Title Page

Clinical Study Protocol 1311.20/M15-989

An Open Label, Single Group, Long Term Safety Extension Trial of BI 655066/ABBV-066 (Risankizumab), in Patients with Moderately to Severely Active Crohn's Disease

Amendment 4

AbbVie Investigational Product:	BI 655066/ABBV-066 (risankizumab)	
Date:	25 July 2018	
Development Phase:	II	
EudraCT Number:	2015-001834-15	
Investigator:	Multicenter Study (Investigator information is on file at AbbVie)	
Sponsor:	Non-European Countries: AbbVie 1 North Waukegan Road North Chicago, IL 60064 USA	European Countries:* AbbVie Deutschland GmbH & Co KG Knollstrasse 50 Ludwigshafen 67061 Germany
Sponsor/Emergency Contact:	[redacted]	

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: AbbVie, Inc.		**Tabulated Trial Protocol**	
Name of finished product: NA			
Name of active ingredient: BI 655066/ABBV-066 (risankizumab)			
Protocol date: 28 Apr 2017	**Trial number:** 1311.20/M15-989		**Revision date:** 25 July 2018

Title of trial:	An open label, single group, long term safety extension trial of BI-655066/ABBV-066 (risankizumab), in patients with moderately to severely active Crohn's disease
Co-ordinating Investigator:	[redacted]
Trial sites:	Multi-centre trial
Clinical phase:	II
Objectives:	Primary objective: To investigate long-term safety of BI 655066/ABBV-066 (risankizumab), in patients with moderately to severely active Crohn`s disease, who showed a clinical response or remission on previous treatment with BI 655066/ABBV-066 (risankizumab) and are now receiving long term treatment. Additional objectives: To further investigate long-term efficacy, tolerability, pharmacokinetics, pharmacodynamics and immunogenicity of BI 655066/ABBV-066 (risankizumab).
Methodology:	Open label, single group, roll-over
No. of patients:	60 (estimated)
total entered:	60 (estimated)
each treatment:	All patients will receive 180 mg of BI 655066/ABBV-066 (risankizumab) every 8 weeks (q8w) as subcutaneous injection. Patients who lost clinical response or remission after end of treatment in 1311.6 and/or at screening for 1311.20/M15-989 will receive open label i.v. re-induction treatment with three infusions of 600 mg each every 4 weeks
Diagnosis:	Moderate to severe active Crohn`s disease with clinical response or remission after previous treatment with BI 655066/ABBV-066 (risankizumab)

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Main criteria for inclusion:

1. Patients with Crohn`s disease, who have successfully completed the preceding trial 1311.6. Successful treatment is defined as:

   Completion of period 2 in 1311.6 with a clinical response (drop in CDAI from baseline by ≥100) but no remission (CDAI < 150) at Visit E1; or

   Completion of period 3 in 1311.6 with a clinical response (drop in CDAI from baseline by ≥100) or remission (CDAI < 150) at Visit E5.
2. Female patients:
   a. Women of childbearing potential (not surgically sterilized and between menarche and 1 year postmenopause), that, if sexually active agree to use one of the appropriate medically accepted methods of birth control in addition to the consistent and correct use of a condom from date of screening until 20 weeks after last administration of study medication. Medically accepted methods of contraception are: ethinyl estradiol containing contraceptives, diaphragm with spermicide substance, and intra-uterine-device, or

   b. Surgically sterilized female patients with documentation of prior hysterectomy, tubal ligation or complete bilateral oophorectomy, or

   c. Postmenopausal women with postmenopausal is defined as permanent cessation ≥ 1 year of previously occurring menses, and

   d. Negative urine pregnancy test at screening. Serum ß-Human Chorionic Gonadotrophin (ß-HCG) pregnancy test will be done at screening only in case when urine pregnancy test is positive.

   Male patients:

   a. Who are documented to be sterile, or

   b. Who consistently and correctly use effective method of contraception (i.e. condoms) during the study and 20-weeks after last administration of study medication.
3. Be able to adhere to the study visit schedule and other protocol requirements.

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Name of finished product: NA			
Name of active ingredient: BI 655066/ABBV-066 (risankizumab)			
Protocol date: 28 Apr 2017	**Trial number:** 1311.20/M15-989		**Revision date:** 25 July 2018
Test products:	BI 655066/ABBV-066 (risankizumab)		
dose:	180 mg every 8 weeks		
mode of admin.:	Subcutaneous injection (maintenance treatment)		
dose:	600 mg every 4 weeks		
mode of admin.:	Intravenous infusion (re- induction treatment)		
Comparator products:	NA		
dose:	NA		
mode of admin.:	NA		
Duration of treatment:	Approximately 4 years		
Extension of Treatment Following Study	Patients who complete the study, including all study procedures for end of trial (EoT), may continue in M16-000 Sub-Study 3.		

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Name of finished product: NA			
Name of active ingredient: BI 655066/ABBV-066 (risankizumab)			
Protocol date: 28 Apr 2017	**Trial number:** 1311.20/M15-989		**Revision date:** 25 July 2018
Criteria for efficacy:	• Clinical remission by visit, defined as a CDAI score of < 150. • Clinical response by visit, defined by either a CDAI score of < 150 or a CDAI reduction from baseline of at least 100 points. • PRO-2 remission by visit, defined by a PRO-2 score of < 75 • PRO-2 response by visit, defined as a decrease from baseline of 50 points or more. • CDEIS remission by visit, defined as a score of 4 or less (for patients with initial isolated ileitis a score of 2 or less) • CDEIS response by visit, defined as a score of 7 or less (for patients with initial isolated ileitis > 50% reduction from baseline). • Mucosal healing by visit, defined as the absence of mucosal ulceration. • Deep remission by visit, defined as clinical remission and endoscopic remission (CDEIS). Change from baseline in CDAI scores by visit. • Change from baseline in PRO-2 scores by visit. • Change in CDEIS by visit. • Change in SES-CD by visit. • CDEIS percentage change from baseline by visit. • SES-CD percentage change from baseline by visit. • Reduction of 75% in CDEIS scores from baseline by visit. • Reduction of 75% in SES-CD scores from baseline by visit. • Change from baseline in stool frequency by visit based on patient diary.		

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Name of finished product: NA			
Name of active ingredient: BI655066/ABBV-066 (risankizumab)			
Protocol date: 28 Apr 2017	**Trial number:** 1311.20/M15-989		**Revision date:** 25 July 2018
Criteria for efficacy:	• Stool consistency by visit based on patient diary. • Change from baseline in abdominal pain score by visit based on patient diary, with possible answers none, mild, moderate and severe. • Change from baseline in IBDQ scores by visit. • Change from baseline in CRP and fecal calprotectin profile by visit. • Reduction in the number of draining fistulas in patients with draining fistulas at baseline.		
Criteria for safety:	Physical examination, vital signs (BP, HR, oral body temperature), 12-lead ECG, laboratory tests (haematology, clinical chemistry and urinalysis), adverse events, immunogenicity.		
Criteria for pharmacokinetics:	Pharmacokinetic parameters of BI 655066/ABBV-066 (risankizumab): PK concentrations, trough levels, descriptive statistics and pharmacokinetic parameters as appropriate.		
Statistical methods:	Endpoints will be summarized descriptively, there is no statistical model.		

FLOW CHART 1: PATIENTS (1) ROLLING-OVER AT WEEK 26 FROM PRECEDING TRIAL 1311.6 (WITH CLINICAL RESPONSE BUT NOT REMISSION AT VISIT E1); OR (2) WHO MAINTAINED RESPONSE OR REMISSION AFTER COMPLETION OF TRIAL 1311.6, VISITS 1-18

Trial Period	**Screening**		**Treatment period**																
Visit	**1**[1,2]	**1.1**[14]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Week	**0**	**1**	**4**	**12**	**20**	**28**	**36**	**44**	**52**	**60**	**68**	**76**	**84**	**92**	**100**	**108**	**116**	**124**	**132**
Time window (days)	+5	+5	± 7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Informed consent	X																		
Assessment of eligibility	X																		
LABS/SAFETY ASSESSMENTS																			
Detailed physical examination	X																		
Targeted physical examination (incl. vital signs)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12 Lead Resting-ECG	X								X						X				
Urine Pregnancy test[4]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests (serum chemistry, hematology, urinalysis)[9]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QuantiFERON-TB Gold In-Tube test[5]	X								X						X				

Trial Period	**Screening**		**Treatment period**																
Visit	**1**[1,2]	**1.1**[14]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Week	**0**	**1**	**4**	**12**	**20**	**28**	**36**	**44**	**52**	**60**	**68**	**76**	**84**	**92**	**100**	**108**	**116**	**124**	**132**
Time window (days)	**+5**	**+5**	± 7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
EFFICACY ASSESSMENTS																			
Dispense patient diary for screening[14]	X																		
Crohn's Disease Activity Index (CDAI), PRO-2	X[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review patient diary	X[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fistula exam	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inflammatory Bowel Disease Questionnaire (IBDQ)[12]			X			X			X			X			X			X	
Ileocolonoscopy (CDEIS)	X[1]								X							X			
OTHER ASSESSMENTS																			
Pharmacokinetics[13]	X			X		X		X		X		X		X		X		X	
Anti-drug antibodies[13]	X			X		X		X		X		X		X		X		X	
CRP[9]	X			X		X		X		X		X		X		X		X	X
Fecal calprotectin	X					X				X				X				X	
Soluble protein biomarkers in serum[9]	X					X				X				X				X	
Previous and concomitant therapy	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[6]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Trial Period	Screening		Treatment period																
Visit	**1**[1,2]	**1.1**[14]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Week	**0**	**1**	**4**	**12**	**20**	**28**	**36**	**44**	**52**	**60**	**68**	**76**	**84**	**92**	**100**	**108**	**116**	**124**	**132**
Time window (days)	**+5**	**+5**	± 7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
TRIAL MEDICATION																			
Contact IRT	X[15]	X[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administration of trial medication[7]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

FLOW CHART 1: PATIENTS (1) ROLLING-OVER AT WEEK 26 FROM PRECEDING TRIAL 1311.6 (WITH CLINICAL RESPONSE BUT NOT REMISSION AT VISIT E1); OR (2) WHO MAINTAINED RESPONSE AFTER COMPLETION OF TRIAL 1311.6, VISITS 19-EOT

Trial Period	**Treatment period**									
Visit	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**EoT[3]**
Week	**140**	**148**	**156**	**164**	**172**	**180**	**188**	**196**	**204**	
Time window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
LABS/SAFETY ASSESSMENTS										
Detailed physical examination										X
Targeted physical examination (incl. vital signs)	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	X
12 Lead Resting-ECG		X						X		X
Urine Pregnancy test[4]	X	X	X	X	X	X	X	X	X	
Laboratory tests (serum chemistry, hematology, urinalysis)[9]	X	X	X	X	X	X	X	X	X	X
QuantiFERON-TB Gold In-Tube test[5]		X						X		
EFFICACY ASSESSMENTS										
Crohn's Disease Activity Index (CDAI), PRO-2	X	X	X	X	X	X	X	X	X	X
Review patient diary	X	X	X	X	X	X	X	X	X	X

Trial Period	**Treatment period**									
Visit	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**EoT[3]**
Week	**140**	**148**	**156**	**164**	**172**	**180**	**188**	**196**	**204**	
Time window (days)	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Fistula exam	X	X	X	X	X	X	X	X	X	X
Inflammatory Bowel Disease Questionnaire (IBDQ)[12]		X			X			X		X
Ileocolonoscopy (CDEIS)			X						X[10]	X[11]
OTHER ASSESSMENTS										
Pharmacokinetics[13]	X		X		X		X		X	X
Anti-drug antibodies[13]	X		X		X		X		X	X
CRP[9]	X		X	X		X	X		X	X
Fecal calprotectin			X				X		X	X
Soluble protein biomarkers in serum[9]			X				X		X	X
Previous and concomitant therapy	X	X	X	X	X	X	X	X	X	X
Adverse events[6]	X	X	X	X	X	X	X	X	X	X
TRIAL MEDICATION										
Contact IRT	X	X	X	X	X	X	X	X	X	X[8]
Administration of trial medication[7]	X	X	X	X	X	X	X	X	X	

1. Visit 1 of this LT extension study should preferably be performed in one visit combined with the last visit of the preceding trial 1311.6 or during the interim period of maximum 5 days after completion of the last visit in 1311.6. If an EoT colonoscopy has not been performed during E1 within 1311.6, it must be performed between V1 and V2 in 1311.20/M15-989.
2. Assessments performed at the last visit in the previous trial do not have to be repeated at visit 1 in this trial. Assessments scheduled but not performed at the last visit in the previous trial should be repeated at Visit 1 in this trial, and the results entered into the CRFs of both trials 1311.6 and 1311.20/M15-989.
3. For patients who discontinue study medication before scheduled EoT visit, an early EoT visit should be performed. After last dose of study medication, a 140 day follow-up call should be scheduled. Upon EC/CA approvals of Study M16-000 protocol amendment 4, patients receiving treatment in M15-989 will have the option to enroll into M16-000 Sub-Study 3 after completing the EoT visit.
4. Must be performed at Visit 1 and starting from Visit 2 prior to each study drug administration in females of childbearing potential. In case of positive result, serum pregnancy test will be performed. Study drug will only be administered if pregnancy is ruled out.
5. Positive QuantiFERON-TB Gold In-Tube tests need not to be repeated. If TB or infection is suspected at any time during the study, a routine work up including chest x-ray and a QuantiFERON-TB Gold In-Tube test or an infection assessment must be performed at investigator's discretion and according to local guidelines.
6. Assessment of AE after subcutaneous injections will also include assessment of local tolerability. The assessment of local tolerability should be done just before the patient leaves the investigator site.
7. All assessments are to be completed prior to study drug administration, unless otherwise specified.
8. An end of trial call should be performed for both patients that agree to enroll into M16-000 Sub-Study 3 OLE or those that do not choose to participate.
9. For details of laboratory tests see Section 5.2.3, Table 5.2.3:1and Table 5.2.3:2.
10. Every effort should be made for the patient to perform a final ileocolonoscopy at the study visit where the last dose of study medication is administered. For patients with early EoT, every effort should be made to perform a final ileocolonoscopy within 2 weeks following the early EoT visit.
11. Colonoscopy is not to be repeated if done at preceding visit.
12. IBDQ should be completed before site staff interaction and study drug administration.
13. Blood samples for PK and ADA will be drawn BEFORE drug administration, i.e. pre-dose, whenever visits coincide.
14. Visit 1.1 is applicable only for those patients that had visit E1 more than 5 days before Visit 1. Visit 1.1 can be performed by phone, fax or email.
15. IRT has to be called only once at V1 or V1.1 after assessment if s.c or i.v. re-induction is needed.
16. In case patient had visit E1 less than 5 days before Visit 1, CDAI assessment and new patient diary dispense should be done at Visit 1.

FLOW CHART 2: PATIENTS (1) ROLLING-OVER AT WEEK 52 FROM PRECEDING TRIAL 1311.6 (WITH CLINICAL RESPONSE OR REMISSION AT VISIT E5) VISITS 1-18

Trial Period	**Screening**		**Treatment period**																
Visit	**1**[1,2]	**1.1**[14]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Week	**0**	**1**	**6**	**14**	**22**	**30**	**38**	**46**	**54**	**62**	**70**	**78**	**86**	**94**	**102**	**110**	**118**	**126**	**134**
Time window (days)	+5	+5	± 7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Informed consent	X																		
Assessment of eligibility	X																		
LABS/SAFETY ASSESSMENTS																			
Detailed physical examination	X																		
Targeted physical examination (incl. vital signs)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12 Lead Resting-ECG	X								X						X				
Urine Pregnancy test[4]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests (serum chemistry, hematology, urinalysis)[9]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QuantiFERON-TB Gold In-Tube test[5]	X								X						X				

Trial Period	**Screening**		**Treatment period**																
Visit	**1**[1,2]	**1.1**[14]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Week	**0**	**1**	**6**	**14**	**22**	**30**	**38**	**46**	**54**	**62**	**70**	**78**	**86**	**94**	**102**	**110**	**118**	**126**	**134**
Time window (days)	**+5**	**+5**	± 7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
EFFICACY ASSESSMENTS																			
Dispense patient diary for screening[14]	X																		
Crohn's Disease Activity Index (CDAI), PRO-2	X[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review patient diary	X[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fistula exam	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inflammatory Bowel Disease Questionnaire (IBDQ)[12]			X			X			X			X			X			X	
Ileocolonoscopy (CDEIS)	X[1]								X							X			
OTHER ASSESSMENTS																			
Pharmacokinetics[13]	X			X		X		X		X		X		X		X		X	
Anti-drug antibodies[13]	X			X		X		X		X		X		X		X		X	
CRP[9]	X			X		X		X		X		X		X		X		X	X
Fecal calprotectin	X					X				X				X				X	
Soluble protein biomarkers in serum[9]	X					X				X				X				X	
Previous and concomitant therapy	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[6]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TRIAL MEDICATION																			
Contact IRT	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administration of trial medication[7]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

FLOW CHART 2: PATIENTS (1) ROLLING-OVER AT WEEK 52 FROM PRECEDING TRIAL 1311.6 (WITH CLINICAL RESPONSE OR REMISSION AT VISIT E5); VISITS 19-EOT

Trial Period	**Treatment period**									
Visit	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**EoT[3]**
Week	**142**	**150**	**158**	**166**	**174**	**182**	**190**	**198**	**206**	
Time window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
LABS/SAFETY ASSESSMENTS										
Detailed physical examination										X
Targeted physical examination (incl. vital signs)	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	X
12 Lead Resting-ECG		X						X		X
Urine Pregnancy test[4]	X	X	X	X	X	X	X	X	X	
Laboratory tests (serum chemistry, hematology, urinalysis)[9]	X	X	X	X	X	X	X	X	X	X
QuantiFERON-TB Gold In-Tube test[5]		X						X		
EFFICACY ASSESSMENTS										
Crohn's Disease Activity Index (CDAI), PRO-2	X	X	X	X	X	X	X	X	X	X
Review patient diary	X	X	X	X	X	X	X	X	X	X

Trial Period	**Treatment period**									
Visit	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**EoT[3]**
Week	**142**	**150**	**158**	**166**	**174**	**182**	**190**	**198**	**206**	
Time window (days)	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Fistula exam	X	X	X	X	X	X	X	X	X	X
Inflammatory Bowel Disease Questionnaire (IBDQ)[12]		X			X			X		X
Ileocolonoscopy (CDEIS)			X						X[10]	X[11]
OTHER ASSESSMENTS										
Pharmacokinetics[13]	X		X		X		X		X	X
Anti-drug antibodies[13]	X		X		X		X		X	X
CRP[9]	X		X	X		X	X		X	X
Fecal calprotectin			X				X		X	X
Soluble protein biomarkers in serum[9]			X				X		X	X
Previous and concomitant therapy	X	X	X	X	X	X	X	X	X	X
Adverse events[6]	X	X	X	X	X	X	X	X	X	X
TRIAL MEDICATION										
Contact IRT	X	X	X	X	X	X	X	X	X	X[8]
Administration of trial medication[7]	X	X	X	X	X	X	X	X	X	

1. Visit 1 of this LT extension study should preferably be performed in one visit combined with the last visit of the preceding trial 1311.6 or during the interim period of maximum 5 days after completion of the last visit in 1311.6. If an EoT colonoscopy has not been performed during E5 within 1311.6, it must be performed between V1 and V2 in 1311.20/M15-989.
2. Assessments performed at the last visit in the previous trial do not have to be repeated at visit 1 in this trial. Assessments scheduled but not performed at the last visit in the previous trial should be repeated at visit 1 in this trial, and the results entered into the CRFs of both trials 1311.6 and 1311.20/M15-989.
3. For patients who discontinue study medication before scheduled EoT visit, an early EoT visit should be performed. After last dose of study medication, a 140 day follow-up call should be scheduled. Upon EC/CA approvals of Study M16-000 protocol amendment 4, patients receiving treatment in M15-989 will have the option to enroll into M16-000 Sub-Study 3 after completing the EoT visit.
4. Must be performed at Visit 1 and starting from Visit 2 prior to each study drug administration in females of childbearing potential. In case of positive result, serum pregnancy test will be performed. Study drug will only be administered if pregnancy is ruled out.
5. Positive QuantiFERON-TB Gold In-Tube tests need not to be repeated. If TB or infection is suspected at any time during the study, a routine work up including chest x-ray and a QuantiFERON-TB Gold In-Tube test or an infection assessment must be performed at investigator's discretion and according to local guidelines.
6. Assessment of AE after subcutaneous injections will also include assessment of local tolerability. The assessment of local tolerability should be done just before the patient leaves the investigator site.
7. All assessments are to be completed prior to study drug administration, unless otherwise specified.
8. An end of trial call should be performed for both patients that agree to enroll into M16-000 Sub-Study 3 OLE or those that do not choose to participate.
9. For details of laboratory tests see Section 5.2.3, Table 5.2.3:1 and Table 5.2.3:2
10. Every effort should be made for the patient to perform a final ileocolonoscopy at the study visit where the last dose of study medication is administered. For patients with early EoT, every effort should be made to perform a final ileocolonoscopy within 2 weeks following the early EoT visit.
11. Colonoscopy is not to be repeated if done at preceding visit.
12. IBDQ should be completed before site staff interaction and study drug administration.
13. Blood samples for PK and ADA will be drawn BEFORE drug administration, i.e. pre-dose, whenever the visits coincide.
14. Visit 1.1 is applicable only for those patients that had visit E5 more than 5 days before Visit 1. Visit 1.1 can be performed by phone, fax or email.
15. In case patient had visit E5 less than 5 days before Visit 1, CDAI assessment and new patient diary dispense should be done at Visit 1.

FLOW CHART 3: PATIENTS ROLLING-OVER WHO HAVE LOST RESPONSE OR REMISSION AFTER COMPLETION OF TRIAL 1311.6 EITHER AT VISIT E1 OR E5, VISITS 1-18

Trial Period	**Screening**		**Re-induction**			**Treatment period**														
Visit	**1**[1, 2]	**1.1**[15]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Week	**0**	**1**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**56**	**64**	**72**	**80**	**88**	**96**	**104**	**112**	**120**	**128**
Time window (days)	**+5**	**+5**	**± 7**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Informed consent	X																			
Assessment of eligibility	X					X[14]														
LABS/SAFETY ASSESSMENTS																				
Detailed physical examination	X																			
Targeted physical examination (incl. vital signs)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12 Lead Resting-ECG	X											X						X		
Urine Pregnancy test[4]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests (serum chemistry, hematology, urinalysis)[9]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QuantiFERON-TB Gold In-Tube test[5]	X									X						X				

Trial Period	Screening		Re-induction			Treatment period														
Visit	**1**[1,2]	**1.1**[15]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Week	**0**	**1**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**56**	**64**	**72**	**80**	**88**	**96**	**104**	**112**	**120**	**128**
Time window (days)	**+5**	**+5**	**± 7**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
EFFICACY ASSESSMENTS																				
Dispense patient diary for screening	X																			
Crohn's Disease Activity Index (CDAI), PRO-2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review patient diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fistula exam	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inflammatory Bowel Disease Questionnaire (IBDQ)[12]						X			X			X			X			X		
Ileocolonoscopy (CDEIS)	X[1]											X							X	
OTHER ASSESSMENTS																				
Pharmacokinetics[13]	X						X		X		X		X		X		X		X	
Anti-drug antibodies[13]	X						X		X		X		X		X		X		X	
CRP[9]	X						X		X		X		X		X		X		X	
Fecal calprotectin	X						X		X				X				X			
Soluble protein biomarkers in serum[9]	X						X		X				X				X			
Previous and concomitant therapy	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[6]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TRIAL MEDICATION																				
Contact IRT	X[16]	X[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administration of trial i.v. medication[7]			X	X	X															
Administration of trial s.c. medication[7]						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

FLOW CHART 3: PATIENTS ROLLING-OVER WHO HAVE LOST RESPONSE OR REMISSION AFTER COMPLETION OF TRIAL 1311.6 EITHER AT VISIT E1 OR E5, VISITS 19-EOT

Trial Period	**Treatment period**											
Visit	**20**	**219**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**EoT[3]**
Week	**136**	**144**	**152**	**160**	**168**	**176**	**184**	**192**	**200**	**208**	**216**	
Time window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
LABS/SAFETY ASSESSMENTS												
Detailed physical examination												X
Targeted physical examination (incl. vital signs)	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X
12 Lead Resting-ECG				X						X		X
Urine Pregnancy test[4]	X	X	X	X	X	X	X	X	X	X	X	
Laboratory tests (serum chemistry, hematology, urinalysis)[9]	X	X	X	X	X	X	X	X	X	X	X	X
QuantiFERON-TB Gold In-Tube test[5]		X						X				
EFFICACY ASSESSMENTS												
Crohn's Disease Activity Index (CDAI), PRO-2	X	X	X	X	X	X	X	X	X	X	X	X
Review patient diary	X	X	X	X	X	X	X	X	X	X	X	X

Trial Period	**Treatment period**											
Visit	**20**	**219**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**EoT[3]**
Week	**136**	**144**	**152**	**160**	**168**	**176**	**184**	**192**	**200**	**208**	**216**	
Time window (days)	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Fistula exam	X	X	X	X	X	X	X	X	X	X	X	X
Inflammatory Bowel Disease Questionnaire (IBDQ)[12]	X			X			X			X		X
Ileocolonoscopy (CDEIS)					X						X[10]	X[11]
OTHER ASSESSMENTS												
Pharmacokinetics[13]	X		X		X		X		X		X	X
Anti-drug antibodies[13]	X		X		X		X		X		X	X
CRP[9]	X	X	X		X	X		X	X		X	X
Fecal calprotectin	X				X				X		X	X
Soluble protein biomarkers in serum[9]	X				X				X		X	X
Previous and concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[6]	X	X	X	X	X	X	X	X	X	X	X	X
TRIAL MEDICATION												
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X[8]
Administration of trial i.v. medication[7]												
Administration of trial s.c. medication[7]	X	X	X	X	X	X	X	X	X	X	X	

1. If an EoT colonoscopy has not been performed during E1/E5 within 1311.6, or if the patient had a treatment interruption followed by a clinical relapse, it must be performed between V1 and V2 in 1311.20/M15-989.
2. Assessments performed at visit E1/E5 in the previous trial do not have to be repeated at Visit 1 in this trial. Assessments scheduled but not performed at Visit E1/E5 in the previous trial should be repeated at visit 1 in this trial, and the results entered into the CRFs of both trials, 1311.6 and 1311.20/M15-989.
3. For patients who discontinue study medication before scheduled EoT visit, an early EoT visit should be performed. After last dose of study medication, a 140 day follow-up call should be scheduled. Upon EC/CA approvals of Study M16-000 protocol amendment 4, patients receiving treatment in M15-989 will have the option to enroll into M16-000 Sub-Study 3 after completing the EoT visit.
4. Must be performed at Visit 1 and starting from Visit 2 prior to each study drug administration in females of childbearing potential. In case of positive result, serum pregnancy test will be performed. Study drug will only be administered if pregnancy is ruled out.
5. Positive QuantiFERON-TB Gold In-Tube tests need not to be repeated. If TB or infection is suspected at any time during the study, a routine work up including chest x-ray and a QuantiFERON-TB Gold In-Tube test or an infection assessment must be performed at investigator's discretion and according to local guidelines.
6. Assessment of AE after intravenous infusions and subcutaneous injections will also include assessment of local tolerability. The assessment of local tolerability should be done just before the patient leaves the investigator site.
7. All assessments are to be completed prior to study drug administration, unless otherwise specified.
8. An end of trial call should be performed for both patients that agree to enroll into M16-000 Sub-Study 3 OLE or those that do not choose to participate.
9. For details of laboratory tests see Section 5.2.3, Table 5.2.3:1 and Table 5.2.3:2.
10. Every effort should be made for the patient to perform a final ileocolonoscopy at the study visit where the last dose of study medication is administered. For patients with early EoT, every effort should be made to perform a final ileocolonoscopy within 2 weeks following the early EoT visit.
11. Colonoscopy is not to be repeated if done at preceding visit.
12. IBDQ should be completed before site staff interaction and study drug administration.
13. Blood samples for PK and ADA will be drawn BEFORE drug administration, i.e. pre-dose, whenever the visits coincide.
14. Clinical response or remission will be compared to 1311.6 baseline (Visit 2), to continue SC medication patients should have response.
15. Visit can be performed by phone, fax or email.
16. IRT has to be called only once at V1 or V1.1 after assessment if s.c or i.v. re-induction is needed.

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ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
AP/ALP	Alkaline Phosphatase
AST	Aspartate aminotransferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
BCG	Bacille Calmette-Guérin
BP	blood pressure
ß-HCG	ß-Human Chorionic Gonadotrophin
CAC	Cardiovascular Adjudication Committee
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CK	Creatine Kinase
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CRF	Case Report Form
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	ethylenediaminetetraacetic acid
ELISA	Enzyme Linked Immunosorbent Assay
EOT	End of Trial
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT/γ-GT	Gamma-Glutamyl Transferase
Hb	Hemoglobin

Hct	Hematocrit
HDL	High density lipoprotein
HPC	Human Pharmacology Centre
HR	heart rate
IB	Investigator's Brochure
IBDQ	Inflammatory Bowel Disease Questionnaire
IEC	Independent Ethics Committee
IFN-γ	Interferon gamma
Ig	Immunglogulin
IRB	Institutional Review Board
IRT	Interactive Response Tool
ISF	Investigator Site File
i.v.	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
LDH	Lactic Dehydrogenase
LDL	Low Density Lipoprotein
LT	Long term
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	milligram
mL	milliliter
MRI	Magnetic Resonance Imaging
MST	Medical Subteam
p.o.	per os (oral)
PCC	Protocol Challenge Committee
PMN	Polymorphonuclear
PRO-2	Patient reported outcome-2
PTT	Partial Thromboplastin Time
q4w	quaque 4 weeks (once in 4 week)
RBC	Red Blood Cell
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual Effect Period
RSI	Reference Safety Information
SAE	Serious Adverse Event
s.c.	subcutaneous
SES-CD	Simple Endoscopic Score in Crohn`s Disease
SOP	Standard Operating Procedures
SPC	Summary of Product Characteristics
TB	Tuberculosis

TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
TMM	Team Member Medicine
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal
xg	times gravity
WBC	White Blood Cells

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Crohn's Disease (CD) is a chronic relapsing, remitting inflammatory disease of the gastrointestinal tract characterized by abdominal pain, fever, and bloody or mucus-containing diarrhea (R13-2231). The disease affects the gastrointestinal tract discontinuously from mouth to anus, but most commonly the ileum and colon (40%), followed by the small bowel only (30%), and the colon only (25%) (R13-2232, R13-2233). It occurs in a relatively young population and there is no marked sex difference.

The annual incidence of CD seems to be increasing with more recent estimates varying from 7.9 to 20.2 cases/100,000, and a prevalence of 161 to 319 cases/100,000 in North America and Europe (R13-2231). Mucosal lesions may be complicated by perforation and fistula formation, which may require hospitalization for medical or surgical management.

Because of myriad symptoms, clinical status is measured using clinical indexes. The most widely used, in clinical trials, is the Crohn's Disease Activity Index (CDAI) (R97-2689). At the mucosal level, the extent of disease can be graded following ileocolonoscopy according to the Crohn's Disease Endoscopic Index of Severity (CDEIS).

Remission of clinical symptoms and endoscopic mucosal healing are predictors of long term improved clinical outcomes, including sustained steroid-free clinical remission, decreased need for surgical intervention, reduction in hospital admissions, improvement in quality of life, and increased work productivity (R13-2413). There is a poor correlation between CDAI and CDEIS. It has been reported that mucosal healing may be better than CDAI for the prediction of long term prognosis (R13-2295, R13-2294).

The mainstay of treatment of moderate to severe CD has been with glucocorticoid therapy, azathioprine, or 6-mercaptopurine (R13-2269). More recently, biologics consisting of monoclonal antibodies directed at cytokines, thought to mediate the pathology, have been used extensively for this indication. In clinical studies of infliximab, adalimumab, and certolizumab pegol, induction of CDAI remission at 4 weeks were in the range of 25 to 35% in contrast to placebo rates of 4 to 12%. At six months, response rates were of approximately 60% and remission rates of 40-50%, compared with 20% in placebo-treated patients. Adverse events reported with these agents include drug-induced lupus, lymphoma, demyelinating diseases, and serious and opportunistic infections, including tuberculosis and systemic fungal infections. Many patients lose response to TNF inhibitors over time, in part due to development of neutralizing or depleting anti-drug antibodies (ADA). Overall, one third of patients fail to respond to initial anti-TNF

therapy (primary non-response), and another third lose their response over time (secondary non-response) (R13-2268, R13-2267, P13-05746, R13-2264, R13-2266, R13-2265). Thus, there remains a significant unmet medical need for better treatments of this disease.

BI 655066/ABBV-066 (risankizumab) is a humanized antibody that is directed against IL-23 p19. Although the etiology of Crohn's Disease (CD) is unknown, data suggest that there is altered immune regulation at the epithelial barrier, leading to overproduction of inflammatory cytokines, tissue destruction, and aberrant tissue repair. Among the cytokines implicated in CD pathogenesis, data at the genetic, human biology and clinical level strongly implicate IL-23 in this disease. In a Phase II placebo-controlled trial of the IL-12/IL-23 antagonist mAb ustekinumab in Crohn's Disease, 34.1 to 39.7% of patients receiving single doses of ustekinumab (1 mg/kg, 3 mg/kg, or 6 mg/kg) had a CDAI response at 6 weeks, compared to 23.5% of patients receiving placebo (R12-5152). In a recent Phase II placebo-controlled trial of the specific IL-23p19 antagonistic mAb MEDI-2070 in moderate to severe Crohn's Disease, 46% of exclusively anti-TNF pretreated patients achieved a clinical response (vs. 25% on placebo) while 27% achieved a clinical remission (vs 15% on placebo) (R15-1973). Therefore, an IL-23 antagonist, whether directed against the p40 or p19 subunit, is likely to be an effective treatment for CD.

1.2 DRUG PROFILE

Preclinical summary

BI 655066/ABBV-066 (risankizumab) binds with high affinity to human and cynomolgus monkey IL-23, but it does not bind to rat or murine IL-23. There was no binding to IL-12 at the highest concentration (100 nM) tested. Binding to human IL-23 was analyzed in the presence of 50% human serum to assess the potential for non-specific binding. BI 655066/ABBV-066 (risankizumab) does not display interference to binding in the presence of 50% serum.

The primary functional cell assay for the IL-23 antibodies measures their ability to inhibit IL-23 stimulated IL-17 production from mononuclear cells isolated from mouse spleens.

Human, cynomologus, rat and mouse recombinant IL-23 are all capable of stimulating IL-17 release from mouse splenocytes with similar EC50 values. The ability of BI 655066/ABBV-066 (risankizumab) to functionally inhibit both a recombinant and natural form of IL-23 was measured in this system. IC50 values for

BI 655066/ABBV-066 (risankizumab) were equivalently low against recombinant (6 pM) and naturally occurring (1 pM) forms of human IL-23 and lower than the IC50 observed with ustekinumab of 167 pM.

BI 655066/ABBV-066 (risankizumab) did not affect IL-12 at a maximum concentration tested of 33 nM and it did not inhibit IL-12 stimulated IFN-γ production, in contrast to a control antibody against IL-12 p70 that completely inhibited IFN-γ output.

A mouse ear inflammation model (R11-1273) of *in vivo* efficacy of BI 655066/ABBV-066 (risankizumab) demonstrated 71% inhibition of ear skin thickness, 100% inhibition of ear tissue IL-17 and 94% inhibition of ear tissue IL-22 after 1 mg/kg of BI 655066/ABBV-066. When ustekinumab was studied in the same model, similar levels of inhibition in IL-17 and IL-22 levels were seen at a dose of 1 mg/kg of ustekinumab as with 0.1 mg/kg of BI 655066/ABBV-066. These results suggest that BI 655066/ABBV-066 (risankizumab) may have higher potency than ustekinumab.

Toxicology summary

No adverse findings have been identified in any of the toxicology studies using BI 655066/ABBV-066 (risankizumab).

In the 26 week monkey toxicity study, marginal but transient test article-related decreases in B lymphocytes were noted only at Month 1 in ≥5mg/kg/week animals (both sexes), but this change was not noted at 3 or 6 month time points. Given the small magnitude of change and the transient nature of the decrease in B lymphocytes, this is not considered an adverse change. Also in the 26 week study, hypospermatogenesis was observed at a low incidence in the testes of ≥ 5 mg/kg/week males and correlated with a reduction in testes weights only in 50 mg/kg/week males. Following 8 weeks of recovery, there was no testicular pathology or testis weight effect in 50 mg/kg/week males. The hypospermatogenesis was not considered as an adverse event given the small magnitude of change and no corresponding decrease of epididymal sperm. In contrast, an external expert panel interpreted these findings as normal variations associated with the onset of puberty that were not considered to represent testicular toxicity related to treatment with BI 655066/ABBV-066 (risankizumab). Moreover, a repeat 26 week male fertility study in sexually mature monkeys demonstrated that weekly subcutaneous administration of BI 655066/ABBV-066 (risankizumab) at 50 mg/kg/week for 26 weeks to sexually mature male cyno monkeys produced no BI 655066/ABBV-066 (risankizumab) related effects on reproductive parameters.

The toxicology data suggest BI 655066/ABBV-066 (risankizumab) can be safely administered to humans, as supported by chronic administration to monkeys for up to

26 weeks. The monkey was identified as the most relevant toxicology species with a NOAEL of 50 mg/kg/dose, corresponding to an exposure (combined sex) of 677 µg/mL for the Cmax and 86,250 µg.h/mL for AUC0-168, respectively.

Clinical summary

BI 655066/ABBV-066 (risankizumab) has been studied in a randomized, double blind, single dose trial in a total of 39 patients with moderate to severe psoriasis (Study 1311.1). BI 655066/ABBV-066 (risankizumab) was administered i.v. in ascending doses ranging 0.01 mg/kg to 5 mg/kg i.v., or s.c. in doses of 0.25 mg/kg or 1 mg/kg. After a single i.v. administration, exposure (Cmax and AUC) to BI 655066/ABBV-066 (risankizumab) increased with dose in an approximately dose-proportional manner. The variability and the estimates of the pharmacokinetic parameters after i.v. dosing of BI 655066/ABBV-066 (risankizumab) appears to be in line with other mAbs binding a soluble target. The geometric mean half-life of BI 655066/ABBV-066 (risankizumab) ranged from approximately 20-28 days. The Tmax occurred at approximately 1 to 2 h from start of i.v. infusion in all patients given BI 655066/ABBV-066 (risankizumab).

Mean Psoriasis Area and Severity Index (PASI) scores showed no relevant change over time among placebo treated patients, but showed marked improvements among the BI 655066/ABBV-066 (risankizumab) treatment groups in Study 1311.1. At doses of 0.25 mg/kg and above, all dose groups showed improvement in mean PASI scores of at least 75% from baseline by week 12, which lasted at least until week 20. Similar improvements were observed in both of the BI 655066/ABBV-066 (risankizumab) subcutaneous dose groups.

In a subsequent randomized double-dummy design phase IIb trial, 166 patients with moderate or severe plaque psoriasis were randomly assigned to one of three dose regimens of BI 655066/ABBV-066 (risankizumab) (18/0, 90/90 or 180/180 mg s.c. at weeks 0 and 4) or ustekinumab (45 or 90 mg, per weight, s.c. at weeks 0 and 4). The primary endpoint was PASI 90 at week 12, comparing BI 655066/ABBV-066 (risankizumab) with ustekinumab. In the pre-specified primary analysis of the 90 and 180 mg BI 655066/ABBV-066 (risankizumab) doses (pooled), BI 655066/ABBV-066 (risankizumab) was superior to ustekinumab (PASI 90 77.1% for BI 655066/ABBV-066 (risankizumab) vs 40.0% for ustekinumab [$p<0.0001$]). Ninety percent of BI 655066/ABBV-066 (risankizumab) patients had sPGA of clear or almost clear compared with 67.5% for ustekinumab. Forty-six percent of BI 655066/ABBV-066 (risankizumab) patients had complete clearing of lesions (PASI 100) compared with 17.5% for ustekinumab. AEs were similar across treatment groups with no drug-related severe or serious AEs. Thus, selective blockade of IL-23p19 with BI 655066/ABBV-066

(risankizumab) was associated with clinical responses superior to ustekinumab in patients with moderate-to-severe plaque psoriasis.

The overall safety profile of risankizumab is consistent with its mechanism of action. Across all indications and doses, the most frequently reported AEs (AEs or serious AEs that received at least 1 dose of risankizumab) were nasopharyngitis, upper respiratory tract infection, headache, and arthralgia. Based on the review of all the risankizumab safety data to date, there are no important identified risks.

For further details see the Investigators Brochure.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

The etiology of CD is unknown but data suggests altered immune regulation at the epithelial barrier leading to overproduction of inflammatory cytokines, tissue destruction and aberrant tissue repair (R13-2231).

Biologic agents targeting TNFα, a cytokine thought to mediate the pathology of CD, have been used extensively for this indication. However, one-third of patients do not respond to anti-TNF agents, and another third of patients have only a transient response (R13-2268, R13-2267, P13-05746, R13-2264, R13-2266, R13-2265). There remains a high unmet medical need for effective therapies for CD, particularly with a different mode of action that overcomes current treatment limitations.

Among the cytokines involved in CD pathogenesis, data at the genetic, human biology and clinical level strongly suggests the role of IL-23 in this disease (R13-2625; R12-5152). Analysis of tissue obtained from surgical biopsies or endoscopies has shown that IL-23 and IL-23R are upregulated in the inflamed mucosa of CD (R12-1009). Data from T cell-driven murine models of colitis support the role of IL-23 in gut pathology (R11-1269; R11-1271). Ustekinumab, an IL-12/IL-23 p40 antagonist mAb, has shown clinical efficacy in Phase II studies of CD (R12-5152). Furthermore, the IL-23 p19 antibody MEDI-2070 has shown very promising activity in patients with CD who have failed one or more anti-TNF treatments before (R15-1973). Finally, BI 655066/ABBV-066 (risankizumab) has shown superior clinical efficacy with comparable safety compared to ustekinumab in a phase II trial in chronic plaque psoriasis, another disease associated with dysregulation of the IL-23 pathway (P15-03262).

Together, these observations suggest that BI 655066/ABBV-066 (risankizumab) may demonstrate efficacy in this disease.

2.2 TRIAL OBJECTIVES

The purpose of this long term safety extension trial is to provide subjects who responded to treatment with BI 655066/ABBV-066 (risankizumab) in a preceding trial with a long-term treatment option.

The primary objective of the study is to investigate long-term safety of BI 655066/ABBV-066 (risankizumab), in patients with moderately to severely active Crohn`s disease, who showed a clinical response or remission on previous treatment with BI 655066/ABBV-066 (risankizumab) and are now receiving long term treatment.

Additional objectives of this study are to further investigate long-term efficacy, tolerability, pharmacokinetics, pharmacodynamics and immunogenicity of BI 655066/ABBV-066 (risankizumab).

Study endpoints are listed in Section 5.1.1.

2.3 BENEFIT - RISK ASSESSMENT

The preclinical and clinical profiles of BI 655066/ABBV-066 (risankizumab) suggest that it profoundly inhibits IL-23 in patients with psoriasis and thus has the potential to address unmet medical need in Crohn's disease, as shown for other IL23 inhibitors before (see Section 1.2) (R15-1973). Since Crohn's disease is a chronic disease that typically requires long-term treatment, a direct benefit for the individual participants in this study can be assumed, since only such patients will be enrolled that have achieved a clinical response to this compound in the preceding trial 1311.6.

In addition, participation in this study may help to generate a group benefit by providing a new treatment modality for the population of patients with moderate or severe Crohn's disease if BI 655066/ABBV-066 (risankizumab) proves to be successful in treating this disease.

Though there are no serious adverse drug reactions known to be associated with risankizumab therapy, risks of participating in this study include risk of infection and risks related to the trial specific procedures blood sampling, infusion and injection of study medication, and ileocolonoscopy.

Blood sampling, intravenous infusions and subcutaneous injections can cause local bruising, inflammation, and pain. Ileocolonoscopy although generally well tolerated, can be associated with diarrhoea, abdominal pain, perforation, bleeding, effects from anaesthetic medications and infection.

As with any immune modulating agent, BI 655066/ABBV-066 (risankizumab) has the potential to impair immune function resulting in an increased risk of infections. This will be addressed by clinical monitoring for AEs during the treatment and observation periods.

Interferon gamma (IFN-γ) release assay to *M. tuberculosis* will be obtained at visit 1, to exclude or discontinue patients with untreated active or latent TB infection. All patients with negative TB screening at baseline will be re-tested once per year in order to exclude possible active or latent TB infection. Patients having current signs or symptoms of infection or history of serious infection will not be included in the study.

Major adverse cardiovascular events, including myocardial infarction, cerebrovascular accident, and cardiovascular death, have been reported in patients with Psoriasis treated with the anti-IL-12/23 agents, ustekinumab and briakinumab, based on their frequent co-morbidities associated with cardiovascular risk. Such an association has not been reported in other diseases and 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. However, all suspected cardio- and cerebro-vascular events (serious or nonserious) observed in this study will be adjudicated by an independent cardiovascular adjudication committee (CAC) during long-term treatment.

Local reactions to s.c. administered biologic agents are uncommon, and are usually limited to redness, swelling or induration at the injection site. Manifestations of systemic infusion reactions include anaphylaxis, pruritus, hypotension, and respiratory distress. Both local and systemic hypersensitivity reactions were rare in phase II, readily detectable, transient in nature, and manageable with standard medical treatment. No systemic hypersensitivity reactions have been reported with BI 655066/ABBV-066 (risankizumab) to date. Patients will be closely monitored for at least 2 to 3 hours after start of i.v. drug administration whereas 30 minutes to 1 hour after s.c. drug administration for signs of redness, swelling or hardness at the injection site or generalized itching, dizziness or difficulty breathing.

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.

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients' safety.

Summary of benefit-risk assessment

The benefit-risk profile is considered appropriate for an experimental therapy at this stage of clinical development. In order to mitigate any safety signals as early as possible, an independent DMC will oversee this study.

The independent external CAC will be adjudicating observed cardio- and cerebro-vascular events. The events that are adjudicated and the adjudication process will be detailed in the Cardiovascular Adjudication Committee Charter. Dedicated eCRFs will be used for events of myocardial infarction-unstable angina, stroke-transient ischemic attack, and death. In addition, the site may be contacted for additional source documentation for relevant events.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This open label long term extension trial investigates the long term safety and efficacy of BI 655066/ABBV-066 (risankizumab). Approximately 60 patients who meet the entry criteria are planned for inclusion in this trial, rolling over from preceding trial 1311.6. The treatment will be open label.

The treatment period will be 204 (Flow chart 1), 206 (Flow chart 2) or 216 (Flow chart 3) weeks, followed by a 140 day follow up period.

Patients rolling over from preceding trial 1311.6 will have to complete period 2 or 3 in that trial and either demonstrate a clinical response without remission at Visit E1 or a clinical response or remission at Visit E5 as defined by that protocol (see Figure 3.1:1).

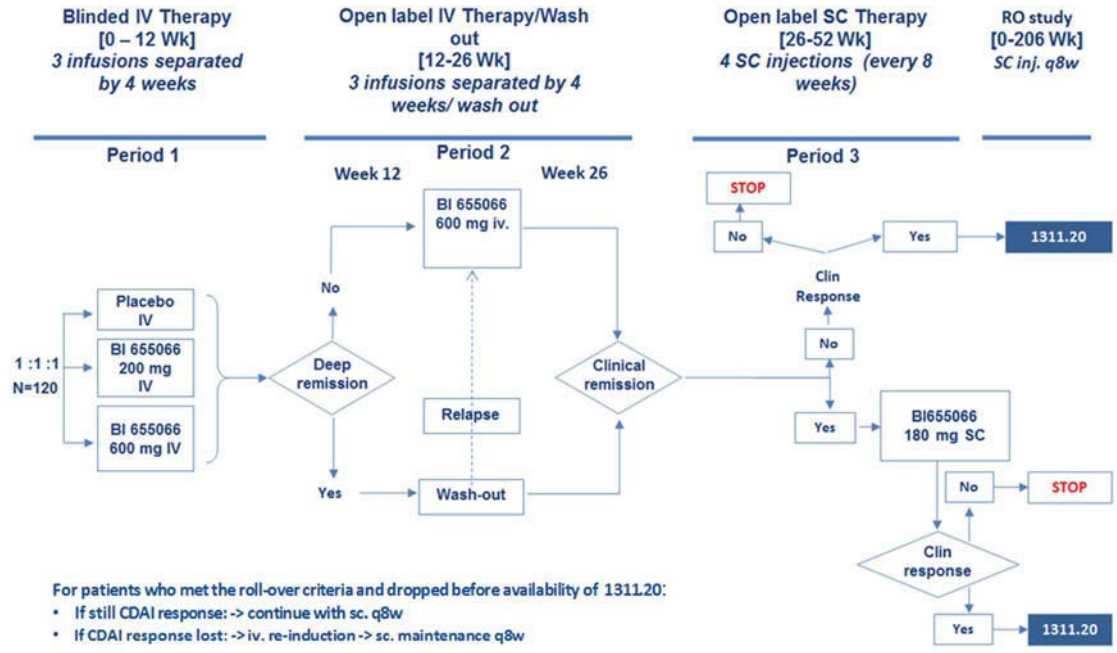


Figure 3.1:1 Guideline for roll over of patients from 1311.6 to long term extension study 1311.20/M15-989

All patients directly rolled over from 1311.6 into 1311.20/M15-989 will receive 180 mg BI 655066/ABBV-066 (risankizumab) subcutaneously from visit 2 onwards every

8 weeks, until the EoT visit is performed. Patients who complete this study may elect to continue in M16-000 Sub-Study 3 (Phase 3 open label extension study).

Patients who have completed 1311.6 qualifying for roll-over into 1311.20/M15-989 before availability of this study, can be enrolled depending on their clinical remission or response. If patients were treated between finishing 1311.6 and entering 1311.20/M15-989 with anti-TNF therapy or any biologic agent an 8 weeks or 5 times the half-life (whichever is longer), wash-out period will be needed before administration of first i.v or s.c. study medication. Patients must maintain their best response status (clinical response or remission) post 1311.6. Patients who dropped from 1311.6 with remission must maintain remission or undergo re-induction while responders will have to maintain their response.

- If clinical response or remission (CDAI drop >100 from baseline of 1311.6 or CDAI < 150) was maintained after end of treatment and is confirmed at screening for 1311.20/M15-989, patients can directly be assigned to open label s.c. maintenance treatment with 180 mg every 8 weeks (FLOW CHART 1) (visit window between last IMP dose in 1311.6 and first IMP dose in 1311.20/M15-989 should be at least 8 weeks).
- If clinical remission (achieved at E5 1311.6) has been lost after end of treatment in 1311.6 and/or at screening for 1311.20/M15-989, patients will receive open label i.v. re-induction treatment with three infusions of 600 mg each every 4 weeks after which eligibility will be re-assessed. If clinical remission or at least response compared to 1311.6 study baseline (V2) is achieved patients will switch to s.c. maintenance treatment with 180 mg s.c. every 8 weeks (Flow chart 3), otherwise an EoT visit has to be performed. After last administration of trial drug in 1311.20/M15-989 trial, a 140 day follow up call should be scheduled for patients who do not elect to enroll in Study M16-000.
- If clinical response (achieved at E1 or E5 1311.6) has been lost after end of treatment in 1311.6 and/or at screening for 1311.20/M15-989, patients will receive open label i.v. re-induction treatment with three infusions of 600 mg each every 4 weeks after which eligibility will be re-assessed. If clinical response or remission compared to 1311.6 study baseline (V2 1311.6) is achieved patients will switch to s.c. maintenance treatment with 180 mg s.c. every 8 weeks (Flow chart 3), otherwise an EoT visit has to be performed. After last administration of trial drug in 1311.20/M15-989 trial, a 140 day follow up call should be scheduled for patients who do not elect to enroll in Study M16-000.

The results from the last colonoscopy done in 1311.6 will serve as baseline for 1311.20/M15-989. A colonoscopy at screening is only required for patients who lost

response or remission during extended follow-up phase after completion of 1311.6. Colonoscopies are repeated once per year to assess the effect of continued treatment on endoscopic response and mucosal healing.

The end of study is defined as the date the last subject completes the End of trial visit

The primary analysis will be performed after all patients have completed their EoT visit. The reference values for the efficacy endpoints clinical or endoscopic response will be the baseline values in 1311.6.

For details regarding Adverse event and serious adverse event reporting, see Section 5.2.2.2

3.1.1 Administrative structure of the trial

The trial is sponsored by AbbVie, Inc.

A Co-ordinating Investigator will be nominated to coordinate investigators at different sites participating in this multicentre trial. Tasks and responsibilities for the Co-ordinating Investigators will be defined in a contract filed before initiation of the trial.

Documents on participating (Principal) investigators and other important participants, especially their curricula vitae, will be filed in the CTMF.

All documentation collected during the trial and filed in the CTMF will be transitioned to AbbVie, Inc.

Details of the trial supplies including responsible institutions are given in Section 4 of this protocol.

Details regarding Interactive Response Tool (IRT) used in this trial are provided in the ISF.

Details regarding procedures pertaining to central laboratory will be provided in the Laboratory Manual in ISF.

External vendors will be contracted to centrally manage videotapes of ileocolonoscopies. Details regarding the procedures pertaining to the central image managing system will be provided in the ISF.

The Investigator Site File (ISF) will be maintained at the sites as required by local regulations. A copy of the ISF documents will be kept as an electronic CTMF document and the CTMF will be transitioned to AbbVie, Inc.

3.1.1.1 Data Monitoring Committee (DMC)

The study will have a DMC independent from the sponsor. The purpose of the DMC is to ensure that the welfare of patients participating in this trial is maintained by:

- Monitoring the trial for possible untoward harmful effects or unexpected frequency of adverse safety events of study drugs;
- Assessing whether the goals of the trial are quite unlikely to be achieved, based on emerging data.

The DMC will perform an evaluation of the accrued patient data in order to recommend whether the trial or program should continue, be modified or stopped for safety concerns or ethical reasons. The DMC will review pertinent trial data, including deaths, SAEs and AEs, laboratory data and efficacy. All materials provided to the DMC are confidential. The tasks and responsibilities of the DMC will be filed in a contract before initiation of the trial and will contain written operating procedures. The DMC will maintain written records of all its meetings. Sponsor will remain blinded to these ongoing data reviews.

Details on the DMC, including the analyses, the composition of the DMC, the procedures, roles, responsibilities and regular meeting planner are provided in the DMC charter in the Investigator Site File (ISF).

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

Study 1311.20/M15-989 is designed as an open label, single group trial and is expected to generate long term safety information to support the submission for registration. As noted in Section 4.1.3 below, the s.c. dose (180 mg every 8 weeks) from the study 1311.6 will be used in all patients for the maintenance treatment. Since study 1311.6 has not been completed and analysed at the time this study has been designed, the highest induction schedule of three 600 mg infusions every 4 weeks that was found safe in 1311.6 will serve as re-induction dose for patients who lost their response or remission between completion of 1311.6 and enrolment in 1311.20/M15-989.

The goal of this study is to obtain initial on-drug, long-term safety data together with early evidence on the durability of the clinical response, that both will be essential for the licensing authorization application. As typical for an open-label, single-group study, neither powered nor controlled analyses can be obtained. However, the study may yield initial tendencies and at the same time permit early study participants to continue a successful therapy.

3.3 SELECTION OF TRIAL POPULATION

Eligible patients from preceding 1311.6 trial will be offered participation in this long term extension trial based on their achievement of clinical response. The check for patient eligibility will be based upon a successful treatment (Section 3.3.2) of the preceding trial and on signing the Informed Consent for the long term extension trial.

Based on the results for the MEDI-2070 compound with identical mode-of-action, it is expected that up to 50 % of patients in 1311.6 will achieve a clinical response after induction treatment. Assuming a 100% maintenance rate of their response, up to 60 patients may be entered in this trial.

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for study entry

3.3.2 Inclusion criteria

1. Patients with Crohn's disease, who have successfully completed the preceding trial 1311.6. Successful treatment is defined as:

- Completion of period 2 in 1311.6 with a clinical response (drop in CDAI from baseline by ≥100) but no remission (CDAI < 150) at Visit E1; or
- Completion of period 3 in 1311.6 with a clinical response (drop in CDAI from baseline by ≥100) **and** / or remission (CDAI < 150) at Visit E5; or
- Completion of period 2 or 3 in 1311.6 per protocol with a clinical response or remission before initiation of 1311.20/M15-989 may roll-over either directly if that response/remission is maintained or through an open-label i.v. re-induction phase if they have lost their previous response/remission.(for more details see Section 3.1)

2. Female patients:
   a. Women of childbearing potential (not surgically sterilized and between menarche and 1 year postmenopause), that, if sexually active agree to use one of the appropriate medically accepted methods of birth control in addition to the consistent and correct use of a condom from date of screening until 20 weeks after last administration of study medication. Medically accepted methods of contraception are: ethinyl estradiol containing contraceptives, diaphragm with spermicide substance, and intra-uterine-device, or
   b. Surgically sterilized female patients with documentation of prior hysterectomy, tubal ligation or complete bilateral oophorectomy, or
   c. Postmenopausal women with postmenopausal is defined as permanent cessation ≥ 1 year of previously occurring menses, and
   d. Negative serum ß-Human Chorionic Gonadotrophin (ß-HCG) test at screening and urine pregnancy test prior to randomization.

   Male patients:
   a. Who are documented to be sterile, or
   b. Who consistently and correctly use effective method of contraception (i.e., condoms) during the study and 20-weeks after last administration of study medication.
3. Be able to adhere to the study visit schedule and other protocol requirements.

3.3.3 Exclusion criteria

Patients meeting any of the following criteria cannot roll over.

1. Patients who were not compliant with key study procedures (colonoscopy, treatment compliance, endpoint assessment, contraception measures) in preceding trial 1311.6

2. Patients who could not tolerate BI 655066/ABBV-066 (risankizumab) treatment for tolerability or safety reasons in the preceding trial

3. Are pregnant, nursing, or planning pregnancy while enrolled in the study, or within 20 weeks after receiving the last dose of study medication.

4. Patients must agree not to receive a live virus or bacterial or BCG vaccination during the study or up to 12 months after the last administration of study drug.

5. Patients who have developed malignancy, or suspicion of active malignant disease during the preceding trial.

6. Are intending to participate in any other study using an investigational agent or procedure during participation in this study.

7. Cannot adhere to the concomitant medication requirements mentioned in Section 4.2.2.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An excessive rate of withdrawals may render the study results uninterpretable; therefore unnecessary withdrawal of patients must be avoided. Patients who discontinue their treatment early should undergo all study required procedures including an early EoT visit and colonoscopy, as defined in Section 6.

Patients have the right to withdraw from the study at any time without the need to justify the decision.

The sponsor reserves the right to terminate a patient from the trial for non-compliance.

The investigator has the right to remove patients from the study for non-compliance.

Furthermore, patients' treatment must be discontinued early due to lack of efficacy (defined as an endoscopically confirmed CDAI re-increase to >100 points above baseline in 1311.6 and a CDEIS >4), or for other reasons (as described below). If, in the investigator's opinion, such a patient requires alternative medical therapy for their Crohn's disease, the study treatment must be stopped and patients may receive conventional treatment for active disease as per investigator's judgment.

Criteria and rules for stopping patient treatment due to reasons other than lack of efficacy include:

- Development of a toxicity or adverse event which warrants drug discontinuation.
- Development of any potentially life-threatening toxicity.
- Any concomitant illness that prevents compliance.
- The patient is unwilling to continue in the trial.

- Pregnancy in a female participant.
- Patient lost to follow-up despite reasonable efforts to make contact with the patient.
- Patient is no longer able to participate for other medical reasons (e.g., surgery, adverse events or other diseases).
- The DMC may recommend termination or re-design of the trial for other relevant issues of safety.

Patients who discontinue from the study after Visit 2 will be considered as "early discontinuations" and the reason for premature discontinuation must be recorded in the eCRFs. The data will be included in the trial database and will be reported.

3.3.4.2 Discontinuation of the trial by the sponsor

Abbvie Inc., reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site,
2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial, or any other administrative reasons, i.e. termination of clinical development of BI655066 in Crohn's disease,
3. Violation of GCP, the CTP, or the contract by a trial site or investigator, 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

BI 655066/ABBV-066 (risankizumab) will be administered intravenously and/or subcutaneously.

4.1.1 Identity of investigational product and comparator product(s)

The characteristics of the test product for i.v. administration are below.

Substance:	BI 655066/ABBV-066 (risankizumab): Anti-human IL-23p19 mAb
Pharmaceutical formulation:	[redacted]
Chemical name:	Anti-human IL-23p19 mAb
Molecular weight:	Approximately 148 kDa
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	[redacted]
Dose (per infusion)	600 mg
Posology	3 infusions separated by 4 weeks
Route of administration:	i.v. infusions

The characteristics of the test product for s.c. administration are below.

Substance:	BI 655066/ABBV-066 (risankizumab): Anti-human IL-23p19 mAb
Pharmaceutical formulation:	[redacted]
Chemical name:	Anti-human IL-23p19 mAb

Molecular weight:	Approximately 148 kDa
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	[redacted]
Dose (per injection)	180 mg
Posology	Every 8 weeks
Route of administration:	s.c.

4.1.2 Method of assigning patients to treatment groups

Patients directly rolled over from 1311.6 into this study will be assigned to open label s.c. treatment via IRT.

For early completers of 1311.6,i.e. patients who have completed 1311.6 qualifying for roll-over into 1311.20/M15-989 before availability of this study and not treated otherwise, will be assigned per clinical response post study treatment and at screening in 1311.20/M15-989 either to i.v. re-induction treatment or directly to open label s.c. treatment via IRT (as described earlier in Section 3.1)

4.1.3 Selection of doses in the trial

Direct roll-over patients from 1311.6 will receive open label treatment with 180 mg s.c. q8w, representing the maintenance dose tested in phase II, that was found safe and effective in preceding study 1311.6.

Early completers of 1311.6 dependent on clinical response post study treatment and at screening in 1311.20/M15-989 will receive either 180 mg s.c. q8w maintenance treatment or re-induction with 3 infusions of 600 mg i.v. q4w followed by180 mg s.c. q8w maintenance treatment.

4.1.4 Drug assignment and administration of doses for each patient

The dose of BI 655066/ABBV-066 (risankizumab) for s.c. and i.v. injections will be fixed.

The subcutaneous study drug will be administered as an injection in the abdomen, thighs, gluteal region, or upper arms. Injections being given in the same area should be at least 2 cm apart and should not be close to a vein. The injection site should avoid sites where the skin is tender, bruised, erythematous, or indurated, and should be alternated to other areas for subsequent doses.

Supplied BI 655066/ABBV-066 (risankizumab) solution for i.v. administration (concentration 10.0 mg/mL) will be injected into a 100 mL i.v. infusion bag of 5% dextrose in water (D5W) and administered as described in detail in the Investigator Site File *(Instructions for Preparation and Handling of BI 655066/ABBV-066 (risankizumab))*.

Subcutaneous administration of biologic agents involves the risk of local (injection site) or systemic hypersensitivity reactions. Therefore patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 30 minutes following study drug administration. Study personnel should observe the injection site for signs of redness, swelling or hardness. They should also ask subjects about itching, dizziness or shortness of breath. Patients should be advised that if they experience redness, swelling or other changes at the injection site, they should notify site personnel. They should further be advised that if they experience itching all over or a feeling of being swollen, dizzy or short of breath, they should notify site personnel or their own healthcare provider immediately.

The i.v. study drug will be administered under immediate supervision of the physician investigator or a designee with a minimum of a nursing degree. In all cases a physician

investigator must be on-site during administration and until at least 2 hours after the start of drug administration. Patients will remain at the trial center for approximately 1 hour following the end of i.v. administration (2 hours after the first administration)

Detailed procedures for preparing and handling of the study drug are provided in the ISF.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Since this is a single group, open label study, there are no blinding issues and the dose received will be visible in the database.

4.1.5.2 Procedures for emergency unblinding

Not applicable.

4.1.6 Packaging, labelling, and re-supply

The clinical trial supply consists of containers (cartons) with trial- identification that hold the trial medication and is labelled as required per country requirements with the following:

- Trial number
- Name of product and strengths or identification code
- Pharmaceutical form
- Route and mode of administration
- Term "for clinical trial use" (domestic language)
- Sponsor name and address
- Storage conditions
- Medication number
- Batch number
- Expiry date (use-by-date)

Labels must remain affixed to the kits.

Drug supply and inventory will be controlled by IRT. Each kit label will contain a unique kit number. The kit is assigned to a subject via IRT at each dispensing visit. For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Both i.v. and s.c. drug supplies will be kept refrigerated (the recommended storage conditions is +2 - +8°C or 36-46°F) in their original packaging. The trial medication must be stored securely, e.g., in a locked refrigerator or at a pharmacy and must be kept protected from light as well as must not be frozen at any time.

The refrigerator temperature must be recorded each business day. Malfunctions or any temperature excursion must be reported to the Sponsor immediately.

Study drug should be quarantined and not dispensed until AbbVie or AbbVie Temperature Excursion Management System (ATEMS) deems the drug as acceptable.

4.1.8 Drug accountability

Drug supplies, which will be provided by *the* sponsor, must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

All unused medication must be returned to the sponsor. Receipt, usage and return must be documented on the respective forms in the ISF. An account must be given for any discrepancies.

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 study protocol by the IRB / ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre,
- 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 or immediately imminent signing of the clinical trial protocol, (in exceptional cases, medication could already be sent to the site, before its activation via IRT)
- if applicable availability of the proof of a medical licence for the principal investigator,
- for USA availability of the Form 1572.

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 disposition of unused product(s).

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) 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 product(s) received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator / pharmacist / investigational drug storage manager must verify that no remaining supplies are in the investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

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

Concomitant therapies should be limited to those essential for the non-gastrointestinal care of the patient. All concomitant medications and the reason(s) for use will be documented throughout the course of the study.

In case of infusion reactions emerging during or after infusion of BI 655066/ABBV-066 (risankizumab), the investigator should consider in accordance with severity of the reaction and local standard of care to

- immediately interrupt the infusion
- treat with systemic anti-histamines and intravenous steroids

Based on patient's clinical course and medical judgment, the infusion may be re-initiated in case of mild or moderate reactions (according to RCTC grading in Appendix 10.3) at

lower speed with gradual increase to complete the infusion as detailed in the Instructions for Preparation and Handling of BI 655066/ABBV-066 (risankizumab) in the Investigator Site File.

In case of adverse events in need of treatment, symptomatic therapy according to the judgment of the investigator will be permitted. All concomitant and/or rescue therapies will be recorded on the appropriate pages of the eCRF.

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Medications	Restriction time period
Investigational products	4 weeks or 5 half-lives, whichever is greater
5-ASA compounds.	• Rectal 5-ASA compounds are not permitted during the study and must have been discontinued at least 4 weeks prior to visit 2. • Oral 5-ASA compounds must have been at a stable dose for at least 4 weeks prior to visit 2. • If oral 5-ASA compounds were recently discontinued, they must have been discontinued at least 4 weeks prior to visit 2.

Immunomodulators	Patients receiving chronic (i.e., ≥ 12 weeks) treatment with AZA, 6-MP, or MTX prior to visit 2 must have been on a stable dose for at least 4 weeks prior to visit 2 and must continue on this same dose during the study. Patients who have discontinued therapy with AZA, 6-MP, or MTX must have stopped the medication at least 4 weeks prior to visit 2 to be considered eligible for randomisation. Patients must not have received therapy with other known immunomodulators (e.g., 6-thioguanine [6-TG], cyclosporine, tacrolimus, sirolimus, pentoxifylline, or mycophenolate mofetil) or experimental agents (e.g., granulocyte macrophage – colony stimulating factor [GM-CSF]) within 8 weeks or 5 half-lives of agent from visit 2, whichever is longer.
monoclonal antibodies or anti-TNF agents	Patients must not have received therapy **≤ 8 weeks or 5 half-lives (whichever is longer)** from visit 2 and during study treatment period.

4.2.2.1 Restrictions regarding concomitant treatment (cont.)

Medications	Restriction time period
Systemic corticosteroids (eg, prednisone, budesonide)	• Parenteral (SC, IM, or IV) or rectal corticosteroids are not permitted during the study and must not have been used within a 4-week period prior to visit 2. • Oral corticosteroids must be at a prednisone-equivalent dose of ≤ 20 mg/day, or ≤ 6 mg/day of budesonide, and have been at a stable dose for at least 4 weeks prior to visit 2. • If oral corticosteroids were recently discontinued, discontinuation must have been completed at least 3 weeks prior to visit 2.

Crohn's disease-specific antibiotics	If using a Crohn's disease-specific antibiotic for treatment of Crohn's disease, patients must have been using the antibiotic for at least 4 weeks before visit 2 at a stable dose. If not currently using a Crohn's disease-specific antibiotic, the stop date must have been at least 4 weeks prior to visit 2.
Opioids	Patients with regular daily opioid use over the past 3 months before screening are excluded due to the interference of such medication with key efficacy endpoints (CDAI)
Live or attenuated vaccines (during study or 140 days after last dose of study drug)	• live attenuated influenza (intranasal) • herpes zoster • rotavirus • varicella (chicken pox) • measles-mumps-rubella (MMR) or measles mumps rubella varicella • (MMRV) • oral polio vaccine (OPV) • smallpox • yellow fever • Bacille Calmette-Guérin (BCG) • oral typhoid

Tapering of corticosteroids

The tapering of prednisone dosage or equivalent (see Appendix 10.2) of other systemic corticosteroids is requested for patients achieving clinical remission the first time while on treatment with BI 655066. In such patients steroids must be tapered at a maximum rate of 2.5 mg per week to a dosage of 0. If a patient experiences a loss of clinical response (decrease in CDAI < 100 points from baseline on 2 consecutive visits) during steroid tapering, the dosage of prednisone may be increased back to the dosage used at study entry.

4.3 TREATMENT COMPLIANCE

Dose administration compliance will be assured by administration of all study medication under supervision of the investigating physician or a designee at the research site. The measured plasma concentrations will provide additional information about compliance.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - PHARMACODYNAMICS

5.1.1 Endpoint of efficacy

Efficacy endpoints are:

- Clinical remission by visit, defined as a CDAI score of < 150.
- Clinical response by visit, defined by either a CDAI score of < 150 or a CDAI reduction from baseline of at least 100 points.
- PRO-2 remission by visit, defined by a PRO-2 score of < 75
- PRO-2 response by visit, defined as a decrease from baseline of 50 points or more.
- CDEIS remission by visit, defined as a score of 4 or less (for patients with initial isolated ileitis a score of 2 or less)
- CDEIS response by visit, defined as a score of 7 or less (for patients with initial isolated ileitis > 50% reduction from baseline).
- Mucosal healing by visit, defined as the absence of mucosal ulceration.
- Deep remission by visit, defined as clinical remission and endoscopic remission (CDEIS).
- Change from baseline in CDAI scores by visit.
- Change from baseline in PRO-2 scores by visit.
- Change in CDEIS by visit.
- Change in SES-CD by visit.
- CDEIS percentage change from baseline by visit.
- SES-CD percentage change from baseline by visit.
- Reduction of 75% in CDEIS scores from baseline by visit.
- Reduction of 75% in SES-CD scores from baseline by visit.
- Change from baseline in stool frequency by visit based on patient diary.
- Stool consistency by visit based on patient diary.
- Change from baseline in abdominal pain score by visit based on patient diary and scored, with possible answers none, mild, moderate and severe.
- Change from baseline in IBDQ scores by visit.
- Change from baseline in CRP and fecal calprotectin profile by visit.
- Reduction in the number of draining fistulas in patients with draining fistulas at baseline.

5.1.2 Assessment of efficacy

CDAI, PRO-2

The investigator will determine and record the CDAI score throughout the study, as denoted (see Flow chart 1, Flow chart 2 and Flow chart 3). Hematocrit evaluations will be made at each visit by the central laboratory as they are integral to the CDAI calculation.

The Patient reported outcome-2 (PRO-2) includes only the two CDAI items stool frequency and abdominal pain and will be analyzed based on the CDAI responses recorded by the investigator for these two dimensions.

Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ (R97-3472) is a 32-item self-report questionnaire for patients with IBD to evaluate the patient reported outcomes across 4 dimensions: bowel symptoms (loose stools, abdominal pain), systemic symptoms (fatigue, altered sleep pattern), social function (work attendance, need to cancel social events), and emotional function (anger, depression, irritability). Scores range from 32 to 224 with higher scores indicating better outcomes.

The patient will complete the IBDQ before site staff interaction and study drug administration as noted in the Flow chart 1, Flow chart 2 and Flow chart 3.

Tapering of corticosteroids

Any change in the corticosteroid co-medication has to be recorded on the appropriate eCRF page for Crohn's disease specific co-medication. The dose of corticosteroid co-medication should remain stable prior to achieving clinical remission.

CRP and Fecal Calprotectin

Concentration of serum CRP and fecal calprotectin will be measured by the central laboratory, and if necessary by additional specialist laboratories.

Ileocolonoscopy, SES-CD and CDEIS

Every effort should be made for the patient to perform a final ileocolonoscopy at the study visit where the last dose of study medication is administered or within 2 weeks following the premature discontinuation visit.

Lesions detected by ileocolonoscopy will be scored by means of the validated Crohn's Disease Endoscopic Index of Severity (CDEIS). The same endoscopist at the study site will complete the CDEIS for each ileocolonoscopy immediately after the procedure. Investigators will record endoscopies and send the videos to the central imaging laboratory. A central reading of endoscopies will be performed by independent blinded reviewer(s) and the findings will be scored using both, the CDEIS and the SES-CD scores. In case of discrepancies between the local endoscopic and central blinded reviewer, the centrally read scores will be used for efficacy assessments and the trial report.

Fistula response

A fistula response is defined as a ≥ 50% reduction in the number of draining fistulas.

Enterocutaneous fistulas (e.g., perianal and abdominal) will be considered no longer draining (i.e., closed) when there is absence of drainage despite gentle compression. Rectovaginal fistulas will be considered closed based on either physical examination, appropriate MRI imaging or absence of relevant symptoms (e.g., passage of rectal material or flatus from the vagina).

5.2 SAFETY

5.2.1 Endpoint(s) of safety

There is no primary endpoint in a statistical sense in this study (see Section 7.2). Instead, safety and tolerability will be assessed in a descriptive way based on:

- Physical examination
- Vital signs (blood pressure (BP), heart rate (HR) and oral body temperature)
- 12-lead ECG (electrocardiogram)
- Clinical laboratory tests (haematology, clinical chemistry and urinalysis)
- Adverse events
- Immunogenicity

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associate with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study drug, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

Adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is life-threatening, results in persistent or significant disability or incapacity, requires inpatient hospitalisation or prolongation of existing hospitalisation, 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 judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

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.

Adverse Events of Special Interest (AESI)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.2.2.2.

The following are considered as AESI:

- Hepatic injury defined by the following alterations of liver parameters:
  - For patients with normal liver function at baseline:
    an elevation of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $\geq$ 3 fold upper limit of normal (ULN) combined with an elevation of total bilirubin $\geq$ 2 fold ULN measured in the same blood draw sample.
  - Hepatic injury defined by the following alterations of liver parameters (for patients with impaired liver function tests at baseline): an elevation of AST and/or ALT $\geq$ 3 times the baseline value combined with an elevation of bilirubin $\geq$ 2 times the baseline value measured in the same blood draw sample.

Patients showing these lab abnormalities need to be followed up according to Section 10.1.2 of this clinical trial protocol and the hepatic injury adverse event form provided via EDC system. These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the hepatic injury AE form via the EDC-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 laboratory results meet the definition of hepatic injury, the investigator will complete the supplemental form.**Cardiac Events/Procedures**

In the case of any of the following reported major cardiovascular adverse events (MACE), the appropriate supplemental eCRFs should be completed:

- Cardiac events;
- Myocardial infarction or unstable angina;
- Cerebral vascular accident and transient ischemic attack;
- Cardiovascular procedures

Tuberculosis (TB)

In the case of any positive TB test or diagnosis of active TB, the appropriate supplemental eCRF should be completed.

Intensity of adverse event

The intensity grading of AEs will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 developed by OMERACT (R13-3515). See Appendix 10.3 for intensity/severity classification.

Causal relationship of adverse event

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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.

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

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

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

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

The reason for the decision on causal relationship for unlisted AEs needs to be provided in the (e)CRF.

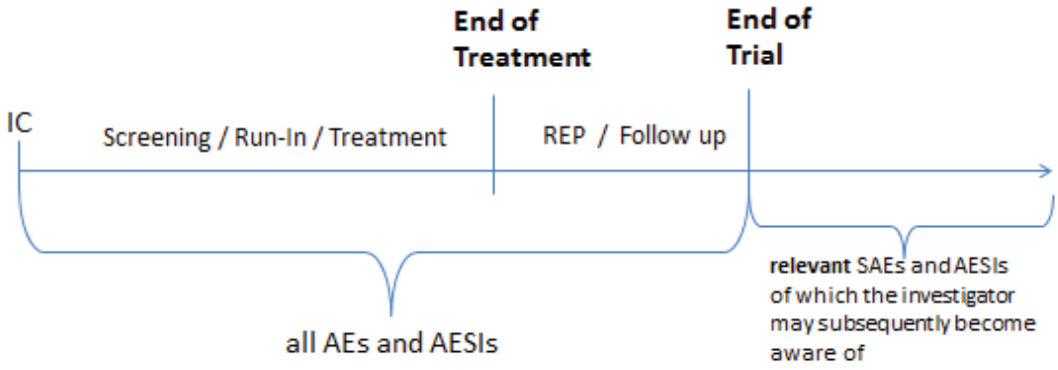
5.2.2.2 Adverse event and serious adverse event reporting

AE Collection

The Investigator shall maintain and keep detailed records of all AEs in their patient files.

The following must be collected and documented on the appropriate CRF(s) / eCRF by the Investigator:

- From signing the informed consent onwards through the Residual Effect Period (REP), until individual patient's end of trial: all AEs (serious and non-serious) and all AESIs.



The residual effect period (REP) for BI 655066/ABBV-066 (risankizumab) is defined as 20 weeks after the last trial medication application. Therefore, all AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment (see Section 7.3.3). Events which occurred after the REP will be considered as post treatment events.

AE reporting to sponsor and timelines

In the event of an SAE, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE system, or if RAVE is not operable, should be documented on the SAE Non-CRF forms and emailed (preferable route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1(847) 938-0660

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

[redacted]

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director:

[redacted]

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie Therapeutic Area Medical Director:

Phone: [redacted]

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines and Appendix A of the Investigator Brochure which will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow up reports, the

RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

Information required

The following should also be recorded as an (S)AE in the (e)CRF and SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after individual patient's end of trial must be followed to a satisfactory conclusion or no further information can be obtained.

Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued from study drug.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

5.2.3 Assessment of safety laboratory parameters

The laboratory tests will be performed as listed in Table 5.2.3: 1and Table 5.2.3: 2. Instructions on sample collection, sample handling/ processing, and sample shipping will be provided to the investigator site file by the central laboratory. For time points of laboratory sampling, see Flow chart 1, Flow chart 2 and Flow chart 3.

Laboratory results of the patients will be available in real time to the respective investigator and to the clinical monitor of each country (central laboratory website), and selected abnormal laboratory alerts will be sent automatically to the sites and to the sponsor in real time. PK, PD and biomarker data will not be available to the investigators or local clinical monitors but the Trial Team (sponsor) in a blinded manner and when relevant, in an unblinded manner to the DMC. Laboratory results will be reported as the absolute value of the measurement obtained on a study patient.

Clinically relevant laboratory values will be commented on in the eCRF. A clinically relevant value may be either in- or outside the reference range. Clinically relevant abnormal laboratory test results must be repeated using an unscheduled visit lab kit and must be repeated until normalisation or stabilisation or until an alternative explanation has been found. Clinically relevant abnormal laboratory values will be also graded for intensity by using RCTC Version 2.0 criteria.

Table 5.2.3: 1 Laboratory tests

Category	**Test name**
H~~a~~ematology	Hematocrit (Hct) Hemoglobin (Hb) Red Blood Cell Count / Erythrocytes Reticulocyte Count White Blood Cells / Leucocytes Platelet Count
Differential automatic (relative and absolute count)	Neutrophils Eosinophils Basophils Monocytes Lymphocytes
Differential manual (relative and absolute count) *(if differential automatic is abnormal)*	Neutrophils, Bands Neutrophils, Polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Coagulation	Partial Thromboplastin Time (PTT) Prothrombin Time (Quick / INR) Fibrinogen
Enzymes	AST/GOT, SGOT ALT/GPT, SGPT Alkaline Phosphatase (AP/ALP) Creatine Kinase (CK) CK-MB if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Lipase Amylase
Specific gamma-globulin quantification	IgE[1], IgG

[1] only in case of allergic reaction

Table 5.2.3: 1 Laboratory tests (con't)

Category	**Test name**
Substrates	Glucose Creatinine and Creatinine Clearance Blood urea nitrogen Bilirubin Total Bilirubin Direct Protein, Total Albumin hsC-Reactive Protein Uric Acid Cholesterol, Total High density lipoprotein (HDL) Cholesterol Calculated Low Density Lipoprotein (LDL) Cholesterol Triglycerides
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate
Hormones	Thyroid stimulating hormone (screening visit only) Free T3, Free T4 if TSH <LLN or >ULN
Urinalysis (Stix)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/Erythrocyte Urine WBC/Leukocytes Urine pH
Urine sediment (microscopic examination) (if urine analysis abnormal)	Urine Sediment Bacteria Urine Casts in Sediment Urine Squamous Epithelial Cells Urine Sediment Crystals, Unspecified Urine Sediment RBC/Erythrocytes Urine Sediment WBC/Leucocytes

Table 5.2.3: 2 Other sampling and testing

Autoantibodies	Human Anti-BI 655066/ABBV-066 (risankizumab) Antibodies (ADA)
Serum Sample for Biomarkers	Refer to Section 5.6
Fecal sample	Calprotectin

5.2.4 Medical examination

Complete physical examination will include vital sign assessment and general appearance as well as evaluation for fistulas and of all organ systems (eyes, ears, nose, mouth, and throat, neck, respiratory, cardiovascular, chest, gastrointestinal, lymphatic, musculoskeletal, skin, neurologic and psychiatric). Targeted physical examination will include vital sign assessment and evaluation for fistulas and of organ systems associated with AE(s) symptoms or laboratory abnormalities.

The medical examination will be carried out at screening. It will include documentation of patient information, informed consent, demographics including height, weight and smoking and alcohol history, relevant medical history and concomitant medication, review of inclusion/exclusion criteria, review of vital signs, 12-lead ECG and laboratory, and a complete physical examination.

5.2.5 Local tolerability

Local tolerability at the administration site of the subcutaneous injection will be assessed by the investigator according to "swelling", "induration", "heat", "redness", "pain", or "other findings".

5.2.6 Infusion reaction

In case of an infusion reaction monitor the patient per standard of care, grade the intensity of the reaction according to RCTC grading (Appendix 10.3) and proceed as described in Section 4.2.2.1. Also draw plasma sample for IgE and ADA (anti-drug antibodies), as detailed in the CTP Section 5.5.2.2. and the Lab Manual.

5.2.7 Electrocardiogram

The 12-lead ECGs will be performed as scheduled in the Flow chart 1, Flow chart 2 and Flow chart 3.

It will be recorded after the patients have rested for at least 5 minutes in supine position at Visit 1. Six limb leads, as specified by Einthoven (I, II and III) and Goldberger (aVR, aVL, aVF), and six pre-cordial leads (V1–V6), according to Wilson, will be used. The investigator or a designate will evaluate whether the ECG is normal or abnormal and whether it is clinically significant, if abnormal. Additionally, any occurrence of re- or depolarization disorders, arrhythmic disorders or other abnormalities will be assessed.

The electronic version of the ECG is regarded as source data. Dated and signed printouts will be stored in the patient's medical file.

ECGs may be repeated for quality reasons and the repeat used for analysis. Additional ECGs may be collected by the investigator for safety reasons. All clinically-significant abnormalities, even transient, must be followed by ECG performed at every subsequent visit.

Clinically relevant abnormal findings will be reported as adverse events.

5.3 OTHER

5.3.1 Other endpoint(s)

Not applicable

5.3.2 Other assessment(s)

Not applicable

5.3.3 Pharmacogenomic evaluation

Not applicable

5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor patients'/patients' safety and to determine pharmacokinetic and pharmacodynamic parameters in an appropriate way.

The scheduled measurements are appropriate to see drug induced changes in vital signs, standard laboratory values and ECG. These endpoints are standard and accepted for evaluation of safety and tolerability of a biologic drug and are widely used in this kind of study.

The pharmacokinetic parameters and measurements outlined in Section 5.5 are generally used assessments of drug exposure. The biomarkers and pharmacodynamic parameters and measurements outlined in Section 5.6 and 5.7 are of an exploratory nature only.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Detailed information on timings for dosing, PK and ADA sampling are listed in Flow chart 1, Flow chart 2 and Flow chart 3. Date and exact clock time of administration as well as of PK sampling times will be recorded.

They will be documented in the CRFs by the medical personnel or sent as electronic files.

These actual sampling times will be used for determination of PK parameters. If the sampling visit represents a drug administration visit, sampling for PK will occur prior to the drug administration.

5.5.1 Pharmacokinetic endpoint(s)

The collected concentrations from all patients will be summarized through descriptive statistics. If data allow, steady state pharmacokinetic parameters of BI 655066/ABBV-066 (risankizumab) will be evaluated as appropriate using non-compartmental analysis methods according to sponsor's standard

Pharmacokinetic data may additionally be analysed using population pharmacokinetic approaches. For this purpose data may also be combined with data from other trials. Modelling activities will be planned and documented separately according to internal and external guidelines and SOPs.

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For the quantification of analyte plasma concentrations, approximately 2.5 mL of blood will be taken from a forearm vein into a K3EDTA (ethylenediaminetetraacetic acid)

anticoagulant blood-drawing tube at the time points listed in the Flow chart 1, Flow chart 2 and Flow chart 3 under PK sampling.

The blood samples must be taken from the forearm vein that is not receiving the i.v. infusion.

Mix the K_3EDTA-anticoagulated blood samples gently and place on ice until centrifugation at approximately +4°C. The blood will be centrifuged to produce plasma as soon as possible after collection, but not later than 30 minutes after withdrawal. Centrifugation will last for approximately 10 minutes (at 2000 x g to 4000 x g) at approximately +4°C. Two aliquots of EDTA plasma samples will be obtained in two labelled (label to include: trial number, patient number, visit, PTM, aliquot 1 or 2, plasma, and PK) polypropylene cryotubes. The two aliquots should contain approximately 0.5 mL of plasma each. The plasma samples will be stored in a freezer set to -20°C or below at the clinical site(s) until shipment on dry ice to the central lab (with dry ice sufficient for 3 days transit), then stored in a freezer set to –70°C or below at the central lab until shipment to the analytical laboratory. Both aliquots will be shipped (in separate shipments with dry ice sufficient for 3 days transit) to the analytical laboratory for the determination of BI 655066/ABBV-066 (risankizumab). Both aliquots will be stored in in a freezer set to –70°C or below at the analytical laboratory until the finalization of the clinical trial report.

5.5.2.2 Plasma sampling for assessment of anti-drug antibody

For the assessment of anti-drug antibody, approximately 2.5 mL of blood will be taken from a forearm vein into a K_3EDTA (ethylendiaminetetraacetic acid) anticoagulant blood-drawing tube at the time points listed in the Flow chart 1, Flow chart 2 and Flow chart 3 under anti-drug antibody (ADA).

Mix the K_3EDTA-anticoagulated blood samples gently and place on ice until centrifugation at approximately +4°C. The blood will be centrifuged to produce plasma as soon as possible after collection, but not later than 30 minutes after withdrawal. Centrifugation will last for approximately 10 minutes (at 2000 x g to 4000 x g) at approximately +4°C. Two aliquots of EDTA plasma samples will be obtained in two labelled (label to include: trial number, patient number, visit, PTM, aliquot 1 or 2, plasma, and ADA) polypropylene cryotubes. Both aliquots will contain approximately 0.5 mL of plasma each. The plasma samples will be stored in a freezer set to -20°C or below at the clinical site(s) until shipment on dry ice to the central lab (with dry ice sufficient for 3 days transit), then stored in a freezer set to -70°C or below at the central lab until shipment to the analytical laboratory. Both aliquots will be shipped (in separate

shipments with dry ice sufficient for 3 days transit) to the analytical laboratory for assessment of potential ADA to BI 655066/ABBV-066 (risankizumab). Following the finalization of the ADA bioanalytical report, selected ADA aliquots will be transferred to long term storage for possible/ additional ADA characterization in the future.

5.5.3 Analytical determinations

BI 655066/ABBV-066 (risankizumab) concentrations will be determined by a validated Enzyme Linked Immunosorbent Assay (ELISA).

The presence of ADA to BI 655066/ABBV-066 (risankizumab) will be assessed via a tiered approach using a validated electrochemiluminescence assay (screening, confirmatory, and titration analysis as appropriate). Samples that are confirmed positive will then be characterized in a validated neutralizing antibody (Nab) assay.

5.6 BIOMARKER(S)

5.6.1 Endpoints based on biomarker(s)

Biomarkers associated with Crohn's disease and the IL-23 pathway will be assessed in serum from patients' pre and post treatment with BI 655066/ABBV-066 (risankizumab). Changes in protein levels of disease specific markers such as but not limited to β defensin 2, neutrophil gelatinase associated lipocalin (NGAL), and S-100 proteins (A7, A8, A12) pre and post treatment with BI 655066/ABBV-066 (risankizumab) will be assessed. These biomarkers are considered exploratory and respective assays will be qualified to meet the required performance criteria.

Serum samples will be collected at time points indicated in Flow chart 1, Flow chart 2 and Flow chart 3 for the analysis of biomarkers. After completion of the study these samples may be used for not yet specified non-genetic biomarker analyses associated with autoimmune diseases as well as method development and evaluation. Samples will be stored for a maximum of 3 years (under consideration of local legislation) upon signature of the final study report.

5.6.2 Methods of sample collection

For the assessment of soluble biomarkers in serum, approximately 8.5 ml of blood will be collected from a forearm vein into a serum separation tube at time points indicated in Flow chart 1, Flow chart 2 and Flow chart 3. The blood will be thoroughly mixed with clotting activation agent by gently inverting the tube not less than five times and will be allowed to clot for at least 30 mins, but for a maximum of 60 mins, with the tube standing

upright. The tube is then centrifuged at 1500 to 2000 xg for 15 mins until clot and serum are separated by a well formed barrier. The serum will then be divided into at least 6 aliquots (in polypropylene tubes) of at least 500 µl and will be frozen immediately at approximately -20°C or below until shipment on dry ice.

5.6.3 Analytical determinations

Characteristics of the analytical methods for the analysis of serum biomarkers will be given in detail in the clinical trial report.

5.7 PHARMACODYNAMICS

5.7.1 Pharmacodynamic endpoints

Serum will be collected to assess changes in the levels of IL-23 pathway and disease specific markers as stated in Section 5.6.1.

5.7.2 Methods of sample collection

See Section 5.6.2

5.8 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

No formal analysis of pharmacokinetic/pharmacodynamic relationships is planned. If the data suggest a pharmacokinetic/pharmacodynamic relationship of special parameters, eg., CDAI, an exploratory analysis may be performed.

Correlation between drug concentration and response may be made if adequate data are available. In addition, exploratory correlations may also be made between drug concentration and AEs.

Data may also be used to develop pharmacokinetic/pharmacodynamic models using nonlinear mixed effect modeling techniques, if feasible. For this purpose data may also be combined with data from other trials. Modeling activities will be planned and documented separately according to internal and external guidelines and SOP.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow chart 1, Flow chart 2 and Flow chart 3. Additional unscheduled visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

For detailed description of the further trial procedures, please refer to the Flow chart 1, Flow chart 2 and Flow chart 3.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

After patients have been informed about the study, written informed consent in accordance with GCP and local legislation must be obtained prior to any study related procedures taking place. Patients will be assigned a number and enrolment must be recorded in eCRF pages.

Visit 1 of this study should preferably be performed in one visit combined with the last visit of preceding trial 1311.6 or during the interim period of maximum 5 days after completion of the last visit in 1311.6.

Patients rolling-over directly from preceding 1311.6 trial eligibility will be assessed based on the patient diary dispensed earlier at the 1311.6 trial containing symptoms over 7 days. Investigators will review the diary in order to assess the CDAI score. The hematocrit result to calculate the CDAI score must be used from visit 1. If an EoT (or at the last preceding trial visit E1 or E5) colonoscopy has not been performed during 1311.6, it must be performed between V1 and V2 in 1311.20/M15-989.

Patients successfully completing the 1311.6 trial before initiation of the 1311.20/M15-989 trial, will be assessed for eligibility based on a newly dispensed patient diary at visit 1. At the following 1.1 visit the investigator will review the diary in order to assess the CDAI score. The hematocrit result to calculate the CDAI score must be used from visit 1. If an EoT colonoscopy has not been performed during 1311.6 or if the patient had a treatment interruption followed by a clinical relapse, it must be performed between V1 and V2 in 1311.20/M15-989.

For detailed description of the trial procedures at screening please refer to Flow chart 1, Flow chart 2 and Flow chart 3.

6.2.2 Treatment periods

If upon completion of screening patient eligibility was confirmed by maintaining clinical response or remission (CDAI drop ≥100 from baseline of 1311.6 or CDAI < 150) patients can directly be assigned to open label s.c. maintenance treatment (see Flow charts 1 and Flow chart 2).

However, if clinical response or remission has been lost after end of treatment in 1311.6 and/or at screening for 1311.20/M15-989, patients will receive open label i.v. re-induction treatment with three infusions of 600 mg each every 4 weeks. After re-induction eligibility will be re-assessed. If clinical response or remission compared to 1311.20/M15-989 study entry is achieved patients will switch to s.c. maintenance treatment (see Flow chart 3).

During the s.c. maintenance treatment patients will be administered BI 655066/ABBV-066 (risankizumab) 180 mg every 8 weeks. Medication will be assigned by IRT. All study medication will be stored and administered on site by authorized study staff only.

For details on the study assessments refer to Flow chart 1, Flow chart 2 and Flow chart 3.

6.2.3 End of trial and follow-up period

The follow up period is 20 weeks after the last administration of study medication. Refer to Flow chart 1, Flow chart 2 and Flow chart 3 for further details.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This trial is a single group, open label extension study of BI 655066/ABBV-066 (risankizumab) in patients with moderately to severely active CD. The patients enrolled in this study are those that achieved clinical response to previous treatment with BI 655066/ABBV-066 (risankizumab). There will be no statistical testing performed.

7.2 NULL AND ALTERNATIVE HYPOTHESES

There is no formal statistical hypothesis test planned.

7.3 PLANNED ANALYSES

Descriptive analyses will be used to analyse the proportion of participants achieving the efficacy endpoints. The study is designed to gain extensive documentation of safety and efficacy.

7.3.1 Primary analyses

There are no primary analyses for efficacy.

7.3.2 Secondary analyses

There is no secondary analyse for efficacy.

Other efficacy endpoints will be summarized descriptively by visit. They will be tabulated and descriptive statistics will be provided.

Additional further endpoints may be defined in the Trial Statistical Analysis Plan (TSAP).

7.3.3 Safety analyses

Since the main objective of this study is long term safety, the primary focus would be on incidence of drug-related AE and serious infection.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. 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 20 weeks 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.

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'. 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 Medical Dictionary for Drug Regulatory Activities (MedDRA). Safety analyses will focus on adverse events related to early discontinuation, immune suppression and injection site effects.

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. Analysis of laboratory measures will focus on haemotologic measures of immune suppression.

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.

7.3.4 Interim analyses

No formal interim analyses are planned. However since this is an open label study, interim analyses may be performed as needed after approximately 20 patients complete the study.

7.3.5 Pharmacokinetic analyses

Refer to Section 5.5.1 for pharmacokinetic parameters to be calculated using noncompartmental analysis (NCA). The derivation of pharmacokinetic parameter is described in sponsor's standard operating procedure.

All evaluable patients who received at least one dose of BI 655066/ABBV-066 (risankizumab) will be included in the pharmacokinetic analysis. Patients who are considered as not evaluable will be listed with their individual plasma concentrations and individual pharmacokinetic parameters, however, will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report. Noncompartmental pharmacokinetic analyses of the plasma concentration-time data will be performed using a validated software program. Only concentrations within the validated concentration range will be used for the calculation of pharmacokinetic parameters.

Plasma concentrations will be plotted graphically versus time for all evaluable patients as listed in the drug plasma concentration-time tables. The actual sampling times will be used for individual drug plasma concentration-time plots. For the presentation of the mean profiles, the arithmetic mean and the planned blood sampling times will be used.

The following descriptive statistics will be calculated for BI 655066/ABBV-066 (risankizumab) concentrations as well as for all pharmacokinetic parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of pharmacokinetic parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the clinical trial report.

7.3.6 Pharmacodynamic analyses

Baseline levels and changes from baseline in serum protein biomarkers will be described over time. Correlations between change from baseline in CDAI scores, endoscopic scores and biomarker levels will be explored. In addition, the relationships, between drug concentrations, clinical efficacy, and selected biomarkers will be explored. The details of these analyses will be included in the SAP.

7.3.7 Pharmacogenomic analyses

Not applicable.

7.4 HANDLING OF MISSING DATA

No imputation will be performed for missing data.

7.5 RANDOMISATION

There is no randomisation for this study. All patients will be assigned to the same regimen and dose of BI 655066/ABBV-066 (risankizumab) , regardless of the treatment and dose received in the 1311.6 trial.

7.6 DETERMINATION OF SAMPLE SIZE

The sample size is determined by the completion of previous trial and the consenting for the extension.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant AbbVie Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/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 general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

Insurance Cover: Insurance certificates are made available to the investigator and the patients via documentation in the ISF (Investigator Site File).

8.1 STUDY 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 (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal trial-related data will be used by AbbVie in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by AbbVie by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs/IECs 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 (CRFs) for individual patients will be provided by the sponsor via remote data capture. 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 entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

For eCRFs all data must be derived from source documents.

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. CRFs/eCRFs 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 CRFs/eCRFs, 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 needs to be provided. The current versions of the Investigator's Brochure reference documents are to be provided in the ISF. No AEs are classified as listed for study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the Investigator Site File.

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 i.e. the CA.

8.6 COMPLETION OF TRIAL

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last patient/patient out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

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10. APPENDICES

10.1 CLINICAL EVALUATION OF LIVER INJURY

10.1.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 (Adverse Events of Special Interest), are to be further evaluated using the following procedures:

10.1.2 Procedures

Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 hours and provide additional blood sample to the central laboratory for automatic reflex testing of the below listed laboratory parameters. Only in case whereby the central laboratory is not immediately available (e.g. if the logistics are such that the patient's repeat specimen would not reach the central laboratory in a reasonable timeframe), ALT, AST, and bilirubin (total and direct) will be evaluated by local laboratory and results are made available to the investigator and to BI as soon as possible. If in such a case ALT and/or AST $\geq$ 3 fold ULN combined with an elevation of total bilirubin $\geq$ 2 fold ULN are confirmed, results of the laboratory parameters described below must be made available to the investigator and to BI as soon as possible.

Clinical chemistry
alkaline phosphatase, albumin, PT or INR, CK, CK-MB, coeruloplasmin, α-1 antitrypsin, transferin, amylase, lipase, fasting glucose, cholesterol, triglycerides

Serology
Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Anti-mitochondrial antibody
<project dependent:> Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM)>

Hormones, tumormarker
TSH

Haematology
Thrombocytes, eosinophils

- Provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm.
- Initiate close observation of subjects by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and / or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices (GCP).

10.2 EQUIVALENT DOSES OF CORTICOSTEROIDS

Drug	Equivalent dose (mg)	Conversion factor
Prednisone	5	X 1
Prednisolone	5	X 1
Triamcinolone	4	X 1.25
6-Methylprednisolone	4	X 1.25
Dexamethasone	1	X 5
Betamethasone	0,75	X 6.7
16-Methylprednisolone	6	X 0.8
Fluocortalon	5	X 1
Cloprednol	3,75-5	X 1.0-1.5
Deflazacort	6	X 0.8
Cortisol (hydrocortisone)	20	X 0.25
Cortisone	25	X 0.20

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

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
	Asymptomatic, or transient Short duration (< 1 week) No change in life style No medication or OTC	Symptomatic Duration (1–2 weeks) Alter lifestyle occasionally Meds relieve. (may be prescription), Study drug continued	Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized < 24h Temporary study drug discontinuation, or/and dose reduced	At risk of death Substantial disability, especially if permanent. Multiple meds Hospitalised > 24h Study drug discontinued
A. ALLERGIC/IMMUNOLOGIC				
A1. Allergic reaction/ hypersensitivity (including drug fever)	Transient rash; drug fever < 38° C, transient asymptomatic bronchospasm	Generalized urticaria responsive to meds; or drug fever > 38° C, or reversible bronchospasm	Symptomatic bronchospasm, requiring meds; symptomatic urticaria persisting with meds, allergy related oedema/angioedema	Anaphylaxis, laryngeal/ pharyngeal edema, requiring resuscitation

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
A. ALLERGIC/IMMUNOLOGIC				
A2. Autoimmune reaction	Serologic or other evidence of autoimmune reaction but patient asymptomatic: all organ function normal and no treatment is required (e.g., vitiligo)	Evidence of autoimmune reaction involving a non-essential organ or functions, requiring treatment other than immunosuppressive drugs (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or toxicity requiring short term immunosuppressive treatment (e.g., transient colitis or anemia)	Causes major organ dysfunction, or progressive, not reversible, or requires long term administration of high dose immunosuppressive therapy
A3. Rhinitis (includes sneezing, nasal stuffiness, post nasal discharge)	Transient, non-prescription meds relieve	Prescription med required, slow	Corticosteroids or other prescription med. with persistent disabling symptoms such as impaired exercise tolerance	NA

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
A. ALLERGIC/IMMUNOLOGIC				
A4. Serum sickness	Transient, non-prescription meds relieve	Symptomatic, slow response to meds (e.g. oral corticosteroids)	Prolonged; symptoms only partially relieved by meds; parenteral corticosteroids required	Major organ dysfunction, requires long-term high-dose immunosuppressive therapy
A5. Vasculitis	Localized, not requiring treatment; or rapid response to meds; cutaneous	Symptomatic, slow response to meds (e.g. oral corticosteroids)	Generalized, parenteral corticosteroids required or/and short duration hospitalization	Prolonged hospitalization, ischemic changes, amputation
B. CARDIAC				
B1. Arrhythmia	Transient, asymptomatic	Transient, but symptomatic or recurrent, responds to meds	Recurrent/persistent; maintenance prescription	Unstable, hospitalization required; parenteral meds

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
B. CARDIAC				
B2. Cardiac function decreased	Asymptomatic decline in resting ejection fraction by > 10%, but < 20% of baseline value	Asymptomatic decline of resting ejection fraction ≥ 20% of baseline value	CHF responsive to treatment	Severe or refractory CHF
B3. Edema	Asymptomatic (e.g., 1+ feet/calves), self-limited, no therapy required	Symptomatic (e.g., 2+ feet/calves), requires therapy	Symptoms limiting function (e.g., 3+ feet/calves, 2+ thighs), partial relief with treatment; prolonged	Anasarca; no response to treatment
B4. Hypertension (new onset or worsening)	Asymptomatic, *transient*, increase by > 20 mm Hg (diastolic),or to > 150/100 if previously normal, no therapy required	Recurrent or persistent increase > 150/100, or by > 10 mmHg (diastolic), requiring and responding readily to treatment	Symptomatic increase > 150/100, > 20 mm Hg, persistent, requiring multi-agent therapy, difficult to control	Hypertensive crisis

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
B. CARDIAC				
B5. Hypotension (without underlying diagnosis)	Transient, intermittent, asymptomatic orthostatic decrease in blood pressure > 20 mmHg	Symptomatic, without interference with function, recurrent or persistent > 20 mmHg decrease, responds to treatment	Syncope, or symptomatic, interferes with function, requiring therapy and sustained medical attention, dose adjustment or drug discontinuation	Shock
B6. Myocardial ischemia	Transient chest pain/ECG changes; rapid relief with nitro	Recurring chest pain, transient ECG ST-T changes; treatment relieves	Angina with infarction, no or minimal functional compromise, reduce dose or discontinue study drug	Acute myocardial infarction, arrthymia or/and CHF
B7. Pericarditis/pericardial effusion	Rub heard, asymptomatic	Detectable effusion by echocardiogram, symptomatic, NSAID required	Detectable on chest X-ray, dyspnea; or pericardiocentesis; requires corticosteroids	Pulsus alternates with low cardiac output; requires surgery

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
B. CARDIAC				
B8. Phlebitis/thrombosis/ embolism (excludes injection site reaction)	Asymptomatic, superficial, transient, local, or no treatment required	Symptomatic, recurrent, deep vein thrombosis, no anticoagulant therapy required	Deep vein thrombosis requiring anticoagulant therapy	Pulmonary embolism
C. GENERAL (constitutional)				
C1. Fatigue/malaise (asthenia)	Increase over baseline; most usual daily functions maintained, short term	Limits daily function intermittently over time	Interferes with basic ADL, persistent	Unable to care for self, bed or wheelchair bound > 50% of day debilitating, hospitalization
C2. Fever (pyrexia) (note: fever due to drug allergy should be coded as allergy)	Transient, few symptoms 37.7–38.5°C	Symptomatic, recurrent, 38.6-39.9°C. Relieved by meds.	≥ 40°C; ≤ 24h, persistent symptoms; partial response to meds	≥ 40°C, debilitating, > 24h, hospitalisation; no relief with meds
C3. Headache	Transient or intermittent, no meds or relieved with OTC	Persistent, recurring, non- narcotic analgesics relieve	Prolonged, with limited response to narcotic medicine	Intractable, debilitating, requires parenteral meds.

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
C. GENERAL (constitutional)				
C4. Insomnia	Difficulty sleeping, short term, not interfering with function	Difficulty sleeping, interfering with function, use of prescription med	Prolonged symptoms, with limited response to narcotic meds	Debilitating, hospitalization; no relief with meds
C5. Rigors, chills	Asymptomatic, transient, no meds, or non-narcotic meds relieve	Symptomatic, narcotic meds relieve	Prolonged symptoms, with limited response to narcotic meds	Debilitating, hospitalization; no relief with meds
C6. Sweating (diaphoresis)	Episodic, transient	Frequent, short term	Frequent, drenching, disabling	Dehydration, requiring i.v. fluids/hospitalization > 24hr
C7. Weight gain	5–9.9%	10–19.9%	20–30%	NA
C8. Weight loss	5–9.9%	10–19.9%	20–30%	NA

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
D. DERMATOLOGIC				
D1. Alopecia	Subjective, transient	Objective, fully reversible	Patchy, wig used, partly reversible	Complete or irreversible even if patchy
D2. Bullous eruption	Localized, asymptomatic	Localized, symptomatic, requiring treatment	Generalized, responsive to treatment; reversible	Prolonged, generalized, or requiring hospitalization for treatment
D3. Dry skin	Asymptomatic, controlled with emollients	Symptoms eventually (1-2 wks) controlled with emollients	Generalized, interfering with ADL > 2 wks, persistent pruritus, partially responsive to treatment	Disabling for extended period, unresponsive to ancillary therapy and requiring study drug discontinuation for relief
D4. Injection site reaction	Local erythema, pain pruritus, < few days	Erythema, pain, oedema, may include superficial phlebitis, 1-2 wks	Prolonged induration, superficial ulceration; includes thrombosis	Major ulceration necrosis requiring surgery
D5. Petechiae (without vasculitis)	Few, transient, asymptomatic	Dependent areas, persistent up to 2 wks	Generalized, responsive to treatment; reversible	Prolonged, irreversible, disabling

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
D. DERMATOLOGIC				
D6. Photosensitivity	Transient erythema	Painful erythema and oedema requiring topical treatment	Blistering or desquamation, requires systemic corticosteroids	Generalized exfoliation, or hospitalization
D7. Pruritis	Localized, asymptomatic, transient, local treatment	Intense, or generalized, relieved by systemic medication	Intense or generalized; poorly controlled despite treatment	Disabling, irreversible
D8. Rash (not bullous)	Erythema, scattered macular/ papular eruption; pruritus transient, OTC or no meds	Diffuse macular/papular eruption or erythema with pruritus; dry desquamation; treatment required	Generalized, moist desquamation, requires systemic corticosteroids; responsive to treatment; reversible	Exfoliative or ulcerating; or requires hospitalization; or parenteral corticosteroids
D9. Induration/fibrosis/ Thickening (not sclerodermal)	Localized, high density on palpation, reversible, no effect on ADL and no disfiguring	Local areas < 50% body surface, not disfiguring, transient interference with ADL, reversible	Generalized, disfiguring, interferes with ADL, reversible	Disabling, irreversible, systemic symptoms

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
E. EAR/NOSE/THROAT				
E1. Hearing loss	Transient, intermittent, no interference with function	Symptomatic, treatment required, reversible	Interferes with function; incomplete response to treatment	Irreversible deafness
E2. Sense of smell	Slightly altered	Markedly altered	Complete loss, reversible	Complete loss, without recovery
E3. Stomatitis	Asymptomatic	Painful, multiple, can eat	Interferes with nutrition, slowly reversible	Requires enteral support, residual dysfunction
E4. Taste disturbance (dysgeusia)	Transiently altered; metallic	Persistently altered; limited effect on eating	Disabling, effect on nutrition	NA
E5. Tinnitus	Intermittent, transient, no interference with function	Requires treatment, reversible	Disabling, or associated with hearing loss	Irreversible deafness
E6. Voice changes (includes hoarseness, loss of voice, laryngitis	Intermittent hoarseness, able to vocalize	Persistent hoarseness, able to vocalize	Whispered speech, slow return of ability to vocalize	Unable to vocalize for extended

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
E. EAR/NOSE/THROAT				
E7. Xerostomia (dry mouth)	Transient dryness	Relief with meds	Interferes with nutrition, slowly reversible	Extended duration interference with nutrition, requires parenteral nutrition
F. EYE/OPHTALMOLOGIC				
F1. Cataract	Asymptomatic, no change in vision, non-progressive	Symptomatic, partial visual loss, progressive	Symptoms impairing function, vision loss requiring treatment, including surgery	NA
F2. Conjunctivitis	Asymptomatic, transient, rapid response to treatment	Symptomatic, responds to treatment, changes not interfering with function	Symptoms prolonged, partial response to treatment, interferes with function	NA
F3. Lacrimation increased (tearing, watery eyes)	Symptoms not requiring treatment, transient	Symptomatic, treatment required, reversible	Unresponsive to treatment with major effect on function	NA

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

F4. Retinopathy	Asymptomatic, non-progressive, no treatment	Reversible change in vision; readily responsive to treatment	Disabling change in vision ophthalmological findings reversible, sight improves over time	Loss of sight
F5. Vision changes (e.g., blurred, photophobia, night blindness, reversible vitreous floaters)	Asymptomatic, transient, no treatment required	Symptomatic, vision changes not interfering with function, reversible	Symptomatic, vision changes interfering with function	Loss of sight
F6. Xerophthalmia (dry eyes)	Mild scratchiness	Symptomatic without interfering with function, requires artificial tears	Interferes with vision/function, corneal ulceration	Loss of sight

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
G. GASTROINTESTINAL				
G1. Anorexia	Adequate food intake, minimal weight loss	Symptoms requiring oral nutritional supplementation	Prolonged, requiring i.v. support	Requires hospitalization for nutritional support
G2. Constipation	Asymptomatic, transient, responds to stool softener, OTC laxatives	Symptomatic, requiring prescription laxatives, reversible	Obstipation, requiring medical intervention	Bowel obstruction. Surgery required.
G3. Diarrhea	Transient, increase of 2–3 stools/day over pre-treatment (no blood or mucus), OTC agents relieve	Symptomatic, increase 4–6 stools/day, nocturnal stools, cramping, requires treatment with prescription meds.	Increase > 6 stools/day, associated with disabling symptoms, e.g. severe cramping, partial response to treatment.	Prolonged, dehydration, unresponsive to treatment, requires hospitalization
G4. Dyspepsia (heartburn)	Transient, intermittent, responds to OTC antacids, H-2 blockers	Prolonged, recurrent, requires prescription meds, relieved by meds	Persistent despite treatment, interferes with function, associated with GI bleeding	NA

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
G. GASTROINTESTINAL				
G5. GI bleed (gastritis, gastric or duodenal ulcer diagnosed — define etiology)	Asymptomatic, endoscopic finding, hemoccult + stools, no transfusion, responds rapidly to treatment	Symptomatic, transfusion ≤ 2 units needed; responds to treatment	Haematemesis, transfusion 3–4 units, prolonged interference with function	Recurrent, transfusion > 4 units, perforation, requiring surgery, hospitalization
G6. Hematochezia (rectal bleeding)	Hemorrhoidal, asymptomatic, no transfusion	Symptomatic, transfusion ≤ 2 units, reversible	Recurrent, transfusion > 3–4 units	> 4 units, hypotension, requiring hospitalization
G7. Hepatitis	Laboratory abnormalities, asymptomatic, reversible	Symptomatic laboratory abnormalities, not interfering with function, slowly reversible	Laboratory abnormalities persistent > 2wks, symptoms interfere with function	Progressive, hepato-renal, anasarca, or pre-coma or coma
G8. Nausea, or nausea/ vomiting (use diagnostic term)	Transient, intermittent, minimal interference with intake, rapid response to meds	Persistent, recurrent, requires prescription meds, intake maintained	Prolonged, interferes with daily function and nutritional intake, periodic i.v. fluids	Hypotensive, hospitalization, parenteral nutrition, unresponsive to out-patient management

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
G. GASTROINTESTINAL				
G9. Pancreatitis	Amylase elevation, intermittent nausea/vomiting, transient, responds rapidly to treatment	Amylase elevation with abdominal pain, nausea, occasional vomiting, responsive to treatment	Severe, persistent abdominal pain with pancreatic enzyme elevation, incomplete or slow response to treatment	Complicated by shock, hemorrhage (acute circulatory failure)
G10. Proctitis	Perianal pruritus, hemorrhoids(new onset), transient, or intermittent, relieved by OTC meds	Tenesmus or ulcerations, anal fissure, responsive to treatment, minimal interference with function	Unresponsive to treatment, marked interference with function	Mucosal necrosis with hemorrhage, infection, surgery required.

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
H. MUSCULOSKELETAL				
H1. Avascular necrosis	Asymptomatic MRI changes, non-progressive	MRI changes and symptoms responsive to rest and analgesia	MRI changes, symptoms requiring surgical intervention	Wheelchair bound; surgical repair not possible
H2. Arthralgia	Intermittent transient symptoms, no meds, or relieved by OTC meds	Persistent or recurrent symptoms, resolve with meds, little effect on function	Severe symptoms despite meds impairs function	Debilitating, hospitalization required for treatment
H3. Leg cramps	Transient, intermittent, does not interfere with function	Recurrent symptoms, minimally interferes with function or sleep, respond to meds	Persistent, prolonged interference with function or sleep, partial or no response to meds	NA

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
H. MUSCULOSKELETAL				
H4. Myalgia	Occasional; does not interfere with function	Frequent, requires meds (non- narcotic); minor effect on function	Major change in function/lifestyle, narcotic pain meds	Debilitating, profound weakness, requires wheelchair, unresponsive to meds
I. NEUROPSYCHIATRIC				
I1. Anxiety or Depression(mood alteration)	Symptomatic, does not interfere with function; no meds	Frequent symptoms, responds to meds; interferes with ADL at times	Persistent, prolonged symptoms, partial or no response to meds, limits daily function	Suicidal ideation, or danger to self
I2. Cerebrovascular ischemia	NA	Single transient ischemic event, responsive to treatment	Recurrent transient ischemic events	Cerebrovascular vascular accident with permanent disability

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
I. NEUROPSYCHIATRIC				
I3. Cognitive disturbance	Subjective symptoms, transient, intermittent, not interfering with function	Objective symptoms, persisting, interferes with daily function occasionally	Persistent, or worsening objective symptoms; interferes with routine daily function	Debilitating/disabling and permanent; toxic psychosis
I4. Depressed consciousness (somnolence)	Observed, transient, intermittent, not interfering with function	Somnolence or sedation, interfering with function	Persistent, progressive, obtundation, stupor	Coma
I5. Inability to concentrate	Subjective symptoms, does not interfere with function	Objective findings, interferes with function	Persistent, prolonged objective findings; or organic cause	NA
I6. Insomnia (in absence of pain)	Occasional difficulty sleeping, transient, intermittent, not interfering with function	Recurrent difficulty sleeping; requires meds for relief; occasional interference with function	Persistent or worsening difficulty sleeping; severely interferes with routine daily function	NA

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
I. NEUROPSYCHIATRIC				
I7. Libido decreased	Decrease in interest	Loss of interest; influences relationship	Persistent, prolonged, interfering with relationship	NA
I8. Peripheral motor neuropathy	Subjective, or transient loss of deep tendon reflexes; function maintained	Objective weakness, persistent, no significant impairment of daily function	Objective weakness with substantial impairment of function	Paralysis
I9. Peripheral sensory (sensory disturbance)	Subjective symptoms without objective findings, transient, not interfering with function	Objective sensory loss, persistent, not interfering with function	Prolonged sensory loss or paresthesias interfering with function	NA
I10. Seizure	NA	Recurrence of old seizures, controlled with adjustment of medication	Recurrence/exacerbation with partial response to medication	Recurrence not controlled, requiring hospitalization; new seizures

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
I. NEUROPSYCHIATRIC				
I11. Vertigo (dizziness)	Subjective symptoms, transient, intermittent, no treatment	Objective findings, recurrent, meds relieve, occasionally interfering with function	Persistent, prolonged, interfering with daily function; partial response to medication	Debilitating, without response to medication, hospitalization

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
J. PULMONARY				
J1. Asthma	Occasional wheeze, no interference with activities	Wheezing, requires oral meds, occasional interference with function	Debilitating, requires nasal O_2	Requires ventilator assistance
J2. Cough	Transient, intermittent, occasional OTC meds relieve	Persistent, requires narcotic or other prescription meds for relief	Recurrent, persistent coughing spasms without consistent relief by meds, interferes with function	Interferes with oxygenation; debilitating
J3. Dyspnea	Subjective, transient, no interference with function	Symptomatic, intermittent or recurring, interferes with exertional activities	Symptomatic during daily routine activities, interferes with function, treatment with intermittent nasal O_2 relieves	Symptomatic at rest, debilitating, requires constant nasal O_2
J4. Pleuritic pain (pleurisy)	Transient, intermittent symptoms, no treatment or OTC meds relieve	Persistent symptoms, requires prescription meds for relief	Prolonged symptoms, interferes with function, requires frequent narcotic pain relief	Debilitating, requiring hospitalisation

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
J. PULMONARY				
J5. Pneumonitis (pulmonary infiltrates)	Asymptomatic radiographic changes, transient, no treatment required	Symptomatic, persistent, requiring corticosteroids	Symptomatic, requiring treatment including O_2	Debilitating, not reversible; or requiring assisted ventilation
J6. Pulmonary function decreased (FVC or carbon monoxide diffusion capacity— DLCO)	76–90% of pre-treatment value	51–75% of pre-treatment value	26–50% of pre-treatment value	≤ 25% of pre-treatment value
LABORATORY DATA				
K. HEMATOLOGY				
K1. Hgb (g/dl) decrease from pre-treatment	1.0–1.4	1.5–2.0	2.1–2.9; or Hgb< 8.0, > 7.0	≥3.0; or Hgb < 7.0
K2. Leukopenia (total WBC) x 1000	3.0–3.9	2.0–2.9	1.0–1.9	< 1.0

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
LABORATORY DATA				
K. HEMATOLOGY				
K3. Neutropenia (x 1000)	1.5–1.9	1.0–1.4	0.5–0.9	< 0.5
K4. Lymphopenia (x 1000)	1.5–1.9	1.0–1.4	0.5–0.9	< 0.5
K5. Platelets (x 1000)	75–LLN	50–74.9	20–49.9; platelet transfusion required	< 20; recurrent platelet transfusions
L. CHEMISTRY				
L1. Hypercalcemia (mg/dl)	1.1 x ULN–11.5	11.6–12.5	12.6–13.5; or symptoms present	> 13.5; or associated coma
L2. Hyperglycemia (mg/dl) Fasting	140–160	161–250	251–500	> 500, or associated with ketoacidosis

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
LABORATORY DATA				
L. CHEMISTRY				
L3. Hyperkalemia (mg/dl)	5.5–5.9	6.0–6.4	6.5–7.0 or any ECG change	> 7.0 or any arrhythmia
L4. Hypocalcaemia (mg/dl)	0.9 x LLN–7.8	7.7–7.0	6.9–6.5; or associated with symptoms	< 6.5, or occurrence of tetany
L5. Hypoglycemia (mg/dl)	55–64 (no symptoms)	40–54 (or symptoms present)	30–39 (symptoms impair function)	< 30, or coma
L6. Hyponatremia (mg/dl)	NA	125–129	120–124	< 120
L7. Hypokalemia (mg/dl)	NA	3.0–3.4	2.5–2.9	< 2.5

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
LABORATORY DATA				
L. CHEMISTRY				
L8. CPK (also if polymyositis-disease	1.2–1.9 x ULN	2.0–4.0 x ULN	> 4.0 x ULN with weakness but without life-threatening signs or symptoms	> 4.0 x ULN with signs or symptoms of rhabdomyolysis or life-threatening
L9.Serum uric acid	1.2–1.6 x ULN	1.7–2.9 x ULN	3.0–5.0 x ULN or gout	NA
L10. Creatinine (mg/dl)	1.1–1.3 x ULN	1.3–1.8 x ULN	1.9–3.0 x ULN	> 3.0 x ULN
L11. SGOT (AST)	1.2–1.5 x ULN	1.6–3.0 x ULN	3.1–8.0 x ULN	> 8.0 x ULN
L12. SGPT (ALT)	1.2–1.5 x ULN	1.6–3.0 x ULN	3.0–8.0 x ULN	> 8.0 x ULN
L13. Alkaline phosphatase	1.1–2.0 x ULN	1.6–3.0 x ULN	3.0–5.0 x ULN	> 5.0 x ULN

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
LABORATORY DATA				
L. CHEMISTRY				
L14. T. bilirubin	1.1–1.4 x ULN	1.5–1.9 x ULN	2.0–3.0 x ULN	> 3.0 x ULN
L15. LDH	1.3–2.4 x ULN	2.5–5.0 x ULN	5.1–10 x ULN	> 10 x ULN
M. URINALYSIS				
M1. Hematuria	Micro only	Gross, no clots	Clots, transfusion < 2 units	Transfusions required
M2. Proteinuria (per 24 h)	300–500 g (tr/1+)	501–1999 g (2+)	2–5.0 g (3+) nephrotic syndrome	> 5.0 g (4+) anasarca
M3. WBC in urine	NA	NA	Indicating acute interstitial nephritis	Associated with acute renal failure

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) (CON'T)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
LABORATORY DATA				
M. URINALYSIS				
M4. Uric acid crystals	Present without symptoms	NA	With stones or symptoms of stones (e.g., renal colic)	Causing renal outflow obstruction and hospitalization

10.4 INVESTIGATOR'S AGREEMENT

1. I have received and reviewed the Investigator's Brochure for BI 655066/ABBV-066 (Risankizumab).
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	An Open Label, Single Group, Long Term Safety Extension Trial of BI 655066/ABBV-066 (Risankizumab), in Patients with Moderately to Severely Active Crohn's Disease
Protocol Date:	25 July 2018

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

10.5 PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Clinical
		Bioanalysis
		Clinical Pharmacology and Pharmacometrics
		Clinical
		Statistics
		Pharma Development

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1.0
Date of CTP revision		*15-Oct-2015*
EudraCT number		2015-001834-15
BI Trial number		1311.20
BI Investigational Product(s)		BI 655066
Title of protocol		An open label, single group, long term safety extension trial of BI 655066, in patients with moderately to severely active Crohn's disease
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		CTP Title
Description of change		[redacted]
Rationale for change		Change of TCM
Section to be changed		Main Criteria for Inclusion
Description of change		1. Deleted: Completion of period 2 or 3 in 1311.6 per protocol with a clinical response or remission before initiation of 1311.20 can roll-over either directly or through an open-label i.v. re-induction phase. 2. d. Deleted: and urine pregnancy test prior to randomization , added: Serum ß-Human Chorionic Gonadotrophin (ß-HCG) pregnancy test will be done at screening only in case when urine pregnancy test is positive
Rationale for change		1. Not a criteria of successful treatment, this statement will remain in section 3.3.2 2. Additional information about serum pregnancy test requirement at screening

Number of global amendment		1.0
Section to be changed		Criteria for Efficacy
Description of change		1. Change from baseline in abdominal pain score by visit based on patient diary, with possible answers none, mild, moderate and severe. 2. Change from baseline in CRP and fecal calprotectin profile by visit
Rationale for change		1. Numeric rating scale was replaced by patient diary with pain scale as none, mild, moderate and severe as numeric scale was mistakenly taken from previous protocol 2. Lactoferin will not be analysed and was removed
Section to be changed		Flowchart 1 (including footnotes)
Description of change		1. Added: who maintained response **OR REMISSION** after completion of Trial 1311.6, 2. 2 additional ECG procedures added at V20 and V26 3. Visit 1.1: footnote mark 16 deleted (2x) 4. Footnote 3: added: **starting from EoT visit** 5. Footnote 4: added: "at Visit 1 and starting from Visit 2" 6. Footnote 15: deleted "completed 1311.6 qualifying for roll-over … this study"; added: **Visit 1.1** is applicable only for those patients **that had visit E1 more than 5 days before Visit 1.** Visit 1.1 can be performed by phone, fax or email 7. Footnote 16 (new one): IRT has to be called only once at V1 or V1.1 after assessment if s.c or i.v. re-induction is needed 8. Visit window for V2 changed to ±7 9. IRT added at visit 1.1
Rationale for change		1. OR REMISSION was added as it was omitted by mistake 2. ECG omitted by mistake in previous version at V20 and V26 3. Visit 1.1. footnote not applicable 4. Footnote 3: additional explanation for VS collection starting point 5. Footnote 4: additional explanation regarding serum pregnancy test 6. Footnote 15: additional explanation needed regarding V 1.1. Footnotes 15 and 16 were joined together. 7. If there is a gap between last visit in 1311.6 trial and first visit in 1311.20 IRT has to be contacted only after assessment if patient kept his best response or not 8. To allow more flexibility to plan V2 9. IRT has to be called first time to register the patient at

Number of global amendment		1.0
		V1.1. in case patient has completed trial 1311.6 before availability of trial 1311.20 after assessment if s.c or i.v. re-induction is needed
Section to be changed		Flowchart 2 (including footnotes)
Description of change		1. Title: deleted "or (2) who maintained response after successful completion of Trial 1311.6," 2. Visit 1.1: footnote mark 16 deleted (2x) 3. 12 Lead Resting-ECG: footnote mark 12 deleted (2x) 4. 2 additional ECG procedures added at V20 and V26 5. Footnote 3: added: **starting from EoT visit** 6. Footnote 4: added: "at Visit 1 and starting from Visit 2" 7. Footnote 15: Added: **Visit 1.1** is applicable only for those patients **that had visit E1 more than 5 days before Visit 1.** Visit 1.1 can be performed by phone, fax or email. Footnote 15: deleted "completed 1311.6 qualifying for roll … this study" 8. Footnote 16: deleted 9. Visit window for V2 changed to ±7
Rationale for change		1. Additional text was removed because this group of pts will follow Flowchart 1 2. Visit 1.1. footnote is not applicable 3. Footnote mark 12 mistakenly entered to ECG 4. ECG omitted by mistake in previous version at V20 and V26 5. Footnote 3: additional explanation for VS collection starting point 6. Footnote 4: additional explanation regarding serum pregnancy test 7. Footnote 15: additional explanation needed regarding V 1.1 8. Footnotes 15 and 16 were joined together. 9. To allow more flexibility to plan V2

Number of global amendment		1.0
Section to be changed		Flowchart 3 (including footnotes)
Description of change		1. Title: added "lost response **OR REMISSION** after" (2x) 2. Visit 1.1: footnote mark 15 deleted (2x) 3. Visit 30: footnote mark 12 added, footnote mark 11 deleted 4. 2 additional ECG procedures added at V23 and V29 5. 12 Lead Resting-ECG: footnote mark 12 deleted 6. Footnote 4: added: "at Visit 1 and starting from Visit 2" 7. Footnote 15: added "1311.6 baseline (visit 2), to continue SC medication patients should have response" 8. Footnote 17 added: IRT has to be called only once at V1 or V1.1 after assessment, if s.c or i.v. re-induction is needed. 9. Visit window for V2 changed to ±7 10. Dispense patient diary for screening: footnote mark 15 deleted
Rationale for change		1. OR REMISSION was added as it was omitted by mistake in previous versions 2. Visit 1.1. footnote 16 not applicable 3. Updated according to Protocol section 3.1 4. ECG omitted by mistake in previous version at V20 and V26 5. 12 Lead Resting-ECG: footnote mark 12 is not applicable 6. Footnote 4: additional explanation regarding serum pregnancy test 7. Footnote 15: additional explanation needed regarding V 1.1 8. If there is a gap between last visit in 1311.6 trial and first visit in 1311.20 IRT has to be contacted only after assessment if patient kept his best response or not. 9. To allow more flexibility to plan V2 10. Dispense patient diary for screening footnote 15 not applicable
Section to be changed		Table of Contents
Description of change		Flowchart 1 added: "who maintained response OR REMISSION after completion of Trial 1311.6" Flow chart 2: removed: " or (2) who maintained response after successful completion of Trial 1311.6," Flow chart 3: added "…OR REMISSION after…" (2x)
Rationale for change		Omitted by mistake in previous version, needed to include all possible patient population
Section to be changed		Section 3.1 Overall Trial Design and Plan

Number of global amendment		1.0
Description of change		1. Figure 3.1:1: Legend: "1311.6" changed to "1311.20" 2. Added: "… an 8 weeks OR 5 times the half-life (whichever is longer) wash-out period…" 3. Added: If clinical response or remission (CDAI drop ≥100 from baseline of 1311.6 or CDAI < 159) was maintained after end of treatment … **(FLOW CHART 1) (visit window between last IMP dose in 1311.6 and first IMP dose in 1311.2 should be at least 8 weeks),** deleted: "Flow Chart 2" 4. Added: "If clinical response or remission compared to 1311.20 study entry …, OTHERWISE VISIT EoT HAS TO BE COMPLETED 15 WEEKS after last administration of trial drug… 5. Deleted: "response or" 2x 6. Added : "(achieved at E5 1311.6)", "or at least response compared to 1311.6 study entry baseline (V2)" 7. Replaced "1311.20 study entry" to "1311.6 study baseline (1311.6 V2)" 8. Added: "If clinical response (achieved at E1 or E5 1311.6) has been lost after end of treatment in 1311.6 and/or at screening for 1311.20, patients will receive open label i.v. re-induction treatment with three infusions of 600 mg each every 4 weeks after which eligibility will be re-assessed. If clinical response or remission compared to 1311.6 study baseline (V2 1311.6) is achieved patients will switch to s.c. maintenance treatment with 180 mg s.c. every 8 weeks (Flow chart 3), otherwise visit EoT has to be completed 15 weeks after last administration of trial drug in 1311.20 trial."
Rationale for change		1. Typos 2. Typos 3. Change of Flowchart number for and additional explanation regarding treatment visit window added. 4. Additional explanations regarding eligibility of patients 5. Additional statement about patient who lost response was added 6. Additional clarifications on eligibility reassessment were added 7. More broad criteria for eligibility reassement at Visit 5 8. Additional clarification added for patients who lost response
Section to be changed		Section 3.3.2 Inclusion Criteria
Description of change		1. Added: "… (drop in CDAI from baseline by ≥100) AND/or remission…"

Number of global amendment		1.0
		2. Added: "… with a clinical response AND/or remission…" 3. Added: "…may roll-over either directly IF THAT RESPONSE / REMISSION IS MAINTAINED or …" 4. Added: "… i.v. re-induction phase IF THEY HAVE LOST THEIR PREVIOUS RESPONSE / REMISSION" 5. Added reference to Section 3.1
Rationale for change		1. AND omitted in previous version by mistake 2. AND omitted in previous version by mistake 3. Additional explanation needed regarding inclusion of patients that have completed trial 1311.6 before initiation of trial 1311.6 4. Additional explanation needed regarding inclusion of patients that have completed trial 1311.6 before initiation of trial 1311.6 5. Reference added for easier handling
Section to be changed		Section 4.1.3 Selection of doses in the trial
Description of change		Changed: "…with 3 infusions **OF** 600mg i.v…."
Rationale for change		Typo
Section to be changed		Section 4.1.4 Drug assignment and administration of doses for each patient
Description of change		1. Deleted: "Placebo" 2. Added: "2 hours after the first administration"
Rationale for change		1. Mistakenly entered in previous version 2. Additional clarification on patient stay at the site after first i.v. IP administration were added
Section to be changed		Section 4.1.7 Storage conditions
Description of change		Added: "…in THE ISF" Added: "…AN account"
Rationale for change		Typos
Section to be changed		Section 4.2.1
Description of change		Deleted: "Placebo"
Rationale for change		Mistakenly entered in previous version
Section to be changed		Section 4.2.2.1
Description of change		Table substantially revised
Rationale for change		Restricted medication table was not complete in previous version in line with restrictions in 1311.6 trial
Section to be changed		Section 4.2.2.1: Tapering of corticosteroids
Description of change		Changed: "…decrease in CDAI <100 points…"
Rationale for change		Typo

Number of global amendment		1.0
Section to be changed		Section 5.1.1 Endpoint(s) efficacy
Description of change		1. Endpoint(s) (s) removed 2. Added: "… WITH POSSIBLE ANSWERS NONE, MILD, MODERATE AND SEVERE" 3. Deleted: "on a numeric rating … pain)" 4. Added: "Change from baseline in CRP **AND fecal** calprotectin …", deleted: " … and lactoferin" 5. Change from baseline in CDAI scores by visit moved as separate endpoint
Rationale for change		1. Typo 2. Numeric rating scale was be replaced by patient diary with pain scale as none, mild, moderate and severe 3. Numeric rating scale was be replaced by patient diary with pain scale as none, mild, moderate and severe 4. Lactoferin will not be analysed and was removed, fecal forgotten by mistake 5. Clarity
Section to be changed		Section 5.1.2 Assessment of Efficacy
Description of change		1. Deleted:" The procedure for handling biopsies will be provided in the laboratory manual." 2. Added fecal to calprotectin
Rationale for change		1. Biopsy is not planned as a part of colonoscopy and was present in the text mistakenly from previous protocol. 2. Fecal forgotten by mistake
Section to be changed		Section 5.2.2.1 Definition of Adverse Events
Description of change		1. Definition of adverse event rephrased 2. Definition of adverse reaction added and additional explanation that medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions
Rationale for change		Adaptation to new Protocol template
Section to be changed		Section 5.2.2.1 Definition of Serious adverse event
Description of change		1. Definition of serious adverse reaction added and also additional explanation what should be considered as serious adverse event. 2. AE considered "Always Serious" rephrased
Rationale for change		Adaptation to new Protocol template

Number of global amendment		1.0
Section to be changed		Section 5.2.2.1 Causal Relationship of AE
Description of change		1. Added Arguments that may suggest that there is / is not a reasonable possibility of a causal relationship 2. Removed statement: the reason for the decision on causal relationship for unlisted AEs needs to be provided in the (e)CRF.
Rationale for change		Adaptation to new Protocol template
Section to be changed		Section 5.2.2.2 Adverse event and serious adverse events reporting
Description of change		Added: The Investigator shall maintain and keep detailed records of all AEs in their patient files.
Rationale for change		Adaptation to new Protocol template
Section to be changed		Section 5.2.2.2 AE Reporting
Description of change		1. Removed: reporting obligations after patient`s individual end of trial 2. Added wording for VS data collection
Rationale for change		Adaptation to new Protocol template
Section to be changed		Section 5.2.2.2 AE Reporting
Description of change		1. Added: After the individual patient's end of the trial: the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of. 2. Figure updated accordingly. 3. Added: Events which occurred after the REP will be considered as post treatment events.
Rationale for change		Adaptation to new Protocol template
Section to be changed		Section 5.2.2.2 Information required
Description of change		Details of AE CRF pages and SAE form as e.g. onset date, end date, intensity, treatment required, outcome, seriousness and action taken with the investigational drug(s) removed
Rationale for change		Adaptation to new Protocol template
Section to be changed		Section 5.2.2.2 AE Reporting / Pregnancy
Description of change		Rephrasing the whole paragraph
Rationale for change		Adaptation to new Protocol template
Section to be changed		Section 5.2.4 Medical examination
Description of change		Changed: "FISTULAS" (2x)

Number of global amendment		1.0
Rationale for change		typo
Section to be changed		Section 5.7.2 Methods of sample collection
Description of change		Deleted: "Not applicable" Added: "SEE SECTION 5.6.2"
Rationale for change		Missing reference to Section 5.6.2
Section to be changed		Section 6.2.1 Screening period
Description of change		1. Several typos/grammar in the paragraph "Patient rolling-over directly …", changed: "…will be assessed FOR ELIGIBILITY" 2. Deleted paragraph: "Demographics and medical history … be recorded in eCRF" 3. Added: "(or at the last preceding trial visit E1 or E5)"
Rationale for change		1. Typos 2. Additional explanation needed for collection of information in eCRF 3. Additional clarifications on colonoscopy requirements between V1 and V2 are added.
Section to be changed		Section 6.2.2 Treatment periods
Description of change		Changed: "(CDAI drop ≥ 100 from baseline…"
Rationale for change		typo
Section to be changed		Section 6.2.3 End of trial and follow-up period
Description of change		Changed: "THE follow up period …"
Rationale for change		Grammar corrected
Section to be changed		Section 7.3.4 Interim analyses
Description of change		Added: However since this is an open label study, interim analyses may be performed as needed after approximately 20 patients complete the study.
Rationale for change		Trial team decision

Number of global amendment		1.0
Section to be changed		Section 8.0
Description of change		Statement: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF (Investigator Site File) Was replaced by: Insurance certificates are made available to the investigator and the patients via documentation in the ISF (Investigator Site File).
Rationale for change		Adaptation to new Protocol template

Number of global amendment		**2.0**
Date of CTP revision		13 October 2016
EudraCT number		2015-001834-15
BI Trial number		1311.20
BI Investigational Product(s)		BI 655066/ABBV-066 (risankizumab)
Title of protocol		An open label, single group, long term safety extension trial of BI BI 655066/ABBV-066 (risankizumab), in patients with moderately to severely active Crohn's disease
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
Description of change 1		The name of TCM changed to [redacted]
Rationale for change		Change of TCM, Study handover from [redacted]
Section to be changed		Whole document
Description of change 2		Changed "Boehringer Ingelheim" into "AbbVie/Boehringer Ingelheim"

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		Whole document
Description of change 3		Added ABBV-066 (risankizumab) after BI 655066
Rationale for change		Refer to rational for first change listed
Section to be changed		Section 3.1.1 Administrative structure of the trial
Description of change 4		"The trial is sponsored by Boehringer Ingelheim (BI)" was changed to "The trial is sponsored by AbbVie in the US and Boehringer Ingelheim (BI) ex-US.
Rationale for change		Refer to rational for first change listed
Section to be changed		Section 3.1.1 Administrative structure of the trial
Description of change 5		"Data Management and Statistical Evaluation will be done by BI according to BI SOPs" was changed to "Data Management will be done by BI according to BI SOPs and the Statistical Evaluation will be done by AbbVie according to their SOPs."
Rationale for change		Refer to rational for first change listed

Number of global amendment		**3.0**
Date of CTP revision		28 April 2017
EudraCT number		2015-001834-15
BI Trial number		1311.20/M15-989
BI Investigational Product(s)		BI 655066/ABBV-066 (risankizumab)
Title of protocol		An open label, single group, long term safety extension trial of ABBV-066 (risankizumab) in patients with moderately to severely active Crohn's disease
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		Cover page
Description of change 1		AbbVie will add their cover page once completed document has been modified by BI. All headers and footers will be changed to reflect AbbVie language and a signature/approval page will be added for AbbVie signatories.
Rationale for change		Change in contact details will be needed for sites.
Section to be changed		Whole document
Description of change 2		Removed reference to Boehringer Ingelheim or BI as sponsor and changed to AbbVie Inc. Added M15-989 after 1311.20.
Rationale for change		At end of June of 2017, AbbVie, Inc will take full sponsorship of this study. Added Abbvie study number for site awareness.
Section to be changed		Abbreviations
Description of change 3		DILI - Drug Induced Liver Injury checklist and OPU - Operative Unit have been deleted
Rationale for change		Abbvie does not follow this checklist for reporting hepatic injury details and does not use OPU terminology.
Section to be changed		Section 1.2 Drug Profile, Section 8.4 Listedness and Expedited reporting of AEs, and Section 9.2 Unpublished References
Description of change 4		Removed link and reference number to the last BI Investigator Brochure.
Rationale for change		AbbVie has written a new version which is now referenced in the unpublished references section.
Section to be changed		Section 3.1.1 Administrative structure of the trial
Description of change 5		Removed reference to BI team structure and their tasks and functions, activities performed by DM and Stats, and reference to BI SOPs. Added a statement that the clinical trial master file (CTMF) documents will be transitioned to AbbVie.

Rationale for change		Team structure and their responsibilities and BI SOPs do not apply to AbbVie. Confirmed that all clinical documents will be transitioned to AbbVie.
Section to be changed		Section 4.1 Treatments to be Administered
Description of change 6		Removed drug to be supplied by BI, added ABBV-066 drug number to substance and removed substance language.
Rationale for change		Supplied by BI removed as part of the sponsor change, Abbvie drug number was missed to be added at last update and substance row is removed as it is duplicate information.
Section to be changed		Section 5.2.2 Assessment of adverse events
Description of change 7		Adverse event definition has been added, AEs considered always serious has been removed, hepatic injury adverse event form has replaced the drug induced liver injury checklist "DILI", adverse event reporting to sponsor and timelines has been modified, emergency contact details have been added and pregnancy language and reporting expectations were changed.
Rationale for change		These changes have been made to follow Abbvie standard language and reporting expectations. The always serious AE list is used for Post Marketing Observational Studies and is not used in clinical trials.
Section to be changed		Safety analyses 7.3.3
Description of change 8		Removed standard BI language for tables and listings and the how safety analyses will be performed.
Rationale for change		BI standards to do not apply to AbbVie.

Number of global amendment		**4.0**
Date of CTP revision		25 July 2018
EudraCT number		2015-001834-15
BI Trial number		1311.20/M15-989
BI Investigational Product(s)		BI 655066/ABBV-066 (risankizumab)
Title of protocol		An open label, single group, long term safety extension trial of ABBV-066 (risankizumab) in patients with moderately to severely active Crohn's disease
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, page 3
Description of change 1		Changed 15 to 20 weeks duration to remain on effective birth control after last dose of medication.
Rationale for change		To reflect updated safety risk language.
Section to be changed		Synopsis, page 4
Description of change 2		Added option for patients to enroll, into M16-000 Sub-Study 3 for those who complete the EoT visit.
Rationale for change		As this study will be terminated, we are allowing patients to enroll into the M16-000 Sub-Study 3 which has similar long-term extension design.
Section to be changed		Synopsis, page 5
Description of change 3		Efficacy endpoints changed from Week 204/206/216 into 'by visit' time points.
Rationale for change		This study will be terminated and not all patients will have the same treatment duration. Using 'by visit' will allow for the different time points when the patient will end treatment.
Section to be changed		Synopsis, page 6
Description of change 4		Removed annual vital status for criteria for long-term safety evaluation of completed patients.
Rationale for change		AbbVie standard does not require and annual vital status or follow up visit to occur after premature discontinuation.
Section to be changed		Synopsis, pages 7-23 flowcharts 1 through 3.
Description of change 5		Removed Week number in EoT flowcharts. Footnote was removed regarding study being conducted until study drug registration, as a result, some footnotes needed to be renumbered. Language was added to accommodate patients that will be allowed to enroll into M16-000 Sub-Study 3. Modified premature discontinuation to early EoT. Removed Vital Status from list of assessments.

Rationale for change		Patients will be ending participation at different weeks so this Week number no longer applies. Study will be terminated and will not continue until study drug registration. Patients will be asked to come in for their EoT visit and provide the option to enroll into the M16-000 Sub-Study 3. Administrative change from premature discontinuation to early EoT to be consistent within the entire document. Vital Status no longer being completed, it is not an AbbVie standard to follow patients annually.
Section to be changed		Abbreviations
Description of change 6		Added Cardiovascular Adjudication Committee (CAC), End Of Trial (EoT), and Reference Safety Information (RSI).
Rationale for change		Language was added to the body of the protocol that included these abbreviations.
Section to be changed		Section 1.2
Description of change 7		Added Clinical summary subheading and provided summary of safety profile.
Rationale for change		To clarify where clinical information begins and to update the safety profile with current information.
Section to be changed		Section 2.3 – Benefit Risk Assessment
Description of change 8		Added clarity on known risks and added a statement about tumor immunity risk. Added the CAC will adjudicate all suspected cardio-and cerebrovascular events.
Rationale for change		To provide the most current safety profile updates. To allow for adjudication of events (aligns with other risankizumab studies) until the study is terminated.
Section to be changed		Section 3.1 – Overall Trial Design and Plan
Description of change 9		Changed the duration of time from 15 weeks to 140 days for follow up period after last dose of study drug. Removed language regarding study being conducted until study drug registration. Added option for patients who complete the EoT visit to enroll into M16-000 Sub-Study 3.

Rationale for change		Change made as a result of IB update and updated RZB half–life of 28 days. Study will be terminated and will not continue until study drug registration. To create efficiencies by moving patients from this study into Study M16-000 Sub-Study 3 (OLE Phase 3), e.g. ensuring long term continuation of all patients within one OLE trial which will minimize the burden on participating sites and patients as well as allow obtaining more robust OLE safety analysis. In addition, the OLE design of M16-000 Sub-Study 3 OLE gives an option of RZB dose escalation if needed.
Section to be changed		Sections 3.3.2 – Inclusion Criteria and 3.3.3 - Exclusion Criteria
Description of change 10		Changed 15 to 20 weeks duration to remain on effective birth control after last dose of medication.
Rationale for change		To reflect updated safety risk language.
Section to be changed		Sections 4.1.6 – Packaging, labelling, and resupply
Description of change 11		Removed drug supplies being provided by BI. Added description of supplies.
Rationale for change		BI no longer provides the drug supplies. Other changes provided for clarity.
Section to be changed		Section 4.1.7 - Storage conditions
Description of change 12		Added language on proper storage and assessing any temperature excursions.
Rationale for change		Changes were made to provide more clarity.
Section to be changed		Section 4.1.8 - Drug accountability
Description of change 13		Added paragraph regarding unused medication.
Rationale for change		Moved paragraph from storage conditions to accountability as this is the proper section.
Section to be changed		Section 4.2.2.1 – Restrictions regarding concomitant treatment
Description of change 14		Added Live or attenuated vaccines 140 days after last study drug dose.
Rationale for change		Added to align with phase 3 protocols and due to product risk language.
Section to be changed		Section 5.1.1 – Efficacy endpoints
Description of change 15		Efficacy endpoints changed from Week 204/206/216 into ‘by visit’ time points.

Rationale for change		This study will be terminated and not all patients will have the same treatment duration. Using "by visit" will allow for the different time points when the patient will end treatment.
Section to be changed		Section 5.2.1 – Endpoints of safety
Description of change 16		Removed annual vital status for criteria for safety evaluation
Rationale for change		AbbVie standard does not require an annual vital status or follow up visit to occur after premature discontinuation.
Section to be changed		Section 5.2.2.1 – Adverse Event and Adverse Event of Special Interest
Description of change 17		Added language to define reporting elective surgery/procedures and language regarding cardiac events and procedures and TB.
Rationale for change		To capture further information on reporting requirements and for suspected cardiac events and TB.
Section to be changed		Section 5.2.2.2 – AE collection
Description of change 18		Removed language regarding annual vital status and reporting of SAEs and AESIs.
Rationale for change		AbbVie standard does not require and annual vital status or follow up visit to occur after premature discontinuation.
Section to be changed		Section 5.2.2.2 – AE collection
Description of change 19		Modified language regarding SUSAR reporting.
Rationale for change		Modified to align with new protocol template language.
Section to be changed		Section 6.2.3 – End of trial and follow-up period
Description of change 20		Changed the duration of time from 15 to 20 weeks for follow up period after last dose of study drug.
Rationale for change		Change made as a result of IB update and updated RZB half–life of 28 days.
Section to be changed		Section 7.3.3 – Safety analysis
Description of change 22		Changed the duration of time from 15 to 20 weeks for follow up period after last dose of study drug.
Rationale for change		Change made as a result of IB update and updated RZB half–life of 28 days.
Section to be changed		Section 9.2 – Unpublished references
Description of change 20		Added versions of the Investigators Brochure that have been approved.
Rationale for change		To ensure complete list of IBs were noted.

Document Approval

Study 131120 (M15-989) - An Open Label, Single Group, Long Term Safety Extension Trial of BI 655066/ABBV-066 (Risankizumab), in Patients with Moderately to Severely Active Crohn's Disease - Amendment 4 - EudraCT 2015-001834-15 - 25Jul2018

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	26-Jul-2018 08:26:15 PM	Approver
	29-Jul-2018 06:05:01 PM	Approver
	02-Aug-2018 02:51:17 P	Approver