CLINICAL TRIAL PROTOCOL

	Document Number:	**c03185695-07**
EudraCT No.:	2014-004932-20	
BI Trial No.:	1311.14	
BI Investigational Product:	BI 655066	
Title:	A phase IIa, randomized, double-blind, placebo controlled, parallel group study to assess the safety and efficacy of subcutaneously administered BI 655066/ABBV-066 (risankizumab) as add-on therapy over 24 weeks in patients with severe persistent asthma.	
Brief Title:	Efficacy and safety of BI 655066/ ABBV-066 (risankizumab) in patients with severe persistent asthma.	
Clinical Phase:	IIa	
Trial Clinical Monitor:	Phone: Fax:	
Coordinating Investigator:	Phone:	
Status:	Final Protocol (revised protocol based on global amendment 5)	
Version and Date:	**Version: 6.0**	**Date: 17 August 2017**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		NA	
Name of active ingredient:		BI 655066	
Protocol date: 13 March 2015	**Trial number:** 1311.14		**Revision date:** 17 August 2017

Title of trial:	A phase IIa, randomized, double-blind, placebo controlled, parallel group study to assess the safety and efficacy of subcutaneously administered BI 655066/ABBV-066 (risankizumab) as add-on therapy over 24 weeks in patients with severe persistent asthma.
Coordinating Investigator	Phone:
Trial sites:	Multi-center, Multi-national
Clinical phase:	IIa
Objectives:	Evaluate efficacy and safety of BI 655066 (risankizumab) compared to placebo in patients with severe persistent asthma over a 24-week treatment period.
Methodology:	Randomized, double-blind, placebo-controlled, parallel-group study with risankizumab compared to placebo, administered subcutaneously in patients with severe persistent asthma.
No. of patients:	Approximately 200
total entered:	Approximately 200
each treatment:	Approximately 100
Diagnosis :	Severe persistent asthma
Main criteria for inclusion:	1. Male or female patients aged at least 18 years but not more than 75 years. 2. Pre-bronchodilator clinic measured FEV_1 of ≥40% and ≤85% of predicted normal at the screening visit. 3. A minimum of one year history of asthma diagnosed by a physician, and have FEV_1 reversibility as defined by an improvement in FEV1 ≥12% and an absolute change of at least 200 ml starting within 15 to 30 minutes after administration of 400 µg salbutamol (albuterol) via MDI. Reversibility testing is performed at the screening Visit (Visit 1B).

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		NA	
Name of active ingredient:		BI 655066	
Protocol date: 13 March 2015	**Trial number:** 1311.14		**Revision date:** 17 August 2017

If reversibility criteria are not met, the patient may still be randomized if there is:

- Documented evidence of reversibility with improvement in FEV_1 ≥12% above baseline and an absolute increase of at least 200 ml in the 2 years prior to Visit 2 (randomization visit)
  or
- Documented evidence of airway hyperresponsiveness (methacholine: PC20 of <8 mg/mL) in the 2 years prior to Visit 2 (randomization visit)
  or
- Documented evidence of airflow variability in clinic FEV1 ≥20% between two clinic visits documented in the 12 months prior to visit 2 (randomization visit).

If reversibility criteria are not met at Visit 1B and if any of the above historic data are not available, reversibility testing can be repeated up to twice during screening period at separate visits. For the first retest, 400 µg salbutamol via MDI should be used, and for the second retest, up to 800 µg salbutamol via MDI or 2.5 mg nebulized albuterol should be used. Reversibility testing must not occur on the day of randomization. Additional guidelines for reversibility testing can be found in Appendix 10.1.

4. Patients must be on at least medium dose inhaled corticosteroids and at least one other asthma controller medication for at least one year prior to the date of screening. Asthma therapy must have been documented and must be stable for at least 4 weeks prior to the date of screening.
5. Patients must have documented history of at least one of the following criteria: a) two or more severe asthma exacerbations in the last 12 months, or b) one severe asthma exacerbation in the last 12 months requiring hospitalization or emergency room visit, or c) one severe asthma exacerbation in the last 6 months not requiring hospitalization or emergency room visit, prior to the date of screening visit (Visit 1B). Patients must not have a severe asthma exacerbation in the 6 weeks prior to screening visit. Patients with only one severe asthma exacerbation in the last 6 months (category c, but not a or b) will be limited to approximately 25% of the total patient population.
6. Patients should be a non-smoker or ex-smoker who stopped smoking at least one year prior to screening. Ex-smokers must have a smoking history of less than 10-pack years

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		NA	
Name of active ingredient:		BI 655066	
Protocol date: 13 March 2015	**Trial number:** 1311.14		**Revision date:** 17 August 2017

Test product(s):	1 mL pre-filled syringe consisting of 90 mg/mL BI 655066
dose:	90 mg, once every 4 weeks: weeks 0, 4, 8, 12, 16, 20
mode of administration:	subcutaneous injection
Comparator products:	1 mL pre-filled syringe consisting of matching placebo
dose:	NA
mode of administration:	subcutaneous injection
Duration of treatment:	24 weeks (last dose at week 20)
Endpoints	**Primary efficacy endpoint:** Time to first asthma worsening during the planned 24-week treatment period. **Secondary efficacy endpoints:** 1. Annualized rate of asthma worsening during the planned 24-week treatment period 2. Annualized rate of severe asthma exacerbation during the planned 24-week treatment period 3. Weekly ACQ_5 score at week 24 4. Trough FEV_1 in-clinic change from baseline at week 24 5. Post-bronchodilator FEV_1 in-clinic change from baseline at week 24 6. Time to first severe asthma exacerbation during the planned 24-week treatment period 7. Time to first asthma worsening (alternative definition 1) during the planned 24-week treatment period
Safety criteria:	Physical examination, vital signs, safety labs, ECG, and adverse events.

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		NA	
Name of active ingredient:		BI 655066	
Protocol date: 13 March 2015	**Trial number:** 1311.14		**Revision date:** 17 August 2017

Statistical methods:	For analysis of time to event data for asthma worsening and severe asthma exacerbation, Cox's proportional hazard model will be used for obtaining hazard ratio estimations, confidence intervals, and p-values. For analysis of annualized rate of asthma worsening and severe asthma exacerbation, a negative binomial model accounting for exposure will be used. Weekly ACQ_5 score will be analyzed using an analysis of covariance (ANCOVA) model. A restricted maximum likelihood (REML) based mixed model repeated measures (MMRM) approach will be used to analyze mean change from baseline in trough and post-bronchodilator FEV_1 at week 24.

FLOW CHART A

	Screening Period[1]		Randomized Treatment Period[2]							Follow-up period[2]			
Visit	**1A**	**1B**	**2**	**3**	**4**	**5**	**6**	**7**	**8 (EOT)**	**9**	**10**	**11** 	**12 (EOO)**
Day	**-28 to -22**	**-21 ±6**	**1**	**29 ±3**	**57 ±3**	**85 ±3**	**113 ±3**	**141 ±3**	**169 ±3**	**197 ±4**	**225 ±4**	**253 ±4**	**281 ±4**
Week	**-4 to -3**	**-3**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**
Informed consent[3]	X												
Inclusion/Exclusion criteria	X	X	X										
Demographics	X												
Med. history/baseline conditions	X	X											
Review smoking status	X								X				X
Physical examination		X	X			X			X				X
Vital signs		X	X	X	X	X	X	X	X	X	X		X
Laboratory assessments[4]		X	X	X	X	X	X	X	X	X	X		X
Pregnancy test[5]		X	X	X	X	X	X	X	X	X	X		X
12-Lead resting ECG		X	X	X		X			X		X		X
Induced sputum[6]		X	X					X	X				X
Randomization			X										
FeNO measurements		X	X	X	X	X	X	X	X	X	X		X
Asthma worsening/exacerbation[7]		X	X	X	X	X	X	X	X	X	X		X
Dispense rescue medication[8]		X	X	X	X	X	X	X	X	X	X		
E-diary/PEF training[9]		X	X										
Dispense asthma monitor (E-diary)		X											
Download E-diary/PEF data			X	X	X	X	X	X	X	X	X		X
Medication washout check[10]		X	X	X	X	X	X	X	X	X	X		X
Asthma medication log review[11]			X	X	X	X	X	X	X	X	X	X	X
Pulmonary function tests[12]		X	X	X	X	X	X	X	X	X	X		X
Administer BI 655066 or placebo			X	X	X	X	X	X					
Adverse events	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
End of treatment period[16]									X				
End of observation period[17]													X

Footnotes:

1. Visit 1A and Visit 1B must occur on separate days and must be separated by at least one day. Visit 1A is the informed consent visit. Visit 1B is the screening visit and referred as such throughout the protocol. Screening period is from Visit 1B to Visit 2.
2. Randomized treatment period will be a total of 24 weeks even if visits within the treatment period are missed or rescheduled. Follow-up period will be a total of 16 weeks.
3. All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which includes medication washout requirements.

4. For tuberculosis screening, refer to Exclusion Criteria 16. Fasting is not required for routine labs.

5. Females (women of child bearing potential only): Serum pregnancy test will be done at the screening visit (Visit 1B). Urine pregnancy test (dipstick) will be done at the clinic at all other visits (except Visit 11) starting at Visit 2. If urine pregnancy test is positive, serum pregnancy test will be done to confirm pregnancy (see Section 6.1).
6. Sputum samples collected at the screening visit (Visit 1B) will be processed on the same day and the primary cytospin slides should be shipped on the same day or no later than the next business day. The central reader will complete the assessment and communicate to the site on patient eligibility (expected to take 5 to 7 business days). Sputum samples from visits other than the screening visit must be processed on the same day and shipped. Sputum induction must be performed only after ECG measurements (if applicable at that visit), FeNO measurements, and PFTs are completed.
7. Asthma worsening check is done by reviewing the downloaded data from the E-diary and also verifying with the patient if there has been any change in asthma symptoms since the last clinic visit.
8. At each clinic visit, starting Visit 1B, study coordinator/nurse must ensure that the patient has access to sufficient rescue medication until the next scheduled clinic visit. The amount of rescue medication needed for the next 4 weeks can be estimated based on the use of rescue medication in the past 4 weeks. Rescue medication should be salbutamol (albuterol) provided by the Sponsor.
9. Patients must be trained in the use of E-diary and PEF measurements at Visit 1B, and 2. If patients are non-compliant in the use of E-diary or if they need more training in PEF measurements, additional training must be provided during clinic visits in the entire duration of the study. Proof of additional training should be documented.
10. Medication washout check is required for the PFTs. Medication washout checklist provided in the ISF must be completed at each visit.
11. Patients will enter any changes in asthma medications (excluding rescue medication) in a medication log provided to them at each visit. At each scheduled visit, the medication log should be collected, reviewed, and a new medication log should be dispensed. At each visit, asthma medication log should be checked to see if patients met any of the asthma exacerbation criteria defined in the protocol.
12. All patients will undergo reversibility testing at Visit 1B (see Appendix 10.1 and Inclusion Criteria 4). Pre-and post-bronchodilator PFTs will also be performed on other clinic visit days (Visits 2 to 12). PFTs must be completed only after ECG measurements (if applicable at that visit), and FeNO measurements are completed. PFT measurements must be completed before sputum induction (if applicable at that visit). PFT measurements should be started in the mornings between 6:00 am and 10:00 am. Please review additional requirements in Section 5.2.

16. If a patient permanently discontinues study medication before the last scheduled dose (Week 20, Visit 7), an early EOT visit should be scheduled approx. 4 weeks after the last dose, and all procedures listed under Visit 8 should be completed. At the completion of the EOT, patient will enter the follow-up period and complete all 4 follow-up visits (Visits 9 to 12, Visit 11 is a phone visit). During the phone call at Visit 11, any adverse events and concomitant therapy will be checked. Any change in asthma medication entered in the asthma medication log will be verified. If the patient is unable to continue all or part of the follow-up period, one additional visit should be scheduled 16 weeks after the EOT.
17. If a patient permanently discontinues from the study during the follow-up period, an EOO visit should be scheduled on the originally scheduled EOO visit date (week 40).

TABLE OF CONTENTS

ABBREVIATIONS

ACQ	Asthma Control Questionnaire
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
BCG	Bacille Calmette-Guerin
BI	Boehringer Ingelheim
BID	Bis in die (twice daily)
CFC	Chlorofluorocarbon
CRO	Contract Research Organization
CTP	Clinical Trial Protocol
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiography
eCRF	Electronic Case Report Form
E-diary	Electronic Diary
EOO	End of Observation
EOT	End of Treatment
ERS	European Respiratory Society
ERT	eResearch Technology
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FeNO	Fractional exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
HFA	Hydrofluroalkane
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
IL	Interleukin
i.m.	Intra-muscular
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File

i.v.	intravenous
Kg	Kilograms
mAB	Monoclonal Antibody
MACE	Major Adverse Cardiovascular Event
MedDRA	Medical Dictionary for Drug Regulatory Activities
Mg	Milligrams
MMRM	Mixed Model Repeated Measures
NA	Not Applicable
OCS	Oral corticosteroids
PEF	Peak Expiratory Flow
PFT	Pulmonary Function Test
QD	Quaque die (once daily)
RDC	Remote Data Capture
REML	Restricted Maximum Likelihood
REP	Residual Effect Period
SAE	Serious Adverse Event
s.c.	subcutaneous
SOP	Standard Operating Procedure
TB	Tuberculosis
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit Normal

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Asthma is a common chronic disease with an estimated 300 million affected individuals. The global prevalence ranges from 1 to 18% of the population in different countries. Asthma is the most common chronic disease in childhood, affecting an estimated 6 million children, and it is a common cause of hospitalization for children in the United States. The World Health Organization has estimated that 15 million disability-adjusted life years (DALYs) are lost annually due to asthma, representing 1% of the total global disease burden. Annual worldwide deaths from asthma have been estimated at 250,000.

The clinical features of asthma include recurrent episodes of wheezing, breathlessness, chest tightness, and cough. The physiologic characteristics are derived from inflammation of the airway mucosa, often involving the infiltration of eosinophils or neutrophils.

Severe asthma represents a high unmet medical need. Despite representing a minority of all asthma patients, severe asthma patients drive the majority of costs and healthcare utilization in asthma. Furthermore, targeting specific clinical phenotypes/endotypes through scientifically rational design is expected to be more successful than broad development in severe asthma since the phenotypic heterogeneity is likely driven by fundamental differences in underlying mechanisms. These clinical phenotypes may show specific pathophysiological associations leading to classifications of endotypes (R14-4225). Accompanying this growing understanding of the diverse nature of asthma is the realization that there are also a diverse range of treatment responses dependent on the underlying nature of an individual's disease. This naturally leads to the concept of the personalized therapy regimes for patients with severe asthma that better target their individual disease. Omalizumab (XOLAIR®) is the first biological asthma treatment to meet that need in patients with severe allergic asthma (R14-2101). Numerous potential biological agents are in development that show promise in targeting patients with particular disease phenotypes / endotypes such as mepolizumab (R14-4224), lebrikizumab (R14-4226), and dupilumab (R14-4232). These approaches have demonstrated clinical benefit in various subsets of asthma, although these agents demonstrated questionable clinical utility in broad asthma when tested in a wider population. The success of these therapies in defined subsets of asthma highlights the need to further refine treating patients in asthma. To date there has been no therapy developed in successfully addressing patients with the known clinical phenotype of neutrophilic asthma despite the fact that this phenotype represents a significant portion of severe asthma.

Cellular heterogeneity has been observed in patients with severe asthma (R14-4187, R14-4184). A number of studies have reported increased numbers of neutrophils in the airways in patients with severe asthma (P03-08188, P99-03282), asthma exacerbations (R14-4216), life threatening severe asthma exacerbations (R98-1426), and fatal asthma (R14-4217). However, a causal association between neutrophils and asthma severity has been difficult to establish. It is not clear if the increased neutrophils are an indicator of a specific inflammatory pattern, a marker of unrecognized airway infection (R14-4215), or the consequence of high doses of corticosteroids used by these patients. Assuming

neutrophilic disease is a targetable clinical entity, a novel biological controller medication in neutrophilic asthma offers a unique opportunity as no other therapy is approved or is near approval in this known clinical phenotype of severe asthma.

The role of IL-23 in maintaining Th-17 cells that secrete the pro-inflammatory cytokines IL-17A and F, IL-22, and IFNγ has increasingly been implicated in chronic inflammatory diseases. The IL-23/Th17 axis is reported to play an important role in the pathogenesis of severe asthma (R14-4183, R14-4182). IL-17A is upstream of the known neutrophil attracting chemokines (e.g. IL-8) which promote a known neutrophilic clinical phenotype described as steroid resistant. Recently induced sputum neutrophil cell counts have demonstrated high predictive value of severe asthma in unbiased clustering approaches of asthma (R14-4315). It is enticing to propose patients with high levels of sputum neutrophils, as a responsive patient population to anti-IL-23 therapy, and testing this hypothesis is a primary aim of the current study. Additionally a readily accessible (e.g. serum) diagnostic biomarker or endotype will likely be required to identify a target population who benefit from use of anti-IL-23 in severe asthma in further clinical studies with this antibody, given the known challenges employing induced sputum assessments in large clinical studies.

This study employs asthma worsening as a more frequent event amenable to measurement in exploratory phase IIa studies of limited size and duration. The ultimate key clinical aim of the program is to reduce the annual rate of exacerbations in patients with severe persistent asthma. Additionally, improvement in symptoms and symptom control is also of clinical importance for severe persistent asthma.

1.2 DRUG PROFILE

BI 655066 (risankizumab) is a fully human monoclonal antibody (mAb) of the IgG1 subclass directed towards IL-23p19. The antibody has been engineered to reduce Fcγ receptor and complement binding and potential charge heterogeneity. Risankizumab binds with high affinity to human IL-23 and inhibits IL-23 stimulated IL-17 production

For this phase 2 trial, risankizumab will be supplied as prefilled syringes containing 1 mL of a 90 mg/mL solution for subcutaneous administration.

1.2.1 General Pharmacology

The role of IL-23 in maintaining Th-17 cells that secrete the pro-inflammatory cytokines IL-17A and F, IL-22, and IFNγ has increasingly been implicated in chronic inflammatory diseases. In addition to psoriasis, there is evidence that the IL-23/Th17 axis plays an important role in the pathogenesis of severe asthma (R14-4183, R14-4182). IL-23 has been shown to be upregulated in pediatric patients with asthma, and negatively correlated with FEV_1 (R14-2349). In animal models of airway hyperreactivity inhibition of IL-23p19 demonstrated a protective effect, and interestingly, blockade of IL-23 unexpectedly reduces the classical Th2 cytokines IL-4, IL-5, IL-13 and IgE in preclinical challenge pharmacology models (R14-2348). More recent reports indicate that IL-21 is essential in the differentiation of Th2 cells able to secrete Th17 cytokines, and that these

cells are specifically pathogenic in severe asthma (P14-14612). Although these pluripotent Th2 cells lack the IL-23 receptor, IL-21 is derived from Th17 cells under the control of IL-23. Targeting p19 has a theoretical advantage in asthma over targeting the p40 subunit of IL-23 in that suppression of IL-12 may be avoided. Although IL-12 suppression has been associated with risk of malignancy in IL-12 knock-out mice, no increased cancer rates have been reported in patients receiving IL-23p40 antibodies for psoriasis over a five year period (R13-3518). Data suggest that a putative risk of infection through suppression of the Th1 pathways and IL-23 is possible, and IL-23 has been shown to play a role in immune response against specific pathogens like Klebsiella and Salmonella (R11-1199, R11-1200). However individuals with genetic perturbations in the IL-12/ IL-23 signaling pathway are not broadly immune compromised. Targeting IL-23p19 that is devoid of IL-12 inhibition could be a preferable approach for asthma as blocking IL-12 could theoretically cause perturbation of the Th1/Th2 balance towards Th2 disease with negative clinical consequences for a major proportion of asthmatics. As an example, TLR 9 agonists demonstrated clinical benefit in asthma by perturbing the Th1/Th2 balance by activating Th1 pathways. The approach of targeting IL-23, the decisive cytokine in Th17 cell propagation, seems to generate a broader suppression of inflammatory pathways including not only Th17 cells, but also Th2 responses in preclinical models, and therefore may be more advantageous than targeting the downstream IL-17 receptor which is a concept currently being clinically tested in severe persistent asthma.

1.2.2 Toxicology

In summary, the toxicology data suggest risankizumab can be safely administered to humans, as supported by chronic administration to monkeys for up to 26 weeks.

1.2.3 Clinical Experience

Risankizumab has been evaluated in a completed phase I study where risankizumab was studied in a single rising dose trial (1311.1 (U12-3066-01) assessing the safety, tolerability, efficacy, PK and PD in male and female patients with moderate to severe psoriasis.

Additionally the 1311.2 (c01651292-07), 1311.6 (c01651690-12), and 1311.8 (c02190287-17) studies evaluating 12-52 week exposure of risankizumab in psoriasis, Crohn's disease, and ankylosing spondylitis respectively are ongoing. The ongoing review of the safety information from these studies taken together with the 12-week unblinded safety data from the 1311.2 study in psoriasis enrolling approximately 120 patients treated with risankizumab was used by an independent Data Monitoring Committee (DMC) to endorse the decision to start this study (1311.14) in patients with severe persistent asthma.

Of interest for potential therapeutic use in asthma, a case report in the literature suggestive of treatment benefit for patients with concomitant asthma and psoriasis whose asthma control is reported to benefit from treatment with STELARA® (R15-0678), but it will be important to evaluate treatment effects of risankizumab in an adequate and well controlled study to explore these anecdotal observations.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Despite the anticipated approval of new therapies targeting Th2 or eosinophil high asthma that will address an important part of the unmet medical need in severe asthma, additional therapy is needed to address the remaining unmet need given the high degree of heterogeneity in asthma, leaving a significant proportion of severe asthma unaddressed.

This study would provide the initial proof of concept for further clinical trials in severe asthma.

2.2 TRIAL OBJECTIVES

The objectives of this trial are primarily to evaluate the efficacy and safety of risankizumab as compared to placebo over a 24-week treatment period in severe asthma patients. The primary endpoint is time to first asthma worsening during the planned 24-week treatment period for active vs. placebo treated patients on top of standard of care therapy. Additional secondary analyses will include time to first severe asthma exacerbation, frequency of asthma worsening and severe asthma exacerbation, effects on trough and post-bronchodilator lung function (FEV_1), and evaluation whether symptomatic benefit can be derived from treatment with risankizumab as compared to placebo treated patients.

2.3 BENEFIT - RISK ASSESSMENT

Severe persistent asthmatics, especially patients who experience frequent exacerbations are associated with substantial morbidity, mortality, and health-care utilization. Recurrent asthma exacerbations are a major problem in severe asthma patients and can predominate in a subgroup characterized by neutrophilic airway inflammation. Neutrophilic asthma may be

specifically non-responsive to corticosteroids. The highest medical value is reduction in exacerbation and hospitalization frequency, and a further improvement in the control of symptoms. In the patient population taking oral corticosteroids (OCS) frequently or continuously, reduction or elimination of steroid use would also mitigate the toxicity associated with these therapies. Assuming neutrophilic inflammation is relevant for severe asthma, neutrophilic severe asthma is currently unaddressed clinically, and it represents both an opportunity of a new therapeutic target population and the challenge of identifying patients likely to respond to a specific therapy. Participation in this study may help to generate future benefit for larger groups of patients with asthma if risankizumab proves to be beneficial in treating this disease.

Although patients enrolled in this study will maintain their standard of care therapy, they will have a 50% chance to receive placebo. Beyond close monitoring of asthma treatment, asthma symptoms, clinical laboratories, and clinical evaluations there is no additional potential benefit for these patients. The decision to include a placebo group is essential for the evaluation of a treatment effect of risankizumab in severe asthma, and all patients are maintained on standard of care therapy.

Clinical data is available from a single rising dose, double-blind, placebo controlled trial with risankizumab in patients with moderate to severe psoriasis. In these studies, risankizumab was generally well tolerated, and there were no clear relationships between the overall frequency of AE and treatment groups. Additional unblinded data, including approximately 120 patients with 12-week exposure to risankizumab from the ongoing phase II study in psoriasis (c01651292-07) was made available for DMC review and a favorable decision was made to initiate this study with severe asthma patients.

As with any immune modulating agent, risankizumab may impair immune function resulting in a risk of infection. This will be monitored by collection of any AEs during the treatment and observation periods. Patients with clinically important active infection will not be included in the study.

The role of IL-23 in tumor immunity is not well established at this time, but an increased risk of cancer from an IL-23 antagonist, though considered small, cannot be excluded.

Major adverse cardiovascular events (MACE), including myocardial infarction, cerebrovascular accident, and cardiovascular death, may be associated with the anti-IL-12/23 agents, ustekinumab and briakinumab in patients with psoriasis. The causal relationship of MACE to treatment with these agents is unclear. The overall risk of MACE in the present study is considered to be low. Patients will have monitoring of electrocardiography (ECG) and vital signs.

Local reactions to s.c administered biologic agents are uncommon, and are usually limited to redness, swelling or induration at the injection site. Although rare, a potential for drug-induced liver injury is under constant surveillance by Sponsors and regulators as in all clinical studies at this stage of clinical development, with no specific increase in risk identified for this antibody. Therefore, this study will require timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety.

High unmet medical need exists in severe asthma, and the vast majority of mechanisms in development focus on Th2 high patients. However, a significant number of severe asthmatics remain unaddressed by current development programs. The exploration of additional mechanisms may provide benefit on top of standard of care. In conclusion, the benefit-risk profile is considered appropriate for this stage of clinical development. In order to detect any safety signals as early as possible, an independent DMC will monitor this study and all other studies where patients are receiving risankizumab.

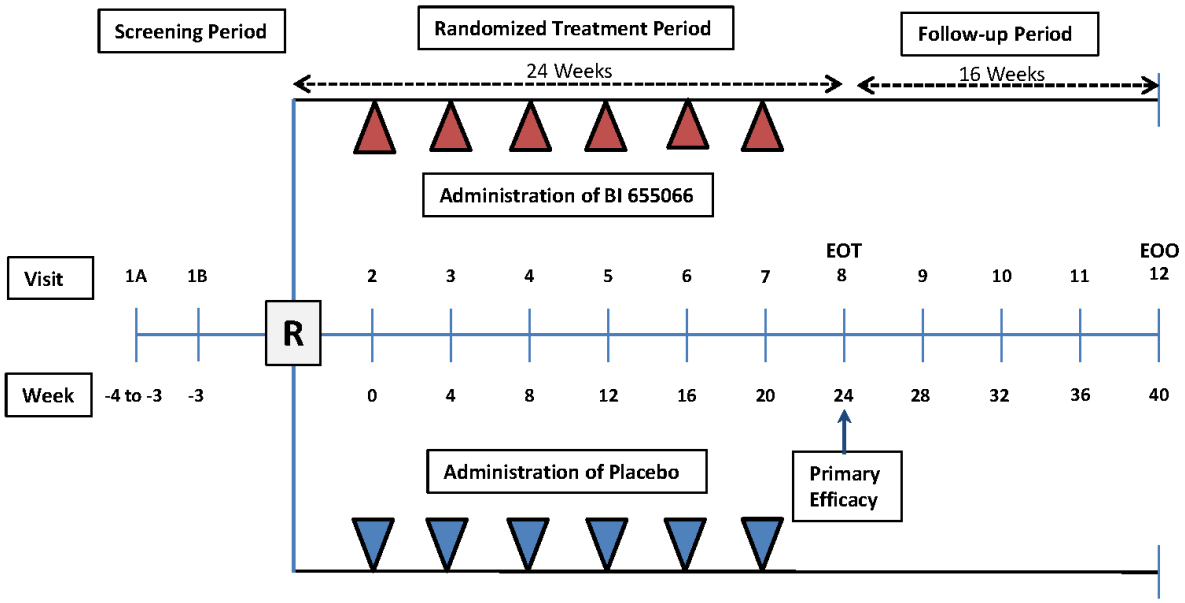
3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a randomized, double-blind, placebo controlled, parallel group, multicenter study to assess the efficacy and safety of risankizumab, an IL-23p19 monoclonal antibody, compared to placebo, in patients with severe persistent asthma. Risankizumab will be administered via subcutaneous injection once every 4 weeks (Week 0, 4, 8, 12, 16, and 20) during the 24-week treatment period. The treatment period will be followed by a 16-week follow-up period. An overview of the trial design is presented in Figure 3.1: 1.

After signing the informed consent at the initial visit, patients will enter a screening period which should last for up to 4 weeks unless extension of the screening period is necessary under certain circumstances (see Section 6.1). Patients who qualify to participate in the study will be randomized into a 24-week treatment period in which they will receive either 90 mg risankizumab or a matching placebo. Patients will be evaluated for an additional 16 weeks following completion of the randomized treatment period. An interim analysis is planned when the last patient completes the 24-week treatment period (see Section 7.4). Treatment groups will remain blinded until the 16-week follow-up period is completed, and trial database is locked.

Figure 3.1: 1 Overview of Trial Design



Visit procedures will be performed as shown in Flow Chart A. All patients will receive an asthma monitor/electronic diary (E-diary) which has an electronic peak flow meter and an electronic diary. The asthma monitor will be dispensed at the screening visit (Visit 1B), and patients will be required to use the device twice daily (morning and evening) to answer questions related to rescue medication use, asthma controller medication use, and also

measure Peak Expiratory Flow (PEF). In addition, patients will complete the first five questions in the Asthma Control Questionnaire (ACQ_5) in the E-diary once a week.

Participation will be blindly stratified by the Interactive Response Technology (IRT) system. The number of patients with a history of only one severe asthma exacerbation in the last 6 months without hospitalization or emergency room visit is limited to approximately 25% of the randomized patients (see Section 3.3.2).

Pre- and post-bronchodilator pulmonary function tests (PFTs) will be performed at all visits on all patients starting at the screening visit. At the screening visit, the pre- and post-bronchodilator measurements will be used to determine reversibility.

Fractional exhaled Nitric Oxide (FeNO) measurements will be done on all patients at all visits starting at the screening visit.

Adverse events will be documented throughout the trial, i.e., starting with the informed consent to the last clinic visit in the follow-up period. For further details, please refer to the safety Section 5.3.7.

All trial related documentation will be stored by Boehringer Ingelheim (BI) in the Trial Master File. Study relevant documentation at the study sites will be filed in the ISF.

3.1.1 Administrative structure of the trial

A DMC, independent of the Sponsor will be established to assess the progress of the clinical trial, including an unblinded safety and efficacy assessment at intervals specified in the DMC charter. Measures are in place to ensure blinding of the Sponsor and all other trial participants. The DMC can recommend to the Sponsor whether to continue, modify, or stop the trial. The tasks and responsibilities of the DMC will be specified in a charter prior to the initiation of the study. The DMC will maintain written records of all its meetings.

The trial is sponsored by AbbVie in the USA and Boehringer Ingelheim (BI) ex-US. AbbVie/Boehringer Ingelheim has appointed a Trial Clinical Monitor, 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,
- order the materials as needed for the trial,
- ensure appropriate training of Local Clinical Monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

Data management and statistical evaluation will be done by BI according to BI SOPs. Tasks and functions assigned in order to organize, manage, and evaluate the trial will be defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A Coordinating Investigator will be nominated and will be responsible to coordinate Investigators at different centres participating in this multicenter trial. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating Investigators and other important participants, including their curricula vitae, will be filed in Trial Master File.

Investigators participating in this study will be pulmonologists, allergists, or physicians who have adequate experience with respiratory clinical studies.

An external vendor, eResearch Technology, Inc. (ERT), will be contracted to manage centralized spirometry. Spirometry, asthma monitor/E-diary (AM3G), ECG, and FeNO measurements are integrated in the Masterscope® CT platform provided by ERT. Each site participating in this study will receive a Masterscope®. Instructions and procedure manuals will be provided in the ISF.

A central laboratory will be responsible for performing the safety laboratory testing (Section 5.3.3), and will also provide the logistics in the receipt, storage, and shipment of other biological samples collected from patients in this study.

A central vendor will be responsible to provide training to all study sites on sputum induction and processing. This vendor will also function as a central reader to assess the sputum

samples for quality, and also characterize them for cellular phenotypes. A sputum induction and processing manual will be provided to all study sites and a copy will be placed in the ISF.

An IRT system from an external vendor will be used for randomization of treatment groups. Trial medication supply and re-supplies will be managed by the IRT. The ability to unblind the treatment group will be available via the IRT system. A copy of the IRT manual will be provided in the ISF.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

The trial design allows the comparison of risankizumab and placebo, on the time to first asthma worsening in patients with severe asthma. The patient population in this study is expected to have frequent episodes of asthma worsening and 1-2 asthma exacerbations per year despite maximal treatment with the current standard of care. All patients in the study will be on asthma maintenance therapy with stable doses of anti-inflammatory medications which must include at least a medium dose inhaled corticosteroid and at least one other asthma controller medication, during the entire screening, treatment, and follow-up periods. Rescue medication (salbutamol/albuterol) will be provided to all patients for as-needed use throughout the course of the trial.

Approximately equal numbers of patients will be randomized to each treatment group. Randomization will be stratified with respect to oral corticosteroid use at baseline, and history of severe asthma exacerbation.

The data collected in this controlled, double-blind, randomized, placebo-controlled study will provide useful information on the efficacy and safety of risankizumab.

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of patients of either sex with the diagnosis of severe persistent asthma will be enrolled in the study to ensure that approximately 200 patients are randomized: approximately 100 in the active treatment arm and 100 in the placebo arm. Approximately 80 study sites will be recruited, and patient recruitment will be competitive. Eligible patients will have the diagnosis of severe asthma being treated with at least medium dose inhaled corticosteroids (ICS) and at least one second controller therapy, and who still experience frequent exacerbations. For the purposes of inclusion (e.g. exacerbation history, and baseline asthma controller medications), “documented” means previously recorded in the patients’ medical history at the Investigator’s site or at another medical facility. Patients must be able to provide an acceptable sputum sample at screening to allow cellular characterization.

Patient recruitment will end when the Trial Clinical Monitor has determined that sufficient number of patients has been randomized. A log of all patients enrolled in the trial (i.e. who have signed informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with the investigational drug.

3.3.1 Main diagnosis for trial entry

Outpatients with a history of asthma and who experience frequent exacerbations despite their current maintenance treatment with at least a medium dose ICS and at least another asthma controller medication are eligible for inclusion if they meet all the inclusion criteria (Section 3.3.2) and none of the exclusion criteria (Section 3.3.3).

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

3.3.2 Inclusion criteria

1. Signed informed consent consistent with ICH-GCP guidelines and local legislation prior to participation in the trial. Medication washout and medication restrictions are allowed only after signed informed consent is obtained.

2. Male or female patients aged at least 18 years but not more than 75 years at the time of informed consent.

3. Pre-bronchodilator clinic measured FEV1 of ≥40% and ≤85% of predicted normal at the screening Visit 1B, and not lower than 40% of predicted normal at randomization visit (Visit 2). Calculations will be based on Global Lung Function Initiative (GLI) formula (R15-0845).

4. A minimum of one year history of asthma, diagnosed by a physician, and have FEV1 reversibility as defined by an improvement in FEV1 ≥12% and an absolute change of at least 200 ml starting within 15 to 30 minutes after administration of 400 µg salbutamol (albuterol) via MDI. Reversibility testing is performed at the screening Visit (Visit 1B).

   If reversibility criteria are not met, the patient may still be randomized if there is:
   - Documented evidence of reversibility with improvement in FEV_1 ≥12% above baseline and an absolute increase of at least 200 ml in the 2 years prior to Visit 2 (randomization visit)
     or
   - Documented evidence of airway hyperresponsiveness (methacholine: PC20 of <8 mg/mL) in the 2 years prior to Visit 2 (randomization visit)
     or
   - Documented evidence of airflow variability in clinic FEV_1 ≥20% between two clinic visits documented in the 12 months prior to visit 2 (randomization visit).

- If reversibility criteria are not met at Visit 1B and if any of the above historic data are not available, reversibility testing can be repeated up to twice during screening period at separate visits. For the first retest, 400 µg salbutamol via MDI should be used, and for the second retest, up to 800 µg salbutamol via MDI or 2.5 mg nebulized albuterol should be used. Reversibility testing must not occur on the day of randomization. Additional guidelines for reversibility testing can be found in Appendix 10.1.

5. Patients must be on at least medium dose ICS (Table 10.1: 1), and at least one other asthma controller medication for at least one year prior to the date of screening. Asthma therapy must have been documented and must be stable for at least 4 weeks prior to the date of screening.

   Note: Some examples of 2nd controller medications are long-acting beta-2-agonist (LABA), leukotriene receptor antagonist (LTRA) or theophylline. Maintenance oral corticosteroid (prednisone or equivalent) with a total daily dose of ≤ 20 mg is also considered as an additional controller therapy.

6. Patients must have documented history of at least one of the following criteria: a) two or more severe asthma exacerbations in the last 12 months, or b) one severe asthma exacerbation in the last 12 months requiring hospitalization or emergency room visit, or c) one severe asthma exacerbation in the last 6 months not requiring hospitalization or emergency room visit, prior to the date of screening visit (Visit 1B). Patients must not have a severe asthma exacerbation in the 6 weeks prior to screening visit. Patients with only one severe asthma exacerbation in the last 6 months (category c, but not a or b) will be limited to approximately 25% of the total patient population.

   Note: Severe asthma exacerbation is defined as initiation of systemic corticosteroids: (prednisone or equivalent) for 3 or more consecutive days for asthma. Additionally, for subjects on maintenance systemic corticosteroids, at least doubling of the maintenance dose resulting in a total daily dose of ≥ 20 mg for three or more consecutive days will be considered a severe asthma exacerbation.

7. Patients should be non-smokers or ex-smokers who stopped smoking at least one year prior to screening. Ex-smokers must have a smoking history of less than 10-pack years (see Appendix 10.1).

8. Patients must be able to perform all trial related procedures including pulmonary function tests, and must be able to use the electronic asthma monitor (E-diary).

3.3.3 Exclusion criteria

1. Patients with a significant disease other than asthma. A significant disease is defined as a disease which in the opinion of the Investigator may a) put the patient at risk because of participation in the trial, or b) influence the results of the trial, or c) cause concern on the patient's ability to participate in the trial.

2. Patients with malignancy for which the patient has undergone resection, radiation, or chemotherapy within the past 5 years. Patients with treated basal cell carcinoma or fully cured squamous cell carcinoma are allowed.
3. Patients with clinically relevant abnormal hematology or blood chemistry laboratory values at screening if the abnormality defines a significant disease as defined in Exclusion Criterion 1.

4. Patients who are not able to produce sputum or sputum samples of sufficient quality at the screening visit. Sputum samples with more than 40% squamous cells or low viability at the screening visit will be considered of insufficient quality. The central reading center will make the final determination on sputum quality.

5. Patients who have history of intubation for asthma exacerbation within one year of the screening visit.

6. Patients diagnosed with concurrent respiratory disease**:** presence of a known pre-existing, clinically important lung condition other than asthma. This includes current infection, bronchiectasis, pulmonary fibrosis, bronchopulmonary aspergillosis, or diagnoses of emphysema or chronic bronchitis (chronic obstructive pulmonary disease other than asthma) or a history of lung cancer.

7. Recent history (i.e., within 6 months) of myocardial infarction or hospitalization for cardiac failure during the past year.

8. Patients who have undergone thoracotomy with pulmonary resection. Patients with a history of thoracotomy for other reasons should be assessed as per Exclusion Criterion 1.

9. Patients who have undergone bronchial thermoplasty or radiotherapy procedure in the year prior to screening or have planned procedures during the study.

10. Patients taking oral corticosteroids with a total daily dose of more than 20 mg prednisone (or equivalent) in the 6 weeks prior to screening visit.

11. Pregnant or nursing (lactating) women.

12. Women of childbearing potential must be ready and able to 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 from date of screening until 20 weeks after last dosing with study medication in this trial. A list of contraception methods meeting these criteria is provided in the patient information.

    Note: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile, i.e. appropriate age range and history of vasomotor symptoms, or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL [for U.S. add estradiol < 20 pg/mL]

13. Patients who have taken an investigational drug within 3 months or six half-lives (whichever is greater) prior to the screening visit.

14. Patients who have been previously randomized in this study.

15. Chronic alcohol or drug abuse or any other condition that in the Investigator's opinion makes these patients unreliable or unlikely to complete the trial.

16. Clinically relevant acute infections or chronic infections including but not limited to HIV, viral hepatitis, and (or) tuberculosis or evidence of tuberculosis infection as defined by a positive QuantiFERON TB test within 2 months prior to or during screening.

    Note: Subjects with a positive QuantiFERON TB test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment must have been initiated and maintained according to local country guidelines.

17. Have received any live bacterial or live viral vaccination in the 12 weeks prior to the date of screening. Patients must agree not to receive a live bacterial or live viral vaccination during the study and up to 12 months after the last administration of study drug.

18. Have received Bacille Calmette-Guerin (BCG) vaccination in the 12 months prior to the date of screening. Patients must agree not to receive BCG vaccination during the study and up to 12 months after the last administration of study drug.

19. Have received treatment with; a) any dose of ustekinumab (Stelara®), or b) any other biological based agents in the 3 months or within 6 times the half-life (whichever is longer) prior to the screening visit.

20. History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients, or a known hypersensitivity to β-adrenergic medications.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An individual patient is to be withdrawn from trial treatment if any of the following criteria apply:

- The patient withdraws consent for study treatment or study participation, without the need to justify the decision
- The patient needs to take concomitant drugs that interfere with the trial medication, and the Investigator wants to discontinue the patient due to safety concerns
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy)
- Sponsor decision to discontinue all or portion of the patients for safety or other reasons

Investigator may discontinue a patient from the study for any unexpected medical conditions that could compromise patient safety.

No patient should be discontinued from the trial for a protocol violation before discussion with the Local Clinical Monitor.

Patients who are intubated for asthma worsening or exacerbation during the course of the study must be discontinued from the study. In addition, the principal Investigator should make an ongoing assessment of the suitability of the patient to continue in the study: any discontinuation should be discussed with the Trial Clinical Monitor.

Given the patient's agreement, the discontinued patient will undergo the procedures for early treatment discontinuation and follow-up. Please refer to Section 6.2 for instructions on early discontinuation visits.

For all patients, the reason for withdrawal (e.g. adverse events) must be recorded in the electronic case report form (eCRF). These data will be included in the trial database and reported.

A patient should be called as lost to follow-up only after three documented attempts have been made to contact the patient.

3.3.4.2 Discontinuation of the trial by the Sponsor

AbbVie/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 enrollment 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. Violation of good clinical practice (GCP), the clinical trial protocol (CTP), or the contract disturbing the appropriate conduct of the trial

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 TREATMENTS TO BE ADMINISTERED

Risankizumab or placebo will be administered subcutaneously. Risankizumab and the matching placebo will be supplied by Boehringer Ingelheim.

4.1.1 Identity of BI investigational product and comparator product

Table 4.1.1: 1 Test Product 1

Substance:	Risankizumab (BI 655066): Anti-human IL-23p19 mAb
Pharmaceutical formulation:	Injection solution of risankizumab (BI 655066) presented in a 1 ml pre-filled syringe
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	90 mg risankizumab (BI 655066) in a 1 ml pre-filled syringe (concentration 90 mg/ml)
Posology	Multiple doses: 6 doses (once every 4 weeks)
Route of administration:	subcutaneous

Table 4.1.1: 2 Test Product 2

Substance:	Placebo
Pharmaceutical formulation:	Injection solution of matching placebo presented in a 1 ml pre-filled syringe
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	NA
Posology	Multiple doses: 6 doses (once every 4 weeks)
Route of administration:	subcutaneous

4.1.2 Method of assigning patients to treatment groups

After the patient's eligibility has been confirmed at Visit 2, each patient will be assigned to a treatment group via the IRT. At Visits 2 to 7, the IRT will assign medication boxes to each patient (based on the assigned treatment) and each medication box will have a unique

number. Site personnel will enter all medication numbers dispensed to each patient in the eCRF. To facilitate the use of the IRT, the Investigator will receive all necessary instructions. Technical features of the treatment allocation are provided in Section 7.6.

4.1.3 Selection of doses in the trial

Each patient will receive six subcutaneous injections of 90 mg each at weeks 0, 4, 8, 12, 16, and 20 (i.e., 90 mg q4wk x 6). The selected dose and regimen were based on the available safety and tolerability established in completed and ongoing clinical trials to support development of risankizumab for other indications. In a single rising dose study (trial 1311.1 (U12-3066-01)), no clinically relevant safety or tolerability issues were observed with risankizumab doses of up to 5 mg/kg i.v. Based on preliminary analysis of concentration response, this dose has been predicted to result in robust reduction in psoriatic lesions (<0.25 mg/kg) based on data from 1311.1 trial.

Dosing of therapeutic monoclonal antibodies is often based on body size with the perception that body weight based dosing would reduce inter-subject variability in drug exposure. While this may be warranted in certain cases, most monoclonal antibodies are target-specific, dosed in antibody/target excess due to target turnover and offer a relatively large therapeutic window. As part of the initial pharmacokinetic analyses (trial 1311.1), there is generally a modest contribution of body size to overall pharmacokinetic variability. Inclusion of body weight in the model as a regressor (i.e., body-weight based dosing) explains only 13% of between subject pharmacokinetic variability of risankizumab with exposures trending higher for individuals with lower body weight (55 kg) vs. typical body weight (75 kg) by 25%. This underscores the general benefits of fixed-dosing vs. body weight dosing which are considered applicable to risankizumab and the aforementioned high drug/target excess (R13-4749, R10-6267, R13-4753, R13-4750, R13-4754).

In three ongoing phase II trials (trials 1311.2, 1311.6, and 1311.8), multiple s.c. doses of risankizumab up to 180 mg are currently being investigated with treatment duration of six months or longer. Based on pharmacokinetic modelling of the dosing regimen proposed for this trial, drug exposure with 90 mg q4wk treatment is not expected to exceed the levels achieved in previous clinical trials

Overall, this trial is designed to evaluate the efficacy of risankizumab in severe asthma patients using a safe and tolerable dose achieved in previous trials and resulting in efficacy in psoriasis.

4.1.4 Drug assignment and administration of doses for each patient

At the visits as indicated in Flow Chart A, each patient will receive a single dose of risankizumab or placebo. The study medication will be allocated by IRT. The design will be double-blind, and patients will receive injections of risankizumab or placebo. All patients will receive a total of 6 subcutaneous injections, one each at week 0, 4, 8, 12, 16, and 20. Even though the last dose is administered at week 20, therapeutic coverage is expected to last until week 24. At week 24, the clinic visit is considered as the end of treatment period, and

patients will enter a 16-week follow-up period. Patients will be seen at the clinic at week 28, 32, and 40, and a phone call at week 36 during the follow-up period. There will be no study drug administration during the follow-up period. Week 40 will be the last clinic visit and is considered as the end of observation. Instruction for medication handling and administration provided in the ISF must be followed.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, Investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomized treatment assignments until after database lock. The randomization code will be kept secret by Clinical Trial Support group until database lock. When interim analysis is performed (Section 7.4), select members of the trial team may be unblinded.

A DMC will be reviewing the trial data periodically (Section 3.1.1), and the committee may have access to unblinded data. Data presented at the DMC will be prepared by an external statistician who will have no direct role in this study.

The randomization codes will be provided to bioanalytics group prior to last patient out to allow exclusion of samples from the placebo arm for the analyses of pharmacokinetic samples. Bioanalytics group will not disclose the randomization code or the results of their measurements until the trial is officially unblinded.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the Investigator / pharmacist / investigational drug storage manager / Sponsor via the 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. A discussion with the Sponsor Trial Clinical Monitor should occur (if possible) prior to the decision to unblind any study subject. The reason for unblinding must be documented in the source documents along with the date and the initials of the person who broke the code. Reason for unblinding should also be recorded in the eCRF. In the case of unblinding an individual patient for safety reasons, appropriate follow-up of safety related events is required.

4.1.6 Packaging, labelling, and re-supply

Risankizumab and the matching placebo will be provided by the Sponsor. Syringes pre-filled with the study medication will be provided in individual boxes. Supply of study medication will be managed by IRT. For details of packaging and the description of the label, please refer to the ISF.

4.1.7 Storage conditions

Study medication supplies will be kept in their original packaging in a secure limited access storage area. Medication must be kept refrigerated in their original packaging. The recommended storage temperature is 2°C to 8°C (36°F to 46° F). A temperature log must be

maintained. If storage conditions are found to be outside the specified range, the Local Clinical Monitor (as provided in the list of contacts in the ISF) must be contacted immediately.

4.1.8 Drug accountability

The Investigator / pharmacist / investigational drug storage manager will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of 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
- Availability of Form 1572 (if applicable)

The Investigator / pharmacist / investigational drug storage manager 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 alternative disposal of unused products.

The records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the Sponsor. At the time of return to the Sponsor and/or appointed contract research organization (CRO), the Investigator / pharmacist / investigational drug storage manager must verify that all remaining supplies are in the Investigator's possession. Detailed instructions will be provided for the return/disposal of unused study medication.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

Rescue medication

Administration of rescue medication is allowed at any time point during the trial except during the washout period before clinic visits for PFTs (see Section 4.2.2). Open-label salbutamol (albuterol) will be provided as rescue medication throughout the course of the trial: screening (from Visit 1B), treatment, and follow-up periods. Only the rescue medication provided by the Sponsor is to be used by the patients. Patients must record the number of inhalations (puffs) of rescue medication used during the daytime and night-time hours in the E-diary. The salbutamol (albuterol) provided as rescue medication is considered a non-investigational medicinal product.

Emergency procedures

Severe asthma exacerbations would be treated according to best medical practice, but would typically include OCS or intra-muscular steroids (and/or antibiotics as appropriate). These patients would be allowed to continue participation in the study.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Table 4.2.2.1: 1 Overview of permitted, restricted, medications and therapies

Drug Class	Washout period[1]	Prior to Visit 1B	Between Visits 1B and 2	Treatment & Follow-up periods
Corticosteroid (nasal/ocular)	NA	Permitted	Permitted	Permitted
Corticosteroid – oral[2]	NA	Permitted[5]	Permitted (stable dose)[7]	Permitted (stable dose) & as needed for exacerbation
Corticosteroid – i.v., i.m.	NA	Permitted[5]	Not permitted[7]	Permitted (as needed for exacerbation)
Short-acting β2-adrenergic agonist -Inhaled	6 hours	Permitted	Only salbutamol /albuterol	Only salbutamol /albuterol
Long-acting β2-adrenergic agonist – Inhaled[3]	12 hours /24hours[4]	Permitted[5]	Permitted[5]	Permitted[5]
Anticholinergic – Inhaled short acting	6 hours	Permitted[5]	Permitted[5]	Permitted[5]
Anticholinergic – Inhaled long acting	24 hours	Permitted[5]	Permitted[5]	Permitted[5]
Leukotriene modifier	24 hours	Permitted[5]	Permitted[5]	Permitted[5]
Cromolyn sodium / nedocromil sodium	6 hours	Permitted[5]	Permitted[5]	Permitted[5]
Methylxanthines	24 hours	Permitted[5]	Permitted[5]	Permitted[5]
Immunomodulators (e.g. methotrexate)	NA	Not Permitted[6]	Not permitted	Not permitted
Immunotherapy (e.g. sub cutaneous or sublingual)	NA	Permitted[5]	Permitted[5]	Permitted[5]
Biologic antagonists (e.g. Omalizumab)	NA	Not permitted[6]	Not permitted	Not permitted
Other investigational drugs	NA	Not permitted[6]	Not permitted	Not permitted

Footnotes:
1. Washout period refer to time before in-clinic PFTs on clinic visit days (including Visit 1B).
2. For patients taking stable maintenance OCS with a total daily dose of ≤ 20 mg prednisone or equivalent.
3. Includes fixed dose combination therapy.
4. 12 hours for patients with BID dosing, and 24 hours for patients with QD dosing.
5. Allowed as stable dose for at least 6 weeks before Visit 1B with no planned changes during the study.
6. Allowed before Visit 1B with a washout period of 3 months or 6 half-lives whichever is greater.
7. Use as needed for exacerbations with extension of screening period (see Section 6.1)

4.2.2.2 Additional treatments

The use of antibiotics is not restricted during the study period for the treatment of asthma exacerbations and/or infections. Investigators should refer to Exclusion Criterion 16 to ensure that patients did not have any active infections before entering the trial.

4.2.2.3 Restrictions on diet and life style

Restrictions prior to PFT visits

Medication washout restrictions should be adhered to as shown in Section 4.2.2.1. Please also see medication washout criteria in Section 6.1.

On clinic visit days, patients should refrain from strenuous activity for at least 12 hours prior to pulmonary function testing and throughout the testing period. Patients should also avoid cold temperatures, environmental smoke, dust or areas with strong odours (e.g. perfumes).

Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods, and ice-cold beverages are not allowed at least 2 hours prior to and during the pulmonary function testing. Decaffeinated beverages are acceptable.

4.2.2.4 Restrictions for women of childbearing potential

Female patients of childbearing potential should use the contraception methods described in Section 3.3.3 (Exclusion Criterion 12).

4.2.2.6 Restrictions before FeNO measurements:

Patients should not drink any fluids or eat any food for about an hour before FeNO measurements. Eating nitrate-containing foods like lettuce are not permitted for about two hours before the measurements.

4.3 TREATMENT COMPLIANCE

Patients are required to complete the scheduled clinic visits within the time windows allowed in the protocol. As the administration of study medication is only at the clinic, and the need to maintain the required intervals between dosing, it is very important to adhere to the time

windows for each visit. Patients who miss scheduled clinic visit(s) within the time window allowed in the protocol will be considered non-compliant. However, they should be allowed to continue in the trial. Persistent non-compliance will have to be discussed with the Local Clinical Monitor.

Patients should be compliant in using the E-diary in the morning and evening. If E-diary compliance is below 75% in the 14 days before Visit 2, randomization visit will be rescheduled (see Section 6.1).

Patients should be compliant in taking their daily asthma controller medications during the course of the study. Dose and regimen of the ICS and additional controller medication(s) should not be changed during the course of the study (screening, treatment, and follow-up periods) except for treatment of an asthma exacerbation or unless absolutely medically necessary. Baseline treatment should be maintained at the same dose and regimen at it was at the time of entry to the study. If changes are absolutely necessary for reasons other than to treat the patient for asthma exacerbation, this should be discussed with the Local Clinical Monitor, and well documented in the patient source data including the medical rationale for the change from the treating physician. The follow up period is also an important part of the study to assess therapeutic efficacy and changes following the last dose of risankizumab should be avoided. After the patient completes the final clinic visit at week-40 (Visit 12), Investigator may adjust the dose or change the asthma controller medications without consequence to the study objectives.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint

The primary endpoint of this study is time to first asthma worsening (in days) during the planned 24-week treatment period (Section 5.2).

5.1.2 Secondary Endpoints

1. Annualized rate of asthma worsening during the planned 24-week treatment period
2. Annualized rate of severe asthma exacerbation during the planned 24-week treatment period
3. Weekly ACQ_5 score at week 24
4. Trough FEV_1 in-clinic change from baseline at week 24
5. Post-bronchodilator FEV_1 in-clinic change from baseline at week 24
6. Time to first severe asthma exacerbation during the planned 24-week treatment period
7. Time to first asthma worsening (alternative definition 1) during the planned 24-week treatment period

5.2 ASSESSMENT OF EFFICACY

Asthma Worsening

For the primary endpoint, asthma worsening is defined as the occurrence of any one of the following four criteria:

a) Decrease from baseline of ≥30% in morning PEF on at least 2 consecutive days
b) Increase from baseline of ≥50% and an increase of least 4 puffs in daily use of rescue medication for at least 2 consecutive days
c) Increase from baseline of ≥0.75 units in ACQ_5
d) Severe asthma exacerbations as defined in the protocol (Section 5.2.1).

Asthma worsening (alternative definition 1) has criteria (c) defined as "Increase from baseline ≥0.5 units in ACQ_5".

Asthma worsening (alternative definition 2) has criteria (c) defined as "Increase from baseline ≥1 units in ACQ_5".

5.2.1 Asthma Exacerbations

The following are protocol definitions for asthma exacerbations based on ATS/ERS criteria (R09-2853)

Moderate asthma exacerbation is defined as a physician directed change or addition in asthma therapy due to asthma worsening: includes change in the dose/regimen of ICS or other asthma controller medications. For patients on maintenance OCS, increase in total

daily dose not meeting the severe asthma exacerbation criteria, will constitute a moderate asthma exacerbation.

Severe asthma exacerbation is defined as initiation of systemic corticosteroids (prednisone or equivalent) for 3 or more consecutive days for asthma. Additionally, for subjects on maintenance systemic corticosteroids, at least doubling of the maintenance dose resulting in a total daily dose of ≥ 20 mg for three or more consecutive days will be considered a severe asthma exacerbation.

Hospitalization for severe asthma exacerbation is patient requiring hospitalization or emergency room/department visit for severe asthma exacerbation.

5.2.2 Efficacy Assessments

Patients will receive an asthma monitor (E-diary) which combines the features of a peak flow meter and an electronic diary. ERT, the central vendor providing the Masterscope® for spirometry will also supply the E-diary to all study sites. Patients will measure the PEF and forced expiratory volume in 1 second (FEV_1) in the morning and evening. In addition, patients will also enter the number of puffs of rescue medication (salbutamol/albuterol) taken, in the morning and evening. Once a day, patient will answer a question in the E-diary to confirm if they have taken the regular asthma controller medications. Once a week, patients will answer in the E-diary, the first 5 self-administered questions from the ACQ (R00-1157). A copy of the ACQ_5 can be found in the ISF.

The E-diary will be dispensed at the screening visit (Visit 1B) and patients will use the E-diary until the end of observation period (Visit 12). Instructions and training for the use of asthma monitor will be provided at Visits 1B and 2. Additional training must be provided if the patient is non-compliant or if the patient has difficulty in using the E-diary.

Data and measurements collected in the E-diary will be automatically transferred to a central server (ERT) each time the patient has completed an assessment on the E-diary. The automated transfer will depend on the availability of the technology in the region, and wireless capabilities at the patient's location. If the automated transfer cannot be completed due to low wireless capabilities, the collected data will be stored in the E-diary and submitted during the next automated transfer after a completed assessment, once wireless connection is available. The E-diary also tries to connect to the central server (ERT) once a day to send a confirmation signal that the device is working properly: if there should be any data available on the device from previous session(s) that were not transmitted due to connection issues, this data will be transferred at this time. In addition, all data collected in the E-diary will be downloaded at each clinic visit on to the Masterscope® and transmitted to the central server. At each clinic visit the principal Investigator or a delegated study staff should review the printed report of all the data downloaded from the E-diary. When reviewing the report, any occurrence of asthma worsening events (Section 5.2) must be identified and discussed with the patient. The principal Investigator is required to sign the printed reports generated from the data downloaded in the Masterscope®. Detailed instructions for the use of the E-diary will be provided in the ISF.

Morning and evening recordings in the E-diary should be performed at approximately the same time of the day (±30 minutes) between 6:00 am and 9:00 am and 6:00 pm and 9:00 pm, respectively. If the patient did not use the E-diary at the specified time, an alarm will sound at 9:00 (am/pm) and 9:30 (am/pm) to remind the patient to enter the data and complete the measurements. If patients forget to use the E-diary in the morning or in the evening, they should be instructed to complete the measurements and enter the data if it is still before 11.59 (am or pm).

The morning measurements should be performed upon arising (after the patient has cleared out any mucus), and measurements will be repeated in the evening, both prior to the administration of the maintenance ICS and any other asthma controller medication(s). On each occasion, patient should perform three peak expiratory flow maneuvers in the standing position. The highest PEF and the highest FEV_1 out of the three acceptable blows, but not necessarily the same blow, will be used for evaluation. On the day prior to the clinic visit and on the morning of the clinic visit, patients must adhere to the medication restrictions (Section 4.2.2.1) that will allow medication washout for the in-clinic PFTs.

During the treatment and follow-up periods, patients will be alerted by the E-diary to contact the Investigator if any of the first three asthma worsening criteria (decrease in PEF, increase in rescue medication use, or increase in ACQ_5 score) specified under the primary efficacy endpoint (Section 5.2) are met. Patients must be instructed to call the study center if they receive an alert in the E-diary. The Investigator or the study coordinator should review the asthma symptoms with the patient when the patient contacts the study site. If deemed necessary, the Investigator may schedule an unscheduled clinic visit. At each clinic visit, the Investigator or the delegated study staff is required to review the data from the E-diary download in the Masterscope® to verify if any asthma worsening criteria have been met.

For asthma worsening, any event that starts within 7 days from the end date of previous event will be considered as the continuation of the previous event, and be collapsed with the previous event into one episode.

Treatment of asthma exacerbations including initiation/addition of systemic corticosteroids should be done according to the medical judgment of the Investigator or the treating physician and should be in line with national and international guidelines. Patients should be instructed to contact the Investigator if they meet any of the asthma exacerbation criteria in between clinic visits. At each clinic visit, the Investigator or the delegated study staff is required to discuss with the patient to verify if any of the asthma exacerbation criteria was met since the previous clinic visit.

It is the responsibility of the Investigator to report any deterioration of asthma as an AE regardless of the definitions provided in this protocol.

For moderate asthma exacerbations, severe asthma exacerbations, and hospitalization for severe asthma exacerbations, any event that starts within 7 days from the end date of previous event will be considered as the continuation of the previous event, and be collapsed with the previous event into one episode.

Asthma Medication Log

All patients will receive an asthma medication log card from Visit 1B onwards to document any changes in asthma controller medications. During the course of the study, if there is any change in the asthma controller medications, patients will record the changes in the asthma medication log. The record should include the name of the medication, start date, end date, dose, and route of intake. Any dose changes in the medications they are already taking for asthma will also be recorded in the log. Any changes to the rescue medication (salbutamol /albuterol) use must not be recorded in this asthma medication log. A copy of the asthma medication log card will be provided in the ISF.

At each clinic visit starting Visit 2 onwards, patients will bring the asthma medication log card to the clinic. The Investigator should review the entries in the medication log and verify if the patient met any of the asthma exacerbation criteria defined in the protocol. The medication log card will be collected and placed in the patient file, and a new card will be issued at each clinic visit. If there are no entries in the medication log, the card should be marked blank, placed in the patient file, and a new card should be dispensed. The asthma medication log will be signed and dated by the Investigator or study staff before placing it in the patient file.

Pulmonary Function Tests

Centralized spirometry services will be made available to all sites by ERT for in-clinic PFTs. The spirometers and their use will meet ATS/ERS criteria [P05-12782]. Spirometry will be conducted in a seated position. It is preferable that the same trained individual performs the PFTs for a given patient at all visits. The best of three efforts will be defined as the highest FEV_1, the highest forced vital capacity (FVC) and the highest PEF, each obtained on any of the three blows meeting the ATS/ERS criteria with preferably a maximum of five maneuvers. However, a maximum of eight maneuvers will be allowed. The highest FEV_1, FVC, and PEF will be selected regardless of whether they come from different spirometric maneuvers or from the same maneuver.

For each patient, PFTs should always be done at approximately the same time of the day at each clinic visit from Visits 2 to 12. The reference time point will be the time of PFTs at the randomization visit (Visit 2). At Visit 2 pulmonary function testing should be started between 06.00 am and 10.00 am. At clinic visits (from Visit 3 onwards), PFTs should be scheduled to start ±30 minutes from the start time of the PFTs at Visit 2. Any deviation from this time window should be documented with the reason for deviation. Every effort must be made to not deviate from the ±30 minutes time window. PFTs should be completed before sputum induction (if applicable at that visit) and dosing with study medication if the patient is scheduled to be dosed at that particular visit.

At Visits 2 to 10 and at Visit 12, following the completion of three acceptable pre-bronchodilator forced expiratory manoeuvers, 400 µg of salbutamol (albuterol) will be administered. There should be at least a 30-second interval between each puff. Post-bronchodilator PFTs (three acceptable manoeuvers) will be started 15 to 30 minutes after the last puff of salbutamol (albuterol) was inhaled.

If a patient is unable to complete the PFTs during a visit, this will be noted in the eCRF indicating the reason for stopping testing. If rescue medication was administered during the PFTs (excluding the administration of salbutamol/albuterol for bronchodilation between pre- and post-measurements), it should be noted in the eCRF.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

A complete physical examination will be completed on all patients at the screening visit (Visit 1B), randomization visit (Visit 2), and at Visit 5, Visit 8 (EOT) and Visit 12 (EOO). Body weight will be measured on the days when physical examination is scheduled, and entered in the eCRF. Relevant asthma history and atopy status will be captured at the screening visit (Visit 1B). All clinically significant findings at screening will be recorded on the Medical History / Baseline Condition page in the eCRF. New clinically significant findings or worsening of preexisting conditions detected at subsequent visits will be recorded as adverse events on the appropriate eCRF page.

An explanation of the etiology of clinically significant abnormal physical findings must be entered on the eCRF. All relevant (in the opinion of the Investigator) abnormal physical findings have to be followed up until they are normalized or sufficiently characterized.

5.3.2 Vital Signs

Pulse rate, systolic and diastolic blood pressure, and body temperature will be measured and recorded at the screening visit and all subsequent visits. Measurements will be obtained before spirometry testing with the patient seated and rested for at least five minutes.

5.3.3 Safety laboratory parameters

The laboratory tests listed in Table 5.3.3: 1 will be performed at the central laboratory service provider, except urine pregnancy test and urinalysis (Stix) that will be performed at the study site. Instructions regarding sample collection, sample handling/processing, and sample shipments are provided in the laboratory manual. For the schedule of routine laboratory tests, please see Flow Chart A. Laboratory results for the samples collected on a clinic visit day will not be available on the same day as they have to be shipped to the central laboratory for analyses.

When the laboratory results are reported by the central laboratory, the Investigator is required to review the reports. Clinically relevant abnormal laboratory values should be commented in the eCRF. It will be responsibility of the Investigator to follow-up with the patient if any findings in the laboratory tests need immediate attention. Laboratory data will be transferred from the central laboratory to the Sponsor periodically. If any local regulations prevent the transfer of certain laboratory parameters tested in this study to the Sponsor, they will not be transferred. Additional laboratory tests not specified in Table 5.3.3.1 may be performed as deemed medically appropriate, and to ensure patient safety.

If screening period is extended, the Investigator should review the laboratory reports from baseline (Visit 1B), and make a determination if any lab tests specified in the protocol must

be repeated before the randomization visit. If deemed necessary, test samples should be drawn and sent to the central laboratory, and results should be reviewed by the Investigator before randomization visit occurs.

During the treatment and follow-up periods, if any of the lab tests specified in the protocol must be repeated for patient safety, test samples should be drawn and sent to the central laboratory.

Table 5.3.3: 1 Laboratory tests

Category	Test name
Haematology[1]	Haematocrit (Hct) Haemoglobin (Hb) Glycosylated Hb (HbA1c)[2] Red Blood Cell Count/ Erythrocytes White Blood Cells / Leukocytes Platelet Count/ Thrombocytes
Diff. Automatic[1]	Neutrophils (absolute and relative count) Eosinophils (absolute and relative count) Basophils (absolute and relative count) Monocytes (absolute and relative count) Lymphocytes (absolute and relative count)
Diff. Manual (if Diff. Automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Enzymes[1]	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)
Electrolytes[1]	Calcium Sodium Potassium Chloride Bicarbonate
Substrates[1]	Glucose Creatinine and Creatinine Clearance eGFR (estimated by CKD-EPI formula) Bilirubin Total Bilirubin Direct Bilirubin Indirect Albumin C-Reactive Protein Cholesterol, total Triglycerides LDL-Cholesterol HDL-Cholesterol Urea
Urine Pregnancy test (only for female patients of childbearing potential) at the clinic, for all scheduled clinic visits except Visit 1A and Visit 1B.	Human Chorionic Gonadotropin in the urine

Table 5.3.3: 1 Laboratory tests (cont.)

Category	Test name
Serum Pregnancy test at screening (Visit 1B) and when urine pregnancy test is positive at other visits	Human Serum Chorionic Gonadotropin
Hormones[4]	TSH, (free T3 and free T4 in case of abnormal TSH results)
Specific gamma-globulin quantification[5]	Total IgE
Urinalysis (Stix)[1]	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urine Bilirubin Urine RBC/ Erythrocytes Urine WBC/ Leukocytes Urine pH Urine specific gravity
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/ Leucocytes
Infections screening[4]	Hepatitis B Surface Antigen (qualitative) Hepatitis C Antibodies (qualitative) HIV-1, and HIV-2 Antibody (qualitative) QuantiFERON-TB Gold

1. Routine laboratory assessments at visits indicated in Flow Chart A.
2. At Visits 2, 5, 8, and 12.

4. At screening only (Visit 1B)
5. At Visits 2 and 8

5.3.4 Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed on all patients at the screening visit (Visit 1B) to obtain patient's baseline condition. ECG procedure will be repeated at the randomization visit (Visit 2), and at Visits 3, 5, 8, 10, and 12. Additional ECGs may be done during the study for safety reasons. ECG equipment provided by ERT (integrated with the Masterscope®) will be used at all the sites for all patients. ECG printouts from the Masterscope® will be read and evaluated locally at the respective study centers by a physician. All ECG data will be transmitted electronically to a central server at ERT and stored. If necessary, the data collected in this study will be readily available for additional evaluations.

ECGs will be recorded after the patient has rested for at least 5 minutes in a supine position, and will always precede blood sampling and PFTs. All clinically significant findings at screening will be recorded on the medical history/baseline condition page in the eCRF. All clinically significant findings at subsequent visits should be documented on the AE page of the eCRF.

5.3.5 Other safety parameters

Local tolerability at the administration site of the subcutaneous injection will be assessed by the Investigator to monitor any swelling, induration, heat, redness, pain, or other findings, and will be recorded in the eCRF.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical 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.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Life-threatening in this context 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.

AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of 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 given above.

The latest list of "Always Serious AEs" can be found in the remote data capture (RDC) system. These events should always be reported as SAEs as described in Section 5.3.6.1.

Adverse events of special interest (AESI)

AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.3.7.

The following are considered as AESIs:

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

- an elevation of AST and/or ALT ≥3 fold upper limit normal (ULN) combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, and/or
- Marked peak 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 "drug-induced liver injury (DILI) checklist" provided in the RDC system. 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.

Intensity of AEs

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Causal relationship of AEs

Medical judgment should be used to determine the relationship, 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.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

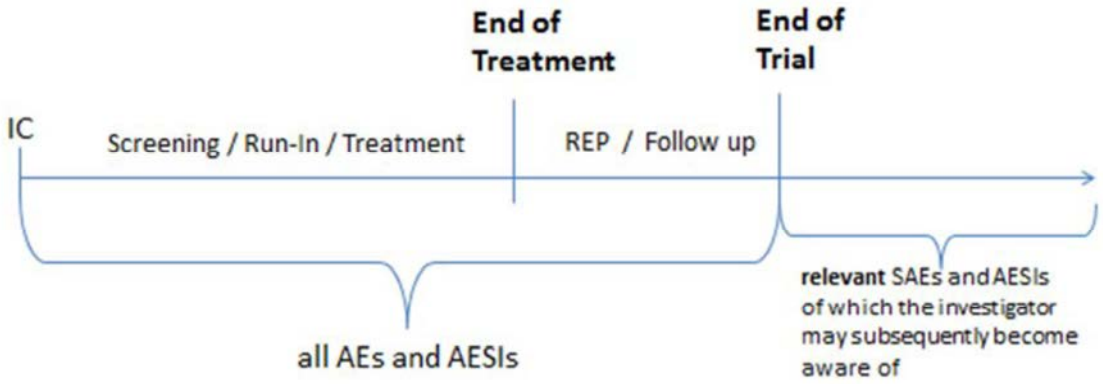
The causal relationship must be provided by the Investigator for all potential trial drugs, i.e. the BI trial drug and for all other trial drugs (such as any active comparator or placebo and for trial procedure). The reason for the decision on causal relationship needs to be provided in the eCRF and on the SAE form.

5.3.7 Adverse event collection and reporting

AE Collection

The following must be collected and documented on the appropriate eCRF by the Investigator:

From signing the informed consent onwards through the Residual Effect period (REP), all AEs (serious and non-serious), and AESIs will be reported.



All AEs which occurred through the treatment phase and throughout the REP will be considered as on-treatment (please see Section 7.3.4). Events which occurred after the REP will be considered as post-treatment events.

After the last per protocol contact (Visit 12), the Investigator does not need to actively monitor patients for AEs. However, if the Investigator becomes aware of SAEs or AESIs that occurred after the last per protocol contact, the SAEs and AESIs should be reported by the Investigator to the Sponsor if considered relevant by the Investigator.

AE reporting to 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). 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.

Information required

For each AE, the Investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The Investigator should determine the causal relationship to the trial medication, the trial procedures outlined under Section 6.2, and any possible interactions between the investigational drug and a non-investigational medicinal product.

The following should also be recorded as an (S)AE in the eCRF and SAE form if they meet the SAE criteria:

- 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 pre-exist prior to trial inclusion they will be considered as baseline conditions. All (S)AEs, including those persisting after trial completion must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

Screening failures

SAEs occurring in patients after having discontinued in the trial due to screening failures, i.e. after the screening period and who did not receive any trial medication, are to be reported if the Investigator considered the SAE related to the screening procedure. SAEs which occurred during the screening period are to be reported according to standard procedures.

Pregnancy

In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the Sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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).

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

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

5.7 APPROPRIATENESS OF MEASUREMENTS

Measurements performed during this trial are standard measurements in patients with severe persistent asthma, and will be performed in order to monitor safety aspects or assess treatment response in an appropriate way.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The trial consists of a screening period, treatment period, and a follow-up period. Following the 3 to 4 week screening period (Visits 1B to Visit 2), patients will be randomized (Visit 2) to one of the two treatment groups: risankizumab or placebo. Additional clinic visits will be scheduled every 4 weeks (Visits 3 to 12, with Visit 11 as a phone visit) until week 40. The first 24 weeks after randomization is the treatment period, and this is followed by a 16-week follow-up period (Figure 3.1: 1).

Patients should make all efforts to complete the study which includes the 16-week follow-up period. Investigators should encourage treatment compliance, E-diary compliance, and adherence to the protocol procedures. All patients should adhere to the visit schedule as specified in Flow Chart A Any deviations from the planned visit schedule should be documented.

Rescheduling clinic visits and study procedures

Medication washout

Medication washout is necessary for the PFTs. Visit 1B (screening visit) may be rescheduled twice within the permitted time windows due to lack of medication washout compliance. For all other clinic visits, rescheduling is not necessary for lack of medication washout. Medication washout checklist provided in the ISF must be completed at each clinic visit. If medication washout requirements (Section 4.2.2) are not met it should be recorded in the Masterscope®. Pre- and post-bronchodilator PFT measurements will be performed during clinic visits (except Visit 1B) even if medication washout criteria are not met. If possible, patients should be contacted by telephone 2 to 3 days before the clinic visit to remind them about the visit schedule and the medication washout requirements.

As reversibility is an inclusion criterion, medication washout must be verified before any study procedures begin at Visit 1B. If washout requirements are not met, the visit will be rescheduled and all Visit 1B procedures will be completed at the rescheduled visit when washout requirements are met.

Sputum induction

If the patient is unable to produce an adequate sample of the sputum or a sputum sample of acceptable quality at Visit 1B (screening visit), a repeat sputum induction may be performed. An interval of at least 3 full days should be observed between repeat sputum induction procedures. Sputum induction procedures at Visits 2, 7, 8, and 12 will not be repeated if the patient is unable to produce sputum or if the sputum sample quality is not acceptable.

If sputum induction procedure at screening (Visit 1B) needs to be repeated, patient will complete only the sputum induction procedure at the repeat visit. All other Visit 1B procedures should have been completed on the originally scheduled Visit 1B date.

Reversibility testing

At Visit 1B (screening visit) if reversibility criterion is not met, and patient does not have a historic reversibility data as defined in Inclusion Criterion 4, reversibility testing can be repeated twice during the screening period.

If reversibility testing is repeated, patient will complete only the reversibility testing when the repeat visit occurs. All other Visit 1B procedures including sputum induction should have been completed on the originally scheduled Visit 1B date.

Asthma exacerbation and respiratory tract infection

If a patient experiences an asthma exacerbation or respiratory tract infection between Visits 1A and 1B, Visit 1B will be postponed until 4 weeks following recovery from the exacerbation or infection. If a patient experiences an asthma exacerbation or respiratory tract infection between Visits 1B and the randomization visit (Visit 2), randomization will be postponed until 4 weeks following recovery from the exacerbation or infection. Screening period may be extended up to six weeks if the patient experiences an asthma exacerbation or respiratory tract infection during the screening period.

If patient has an asthma exacerbation or respiratory tract infection during the treatment period or follow-up period, study visits will not be rescheduled. In this case, the investigator will make a determination on what study procedures can be completed on the scheduled clinic visits.

E-diary compliance

If at the randomization visit (Visit 2), E-diary compliance is below 75% and two completed ACQ_5 sessions are not available, rescheduling of Visit 2 is required. The timing of the rescheduled visit will depend on the data already available in the E-diary, and what is needed to achieve at least 75% compliance. The goal should be that patient meets the required compliance level at the next rescheduled visit. Rescheduling Visit 2 for lack of E-diary compliance is allowed twice. Screening period may be extended up to four weeks if Visit 2 is rescheduled for lack of E-diary compliance.

When patient arrives for Visit 2, the E-diary data should be downloaded first in the Masterscope® to determine if the patient met the E-diary compliance criteria. If the compliance criteria are not met, randomization visit must be rescheduled, and no other Visit 2 procedures should be performed.

The calculation of E-diary compliance during the screening period will be based on the data collected in the last 14 days prior to Visit 2. E-diary compliance is derived from the number of acceptable sessions. An acceptable session is one in which at least two acceptable PEFs were stored and the question on rescue medication use is answered in the E-diary. In addition, to meet the required E-diary compliance, at least two ACQ_5 sessions in the 14 days prior to Visit 2 (including the morning session of Visit 2 before randomization visit) must have been completed. ACQ_5 will be displayed in the E-diary only once every week as this is a weekly

recall. If the patient misses a scheduled ACQ_5 session in the E-diary, patient will be able to complete the questionnaire in the evening of the same day or in the morning or evening sessions in the following day.

Patients should be instructed to maintain full compliance with the E-diary during the entire study period. From Visit 3 onwards, study visits will not be rescheduled for lack of E-diary compliance.

Rescheduling clinic visits after randomization

If a clinic visit after Visit 2 and the phone call at Visit 11 is out of the time window allowed by the protocol, subsequent visits should occur at the originally scheduled date to ensure a 24-week treatment period, and a 16-week follow-up period. Any visits outside the time window allowed by the protocol should be discussed with the Local Clinical Monitor. All patients are expected to complete the treatment period in 24 weeks, and the follow-up period in 16 weeks.

All clinic visits and the phone call at Visit 11 should be completed at the time window allowed in the protocol. Under extraordinary circumstances, if a scheduled clinic visit is delayed (i.e., occurs after the scheduled visit date) during the treatment period, and the visit date is more than 14 days from the scheduled visit that was missed, study drug will not be administered and the dose should be skipped. However, all other visit procedures should be completed. Patient will have to wait until the next scheduled visit to receive the next dose of study medication. The time interval between two consecutive doses of the study medication must be at least 14 days.

Pregnancy tests

All women of child bearing potential will undergo serum pregnancy test at the screening visit (Visit 1B). Patients who test positive for the serum pregnancy test will be excluded from the study. Urine pregnancy tests will be done at all visits in the clinic starting from Visit 2. If the urine pregnancy test is positive, a serum pregnancy test will be done to confirm pregnancy. If the serum pregnancy test is positive, patient will be discontinued from the study. If serum pregnancy is negative, patient may continue in the study.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

At Visit 1A, informed consent will be obtained prior to patient participation in the trial. Medication washout procedures are allowed only after the patient signs the informed consent. If the patient is willing to provide a sample for pharmacogenomic testing, a separate consent must be obtained.

Each patient will be assigned a unique patient number and enrollment will be recorded in eCRF.

Baseline conditions, medical history, and eligibility criteria will be assessed at Visit 1A. Concomitant therapy and AE (if any) will be recorded. Visit 1B will be scheduled. At the conclusion of Visit 1A, patients should receive instructions on medication washout requirements for Visit 1B and they should also be briefed about all the procedures to be performed at Visit 1B.

Procedures indicated under Visit 1B in Flow Chart A should be completed at Visit 1B. The E-diary will be dispensed at Visit 1B after the patient is trained on how to use the E-diary including PEF measurements. An E-diary will be available at all sites exclusively for training purposes. Rescue medication will be provided starting at Visit 1B. An asthma medication log card will be dispensed, and patient will record any change in asthma medications (Section 5.2.2). Patient should be trained on when entries should be made in the asthma medication log.

Visit 1B should be scheduled in the morning between 6:00 am and 10:00 to ensure completion of the reversibility testing in the morning. The sequence of procedures in the Masterscope® provided by ERT will be ECG followed by FeNO measurements, and then PFTs for reversibility testing. Blood samples should be collected after the ECG procedure is completed. Sputum induction should be done only after completing ECG, FeNO measurements, and PFTs for reversibility testing. The Masterscope® will be used to do the PFTs and monitor patient's lung function during sputum induction. Processing of the sputum samples will be done as specified in a separate sputum procedures manual provided in the ISF. Instructions for shipping of laboratory samples and sputum samples/slides will be provided in the manual.

If the patient has met all the eligibility criteria (pending sputum assessment and safety laboratory results), randomization visit will be scheduled. If patients do not meet the sputum criteria, they should be informed about their ineligibility and must be marked as screen failed. Sputum quality and acceptability will be made by the external vendor who has been contracted to make the assessments centrally and the central reader's decision will be final.

If rescheduling Visit 1B or Visit 2 is required for reasons specified in Section 6.1, screening period can be extended by two weeks unless otherwise a specific period is stated in the protocol. Screening period may be extended by four weeks for administrative reasons after consultation with the Local Clinical Monitor. The typical screening period allowed by the

protocol is 3 to 4 weeks
However, if the screening period is extended due to rescheduling allowed per protocol, the total screening period should not exceed 10 weeks (informed consent to randomization) unless written approval is obtained from the Trial Clinical Monitor.

If screening period is extended for any reasons, the Investigator should review the laboratory reports from baseline (Visit 1B), and make a determination if any labs specified in the protocol must be repeated before the randomization visit. If deemed necessary, test samples should be drawn and sent to the central laboratory.

Discontinuation during the screening period

If patients discontinue from the study during the screening period, no additional clinic visits are required, and they will be marked as screen failures.

Re-screening

Patients may be re-screened once with approval from the Local Clinical Monitor. Patients who met all the inclusion criteria but were screen failed due to acute medical conditions that have since been resolved or those who were screen failed for administrative reasons (e.g., extended travel, life events) will be good candidates for re-screening.

6.2.2 Treatment period

All eligibility criteria must be checked before proceeding with the randomization visit. Patients will be randomized only if their pre-bronchodilator FEV_1 is not below 40% (Inclusion Criterion 3), met the E-diary compliance criteria (Section 6.1), and were able to produce sputum that could be characterized (Exclusion Criterion 4).

Treatment period begins after the patient is dosed with the study medication at Visit 2 and ends after completion of the End of Treatment visit (Visit 8) at Week 24. Each patient will be assigned to one of the two treatment groups: risankizumab or placebo. Procedures listed under each visit in Flow Chart A and Flow Chart B should be completed from Visit 2 until Visit 8. Visit windows should be adhered as specified in Flow Chart A.

Patient will be dosed with the study medication every 4 weeks (Visits 2 to 7) in the clinic. At each one of these visits, medication should be administered after completion of all other visit procedures. The study drug will be administered by a physician Investigator or a person who is designated by the principal Investigator. The designated person must be medically qualified to administer the injection, and all study drug administration should be under the supervision of a physician. Patients will remain in the clinic for observation for approximately an hour after the medication is administered. The instructions for medication handling and administration provided in the ISF must be followed.

All visits during the treatment period should be scheduled in the mornings. For more instructions on the timing of each visit, please refer Section 5.2.2. Medication washout checklist should be completed at each visit. The sequence of procedures in the Masterscope® provided by ERT will be ECG followed by FeNO measurements, and then the PFTs.

Sputum induction (at applicable visits) should be done only after completing ECG, FeNO measurements, and PFTs. The Masterscope® will be used to do the PFTs and monitor patient's lung function during sputum induction. ECG and sputum induction will be performed only at visits shown in Flow Chart A. Processing of the sputum samples will be done as specified in the manual provided in the ISF. Instructions for shipping of laboratory samples and sputum samples/slides will be provided in the respective manuals. Sputum samples/specimens will be assessed by the central reader.

At each visit, data downloaded from the E-diary must be reviewed to check for any asthma worsening events (Section 5.2) since the previous clinic visit. Asthma medication log should be reviewed for any changes in asthma medications since the last clinic visit. Patients should be asked if there were any other change in asthma medications or if they had to seek medical help (visit to doctor's office, hospital, etc.) since the previous clinic visit. Any information written in the medication log or collected during the discussion with the patient should be assessed to see if they meet any of the asthma exacerbation criteria specified in the protocol.

If the scheduled visit does not occur within the protocol allowed time window, follow instructions provided in Section 6.1 for rescheduling and study drug administration. Unscheduled visits may be arranged if necessary and the procedures completed during the unscheduled visit will depend on the circumstances under which the visit was scheduled.

After completion of the End of Treatment visit (Visit 8), all patients will enter the 16-week follow-up period.

Discontinuation during the treatment period:

If patients discontinue from the study during the treatment period, an EOT visit (corresponding to Visit 8) will be scheduled 4 weeks after the last dose of study medication. Every effort should be made to complete all the procedures (including sputum induction) listed under EOT visit. After completing the EOT visit, patients should be allowed to enter the follow-up period of 16 weeks, and they will complete the four visits (Visit 11 is a phone visit) and the associated procedures ending in the End of Observation (EOO) visit. If the patient is not willing to enter the follow-up period, one additional follow-up visit should be scheduled 16 weeks after the EOT visit and this will be considered as the EOO visit. During the EOO visit, every effort should be made to complete all procedures listed under the EOO visit (Visit 12).

6.2.3 Follow Up Period and Trial Completion

The follow-up period extends from week 24 (Visit 8) until week 40 (Visit 12). The first follow-up visit (Visit 9) will be scheduled 4 weeks after the EOT visit. Visits will be scheduled every 4 weeks (Visits 9 to 12, Visit 11 being a phone visit). Procedures for each visit can be found in Flow Chart A and Flow Chart B. Patients will not be dosed with the study medication (risankizumab or placebo) during the follow-up visits. The sequence of visit procedures will be the same as in the treatment period. All visits during the follow-up period should be scheduled in the mornings and the criteria for the PFTs including the timing will be the same as in the treatment period. For more instructions on the timing of the PFTs at each visit, please refer Section 5.2.2. Patients will continue to receive the rescue medication and will continue to use the E-diary, and the asthma medication log as in the treatment period. The last clinic visit will be at week 40 (Visit 12), and this will mark the End of Observation period, and the patient has completed the study.

Discontinuation during the follow-up period:

If patients discontinue from the study during the follow-up period, an EOO visit will be scheduled at the date Visit 12 would have been originally scheduled. All procedures scheduled for the EOO visit should be completed during this visit.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a randomized, double-blind, placebo-controlled, parallel group trial with a 24-week treatment period which is followed by a 16-week follow-up period. Risankizumab will be compared to placebo in patients with severe persistent asthma.

The primary endpoint is the time to first asthma worsening during the planned treatment period and will be analyzed using Cox-proportional hazards model. Detailed specifications are provided in Section 7.3.

The primary endpoint and secondary endpoints are defined in Section 5.1.

Baseline

The baseline for the diary data: rescue medication, PEF, FEV_1 (except ACQ_5) is defined as the mean of the measurements at corresponding time point (if any) as specified in the endpoints in the last two weeks prior to Visit 2, i.e., 14 days prior to the administration of the first dose of randomized treatment.

The baseline for ACQ_5 is defined as the mean of the last two available measurements in the last two weeks prior to Visit 2 (including the morning session before randomization visit), i.e., 14 days prior to the administration of the first dose of randomized treatment.

For all clinical spirometry endpoints, the pulmonary function test at the randomization visit (Visit 2), measured prior to the first administration of the randomized treatment, is defined as baseline.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The following hypotheses will be tested for the primary endpoint with 1-sided $\alpha = 0.1$:

H_0: $S_{BI}(t)=S_{PBO}(t)$, for $t>0$
H_1: $S_{BI}(t)>S_{PBO}(t)$, for $t>0$,

where S(t) is the probability that a patient has no asthma worsening up to time t, i.e., the survival function. The subscripts represent the two treatment groups of either risankizumab or placebo.

7.3 PLANNED ANALYSES

7.3.1 Primary endpoint analyses

The primary analyses will be performed in all randomized patients who receive at least one dose of treatment. This set will be called Full Analysis Set (FAS) for all patients.

Time to first asthma worsening during the planned 24-week treatment period will be analyzed using Cox proportional-hazards model including treatment and stratification factor of OCS use at baseline as fixed effects to provide hazard ratio, confidence interval, and test statistic to compare the treatment groups in FAS. Kaplan-Meier curves will be provided. For patients who prematurely discontinue from the trial during the treatment period not due to consent withdrawal, the asthma worsening events collected after treatment discontinuation until 24 weeks (if available) from the start of the treatment will be included in the analysis. A sensitivity analysis which includes all asthma worsening events during the actual on-treatment period including 4 weeks after last drug administration will be conducted.

7.3.2 Secondary endpoint analyses

The analyses of secondary endpoints will be performed in FAS.

The annualized rate of asthma worsening and severe asthma exacerbation during the planned 24-week treatment period will be analyzed using negative binomial regression with logarithm of the exposure as an offset. The analyses will include treatment and the stratification factor of OCS use at baseline as fixed effects. The mean number of events per patient year by treatment arm, the rate ratio, and corresponding 95% confidence interval will be presented along with the p-value.
The same model for primary endpoint will be used to analyze time to first severe asthma exacerbation during the planned 24-week treatment period.

An analysis of covariance (ANCOVA) model will be used to analyze ACQ_5 score, separately for each week (including the secondary endpoint measured at week 24). The model will include the fixed categorical effects of treatment and the stratification factor of OCS use at baseline, and baseline ACQ_5 as a continuous covariate.

Mean change from baseline in trough and post-bronchodilator FEV_1 at each clinic visit (including secondary endpoint measured at week 24) during the planned treatment period will be analyzed using a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach. Analyses will include the fixed, categorical effects of treatment, stratification factor of OCS use at baseline, test day, and treatment-by-test day interaction, as well as the continuous, fixed covariates of baseline and baseline-by-test day interaction. Patient will be considered as a random effect. The planned test days during the 24-week planned treatment period will be used for values of test day. An unstructured co(variance) structure will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Analyses will be implemented using SAS. The FAS population will be used. A plot and table over time will be provided to describe the profile of trough and post-bronchodilator FEV_1.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 130 days after the last dose of trial medication, will be assigned to the treatment period for evaluation. All 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. 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 is defined as 130 days. 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 and preferred term after coding according to the current version of the MedDRA.

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.

7.4 INTERIM ANALYSES

Interim analyses may be performed when the last patient completes the 24-week treatment period. The data from interim analysis will allow planning future trials and reporting key results. Select members of the Sponsor trial team will be unblinded during interim analysis. Investigators, study site staff, and patients will remain blinded. No alpha adjustment is needed because the primary endpoint will have been reached for all patients in the study. More details will be specified in the interim analysis logistics plan.

7.5 HANDLING OF MISSING DATA

For Patient Daily Record data, when the number of salbutamol (albuterol) doses is missing but other data are entered on any given day, then these data will be imputed by zero (because the presence of other data is interpreted as meaning that the patient did not take rescue medication).

Additional details on the imputation of missing data will be specified in the TSAP prior to unblinding.

7.6 RANDOMIZATION

Patients will be randomized in blocks to double-blind treatment. Approximately equal numbers of patients will be randomized to each treatment group. Randomization will be stratified based on OCS use at baseline, and history of severe asthma exacerbation in the past 12 months. BI will arrange for the randomization and the packaging and labelling of trial medication.

The randomization 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.

7.7 DETERMINATION OF SAMPLE SIZE

Based on the previous studies in asthma with tiotropium: trials 205.416 and 205.417 (U12-2037-01), the proportion of patients with asthma worsening within 6 months, derived using the definition in this study, was around 55% in tiotropium treated patients, with history of frequent severe asthma exacerbations. It is assumed that risankizumab would reduce the risk of asthma worsening by 40% (HR = 0.6) in patients. Given 1-sided type-I error $\alpha = 0.1$, this trial requires a total of 89 events and 100 patients per treatment arm to achieve 87% power.

Table 7.7: 1 Sample size calculation with 1-sided $\alpha = 0.1$, event rate = 55% in placebo group using nQuery Advisors 6.01 STT0 (log rank test)

Hazard ratio	0.5		0.6	
n per group	47	40	100	90
Total number of events needed	38	32	89	80
Power	80%	75%	87%	84%

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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 Tripartite Guideline for GCP and relevant BI Standard Operating Procedures (SOPs).

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 subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

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 finalization of the Clinical Trial Report.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND 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 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.

8.2 DATA QUALITY ASSURANCE

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

Case Report Forms (eCRF) 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

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site. Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records; current medical records must also be available.

For the eCRF, the following data need to be derived from source documents:

- Patient identification
- 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)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date
- Serious adverse events (onset date (mandatory), and end date
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results
- Completion of Patient's Participation in the trial
- 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 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 permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRF and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all eCRF, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness is provided. For risankizumab, this is the current version of the Investigator's Brochure (c15197475). The current version of this reference document is provided in the ISF. For non-investigational medicinal product (salbutamol/albuterol), the reference document is the United States prescribing information or another regulatory label document. The current version of this

reference document is provided in the ISF. No AEs are classified as listed for matching placebo, trial design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IEC / IRB

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IEC / IRB, will be done according to local regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers. 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 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.

8.6 END OF TRIAL

The end of the trial is defined as the last patient completing the last visit (Visit 12) of the follow-up period.

The IEC / competent authority in each participating EU member state needs to be notified about the end of the trial or early termination of the trial.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P03-08188 Holgate ST The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. Eur Respir J 22 (3), 470 - 477 (2003)

P05-12782 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 26 (2), 319 - 338 (2005)

P14-07215 Global Initiative for Asthma (GINA) Global strategy for asthma management and prevention (updated 2014). http://www.ginasthma.org (2014)

P14-14612 Irvin C, Zafar I, Good J, Rollins D, Christianson C, Gorska MM, et al. Increased frequency of dual-positive TH2/TH17 cells in bronchoalveolar lavage fluid characterizes a population of patients with severe asthma. J Allergy Clin Immunol, (2014)

P99-03282 Jatakanon A, Uasuf C, Maziak W, Lim S, Chung KF. Neutrophilic inflammation in severe persistent asthma. Am J Respir Crit Care Med 160 (5, Part 1), 1532 - 1539 (1999)

R00-1157 Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 14, 902 - 907 (1999)

R08-5197 Lange P, Nyboe J, Appleyard M, Jensen G, Schnohr P. Relationship of the type of tobacco and inhalation pattern to pulmonary and total mortality. Eur Respir J 5, 1111 - 1117 (1992)

R09-2853 Reddel HK, Taylor DR, Bateman ED, Boulet L, Boushey HA, Busse WW et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations. Am J Respir Crit Care Med 180, 59-99(2009)

R10-6267 Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 49, 1012 - 1024 (2009)

R11-1199 Vosse E van de, Ottenhoff THM. Human host genetic factors in mycobacterial and Salmonella infection: lessons from single gene disorders in IL-12/IL-23-dependent signaling that affect innate and adaptive immunity. Microbes Infect 8, 1167 - 1173 (2006)

R11-1200 Happel KI, Dubin PJ, Zheng M, Ghilardi N, Lockhart C, Quinton LJ, et al. Divergent roles of IL-23 and IL-12 in host defense against Klebsiella pneumoniae. J Exp Med 202 (6), 761 - 769 (2005)

R13-3518 Papp KA, Griffiths CEM, Gordon K, Lebwohl M, Szapary PO, Wasfi Y, et al. PHOENIX 1 Investigators, PHOENIX 2 Investigators, ACCEPT Investigators Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. Br J Dermatol 168, 844 - 854 (2013)

R13-4749 Bai S, Jorga K, Xin Y, Jin D, Zheng Y, Damico-Beyer LA, et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 51 (2), 119 - 135 (2012)

R13-4750 Joos B, Trkola A, Kuster H, Aceto L, Fischer M, Stiegler G, et al. Long-term multiple-dose pharmacokinetics of human monoclonal antibodies (MAbs) against human immunodeficiency virus type 1 envelope gp120 (MAb 2G12) and gp41 (MAbs 4E10 and 2F5). Antimicrob Agents Chemother 50 (5), 1773 - 1779 (2006)

R13-4753 Deng R, Iyer S, Theil FP, Mortensen DL, Fielder PJ, Prabhu S. Projecting human pharmacokinetics of therapeutic antibodies from nonclinical data: what have we learned? MAbs 3 (1), 61 - 66 (2011)

R13-4754 Xin Y, Gordon MS, Jin D, Wakshull E, Chen DS, Rosen LS, et al. Population pharmacokinetic (PK) analysis supports fixed dosing for the humanized monoclonal antibody (huMAb) anti-EGFL7 (MEGF0444A) administered intravenously in patients with advanced solid tumors. 47th Ann Mtg of the American Society of Clinical Oncology (ASCO), Chicago, 3 - 7 Jun 2011 J Clin Oncol 29 (15) (Suppl),, Abstr 2586 (2011)

R14-2101 Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 60, 309 - 316 (2005)

R14-2348 Wakashin H, Hirose K, Maezawa Y, Kagami S, Suto A, Watanabe N, et al. IL-23 and Th17 cells enhance Th2-cell-mediated eosinophilic airway inflammation in mice. Am J Respir Crit Care Med 178 (19), 1023 - 1032 (2008)

R14-2349 Ciprandi G, Cuppari C, Salpietro AM, Tosca MA, Rigoli L, Grasso L, et al. Serum IL-23 strongly and inversely correlates with FEV_1 in asthmatic children. Int Arch Allergy Immunol 159 (2), 183 - 186 (2012)

R14-4182 Seys SF, Grabowski M, Adriaensen W, Decraene A, Dilissen E, Vanoirbeek JA, et al. Sputum cytokine mapping reveals an 'IL-5, IL-17A, IL-25-high'

pattern associated with poorly controlled asthma.
Clin Exp Allergy 43, 1009 - 1017 (2013)

R14-4183 Agache I, Ciobanu C, Agache C, Anghel M. Increased serum IL-17 is an independent risk factor for severe asthma. Respir Med 104, 1131 - 1137 (2010)

R14-4184 Brasier AR, Victor S, Boetticher G, Ju H, Lee C, Bleecker ER, et al. Molecular phenotyping of severe asthma using pattern recognition of bronchoalveolar lavage-derived cytokines. J Allergy Clin Immunol 121 (1), 30 - 37.e6 (2008)

R14-4187 Hastie AT, Moore WC, Meyers DA, Vestal PL, Li H, Peters SP, et al. NHLBI Severe Asthma Research Program (SARP) Analyses of asthma severity phenotypes and inflammatory proteins in subjects stratified by sputum granulocytes. J Allergy Clin Immunol 125 (5), 1028 - 1036.e13 (2010)

R14-4215 Wood LG, Baines KJ, Fu J, Scott HA, Gibson PG. The neutrophilic inflammatory phenotype is associated with systemic inflammation in asthma. Chest 142 (1), 86 - 93 (2012)

R14-4216 Boushey HA, Fahy JV. Basic mechanisms of asthma. Environ Health Perspect 103 (Suppl 6), 229 - 233 (1995)

R14-4217 Carroll N, Lehmann E, Barret J, Morton A, Cooke C, James A. Variability of airway structure and inflammation in normal subjects and in cases of nonfatal and fatal asthma. Pathol Res Pract 192, 238 - 248 (1996)

R14-4224 Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 380, 651 - 659 (2012)

R14-4225 Lotvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immunol 127 (2), 355 - 360 (2011) R14-2101

R14-4226 Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, et al. Lebrikizumab treatment in adults with asthma. N Engl J Med 365 (12), 1088 - 1098 (2011)

R14-4232 Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med 368 (26), 2455 - 2466 (2013)

R14-4315 Moore WC, Hastie AT, Li X, Li H, Busse WW, Jajour NN, et al. National Heart, Lung, and Blood Institute's Severe Asthma Research Program Sputum neutrophil counts are associated with more severe asthma phenotypes using cluster analysis. J Allergy Clin Immunol 133 (6), 1557 - 1563 (2014)

R15-0678 Amarnani A, Rosenthal KS, Mercado JM, Brodell RT. Concurrent treatment of chronic psoriasis and asthma with ustekinumab. J Dermatol Treat 25 (1), 63 - 66 (2014)

R15-0845 Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH et al. Multi-ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations: report of the Global Lung Function Initiative (GLI), ERS Task Force to establish improved lung function reference values. Eur Respir J. 40(6):1324-1343 (2012)

R98-1426 Lamblin C, Gosset P, Leblond IT, Saulnier F, Marquette CH, Wallaert B, Tonnel AB. Bronchial neutrophilia in patients with noninfectious status asthmaticus. Am J Respir Crit Care Med 157, 394 - 402 (1998)

9.2 UNPUBLISHED REFERENCES

c01651292-07 48 weeks study of three different dose regimens of BI 655066 administered subcutaneously in patients with moderate to severe chronic plaque psoriasis (randomised, dose-ranging, active-comparator controlled (ustekinumab), double-blind within dose groups of BI 655066). 1311.2. Version: 4.0. 03-Jul-2014.

c01651690-12 . A phase II, multicenter, randomized, double-blind, multiple dose, placebo-controlled, parallel-group study to evaluate the efficacy, pharmacokinetics and safety of BI 655066, an IL-23p19 antagonist monoclonal antibody, in patients with moderately to severely active Crohn's disease, who are naïve to, or were previously treated with anti-TNF therapy. 1311.6. Version: 5.0. 04-Dec-2014.

c02190287-17 . A 48 weeks, phase II, randomized, double-blind, placebo-controlled, proof of concept and dose finding study of three different dose regimens of BI 655066 administered subcutaneously in patients with ankylosing spondylitis. 1311.8. Version:3.0. 18-Jun-2014.

U12-2037-01 . Combined Clinical Trial Report. BI Trial No. 205.416 and 205.417. A Phase III randomized, double-blind, placebo-controlled, parallel group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler

(5µg/day) over 48 weeks as add-on controller therapy on top of usual care in patients with severe persistent asthma. 31 Aug 2012.

U12-3066-01 . Safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of single rising i.v. (Stage 1) and s.c. (Stage 2) doses of BI 655066 in male and female patients with moderate to severe psoriasis (randomized, double-blind, placebo-controlled within dose groups). 1311.1. 25-Jan 2012.

10. APPENDICES

10.1 ADDITIONAL INFORMATION REGARDING INCLUSION/EXCLUSION CRITERIA

Table 10.1: 1 Definition of medium daily doses of ICS adapted from Global Initiative for Asthma (GINA) 2014 (P14-07215)

Drug	Medium daily Dose (µg)*
Beclometasone dipropionate (CFC)	>500 - 1000
Beclometasone dipropionate (HFA)	>200 - 400
Budesonide (DPI)	>400 - 800
Ciclesonide (HFA)	>160 - 320
Fluticasone propionate (DPI)	>250 - 500
Fluticasone propionate (HFA)	>250 - 500
Mometasone furoate	>220 - 440
Triamcinolone acetonide	>1000 - 2000

*Protocol requires patients to be on at least medium dose. There is no restriction on the maximum dose. Prescribing information should be carefully reviewed by the Investigator for the correct equivalent dose.

Reversibility testing (P05-12782): At the screening visit (Visit 1B) following the completion of three acceptable pre-bronchodilator forced expiratory maneuvers, salbutamol (albuterol) will be administered to each patient in order to document the degree of reversibility. Immediately after (within 10 min) pre-bronchodilator forced expiratory maneuvers and after a gentle and incomplete expiration, a dose of 100 µg of salbutamol is inhaled in one breath to total lung capacity. The breath is then held for 5–10 s before the subject exhales. Four separate doses (total dose 400 µg) are delivered at approximately 30-second intervals (this dose ensures that the response is high on the salbutamol dose–response curve). Three additional, acceptable post-bronchodilator forced expiratory maneuver tests are recorded starting ≥15 min to 30 min later after the last dose of salbutamol is inhaled.

If reversibility criteria are not met at Visit 1B and if any of the historic data is not available as stated in inclusion criterion 4, reversibility testing can be repeated twice during screening period at separate visits. For the first retest, 400 µg salbutamol via MDI should be used, and for the second retest, either 800 µg salbutamol via MDI or 2.5 mg nebulized albuterol should be used.

During the second retest, the first 400 µg is administered as described above and tested for reversibility. If the patient did not meet the reversibility criteria, another 200 µg salbutamol is administered and tested for reversibility: post-bronchodilator measurements should begin 10 to 20 minutes after the last dose of salbutamol is inhaled. If the patient did not meet the reversibility criteria after a total of 600 µg salbutamol, another 200 µg salbutamol is administered and tested for reversibility: post-bronchodilator measurements should begin 10 to 20 minutes after the last dose of salbutamol is inhaled. Reversibility testing must not occur on the day of randomization.

Smoking: calculation of number of pack years

Calculation of pack years based on number of cigarettes:

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

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:

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

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		22 October 2015
EudraCT number		2014-004932-20
BI Trial number		1311.14
BI Investigational Product(s)		BI 655066
Title of protocol		A phase IIa, randomized, double-blind, placebo controlled, parallel group study to assess the safety and efficacy of subcutaneously administered BI 655066 as add-on therapy over 24 weeks in patients with severe persistent asthma.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Synopsis Section 3.3 Section 7.7
Description of change 1		Total number of patients, and patients entered **changed** from 300 to 270, Patients in each treatment **changed** from 150 to 135.
Rationale for change		In studies with tiotropium in asthma, the observed event rate in patients treated with tiotropium was 55%: however, these studies did not have the same definition as in this study for the ACQ component. The original protocol assumed the event rate of 50% to account for the change in the way ACQ is administered in this study. After additional considerations, due to the exploratory nature of the study, a less conservative approach was adopted with an assumption of an event rate of 55% for the primary endpoint. Change in the

Number of global amendment		1
		expected event rate from 50% to 55%, resulted in the reduction of sample size.
Section to be changed		Flow Chart A
Description of change 2		Clinic visit 11 replaced with a phone visit. Footnote #16, **added** the following: during the phone call, any adverse events and concomitant therapy will be checked, and any change in asthma medication entered in the asthma medication log will be verified.
Rationale for change		In order to reduce the burden of multiple clinic visits for the patient during the follow-up period, Visit 11 at week 36 (16 weeks after the last dose of study drug) was converted to a phone visit.
Section to be changed		Flow Chart A
Description of change 3		Removal of AQLQ administration
Rationale for change		Being a proof-of-concept Phase 2a study, data from AQLQ may not add much value. To reduce some burden on the patient during clinic visits, the questionnaire was removed.
Section to be changed		
Description of change 4		
Rationale for change		
Section to be changed		Flow Chart A, Footnotes
Description of change 5		Serum pregnancy added to Visit 1B for women of child bearing potential.
Rationale for change		To ensure exclusion of patients who are pregnant. Also, this was a request made by regulatory authorities.

Number of global amendment		1
Section to be changed		
Description of change 6		
Rationale for change		
Section to be changed		
Description of change 7		
Rationale for change		
Section to be changed		Section 3.3.2 Section 5.2.1
Description of change 8		Section 3.3.2: Inclusion criterion #6: first part of severe asthma exacerbation definition: Severe asthma exacerbation is defined as initiation of systemic corticosteroids: oral (prednisone or equivalent) or i.v. for 3 or more consecutive days, or a single i.m dose for asthma. **Changed to:** *Severe asthma exacerbation is defined as initiation of systemic corticosteroids: (prednisone or equivalent) for 3 or more consecutive days for asthma.*

Number of global amendment		1
		Section 5.2.1 Definition of severe asthma exacerbation changed to be consistent with the definition for the same in Section 3.3.2
Rationale for change		To be consistent with ATS/ERS definitions.
Section to be changed		Section 3.3.3, Exclusion Criteria #12
Description of change 9		Women of childbearing potential that, if sexually active, are unwilling to use a highly effective method of birth control which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly from date of screening until 20 weeks after last dosing with study medication in this trial. Highly effective methods of birth control include: ethinyl estradiol containing contraceptives, diaphragm with spermicide substance, intra-uterine device, and male sterilization. **Changed to:** *Women of childbearing potential must be ready and able to 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. A list of contraception methods meeting these criteria is provided in the patient information.*
Rationale for change		To allow having a comprehensive list of highly effective methods of birth control (available locally and aligned with local regulations) in the "patient information". This change was also requested by regulatory authorities.
Section to be changed		Section 3.3.3
Description of change 10		**Added** the following exclusion criterion: *History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients, or a known hypersensitivity to β-adrenergic medications.*
Rationale for change		To exclude patients who are at high risk. The addition of this exclusion criterion was also requested by regulatory authorities.
Section to be changed		Section 3.3.4

Number of global amendment		1
Description of change 11		**Added:** *Investigator may discontinue a patient from the study for any unexpected medical conditions that could compromise patient safety.*
Rationale for change		Additional criterion added to ensure patient safety. The addition of this criterion was also requested by regulatory authorities.
Section to be changed		
Description of change 12		
Rationale for change		

Number of global amendment		1
Section to be changed		Section 5.1.3
Description of change 13		Removal of endpoints related to AQLQ
Rationale for change		AQLQ administration was removed from the study.
Section to be changed		Section 5.2.2
Description of change 14		Section 5.2.2, paragraph 3: Data and measurements collected in the E-diary will be automatically transferred to a central ERT (vendor) server at a designated time, once every day as technically feasible. The daily transfer will depend on the availability of the technology in the region, and wireless capabilities at the patient's location. **Changed to:** *Data and measurements collected in the E-diary will be automatically transferred to a central server (ERT) each time the patient has completed an assessment on the E-diary. The automated transfer will depend on the availability of the technology in the region, and wireless capabilities at the patient's location. If the automated transfer cannot be completed due to low wireless capabilities, the collected data will be stored in the E-diary and submitted during the next automated transfer after a completed assessment, once wireless connection is available. The E-diary also tries to connect to the central server (ERT) once a day to send a confirmation signal that the device is working properly: if there should be any data available on the device from previous session(s) that were not transmitted due to connection issues, this data will be transferred at this time.*
Rationale for change		The timing of the automatic transfer of data from patient E-diary to the central server is corrected.
Section to be changed		Table 5.3.3: 1
Description of change 15		a) Urine Pregnancy test (only for female patients of childbearing potential) at the clinic, for all scheduled clinic visits except Visit 1A. **Changed to:** *Urine Pregnancy test (only for female patients of childbearing potential) at the clinic, for all scheduled clinic visits except Visit 1A and Visit 1B.*

Number of global amendment		1
		b) Urobilinogen test removed from the urinalysis
Rationale for change		a) Urine pregnancy test not required at Visit 1B as serum pregnancy test is done. b) Direct bilirubin is quantitatively measured as part of the chemistry profile.
Section to be changed		
Description of change 16		

Number of global amendment		1
Rationale for change		
Section to be changed		
Description of change 17		

Number of global amendment		1
Rationale for change		
Section to be changed		
Description of change 18		

Number of global amendment		1

Number of global amendment		1
Rationale for change		
Section to be changed		
Description of change 19		

Number of global amendment		1
Rationale for change		
Section to be changed		
Description of change 20		

Number of global amendment		1

Number of global amendment		1
Rationale for change		
Section to be changed		
Description of change 21		
Rationale for change		
Section to be changed		1) Footnotes for Flow Chart A 3) Abbreviations 5) Section 2.3 6) Section 3.1 7) Section 3.3.2 9) Section 4.1.4 10) Section 5.2.2 11) Section 5.2.2 12) Section 5.2.2 13) Section 5.3.3 14) Table 5.3.3: 1 15) Section 5.5 16) Section 6.1 17) Section 6.1 18) Section 6.1 19) Section 6.1 20) Section 6.2.2 21) Section 6.2.3 22) Section 7.1 23) Section 7.3.3 24) Section 7.5

Number of global amendment		1
Description of change 22		1) Footnote #5 now indicates that urine pregnancy test will not be done for Visit 11. Footnote #6: **Added** "*the primary cytospin slides should be*". Footnote on AQLQ **deleted**. In footnote #12, "PFT measurements should be completed" **changed to** "PFT measurements should be started". Footnote #16 now states that Visit 11 is a phone visit. 2) In the column "event and comment", BI 655066 administration was **changed to** BI 655066/Placebo administration. Visit 11 is marked as "NA, Phone visit". 3) AQLQ **removed** from the abbreviation list. 5) In Section 2.3, paragraph 2, "no additional potential additional" **changed to** "no additional potential". 6) In Section 3.1, paragraph 2, "and trial database is locked" was **added** in the last sentence. 7) In Section 3.3.2, inclusion criteria #3, "Global Lung Function" **changed to** Global Lung Function Initiative". 9) In Section 4.1.4, first paragraph, Patients will be seen at the clinic at week 28, 32, 36, and 40 during the follow-up period

Number of global amendment		1
		Changed to Patients will be seen at the clinic at week 28, 32, and 40 and a phone call at week 36 during the follow-up period. 10) In Section 5.2.2, the section on AQLQ is **deleted.** 11) In Section 5.2.2, in the section on Pulmonary Function Tests, paragraph 2, "At Visits 3 to 12" **changed to** "At clinic visits (from Visit 3 onwards)". 12) In Section 5.2.2, in the section on Pulmonary Function Tests, paragraph 3, "At Visits 2 to 12" **changed to** "At Visits 2 to 10 and at Visit 12" 13) In Section 5.3.3, paragraph 1, "The laboratory tests listed in Table 5.3.3: 1 will be performed at the central laboratory service provider". **Changed to:** "The laboratory tests listed in Table 5.3.3: 1 will be performed at the central laboratory service provider, except urine pregnancy test and urinalysis (Stix) that will be performed at the study site". 14) In Table 5.3.3: 1, "Serum Pregnancy test (only when urine pregnancy test is positive)" **Changed to**: "Serum Pregnancy test at screening (Visit 1B) and when urine pregnancy test is positive" 15) In Section 5.5, in the section "Methods of Sample Collection", Sputum will be collected via sputum induction procedures described in the manual. **Changed to:** Sputum will be collected via sputum induction procedures described in the sputum induction and processing manual. 16) In section 6.1, "Visits 3 to 12" **Changed to:** "Visits 3 to 12, with Visit 11 as a phone visit" 17) In Section 6.1, in the section on "Medication washout"

Number of global amendment		1
		For all other visits (Visit 2 to 12), rescheduling is not necessary for lack of medication washout. Medication washout checklist provided in the ISF must be completed at each clinic visit. If medication washout requirements (Section 4.2.2) are not met (for Visits 2 to 12) it should be recorded in the eCRF. Pre- and post-bronchodilator PFT measurements will be performed during Visits 2 to 12 even if medication washout criteria are not met. **Changed to:** For all other clinic visits, rescheduling is not necessary for lack of medication washout. Medication washout checklist provided in the ISF must be completed at each clinic visit. If medication washout requirements (Section 4.2.2) are not met it should be recorded in the Masterscope®. Pre- and post-bronchodilator PFT measurements will be performed during clinic visits (except Visit 1B) even if medication washout criteria are not met. 17) In Section 6.1, in the section on "Rescheduling clinic visits after randomization" If a clinic visit after Visit 2 is out of the time window allowed by the protocol, subsequent visits should occur at the originally scheduled date to ensure a 24-week treatment period, and a 16-week follow-up period. Any clinic visits outside the time window allowed by the protocol should be discussed with the Local Clinical Monitor. **Changed to:** If a clinic visit after Visit 2 and the phone call at Visit 11 is out of the time window allowed by the protocol, subsequent visits should occur at the originally scheduled date to ensure a 24-week treatment period, and a 16-week follow-up period. Any visits outside the time window allowed by the protocol should be discussed with the Local Clinical Monitor. 18) In Section 6.1, in the section on "Rescheduling clinic visits after randomization", paragraph 2: All clinic visits should be completed at the time

Number of global amendment		1
		window allowed in the protocol. **Changed to:** All clinic visits and the phone call at Visit 11 should be completed at the time window allowed in the protocol. 19) In Section 6.1, in the section on "Pregnancy tests", the following sentence is added: All women of child bearing potential will undergo serum pregnancy test at the screening visit (Visit 1B). Patients who test positive for the serum pregnancy test will be excluded from the study. 20) In Section 6.2.2, in the section "Discontinuation during treatment period" After completing the EOT visit, patients should be allowed to enter the follow-up period of 16 weeks, and they will complete the four clinic visits and the associated procedures ending in the End of Observation (EOO) visit. **Changed to:** After completing the EOT visit, patients should be allowed to enter the follow-up period of 16 weeks, and they will complete the four visits (Visit 11 is a phone visit) and the associated procedures ending in the End of Observation (EOO) visit. 21) In section 6.2.3, Clinic visits will be scheduled every 4 weeks (Visits 9 to 12). **Changed to:** Visits will be scheduled every 4 weeks (Visits 9 to 12, Visit 11 being a phone visit). 22) In Section 7.1, the text related to AQLQ is **deleted.** 23) In Section 7.3.3, the text related to AQLQ is **deleted.** 24) In Section 7.5, the text related to AQLQ is **deleted.**

Number of global amendment		1
Rationale for change		

Number of global amendment		2
Date of CTP revision		04 December 2015
EudraCT number		2014-004932-20
BI Trial number		1311.14
BI Investigational Product(s)		BI 655066
Title of protocol		A phase IIa, randomized, double-blind, placebo controlled, parallel group study to assess the safety and efficacy of subcutaneously administered BI 655066 as add-on therapy over 24 weeks in patients with severe persistent asthma.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		Section 3.3.3
Description of change 1		**Exclusion criterion 12** Women of childbearing potential must be ready and able to 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. A list of contraception methods meeting these criteria is provided in the patient information. **Changed to** Women of childbearing potential must be ready and able to 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 from date of screening until 20 weeks after last dosing with study medication in this trial. A list of contraception methods meeting these criteria is provided in the patient information.

Number of global amendment		2
Rationale for change 1		Clarification that birth control use must continue for the 20 weeks after the last dose of study medication.

Number of global amendment		3
Date of CTP revision		11 July 2016
EudraCT number		2014-004932-20
BI Trial number		1311.14
BI Investigational Product(s)		BI 655066
Title of protocol		A phase IIa, randomized, double-blind, placebo controlled, parallel group study to assess the safety and efficacy of subcutaneously administered BI 655066 (risankizumab) as add-on therapy over 24 weeks in patients with severe persistent asthma.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Throughout the document
Description of change 1		BI 655066 changed to risankizumab
Rationale for change 1		New name for BI 655055 added for completeness
Section to be changed		Flow Chart A (Footnote #1) Section 6.1
Description of change 2		Screening period is defined as the period between Visit 1B and Visit 2.
Rationale for change 2		Clarification
Section to be changed		Synopsis Section 3.3 Section 7.2 Section 7.4 Section 7.7
Description of change 3		Total number of patients, and patients entered **changed** from 270 to 200, Patients in each treatment **changed** from 135 to 100.

Number of global amendment		3
		Change in statistical parameters and sample size calculations. In Section 7.4, "interim analyses will be performed" changed to "interim analyses may be performed".
Rationale for change 3		The sample size for the study was re-evaluated in the context of an initial exploratory proof of concept study to investigate efficacy and effects in subsets of patients. The type-I error was changed from a confirmatory alpha of 0.05 to 0.1 (1-sided). A change in the type-I error resulted in the reduction of sample size. Change in Section 7.4 still allows the conduct of interim analyses.
Section to be changed		Synopsis Section 3.3.2
Description of change 4		A minimum of one year history of asthma, diagnosed by a physician, and have FEV_1 reversibility of at least 12% and an absolute change of at least 200 mL starting within 15 to 30 minutes after administration of 400 µg salbutamol (albuterol) at the screening Visit 1B (see Appendix 10.1). If reversibility cannot be achieved, documented evidence of reversibility in the 12 months prior to the screening visit is acceptable. *Note: Reversibility testing can be repeated twice during the screening period if reversibility cannot be achieved at the screening visit and if documented evidence of historic reversibility (in the past 12 months) is not available.* Changed to A minimum of one year history of asthma, diagnosed by a physician, and have FEV_1 reversibility as defined by an improvement in FEV1 ≥12% and an absolute change of at least 200 ml starting within 15 to 30 minutes after administration of 400 µg salbutamol (albuterol) via MDI. Reversibility testing is performed at the screening Visit (Visit 1B). If reversibility criteria are not met, the patient may still be randomized if there is: • Documented evidence of reversibility with improvement in FEV1 ≥12% above baseline and an absolute increase of at least 200 ml in the 2 years prior to Visit

Number of global amendment		3
		2 (randomization visit) **or** • Documented evidence of airway hyperresponsiveness (methacholine: PC20 of <8 mg/mL) in the 2 years prior to Visit 2 (randomization visit) **or** • Documented evidence of airflow variability in clinic FEV1 ≥20% between two clinic visits documented in the 12 months prior to visit 2 (randomization visit). If reversibility criteria are not met at Visit 1B and if any of the above historic data are not available, reversibility testing can be repeated up to twice during screening period at separate visits. For the first retest, 400 µg salbutamol via MDI should be used, and for the second retest, up to 800 µg salbutamol via MDI or 2.5 mg nebulized albuterol should be used. Reversibility testing must not occur on the day of randomization. Additional guidelines for reversibility testing can be found in Appendix 10.1.
Rationale for change 4		To align with current GINA guidelines and current practice for reversibility testing in a severe asthma patient population with higher degree of fixed airflow. History of reversibility increased to allow as reversibility testing not routinely performed yearly for this patient population with diagnosis of asthma over many years.
Section to be changed		Synopsis Section 3.3.2
Description of change 5		Patients must be on at least medium dose ICS (Table 10.1: 1), and at least one other asthma controller medication for at least one year prior to the date of screening. Asthma therapy must have been documented and must be stable for at least 6 weeks prior to the date of screening. Changed to, Patients must be on at least medium dose ICS (Table 10.1: 1), and at least one other asthma controller medication for at least one year prior to the date of screening. Asthma therapy must have been documented and must be stable for at least 4

Number of global amendment		3
		weeks prior to the date of screening.
Rationale for change 5		The requirement for 6 weeks of stable medication was changed to 4 weeks to reflect the treatment practice for severe asthma patients with frequent exacerbations requiring medication adjustments to achieve control.

Number of global amendment		3
Section to be changed		Synopsis Section 3.3.2
Description of change 6		Patients must have documented history of two or more severe asthma exacerbations in the 12 months prior to the date of screening, but not within 6 weeks prior to screening. Changed to Patients must have documented history of at least one of the following criteria: a) two or more severe asthma exacerbations in the last 12 months, or b) one severe asthma exacerbation in the last 12 months requiring hospitalization or emergency room visit, or c) one severe asthma exacerbation in the last 6 months not requiring hospitalization or emergency room visit, prior to the date of screening visit (Visit 1B). Patients must not have a severe asthma exacerbation in the 6 weeks prior to screening visit. Patients with only one severe asthma exacerbation in the last 6 months (category c, but not a or b) will be limited to approximately 25% of the total patient population.
Rationale for change 6		To allow patients with a history of less than 2 exacerbations in the previous year but at the same time where asthma is still not adequately controlled.
Section to be changed		Section 3.1 Section 3.2 Section 7.3.1 Section 7.6
Description of change 7		Description of severe asthma exacerbation history related to inclusion criterion # 6
Rationale for change 7		Clarification in sections impacted by change in inclusion criterion #6.
Section to be changed		Section 9.1 Section 9.2
Description of change 8		References R04-1001 and R08-0092 deleted. Reference updated with the revised version of the

		investigator's brochure
Rationale for change 8		References that were not applicable are deleted. Current version of the investigator's brochure referenced
Section to be changed		Appendix 10.1
Description of change 9		Additional instructions provided for reversibility testing
Rationale for change 9		Additional instructions needed as the inclusion criteria for reversibility testing was changed.

Number of global amendment		4
Date of CTP revision		13 October 2016
EudraCT number		2014-004932-20
BI Trial number		1311.14
BI Investigational Product(s)		BI 655066
Title of protocol		A phase IIa, randomized, double-blind, placebo controlled, parallel group study to assess the safety and efficacy of subcutaneously administered BI 655066/ABBV-066 (risankizumab) as add-on therapy over 24 weeks in patients with severe persistent asthma.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		Title page, Synopsis
Description of change 1		Changed BI drug or BI investigational product or BI 655066 to refer to either names for this compound: BI 655066/ ABBV-066/risankizumab
Rationale for change		In February 2016, AbbVie entered into a license agreement with BI related to risankizumab, and in October 2016, the US IND for risankizumab transitioned from BI to AbbVie. This protocol change reflects that AbbVie will now be the Sponsor of this study in the US, as well as the modifications to certain study conduct responsibilities as a result of that license agreement are listed as separate changes below.
Section to be changed		Section 3.1.1
Description of change 2		Changed sponsor from Boehringer Ingelheim (BI) to AbbVie in the US and BI for all other participating countries.
Rationale for change		Refer to rationale for change 1
Section to be changed		Section 3.3.4.2
Description of change 3		Updated text to: “AbbVie/Boehringer Ingelheim reserves the right to discontinue the trial overall or

Number of global amendment		4
		at a particular trial site at any time for the following reasons”.
Rationale for change		Refer to rationale for change 1
Section to be changed		
Description of change 4		
Rationale for change		

Number of global amendment		5
Date of CTP revision		17 August 2017
EudraCT number		2014-004932-20
BI Trial number		1311.14
BI Investigational Product(s)		BI 655066
Title of protocol		A phase IIa, randomized, double-blind, placebo controlled, parallel group study to assess the safety and efficacy of subcutaneously administered BI 655066/ABBV-066 (risankizumab) as add-on therapy over 24 weeks in patients with severe persistent asthma.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Protocol Synopsis, Sections 5.1.2, 5.1.3, and 5.2.
Description of change 1		Asthma worsening criteria (ACQ_5): increase of 0.5 units from baseline changed to 0.75 units. Addition of secondary and further endpoints. Addition of "alternative definitions 1 and 2" for asthma worsening in Section 5.2.
Rationale for change		The event rate of asthma worsening and the time to first asthma worsening were monitored in a blinded manner during the course of the study. With a 0.5 units change from baseline in ACQ_5, the event rate and the number of asthma worsening events were primarily driven by change in the ACQ_5 score.
Section to be changed		Section 7.3
Description of change 2		Only one stratification factor – OCS use at baseline will be included in the primary model as a fixed effect. In Section 7.3.2, using baseline ACQ_5 as a continuous covariate is not a change but a clarification.
Rationale for change		The statistical model for analysis of primary, secondary, and further endpoints include all the stratification factors as fixed effects. However, the

Number of global amendment		5
		numbers of patients in one level of two stratification factors, i.e., with only one exacerbation not requiring hospitalization in the past 6 month are very low (approximately 10).
Section to be changed		Sections 1.2.2, 1.2.3, 8.4.1, and 9.2
Description of change 3		Reference to Investigator's Brochure has been updated to reflect the current version.
Rationale for change		The study is conducted under the current version of the Investigator's Brochure.

APPROVAL / SIGNATURE PAGE

Document Number: c03185695 **Technical Version Number:7.0**

Document Name: clinical-trial-protocol-version-06

Title: A phase IIa, randomized, double-blind, placebo controlled, parallel group study to assess the safety and efficacy of subcutaneously administered BI 655066 (risankizumab) as add-on therapy over 24 weeks in patients with severe persistent asthma.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		18 Aug 2017 15:08 CEST
Approval-Biostatistics		18 Aug 2017 15:23 CEST
Approval-Therapeutic Area		18 Aug 2017 15:32 CEST
Author-Trial Clinical Pharmacokineticist		18 Aug 2017 15:53 CEST
Approval-Team Member Medicine		18 Aug 2017 17:46 CEST
Verification-Paper Signature Completion		18 Aug 2017 20:06 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**