and Severity Index
PPP PGA	Palmoplantar Pustulosis Physician Global Assessment

PPP SI	Palmoplantar Pustulosis Severity Index
[redacted]	
PPS	per-protocol set
PRO	Patient Reported Outcome
[redacted]	
q4w	every four weeks
q8w	every eight weeks
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual Effect Period
RNA	Ribo Nucleid Acid
s.c.	subcutaneous
SAE	Serious Adverse Event
SAF	safety analysis set
[redacted]	
SOP	Standard Operating Procedure
[redacted]	
SRD	Single Rising Dose
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Events
[redacted]	
TSAP	Trial Statistical Analysis Plan
ULN	Upper Level of Normal
VAS	Visual Analogue Scale
vs	versus
WBC	white blood count
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

The target indication is Palmoplantar Pustulosis (PPP), a disease with a high unmet medical need. PPP is a chronic disease and a form of pustular psoriasis (as is Generalized Pustular Psoriasis, GPP). Recent evidence suggests that PPP and GPP are genetically distinct from chronic plaque psoriasis as the major genetic determinant PSORS1 for plaque psoriasis has not been found in PPP and GPP patients [R16-3560; R16-3546]. Gene expression [R16-3543] and human genetic [R16-3553, R15-1421, R16-0950, R16-3544] and clinical data imply that the IL36 pathway (targeted by BI 655130) drives the pustular psoriasis diseases of PPP and GPP [P19-01888, R16-0950, R16-3561, R16-3544].

PPP may be considered a rare disease. PPP is characterised by the presence of sterile pustules on palms and/or soles [R16-0927], in some cases evolve from vesicles [R19-0961]. Despite the limited area of skin involvement in PPP, the disease is very debilitating with a large impact on quality of life including ability to work. PPP symptoms include pruritus, burning sensations, and pain. In severe cases, the skin affliction makes walking or other activities of daily living challenging if not impossible. No approved treatment is available for PPP except for guselkumab in Japan, further highlighting the high need for an effective treatment option. PPP can be associated with plaque psoriasis elsewhere on the body.

Genetic human studies have established a link between IL36R signalling and PPP: The same hypomorphic missense mutation in IL36RN reported for GPP [R16-0950; R16-3561] has also been observed in PPP, albeit to a lesser extent as compared to GPP [R16-3544].

Further genetic linkage between PPP and the IL36 pathway has been recently disclosed. For example, mutations in other genes linked to the IL36 pathway such as CARD14 [R16-3544] and AP1S3 [R16-0928] have been linked to the pathogenesis of all forms of pustular psoriasis including PPP. CARD14 is specifically and predominantly expressed in keratinocytes in the skin. It acts downstream of the IL36 pathway and is a known activator of NF-kB signalling. Mutations in the coding sequence (c.11T>G and c.97C>T) in AP1S3 have been linked to the pathogenesis of all forms of pustular psoriasis including PPP. The gene encodes a subunit of the AP-1 complex. Functionally the occurrence of these rare mutations causes a destabilizing of the AP-1 complex and could be linked to impaired Toll-like receptor 3 signalling and subsequent expression of the anti-inflammatory mediator IFN-β [R16-0928].

It is planned to enroll PPP patients irrespective of their mutation status of these three genes. However the genotypes of all patients will be determined in order to investigate the influence of their genetic background on the result of BI 655130 treatment.

Currently there is no standard of care available for the treatment of PPP (i.e., no approved therapy except for guselkumab in Japan). PPP is notoriously difficult to treat. Patients usually end up being treated with the currently available systemic treatment options including retinoids, PUVA, methotrexate, ciclosporine and topical corticosteroids. Unfortunately, these options are usually not effective in reducing duration and severity of PPP.

Thus, there is high unmet medical need for PPP.

Secukinumab (anti-IL17A; EU), ANBO19 (IL36R mAb), along with BI 655130, are the only treatments currently being tested in the clinic for the PPP indication. Guselkumab has been recently approved for the treatment of PPP in Japan. No other anti-IL36R treatments are known to have been tested or are being tested in the clinic in PPP.

BI 655130 will target as a first in class compound the IL36 pathway which is genetically linked to PPP disease pathogenesis and will be investigated in the clinical program for treatment of PPP, a disease with significant unmet medical need.

1.2 DRUG PROFILE

Mode of action
BI 655130 is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL36R signalling. Binding of BI 655130 to IL36R is anticipated to prevent the subsequent activation of IL36R by cognate ligands (IL36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways with the aim to reduce epithelial cell/ fibroblast/ immune cell-mediated inflammation and interrupt the inflammatory response that drives pathogenic cytokine production in inflammatory skin diseases including generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP) and atopic dermatitis, and inflammatory bowel disease (IBD).

Key pharmacokinetic characteristics
PK analysis showed that exposure (AUC0-tz and Cmax) to BI 655130 increased with increasing dose in an approximately dose-proportional manner from 0.3 to 10 mg/kg. Overall, PK data so far suggests target-mediated drug disposition (TMDD) kinetics for BI 655130. The effective half-life of BI 655130 is approximately 4 weeks in the linear dose range in healthy volunteers and approximately 3 weeks in GPP patients. For details please see the IB.

Drug interactions
There is no information available. A drug interaction study is planned within the ulcerative colitis program.

Residual Effect Period
The Residual Effect Period (REP) of BI 655130 is 16 weeks. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present. The consideration behind the REP derivation is that the half-life of ~4 weeks for BI 655130 was observed in the healthy volunteer SRD study of 1368.1. However, in the patient trial 1368.11 where BI 655130 was tested in GPP patients, the effective half-life was 23.9 days, ie. ~3.4 weeks. Therefore 16 weeks would correspond to approximately 5 half-lives in patients, after which time most drug will have been cleared and only less than 3.125% of BI 655130 will still be available.

Data from non-clinical studies

Preclinical studies
BI 655130 binds to human IL36R with a binding avidity of less than 1 pM. BI 655130 inhibits IL36 ligand-stimulated NF-κB activation in HT29 and transformed epithelial cells and in primary human dermal fibroblasts or intestinal myofibroblasts with IC90 values in a consistent range of 0.7 to 3.7 nM. BI 655130 also inhibits IL8 release in primary human intestinal myofibroblasts and IFNγ secretion in human peripheral blood mononuclear cells (PBMCs) stimulated with IL36α, IL36β, or IL36γ combined with IL12.

Mutations of two key residues (L234 and L235) to alanine were made to BI 655130 to abrogate FcR binding activity and function. Direct assessment of the impact of the mutations in the IgG1 FcR binding sites on both antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) effector functions revealed that the mutations abrogate both ADCC and CDC effector functions and indicate that BI 655130 will be a non-depleting therapy *in vivo*.

Toxicology studies
BI 655130 does not bind to IL-36R from common toxicology species. Therefore, meaningful toxicity studies of the molecule cannot be performed in any animal species with BI 655130. However, hazard identification studies of the mode-of-action (MoA) of IL-36R inhibition were performed in mice using a mouse specific anti-IL-36R monoclonal antibody (BI 674304), which is a mouse IgG2a monoclonal antibody with rat variable regions. In a 13-week intravenous toxicity study of BI 674304 in mice, no adverse effects of IL-36R antagonism were seen at a dose (50 mg/kg, twice weekly) that was 5 fold higher than the dose that was protective in an experimental mouse colonic inflammation model. In the 26-week toxicity study, male and female mice (20-30/sex/group at 0, 10 and 50 mg/kg/day) were administered BI 674304 twice weekly for 26 weeks by intravenous injection via the caudal vein. There were no BI 674304-related changes in clinical observations, body weights, food consumption, ophthalmology, clinical pathology parameters (haematology, clinical chemistry), organ weights, macroscopic or microscopic examinations. The no-observed-adverse-effect level (NOAEL) was considered to be 50 mg/kg/day.

The *in vitro* cytokine release and tissue cross-reactivity assays demonstrate that the risk of transient cytokine release in humans is low and that, as expected, BI 655130 stains epithelium in a variety of tissues. There were no signs of local irritation after single, 1 mL injections of the subcutaneous formulation in rabbits. These preclinical toxicology data support chronic BI 655130 dosing in humans.

Data from clinical studies

Studies in Healthy Volunteers
BI 655130 or placebo (PBO) was administered to 78 healthy volunteers at single ascending i.v. doses from 0.001 mg/kg to 10 mg/kg body weight (1368.1). Safety and tolerability of all tested i.v. doses was good. There were no drug-related Serious Adverse Events (SAEs). Adverse Events (AEs) categorized as related to treatment were observed in 3/19 (15.8%) subjects in the placebo group and in 7/59 (11.9%) subjects treated with BI 655130. The most frequent treatment-emergent AEs were nasopharyngitis (BI 655130: 21%; PBO: 15%), headache (BI 655130: 9%; PBO: 15%), influenza like illness (BI 655130: 7%; PBO: 10%),

and diarrhoea (BI 655130: 3%; PBO: 10%). There were two AEs of moderate intensity (injection site haematoma, headache), all remaining AEs were of mild intensity. There was no apparent relationship between the frequency of AEs and the dose. There were no relevant changes compared to placebo for laboratory safety, including clinical chemistry, haematology, coagulation parameters, and urinalysis. No clinically relevant changes were observed in 12-lead ECGs, vital signs, and cardio-monitoring.

PK analysis showed that exposure (AUC0-tz and Cmax) to BI 655130 increased with increasing dose in an approximately dose-proportional manner from 0.3 to 10 mg/kg. The effective half-life of BI 655130 is approximately 4 weeks in the linear dose range. Overall, PK data so far suggests target-mediated drug disposition (TMDD) kinetics for BI 655130. Anti-drug antibodies (ADA) were detected in 8 patients, 3 of those had pre-existing levels. Pharmacodynamic effects in this first in human (FIH) single rising dose (SRD) trial [c03361085-07] were assessed by indirect target engagement (ITE) of IL36R by BI 655130 using an ex-vivo whole blood stimulation assay. All doses higher than 0.001 mg/kg were biologically active, corresponding to the minimum anticipated biological effect level, MABEL.

In a multiple rising dose (MRD) trial (1368.2), BI 655130 or placebo have been administered to healthy volunteers at multiple ascending i.v. doses of 3, 6, 10 and 20 mg/kg given once weekly (qw) for 4 weeks (i.e. 4 administrations) or a single dose of 20 mg/kg (8 subjects each, 3:1 on active or PBO). Overall, BI 655130 was well tolerated. There were no dose dependent AEs, AEs considered to be dose limiting and no SAEs. In all cases the AEs were of mild or moderate intensity. Furthermore, there were no clinically relevant abnormalities on treatment with BI 655130 with respect to safety laboratory, vital signs, or ECGs as assessed by a central reader. Importantly, based on the analysis of the ITE studies, more than 90% of peripheral IL36R was engaged for at least 22 weeks after the last application of four weekly doses. For further details and most recent results refer to the current Investigator`s Brochure [c03320877].

Study 1368.3 explored pharmacokinetics as well as safety and tolerability of a subcutaneous formulation of BI 655130 at two different dose strengths of 150 mg (1 mL) and 300 mg (2 mL) using an open-label, single dose, parallel group, matched pair design to determine the relative bioavailability of the 300 mg s.c. compared to one single 300 mg i.v. dose of BI 655130. In this study, 36 healthy male and female subjects have been treated with BI 655130, with 12 subjects per dose group. 35 subjects completed the study per protocol, one subject discontinued for logistical reasons (work-related issues).
Although the evaluation of the study is still ongoing, the local tolerability of the s.c. formulation can be considered as well tolerated. Following an s.c. injection of 150 mg of BI 655130, there were two cases of redness and one case of swelling at the injection site in 12 subjects dosed. For the 300 mg s.c. dose there was one further report of redness in 12 subjects dosed. All local events were of mild intensity, occurred within 30 minutes after injection and completely resolved within 4 hours. There were no reports of injection site pain.
The type, intensity and duration of systemic adverse events were similar to what has been observed in the preceding SRD/MRD studies 1368.1 and 1368.2. Most of the AEs were of mild intensity, there were no AEs considered to be dose limiting, and no SAEs. One subject in the 300 mg i.v. group discontinued during the infusion due to a panic attack, another one in

the 300 mg i.v. group discontinued his participation two months after dosing for personal reasons.

In 1368.9 trial, 32 healthy Japanese male subjects were enrolled in 4 dose groups comprising 8 subjects per group. The study consisted of three dose groups receiving single rising intravenous doses of BI 655130 (300 mg, 600 mg, and 1200 mg) and one dose group receiving single subcutaneous doses of BI 655130 (300 mg). In each dose group, 6 subjects received BI 655130 and 2 subjects placebo.
Treatments were administered in a double-blind fashion within dose groups. In total, 24 subjects received BI 655130 and 8 subjects placebo. Three subjects in the 600 mg i.v. group (1 of them allocate to placebo) and 1 subject in the 1200 mg i.v. group discontinued the trial prematurely due to personal reasons.
A total of 3 out of 18 subjects (16.7%) on intravenous doses of BI 655130 (1 subject per i.v. dose level) were reported with an AE compared with 2 out of 8 subjects (25%) on placebo. No subject was reported with an AE following subcutaneous administration of BI 655130. Adverse events by preferred term reported on placebo were vomiting, chest comfort, and allergic rhinitis, while AEs reported on BI 655130 were upper respiratory infection (300 mg i.v.), contusion (600 mg i.v.), gastroenteritis (1200 mg i.v.), and temporomandibular joint syndrome (1200 mg i.v.). None of the observed AEs were judged by the investigator as related to the trial medication.

Studies in Patients
In a multi-center, open-label single arm phase I study (1368.11) to investigate safety, tolerability, pharmacokinetics, pharmacogenomics, and efficacy of a single intravenous dose of BI 655130 (10 mg/kg) in patients with an acute flare of Generalized Pustular Psoriasis (GPP), 7 patients were treated. This trial could demonstrate that BI 655130 treatment rapidly stops the flare and clears pustules, the primary lesions in GPP, a disease closely linked to loss-of-function mutations in the natural IL36R antagonist.
In a multi-center, double-blind, randomised, placebo-controlled, phase IIa study (1368.15) to investigate efficacy, safety, tolerability, pharmacokinetics and pharmacogenomics of multiple intravenous doses of BI 655130 in patients with Palmoplantar Pustulosis (PPP), 59 patients were randomised and treated with BI 655130 for 12 weeks. This trial showed a good safety and tolerability profile (see IB for details).

1368.15 was a double-blind, randomised and placebo-controlled trial with 59 patients that was intended to explore safety, tolerance, PK and efficacy in PPP patients. Patients were enrolled in Europe and Canada and randomised in a 1:1:1 allocation ratio and received either 900 mg BI 655130, 300 mg BI 655130 or placebo intravenously every 4 weeks over a period of 12 weeks and were monitored for up to 32 weeks.
As there are currently no established nor validated endpoints available to specifically assess clinician- or patient reported outcomes in PPP, several endpoints were explored in this proof of concept trial. The endpoints included a PPP-specific PASI (ppPASI = PPP ASI in the nomenclature of trial 1368-0016) where induration was replaced with pustulation, as the sterile pustule is the primary component of PPP (as it is in GPP), while the scaling and erythema components remained unchanged. The primary efficacy endpoint was PPP ASI50 at Week 16.

As PPP is a neutrophilic dermatosis characterised by sterile pustules on palms and soles and in light of the rapid response observed on pustule clearance in trial 1368.11 (GPP), change from baseline in pustule severity was also included in the efficacy assessment. The focus on pustules allows to specifically address the impact and benefit of BI 655130 treatment on PPP disease.
Overall, the baseline disease severity within the trial population was lower than expected because few patients with severe disease were enrolled in the trial. More specifically, half of the patients had a PPP ASI total score at baseline ≤16.70, which was close to the minimum required PPP ASI score of 12 for inclusion. The proportion of patients who achieved PPP ASI50 at Week 16 in the total population was similar in all treatment groups (6 of 19 in 900 mg BI 655130 arm, 6 of 19 in 300 mg BI 655130 arm, and 5 of 21 in placebo arm). However, post-hoc subgroup analyses indicated efficacy of both doses of BI 655130 in patients with more severe PPP disease at baseline (above the median PPP ASI value of 16.7). In particular, the results on pustule severity were pronounced with a rapid reduction in pustule severity with evidence of a dose response relationship (Figure 1.2: 1). In the same subgroup, a mean percent reduction from baseline in PPP ASI has been observed. For details please see the current Investigator´s Brochure, c03320877.

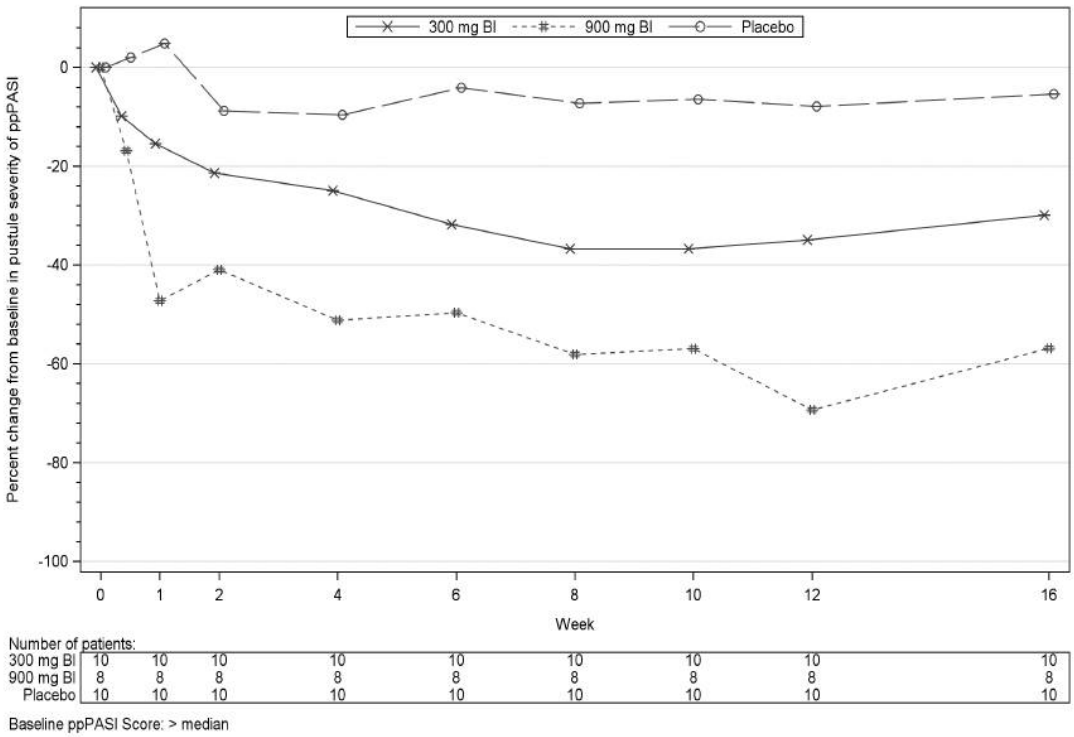


Figure 1.2: 1: Mean of change from baseline (%) in pustule severity of PPP ASI (average across regions) by baseline PPP ASI score (> median of 16.7) over time – FAS (LOCF)

Summary
BI 655130 is an anti IL36R antibody with a high clinical activity to block IL36R signalling, as demonstrated in patients with GPP and PPP. IL36R inhibition shows a favorable nonclinical safety profile in healthy volunteers and in patients tested. BI 655130 has been

tested in healthy volunteers with single or multiple dosing up to 4 weeks of 20 mg/kg i.v. qw, in GPP patients (1368.11 trial, N=7 in a single i.v. dose of 10 mg/kg) and in PPP patients (1368.15 trial, N=59, i.v. doses 300 mg and 900 mg every 4 weeks) which were all safe and well tolerated.

For a more detailed description of the BI 655130 profile, please refer to the current Investigator's Brochure (IB) [c03320877].

1.3 RATIONALE FOR PERFORMING THE TRIAL

BI 655130 is in development for the treatment of Palmoplantar Pustulosis. The rationale of this trial is to demonstrate proof of concept with respect to a non-flat dose response curve and to define a suitable dose range for BI 655130 regarding efficacy and safety for further pivotal testing in phase III in patients with PPP. For this purpose, a multiple comparison procedure with modelling techniques (MCPMod) approach is considered.

The rationale to perform this trial is based on the proof-of-concept, phase IIa trial 1368.15. In this trial, the intravenous regimens proved activity. More pronounced clinical effects were seen in patients with higher disease activity (as shown in Fig 1.2: 1). By optimised inclusion criteria, it is intended to recruit in this trial patients with a higher disease intensity with a focus on fresh pustulation and the requirement to have a certain threshold of fresh pustulation (see Inclusion criteria).

As there is high prevalence of PPP in Japan, evidence for phenotypic differences (clear pustular phenotype with no association with plaque psoriasis, focal infection as a trigger, and association with pustulotic arthro-osteitis, PAO) and treatment efficacy observed with guselkumab in Japan [R19-0861], a proof-of-concept is planned to be evaluated in Japan in this trial and therefore the trial will be stratified (Japan vs non-Japan).
Of note, the studies so far have a deficiency in being either exclusively Japan (guselkumab) or exclusively non-Japan (secukinumab) [R19-0676, R19-0677, and R19-0678].

We restrict further exploration of BI 655130 in this indication to a subcutaneous formulation to better meet the needs of patients and a good alignment with the primary dermatology care treatment procedures. The pharmacokinetics and pharmacodynamics of different subcutaneous loading and maintenance dose regimens of BI 655130 in patients with PPP will be investigated.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see Section 5.4). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Preclinical profiles of BI 655130 and clinical data from healthy volunteer and patient trials suggest that BI 655130 is safe, tolerable and may address an unmet medical need in PPP patients by an anti-inflammatory mechanism of action, cf. Section 1.2 and the IB [c03320877]. The data from the completed PoC trial 1368.11, in patients with an acute flare of generalized pustular psoriasis (GPP), demonstrate that BI 655130 treatment rapidly stops the flare and clears pustules, the primary lesions in GPP, a disease closely linked to loss-of-function mutations in the natural IL36R antagonist. This and the data from 1368.15 indicates that BI 655130 inhibits IL36R signalling also in human disease and thus has the potential to be further investigated also in PPP patients (see Section 1.2 and IB).

No relevant animal species is available for toxicology testing of the highly human specific antibody BI 655130. However, preclinical toxicology studies with a mouse surrogate antibody have demonstrated the safety of IL-36R inhibition in mice, please refer to the IB Section 5.1.2 [c03320877].

A total of more than 212 subjects have been exposed to single or multiple i.v. doses of BI 655130 as of September 2018 (see IB). BI 655130 was safe and well tolerated in four healthy volunteers trials evaluating the i.v. and s.c. formulation.
In trial 1368.15 there were no clinically relevant abnormalities on treatment with BI 655130 with respect to safety laboratory and vital signs. BI 655130 was well tolerated and no safety signal was identified. For details refer to IB [c03320877].

1.4.2 Risks

There are no identified or potential risks for BI 655130, based on the toxicology program or any clinical trials conducted for this product to date (see also Section 1.2). No other IL-36 receptor antagonist is currently approved, providing information on identified risks in molecules of this class.

The risks shown in the table below are hypothetical in nature; these are derived from general safety considerations of immunomodulatory drugs.

In order to protect the patient's safety during conduct of this trial, an independent Data Monitoring Committee has been established for the periodic review of clinical trial safety data.

Hypothetical risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product		
Drug-induced liver	Rare but severe event, thus	Timely detection, evaluation, and

injury (DILI)	under constant surveillance by sponsors and regulators.	follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety. See also Section 5.2.6, adverse events of special interest
Systemic hypersensitivity reaction	After administration of any biologic agent or protein, there is a possibility of occurrence of adverse immune reactions which can be local (e.g. redness, pruritus, and or swelling at the injection site) or systemic (e.g. anaphylactic reactions).	Patients with a history of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients are excluded from the trial. In case of systemic hypersensitivity reactions including anaphylactic reaction emerging during or after administration of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care to interrupt and treat the condition. Systemic hypersensitivity reaction is defined as AESI. It is subject to close monitoring and investigators are requested to assess these conditions using the criteria discussed in the statement paper from Sampson HA [R11-4890].
Infections	Inhibition of the immune response with an immune-modulating biologic may increase the risk of infections. A recent characterisation of individuals with homozygous IL36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL36 signallingpathway inhibition does not compromise host defences [R17-3632].	Screening procedures for infections will be established for this trial. Patients with any relevant chronic or acute infections including human immunodeficiency virus (HIV), viral hepatitis or tuberculosis (including a positive Quantiferon test in early trials) are excluded from the trial. Treatment of infections should be initiated promptly according to standards of care. Severe infections and opportunistic infections are considered AESI for this trial. These conditions and serious

		infections are subject to close monitoring. An independent data monitoring committee (DMC) is in place to periodically evaluate clinical trial safety data.
Malignancies	Inhibition of the immune response with an immune-modulating biologic may increase the risk of a decreased immune defense against malignancies. A recent characterisation of individuals with homozygous IL36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL36 signalling pathway inhibition does not compromise host defences [R17-3632].	Patients with a recent history of malignancy will be excluded from participation in this trial. In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue treatment with BI 655130. Diagnostics and treatment have to be initiated according to local standard of care. Malignancies represent always serious adverse events and are subject to close monitoring
Trial procedures		
Blood Sampling	As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain.	These risks will be addressed by careful safety monitoring and risk mitigation measures such as (a) close clinical monitoring for AEs; (b) selection of experienced sites and site staff; (c) training.
Skin Biopsy	Can cause local bruising, imflammation, nerve damage and pain.	These risks will be addressed by careful monitoring and risk mitigation measures such as (a) close clinical monitoring for AEs;

		(b) selection of sites with experienced site staff; (c) training.
Other risks		
Administration of Placebo	If the patient is randomised to receive a placebo, the patient´s condition could get worse during the course of the trial.	[redacted] Please refer to Section 3.1.

Based on the findings in the nonclinical studies conducted to date and in accordance with international regulatory guidelines, the inclusion of Women of Child Bearing Potential (WOCBP) in this study is justified. To minimize the risk of unintentional exposure of an embryo or fetus to the investigational drug, WOCBP must agree to the requirements for the pregnancy testing and contraceptive methods described in Section 4.2.2.3.

1.4.3 Discussion

Due to the lack of mechanism- or compound-related safety signals and the antagonistic mode of action of BI 655130 it is considered likely that PPP patients will not be exposed to undue risks and adverse events in relation to the information that is expected to be gained from this trial. Considering the medical need of the development of an effective and well tolerated drug specifically and directly treating PPP, the benefit of this trial is considered to outweigh the potential risks for individual PPP patients participating in this trial. The benefit-risk profile is thus considered appropriate for an experimental therapy at this stage of clinical development.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The present trial will be performed to demonstrate proof of concept with respect to a non-flat dose response curve, and to define a suitable dose range for BI 655130 regarding efficacy and safety for further pivotal testing in Phase III in patients with PPP. For this purpose, a multiple comparison procedure with modelling techniques (MCPMod) approach is considered.

The primary objective is to provide dose-ranging data for 4 dose regimens of BI 655130 (with each regimen consisting of a loading and a separate maintenance subcutaneous dose) compared to placebo on the primary endpoint of percentage change from baseline in PPP ASI at Week 16. The target dose(s) will be estimated from the model by incorporating information on the minimum clinically relevant effect and accounting for safety. Supportive dose-ranging assessments will also be done on pre-specified secondary endpoints.

The primary endpoint comparison will be performed for all randomised and treated patients who have a baseline value for the primary endpoint. The primary treatment comparison will be performed as if all patients took randomised treatment for the duration of the trial that is excluding the effects of either treatment discontinuation or use of rescue therapy.

The additional objectives are to explore long-term efficacy, safety and tolerability of multiple dose regimens of BI 655130 in patients with PPP.

2.1.2 Primary endpoint(s)

The primary endpoint to assess efficacy of BI 655130 is % change in PPP ASI from baseline at Week 16. Any data collected after use of any rescue therapy or after 6 weeks following discontinuation of treatment (to allow for incorporation of the continuing maximum treatment effect period) are censored for the purpose of the primary estimand.

2.1.3 Secondary endpoint(s)

Secondary endpoints are defined as described below. Note that for the secondary endpoints, any data collected after use of any rescue therapy or after 6 weeks following discontinuation of treatment (to allow for incorporation of the continuing maximum treatment effect period) are censored for the purpose of the primary estimand.

- Change from baseline in PPP Pain Visual Analog Scale (VAS) score at Week 4 and 16
- PPP SI change from baseline at Week 16
- PPP ASI50 at Week 16
- PPP ASI75 at Week 16
- PPP PGA clear/almost clear at Week 16
- PPP PGA pustules clear/almost clear at Week 16
- Percent change in PPP ASI from baseline at Week 52

[redacted]

- The occurrence of Treatment Emergent Adverse Events (TEAEs)

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a randomised, double-blind, placebo-controlled, parallel-design dose-finding trial comprising of 4 active doses compared to placebo. Active treatment arms consist of active loading dose and active maintenance treatment. Two different loading doses and two different maintenance treatment doses are to be tested up to Week 16 (to give four different BI 655130 dose regimens). From Week 16 onwards, three different maintenance treatment doses are to be tested. The trial design is illustrated in Figure 3.1: 1.

Approximately 140 eligible patients with Palmoplantar Pustulosis will be randomised in a 2:1:1:1:2 ratio to one of the 5 following treatment arms:

Arm 1: BI 655130 [redacted] (N=40)

Arm 2: BI 655130 [redacted] (N=20)

Arm 3: BI 655130 [redacted] (N=20)

Arm 4: BI 655130 [redacted] (N=20)

Arm 5: Placebo [redacted] (N=40)

The randomisation will be stratified for Japan versus non-Japan and will be done to assure that sufficient patients per treatment arm are recruited specifically within each region (Japan vs non-Japan). Screening of patients into any single region (Japan or non-Japan) will be closed in order to ensure that not more than 91 patients are randomised into that region. The rationale is to allow for a thorough assessment in the Japanese population and to assess whether there is a difference in treatment effect between Japanese vs non-Japanese patients (which is hypothesized based on clinical trials in Japan which tend to show larger treatment effects in PPP patients than have been observed in European clinical trials). This stratum will be included into the analyses of the primary endpoint.

[redacted] This is required to keep the blinding. Please refer to Sections 4.1.1 and 4.1.5.1 for details.
An overview of all relevant trial activities is provided in the Flow Chart. For visit schedules and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

The patients are followed-up until Week 68 which is 16 weeks after the last dose of the study drug at week 52 (Residual Effect Period of 16 weeks).

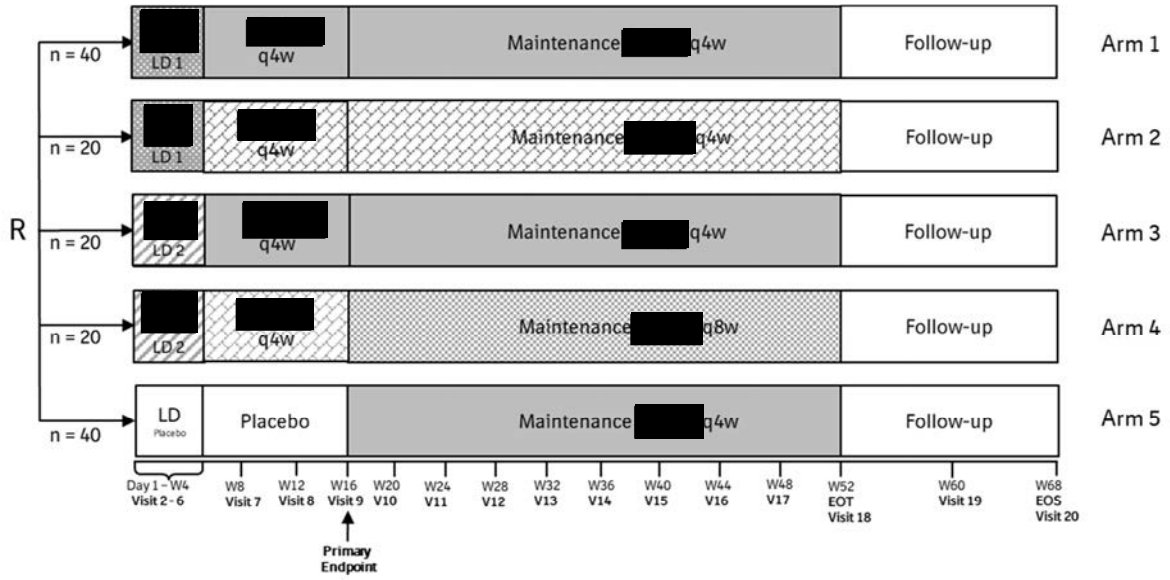


Figure 3.1: 1 Trial design

[redacted]

An independent Data Monitoring Committee will evaluate safety and efficacy data on a continuous basis. For details please refer to Section 8.7.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

The selection of PPP patients is based on the high unmet medical need in these patients.The trial design has been chosen to aid in selecting the appropriate dose regimens for a subsequent Phase III trial in PPP. The doses to be studied in this trial are expected to generate sufficient information to allow the selection of a reasonable number of doses/dose regimens for the phase III trial. The loading dose is selected to maximize the treatment response, the duration of response, and to bring the effect earlier to steady state.

A MCPMod approach will be employed in a parallel group, double-blind, placebo controlled trial to select one or two doses for subsequent confirmation of the efficacy and safety of BI 655130 in Palmoplantar Pustulosis. As only limited treatment options are available for PPP patients in a global trial setting, the placebo control group in 1368-0016 is required to compare both the efficacy and safety of BI 655130 in this population.

The treatment duration of 52 weeks with BI 655130 (with primary endpoint at Week 16) was selected with the aim to maximize treatment efficacy (continued or improved efficacy after the primary endpoint) with this new mode of action and to explore the long-term efficacy and safety.

3.3 SELECTION OF TRIAL POPULATION

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients across the regions has been screened. Screening of patients into any single region (Japan or non-Japan) will be closed in order to ensure that not more than 91 patients are randomised into that region. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.

If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

3.3.1 Main diagnosis for trial entry

The trial will be performed in adult patients diagnosed with Palmoplantar Pustulosis defined as presence of primary, persistent (>3 months duration), sterile, macroscopically visible pustules on the palms and/or soles, without or with plaque psoriasis elsewhere on the body.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. 18 to 75 years of legal age (according to local legislation) at screening.
2. Diagnosis of Palmoplantar Pustulosis defined as presence of primary, persistent (>3 months duration), sterile, macroscopically visible pustules on the palms and/or soles, without or with plaque psoriasis elsewhere on the body.
3. Presence of white or yellow pustules on palms and/or soles at screening and baseline.
4. Pustular severity score ≥2 in at least one region and ≥10 well-demarcated pustules (white or yellow pustules) across all regions at screening and baseline.
5. PPP PGA of at least moderate severity (≥3) at screening and baseline.
6. A minimum PPP ASI score of 12 at screening and baseline.
7. Male or female patients. Women of childbearing potential (WOCBP)[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.

failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information and in Section 4.2.2.3.

8. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.

3.3.3 Exclusion criteria

1. Reduction in PPP ASI total score ≥ 5 from screening visit (Visit 1) to baseline (randomisation visit, Visit 2).
2. Patients with plaque psoriasis with worsening of plaque psoriasis within the last 3 months prior to screening.
3. Skin conditions that affect ability to score area and severity of PPP components (such as dyshidrotic eczema, calluses, tinea, xerotic scaling on heels, or maceration of interdigital areas).
4. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
5. Severe, progressive, or uncontrolled condition such as renal, hepatic, haematological, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease, or signs and symptoms thereof.
6. Presence or known history of anti-TNF-induced PPP-like disease.
7. Patient with a transplanted organ (with exception of a corneal transplant >12 weeks prior to screening) or who have ever received stem cell therapy (e.g., Prochymal).
8. Known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
9. 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, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
10. Use of any restricted medication as specified in Table 4.2.2.1: 1 or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator.
11. Plans for administration of live vaccines during the study period or within 6 weeks prior to randomisation.
12. History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients.
13. Active systemic infections during the last 2 weeks (exception: common cold) prior to randomisation, as assessed by the investigator.
14. Chronic or relevant acute infections including human immunodeficiency virus (HIV), viral hepatitis and (or) active or latent tuberculosis (TB):
    QuantiFERON® TB test will be performed at screening. If the result is positive, the patient may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. Active TB patients must be excluded. If presence of latent tuberculosis is established, then treatment should have been initiated and maintained according to local country guidelines.

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

15. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomisation or planned within 52 weeks after randomisation (e.g. hip replacement, aneurysm removal, stomach ligation), as assessed by the investigator.
16. Patient has received surgical treatment of focal infection (e.g. tonsillectomy or dental therapy) within 6 months of randomisation.
17. Total white blood count (WBC) <3,000/µL, or platelets <100,000/µL or neutrophils <1,500/µL, or hemoglobin <8.5 g/dL at screening.
18. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2x the upper limit of normal, or total bilirubin >1.5x the upper limit of normal (patients with Gilbert's syndrome are not excluded) at screening.
19. Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational treatment(s).
20. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes the patient an unreliable trial participant or unlikely to complete the trial Section 4.2.2.1.
21. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled.
22. Previous randomisation in this trial.

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.
Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect important trial data.
Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.
The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see Sections 5.2.6.2.1 and 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:
- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take rescue therapy, see Section 4.2.2.1.
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy).

Even if the trial treatment is discontinued, the patient remains in the trial and, given his/her agreement, ideally should follow the visits and procedures outlined in the Flow Chart, including the EOT and EOS visits.

If the patient is not willing to follow the whole visit schedule, at least the EOT should be conducted either immediately or as soon as possible followed by the EOS visit 16 weeks after the EOT visit.

The trial treatment discontinuation criteria apply from Week 24 onwards and require assessment and confirmation at 2 consecutive visits (discontinuation itself will apply at the second visit in the sequence)

- No reduction in pustulation severity compared to baseline

AND

- No reduction in PPP ASI of ≥ 5 points compared to baseline

A patient who meets the trial treatment discontinuation criteria may be discontinued from the trial treatment and administered rescue therapy as judged by the investigator.
The earliest trial treatment discontinuation timepoint according to this rule is at Week 28.

For individual stopping rules related to specific adverse events, please see Section 4.2.1 (Other treatments and emergency procedures).

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.
If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.
4. Termination of the development of the compound in this indication.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product has been manufactured by BI Pharma GmbH & Co. KG, Biberach, Germany. The BI 655130 molecule is an anti-human IL-36 receptor monocloncal antibody heterodimer with a molecular weight of approximately 146 kDa.

4.1.1 Identity of the Investigational Medicinal Products

The investigational product (test product and matching placebo) is provided in prefilled syringes of 1 mL volume.

Table 4.1.1: 1 Test product **BI 655130**

Substance:	BI 655130
Pharmaceutical formulation:	Solution for injection
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Anti-human IL-36 Receptor mAb
Molecular weight:	146 kDa
Unit strength:	BI 655130 [redacted]
Posology:	[redacted]
Mode of administration:	Subcutaneous injections

Table 4.1.1: 2 Test product **Placebo to BI 655130**

Substance:	Placebo to BI 655130
Pharmaceutical formulation:	Solution for injection
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Not applicable
Molecular weight:	Not applicable
Unit strength:	Not applicable
Posology:	[redacted]
Method and route of administration:	Subcutaneous injections

4.1.2 Selection of doses in the trial and dose modifications

The aim of the trial 1368-0016 is to select dose regimens for a confirmatory phase III trial using a MCPMod based dose finding approach.

The BI 655130 subcutaneous dose regimens in 1368-0016 are selected to represent one subcutaneous dose in the range of the optimal i.v. dose identified in PoCC trial 1368.15, two

lower effective doses (different loading and different maintenance doses) and one dose with suboptimal efficacy for the Week 16 primary analysis. Additionally, the loading dose is selected to maximize the treatment response, the duration of response, and to bring the effect earlier to steady state.

Exposure response modelling was conducted on data from 1368.15 to support dose regimen selection in 1368-0016. Specifically, a graphical analysis of the average pustule severity (subcomponent of PPP ASI) suggested an increasing dose-exposure-response relationship in a severe subgroup of PPP patients in 1368.15 (presenting with a baseline PPP ASI > 16.7). A longitudinal PK/PD model linking plasma concentration to pustule severity was developed in this subgroup to describe the observed dose-exposure-response relationship and to predict the response to various subcutaneous dosing regimens.

The highest dose regimen [redacted] chosen because it is the highest dose and frequency that can be conveniently administered subcutaneously without imposing undue burden on PPP patients. This regimen with a loading dose allows to maximize the dose, exposure and pustule severity response that can be obtained following extravascular administration of BI 655130. A loading dose may also allow for an earlier onset of response while also theoretically reducing the high inflammatory burden associated in patients with PPP.

The second dosing regimen [redacted] was chosen because a high loading dose along with a more convenient, lower maintenance subcutaneous regimen should also be therapeutic, and with an effect which is similar to that of the highest dose regimen over 16 weeks.

The third dosing regimen [redacted] was chosen because a lower loading dose alongside the highest proposed maintenance dose, as well as being therapeutic, should have an effect over 16 weeks which is similar to but less than the effects of the two selected highest dosing regimens.

The lowest dose selected [redacted] is considered to be a clinically subtherapeutic dose but is still expected to provide some relief in terms of reducing the average severity of pustules. For endpoints other than pustule severity (such as PPP ASI or pain VAS), this dose may not provide significant clinical benefit based on data from 1368.15.

A longitudinal PK/PD model was also developed to describe the % change in PPP ASI at Week 16 (primary endpoint of this trial). Although the pustule severity model is used as the primary model for dose selection, the PPP ASI model supplemented the selection of the 4 dosing regimens for 1368-0016. The predicted % change in PPP ASI at Week 16 is expected to show more separation between the 4 dose groups identified, albeit with lower overall drug effects compared to the pustule severity subcomponent.

The pharmacokinetic profiles for the regimens selected are also expected to have a wide exposure range over the span of the trial duration. It is expected with the proposed 4 doses that the PK and PD data obtained over the entire 52 weeks duration may provide a robust characterisation of the exposure-response relationship.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria, each eligible patient will be randomised to blinded treatment arms according to a randomisation plan in a 2:1:1:1:2 ratio at Visit 2 via Interactive Response Technology (IRT). This randomisation will be stratified according to region (i.e. Japan vs non-Japan).

Note that the medication number is different from the patient number (the latter is generated during screening via the IRT system). Each syringe will have an individual medication number for dispensation.

4.1.4 Drug assignment and administration of doses for each patient

Study drugs will be administered subcutaneously. Injections will be given in a double blind fashion.

At randomisation as well as at subsequent medication dispensation visits, IRT will assign medication numbers. Site personnel will enter the medication numbers in the eCRF.

BI 655130 will be administered as a subcutaneous injection by the investigator or authorized study personnel. The date and time of the administration will be recorded in the eCRF. Details are described in the drug administration manual located in ISF.

The injection sites should avoid sites of psoriasis involvement as well as sites where the skin is tender, bruised, erythematous, or indurated, and should be alternated to other areas for subsequent doses.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients and investigators involved in the trial conduct will remain blinded with regard to the randomised treatment assignments until after database lock for the final trial analysis.

To maintain the treatment blind during the trial, all patients will receive 4 injections at all dosing visits in the every 4 weeks schedule, as indicated in the Flow Chart. [redacted]

The primary analysis of the trial will be performed once all randomised patients have completed through 16 weeks of trial treatment. At this time, a database lock for the primary analysis will be done and treatment will be unblinded. In order to confirm the integrity of the treatment blind while the trial continues through to completion, a logistics plan will be developed to describe the mechanisms that are to be put in place to assure that the patients and investigators remain blinded to both individual patient data, as well to the primary analysis results. The blind status of trial and project team members at this time will also be clarified. The logistics plan will be finalized prior to the treatment unblind for the primary analysis.

The access to the randomisation code will be kept restricted until its release at the time of the final trial analysis once all patients have completed the trial.

[redacted]

A fully independent DMC will perform an un-blinded safety and efficacy assessment at specified intervals in order to ensure that patients are protected from potential harm, please refer to Section 8.7 for further details.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance (PV) group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives for processing in the PV database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.
For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the Clinical Trial Manager (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator (if applicable),
- Availability of FDA Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics.
The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor <and/or> appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Systemic hypersensitivity including anaphylactic reaction
In case of systemic hypersensitivity including anaphylactic reaction emerging during or after injection(s) of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care to

- Stop further injection(s)

- Treat with systemic anti-histamines, i.v. steroids, and in case of a severe allergic reaction (e.g., anaphylactic reaction) epinephrine

Also draw a plasma sample for IgE and ADA as detailed in the laboratory manual (ISF) and consider the evaluation of histamine, serum tryptase, and complement components.

In case of systemic hypersensitivity, based on patient's clinical course and medical judgment, injections may be cautiously re-initiated or continued in case of mild or moderate systemic hypersensitivity (according to RCTC grading, provided in the ISF).
In case of anaphylactic reaction based on the criteria discussed in the statement paper from Sampson HA (Appendix 10.2, R11-4890) suspected to be caused by the trial medication, the investigator should discontinue treatment with study drug.
When a non-acute hypersensitivity reaction related to immune complexes (i.e., serum sickness) is suspected, please draw a sample for the laboratory assessment for circulating immune complexes.

Severe infections (according to RCTC grading in Appendix 10.3), serious infections, opportunistic or mycobacterium tuberculosis infection
Treatment of the infection should be initiated promptly according to local standard of care. No further trial medication should be administered until the active infection has resolved. Treatment with study drug may be restarted when the patient has recovered according to investigator's assessment.

Malignancies
In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue treatment with study drug. Diagnostics and treatment have to be initiated according to local standard of care.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

This section provides information on restrictions regarding concomitant treatment before randomisation and during the trial (after randomisation), including a definition on rescue therapy for the treatment of worsening of PPP.

Restrictions regarding concomitant treatment before randomisation

The medications (or classes of medications) listed in Table 4.2.2.1: 1 must not be taken for the time periods as specified for washout.

Table 4.2.2.1: 1 Restricted Medications before randomisation

Medication or class of medications	**Restriction duration**
IL36R inhibitors other than the study drug	not allowed

Table 4.2.2.1: 1 (cont.) Restricted Medications before randomisation

Medication or class of medications	**Restriction duration**
Biologic treatment, e.g. Secukinumab (Cosentyx®), ustekinumab (Stelara®), guselkumab (Tremfya®), ixekizumab, tildrakizumab, brodalumab Adalimumab, infliximab Natalizumab or agents that deplete B or T cells (e.g. rituximab, alemtuzumab or visilizumab)	12 weeks or 5 half-lives, whichever is greater, prior to randomisation
Investigational products for psoriasis	12 weeks or 5 half-lives, whichever is greater, prior to randomisation
Etanercept Live virus vaccinations[3]	6 weeks prior to randomisation
Other systemic immunomodulating treatments (e.g. corticosteroids[1], methotrexate, fumaric acid esters, acitretin, ciclosporin, apremilast) Any investigational device or product (excludes psoriasis products)	4 weeks prior to randomisation
Phototherapy (e.g., UVA, UVB), topical treatment for psoriasis or any other skin condition affecting palms/soles (e.g. corticosteroids[2], vitamin D analogues, salicylic acid, tar, anthralin)	14 days prior to randomisation
Anakinra	7 days prior to randomisation

[1] There is no restriction on corticosteroids with only a topical effect (e.g. inhaled corticosteroids to treat asthma or corticosteroids drops administered in the eye or ear).

[2] Exception: topical steroids for use on the face, axilla, and/or genitalia with a restriction of use within 24 hours prior to trial visit in which PPP ASI is assessed.

[3] Live virus vaccination should be restricted until the end of the trial.

In the event a patient with prior use of biologic treatment, systemic steroids or immunomodulating treatments is enrolled, past medical records are required to document when these treatments were stopped. All concomitant or rescue therapies will be recorded (including time of intake and dose on study days) on the appropriate pages of the CRF.

Restrictions regarding concomitant treatment during the trial

Topical treatment

Topical treatment for PPP is not allowed throughout the study. Topical treatment for other conditions is not restricted, however, the patient should avoid applying it with bare hands (e.g. use gloves) when the topical treatment is applied on affected body areas.

Topical corticosteroids
Topical corticosteroids for the treatment of PPP are not allowed during the trial unless they are needed as rescue therapy. Topical corticosteroids for body area other than palms and soles are allowed. The dose and mode of administration should be kept unchanged, if possible. The patient should avoid applying it with bare hands (e.g. use gloves).

Systemic immunomodulating treatments
Systemic corticosteroids and other immunomodulating agents (such as methotrexate, fumaric acid acitretin, ciclosporin, apremilast) for the treatment of PPP are not allowed unless they are needed as rescue therapy.

Biologic treatment
Biologic treatment is not allowed throughout the study, unless it is needed as rescue therapy.

Non-steroidal anti-inflammatory drugs (NSAIDs)
The use of NSAIDs is allowed, however it is recommended that a stable dose is maintained and the drug is not changed throughout the study up to at least the primary endpoint at Week 16.

Rescue therapy for the treatment of worsening of PPP

Rescue therapy is defined as both the use of medication such as topical corticosteroids or other topical treatment applied on the palms and/or soles, systemic immunomodulating treatments or biologics and therapy such as tonsillectomy, for the treatment of worsening of PPP.
The use of the rescue therapy leads to the discontinuation of the trial treatment, but the patient should remain in the trial observation.

4.2.2.2 Restrictions on diet and life style

No specific restrictions on diet or life style of the patients are required.
Emollients will be provided by the sponsor for the patient´s use during the trial. However, emollients must not be used on all visit days prior to the PPP assessments. Further details will be provided in ISF

4.2.2.3 Contraception requirements

Women of childbearing potential (for the definition of WOCBP, please refer to Section 3.3.3) 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 during the trial, and for a period of at least 16 weeks after the last study drug administration. A double barrier method of contraception is not required. A list of contraception methods meeting these criteria is also provided in the patient information.

Female Patients:
Acceptable methods of birth control for this trial are:

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable)
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised sexual partner with documented absence of sperm

Or

Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.

Male Patients:
Contraception of male trial participants and female partners of male trial participants are not required.

4.3 TREATMENT COMPLIANCE

Treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the Clinical Research Associate (CRA) authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of actual injections} \times 100}{\text{Number of per protocol planned injections}}$$

The measured plasma concentrations will provide additional information about compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Palmoplantar Pustulosis Area and Severity Index (PPP ASI)

The Palmoplantar Pustulosis Area and Severity Index (PPP ASI) is an investigator assessment of the extent and severity of pustular and plaque lesions on the palms and soles presenting in PPP patients. The adaptation from [redacted] an established measure of severity and area of psoriatic lesions in patients with psoriasis, by Bhushan et.al [R16-5334] will be used in this trial.
This tool provides a numeric scoring for patients overall PPP disease state, ranging from 0 to 72. It is a linear combination of the percent of surface area of skin that is affected on the palms and soles of the body and the severity of erythema, pustules, and scaling (desquamation).
The PPP ASI will be measured at the timepoints noted in the Flow Chart. The PPP ASI is provided in Appendix 10.1.1.

5.1.2 Palmoplantar Pustulosis Physician Global Assessment (PPP PGA)

The Palmoplantar Pustulosis Physician Global Assessment (PPP PGA) relies on clinical assessment of the patient's skin presentation on the palms and soles. The investigator scores the individual components (erythema, pustules and scaling/crusting) from 0 to 4 as clear, almost clear, mild, moderate or severe.
PPP PGA is using severity scores for erythema, pustules, and scaling. The PPP PGA will be analyzed as PPP PGA total score including erythema, pustules and scaling, and as PPP PGA pustules score for pustules only. Further details and practical guidance will be available in the ISF.

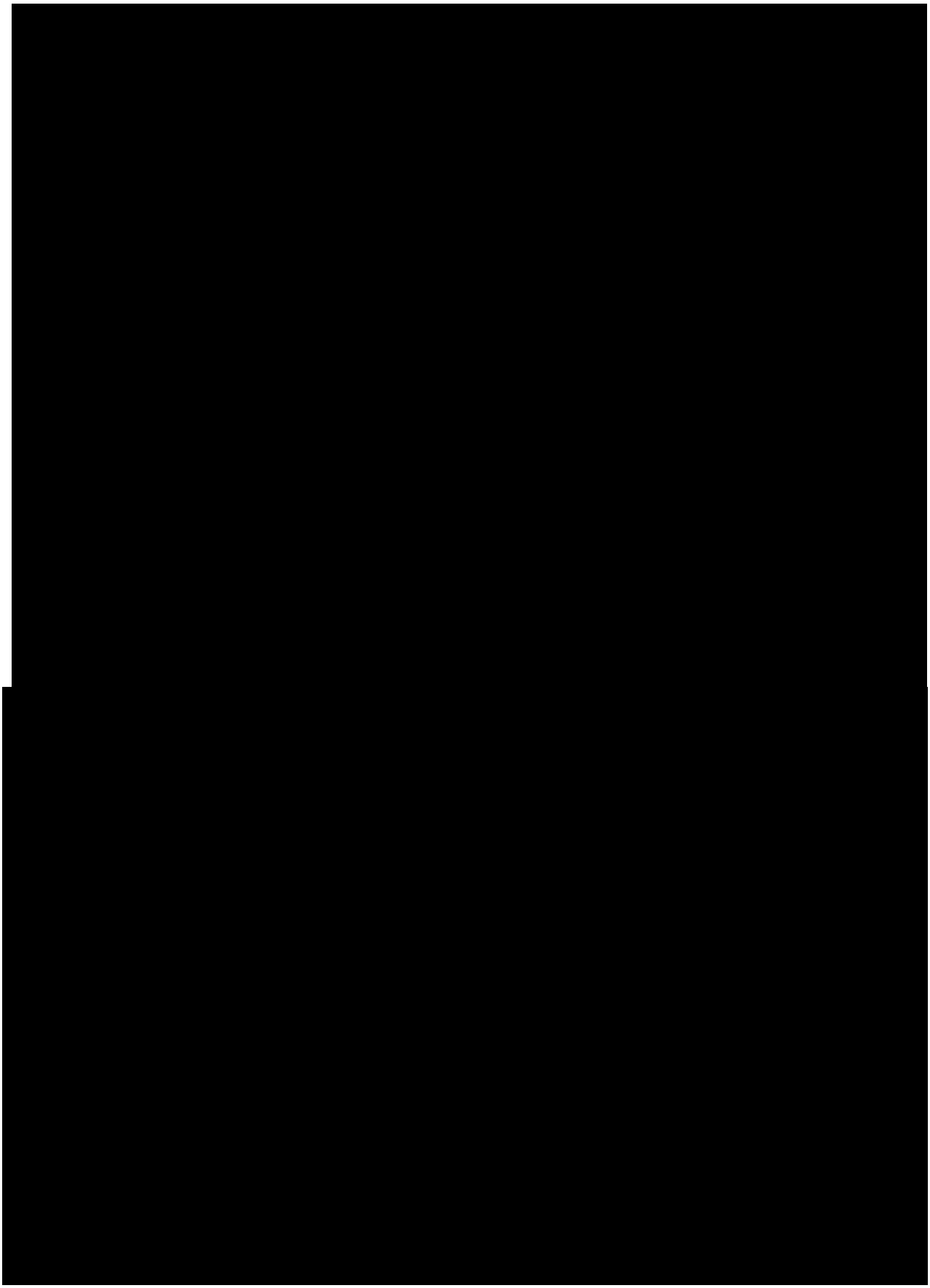
The PPP PGA will be measured at the timepoints noted in the Flow Chart. The PPP PGA is provided in Appendix 10.1.2.

5.1.3 Pain VAS (Visual Analogue Scale)

The pain VAS is a unidimensional measure of pain intensity [R18-1989]. It is a continuous scale comprised of a horizontal or vertical line, usually 10 centimeters (100 mm) in length, anchored by word descriptors at each end ("no pain", "very severe pain"). The pain VAS is self-completed by the patient.The patient is asked to place a vertical (|) mark on the horizontal line to indicate the severity of the pain. Using a ruler, the score is determined by measuring the distance (mm) on the 10-cm line between the "no pain" anchor and the patient's mark, providing a range of scores from 0–100. A higher score indicates greater pain intensity.

Pain VAS will be measured at the timepoints noted in the Flow Chart. The Pain VAS instrument to assess is provided in Appendix 10.1.3. Of note, there will be two pain VAS questionnaires, one specifically asking for pain on palms and/or soles (PPP Pain VAS) and one for muscular and joint pain.

[redacted]



[redacted]

5.1.10 Palmoplantar Pustulosis Severity Index (PPP SI)

The Palmoplantar Pustulosis Severity Index (PPP SI) is based on the severity score of individual components (erythema, pustules, and scaling/desquamation) of PPP ASI assessments. The most severe skin lesion location is identified by the investigator at baseline and assessed at all subsequent visits.

The PPP SI will be calculated by summing up the individual components of PPP ASI assessment (range 0-12) at each visit for the identified location.

PPP SI will be measured at the timepoints noted in the Flow Chart. Details are provided in Appendix 10.1.10.

[redacted]

5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

- Adverse events (including drug-related AEs and AEs leading to discontinuation)
- Adverse events of special interest (AESIs)
- Serious adverse events (SAEs)
- Intensity of adverse events will be assessed by Rheumatology Common Toxicity Criteria (RCTC) version 2.0 (refer to Appendix 10.3 and ISF for details)
- Safety laboratory tests
- Physical examination
- Vital signs (blood pressure, pulse rate, body temperature, respiratory rate)
- 12-lead Electrocardiogram (ECG)
- Local tolerability
- Immunogenicity (ADA/Nab)

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

Targeted physical examination will include vital sign assessment and evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities.
Measurement of height and body weight will be performed at the time points specified in the Flow Chart.
The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, prior to blood sampling. Measurements of vital signs should be assessed at screening. At dosing visits, vital signs evaluations will be performed pre-dose and additional evaluations will be taken at 10 minutes post-dose and 1 hour after the end of the study drug administration.

This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest, and additionally temperature and respiratory rate. The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1. For the sampling timepoints please see the Flow Chart.

All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.
Patients do not have to be fasted for the blood sampling for the safety laboratory.

Instructions regarding blood and urine sample collection, sample handling/ processing and sample shipping are provided in the laboratory manual in the ISF.
The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1 and the DILI Checklist provided in the ISF). The amount of blood taken from the patient concerned will be increased due to this additional sampling.
The central laboratory will transfer the results of the analysis to the sponsor.

Table 5.2.3: 1 Safety laboratory tests

Category	Test name
Haematology	Haematocrit (Hct) Haemoglobin (Hb) Glycosylated Hbc (HbA1c) (only at screening) Red Blood Cell Count Reticulocyte Count White Blood Cells / Leukocytes Platelet Count / Thrombocytes

Table 5.2.3: 1 (cont.) Safety laboratory tests

Category	Test name
Diff. Automatic	Neutrophils (relative and absolute) Eosinophils (relative and absolute) Basophils (relative and absolute) Monocytes (relative and absolute) Lymphocytes (relative and absolute)
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Coagulation	Partial Thromboplastin Time (aPTT) Prothrombin time (INR) Fibrinogen
Enzymes	AST (GOT) ALT (GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Amylase Lipase Serum Tryptase[1]
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate
Substrates	Glucose BUN (blood urea nitrogen) Uric acid Creatinine eGFR (estimated by CKD-EPI formula) (only at screening) Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Troponin (Reflex, in case of elevated CK) Protein, Total Albumin C-Reactive Protein (CRP) (high sensitivity) Cholesterol, total Triglycerides LDL-Cholesterol HDL-Cholesterol
Specific gamma-globulin quantification	IgE[3]
Urine Pregnancy test[2] (only for female patients of childbearing potential). At the drug administration visits, the test will be performed prior to the administration of study drug	Human Chorionic Gonadotropin in urine
Serum Pregnancy test[2] (only for female patients of childbearing potential)	Human Serum Chorionic Gonadotropin

Table 5.2.3: 1 (cont.) Safety laboratory tests

Category	Test name
Hormones (only at screening)	TSH (free T3 and free T4 in case of abnormal TSH result)
Urinalysis	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC / Erythrocytes Urine WBC / Leukocytes Urine pH Urine Creatinine
Urine-Sediment (microscopic examination, only if urine analysis abnormal)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sed. Crys., Unspecified Urine Sediment RBC / Erythrocytes Urine Sediment WBC / Leukocytes
Urine (only at screening)	Albumin (quantitative)
Infections testing	Hepatitis B Surface Antigen (qualitative), Hepatitis B core Antibody HBV-DNA (quantitative) at screening (Visit 1) and EOT Visit[4] Hepatitis C Antibodies (qualitative), HIV-1, and HIV-2 Antibody (qualitative), QuantiFERON®-TB[5,6]

[1] Performed only at the randomisation visit (Visit 2).

[2] Urine and serum pregnancy testing will be performed as indicated in the Flow Chart.

[3] IgE will be taken in case of systemic hypersensitivity reaction together with ADA (anti-drug antibodies) sample.

[4] A HBV-DNA should be conducted if Hepatitis B core Antibody is positive and Hepatitis B Surface Antigen is negative. These evaluations should be conducted at screening and at the EOT Visit.

[5] If the 1st QuantiFERON®-TB test result is indeterminate, a retest should be performed

[6] In patients with a negative QuantiFERON®-TB test, the test should be repeated at EOT visit.

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the Flow Chart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for analysis. Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.
Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

All cases of malignancies that are detected during the trial will be reported as SAEs. Patients with a history of malignancy (except for specific cancers) will be excluded from this trial per the exclusion criteria (Section 3.3.3).

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):
- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:
- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

For Japan only: the following events will be handled as “deemed serious for any other reason”. AEs which possibly lead to disability will be reported as SAEs.

5.2.6.1.3 AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.
The latest list of "Always Serious AEs" can be found in the eDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described above.
Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in Section 5.2.6.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.6.2.2.

The following are considered as AESIs:

Systemic hypersensitivity reactions including anaphylactic reaction
Any suspicion of severe systemic hypersensitivity reaction and of any potential cases of anaphylaxis should be defined and assessed using the criteria discussed in the statement paper from Sampson HA (Appendix 10.1, R11-4890).

Severe infections (according to RCTC grading in Appendix 10.2)

Opportunistic and mycobacterium tuberculosis infections
These include pneumocystis jirovecii, BK virus disease including PVAN, CMV, post-transplant lymphoproliferative disorder (EBV), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), HCV progression [R17-2617].

Hepatic injury

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

- an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

5.2.6.1.5 Intensity (severity) of AEs

The intensity grading of AEs will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 developed by OMERACT [R13-3515]. Refer to the ISF for intensity/severity classification. Intensity options are:

Grade 1	mild
Grade 2	moderate
Grade 3	severe
Grade 4	life-threatening

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
- Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files. The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial: all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

[redacted]

5.5 BIOBANKING

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will only occur after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements.

Unspecified DNA Banking:
An additional blood sample for DNA banking will be collected in PAXgene Blood DNA tube at Visit 2 (see Flow Chart). The DNA Banking sample, derived from the original blood sample, will be stored at Boehringer Ingelheim. The stored DNA may be retrospectively analysed.

5.6 OTHER ASSESSMENTS

Photographs of palmoplantar lesions
Photographs of palms and soles (with or without palmar or plantar lesions) and, if applicable, selected area with plaque psoriasis target lesion elsewhere on the body (in patients with concurrent plaque psoriasis only) will be taken at time points specified in the Flow Chart. The images must not be identifiable to the patients (e.g. by tattoos). Photographs will be used for monitoring the study quality and explore diagnostic accuracy by clinical experts, Clinical Trial Physician or designated functions. The monitoring of images will not have any impact on patient selection by investigators and on data analyses. Details are described in the photo documentation instruction manual in the ISF.

5.7 APPROPRIATENESS OF MEASUREMENTS

The measurements performed during this trial are standard measurements in PPP treatment trials and will be performed in order to monitor safety aspects or assess treatment response in an appropriate way. The PROs included in this trial have been used and described in other diseases, including dermatologic conditions, where they have demonstrated adequate measurement properties. They were included because they explore concepts of PPP that patients and physicians have highlighted as relevant and important.

Therefore, the appropriateness of all measurements applied in this trial is given.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow Chart. Each visit data (with its window) up to EOS is to be counted from Day 1 (Visit 2). If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart and respective protocol sections.

Measurement of vital signs should precede blood sampling and be assessed pre-dose at all dosing visits.

Patient Reported Outcomes (PROs) such as [redacted] Pain VAS, [redacted] should be completed by the patient on his/her own in a pre-specified order in a quiet area/room before any other visit assessments or treatments, and, if possible, before any interaction with the investigator or other members of the study team. This applies also to the randomisation visit (V2).

The following sequence of procedures at each visit (where applicable) is recommended:

1. PROs (prespecified order: [redacted] Pain VAS, [redacted]
2. AE and concomitant therapy collection; smoking status
3. Physical examinations (including predose vital signs)
4. PPP PGA, PPP ASI, [redacted]
6. Photographs of skin lesions
7. ECG
8. Urine pregnancy testing (if applicable)
9. Blood and urine sampling, including [redacted] ADA/Nab, [redacted]
10. Skin biopsies
11. Assign (IRT call) /Administer study drug
12. Local tolerability
13. Post-dose vital signs

6.2.1 Screening and run-in period(s)

Screening Period
Study requirements, including the procedure for the follow-up of prematurely withdrawn patients must be fully explained to the patient and written informed consent obtained prior to initiating any study-related evaluation. The importance of staying in the trial until completion

of all study requirements will be emphasized. No trial procedures should be done unless the patient has consented to taking part in the trial.

Once consented, the patient is considered to be enrolled in the trial and has started screening. The patient should be recorded on the enrolment log and be registered in IRT as a screened patient. Patients will be assigned a patient number generated via the IRT system.

Screening (Visit 1) should normally take place no more than 28 days before Visit 2 and be completed no less than 14 days prior to Visit 2. Visit 1 procedures may be completed over multiple physical visits, if needed. The time window for Visit 1 may be extended at the discretion of the CT Manager in conjunction with the CT Leader on a case by case basis.

For the comprehensive list of the trial procedures required at the Screening Visit (Visit 1) please refer to Flow Chart. Patients who have a laboratory test value that makes their participation uncertain may have the test repeated to determine eligibility; however, the result must be available prior to Visit 2 (Day 1). Baseline conditions and medical history will be assessed during screening.

Demographics:
Informed consent date, gender, ethnicity and race (if allowed by local law) will be collected and reported in the eCRF.

Baseline Conditions
Chronic diseases, current observable conditions, any new clinically relevant findings discovered from the physical examination, ECG, safety labs, and any condition requiring therapy (excluding PPP, and if applicable concurrent plaque psoriasis) will be reported on the Baseline Condition eCRF page. The smoking status and history based on the calculation of pack-years will be collected as well; see Appendix 10.4 for details.

Infections screening
Infections testing will include tuberculosis, hepatitis B, hepatitis C, and HIV assessments (see Section 3.3.3 and Table 5.2.3: 1).

Medical History
Medical history of PPP, including the previous treatment, will be collected and reported in the eCRF.
Information on clinically significant previous and concomitant illnesses, other than PPP, or any clinically significant signs or symptoms that are present before informed consent, or pre-existing conditions identified through findings from assessments and examinations done during the screening visits will be recorded as medical and surgical history at screening on the Baseline Condition page in the eCRF.

Patients who fail screening (i.e. does not meet the eligibility criteria) following Visit 1 assessments should be registered as a screen failure in IRT.

Re-Screening

If a patient results in a screen failure the patient must be registered as a screen failure in IRT system.
However, re-screening of a previously screen failed patient will be permitted once. Details of IRT procedures can be found in the IRT manual located in the Investigator Site File (ISF).
For the comprehensive list of the trial procedures required at the Screening Visit (Visit 1) please refer to the Flow Chart.

6.2.2 Treatment period(s)

When eligibility of the patient to participate in the trial is confirmed, randomisation via IRT will be performed at Visit 2. The treatment period is from Day 1 to Week 52 (End of Treatment, EOT). Procedures described in the Flow Chart for each visit should be performed.

[redacted]

At visits during the treatment period, venepuncture (i.e. safety laboratories, [redacted] ADA, [redacted]) and skin biopsies should be the last procedures performed prior to study drug administration. Only after all blood specimens are collected, will each eligible patient receive a dose of the assigned trial medication.

6.2.3 Follow-up period and trial completion

For all randomised patients termination of trial medication and trial completion must be recorded on the corresponding CRFs.

For patients completing the randomised trial treatment regularly at Week 52 (EOT), safety follow-up visits will be performed at Week 60 (FU1 Visit) and at Week 68 (End of Study, EOS Visit).

Early treatment discontinuation
Patients who discontinue treatment prematurely prior to the planned EOT visit (Week 52, the last planned treatment visit) should be registered as withdrawn from treatment in IRT.
Patients should follow the scheduled visits as much as possible as defined in the Flow Chart.
If the patient is not willing to follow the whole visit schedule, at least the EOT should be conducted either immediately or as soon as possible followed by the EOS visit 16 weeks after the EOT visit. All efforts should be made to keep the patient in the observation for at least 16 weeks after the last dose of the study drug.

Treatment completion
Treatment completion is defined as a patient having completed treatments till planned EOT visit (Week 52).

Trial completion:
Trial completion is defined as a patient having reached the EOS Visit per protocol (Week 68).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This trial is designed as a randomised, parallel-group, double-blind, and placebo-controlled trial with 4 active doses of BI 655130 in patients with moderate to severe Palmoplantar Pustulosis.

The purpose of this trial is to demonstrate proof of concept of clinical activity of BI 655130 on the primary endpoint of % PPP ASI change at Week 16. For the proof of concept a combined criterion of MCPMod testing (with respect to achieving a non-flat dose response curve) and evaluation of a minimum relevant benefit is implemented. In detail, for PoC, at first a statistically significant non-flat dose-response needs be detected. For this purpose, a multiple comparison procedure with modelling techniques (MCPMod) approach is applied. Subsequently, at least one dose should show a benefit of at least 20% compared to placebo (i.e. the maximum benefit of BI 655130 for achieving the primary endpoint, based on modelled dose-response curve using model averaging across the statistically significant models (see Section 7.2.2), shows a ≥ 20% larger reduction compared to placebo).

Overall this approach is applied to define suitable dose regimens for BI 655130 regarding efficacy and safety for further pivotal testing in a subsequent study. Further assessment on the efficacy of BI 655130 at time-points after Week 16 will be performed in an exploratory manner.

Baseline refers to the measurement recorded at randomisation (Visit 2); if data at Visit 2 is missing, then data from Visit 1 will be considered baseline. The percent change from baseline of the PPP ASI score, at all follow-up visits (X), is calculated as:

% PPP ASI change from baseline = ((PPP ASI at Visit X – PPP ASI at baseline) / PPP ASI at baseline) * 100.

For the derivation of the primary endpoint, all measurements collected after treatment discontinuation, or after the use of rescue therapy for the purpose of disease worsening, will be censored. The primary endpoint is then evaluated based on the results of a mixed effect model for repeated measurements (MMRM) which assumes that missing data up to Week 16 are handled via a missing at random approach. The estimated dose effects at Week 16 will then be analysed using the MCPMod approach techniques [R10-1424, R15-1961].

Randomisation will be stratified, and analysis will be performed, based on a stratification according to Japan versus non-Japan.

7.1 NULL AND ALTERNATIVE HYPOTHESES

The null hypothesis of the MCPMod test is that there is a flat dose response curve comparing the placebo and the BI 655130 dose groups on the primary endpoint of % PPP ASI change at Week 16. The alternative hypothesis is that there is a non-flat dose response curve indicating a (clinically relevant) benefit of BI 655130 over Placebo.

The MCPMod procedure allows for simultaneous evaluation of different potential dose response patterns, whilst protecting the overall probability of Type I error (one sided α of 5%). The pre-specified models and their parameters used for this test are outlined in Section 7.2.2 and Section 7.5.

Additionally, the probability of making a positive decision to continue the program with a non-effective drug is further limited by requesting that an effect of at least "delta" relative to placebo is achieved (see Section 7.5 for details). This consequently leads also to a reduction of the probability for having a false positive decision.

7.2 PLANNED ANALYSES

7.2.1 General considerations

There will be 3 main patient populations in this trial for analyses: the full analysis set (FAS), the safety analysis set (SAF), and the per-protocol set (PPS).

Safety Analysis Set (SAF)
This patient set includes all patients who were randomised and received at least one dose of study drug. It will be the main analysis set for presentation of safety. Patients will be analyzed according to the actual treatment.

Full Analysis Set (FAS)
This patient set includes all patients in the SAF who had a baseline for the primary efficacy endpoint. Treatment assignment will be as randomised. This is the main analysis set for presentation of efficacy data.

Per-Protocol Set (PPS)
This patient set includes all patients in the FAS who adhered to the CTP without any IPDs (potentially affecting the study outcome) which lead to exclusion from the PPS. This set will be used for sensitivity analysis on the primary efficacy endpoint. Important deviations of the protocol will include violations of the key inclusion and exclusion criteria, incorrect medications taken, concomitant use of restricted medications, and any other deviations of the protocol deemed important by the study team. All decisions concerning important protocol deviations will be made prior to un-blinding of the database for the primary endpoint analysis at week 16, and a full list of such deviations will be provided in the trial Integrated Quality and Risk Management Plan (IQRMP).

Further analysis sets, [redacted], will be defined in the Trial Statistical Analysis Plan (TSAP).

Standard statistical parameters (number of non-missing values, mean, standard deviation (SD), median, quartiles, minimum and maximum) or frequency tables (including patient frequencies and percentages) will be calculated where appropriate.

The following analyses of this trial protocol, in chronological order, are planned:

Week 16 Primary Analysis

The primary analysis of the trial will be performed once all randomised patients have completed the first 16 weeks of the trial, and a database lock will be done. Details of the analysis to be performed will be described in the TSAP which is planned to be finalized prior to achieving database lock for this primary analysis. Treatment will be unblinded at this time. For further details regarding the maintenance and protection of the blind through the continuing trial subsequent to performance of the primary analysis, refer to Section 4.1.5.1.

Final Trial Analysis
The final analysis of the trial will be performed once all randomised patients have completed the trial. At this time, the treatment will be officially unblinded.

A Clinical Trial Report will be prepared at the end of the trial.

7.2.2 Primary endpoint analyses

The % change in PPP ASI at Week 16 is the primary endpoint of efficacy in this trial.

The primary analysis consists of a combination of MCPMod-based testing (with respect to a non-flat dose response curve) and an evaluation of the dose-wise benefit at Week 16. As a basis for the MCPMod analysis a mixed effect model for repeated measurements (MMRM) is used.

MMRM model
The % change in PPP ASI from baseline (Visit 2), at Visits 6, 7, 8 and 9 (Weeks 4, 8, 12 and 16 only) will be evaluated using an MMRM accounting for the following sources of variation: 'baseline' as a continuous covariate, and 'visit', 'treatment', 'region' (stratification according to Japan vs. non-Japan), 'visit*treatment' and 'visit*baseline' interaction as fixed effects as well as the random 'subject' effect. The unstructured covariance structure will be used to model the within patient measurements. To estimate denominator degrees of freedom the Kenward-Roger approximation will be used. In the event of model non-convergence (following application of suitable methods to attempt to resolve this – as will be specified in the TSAP), first, the strata for region will be dropped from the model, and then, if non-convergence persists, an ANCOVA (Analysis of Covariance) model at Week 16 only will instead be performed.

MCPMod analysis
The dose-response relationship of the Week 16 estimates from MMRM will then be analysed using MCPMod [R10-1424, R15-1961]. Thereby, several possible dose response models (patterns) will be evaluated (while keeping full control of the type I error at 5%, one-sided) to identify the best-fitting model.

Dosing is planned to be administered in two phases, a loading phase followed by a maintenance phase (for details see Section 3.1). For modelling purposes the different active dose groups will be approximated by the planned total [redacted] Consequently, the total doses which are included are BI 655130 [redacted] (Arm 1: "high dose" regimen), [redacted] (Arm 2: "medium-

high dose" regimen), [redacted] (Arm 3: "medium-low dose" regimen), [redacted] (Arm 4: "low dose" regimen) and placebo (Arm 5).

For the PoC testing and for the sample size calculation the following model assumptions and resulting graphs (see Figure 7.2.2: 1) have been selected to cover both the plausible and a diverse range of potential dose response patterns:

- Linear
- Emax: assumes 70% of the maximum effect is achieved at the "low dose" regimen [redacted]
- Exponential: assumes 25% of the maximum effect is achieved at the "medium-low dose" regimen [redacted]
- Logistic: assumes 20% of the maximum effect is achieved at the "low dose" regimen (Arm 4) and 95% of the maximum effect is achieved at "medium high dose" regimen (arm 2, i.e. [redacted]
- Sigmoid Emax: assumes 10% of the maximum effect is achieved at "low dose" regimen (Arm 4) and 80% of the maximum effect is achieved at the "medium-high dose" regimen (Arm 2))

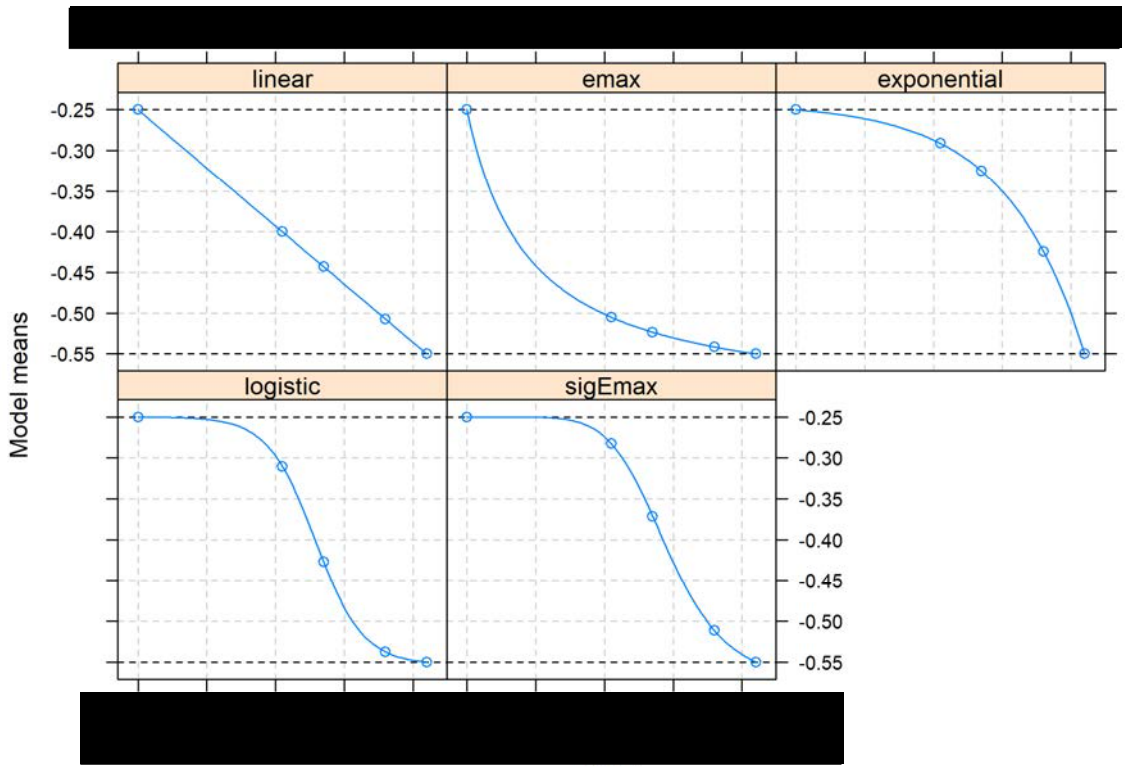


Figure 7.2.2: 1: Defined MCPMod shapes to be used.

The optimal contrasts corresponding to the candidate models will be shown in the TSAP. For the final evaluation, these contrasts will be updated using the expected model means from the candidate set and the estimated variance-covariance matrix extracted from the MMRM model.

A non-flat dose response is established if at least one dose response pattern is statistically significant, rejecting the null hypothesis of a flat dose response relationship on % PPP ASI change at Week 16 jointly for each of the candidate dose response models, with a contrast test controlled for the family–wise type I error rate at a one sided $\alpha = 5\%$. If a non-flat dose response is established, the statistically significant model(s) from the above candidate set are refitted to the data to generate new estimates for all model parameters. The dose-response curve is then fitted based on model averaging across the statistically significant models.

If considered necessary and for the purpose of further model refinement, MCPMod might be repeated on the primary endpoint but with an extended set of shapes including the original candidates. [redacted]

Other analyses of the primary endpoint will include:

[redacted]

7.2.3 Secondary endpoint analyses

The following continuous secondary endpoints will be evaluated in the same manner as described for the primary endpoint:

- Change from baseline in PPP Pain VAS score at Week 4
- Change from baseline in PPP Pain VAS score at Week 16
- PPP SI change from baseline at Week 16

Hereby the same model shapes as for the primary endpoint will be used. The corresponding contrasts and further details will be described in the TSAP.

For the continuous secondary endpoint of percent change in PPP ASI from baseline at Week 52, the following maintenance treatment comparisons will be performed using an MMRM (incorporating weeks 4, 12, 20, 28, 36, 44, and 52) as well as descriptive methods:

- Arm 1 vs Arm 2: to compare the effect of [redacted] q4w vs [redacted] q4w on a loading dose of [redacted]
- Arm 3 vs Arm 4: to compare the effect of [redacted] q4w vs [redacted] q8w on a loading dose of [redacted]
- Arm 1 +Arm 3 +Arm 5 vs Arm 4: to compare the global effect of [redacted] q4w vs. [redacted] q8w maintenance dose used after Week 16.

- Arm 1 +Arm 3 +Arm 5 vs Arm 2: to compare the global effect of [redacted] q4w vs. [redacted] q4w maintenance dose.
- Arm 2 vs Arm 4: to compare the effect of [redacted] q4w vs. [redacted] q8w maintenance dose used after Week 16.

For each of the binary secondary endpoints at Week 16, a MCPMod approach will also be used to evaluate the treatment effect of multiple doses of BI 655130 vs. placebo. This method will be implemented for MCPMod in a binary setting. The assessments will be performed using the identical dose response assumptions to those described for the primary endpoint analysis and will be done based upon the response proportions collected at Week 16 only. The contrasts applicable to each dose response shape for each of the binary secondary endpoints, will be specified, along with further details on the implementation of a binary MCP-Mod approach, in the TSAP. [redacted]

As a further analysis, a logistic regression model on each binary endpoint at Week 16 with fixed factors for 'treatment', and 'region' as strata will also be applied for the FAS. 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 [R16-4414]; further details will be provided in the TSAP.

[redacted]

7.2.5 Safety analyses

Adverse events will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced.

All randomised and treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned. Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events (TEAE). To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'; the residual effect period (REP) is defined as 16 weeks after the last dose of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class (SOC) and preferred term after coding according to the current version of the MedDRA at database lock.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Immunogenicity data will be analysed in a descriptive way.

[redacted]

7.2.7 Interim Analyses

There are no interim analyses of this trial planned to be performed.

Once all randomised patients have completed the first 16 weeks of study, a database lock will be done for safety and efficacy data collected up to Week 16. At this time, the primary analysis of these data through Week 16 will be performed. Since the study is planned to continue, and will remain blinded, a logistics plan as described in Section 4.1.5.1 will be developed in order to protect the integrity of the ongoing trial data and reporting subsequent to treatment un-blind for the Week 16 primary analysis. Details of the analysis to be performed will be described in the TSAP which is planned to be finalized prior to achieving database lock for the Week 16 primary analysis. The primary analysis is planned to be described in a Clinical Trial Report (CTR).

A final analysis of the entire trial data will be performed once all randomised patients have completed the 68 weeks of study. The final analyses are planned to be documented in a CTR which is to be prepared at the end of the trial.

7.3 HANDLING OF MISSING DATA

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

In order to check the robustness of the primary MCPMod analysis to missing data, a sensitivity analysis will be performed using adjusted multiple imputation. Non-monotone missing data will initially be multiply imputed as missing-at-random. For monotone missing data, a Jump to Reference method will then be implemented via a sequential regression MI approach. For such missing data, patients in the active treatment groups are assumed to lose any treatment effect with their missing observations and to then assume a trajectory similar to that of the placebo group. For each imputed complete dataset, an ANCOVA (Analysis of Covariance) model for Week 16 data analogous to the primary MMRM model will be used for the analysis. The results will be pooled using Rubin's rules and the primary MCPMod analysis will be repeated on the summarized outcomes. Further details on the procedure will be included in the TSAP.

For secondary efficacy endpoints of a binary nature, a Non Response Imputation (NRI) approach, will be applied to the missing visits up to Week 52 that is, imputing as a failure to achieve a response in the visits with missing endpoint score, however:

- If there are available data at the visits both before and after the visit with a missing outcome, then impute as a success only if both the preceding and the following measurement indicate success (that is, score of 1) and there is no use of rescue therapy for disease worsening within this imputation period;
- Otherwise, impute as a failure to achieve a response (i.e. no response imputation).

Multiple imputation will be used as a sensitivity analysis to handle missing secondary binary data. Detailed description of multiple imputation will be included in the TSAP.

With respect to safety evaluations, it is not planned to impute missing values.

7.4 RANDOMISATION

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

Stratification of the randomisation will be performed for Japan versus non-Japan.

Within each stratum, patients will be randomised in a 2:1:1:1:2 randomisation ratio to receive either placebo or one of four BI 655130 dose regimens (“high dose” regimen; “medium-high dose” regimen; “medium-low dose” regimen; “low dose” regimen). The randomisation will be done in blocks to achieve balanced allocation.

The process of randomisation is done via an IRT. Practical aspects of the treatment allocation process are detailed in Section 4.1.3.

7.5 DETERMINATION OF SAMPLE SIZE

Calculations were performed using R Version 3.5.1.

The study is intended to show a benefit of BI 655130 over placebo in terms of the difference in % PPP ASI change at Week 16.

The aims of this study are two-fold. A first aim is to show a significant non-flat dose-response curve across the different doses and placebo. Additionally to that at least one modelled dose within the dose range considered should show a benefit of at least "Delta" % PPP ASI change compared to placebo. The probability of success of this trial is therefore defined as the probability to (1) obtain a significant test for non-flat dose-response curve and (2) to observe for at least one of the modelled doses an effect difference of at least delta compared to placebo.

The sample size calculation is based on an assumed maximum difference in % PPP ASI change of placebo vs. BI 655130 of 30%, as well as on the pre-specified models listed in Section 7.2.2. The standardized deviation of the % PPP ASI change is assumed to be 35%.

For placebo, a fixed rate of -25% PPP ASI change at Week 16 will be considered. These estimates are derived from trial 1368.15 in PPP.

Using a total sample size of 140 evaluable patients (40, 20, 20, 20 and 40 for placebo and low to high dose regimes respectively), the probability for a successful trial (as defined above) was estimated using simulations. For each dose group, samples of the required size were drawn from a normal distribution. Values smaller than -100% (which corresponds to complete recovery of a patient) were set to -100%. The expected values of the original normal distribution were chosen such that the expected dose group means after truncation correspond to the model assumptions. In the following, the reported dose means will always refer to dose means after truncation. The standard deviation of the untruncated normal distribution was set to 35% for all simulations. This will result in slightly reduced standard deviations after truncation (of approx. 30% for the highest dose group).

Based on these assumptions, the success probability under a delta of 25% (i.e. non-flat curve achieved, and at least one BI 655130 dose shows a difference to placebo of at least 25%) is approximately 77% when assuming a linear dose response curve (i.e. -25, -40, -44, -51 and -55% PPP ASI change for placebo and low to high dose regimens, respectively). Assuming one of the other dose response curves listed in Section 7.2.2 the success probability is between 79% and 84%. For a delta of 20% the respective success probabilities are between 93 and 96%.

If the difference between placebo and active doses is low, i.e. 10% (which is assumed to be clinically not relevant) the success probability is approximately 2% and 9% for a delta of 25% and 20%, respectively (assuming a linear dose response curve). In the case that there is no treatment benefit, the false positive probability is limited by the α-level for the significance testing of the non-flat dose-response curve of 5% (one-sided). Additionally, this probability is further reduced by requesting an effect of at least delta. Thereby, the probability of a false decision for a non-effective drug is reduced to less then 1%.

The following Table 7.5: 1 provides success probabilities under different scenarios (i.e. different treatment effects and dose-response curves).

Table 7.5: 1 Probability of multiplicity-adjusted success probability given expected % change in PPP ASI at week 16 and a total sample size of 140 patients (with 40/20/20/20/40 per dose group) based on MCPMod nominal alpha-level of 5% (one-sided) and additional treatment effect threshold (Delta).

(Assumed) True Model	**Expected % change in PPP ASI (in %)**					**Exp. max. Response Difference**	**Delta**	**Multiplicity adjusted Success probability***
	Placebo	Low dose BI	Medium-low dose BI	Medium-high dose BI	High dose BI			
Linear30	-25	-40	-44	-51	-55	30	25	77,1%
Emax30	-25	-51	-52	-54	-55	30	25	80,7%
Exp30	-25	-29	-33	-42	-55	30	25	79,0%
Logistic30	-25	-31	-43	-54	-55	30	25	84,4%

Table 7.5: 1 (cont.) Probability of multiplicity-adjusted success probability given expected % change in PPP ASI at week 16 and a total sample size of 140 patients (with 40/20/20/20/40 per dose group) based on MCPMod nominal alpha-level of 5% (one-sided) and additional treatment effect threshold (Delta).

(Assumed) True Model	Expected % change in PPP ASI (in %)					Exp. max. Response Difference	Delta	Multiplicity adjusted Success probability*
	Placebo	Low dose BI	Medium-low dose BI	Medium-high dose BI	High dose BI			
SigEmax30	-25	-28	-37	-51	-55	30	25	83,6%
Linear40	-25	-45	-51	-59	-65	40	25	98,2%
Linear0	-25	-25	-25	-25	-25	0	25	<0,1%
Linear10	-25	-30	-31	-34	-35	10	25	1,8%
Linear30	-25	-40	-44	-51	-55	30	20	93,2%
Emax30	-25	-51	-52	-54	-55	30	20	94,6%
Exp30	-25	-29	-33	-42	-55	30	20	93,8%
Logistic30	-25	-31	-43	-54	-55	30	20	95,8,%
SigEmax30	-25	-28	-37	-51	-55	30	20	95,5%
Linear40	-25	-45	-51	-59	-65	40	20	99,8%
Linear0	-25	-25	-25	-25	-35	0	20	0,4%
Linear10	-25	-30	-31	-34	-25	10	20	8,7%

*Success probabilities under different efficacy assumptions for the defined success criteria of 1) Significant non-flat dose-response achieved based on at least one of the candidate set models AND 2) Treatment benefit of at least 'delta' compared to placebo for at least one modelled dose within the considered dose range. Success probabilities have been calculated using R Version 3.5.1 based on simulations (10000 simulations per scenario). Thereby the calculations for the MCPMod step have been performed using DoseFinding R-package 0.9-16 [R15-2001].

"Linear30: Main scenario reflecting the assumption of maximum effect difference of 30% compared to placebo assuming a linear dose-response curve as defined in Section 7.2.2.

"Emax30: Alternative scenario reflecting the assumption of maximum effect difference of 30% compared to placebo assuming an Emax dose-response curve as defined in Section 7.2.2.

"Exp30: Alternative scenario reflecting the assumption of maximum effect difference of 30% compared to placebo assuming an exponential dose-response curve as defined in Section 7.2.2.

"Logistic30: Alternative scenario reflecting the assumption of maximum effect difference of 30% compared to placebo assuming a logistic dose-response curve as defined in Section 7.2.2.

"SigEmax30: Alternative scenario reflecting the assumption of maximum effect difference of 30% compared to placebo assuming a sigmoid dose-response curve as defined in Section 7.2.2.

“Linear40: Alternative scenario reflecting the assumption of a higer maximum effect difference of 40% compared to placebo assuming a linear dose-response curve.

“Linear0: Alternative scenario reflecting the assumption of no difference compared to placebo assuming a linear dose-response curve.

“Linear10: Alternative scenario reflecting the assumption a clinically not relevant maximum effect difference of 10% compared to placebo assuming a linear dose-response curve.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as “protocol deviation”.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient’s legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient’s legally accepted representative.”

The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.
The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient’s own free will with the

informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.
A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.
Before providing any copy of patient´s source documents to the sponsor the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.
Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular

- Sample and data usage has to be in accordance with the separate biobanking informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").
The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site.**Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.
The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A DMC will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician.
The DMC will evaluate safety and efficacy data. The DMC will receive urgent significant safety concerns for immediate evaluation. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs)/Health Authorities (HAs), IRBs/IECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.
A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and central laboratory manual, available in the ISF.

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10. APPENDICES

10.1 INSTRUCTIONS FOR USE

10.1.1 Palmoplantar Pustulosis Area and Severity Index (PPP ASI)

Score	0	1	2	3	4	5	6
Erythema (E)	None	Slight	Moderate	Severe	Very severe		
Pustules (P) (total)	None	Slight	Moderate	Severe	Very severe		
Desquamation (D) (scaling)	None	Slight	Moderate	Severe	Very severe		
Area affected (%)*	0	<10	10<30	30<50	50<70	70<90	90 - 100

* where area assessed is glabrous skin on the palms/ soles

PPP ASI = [(E+P+D) Area x 0.2 (right palm)] + [(E+P+D) Area x 0.2 (left palm)] + [(E+P+D) Area x 0.3 (right sole)] + [(E+P+D) Area x 0.3 (left sole)]

10.1.2 Palmoplantar Pustulosis Physician Global Assessment (PPP PGA)

Components	
Erythema*	0=Clear; 1=Almost Clear; 2=Mild, 3=Moderate, 4=Severe
Pustules	0=Clear; 1=Almost Clear; 2=Mild, 3=Moderate, 4=Severe
Scaling/Crusting	0=Clear; 1=Almost Clear; 2=Mild, 3=Moderate, 4=Severe

*Do not score eroded area, physiological erythema, frictional hyperkeratosis and calluses

Each of the components (erythema, pustules, scaling/crusting) should be scored and recorded.

The PPP PGA total score is derived as the mean of all individual components.

PPP PGA Total Score:

0 = If mean=0 for all three components
1 = If 0 < mean <1.5
2 = If (1.5 <= mean <2.5)
3 = If 2.5 <= mean <3.5
4 = If mean >=3.5

10.1.3 Pain Visual Analogue Scale (VAS)

10.1.3.1 Pain VAS because of PPP on the palms and/or soles (PPP Pain VAS)

How much pain have you had because of your palmoplantar pustulosis (PPP) on the palms and/or soles in the past week?

Place a vertical (|) mark on the line to indicate the severity of the pain.

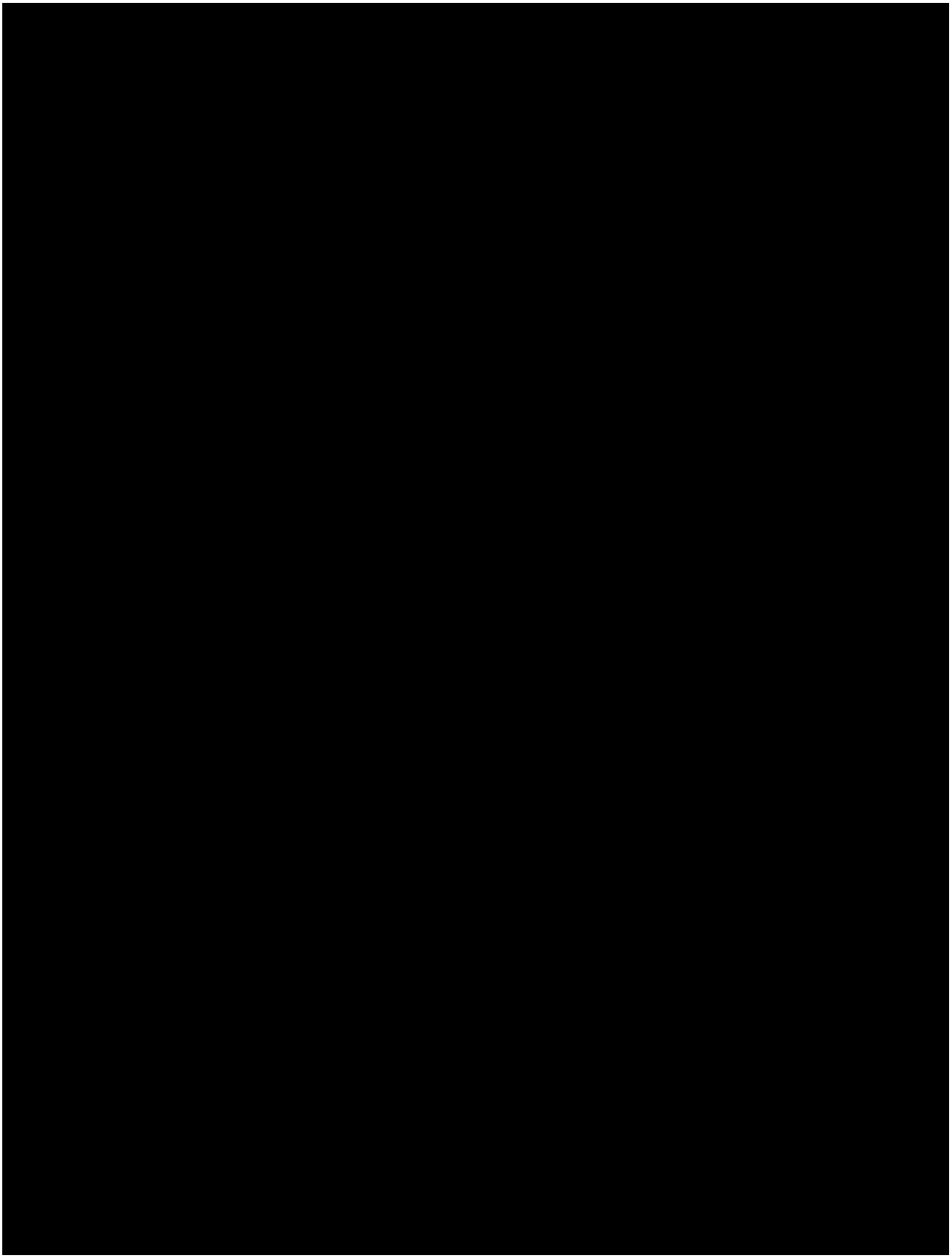
No pain Severe pain
0 ——————————————————— 100

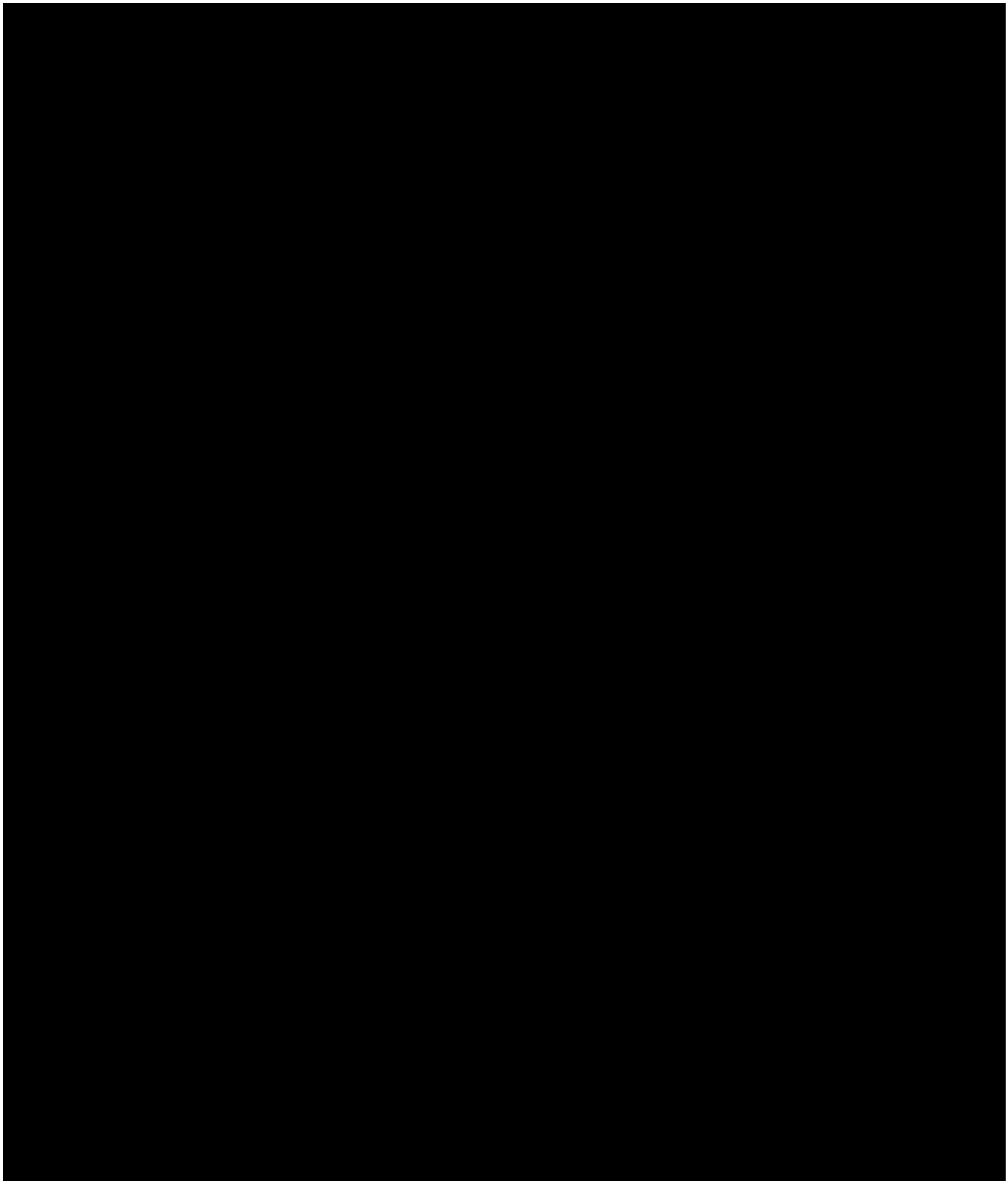
10.1.3.2 Pain VAS for muscular or joint pain

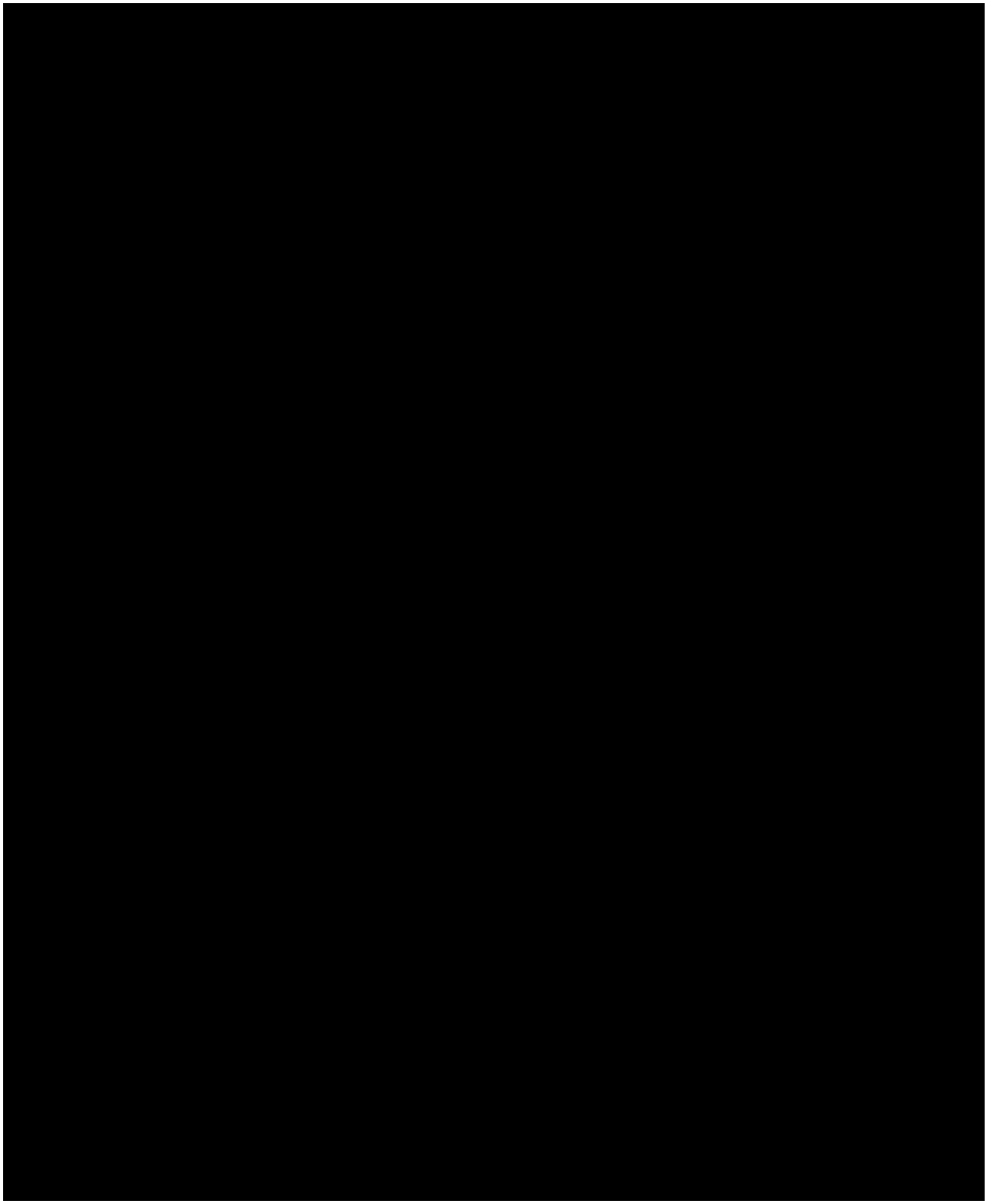
How much muscular or joint pain have you had in the past week?
Place a vertical (|) mark on the line to indicate the severity of the pain.

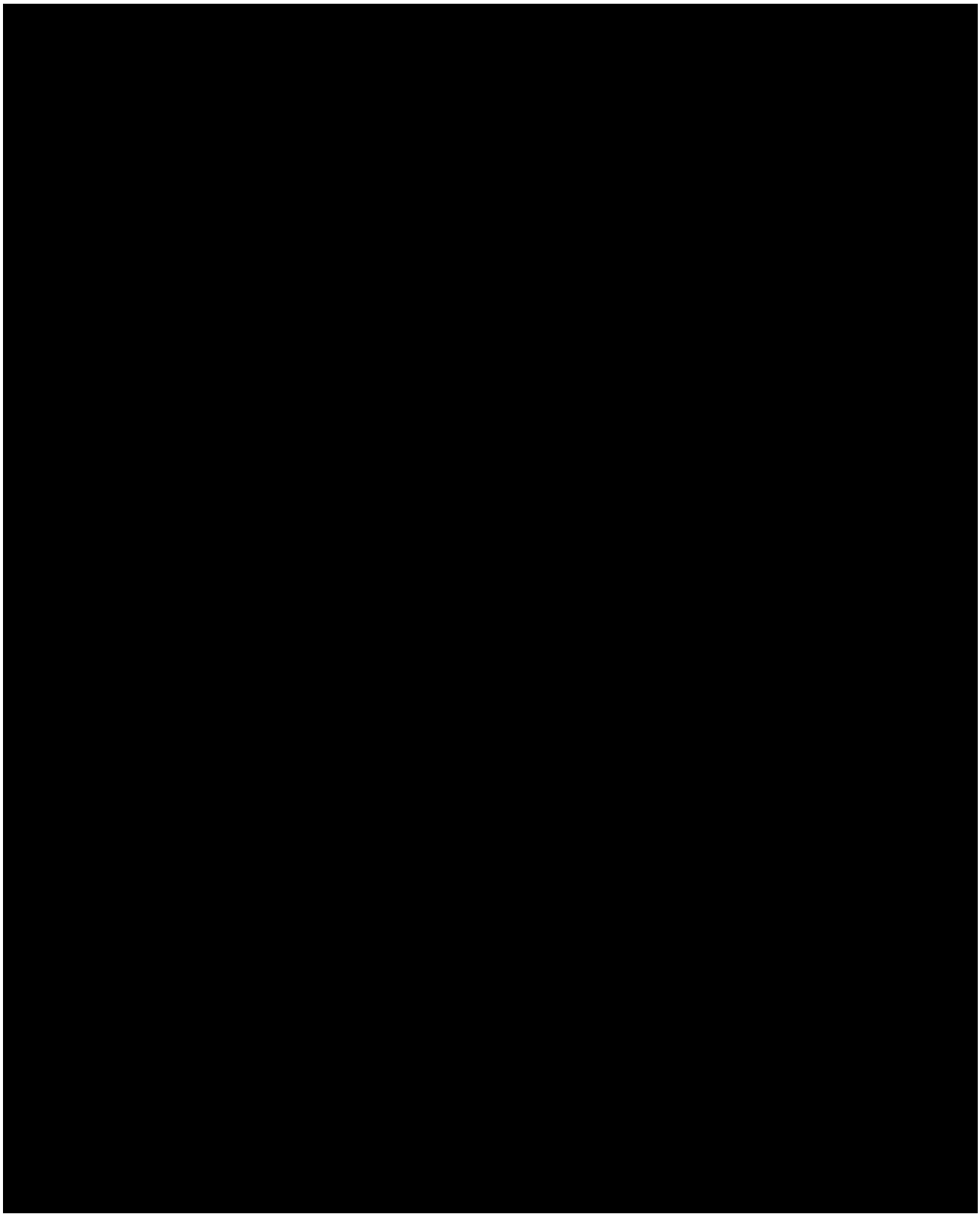
No pain Severe pain
0 ——————————————————— 100

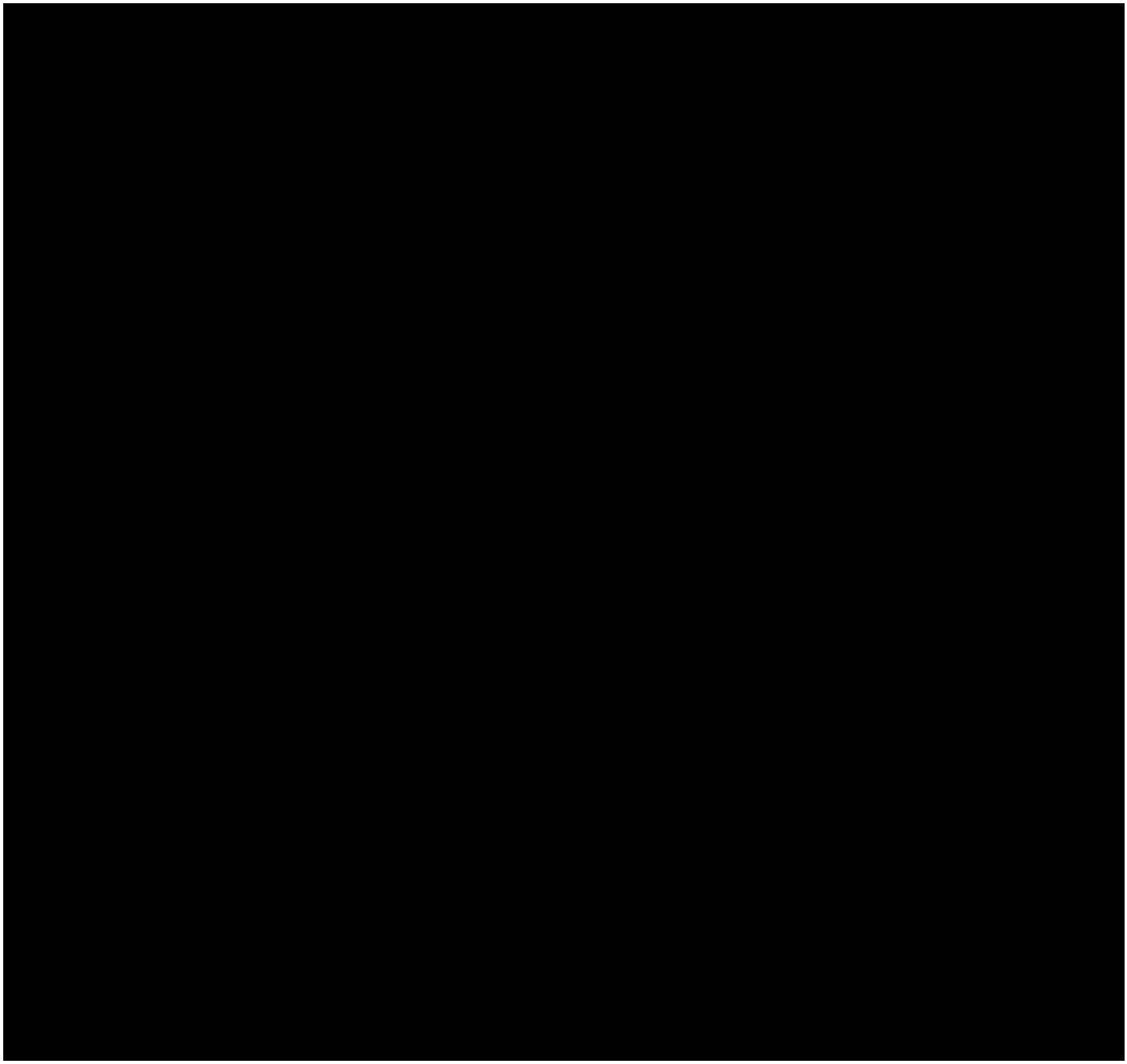
Source: (R18-1989).











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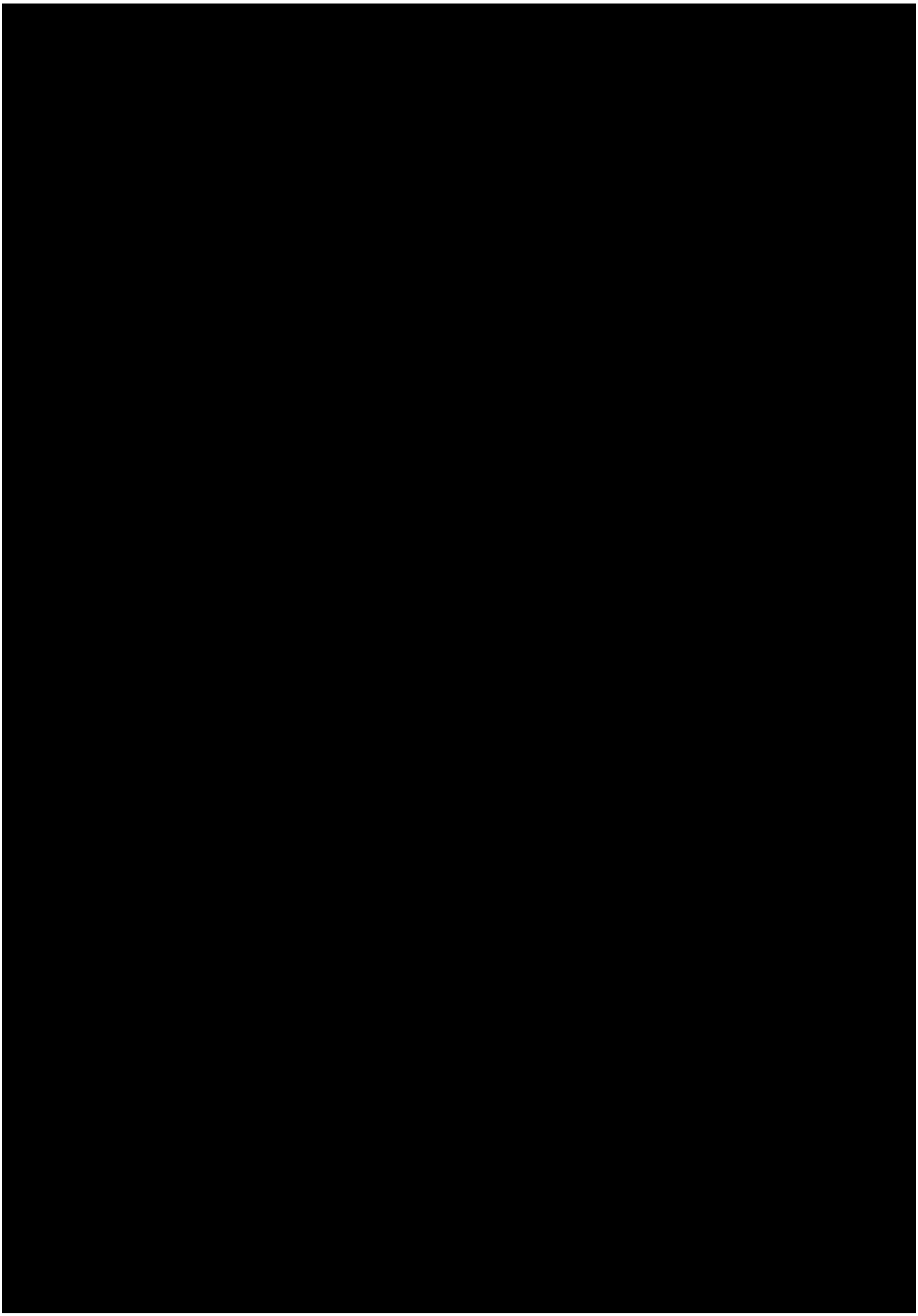
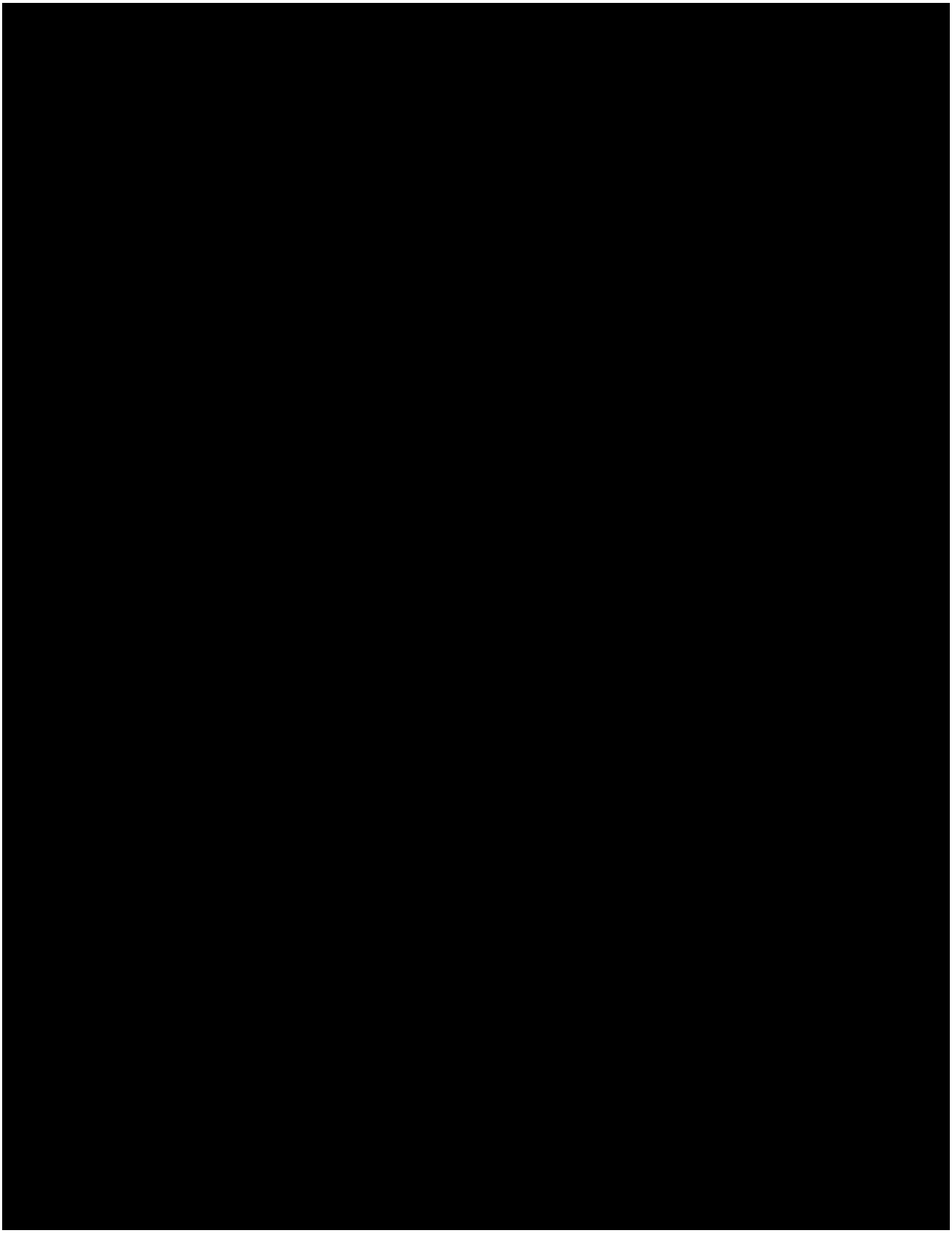
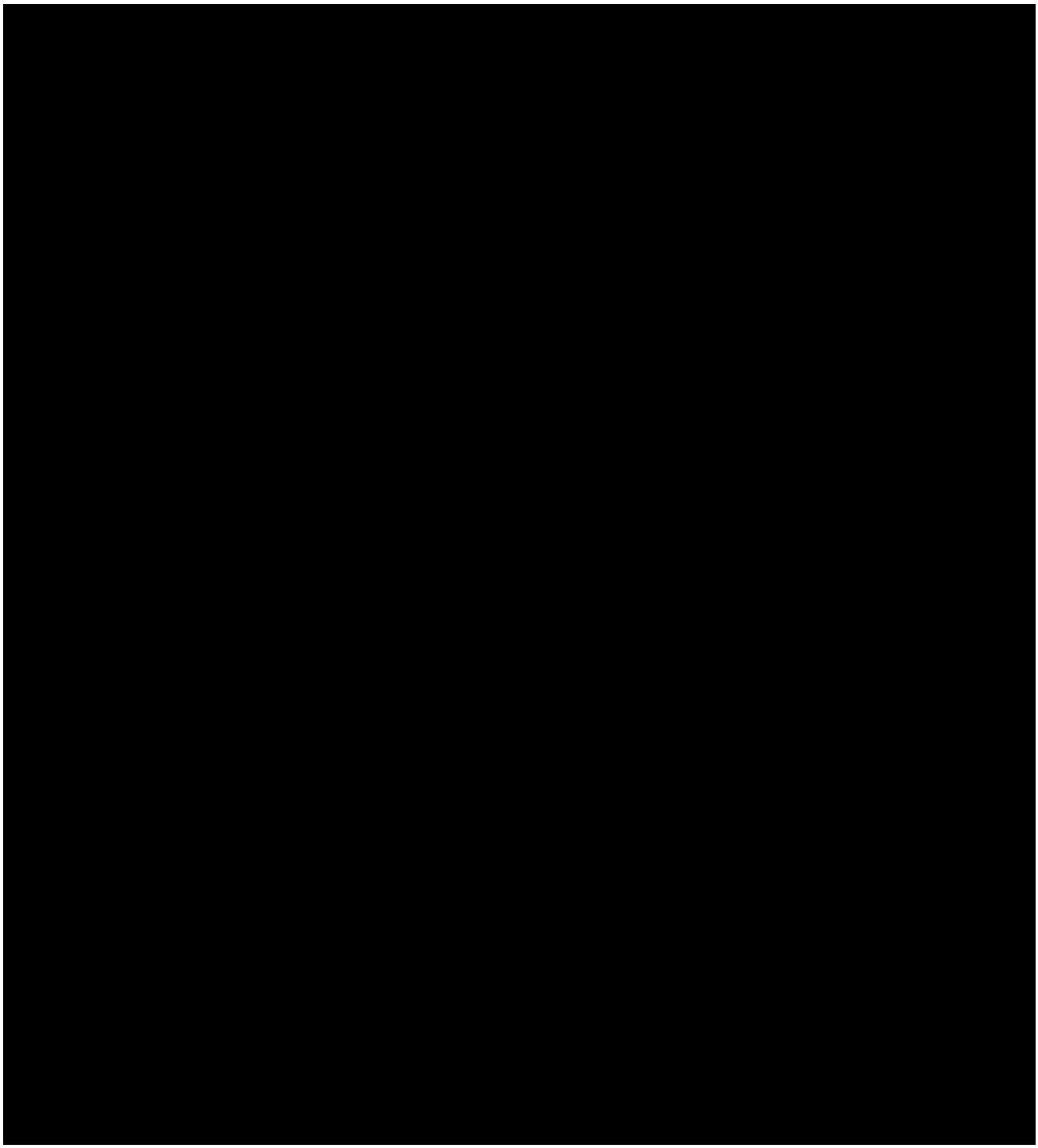
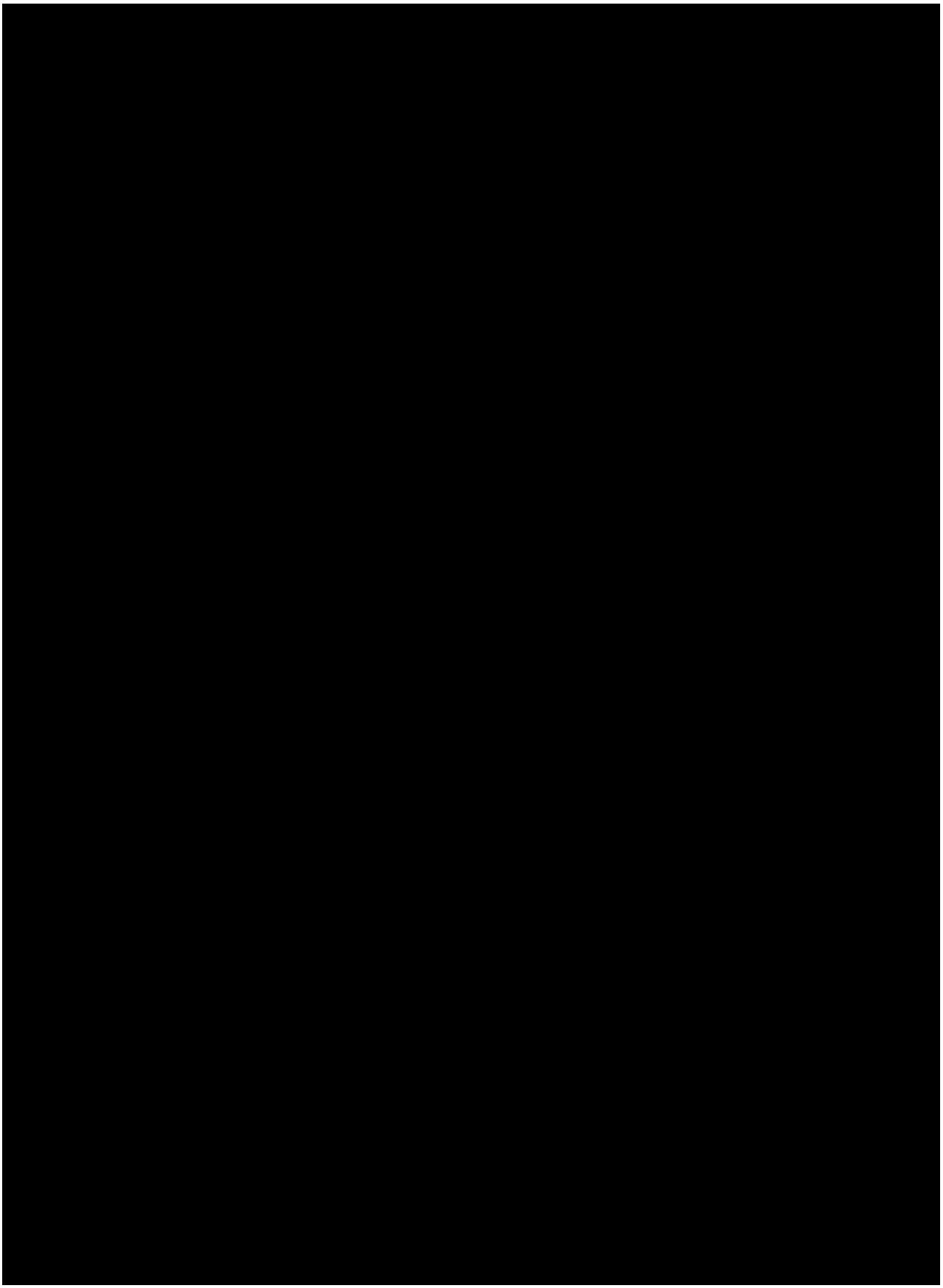
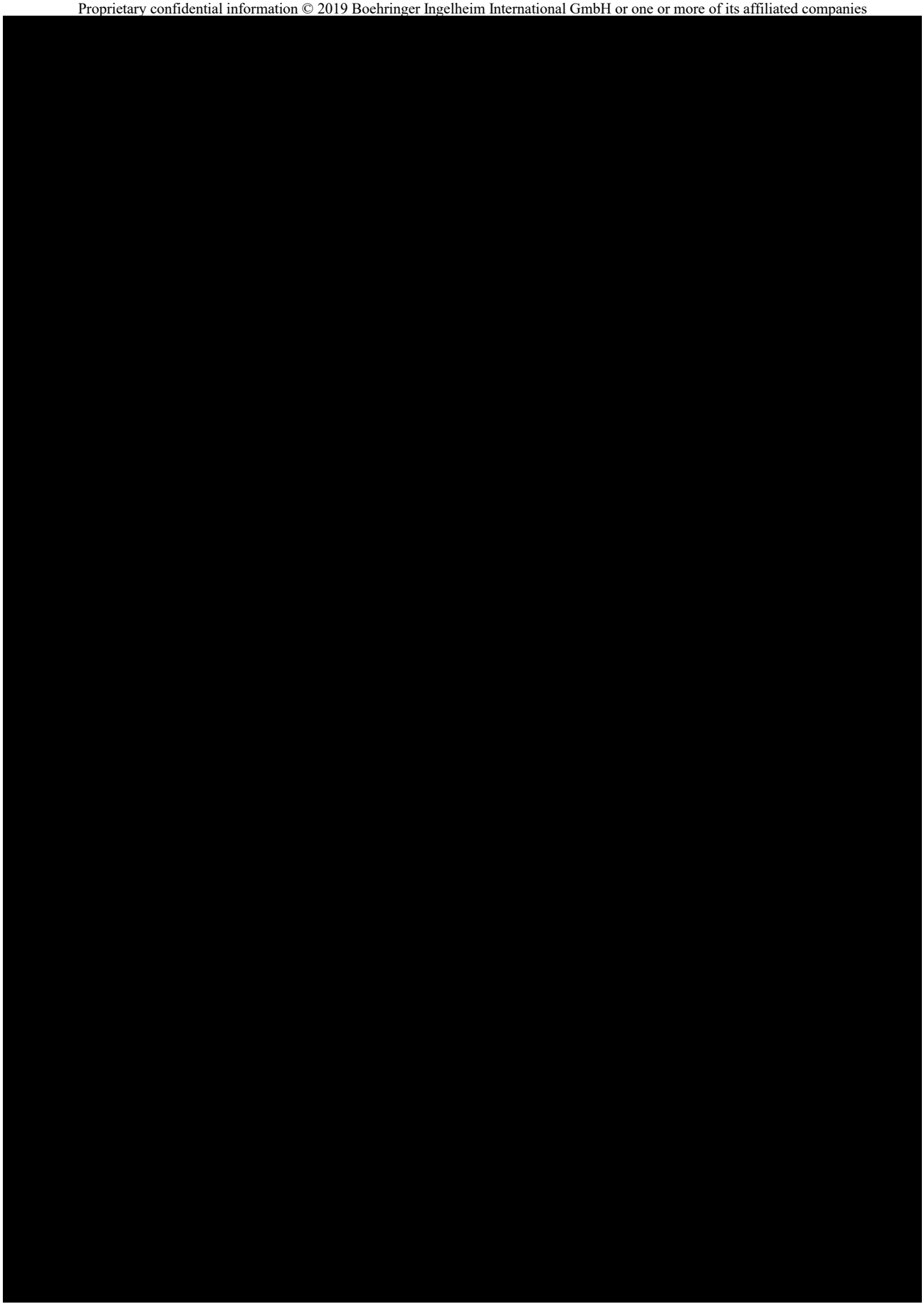
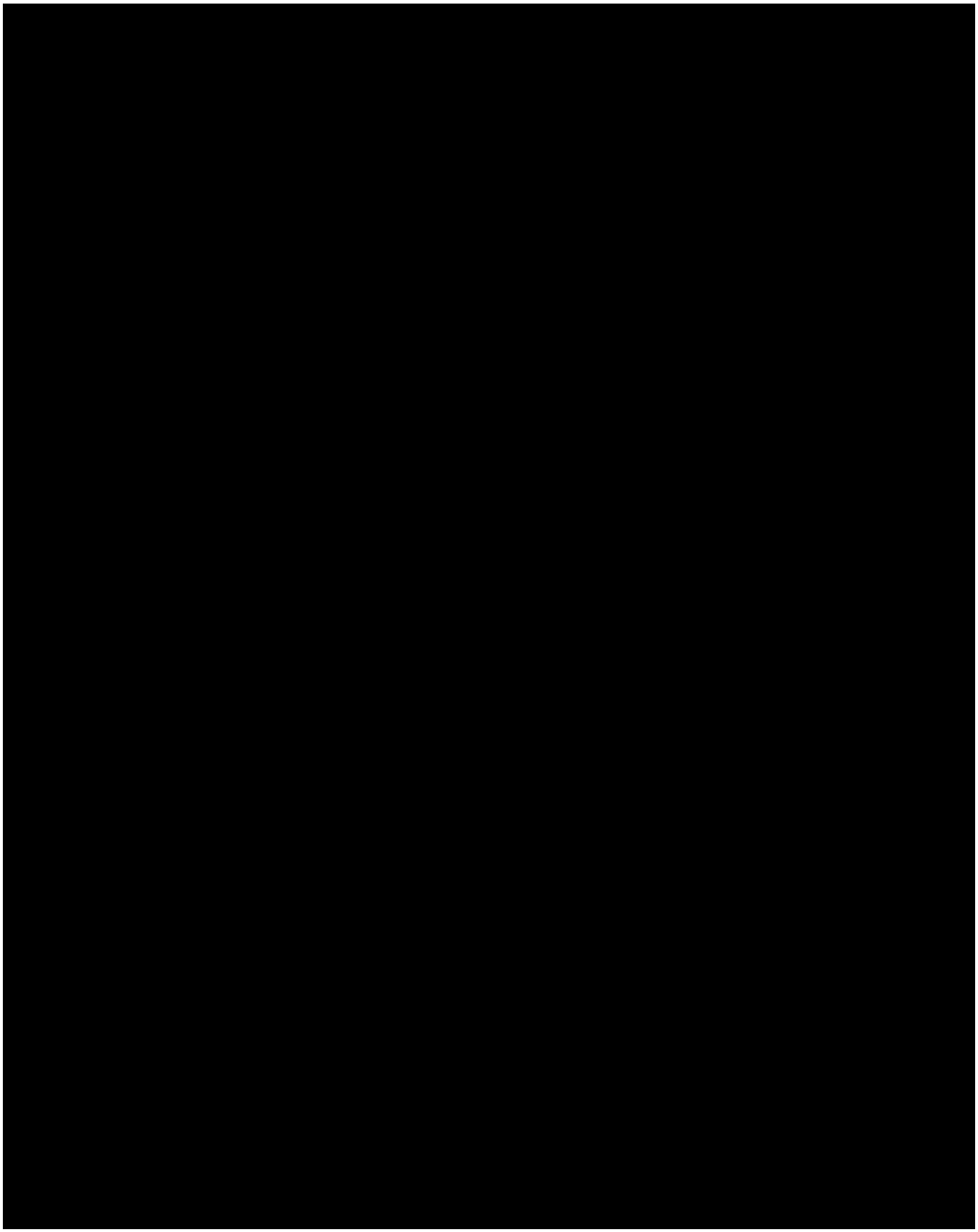


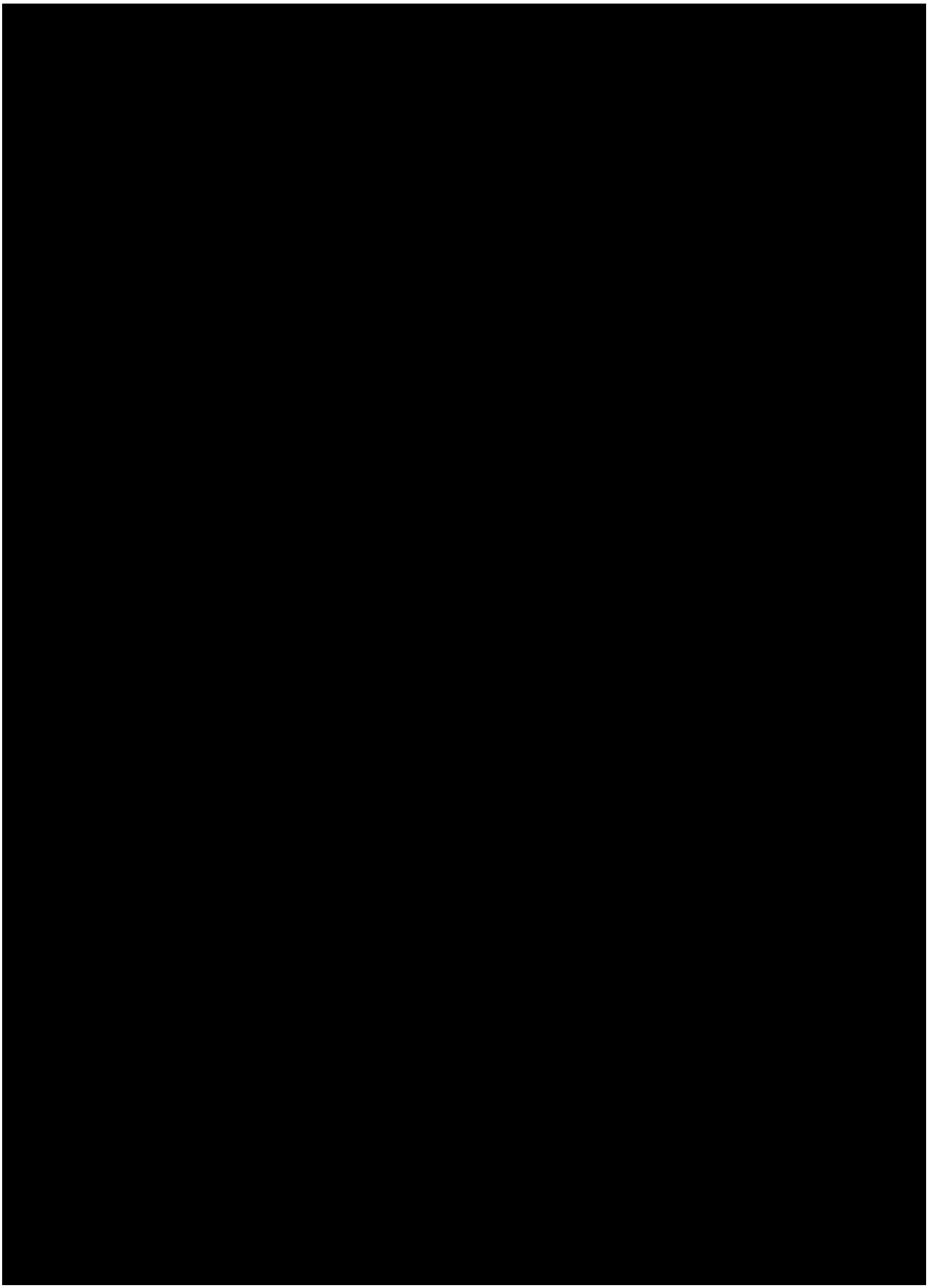


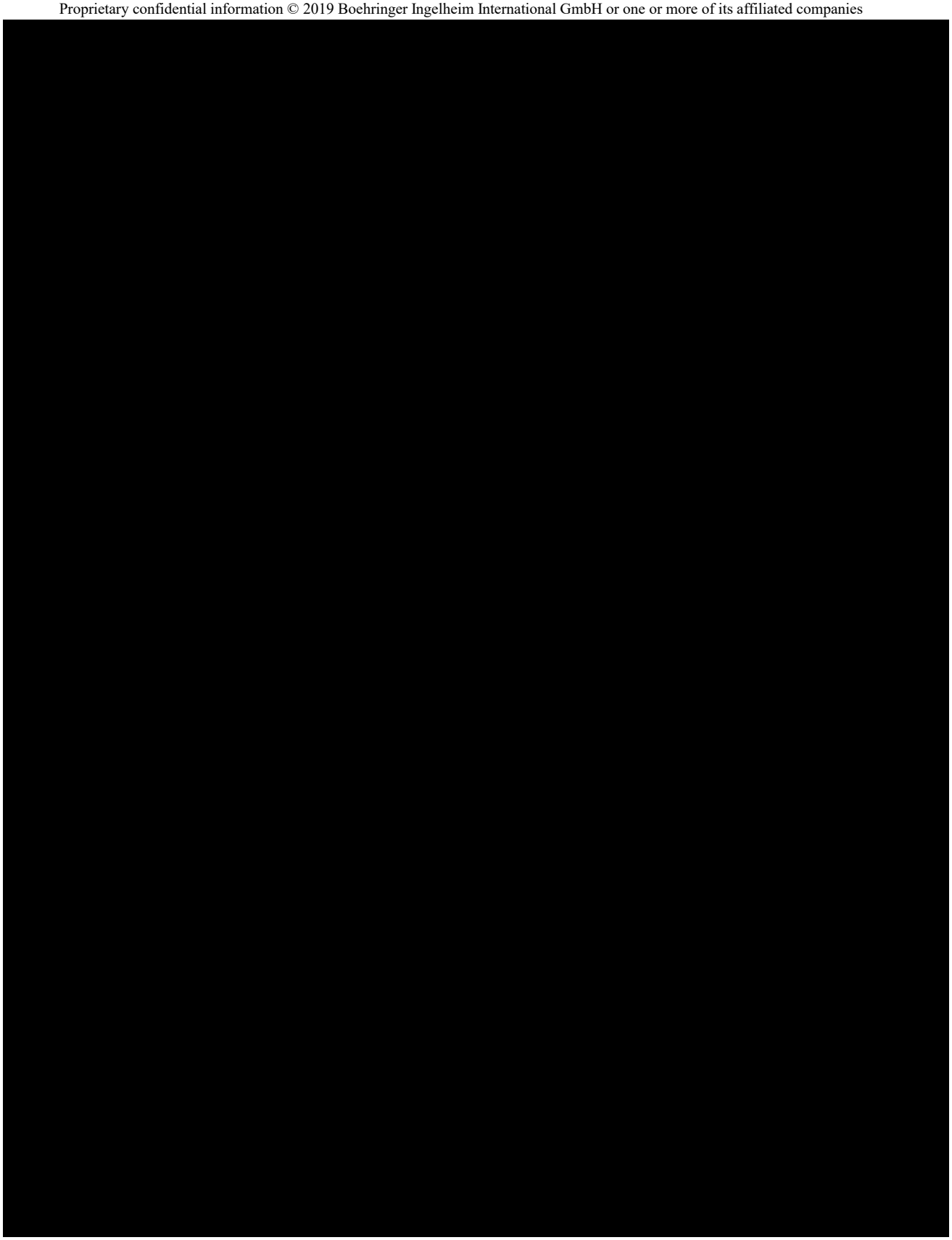


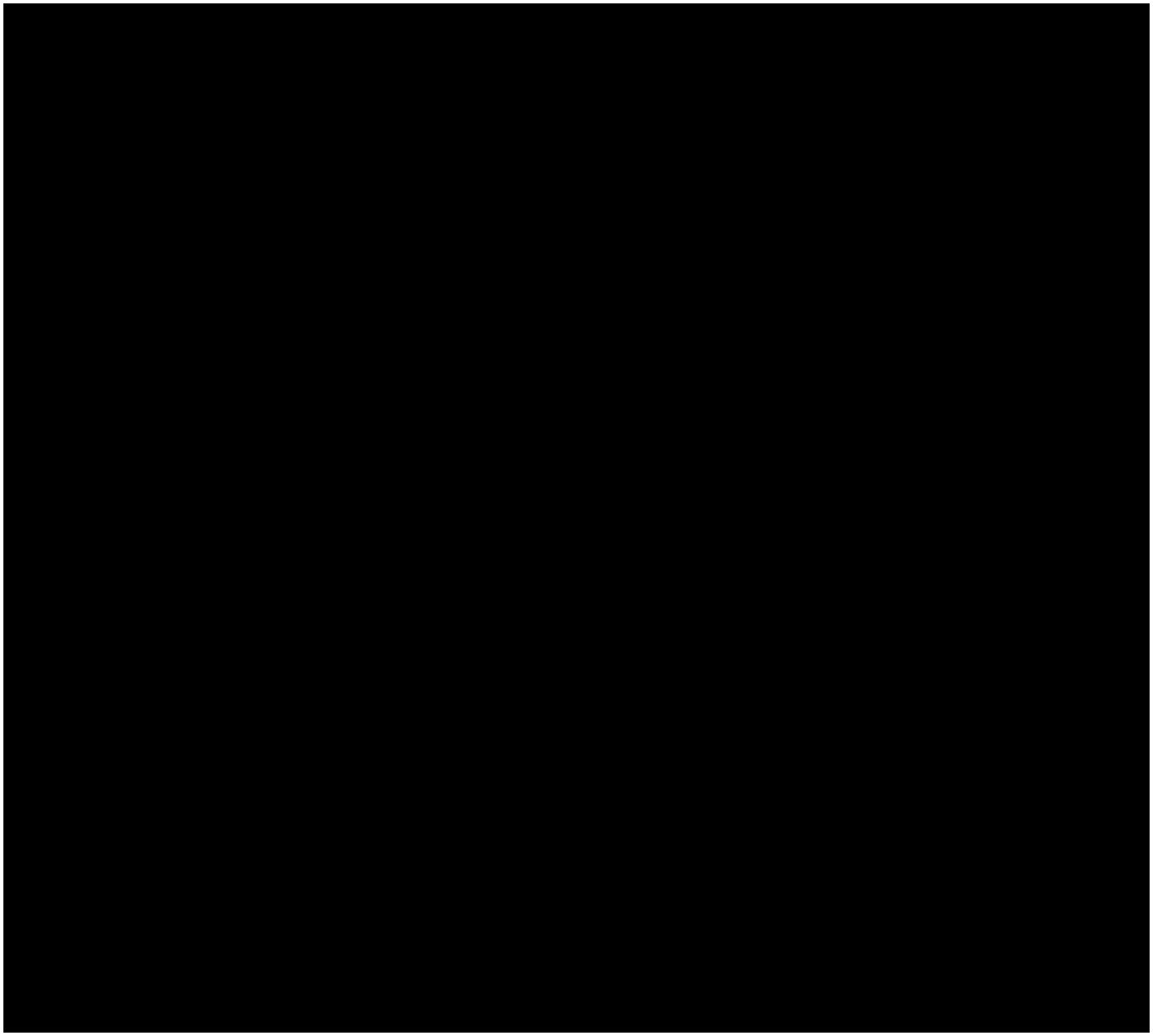


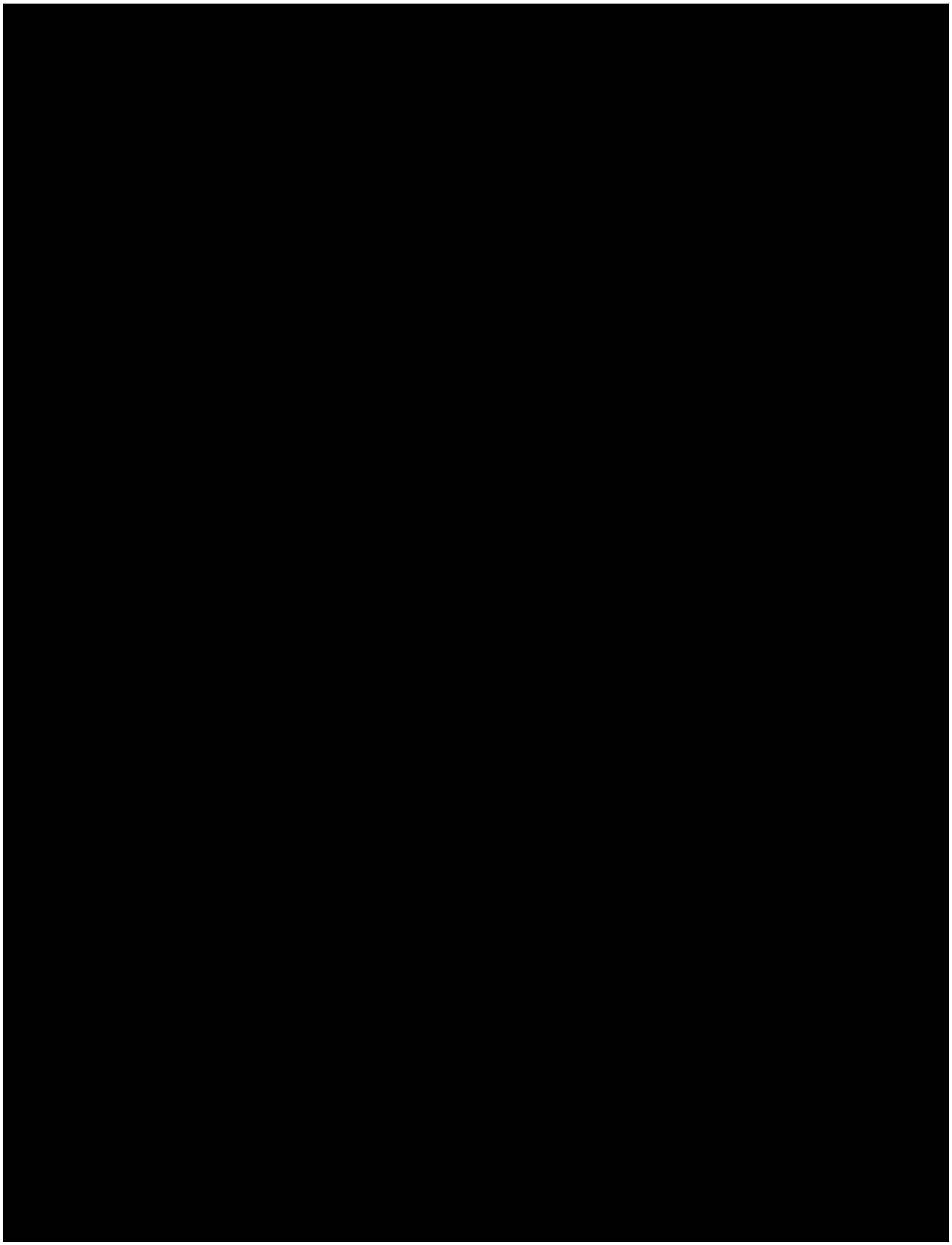


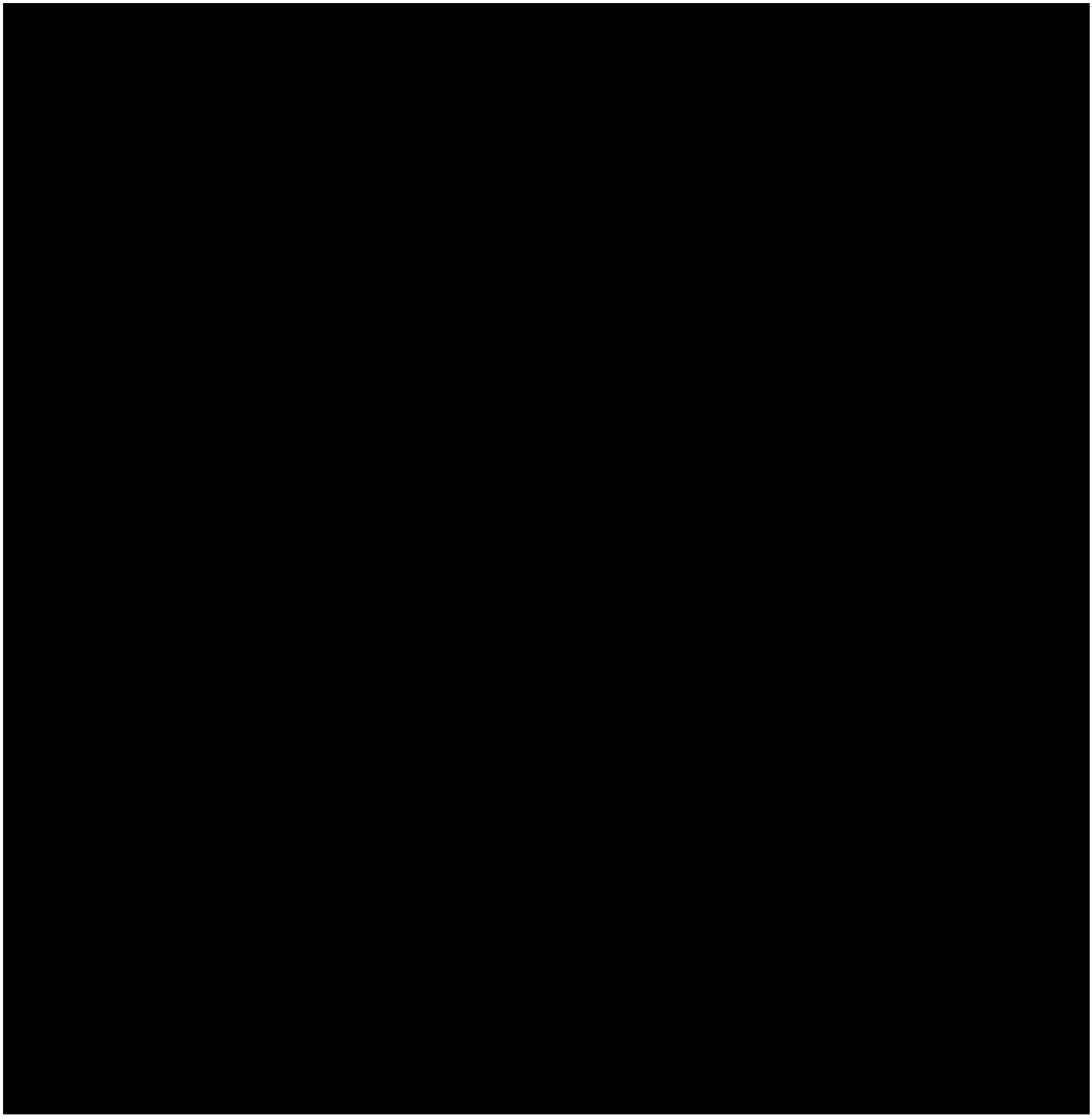


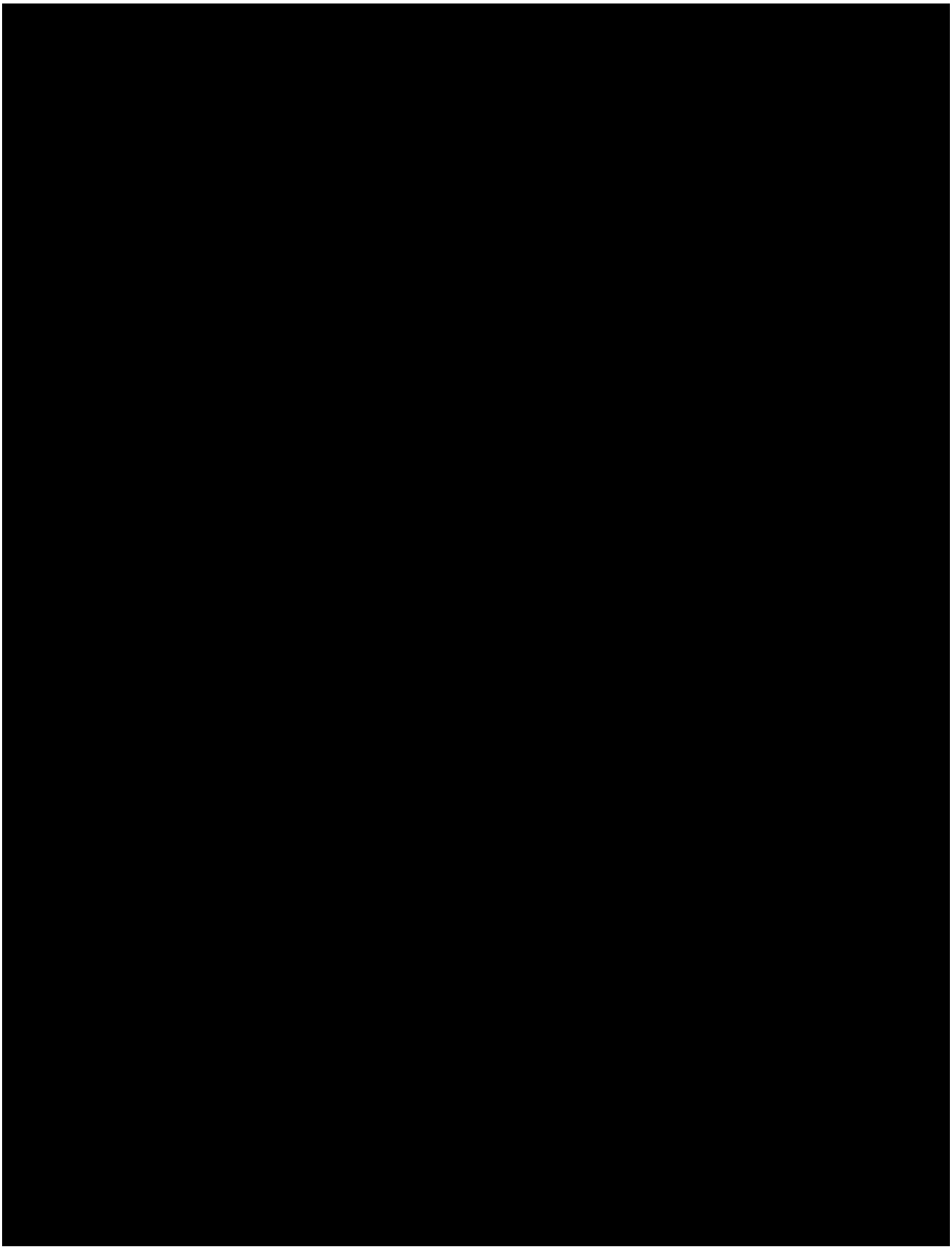












10.2 DIAGNOSIS OF ANAPHYLAXIS

Clinical Criteria for diagnosing anaphylaxis [R11-4890]

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; BP, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg +[2 x age] from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
	Asymptomatic, or transient Short duration (< 1 week) No change in life style No medication or OTC	Symptomatic Duration (1–2 weeks) Alter lifestyle occasionally Meds relieve. (may be prescription), Study drug continued	Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized<24h Temporary study drug discontinuation, or/and dose reduced	At risk of death Substantial disability, especially if permanent. Multiple meds Hospitalised >24h Study drug discontinued
A.ALLERGIC/IMMUNOLOGIC				
A1. Allergic reaction/ hypersensit-vity (including drug fever)	Transient rash; drug fever < 38° C, transient asymptomatic bronchospasm	Generalized urticaria responsive to meds; or drug fever > 38° C, or reversible bronchospasm	Symptomatic bronchospasm, requiring meds; symptomatic urticaria persisting with meds, allergy related oedema/angioedema	Anaphylaxis, laryngeal/ pharyngeal edema, requiring resuscitation
A2. Autoimmune reaction	Serologic or other evidence of autoimmune reaction but patient asymptomatic: all organ function normal and no treatment is required (e.g., vitiligo)	Evidence of autoimmune reaction involving a non-essential organ or functions, requiring treatment other than immunosuppressive drugs (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or toxicity requiring short term immunosuppressive treatment (e.g., transient colitis or anemia)	Causes major organ dysfunction, or progressive, not reversible, or requires long term administration of high dose immunosuppressive therapy
A3. Rhinitis (includes sneezing, nasal stuffiness, post nasal discharge)	Transient, non-prescription meds relieve	Prescription med required, slow	Corticosteroids or other prescription med. with persistent disabling symptoms such as impaired exercise tolerance	NA

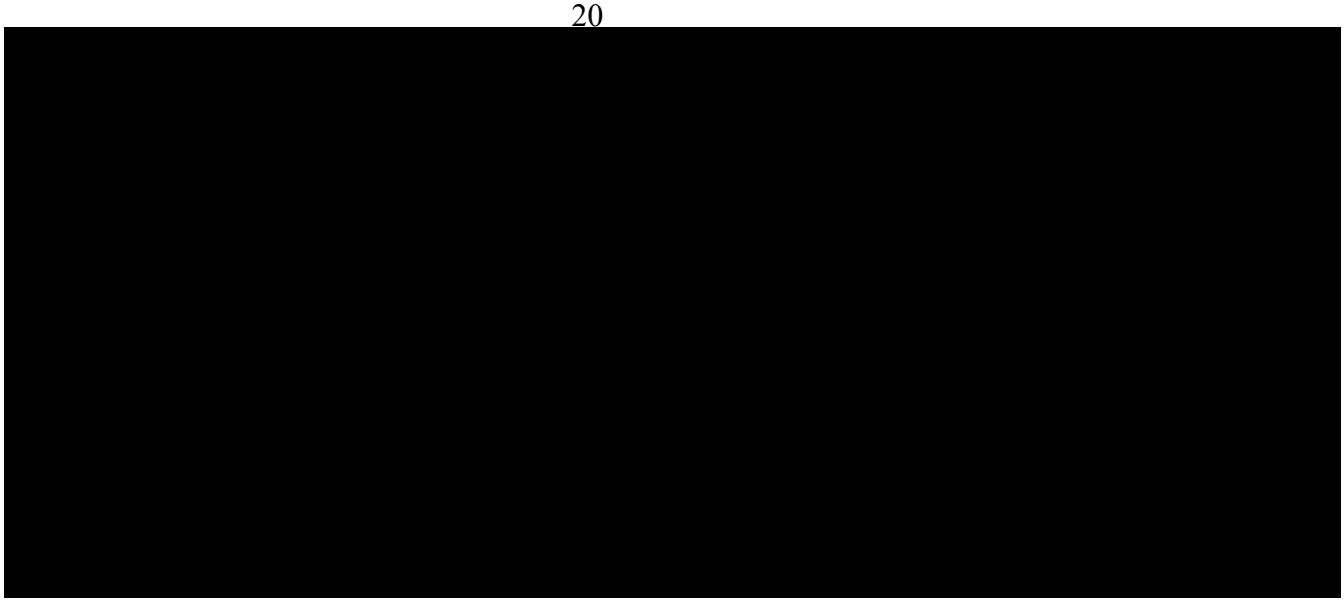
10.4 SMOKING HISTORY BASED ON CALCULATION OF PACK YEARS

Calculation of pack years based on number of cigarettes:

$$\text{Pack years} = \frac{\text{Number of cigarettes/day} \times \text{years of smoking}}{20}$$

The following equivalents for the tobacco content should be used for smokers other than cigarettes smokers (R08-5197):
One plain or filter cigarette = 1 gram of tobacco
One cigar = 5 grams of tobacco
One cheroot or cigarillo = 3 grams of tobacco
One gram of pipe tobacco = 1 gram of tobacco
Calculation of pack years based on tobacco contents:

$$\text{Pack years} = \frac{\text{Number of grams/day} \times \text{years of smoking}}{20}$$



11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

APPROVAL / SIGNATURE PAGE

Document Number: c18863881 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-version-01

Title: Multi-center, double-blind, randomised, placebo-controlled, phase IIb dose-finding study to evaluate efficacy and safety of different subcutaneous doses of BI 655130 in patients with moderate to severe Palmoplantar Pustulosis (PPP)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	04 Apr 2019 14:04 CEST
Approval-Team Member Medicine		04 Apr 2019 14:24 CEST
Author-Trial Clinical Pharmacokineticist		04 Apr 2019 15:32 CEST
Author-Trial Statistician		05 Apr 2019 05:26 CEST
Approval-Therapeutic Area [redacted]		05 Apr 2019 10:10 CEST
Verification-Paper Signature Completion		11 Apr 2019 14:53 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed