1.0 Title Page

Statistical Analysis Plan

Study 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

Date: 15 July 2019

Version 1.0

2.0 Table of Contents

List of Tables

List of Figures

3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by the Data and Statistical Science Department for ABBV-066 Study M15-989. It provides details to further elaborate statistical methods as outlined in the protocol and describes analysis conventions to guide the statistical programming work.

Unless noted otherwise, all analyses will be performed using SAS version 9.2 or later (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

4.0 Study Background

4.1 Objectives

The purpose of this long-term safety extension trial is to provide patients 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 achieved 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).

4.2 Study Design

This open label long term extension trial investigates the long-term safety and efficacy of BI 655066/ABBV-066 (risankizumab). Approximately 60 patients who met the entry criteria were planned for inclusion in this trial, rolling over from preceding trial Study M15-993/1311.6.

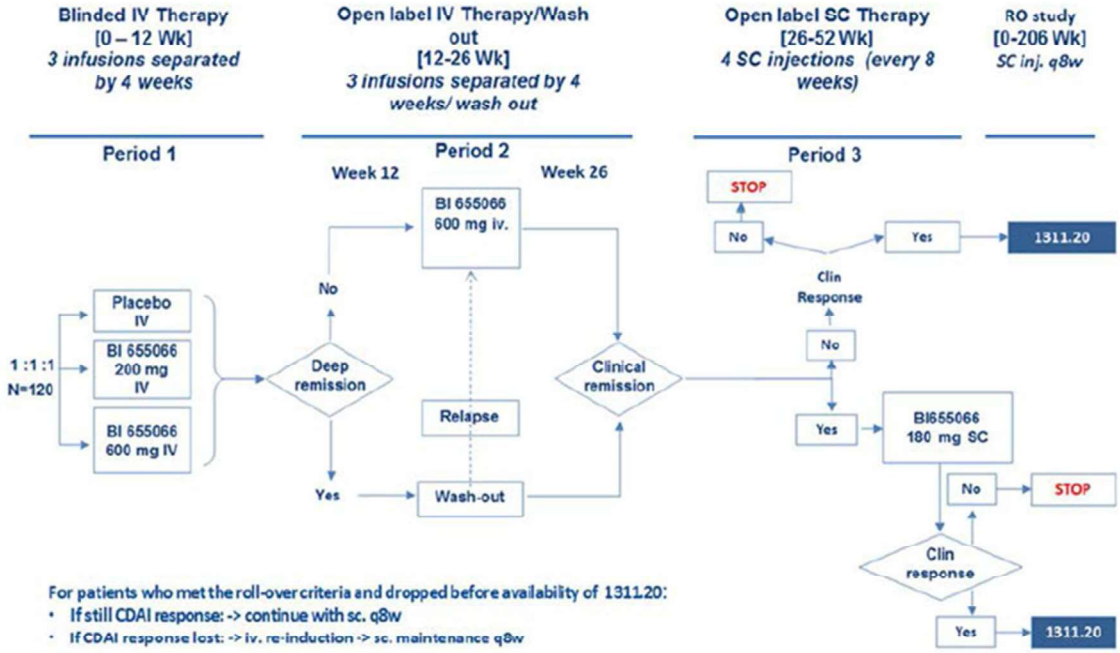
All patients directly rolled over from Study M15-993/1311.6 into Study M15-989/1311.20 received 180 mg BI 655066/ABBV-066 (risankizumab) subcutaneously (SC) from Visit 2 onwards every 8 weeks. Patients who lost clinical response or remission after the end of treatment in Study M15-993/1311.6 and/or at screening for Study 1311.20/M15-989 received open label, i.e., re-induction treatment with three intravenous infusions (IV) of 600 mg each every 4 weeks. Patients who complete this study may elect to continue in Study M16-000 Sub-Study 3 (Phase 3 open label extension study).

4.2.1 Study Design and Design Diagram

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).

Patients rolling over from preceding trial Study M15-993 completed Period 2 or 3 in that trial and either demonstrated a clinical response without remission at Visit E1 (Week 26 visit of Period 2) or a clinical response or remission at Visit E5 (Week 52 visit of Period 3) as defined by that protocol (see Figure 1).

Figure 1. Guideline for rolling over of patients from Study M15-993/1311.6 to long term extension Study M15-989/1311.20.



The scheduled activities during the whole study are shown in Flow Chart 1, Flow Chart 2 and Flow Chart 3 respectively for different types of rolling over.

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[15]**	**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				
EFFICACY ASSESSMENTS																			
Dispense patient diary for screening[15]	X																		
Crohn's Disease Activity Index (CDAI), PRO-2	X[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review patient diary	X[17]	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)[13]			X			X			X			X			X			X	
Ileocolonoscopy (CDEIS)	X[1]								X							X			
OTHER ASSESSMENTS																			
Pharmacokinetics[14]	X			X		X		X		X		X		X		X		X	
Anti-drug antibodies[14]	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[16]	X[16]	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
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[15]	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				
EFFICACY ASSESSMENTS																			
Dispense patient diary for screening[15]	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)[13]			X			X			X			X			X			X	
Ileocolonoscopy (CDEIS)	X[1]								X							X			
OTHER ASSESSMENTS																			
Pharmacokinetics[14]	X			X		X		X		X		X		X		X		X	
Anti-drug antibodies[14]	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
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[16]	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[15]														
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				
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)[13]						X			X			X			X			X		
Ileocolonoscopy (CDEIS)	X[1]											X							X	
OTHER ASSESSMENTS																				
Pharmacokinetics[14]	X						X		X		X		X		X		X		X	
Anti-drug antibodies[14]	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[8]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TRIAL MEDICATION																				
Contact IRT	X	X[17]	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
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.

4.2.2 Variables Used for Stratification of Randomization

Not applicable.

4.3 Endpoints

4.3.1 Primary Efficacy Endpoint

There is no primary efficacy endpoint specified.

4.3.2 Secondary Efficacy Endpoint

- Clinical remission by visit defined as a CDAI < 150.
- Clinical response by visit, defined by either a CDAI < 150 or a CDAI reduction from baseline of at least 100 points.
- PRO-2 remission by visit, defined by a PRO-2 score < 75
- PRO-2 response by visit, defined as a decrease from baseline of 50 points or more.
- CDEIS remission, defined as a score of 4 or less, by visit (for patients with initial isolated ileitis a score of 2 or less)
- CDEIS response, defined as a score of 7 or less, by visit (for patients with initial isolated ileitis > 50% reduction from baseline).

- Mucosal healing, using CDEIS defined as the absence of mucosal ulceration, i.e., ulceration sub-score (deep ulceration, superficial ulceration, ulcerated stenosis) is 0, by visit.
- Deep remission, defined as clinical remission and CDEIS remission by visit.
- IBDQ remission (IBDQ total score > 170 points) by visit.
- IBDQ response (increase in IBDQ total score > 16 points from baseline) by visit.
- Change from baseline in CDAI by visit.
- Change from baseline in PRO-2 scores by visit.
- Change from baseline in CDEIS by visit.
- Change from baseline in SES-CD by visit.
- Change from baseline in stool frequency (SF) by visit based on patient diary.
- Change from baseline in abdominal pain (AP) score by visit based on patient diary.
- Change from baseline in IBDQ total scores by visit.
- Change from baseline in IBDQ domain scores by visit.
- Change from baseline in hs-CRP by visit.
- Change from baseline in fecal calprotectin profile by visit.

Note: For the composite endpoints such as deep remission, please refer to Appendix 12.9 for detailed analysis convention.

4.3.3 Exploratory Efficacy Endpoint

The following endpoints will be summarized in subjects with baseline SF ≥ 4 or AP ≥ 2, and baseline SES-CD, excluding the presence of narrowing component, ≥ 6 (≥ 4 for subjects with initial isolated ileitis).

- Proportion of subjects with average daily SF ≤ 2.8 and not worse than baseline and average daily AP score ≤ 1 and not worse than baseline, by visit.
- Proportion of subjects with decreasing in SES-CD > 50% from baseline (or for a baseline SES-CD of 4, at least a 2 point reduction from Baseline), by visit.

- Proportion of subjects with ≥ 60% decrease in average daily SF and/or ≥ 35% decrease in average daily AP score and both not worse than baseline, and/or achievement of average daily SF ≤ 2.8 and AP ≤ 1 and both not worse than baseline, by visit.
- Proportion of subjects with SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore ≥ 1 at baseline, by visit.
- Proportion of subjects with SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable, by visit.
- Proportion of subjects who discontinued corticosteroid use for at least 90 days before or at visit and achieved average daily SF ≤ 2.8 and AP ≤ 1 and both not worse than baseline in subjects taking steroids at baseline, by visit.

Note: To summarize discontinuing corticosteroid use for at least 90 days before or at visit in Study M15-989, the concomitant medication records from the feeder Study M15-993 need to be taken into account.

4.3.4 Safety Endpoint

- Vital signs
- Clinical laboratory tests
- Adverse events

4.3.5 Pharmacological Endpoint (Optional)

Pharmacological Endpoint will be analyzed separately and not included in this SAP.

4.4 Sample Size Justification

The sample size is determined by the completion of previous trial Study M15-993/1311.6 and the consenting for the extension.

4.5 Interim Analysis

There will be no formal efficacy interim analysis planned for this study. Since this is an open label study, interim analyses may be performed for publication purpose.

An external independent data monitoring committee (DMC) reviewed safety data throughout the course of the study. A separate DMC charter was prepared outside of the protocol and approved by AbbVie and the DMC members. The DMC is responsible for monitoring safety data, alerting AbbVie to possible safety concerns related to the conduct of the study, and recommending appropriate actions for study conduct and management.

4.6 Multiplicity Testing Procedures for Type-I Error Control

Not applicable.

5.0 Analysis Populations

5.1 Definition of Analysis Populations

5.1.1 Efficacy Populations

Intent-to-Treat Analysis Set

The Intent-to-Treat Analysis Set (ITT) includes all subjects who received at least one dose of risankizumab in the current study.

- The Intent-to-Treat Analysis Set for IV (ITT_IV) includes all subjects who received at least one dose of risankizumab IV in the current study.
- The Intent-to-Treat Analysis Set for SC (ITT_SC) includes all subjects who received at least one dose of risankizumab SC in the current study.

The ITT population will primarily be used for all efficacy analyses. Any by-period analyses on IV (or SC treated population) will be based on ITT_IV set (or ITT_SC set).

5.1.2 Safety Populations

The safety analysis set (SA) consists of all subjects who received at least one dose of risankizumab in the current study. Further define two subsets within SA:

- The Safety Analysis Set for IV (SA_IV) includes all subjects who received at least one dose of risankizumab IV in the current study.
- The Safety Analysis Set for SC (SA_SC) includes all subjects who received at least one dose of risankizumab SC in the current study.

5.2 Definition of Treatment Groups

The treatment groups for efficacy analysis are as below:

During IV period: Risankizumab 600 mg IV

During SC period: Risankizumab 180 mg SC

The treatment groups for safety analysis are as below:

During IV period: Risankizumab 600 mg IV

During SC period: Risankizumab 180 mg SC

During the current study: All Risankizumab

6.0 Analysis Conventions

6.1 Definition of Baseline

Efficacy analysis:

For efficacy analysis, the baseline is defined as the last measurement prior to the first dose of the study drug in the feeder Study M15-993 (1311.6).

Safety analysis:

For safety analyses, the baseline is defined as the last measurement prior to the first dose of risankizumab in the feeder Study M15-993 (1311.6).

Demographics and Baseline Characteristics:

For Demographics and Baseline Characteristics, the data will be from the baseline of the feeder Study M15-993 (1311.6).

6.2 Definition of Final Observation

The final observation for each patient will be defined as the last non-missing post-baseline value collected no more than 140 days after the last dose of the study drug in Study M15-989. Any data collected beyond 140 days after the last dose of study drug in Study M15-989 will not be used for analysis but will be displayed in the data listings.

6.3 Definition of Rx Days

The Rx Day is calculated as the event date minus the date of first dose of study drug plus 1 when the time point of interest is after the date of first dose of study drug, or the event date minus the date of first dose of study drug when the time point of interest is prior to the date of first dose of study drug. It provides a quantitative measure of days between the time point of interest and the first study drug dose date. The day of the first dose of study drug is defined as Rx Day 1, while the day prior to the first study drug dose is defined as Rx Day –1 (there is no Rx Day 0).

6.4 Definition of Visit Windows

Since subjects do not always adhere to the study visit schedule, the following rules will be applied to assign actual visits to protocol-specified visits including early termination visits. For each study visit mentioned in the protocol, a nominal or target day will be selected to represent the corresponding visit along with a window around the target day. Windows will be selected in a non-overlapping fashion so that a date collected on the case

report form (CRF) does not correspond to multiple visit windows. Moreover, windows will not discard any post-baseline measurement recorded on the CRF. If a subject had 2 or more actual visits in one visit window, the visit closest to the target will be used as the study visit for that window. If two visits are equidistant from the target day, then the later visit will be used for reporting.

The visit windows and the target/nominal day for each study visit are shown in the tables below. The visit windows defined below will be based on relative days to either first dose on IV or first dose on SC.

Table 1. Windows for subcutaneous injection period for ITT_SC (SA_SC) population, using for Vital sign, Lab Values, Fistula exam, CDAI, Review patient diary (PRO data).

Nominal Visit Week[d]	Lower Bound	Nominal Day	Upper Bound
0	–999	1[a]	1
8	2	57	85
X[c]	1 + 7*(X - 4) + 1	1 + 7*X	1 + 7*(X + 4)
200	1374	1401	9999[b]

a. Day of first dose of study drug for subcutaneous injection.

b. It is minimum of (the last dose date + 140 days, the first dose date of Study M16-000 sub-Study 3) for the subjects who entered the Study M16-000 sub-Study 3; otherwise it is the last dose date +140 days.

c. X = 8*i, i = 2,…, 24.

d. Nominal visit week is a transformation of the protocol-specified week. For the patients' schedule following the Flow Chart 1, nominal visit week = protocol-specified week – 4. For the patients' schedule following the Flow Chart 2, nominal visit week = protocol-specified week – 6. For the patients' schedule following the Flow Chart 3 (only for subcutaneous injection period), nominal visit week = protocol-specified week – 16.

Table 2. Windows for subcutaneous injection period for ITT_SC population, using for CDEIS and SES-CD.

Nominal Visit Week[c]	Lower Bound	Nominal Day	Upper Bound
0	–999	1[a]	1
48	2	337	533
104	534	729	897
152	898	1065	1233
200	1234	1401	9999[b]

a. Day of first dose of study drug for subcutaneous injection.

b. It is minimum of (the last dose date + 140 days, the first dose date of Study M16-000 sub-Study 3) for the subjects who entered the Study M16-000 sub-Study 3; otherwise it is the last dose date +140 days.

c. Nominal visit week is a transformation of the protocol-specified week. For the patients' schedule following the Flow Chart 1, nominal visit week = protocol-specified week – 4. For the patients' schedule following the Flow Chart 2, nominal visit week = protocol-specified week – 6. For the patients schedule following the Flow Chart 3 (only for subcutaneous injection period), nominal visit week = protocol-specified week – 16.

Table 3. Windows for subcutaneous injection period for ITT_SC population, using for IBDQ.

Nominal Visit Week[d]	Lower Bound	Nominal Day	Upper Bound
0	–999	1[a]	1
24	2	169	253
X[c]	1 + 7*(X - 12) + 1	1 + 7*X	1 + 7*(X + 12)
192	1262	1345	9999[b]

a. Day of first dose of study drug for subcutaneous injection.

b. It is minimum of (the last dose date + 140 days, the first dose date of Study M16-000 sub-Study 3) for the subjects who entered the Study M16-000 sub-Study 3; otherwise it is the last dose date + 140 days.

c. X = 24*i, i = 2, 3, 4, 5, 6, 7.

d. Nominal visit week is a transformation of the protocol-specified week. For the patients' schedule following the Flow Chart 1, nominal visit week = protocol-specified week – 4. For the patients' schedule following the Flow Chart 2, nominal visit week = protocol-specified week – 6. For the patients' schedule following the Flow Chart 3 (only for subcutaneous injection period), nominal visit week = protocol-specified week – 16.

Table 4. Windows for subcutaneous injection period for ITT_SC population, using for Fecal Calprotectin

Nominal Visit Week[d]	Lower Bound	Nominal Day	Upper Bound
0	–999[e]	1[a]	1
24	2	169	281
X[c]	1 + 7*(X - 16) + 1	1 + 7*X	1 + 7*(X + 16)
184	1178	1289	1345
200	1346	1401	9999[b]

a. Day of first dose of study drug for subcutaneous injection.

b. It is minimum of (the last dose date + 140 days, the first dose date of Study M16-000 sub-Study 3) for the subjects who entered the Study M16-000 sub-Study 3; otherwise it is the last dose date + 140 days.

c. X = 24 + 32*i, I = 1, 2, 3, 4.

d. Nominal visit week is a transformation of the protocol-specified week. For the patients' schedule following the Flow Chart 1, nominal visit week = protocol-specified week – 4. For the patients' schedule following the Flow Chart 2, nominal visit week = protocol-specified week – 6. For the patients' schedule following the Flow Chart 3 (only for subcutaneous injection period), nominal visit week = protocol-specified week – 16.

e. Since some fecal calprotectin data at screening visit are loaded into the last visit of the feeder Study M15-993, the combined fecal calprotectin data from the feeder Study M15-993 and the current Study M15-989 will be used to derive the value at Week 0.

Table 5. Windows for subcutaneous injection period for ITT_SC population, using for hs-CRP.

Nominal Visit Week[d]	Lower Bound	Nominal Day	Upper Bound
0	–999[e]	1[a]	1
8	2	57	113
X[c]	1 + 7*(X - 8) + 1	1 + 7*X	1 + 7*(X + 8)
120	786	841	869
128	870	897	925
136	926	953	985
152	986	1065	1093
160	1094	1121	1177
176	1178	1233	1261
184	1262	1289	1345
200	1346	1401	9999[b]

a. Day of first dose of study drug for subcutaneous injection.

b. It is minimum of (the last dose date + 140 days, the first dose date of Study M16-000 sub-Study 3) for the subjects who entered the Study M16-000 sub-Study 3; otherwise it is the last dose date + 140 days.

c. X = 8 + 16*i, i = 1, 2, 3, 4, 5, 6.

d. Nominal visit week is a transformation of the protocol-specified week. For the patients' schedule following the Flow Chart 1, nominal visit week = protocol-specified week – 4. For the patients' schedule following the Flow Chart 2, nominal visit week = protocol-specified week – 6. For the patients' schedule following the Flow Chart 3 (only for subcutaneous injection period), nominal visit week = protocol-specified week – 16.

e. Since some hs-CRP data at screening visit are loaded into the last visit of the feeder Study M15-993, the combined hs-CRP data from the feeder Study M15-993 and the current Study M15-989 will be used to derive the value at Week 0.

Table 6. Windows for IV injection period for ITT_IV (SA_IV) population, using for Vital sign Lab Values, Fistula exam, CDAI, Review patient diary (PRO data)

Nominal Visit Week[b]	Lower Bound	Nominal Day	Upper Bound
0	–999	1[a]	1
4	2	29	43
8	44	57	71

a. Day of first dose of study drug for IV injection.

b. Nominal visit week is a transformation of the protocol-specified week. For the patients' schedule following the Flow Chart 3 (only for IV injection period), nominal visit week = protocol-specified week – 4.

6.5 Dealing with Multiple Measurements Collected on the Same Day

For efficacy related analysis, if multiple measurements for a particular parameter are collected on the same day for the same subject, the average of those measurements will be used in analyses.

For safety related analysis, if multiple measurements are made for a particular laboratory or vital sign parameter on the same day for the same subject, the average of the values will be used in the analyses. For summaries and listings for shift from baseline and potentially significant values, all values will be considered in the analyses.

7.0 Demographics, Baseline Characteristics, Medical History, and Previous and Concomitant Medications

7.1 Demographic and Baseline Characteristics

The following demographic and baseline characteristics, as measured at baseline of the feeder Study (M15-993), will be summarized.

Demographics

- Gender (Male, Female)
- Race [American Indian/Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Multiple]
- Ethnicity [Hispanic/Latino, Non-Hispanic/Latino]
- Age [years]
- Country

Tobacco/Nicotine and Alcohol Use

- Tobacco/Nicotine Use [currently smokes, ex-smoker, never smoked]

- Alcohol Use [Non-drinker, drinks - no interference, drinks - possible interference]

Vital Signs

- Height [cm]
- Weight [kg]
- Weight by sex
- Weight category (< 60 kg, ≥ 60 kg)
- Body mass index [kg/m2] (defined as weight/(height/100)^2)
- BMI Category
  - Underweight [< 18.5 kg/m^2]
  - Normal [≥ 18.5 and < 25 kg/m^2]
  - Overweight [≥ 25 and < 30 kg/m^2]
  - Obese [≥ 30 kg/m^2]

Patient Reported Outcomes at Baseline

- Inflammatory Bowel Disease Questionnaire (IBDQ)
- Average Daily Stool Frequency
- Average Daily Abdominal Pain
- PRO-2

Other Assessments at Baseline

- CDAI
- SES-CD
- CDEIS
- hs-CRP [mg/L]
- Fecal calprotectin
- TNF antagonist exposure (anti-TNF experienced, anti-TNF naive)

- Frequency distribution of draining fistula
- Baseline corticosteroid use (yes, no)
- Crohn's disease duration [year]
- Crohn's disease location (Colon only, Ileum only, Ileocolonic) based on CDEIS

7.1.1 Analysis of Demographic Data and Baseline Characteristics

Demographic and Baseline characteristics will be summarized with descriptive statistics. The number of non-missing observations, mean, standard deviation, median, minimum and maximum will be summarized for continuous variables. Categorical or discrete variables will be summarized by counts and percentages.

7.2 Medical History

Medical history data will be summarized using primary Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) and preferred terms (PTs) for each treatment group according to Version 18.0 or higher of the MedDRA coding dictionary. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC. A subject who reports 2 or more different PTs, which are in the same SOC, will be counted only once in the SOC total. Subjects reporting more than one condition for a given PT will be counted only once for that term. No statistical comparison will be performed on medical history.

7.3 Previous Treatment and Concomitant Medications

The number and percent of subjects who received concomitant medication listed below will be tabulated by the generic name assigned by the most current version of the World Health Organization (WHO) Drug Dictionary in alphabetical order for concomitant medications. The prior medication, which is defined as any medication taken prior to the first dose of current study drug, has been reported in the feeder Study M15-993 and will not be evaluated here. No statistical comparisons will be performed.

A concomitant medication is defined as any medication other than study drug and the rescue medication that (1) was started prior to the first dose of study drug and continued to be taken after the first dose of study drug or (2) was started after the first dose of study drug, but was not started after the last dose of study drug. The definition of a concomitant medication for each of IV period and SC period can be defined similarly using the first dose of study drug in that period and the last dose of study drug in that period. A particular medication will be classified as "prior" or "concomitant" or "both" according to the rules provided in Table 7, where "FD" is the date of the first dose of study drug and "LD" is the date of last dose of study drug plus 140 days.

Table 7. Rules for Prior and Concomitant Medication Classification

Medication Start Date	Ongoing?	Medication Stop Date					
		Missing	< FD	= FD	(FD, LD)	= LD	> LD
Missing	YES	1, 2					
	NO/Missing	1, 2	1	1, 2	1, 2	1, 2	1, 2
< FD	YES	1, 2					
	NO/Missing		1	1, 2	1, 2	1, 2	1, 2
= FD	YES	2					
	NO/Missing			2	2	2	2
(FD, LD)	YES	2					
	NO/Missing				2	2	2
= LD	YES	2					
	NO/Missing					2	2
> LD	YES	3					
	NO/Missing						3

1. 1 = Prior, 2 = Concomitant, 3 = Post-treatment.
2. "FD" is the date of the first dose of study drug.
3. "LD" is the date of last dose of study drug plus 140 days.

Concomitant medications at baseline of Study M15-989 include prior medications that have a start date before first dose of study drug of Study M15-989 and are ongoing or have a stop date after first dose of study drug of Study M15-989.

Particularly, a concomitant medication for IV period should have the start date before the date of last dose of study drug in IV period plus 140 days or the date of the first dose in SC period, whichever occurs earlier. A concomitant medication for SC period should have the start date before the date of last dose of study drug in SC period plus 140 days or the date of the first dose in Study M16-000 sub-Study 3 if any, whichever occurs earlier.

7.3.1 Reporting Special Medications

The number and percent of subjects using Crohn's disease specific medications (including corticosteroids, aminosalicylates, immunomodulators [defined as azathioprine, 6 mercaptopurine, or methotrexate], and antibiotics) within past 90 days prior to baseline (of the Study M15-993), and at baseline will be tabulated.

8.0 Patient Disposition and Study Drug Exposure

8.1 Patient Disposition

The number of subjects will be tabulated by country, investigator site and overall for the following sets: efficacy population, safety population, subjects who completed study, and subjects who prematurely discontinued study drug, as appropriate.

In addition, the number and percentage of subjects who prematurely discontinued study drug will be summarized by reason. All reasons and primary reasons for discontinuation of study drug will be summarized as recorded on the eCRF by the following categories:

- Adverse event (AE)
- Protocol violation
- Lost to follow-up
- Withdrew by subject
- Other

Subjects may have more than one reason for discontinuing study drug, but they will be counted once for the total number of premature discontinuations. Subjects have only one primary reason for discontinuing study drug or discontinuing from the study.

8.2 Study Drug Exposure and Compliance

8.2.1 Study Drug Exposure

For the safety population, the duration of exposure to study drug will be summarized. Duration of exposure of risankizumab SC is defined for each subject as number of days since first dose of risankizumab SC through min (the last risankizumab SC dose date + 56 days, the first dose date of study drug in Study M16-000 sub-Study 3). Duration of exposure of risankizumab IV is defined as number of days since first dose of risankizumab IV drug through min (the last risankizumab IV dose date + 28 days, the first dose date of risankizumab SC). Duration of exposure of all risankizumab is defined for each subject as number of days since first dose of study drug through min (the last study drug dose date + 56 days, the first dose date of study drug in Study M16-000 sub-Study 3). Study drug dose date refers to recorded dates of administration of study drug.

For each treatment group and total, the duration of exposure will be summarized by the number of subjects treated, as well as the mean, standard deviation, median, minimum and maximum values. In addition, the number and percentage of subjects exposed to study drug will be summarized for the following exclusive duration intervals:

1 – 84 days
85 – 140 days
141 – 196 days
197 – 252 days
253 – 308 days
309 – 364 days
365 – 420 days

421 – 476 days
477 – 532 days
533 – 588 days
589 – 644 days
645 – 700 days
701 – 756 days
757 – 812 days
813 – 868 days
869 – 924 days
> 924 days

8.2.2 Study Drug Compliance

The treatment compliance (%) of risankizumab dose information will be summarized for safety population:

8.2.2.1 Intravenous Therapy

Total number of infusions received
Cumulative risankizumab dose (mg)

8.2.2.2 Subcutaneous Therapy

Total number of injections received
Cumulative risankizumab dose (mg)

9.0 Efficacy Analysis

9.1 General Considerations

There is no formal statistical hypothesis test planned. Descriptive analyses will be used to analyze the proportion of participants achieving the efficacy endpoints. The study is designed to gain extensive documentation of safety and efficacy.

9.1.1 Analysis of Efficacy Endpoints by Variable Type

9.1.2 Missing Data Imputation for Efficacy Endpoints

Missing data imputation will be done only for categorical efficacy variables. For the analysis other than efficacy, no imputation will be done for missing values.

Non-Responder Imputation (NRI)

The NRI approach is used for binary efficacy variables. These variables can take values of 'Achieved' or 'Not Achieved' or may be missing for any reason including discontinuation from study. According to the NRI imputation approach, all missing values will be considered as 'Not Achieved.' If a subject has missing value for a specific visit, the data will be imputed using NRI only for the period which the visit belongs to.

Observed Case (OC)

Observed case analysis will be performed, i.e., missing values will not be imputed. An analysis using only the observed data will be performed as a sensitivity analysis for primary and secondary efficacy endpoints.

Imputation of Missing Dates

For baseline, efficacy, and safety parameters, if the day and/or month are missing, the following conventions will be used to impute the missing dates:

01 for missing start day
End of month for missing end day
January 1st for missing start month
December 31st for missing end month

In case of partially missing AE start and stop dates, the dates will be imputed by comparing to first dose date of study medication so than the corresponding AEs will be made treatment-emergent whenever possible. If the start date of an AE is partially

missing and the month is the same as the start date of a new therapy, the AE will be made treatment emergent to the new therapy.

In case of missing or partially missing study drug dosing dates, the dates will not be imputed. Subjects will be treated as not receiving dose on that date.

9.1.3 Dose Response Model and Dose Selection (if applicable)

Not applicable.

9.2 Primary Efficacy Analysis

There are no primary analyses for efficacy.

9.3 Secondary Efficacy Analyses

Secondary efficacy endpoints will be summarized descriptively by visit. They will be tabulated and descriptive statistics will be provided. Both Observed Case (OC) and Non-responder imputation (NRI) method will be used in the analysis.

9.4 Other Efficacy Analysis

There are no other efficacy analyses.

9.5 Efficacy Subgroup Analysis

The exploratory efficacy endpoints will be summarized descriptively by visit in the subgroup indicated. They will be tabulated and descriptive statistics will be provided. Both Observed Case (OC) and Non-responder imputation (NRI) method will be used in the analysis.

10.0 Safety Analysis

10.1 General Considerations

Safety analyses will include reporting of adverse events, laboratory, and vital signs measurements. All safety analyses will be performed on the safety analysis set.

The following summary statistics will be presented for subjects who have both baseline and post-baseline values for laboratory parameters and vital signs: the mean value at baseline and at each respective protocol specified visit, and the mean, standard deviation and median for changes from baseline. Categorical data will be summarized using frequencies and percentages.

10.2 Analysis of Adverse Events

10.2.1 Treatment-Emergent Adverse Events

Treatment emergent AEs (TEAEs) are defined as events that begin or worsen either on or after the first dose of the study drug in the current study and within 140 days after the last dose administration of the study drug in the current study for subjects not rolling over into Study M16-000 Sub-Study 3 or until the first dose of the study drug of Study M16-000 sub-Study 3 if the subject is enrolled into Study M16-000 Sub-Study 3.

Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent, unless the study drug start time and the adverse event start time are collected and the adverse event start time is prior to the study drug start time. If an incomplete onset date was collected for an adverse event, the event will be assumed to be treatment-emergent unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

All analyses of AEs will be based on the number of patients with AEs (not the number of AEs).

10.2.1.1 Adverse Event Overview

The number and percentage of subjects experiencing TEAEs will be summarized for the following AE categories.

Any treatment-emergent adverse event.

Any treatment-emergent adverse event that was assessed with a Reasonable Possibility of being related to study drug by the Investigator.

Any treatment-emergent severe adverse event.

Any treatment-emergent serious adverse event.

Any treatment-emergent adverse event leading to discontinuation of study drug.

Any treatment-emergent adverse event leading to death.

Any treatment-emergent adverse event of safety interest.

Any event with an unknown severity will be considered severe and any AE with an unknown relationship will be considered drug related.

10.2.1.2 Adverse Events by System Organ Class and Preferred Term

The number and percentage of subjects experiencing TEAEs will be tabulated using primary Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) and preferred terms (PTs) for each treatment group according to Version 18.0 or higher of the MedDRA coding dictionary. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

A subject who reports more than 1 AE in different SOCs will be counted only once in the overall total. A subject who reports 2 or more different PTs, which are in the same SOC, will be counted only once in the SOC total. Subjects reporting more than 1 AE for a given PT will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables).

10.2.1.3 Adverse Events by Maximum Severity

The severity grading of AEs follows Rheumatology Common Toxicity Criteria (RCTC).

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

TEAEs will be summarized and tabulated by maximum severity in three categories: mild (Grade 1), moderate (Grade 2) and severe (Grade 3 or above) for data presentation. If a subject has an AE with an unknown severity, then the subject will be counted in the severity category of unknown, even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same AE with the most extreme severity – severe. In this case, the subject will be counted under the severe category.

AEs with Grade 3 or higher will be described in detail.

10.2.1.4 Adverse Events by "Reasonably Possibly Related" Relationship

TEAEs will also be summarized by MedDRA SOC and MedDRA PT, assessed with a Reasonable Possibility of being related to study drug by the Investigator. If a subject has an AE with an unknown relationship, then the subject will be counted in as 'related.'

10.2.1.5 Adverse Events by Preferred Term in Decreasing Frequency

TEAEs will be summarized for each treatment group by MedDRA PT in decreasing frequency of all risankizumab group.

10.2.1.6 Areas of Safety Interest

The Areas of Safety Interest (ASI) categories are listed in Appendix 12.7. These will be summarized and presented using primary MedDRA query and MedDRA PT.

Additional ASIs may be considered for tabulation/summary based on recommendations from Clinical and Safety teams, as deemed appropriate.

10.2.1.7 Adverse Events by 100 Patient Years

TEAEs will be summarized by event rate per 100 patient years, defined as

$$100 \times \frac{Number\ of\ TEAEs}{Total\ Patient\ Years}$$

where total patient years is defined as below.

- Total patient years of SC period is defined as (min (the last risankizumab SC dose date in Study M15-989 + 140 days, the first dose date of risankizumab in Study M16-000 sub-Study 3) - the first dose date of risankizumab SC in Study M15-989)/365.25.
- Total patient years of IV period is defined as (min (the last risankizumab IV dose date + 140 days, the first dose date of risankizumab SC) - the first dose date of risankizumab IV in Study M15-989)/365.25.
- Total patient years of "all risankizumab" is defined as (min (the last risankizumab dose date in Study M15-989 + 140 days, the first dose date of risankizumab in Study M16-000 sub-Study 3) - the first dose date of risankizumab in Study M15-989)/365.25.

10.2.2 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

The number and percentage of subjects experiencing treatment-emergent SAEs and adverse events leading to discontinuation of study drug will be tabulated according to the primary MedDRA SOC and PT for each treatment group.

10.2.3 Listing of Adverse Events

The following summaries of AEs will be prepared.

Listing of Subjects with Treatment-Emergent Adverse Events of Special Interest

Listing of Subjects with Treatment-Emergent Serious Adverse Events

Listing of all adverse events that led to discontinuation of study drug.

Listing of all deaths.

10.3 Analysis of Laboratory Data

Data collected from the central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses.

Hematology parameters: White Blood Cell (WBC) count, Neutrophils, Lymphocytes, Red Blood Cell (RBC) count, Hematocrit, Hemoglobin, Platelets count.

Chemistry parameters: Total Bilirubin (TBL), Direct Bilirubin, Gamma Glutamyl Transferase (GGT), Alkaline Phosphatase (ALP), Serum glutamic oxaloacetic transaminase (SGOT)/Aspartate Aminotransferase (AST), Serum glutamic pyruvic transaminase (SGPT)/Alanine aminotransferase (ALT), Total Protein, Albumin, Glucose, Creatinine, Potassium, Sodium, Calcium, Creatine Phosphokinase (CPK), Cholesterol, LDL cholesterol, HDL cholesterol, Triglycerides.

Urinalysis parameters: PH value.

10.3.1 Variables and Criteria Defining Abnormality

The liver-specific laboratory tests include the serum glutamic pyruvic transaminase (SGPT/ALT), serum glutamic-oxaloacetic transaminase (SGOT/AST), alkaline phosphatase, and total bilirubin.

The number and percentage of subjects meeting the criteria for potentially clinically significant liver function laboratory values will be summarized and a listing of potentially clinically significant liver function laboratory values will be provided. The table and listing will include all subjects who met any of the following 4 criteria:

ALT $\geq$ 3 $\times$ ULN, or
AST $\geq$ 3 $\times$ ULN, or
Alkaline phosphatase $\geq$ 1.5 $\times$ ULN, or
Total bilirubin $\geq$ 2 $\times$ ULN.

A listing of potential Hy's Law cases, defined as those who meet all of the following conditions will be provided.

- ALT of > 3 × ULN or AST of > 3 × ULN,
- associated with an increase in bilirubin ≥ 2 × ULN.

Additional listing of patients who met all of the following 3 criteria will be provided:

- ALT of > 3 × ULN or AST of > 3 × ULN,
- associated with an increase in bilirubin ≥ 2 × ULN,
- Alkaline phosphatase < 2 × ULN.

10.3.2 Statistical Methods

Changes from baseline in continuous laboratory parameters will be summarized by n, mean, standard deviation, minimum value, median, and maximum value for each treatment group.

Shift tables from baseline to the final value (the last assessment during each treatment period) according to the normal range will be provided for each hematology, clinical chemistry parameter and urinalysis parameter. The laboratory data will be categorized as low, normal, or high based on the normal ranges of the central laboratory used in this study. The shift tables will tabulate the number and percentage of subjects with baseline values below/within/above the normal range versus final values below/within/above the normal range.

For selected laboratory parameter with Common Toxicity Criteria (CTC) a listing of all subjects with any laboratory determinations meeting CTC Grade ≥ 3 as well as being a higher grade than the baseline CTC grade will be provided. For each of these subjects, the whole course of the parameter of the current study along with the baseline value will be listed.

Pre-defined criteria of CTC Grade 3 or greater are given in Table 8 and Table 9 below for selected chemistry variables and hematology variables respectively based on CTC Version 4.0. Please refer to Appendix 12.8 for the CTC Grades 1 - 4 for these variables based on CTC Version 4.0.

Table 8. Criteria for CTC Grade 3 or Greater for Chemistry Values

		Definition of CTC Grade 3 or Greater	
Chemistry Variables	**Units**	**Very Low**	**Very High**
TBL	mcmol/L		> 3.0 × ULN
SGOT/AST	U/L		> 5.0 × ULN
SGPT/ALT	U/L		> 5.0 × ULN
Albumin	g/L	< 20	
Glucose	mmol/L	< 2.2	> 13.9
Triglycerides	mmol/L		> 5.7
Creatinine	mcmol/L		> 3.0 × ULN
Sodium	mmol/L	< 130	> 155
Potassium	mmol/L	< 3.0	> 6.0
Calcium	mmol/L	< 1.75	> 3.1
CPK	U/L		> 5.0 × ULN
Total Cholesterol	mmol/L		> 10.34
GGT			> 5.0 × ULN
ALP			> 5.0 × ULN

Table 9. Criteria for CTC Grade 3 or Greater for Hematology Values

		Definition of CTC Grade 3 or Greater
Hematology Variables	**Units**	**Very Low**
Hemoglobin	g/L	< 80.0
Platelets count	10^9/L	< 50.0
WBC count	10^9/L	< 2.0
Neutrophils	10^9/L	< 1.0
Lymphocytes	10^9/L	< 0.5

10.4 Analysis of Vital Signs

10.4.1 Variables and Criteria Defining Abnormality

Vital sign variables include systolic blood pressure, diastolic blood pressure, pulse rate, body temperature, and weight. The criteria for potentially clinically significant key vital sign findings are presented in Table 10.

Table 10. Criteria for Potentially Clinically Significant Vital Sign Findings

Vital Sign	Category	Criteria for Potential Clinically Significant Vital Signs
Systolic blood pressure (mmHg)	Low	Value ≤ 90 mmHg and decrease ≥ 20 mmHg from Baseline
	High	Value ≥ 160 mmHg and increase ≥ 20 mmHg from Baseline
Diastolic blood pressure (mmHg)	Low	Value ≤ 50 mmHg and decrease ≥ 10 mmHg from Baseline
	High	Value ≥ 100 mmHg and increase ≥ 10 mmHg from Baseline
Pulse rate (bpm)	Low	Value ≤ 50 bpm and decrease ≥ 15 bpm from Baseline
	High	Value ≥ 120 bpm and increase ≥ 15 bpm from Baseline

10.4.2 Statistical Methods

The following summary statistics for all vital sign variables will be presented by treatment group: baseline mean, the mean at each visit, mean change from baseline, standard deviation, median, minimum, and maximum. The number and percentage of subjects meeting the criteria for potentially clinically significant key vital sign values will be summarized.

Vital sign results for subjects with values meeting the criteria for potentially clinically significant vital sign findings will be identified in a listing.

10.5 Analysis of ECG Parameters

ECG abnormalities if assessed by the Investigator as clinically significant will be reported as AE. ECG abnormalities assessed by the Investigator as no clinically significant, will not be captured. Hence no ECG analyses (categorical or outlier) will be performed.

11.0 Summary of Changes

Boehringer Ingelheim Pharma GmbH & Co. KG (BIP) and AbbVie S.A.R.L. (AbbVie) have entered into an agreement whereby AbbVie will take on the responsibilities for the development and commercialization of risankizumab (BI 655066/ABBV-066).

The current SAP has adapted the TSAP initial version developed by Boehringer Ingelheim (BI) which was dated by July 15, 2016. AbbVie analysis conventions are applied.

12.0 Appendix

12.1 Crohn's Disease Activity Index (CDAI)

The Crohn's Disease Activity Index (CDAI) is a composite instrument that includes patient symptoms evaluated over 7 days (abdominal pain, stool frequency and general well-being), as well as physical and laboratory findings. These items are scored individually, weighted, and do not contribute equally to the overall score. The CDAI is derived from summing up the weighted individual scores of eight items as outlined below:

Variable	Description		Weight
Number of liquid stools	Sum of 7 days		2
Abdominal pain	Sum of 7 days ratings	Range: 0 (none) to 3 (severe)	5
General well being	Sum of 7 days ratings	Range: 0 (generally well) to 4 (terrible)	7
Extraintestinal complications	Number of listed complications	arthritis/arthralgia, iritis/uveitis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, anal fissure/fistula/abscess, fever > 37.8°C	20
Antidiarrhoeal drugs	Use in previous 7 days	0 (no) or 1 (yes)	30
Abdominal mass		0 (no), 2 (questionable) or 5 (definite)	10
Hematocrit	Expected minus observed hematocrit	Males: 47 minus observed Females: 42 minus observed	6
Body weight[#]	Observed/ideal ratio	[1 – (observed/ideal)] × 100	1

[#] For body weight, if the calculated value is less than –10 then the value is set to –10.

CDAI approximately ranges from 0 to 600 with higher scores indicating more severe disease. For the calculation of CDAI and components at each visit, the following rules will be applied:

- The 7 most recent useable days out of the 14 days preceding the visit will be used.
- If 7 useable days are not available, an average will be calculated based on the number of days with available data as follows:
  - An average for the most recent 6 days will be calculated if data for only 6 days are available,
  - An average for the most recent 5 days will be calculated if data for only 5 days are available,
  - An average for the most recent 4 days will be calculated if data for only 4 days are available,
  - Data for days with missing diary entries will be imputed using the average of the non-missing days, in order to calculate a CDAI and components based on 7 days.
- If the minimum number of days of diary data (i.e., 4 days for CDAI and components) are not available, then the subject's score for that visit will be considered missing and NRI will be used for any endpoints relating to data for this visit.

The CDAI score is set to missing under the following conditions:

1. If there are less than 4 days of any diary data.
2. If any component other than the diary data is missing.

12.2 Patient Reported Outcome (PRO-2)

The PRO-2 is calculated based on the sum of the weighted patient-reported subscores of CDAI for liquid or soft stool frequency [SF] plus abdominal pain [AP] in the 7 days prior to the study visit. PRO-2 is calculated (as in the CDAI) by adding the values of the

summed stool frequency scores multiplied by 2 plus the summed abdominal pain scores multiplied by 5.

The SF and AP score at an assessment visit will be the average of the daily values reported during the 7 days preceding the scheduled assessment visit.

- If 7 days daily values are not available, an average will be calculated based on the number of days with available data as follows:
  - An average for the most recent 6 days will be calculated if data for only 6 days are available,
  - An average for the most recent 5 days will be calculated if data for only 5 days are available,
  - An average for the most recent 4 days will be calculated if data for only 4 days are available.
- If the minimum number of days of diary data (i.e., 4 days for SF and AP) are not available, then the subject's score for that visit will be considered missing and NRI will be used for any endpoints (e.g., clinical remission) relating to data for this visit. Subjects who discontinue prior to the endpoint for any reason will be considered as "not achieved" for the endpoint.

12.3 Crohn's Disease Endoscopic Index of Severity (CDEIS)

Scoring System for Crohn's Disease Endoscopic Index of Severity (CDEIS)

	Rectum	Sigmoid and Left Colon	Transverse Colon	Right Colon	Ileum	Total
Deep ulcerations (12 if present)						Total 1
Superficial ulcerations (6 if present)						Total 2
Surface involved by disease (cm)						Total 3
Surface involved by ulcerations (cm)						Total 4
					Total 1 + Total 2 + Total 3 + Total 4 =	Total A
					Number of segments totally or partially explored	N
					Total A/n =	Total B
					If an ulcerated stenosis is present anywhere add 3 =	C
					If a nonulcerated stenosis is present anywhere add 3 =	D
					Total B + C + D =	CDEIS

If deep ulceration is present the value is 12. Sum the present values for rectum, sigmoid and left colon, transverse colon, right colon and ileum.

If superficial ulceration is present the value is 6. Sum the present values for rectum, sigmoid and left colon, transverse colon, right colon and ileum.

Sum the surface involved by the disease (cm from 0 – 10) for rectum, sigmoid and left colon, transverse colon, right colon and ileum. The sum has one decimal place.

Sum the surface involved by ulcerations (cm from 0 – 10) for rectum, sigmoid and left colon, transverse colon, right colon and ileum. The sum has one decimal place.

A is the sum of the sum for deep ulceration + sum for superficial ulceration + sum for surface involved by disease + sum for surface involved by ulceration.

n is the number of segments totally or partially explored.

B is A/n.

C if ulcerated stenosis is present anywhere add 3.

D if non ulcerated stenosis is present anywhere add 3.

The total score (CDEIS) is the sum of the sum for deep ulceration + sum for superficial ulceration + sum for surface involved by disease + sum for surface involved by ulceration (for all examined segments) divided by the number of segments totally or partially explored + 3 if an ulcerated stenosis present (> 0) + 3 if a non-ulcerated stenosis present (> 0).

Please use baseline CDEIS score for the disease location (pattern) analysis:

a. Ileum only: at least one component score > 0 in ileum and all component scores = 0 in colon (left, transverse, right, sigmoid, rectum)
b. Colonic only: all component scores = 0 in ileum and at least one component score > 0 in colon (left, transverse, right, sigmoid, rectum)
c. Ileocolonic: at least one component score > 0 in ileum and at least one component score > 0 in colon (left, transverse, right, sigmoid, rectum)

The following convention applies to Crohn's Disease Endoscopic Index of Severity (CDEIS):

If any item among the explored segments is missing, then set the total score to missing.

12.4 Simple Endoscopic Score – CD (SES-CD)

SES-CD is calculated based the sum of individual segment values for four endoscopic variables (presence and size of ulcers, ulcerated surface, affected surface and presence of narrowing). Each variable in each segment be scored 0 to 3 resulting in SES-CD values ranging from 0 to 56 with higher scores indicating more severe disease.

Variable	Score			
	0	1	2	3
Size of ulcers (cm)	None	Aphthous ulcers (diameter 0.1–0.5)	Large ulcers (diameter 0.5–2)	Very large ulcers (diameter >2)
Ulcerated surface (%)	None	<10	10–30	>30
Affected surface (%)	Unaffected segment	<50	50–75	>75
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

*Total SES-CD: sum of the values of the 4 variables for the 5 bowel segments. Values are given to each variable and for every examined bowel segment (for example, rectum, left colon, transverse colon, right colon and ileum).

Medscape Source: Nat Rev Gastroenterol Hepatol ©2009 Nature Publishing Group

SES-CD Scoring:

	Rectum	Sigmoid and Left Colon	Transverse Colon	Right Colon	Ileum	Total
Size of Ulcers Enter: 0 if none 1 if aphthous ulcers (Ø 0.1 to 0.5 cm) 2 if large ulcers (Ø 0.5 to 2 cm) 3 if very large ulcers (Ø > 2 cm)						
Ulcerated Surface Enter: 0 if none 1 if < 10% 2 if 10% – 30% 3 if > 30%						
Affected Surface Enter: 0 if unaffected segments 1 if < 50% 2 if 50% – 75% 3 if > 75%						
Presence of Narrowing Enter: 0 if none 1 if single, can be passed 2 if multiple, can be passed 3 if cannot be passed						
					TOTAL =	

The following convention applies to Simple Endoscopic Score – CD (SES-CD) total score:

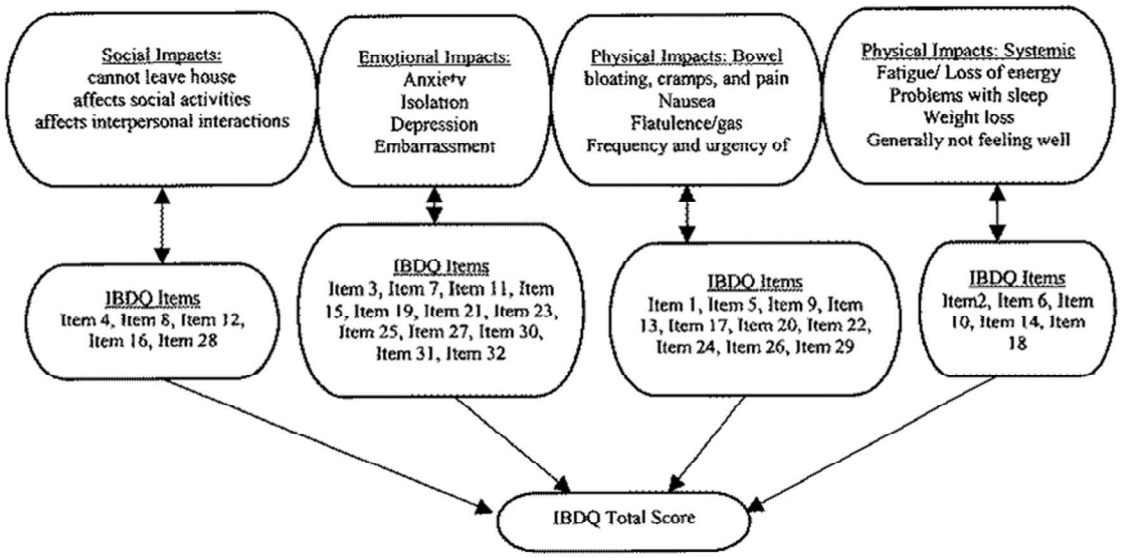
- Baseline missing variables are imputed as 0
- Post-baseline total score will be missing if > 8 individual variables are missing. Otherwise, missing variables will be imputed as 0.

The following convention applies to Simple Endoscopic Score – CD (SES-CD) subscore (Size of Ulcers, Ulcerated Surface, Affected Surface, Presence of Narrowing) if the endpoint is only related to the subscores:

- Baseline missing variables in any subscore are imputed as 0
- Post-baseline subscore will be missing if > 2 individual variables for this subscore are missing. Otherwise, missing variables for this subscore will be imputed as 0.

12.5 Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ is a 32-item (ranges 1 – 7) self-report questionnaire for patients with IBD to evaluate the patient reported outcomes across 4 domains: 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), as shown in the figure below. The IBDQ total score ranges from 32 to 224 with a higher score indicating better outcome.



The derivation of the IBDQ total score and the four IBDQ domain scores are as follows:

Domain Scores:

S1. BOWEL SYMPTOM: Q1 + Q5 + Q9 + Q13 + Q17 + Q20 + Q22 + Q24 + Q26 + Q29
[score ranges from 10 - 70],

S2. SOCIAL FUNCTION: Q4 + Q8 + Q12 + Q16 + Q28
[score ranges from 5 - 35],

S3. SYSTEMIC SYMPTOM: Q2 + Q6 + Q10 + Q14 + Q18
[score ranges from 5 - 35],

S4. EMOTIONAL FUNCTION: Q3 + Q7 + Q11 + Q15 + Q19 + Q21 + Q23 + Q25 + Q27 + Q30 + Q31 + Q32
[score ranges from 12 - 84].

Total Score:

IBDQ Total Score = SUM of (bowel symptom domain score, social function domain score, systemic symptom domain score, emotional function domain score).

The following convention applies to Inflammatory Bowel Disease Questionnaire (IBDQ):

When not more than 20% of items in a domain of IBDQ were missing, it was substituted with the mean values from the items completed in the particular domain; otherwise, they were treated as missing. The 20% threshold in each domain is: bowel symptom domain: 2 items, systemic symptom domain: 1 item, social function domain: 1 item, emotional function domain: 2 items. If any of the 4 domain scores is missing, the total IBDQ score will be set to missing.

12.6 Isolated Ileitis

- For isolated ileitis in the analysis using CDEIS: Patients who have CDEIS = 0 in all segments other than ileum are considered to have isolated ileitis.
- For isolated ileitis in the analysis using SESCD: Patients who have SESCD = 0 in all segments other than ileum are considered to have isolated ileitis.

12.7 Area of Safety Interest (ASI)

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Adjudicated CV Events	MACE	Adjudicated terms will be identified using CECAT and CETERM from the CE SDTM dataset.	Display underlined terms defined by the following adjudicated terms: • CV Death which includes adjudicated results of: Sudden Cardiac death, Death due to Acute MI, Death due to Heart Failure, Death due to CV Procedures, Death due to CV Hemorrhage, Death due to Other CV Causes (specify), Undetermined Death, fatal stroke (ischemic, hemorrhagic, undetermined) • Myocardial infarction • Stroke: Ischemic stroke, Hemorrhagic stroke, Undetermined stroke	Y
	Extended MACE	Adjudicated terms will be identified (for MACE +) using CECAT and CETERM from the CE SDTM dataset.	Display underlined terms from MACE and underlined terms below: • Hospitalization for Unstable Angina • PCI • CABG	N
Serious infections, TB, fungal and opportunistic infections (including herpes zoster)	Serious infections	Infections and Infestations SOC	PTs	Y
	TB	Tuberculosis (including Investigations) CMQ (code 80000033)	PTs	Y
	Opportunistic infections	Opportunistic infections CMQ (code 80000073)	PTs	Y
	Fungal infections	Fungal infections CMQ (code 80000063)	PTs	N
	Herpes Zoster	Herpes zoster CMQ (code 80000175)	PTs	N

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Malignancies	All possible malignancies	Narrow Malignancies (SMQ 20000090)	PTs	N
	Malignant Tumors	Narrow Malignant tumors (SMQ 20000194)	PTs	Y
	Non-melanoma skin cancer (NMSC)	Broad Skin malignant tumors (SMQ 20000204) excluding terms identified by the Melanoma CMQ (code 80000119)	PTs	N
	Malignancies excluding NMSC	'Malignancies excluding NMSC' is identified by the 'Malignant Tumours' search excluding terms identified by the 'Non-melanoma skin cancer' (NMSC) search.	PTs	Y
Hypersensitivity Reaction	Hypersensitivity	Narrow Hypersensitivity (SMQ 20000214)	PTs	Y
	Anaphylactic Reaction	Narrow Anaphylactic reaction (SMQ 20000021)	PTs	Y

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Hepatic Event	Hepatic Event	Broad Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ 20000013) Broad Hepatitis, non infectious (SMQ 20000010) Broad Cholestasis and jaundice of hepatic origin (SMQ 20000009) Broad Liver related investigations, signs and symptoms (SMQ 20000008) Narrow Liver-related coagulation and bleeding disturbances (SMQ 20000015)	PTs	N

12.8 Common Toxicity Criteria (CTC) Grade for Laboratory Data

Test	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry Variables				
SGPT/ALT increased	> ULN – 3.0 × ULN	> 3.0 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
SGOT/AST increased	> ULN – 3.0 × ULN	> 3.0 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
GGT increased	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
ALP increased	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
TBL increased	> ULN – 1.5 × ULN	> 1.5 – 3.0 × ULN	> 3.0 – 10.0 × ULN	> 10.0 × ULN
Creatinine increased	> ULN – 1.5 × ULN	> 1.5 – 3.0 × ULN	> 3.0 – 6.0 × ULN	> 6.0 × ULN
CPK increased	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 10.0 × ULN	> 10.0 × ULN

Test	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry Variables				
Total Cholesterol increased	> ULN - 7.75	> 7.75 - 10.34	> 10.34 - 12.92	> 12.92
Albumin decreased	< LLN - 30	< 30 - 20	< 20	N/A
Triglycerides increased	1.71 - 3.42	> 3.42 - 5.7	> 5.7 - 11.4	> 11.4
Glucose	< LLN - 3.0 or > ULN - 8.9	< 3.0 - 2.2 or > 8.9 - 13.9	< 2.2 - 1.7 or > 13.9 - 27.8	< 1.7 or > 27.8
Sodium	< LLN – 130 or > ULN - 150	> 150 – 155	< 130 – 120 or > 155 - 160	< 120 or > 160
Potassium	< LLN - 3.0 or > ULN - 5.5	< LLN - 3.0 or > 5.5 - 6.0	< 3.0 - 2.5 or > 6.0 - 7.0	< 2.5 or > 7.0
Calcium	< LLN - 2.0 or > ULN -2.9	< 2.0 - 1.75 or > 2.9 - 3.1	< 1.75 - 1.5 or > 3.1 - 3.4	< 1.5 or > 3.4
Hematology Variables				
Hemoglobin decreased	< LLN – 100.0 g/L	< 100.0 – 80.0 g/L	< 80.0 g/L	N/A
Neutrophil count decreased	< LLN – 1.5 × 10^9/L	< 1.5 – 1.0 × 10^9/L	< 1.0 – 0.5 × 10^9/L	< 0.5 × 10^9/L
WBC decreased	< LLN – 3.0 × 10^9/L	< 3.0 – 2.0 × 10^9/L	< 2.0 – 1.0 × 10^9/L	< 1.0 × 10^9/L
Lymphocyte count decreased	< LLN – 0.8 × 10^9/L	< 0.8 – 0.5 × 10^9/L	< 0.5 – 0.2 × 10^9/L	< 0.2 × 10^9/L
Platelets count decreased	< LLN - 75.0 × 10^9/L	< 75.0 - 50.0 × 10^9/L	< 50.0 - 25.0 × 10^9/L	< 25.0 × 10^9/L

12.9 Analysis Convention for Composite Endpoints

The value of composite endpoints, such as deep remission, is decided by the value of each component at the visits with planned measurements for all components. In details, taking deep remission as an example, one of its components, clinical remission, is measured every eight weeks, i.e., Week 0, 8, 16, 24 etc. The other component, CDEIS remission, is measured every year, i.e., Week 0, Week 48, Week 104, Week 152, Week 200. Hence the observed value of deep remission will be evaluated at Week 0, Week 48, Week 104,

Week 152, Week 200 based on the value of each component endpoint at the corresponding visit, according to Table 11 below, where, for deep remission, the endpoint A = Clinical remission, the endpoint B = CDEIS remission.

Table 11. How to calculate the observed value of endpoint C = A and B for different scenarios

Scenarios	A at Week X*	B at Week X*	C at Week X*
Scenario 1	1	1	1
Scenario 2/3/4	1/0/0	0/1/0	0/0/0
Scenario 5/6	1/Missing	Missing/1	Missing/Missing
Scenario 7/8	0/Missing	Missing/0	0
Scenario 9	Missing	Missing	Missing

* X = The visits with both measurements A and B planned. It will be 0, 48, 104, 152, 200 for deep remission.

The other endpoints which have multiple components, i.e., "A and B and C…," such as "Proportion of subjects with average daily SF $\leq$ 2.8 and not worse than baseline and average daily AP score $\leq$ 1 and not worse than baseline," could follow the similar logic.

For endpoints with the structure of "A or B," such as "Proportion of subjects with $\geq$ 60% decrease in average daily SF and/or $\geq$ 35% decrease in average daily AP score and both not worse than baseline, and/or achievement of average daily SF $\leq$ 2.8 and AP $\leq$ 1 and both not worse than baseline," the observed value of such endpoint "C = A or B" can be determined following the logic displayed in Table 12 below.

Table 12. How to calculate the observed value of endpoint C = A or B for different scenarios.

Scenarios	A at Week X*	B at Week X*	C at Week X*
Scenario 1	0	0	0
Scenario 2/3/4	1/0/1	1/1/0	1/1/1
Scenario 5/6	1/Missing	Missing/1	1/1
Scenario 7/8	0/Missing	Missing/0	Missing/Missing
Scenario 9	Missing	Missing	Missing

* X = The visits with both measurements A and B planned.

Document Approval

Study M15989 - Statistical Analysis Plan Version 1 - 15Jul2019 (E3 16.1.9)

Version: 1.0 **Date:** 17-Jul-2019 03:46:15 AM **Company ID:** 07172019-00F9F6842AA885-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	16-Jul-2019 09:30:39 AM	Approver
	16-Jul-2019 03:17:43 PM	Approver
	16-Jul-2019 03:19:44 PM	Author
	17-Jul-2019 03:46:14 AM	Approver