



Title: A Phase 3, Open-label Study to Determine the Long-term Safety and Efficacy of Vedolizumab (MLN0002) in Patients With Ulcerative Colitis and Crohn's Disease

NCT Number: NCT00790933

Protocol Approve Date: 22 August 2016

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CLINICAL STUDY PROTOCOL C13008

Vedolizumab (MLN0002)

A Phase 3, Open-label Study to Determine the Long-term Safety and Efficacy of Vedolizumab (MLN0002) in Patients With Ulcerative Colitis and Crohn's Disease

Protocol Number: C13008
Indication: Ulcerative colitis and Crohn's disease
Phase: 3
Sponsor: Takeda Development Center Americas, Inc.,
Takeda Development Centre Europe, Ltd.,
Takeda Development Center Asia Pte. Ltd
EudraCT Number: 2008-002784-14
Therapeutic Area: Inflammation

Protocol History

Original		26 June 2008
Amendment 1		14 October 2008
Amendment 2		28 April 2009
Amendment 3	<i>for use only outside of the US</i>	28 April 2009
Amendment 4	<i>for use only in Norway and the United Kingdom</i>	17 November 2009
Amendment 5	<i>for use in all countries except the US, Norway, and the United Kingdom</i>	23 November 2010
Amendment 6	<i>for use in the US only</i>	23 November 2010
Amendment 7	<i>for use only in Norway and the United Kingdom</i>	21 January 2011
Amendment 8	<i>for use in all countries outside the US</i>	15 February 2012
Amendment 9	<i>for use in the US only</i>	15 February 2012
Amendment 10	<i>for use in all countries outside the US that are enrolling de novo patients</i>	15 February 2012
Amendment 11	<i>for use in Germany only</i>	04 May 2012
Amendment 12	<i>for use only in Norway and the United Kingdom</i>	11 May 2012
Amendment 13	<i>for use in Spain only</i>	05 November 2012
Amendment 14	<i>for use in all countries currently/previously working to Amendment 8 where vedolizumab is either not commercially available or is not reimbursed</i>	26 November 2015
Amendment 15	<i>for use in the US only</i>	26 November 2015
Amendment 16	<i>for use in all countries currently/previously working to Amendment 10 where vedolizumab is either not commercially available or is not reimbursed</i>	26 November 2015

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Amendment 17	<i>for use in the US only</i>	19 February 2016
Amendment 18	<i>for use in all countries currently/previously working to Amendment 14 where vedolizumab is either not commercially available or is not reimbursed</i>	22 August 2016
Amendment 19	<i>for use in India only</i>	22 August 2016
Amendment 20	<i>for use in all countries currently/previously working to Amendment 16 where vedolizumab is either not commercially available or is not reimbursed</i>	22 August 2016

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Approval Page

Note: If this document was approved electronically, the electronic approval signatures may be found at the end of the document.

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Rationale for Amendment 20

Amendment 20 is an update to Amendment 16 of the C13008 protocol to be implemented in countries where vedolizumab is either not commercially available or is not reimbursed. With this amendment, patients participating in these countries will have continued access to vedolizumab in Study C13008 until either:

- July 2017, or
- The Extended Access Program (XAP) study is available at the site, or
- Patient withdrawal, or
- Vedolizumab is available to the patient through commercial channels (including reimbursement) for the patient's clinical scenario, or
- The study is terminated early by the sponsor, as described in Section 11.12,

whichever comes first.

Purposes for Amendment 20

The purpose of this amendment is to:

- Extend the duration of this study to allow all patients in countries where vedolizumab is either not commercially available or is not reimbursed continued access to vedolizumab until July 2017, or until the XAP study is available at the site, or until patient withdrawal, or until vedolizumab is available to the patient through commercial channels (including reimbursement) for the patient's clinical scenario, or unless the study is terminated early by the sponsor, as described in Section 11.12, whichever comes first.
- Remove the requirement for patients who transition into the XAP study to attend the Final Safety Visit in the C13008 study. The safety of these patients will be monitored as part of the XAP study.
- Amendment of the pregnancy and contraception language in line with updated safety information.
- Amend the adverse event, serious adverse event, and concomitant medication reporting instructions for patients in Study C13008 who transition into the XAP study, such that the C13008 collection period ends at the time the patient is consented into the XAP study.

For specific examples of changes in text and where the changes are located, see Section 15.14.

PROTOCOL SUMMARY

Study Title: A Phase 3, Open-label Study to Determine the Long-term Safety and Efficacy of Vedolizumab (MLN0002) in Patients With Ulcerative Colitis (UC) and Crohn's Disease (CD)

Study Phase: Phase 3

Number of Patients: up to approximately 2200

Study Objectives:

Primary Objective

- To determine the safety profile of long-term MLN0002 treatment

Resource Utilization and Patient-Reported Outcome Objectives

- To determine the effect of long-term MLN0002 treatment on time to major inflammatory bowel disease (IBD)-related events (hospitalizations, surgeries, and procedures)
- To examine the effect of long-term MLN0002 treatment on health-related quality of life (QOL) measurements

Exploratory Objective

- To obtain data regarding the effect of long-term MLN0002 treatment on maintaining clinical response and remission

Overview of Study Design:

Enrolled patients will receive 300 mg MLN0002 every 4 weeks, starting at Week 0, until July 2017, or until an Extended Access Program (XAP) study is available at the site, or until patient withdrawal, or until vedolizumab is available to the patient through commercial channels (including reimbursement) for the patient's clinical scenario, unless the study is terminated early by the sponsor, as described in Section 11.12, whichever comes first. For subjects who do not transition into the XAP study, the dosing period will be followed by a 16-week posttreatment observation and safety assessment period.

Patients may receive allowed concomitant medications for the treatment of IBD as detailed in Section 6.2.1, as determined by the principal investigator, at any time point during the study. Medications may be discontinued during the study, but if discontinuation is planned, it should be done prior to the first dose of vedolizumab.

It is strongly recommended that patients receiving oral corticosteroids should begin an oral corticosteroid tapering regimen once they achieve clinical response or if, in the opinion of the investigator, they demonstrate sufficient improvement in clinical signs and symptoms.

Patients who require rescue medication or major surgery for the treatment of their IBD (as defined in Section 6.4.9) or who, in the opinion of the investigator or patient, are not benefiting from therapy will be withdrawn from the study. Investigators should also strongly consider withdrawing patients who require recurrent courses of oral corticosteroids with an inability to taper.

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Safety assessments, including safety labs, and exploratory efficacy assessments (using the partial Mayo Score [for patients with UC] or the Harvey-Bradshaw Index (HBI) score [for patients with CD]) will be made throughout the treatment period, and at the Final Safety visit. Serious adverse events (SAEs) and adverse events (AEs) will be collected throughout the study (as applicable). For patients enrolling to the XAP study, AEs/SAEs and concomitant medications will be collected until in Study C13008 the patient is consented into the XAP study. Data pertaining to health care utilization and patient-reported outcomes will also be collected regularly throughout the study. In addition, safety data from this study will be benchmarked with data from external databases.

Study Population:

Most patients enrolling in this study will have participated in a previous qualifying MLN0002 study (rollover patients):

- Patients with UC or CD who participated in the phase 2, open-label, long-term safety study (Study C13004)
- Patients who withdrew early from a phase 3 UC or CD induction and maintenance study (Study C13006 or Study C13007) due to sustained nonresponse, disease worsening, or the need for rescue medications
- Patients who completed Study C13006, Study C13007, or Study C13011

In addition, up to 400 patients without previous treatment with vedolizumab may be enrolled directly (de novo patients):

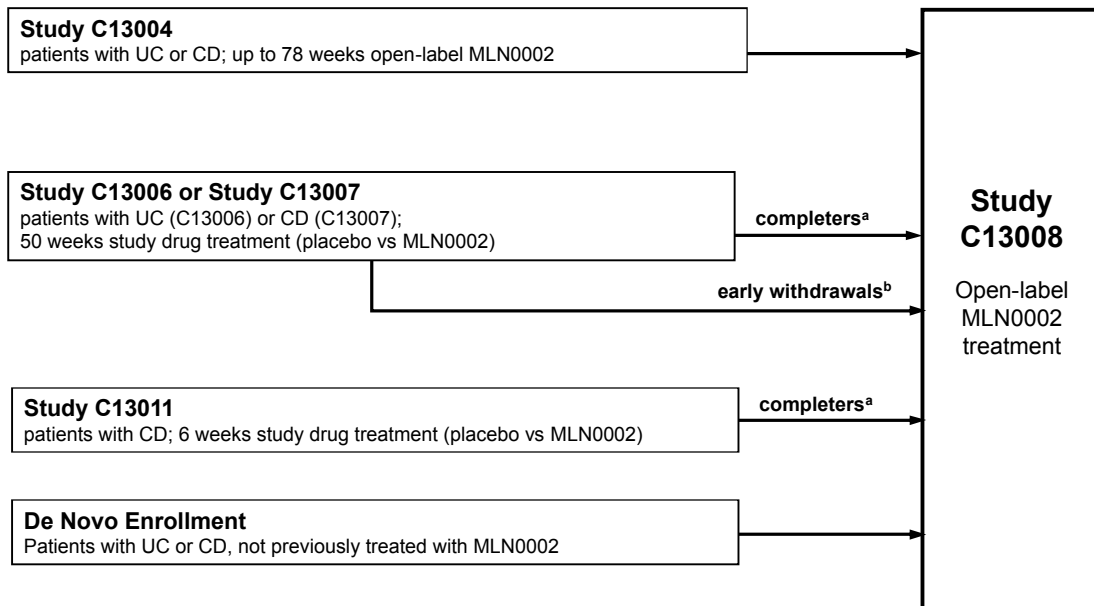
- Patients with UC or CD who meet the inclusion/exclusion criteria for de novo patients

Number of Study Center(s): approximately 400 sites worldwide; de novo patients will be enrolled at approximately 150 of the existing sites.

Duration of Study:

It is anticipated that the duration of MLN0002 treatment will vary by patient based on continued benefit. Treatment duration may continue until July 2017, or until XAP study is available at the site, or until patient withdrawal, or until vedolizumab is available to the patient through commercial channels (including reimbursement) for the patient's clinical scenario, or unless the study is terminated early by the sponsor, as described in Section 11.12, whichever is sooner. After the final dose of MLN0002, patients who do not transition into the XAP study will complete the 16-week post treatment observation and assessment period. Additionally, upon completion of or termination from this study, patients will participate in a 2-year follow-up survey during which time a safety questionnaire will be administered by telephone. Patients who transition into the XAP study are not required to attend the Final Safety Visit of C13008. The safety of these patients will be monitored as part of the XAP study.

Study Diagram: Sources of Study Participants



- a Patients who completed the Week 52 assessments in Study C13006 or Study C13007, or the Week 10 assessments in Study C13011.
- B Patients who met the criteria for sustained nonresponse or disease worsening, or required rescue medications in a phase 3 UC or CD induction and maintenance study (Study C13006 or Study C13007) and withdrew early from that study.

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Schedule of Events: Pre-enrollment Through Year 2

Study Procedures	Pre-enrollment		Treatment																								Unscheduled Visit (Disease Exacerbation)			
	Rollover Patients ^a (P) = obtained from prior study	De Novo Screening ^b	YEAR 1												YEAR 2															
			Weeks (± 1 week)												Weeks (± 1 week)															
			0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100		
Informed consent	X	X																												
Wallet card	X	X																												
Demographics	(P)	X																												
Tobacco use	(P)	X																												
Medical history	(P)	X																												
Prior therapies	(P)	X																												
UC/CD Disease history	(P)	X																												
Physical exam ^c	(P)	X		X				X				X			X				X				X				X		X	
Neurological exam ^c	(P)	X		X				X				X			X				X				X				X		X	
Vital signs ^d		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight ^d		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PML checklist		X	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g		
Patient assessment of disease activity		X	X ^g	X ^g	X ^g	X ^g		X ^g		X ^g		X ^g		X ^g		X ^g		X ^g		X ^g		X ^g		X ^g		X ^g		X		
Concomitant medications ^e	(P)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Study Procedures	Pre-enrollment		Treatment																								Unscheduled Visit (Disease Exacerbation)				
	Rollover Patients ^a (P) = obtained from prior study	De Novo Screening ^b	YEAR 1												YEAR 2																
			Weeks (± 1 week)												Weeks (± 1 week)																
			0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100			
Urinalysis	(P)	X														X ^g															
CRP	(P) ¹	X										X ^g								X ^g	X ^g									X ^g	
HAHA ^m	(P)	X		X ^g				X ^g				X ^g				X ^g				X ^g	X ^g				X ^g	X ^g				X ^g	X
Fecal calprotectin		X ^o																													
Stool sample ^k		X																													X ^k
End-of-study eCRF			p												p																

Abbreviations: AEs = adverse events, CD = Crohn’s disease, CRP = C-reactive protein, EQ-5D = EuroQual, ECG = electrocardiogram, HAHA = human anti-human antibodies, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IBDQ = Inflammatory Bowel Disease Questionnaire, HBI = Harvey-Bradshaw Index, PML = progressive multifocal leukoencephalopathy, SAEs = serious adverse events, SF-36 = Short Form-36, TB = tuberculosis, UC = ulcerative colitis.

Note: Patients will return 16 weeks after the last dose of MLN0002 for final safety assessments at the Final Safety visit, as described in the Schedule of Events for Years 5 and beyond. This visit is not required for patients transitioning from Study C13008 into the XAP study.

a For rollover patients, the first dose of MLN0002 in this study (ie, Week 0) should occur no more than 9 weeks after the last dose of study drug in the previous study; the preferable period is within 3 to 5 weeks after the last dose in the previous study. Pre-enrollment procedures marked with an X will be completed within 5 weeks prior to Week 0 for rollover patients. Pre-enrollment assessments marked with (P) will not be performed; data for these assessments will be obtained from the previous study.

b For de novo patients, all screening procedures will be done between Day -21 and Day -1.

c Clinically significant findings will be recorded as AEs.

d On dosing days, vital signs and weight will be obtained prior to dosing.

e For rollover patients, any medications that are ongoing at the end of the previous study and that are still present at the time of enrollment into the C13008 study will be recorded in the eCRF for Study C13008.

f For patients with UC.

g To be performed prior to dosing.

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Study Procedures	Pre-enrollment		Treatment																								Unscheduled Visit (Disease Exacerbation)
	Rollover Patients ^a (P) = obtained from prior study	De Novo Screening ^b	YEAR 1												YEAR 2												
			Weeks (± 1 week)												Weeks (± 1 week)												
0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100		
<p>h For patients with CD.</p> <p>i AE and SAE collection will begin at the time of enrollment (with the exception of SAE collection for de novo patients, which will begin at the signing of informed consent).</p> <p>j All females must have a serum pregnancy test at screening for de novo patients and at the Final Safety visit for all patients (as applicable). A urine pregnancy test will be performed prior to each dose of MLN0002.</p> <p>k A stool sample for culture, ova and parasite evaluation, and <i>C. difficile</i> assay will be obtained at screening for de novo patients and (if indicated) at any point during the study when a patient becomes symptomatic, including worsening or return of disease activity.</p> <p>l For rollover patients, CRP results will be obtained from previous study as applicable.</p> <p>m Drug concentration may be determined as part of the HAHA testing.</p> <p>n Patients with no history of TB will have either a QuantiFERON test or a tuberculin skin test within 1 month of enrollment.</p> <p>o As needed for study eligibility.</p> <p>p If the patient is transitioning from Study C13008 into the XAP study, complete the end-of-study eCRF page at their last dosing visit in C13008. For all other patients, complete the end-of-study page at the Final Safety Visit.</p>																											

Schedule of Events: Years 3 and 4

Study Procedures ^a	Treatment																							Unscheduled Visit (Disease Exacerbation)	
	YEAR 3												YEAR 4												
	Weeks (± 1 week)												Weeks (± 1 week)												
	104	108	112	116	120	124	128	132	136	140	144	148	152	156	160	164	168	172	176	180	184	188	192	196	
Physical exam ^b				X				X				X				X				X				X	X
Neurological exam ^b				X				X				X				X				X				X	
Vital signs ^c	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight ^c	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PML checklist	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	
Patient assessment of disease activity		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Partial Mayo score ^e		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d	X
HBI ^f		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d		X ^d	X
IBDQ						X ^d						X ^d							X ^d					X ^d	
SF-36						X ^d						X ^d							X ^d					X ^d	
EQ-5D						X ^d						X ^d							X ^d					X ^d	
12-lead ECG	X ^d												X ^d												
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Samples for:																									
Pregnancy test ^g	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	
Clinical chemistry				X ^d				X ^d				X ^d				X ^d				X ^d				X ^d	X
Hematology				X ^d				X ^d				X ^d				X ^d				X ^d				X ^d	X
Coagulation	X ^d												X ^d												

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Study Procedures ^a	Treatment																								Unscheduled Visit (Disease Exacerbation)	
	YEAR 3												YEAR 4													
	Weeks (± 1 week)												Weeks (± 1 week)													
	104	108	112	116	120	124	128	132	136	140	144	148	152	156	160	164	168	172	176	180	184	188	192	196		
Urinalysis	X ^d												X ^d													
CRP								X ^d								X ^d									X ^d	
HAHA ^h				X ^d				X ^d				X ^d				X ^d					X ^d				X ^d	X
Stool sample ⁱ																										X ⁱ
End-of-study eCRF	j												j													

Abbreviations: AEs = adverse events, CD = Crohn’s disease, CRP = C-reactive protein, EQ-5D = EuroQual, ECG = electrocardiogram, HAHA = human anti-human antibodies, IBDQ = Inflammatory Bowel Disease Questionnaire, HBI = Harvey-Bradshaw Index, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, PML = progressive multifocal leukoencephalopathy, SAEs = serious adverse events, SF-36 = Short Form-36, UC = ulcerative colitis.

a Patients will return 16 weeks after the last dose of MLN0002 for final safety assessments at the Final Safety visit, as described in the Schedule of Events for Years 5 and beyond. This visit is not required for patients transitioning from Study C13008 into the XAP study.

b Clinically significant findings will be recorded as AEs.

c On dosing days, vital signs and weight will be obtained prior to dosing.

d To be performed prior to dosing.

e For patients with UC.

f For patients with CD.

g All female subjects of childbearing potential must have a serum pregnancy test at the Final Safety visit (as applicable). A urine pregnancy test for women of childbearing potential will be performed prior to each dose of MLN0002.

h Drug concentration may be determined as part of the HAHA testing.

i A stool sample for culture, ova and parasite evaluation, and *C. difficile* assay will be obtained (if indicated) at any point during the study when a patient becomes symptomatic, including worsening or return of disease activity.

j If the patient is transitioning from Study C13008 into the XAP study, complete the end-of-study eCRF page at their last dosing visit in C13008. For all other patients, complete the end-of-study page at the Final Safety Visit.

Schedule of Events: Years 5 and Beyond, and the Final Safety Visit

Study Procedures	Treatment: YEARS 5 and Beyond													Final Safety Visit ^{a,b}	Unscheduled Visit (Disease Exacerbation)	
	Weeks (± 1 week)															
	Year 5	200	204	208	212	216	220	224	228	232	236	240	244			248
	Year 6	252	256	260	264	268	272	276	280	284	288	292	296	300	16 (± 2) wks after last dose	
	Year 7	304	308	312	316	320	324	328	332	336	340	344	348	352		
	Year 8	356	360	364	368	372	376	380	384	388	392	396	400	404		
Physical exam ^b				X				X					X	X		X
Neurological exam ^b				X				X					X	X		
Vital signs ^c		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight ^c		X			X				X				X			
12-lead ECG														X		
PML checklist		X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X	
Patient assessment of disease activity			X ^d		X ^d		X ^d		X ^d		X ^d		X ^d	X ^d		X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant procedures		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dosing		X	X	X	X	X	X	X	X	X	X	X	X	X		
Partial Mayo score ^e			X ^d		X ^d		X ^d		X ^d		X ^d		X ^d	X ^d		X
HBI ^f			X ^d		X ^d		X ^d		X ^d		X ^d		X ^d	X ^d		X
IBDQ														X ^d		
SF-36														X ^d		
EQ-5D														X ^d		
AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Samples for:																
Pregnancy test ^g		X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^g	
Clinical chemistry					X ^d				X ^d					X ^d	X	X
Hematology					X ^d				X ^d					X ^d	X	X

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	Treatment: YEARS 5 and Beyond													Final Safety Visit^{a,b}	Unscheduled Visit (Disease Exacerbation)
	Weeks (± 1 week)														
Year 5	200	204	208	212	216	220	224	228	232	236	240	244	248	16 (± 2) wks after last dose	
Year 6	252	256	260	264	268	272	276	280	284	288	292	296	300		
Year 7	304	308	312	316	320	324	328	332	336	340	344	348	352		
Year 8	356	360	364	368	372	376	380	384	388	392	396	400	404		
Coagulation														X	
Urinalysis														X	
HAHA ^h						X ^d							X ^d	X	X
Stool sample ⁱ															X ⁱ
End-of-study eCRF	j													j	
<p>Abbreviations: AEs = adverse events, CD = Crohn’s disease, EQ-5D = EuroQual, HAHA = human anti-human antibodies, IBDQ = Inflammatory Bowel Disease Questionnaire, HBI = Harvey-Bradshaw Index, PML = progressive multifocal leukoencephalopathy, SAEs = serious adverse events, SF-36 = Short Form-36, UC = ulcerative colitis.</p> <p>a Patients will return 16 weeks after the last dose of MLN0002 for final safety assessments at the Final Safety visit. This visit is not required for patients transitioning from Study C13008 into the XAP study.</p> <p>b Clinically significant findings will be recorded as AEs.</p> <p>c On dosing days, vital signs and weight (weight only at specified visits) will be obtained prior to dosing.</p> <p>d To be performed prior to dosing.</p> <p>e For patients with UC.</p> <p>f For patients with CD.</p> <p>g All female subjects of childbearing potential must have a serum pregnancy test at the Final Safety visit (as applicable). A urine pregnancy test will be performed for female subjects of childbearing potential prior to each dose of MLN0002.</p> <p>h Drug concentration may be determined as part of the HAHA testing.</p> <p>i A stool sample for culture, ova and parasite evaluation, and <i>C. difficile</i> assay will be obtained (if indicated) at any point during the study when a patient becomes symptomatic, including worsening or return of disease activity.</p> <p>j If the patient is transitioning from Study C13008 into the XAP study, complete the end-of-study eCRF page at their last dosing visit in C13008. For all other patients, complete the end-of-study page at the Final Safety Visit.</p>															

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LIST OF ABBREVIATIONS

Abbreviation	Term
5-ASAs	5-aminosalicylates
AEs	adverse events
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CD	Crohn's disease
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
C _{min}	minimum plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
CRP	C-reactive protein
CV	coefficient of variation
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EQ-5D	EuroQual
ET	early termination
GCP	good clinical practice
GI	gastrointestinal
h	hours
HAHA	human anti-human antibody
HBI	Harvey-Bradshaw Index
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLT	high level term
IAC	Independent Adjudication Committee
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFN	interferon
IL	interleukin
IRB	institutional review board
IV	intravenous
JCV	JC virus, a neurotropic DNA polyomavirus
IVRS	interactive voice response system

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Abbreviation	Term
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MLN0002	vedolizumab
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamics
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PVC	polyvinylchloride
QOL	quality of life
RAMP	Risk Assessment and Minimization for PML
RBC	red blood cell(s)
SAEs	serious adverse events
SF-36	Short-Form 36
SOC	system organ class
TB	tuberculosis
TNF α	tumor necrosis factor alpha
UC	ulcerative colitis
UCCS	Ulcerative Colitis Clinical Score
ULN	upper limit of normal
US	United States
WBC	white blood cell(s)
XAP	Extended Access Program

Study Definitions

Pertaining to Patients With UC

Term	Definition
Clinical Remission	A partial Mayo score of ≤ 2 with no individual subscore > 1 .
Clinical Response	A decrease in the partial Mayo Score of at least 2 points and $\geq 25\%$ from baseline, with an accompanying decrease in rectal bleeding subscore of ≥ 1 point from baseline or absolute rectal bleeding subscore of ≤ 1 point
Rescue Medication(s)	Any new medication to treat a new or unresolved luminal manifestation of ulcerative colitis (UC), with the following exceptions: <ul style="list-style-type: none">• oral and topical (rectal) 5-aminosalicylate (ASA) treatment• oral corticosteroids per the guidelines outlined in Section 6.2.3• topical (rectal) corticosteroid enemas/suppositories• azathioprine or 6-mercaptopurine; stable doses are recommended• antibiotics• antidiarrheals for control of chronic diarrhea• probiotics (eg, Culturelle, <i>Saccharomyces boulardii</i>)
Long-term Treatment Failure	Need for rescue medications, or major surgical intervention for treatment of UC, or a study drug-related adverse event leading to discontinuation from the study

Pertaining to Patients With CD

Term	Definition
Clinical Remission	A Harvey-Bradshaw Index (HBI) score ≤ 4 points
Clinical Response	A ≥ 3 -point decrease in HBI score from baseline
Rescue Medication(s)	Any new medication to treat a new or unresolved luminal manifestation of Crohn's disease (CD), with the following exceptions: <ul style="list-style-type: none">• oral and topical (rectal) 5-ASA treatment• oral corticosteroids per the guidelines outlined in Section 6.2.3• topical (rectal) corticosteroid enemas/suppositories• azathioprine, 6-mercaptopurine, or methotrexate; stable doses are recommended• antibiotics• antidiarrheals for control of chronic diarrhea• probiotics (eg, Culturelle, <i>S. boulardii</i>)
Long-term Treatment Failure	Need for rescue medications, or major surgical intervention for treatment of CD, or a study drug-related adverse event leading to discontinuation from the study

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 The Inflammatory Bowel Diseases: Ulcerative Colitis and Crohn's Disease

Ulcerative colitis (UC) is a relapsing, remitting inflammatory disease of the colonic mucosa and submucosa. The prevalence of UC is approximately 200/100,000 of population in the United States (US) and approximately 150/100,000 of population in Western Europe.^(2, 3, 4) A genetic contribution to the disease is indicated by the increased incidence of UC (of 30 to 100 times that of the general population) among first-degree relatives of patients with UC. The characteristic pathology is one of chronic inflammation characterized by large numbers of lymphocytes and histiocytes in the diseased mucosa and submucosa with an acute inflammatory infiltrate composed of neutrophils variably present.

Crohn's disease (CD) is a relapsing, remitting inflammatory disease that may involve any portion of the length of the gastrointestinal tract from mouth to anus in a transmural fashion from mucosa to serosa. The prevalence of CD is approximately 150/100,000 of population in the US and approximately 125/100,000 of population in Western Europe.^(2, 3, 4) The characteristic pathology involves a chronic inflammatory infiltrate consisting of neutrophils and macrophages. Hallmarks of CD include granulomatous inflammation and aphthous ulceration.

Clinical manifestations of both diseases include diarrhea (typically bloody in patients with UC), as well as abdominal pain, fecal urgency, and incontinence. Systemic features such as fever, weight loss, malaise, and fatigue are indicators of more extensive disease.

Extra-intestinal manifestations such as uveitis, arthritis, ankylosis spondylitis, or primary sclerosing cholangitis may also be seen in conjunction with inflammatory bowel disease (IBD). The diagnosis of UC or CD is usually made by histopathologic examination of endoscopic mucosal biopsy specimens obtained on ileocolonoscopy.

Current treatments have been effective for many patients with UC or CD but have numerous limitations for patients with moderate to severe disease. 5-Aminosalicylates (5-ASAs) are the mainstay of UC pharmacotherapy for induction and maintenance of remission for patients with mild to moderate disease, but are less effective in severe disease. The National Cooperative Crohn's Disease Study demonstrated a role for sulfasalazine (a 5-ASA containing molecule) in moderate to severe Crohn's disease⁽⁵⁾; however, the efficacy of 5-ASAs in CD has been called into question by a recent meta analysis.⁽⁶⁾ Corticosteroids are

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often required for the one-third of patients who fail to respond to 5-ASAs. While highly effective for induction of remission, corticosteroids are not useful in either disease for maintenance of remission and carry significant undesirable side effects, including osteoporosis, glucose intolerance, and increased risk of infection.

Immunomodulatory agents, including 6-mercaptopurine and azathioprine, have a role in maintenance of remission in moderate to severe UC and moderate to severe CD. Their relatively slow onset of action precludes their use during flares of disease, and the use of these agents has been reported to potentially increase the risk of lymphoma in patients with IBD.⁽⁷⁾ Intravenous cyclosporine has a role in the management of severe UC; however, it is impractical in nonhospitalized patients, requires intense monitoring, and may cause irreversible nephrotoxicity, all of which limit its use to severe cases. Methotrexate, while ineffective in UC, has a role in the management of refractory CD; however, it also demonstrates a number of dose-limiting toxicities. Antibiotics have marginal efficacy in maintenance of remission in CD and are not effective in UC.

Biologic agents, including monoclonal antibodies against tumor necrosis factor alpha (TNF α), such as infliximab (Remicade[®]) and adalimumab (Humira[®]), have been studied and have proven useful for both induction and maintenance of remission in CD. Infliximab is also useful for induction and maintenance of remission in UC. However, only approximately one-third of patients have a sustained remission at 1 year following treatment with these agents. In addition, treatment with TNF α antagonists has been associated with a number of serious adverse events (SAEs) involving hypersensitivity and infection. Reactivations of latent tuberculosis (TB)⁽⁸⁾ and disseminated histoplasmosis have been reported, and in some cases have been fatal.⁽⁹⁾ Induction of remission with infliximab occurs in only 31% to 39% of patients with UC⁽¹⁰⁾ and durable clinical remission (at 1 year) occurs in only 26% of patients with UC. Efficacy data for both infliximab and adalimumab in CD are quite similar to the infliximab data in UC with only a minority of patients having a durable response at 1 year.^(11, 12)

Failure of medical therapy leads to colectomy in 9% to 35% of patients with UC within 5 years. Colectomy is considered to be an important adjunct treatment for refractory UC; however, colectomy with ileal pouch anal anastomosis (the standard surgical therapy) has many limitations and is associated with its own set of complications, including high stool frequency,⁽¹³⁾ female infertility,⁽¹⁴⁾ and a cumulative incidence of pouchitis of 50% at 10 years.⁽¹⁵⁾ Surgical removal of highly diseased, strictured, or stenotic segments of bowel

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in CD is not curative. Relapse occurs in a majority of patients with CD who undergo segmental resections, and the need for reoperation is the rule rather than the exception.⁽¹⁶⁾

The limitations of current therapies for IBD indicate that there is a significant need for safer and more effective therapies. MLN0002 (vedolizumab) is being developed to fulfill this important unmet medical need.

1.1.2 Study Drug: Vedolizumab (MLN0002)

MLN0002 is a humanized monoclonal antibody that binds to the $\alpha_4\beta_7$ integrin, which is expressed on discrete populations of leukocytes involved in gut mucosal immunity.⁽¹⁷⁾ One of the adhesion ligands of $\alpha_4\beta_7$, mucosal addressin cell adhesion molecule-1 (MAdCAM-1) is preferentially expressed on high endothelial venules at sites of lymphocyte extravasation in the gastrointestinal (GI) mucosa and associated lymphoid tissue. Binding of MAdCAM-1 by $\alpha_4\beta_7$ mediates migration of leukocytes into GI mucosa and associated lymphoid tissue.^(18, 19, 20) The $\alpha_4\beta_7$ integrin has received particular attention in the context of mucosal immune responses given its unique role in mediating infiltration of the GI tract by leukocytes.

MLN0002 antagonizes both the $\alpha_4\beta_7$ -MAdCAM-1 interaction, and the associated migration of leukocytes into GI mucosa. This mechanism of action of MLN0002 reduces pathological bowel inflammation, thus providing a potential therapeutic option for patients with IBD. A unique feature of MLN0002 is that it binds exclusively to an epitope that is unique to $\alpha_4\beta_7$; it does not bind to α_4 or β_7 in association with other integrins, for example $\alpha_4\beta_1$ or $\alpha_E\beta_7$.

1.2 Preclinical Experience

Detailed information regarding the nonclinical pharmacology and toxicology of MLN0002 is found in the Investigator's Brochure (IB).

1.3 Clinical Experience

More than 1800 people have participated or are participating in clinical trials with MLN0002. In completed studies, nearly 600 men and women are known to have received at least 1 dose of MLN0002, which includes more than 300 people with UC or CD. Further details are provided in the IB.

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1.3.1 MLN0002 Efficacy

MLN0002 efficacy has been established in patients with UC and CD. Specifically, in a phase 2 study in patients with moderately active UC (Study M200-022), MLN0002 treatment (administered at doses of 0.5 and 2.0 mg/kg IV on Days 1 and 29) induced a statistically significant increase in rates of clinical remission compared with placebo.⁽²¹⁾ Clinical remission rates at Week 6 were 33%, 32%, and 14% for patients who received 0.5 mg/kg MLN0002, 2.0 mg/kg MLN0002, and placebo, respectively ($p = 0.017$ for 0.5 mg/kg dose group, $p = 0.023$ for 2.0 mg/kg dose group, and $p = 0.009$ for the combined MLN0002 groups vs placebo group). Twenty-eight percent of patients receiving 0.5 mg/kg and 12% of those receiving 2.0 mg/kg had evidence of endoscopic remission compared to 8% of patients receiving placebo ($p = 0.007$ for the combined MLN0002 groups vs placebo group). Results from this study demonstrated proof-of-concept for the use of MLN0002 as a novel agent for the treatment of UC.⁽²²⁾

Similarly, in a phase 2 study in patients with moderately active CD (Study L299-016), MLN0002 treatment (administered at doses of 0.5 and 2.0 mg/kg IV on Days 1 and 29), did not achieve its prospectively-defined primary endpoint of clinical response at 8 weeks (a 70-point decline in Crohn's Disease Activity Index [CDAI] from baseline), but did achieve the more rigorous secondary endpoints of clinical remission ($CDAI \leq 150$ points) at 8 weeks and enhanced clinical response (CDAI decrease of ≥ 100 points) at 8 weeks for the 2.0 mg/kg MLN0002 group versus placebo.⁽²³⁾ Clinical remission rates were 30%, 37%, and 21%, for patients who received 0.5 mg/kg MLN0002, 2.0 mg/kg MLN0002, and placebo, respectively ($p = 0.044$ for 2.0 mg/kg dose group vs placebo). Other secondary endpoints also showed dose-dependent trends that achieved statistical significance in the 2.0 mg/kg MLN0002 dose group. These include time to response, percentage of patients with normalization of C-reactive protein (CRP), and mean decline in CDAI score. Together, these results suggest biologic activity of MLN0002 in CD.

1.3.2 MLN0002 Safety

Vedolizumab has shown an acceptable safety profile based on an integrated analysis of all adverse events and select safety laboratories for all completed phase 1 and phase 2 clinical studies. In addition, the blinded, aggregate safety data in the phase 3, placebo-controlled, UC and CD studies has been similar to the safety experience in the open-label, phase 3, safety extension study C13008. Of note, approximately 1800 patients have participated in Study C13008, the majority of whom have received multiple doses of vedolizumab. The

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integrated summary of safety for the completed studies, as well as a summary of safety from the ongoing phase 3 program (based on a data cutoff of 16 April 2010), are detailed in the current version of the IB. The current experience with vedolizumab, based on review of data from the blinded safety data in Studies C13006, C13007, C13011, and from the open-label study C13008, is consistent with the findings as detailed in the IB. The phase 3 trials are also independently monitored for safety as described below.

In the completed studies, overall, percentages of subjects who reported AEs and SAEs, or who discontinued due to an adverse event (AE), were similar between MLN0002- and placebo-treated groups. Throughout the MLN0002 program, there has been no overt relationship between dose and specific AEs.

The safety profile of MLN0002 in the target patient populations is generally reflective of the indication under study. That is, there are more reports of GI events in patients with IBD (UC, CD) compared with the experience in healthy subjects. Baseline disease activity in patients with IBD did not influence the overall rate of AEs, although SAEs, severe AEs, and discontinuations due to AEs were reported more commonly in patients with more severe disease activity regardless of whether they received MLN0002 or placebo.

Patients in the completed and ongoing trials have been and are closely monitored for infection.

Additionally, in the completed studies, an analysis of concomitant use of immunosuppressants (ie, corticosteroids, azathioprine/6-mercaptopurine [6-MP], methotrexate, cyclosporine, or infliximab within 90 days of patients' last dose of study drug) has not identified an acute, additive risk of infection attributable to MLN0002.

Similarly, concomitant use of corticosteroids and/or conventional immunomodulators does not appear to be associated with a clinically meaningful increased rate of infections based on the comparative rates of infections in the blinded phase 3 trials among patients who have and have not received these medications.

As shown in [Table 1-1](#), overall rates of infection are relatively constant regardless of the use of these concomitant medications. Most infections (by preferred term) were reported by either 1 or 2 individuals, and no trends were observed when comparing the blinded aggregate data from C13006 and C13007 to the open-label experience (C13008).

Concomitant use of these medications does not appear to be associated with any increased rate of specific infections.

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Table 1-1 Overview of Subjects Reporting at Least 1 Infection According to Concomitant Medication Use

Study Population	C13006 n/N (%)	C13007 n/N (%)	C13008 n/N (%)
All patients	56/300 (19)	100/454 (22)	32/203 (16)
Neither steroids or immunomodulators	19/94 (20)	40/169 (24)	17/135 (13)
Steroids only	19/106 (18)	29/143 (20)	10/43 (23)
Immunomodulator only	5/30 (13)	16/76 (21)	2/13 (15)
Both steroids and immunomodulators	13/60 (22)	15/66 (23)	3/12 (25)
Either steroids, immunomodulators or both	37/206 (18)	60/285 (21)	15/68 (22)
Any steroids (with or without immunomodulators)	32/166 (19)	44/209 (21)	13/55 (24)
Any immunomodulator (with or without steroids)	18/100 (18)	31/142 (22)	5/25 (20)

In addition, all patients enrolled in the vedolizumab trials are actively monitored for progressive multifocal leukoencephalopathy (PML) through the Risk Assessment and Minimization for PML (RAMP) program. No cases of PML have been reported in any clinical trial.

Deaths have occurred in patients participating in MLN0002 clinical trials, 2 of which were thought to be related to the study drug by the treating physicians. However, the treating physicians do not know if these subjects received MLN0002 or placebo.

The phase 3 vedolizumab clinical program is overseen by an independent Data Safety Monitoring Board (DSMB) composed of 2 gastroenterologists, an infectious diseases physician, a physician with training in epidemiology, and a statistician. The DSMB reviews all SAEs monthly and unblinded safety data from all phase 3 trials every 6 months at a minimum. The DSMB convened on 13 December 2011, and after reviewing unblinded safety data, recommended that the trials proceed without modification.

In conclusion, substantial clinical exposures to vedolizumab have been accrued in patients with moderate to severe IBD, and the clinical safety experience with vedolizumab has been consistent with its mechanism of action as a selective integrin antagonist. In consideration of the greater severity of disease of patients enrolled in the phase 3 studies, the overall safety profile of vedolizumab (MLN0002) remains consistent with the favorable safety experience in the phase 2 trials, and remains compatible with vedolizumab's gut-selective anti-inflammatory effects.

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Refer to Section 1.5 for the identified, potential, and hypothetical risks of MLN0002 based on clinical experience as of 16 April 2010. Further details are provided in the current IB.

1.4 Study Rationale

Establishing the long-term safety and tolerability of MLN0002 is a key component of the pivotal development programs in both UC and CD. From this long-term open-label study of active MLN0002 therapy, data regarding the occurrence of important clinical events resulting from chronic MLN0002 administration will be obtained. Important clinical events including those related to safety (eg, opportunistic infections, malignancy, long-term immunogenicity profile) as well as efficacy (eg, maintenance of remission, quality of life, and various other health outcomes measures) will be collected. The probability of experiencing uncommon safety events that occur at a frequency on the order of 1/100-1/1500 that might not ordinarily be detected in year-long induction and maintenance studies may be estimated from this study data. The probability of detecting at least 1 uncommon adverse event with 2000 patients will be 0.9999, 0.9818, 0.8648, and 0.6322 when the true rates are 1/100, 1/500, 1/1000, and 1/2000, respectively.

This study will allow patients with prior enrollment in a qualifying MLN0002 study (rollover patients, as detailed in Section 4.1) to receive long-term MLN0002 treatment.

Although the study was due to complete in December 2016, Takeda has agreed to extend the treatment period until July 2017 to allow continued access for patients in countries where vedolizumab is either not commercially available or is not reimbursed, or for which the XAP study is not yet available at the site. For this reason, this amendment is being submitted in all countries currently following Amendment 16 except the following: Austria, France, Germany, Israel, Netherlands, Norway, Spain, Sweden, Switzerland and the United Kingdom. Current safety information is available in the latest version of the Investigator Brochure.

A control group has not been included in this study based on the following considerations. First, since the observed rates of rare safety events such as those listed above can be estimated from an observational study, a controlled study is unnecessary. Second, most of the patients participating in this long-term safety study will have participated in a previous MLN0002 study in which they may have been randomized to placebo therapy; therefore, the opportunity for these patients to receive active treatment should not be unnecessarily delayed. Third, data from the study will be benchmarked with data from external databases (see Section 8.7 for further details on safety analyses that will be performed).

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UC disease activity will be followed throughout this study using the partial Mayo score, a standardized measure for UC trials that includes 3 of the 4 components of the complete Mayo score.⁽¹⁰⁾ CD disease activity will be followed throughout this study using the Harvey-Bradshaw Index (HBI), a standardized measure for CD trials that has previously been demonstrated to correlate highly with the Crohn's Disease Activity Index (CDAI).⁽²⁴⁾ Exploratory efficacy outcomes such as clinical remission, clinical response, and decrease in corticosteroid use will be assessed in subgroups of patients to whom these endpoints are relevant.

Dose Selection Rationale

The strategy for dose selection in this phase 3 study was based on the following parameters:

- Clinical efficacy and dose response in phase 2
- Suppression of human anti-human antibody (HAHA) formation
- Serum concentration of MLN0002 at the efficacious doses in phase 2 trials (pharmacokinetic considerations)
- Maintenance of $\alpha_4\beta_7$ receptor saturation (pharmacodynamic considerations)

A dose of 300 mg MLN0002 (roughly equivalent to 4 mg/kg MLN0002 for a 75 kg patient) every 4 weeks has been selected for evaluation. This selection is based on the phase 2 findings that 2 mg/kg MLN0002 administered every 4 weeks as induction therapy was an efficacious dose for both UC and CD, but that maximal efficacy may not have been achieved. Also, formation of HAHA following MLN0002 treatment has an inverse dose relationship, with higher doses within the tested range having a suppressive effect on immunogenicity (refer to the IB). Therefore, doses higher than those that might ordinarily be acceptable short-term in the absence of HAHA are required to sustain remission throughout the dosing interval. Therefore, as a strategy to maximally suppress HAHA formation with MLN0002, 300 mg MLN0002 will be administered every 4 weeks.

MLN0002 treatment was generally well tolerated in 79 healthy subjects and patients with IBD that were treated with doses and/or dose regimens resulting in concentrations that exceed the median predicted steady-state MLN0002 peak and trough concentrations for the proposed dose (300 mg MLN0002 administered every 4 weeks). The favorable safety profile of MLN0002 doses up to 10 mg/kg supports selection of this dose for evaluation in this study (for additional details, see Section 1.3.2).

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A dose of 300 mg MLN0002 every 4 weeks is expected to suppress immunogenicity during multiple dosing, thereby maintaining sufficient MLN0002 exposure and $\alpha_4\beta_7$ receptor saturation throughout the dosing interval which, in previous efficacy studies, have been shown to result in clinical efficacy. It is also one of the dose regimens currently being evaluated in the phase 3 induction and maintenance Studies C13006 and C13007 and the induction Study C13011. This long-term safety study will provide additional supportive data for 300 mg MLN0002 administered every 4 weeks in patients with IBD and will ensure an adequate safety database for the eventual registration of MLN0002 in UC and CD.

1.5 Potential Risks and Benefits

As described in Section 1.3, 2 well-powered, phase 2 studies have shown the benefit of MLN0002 treatment in inducing response and remission in UC and CD. An integrated safety analysis was conducted using data from completed and unblinded clinical trials as of 16 April 2010. This analysis of 742 healthy subjects and patients with IBD, of whom 560 received at least 1 dose of MLN0002, demonstrated an acceptable safety profile for MLN0002. Thus, MLN0002 has a favorable risk to benefit profile to date. Section 10.5 describes the comprehensive risk management program for this study.

1.5.1 Identified Risk of MLN0002 Treatment: Infusion-Related Reaction

As of 16 April 2010, no anaphylactic or anaphylactoid reactions have been observed following initial dosing of MLN0002. There is an identified risk of infusion-related reaction with vedolizumab, largely limited to individuals who develop clinically significant titers of HAHA. Three (< 1%) of more than 300 subjects known to have received 2 or more infusions of MLN0002 developed an infusion-related reaction, 1 of which was reported as serious. Following a second administration of the MLN0002 formulation used during earlier development, 2 patients experienced signs and symptoms consistent with an acute infusion-related reaction either during or within minutes of administration. These symptoms included rash, facial numbness, urticaria, pruritus, puffiness and pressure to the eye, angioedema of the lip, and throat tightness. The third patient, who developed an acute infusion-related reaction after receiving a recent version of MLN0002, had been sensitized by exposure to an earlier version of MLN0002 in a previous study. All of these infusion-related reactions were mild to moderate in intensity and were managed medically with either antihistamines alone or with the addition of steroids. Please refer to the current IB for further information.

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Immunogenicity

Based on existing data from clinical studies with MLN0002, there is the possibility of developing HAHA to vedolizumab that may cause infusion-related reactions, other nonspecific AEs, and/or reduced efficacy. The data from clinical studies with MLN0002 demonstrate dose dependence in clinically relevant HAHA formation (HAHA associated with PK and/or pharmacodynamic changes). Thus, the immunogenicity of vedolizumab may be substantially reduced at higher doses of MLN0002.

More data are required to fully characterize the immunogenicity profile of vedolizumab and the relationship between HAHA levels, efficacy, and AEs, including infusion-related reactions.

1.5.2 Potential Risk of MLN0002 Treatment: Increased Rates of Infections

As observed in the phase 1 and 2 studies, patients with IBD receiving MLN0002 may have an increased rate of upper respiratory and mucosal infections. Upper respiratory infections, *Herpes labialis*, and mucosal candidiasis were more common in subjects who received MLN0002 in the phase 1 and 2 studies. Given the known distribution of the MAdCAM-1 binding sites in the nasopharyngeal and oropharyngeal tissue and vagina, it is possible that upper respiratory tract, esophageal, and vaginal infections may be more common based on the mechanism of action of MLN0002.

1.5.3 Hypothetical Risks of MLN0002 Treatment (Not Observed to Date)

Gastrointestinal Infections

There is a hypothetical risk that MLN0002 may increase GI infections, as well as systemic infections against which the gut constitutes a defensive barrier. Examples of such infections include those caused by enteric pathogens (eg, *Listeria*, *Salmonella*, *Campylobacter*, *Yersinia*, *C. difficile*), viral infections such as CMV, and opportunistic infections (eg, cryptosporidiosis, *Mycobacterium avium* complex).

As of 16 April 2010, however, increased rates of GI infections or severe infections have not been observed among healthy subjects or patients administered MLN0002. No systemic opportunistic infections with a portal of entry outside the GI tract have been reported. In the subset of patients who received concomitant steroids and immunosuppressants while MLN0002 serum levels were still detectable, no increased rate of infections was seen.

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Progressive Multifocal Leukoencephalopathy

The cases of progressive multifocal leukoencephalopathy (PML) reported in patients being treated with the pan- α_4 integrin antagonist natalizumab (Tysabri[®]) have focused safety concerns on integrin antagonists. The gut-selective anti-inflammatory activity of MLN0002, as a specific $\alpha_4\beta_7$ integrin antagonist, may not predispose patients to an increased risk of PML. Nevertheless, all ongoing MLN0002 clinical studies use the Risk Assessment and Minimization for PML (RAMP) program as a Risk Minimization Action Plan for PML. Details of the RAMP program are provided in Section 10.5.3 and in the Study Manual.

Malignancy

The incidence of certain malignancies, in particular lymphoma and colorectal cancer, may, in theory, increase in patients on long-term immunosuppressive therapies, particularly those which target cell-mediated immunity.

As of 16 April 2010, the percentages of MLN0002 and placebo subjects who have developed a malignancy during the long-term study follow-up are similar. There have been 4 cases of malignancies reported posttreatment in the completed studies: 2 cases of breast cancer, 1 case of cervical cancer, and 1 case of endometrial cancer, the latter of which was present before study entry. No cases of lymphoma or neoplasia of another organ system were reported during the long-term follow-up periods (through 2 years from last dose of study drug) in any of the clinical studies for which these data are available.

A number of malignancies have occurred over the duration of the phase 3 program, which remains blinded at the time of the writing of this amendment. At the meeting in December 2011, the DSMB for the phase 3 program reviewed unblinded data, and no modifications to the trial were requested.

1.5.4 Summary of Risks and Benefits

The safety analysis of all completed trials, as well as the current safety experience from the ongoing phase 3 trials, demonstrate that MLN0002 has an acceptable safety profile. Phase 2 studies have demonstrated efficacy in UC and CD. These data support a favorable benefit-to-risk profile for MLN0002. In addition, based on its targeted mechanism of action, MLN0002 may prove to have a superior benefit-to-risk profile compared with conventional systemic immunosuppressive therapies for IBD, such as corticosteroids and TNF α .

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antagonists. On this basis, as well as the risk management procedures implemented in this study, further investigation of this novel compound for the treatment of IBD is warranted.

2. STUDY OBJECTIVES

2.1 Primary Objective

- To determine the safety profile of long-term MLN0002 treatment

2.2 Resource Utilization and Patient Reported Outcome Objectives

- To determine the effect of long-term MLN0002 treatment on time to major IBD-related events (hospitalizations, surgeries, and procedures)
- To examine the effect of long-term MLN0002 treatment on health-related quality of life (QOL) measurements

2.3 Exploratory Objective

- To obtain data regarding the effect of long-term MLN0002 treatment on maintaining clinical response and remission

3. STUDY ENDPOINTS

3.1 Primary Endpoints

- SAEs, AEs, vital signs, results of standard laboratory tests (clinical chemistry, hematology, coagulation, urinalysis, and HAHA), and results of electrocardiograms (ECGs)

3.2 Resource Utilization and Patient Reported Outcome Endpoints

- Time to major IBD-related events (hospitalizations, surgeries, or procedures)
- Changes from baseline in IBDQ, SF-36, and EuroQual (EQ-5D) scores

3.3 Exploratory Endpoint

- Partial Mayo scores and HBI scores will be used to monitor changes in IBD activity during long-term MLN0002 treatment

4. STUDY DESIGN

4.1 Overview of Study Design

This is an open-label phase 3 study to determine the long-term safety and efficacy of vedolizumab (MLN0002) for the treatment of patients with moderate to severe UC or CD. All enrolled patients will receive 300 mg MLN0002 administered every 4 weeks.

Most patients enrolling in this study will have participated in a previous qualifying MLN0002 study (rollover patients):

- Patients with UC or CD who participated in the phase 2, open-label, long-term safety study (Study C13004), which includes up to 78 weeks of open-label treatment with MLN0002
- Patients who withdrew early from a phase 3 induction and maintenance study (Study C13006 [patients with UC] or Study C13007 [patients with CD]), which includes up to 50 weeks of blinded study treatment (MLN0002 or placebo). These patients must have withdrawn due to sustained nonresponse, disease worsening, or the need for rescue medications
- Patients who completed Study C13006, Study C13007, or Study C13011

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For rollover patients, the first dose of MLN0002 in this study (ie, Week 0) should occur no more than 9 weeks after the last dose of study drug in the previous study; the preferable period is within 3 to 5 weeks after the last dose in the previous study. Patients will be consented and receive wallet cards prior to or at the Week 0 Visit. Results of assessments from the last visit in the previous qualifying study will be used to determine their eligibility to participate in this study. Baseline data will also be obtained from the previous study, including medical history, disease history, demographics, tobacco use, and prior therapies.

In addition, up to 400 patients without previous treatment with vedolizumab may be enrolled directly into this study (de novo patients). Patients with UC or CD must meet the inclusion/exclusion criteria for de novo patients (Section 5). Baseline data will be obtained during the Screening period.

Enrollment in this study is defined as the time the patient is entered into the Interactive Voice Response System (IVRS) at Week 0.

Following enrollment all patients will be administered 300 mg vedolizumab every 4 weeks for the duration of the study. The total duration of MLN0002 treatment will vary by patient based on continued benefit until July 2017, or until the XAP study is available at the site, or until patient withdrawal, or until vedolizumab is available to the patient through commercial channels (including reimbursement) for the patient's clinical scenario, or unless the study is terminated early by the sponsor, as described in Section 11.12, whichever is sooner.

Patients may receive allowed concomitant medications for the treatment of IBD as detailed in Section 6.2.1, as determined by the principal investigator, at any time point during the study. Medications may be discontinued during the study, but if discontinuation is planned, it should be done prior to the first dose of vedolizumab.

It is strongly recommended that patients receiving oral corticosteroids should begin an oral corticosteroid tapering regimen once they achieve clinical response or if, in the opinion of the investigator, they demonstrate sufficient improvement in clinical signs and symptoms.

Patients will be withdrawn from the study for long-term treatment failure as described in the [study definitions](#) or if (in the opinion of the investigator or patient) they are not benefiting from therapy (see Section 6.2.3, Section 6.4.10, and Section 7.4). Additionally, investigators should strongly consider withdrawing patients who require recurrent courses of corticosteroids with inability to taper.

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Patients who do not transition into the XAP study will return 16 weeks after their last dose of MLN0002 for the Final Safety visit. Patients who transition into the XAP study are not required to attend the Final Safety Visit. The safety of these patients will be monitored as part of the XAP study. The end-of-study eCRF page must be completed for all patients regardless of whether they transition into the XAP study or not.

Safety assessments and efficacy assessments using the partial Mayo Score (for patients with UC) or the HBI score (for patients with CD) will be made throughout the treatment period. Detailed visit-by-visit study procedures and assessments are provided in the [Schedule of Events](#) and Section 7.

This trial will be conducted in compliance with the protocol, good clinical practice (GCP), and the applicable regulatory requirements (including International Conference on Harmonisation [ICH] guidelines).

4.2 Number of Patients

Approximately 1800 rollover patients with UC or CD will enroll in this study from approximately 400 study centers worldwide following participation in other qualifying MLN0002 studies. In addition, up to 400 de novo patients with UC or CD (not previously treated with vedolizumab) will enroll in this study. These patients will be enrolled from approximately 150 of the 400 worldwide centers noted above. Those sites selected to enroll de novo patients will be notified by the sponsor.

4.3 Duration of Study

It is anticipated that the duration of MLN0002 treatment will vary by patient based on continued benefit. Treatment duration may continue until July 2017, or until the XAP study is available at the site, or until patient withdrawal, or until vedolizumab is available to the patient through commercial channels (including reimbursement) for the patient's clinical scenario, or unless the study is terminated early by the sponsor, as described in Section 11.12, whichever is sooner. After the final dose of MLN0002, patients who do not transition into the XAP study will complete the 16-week posttreatment observation and safety assessment period (not applicable to patients who transition to the XAP study). Concomitant vedolizumab (Entyvio) taken during the 16-week follow-up period will be recorded as a concomitant medication and will not be considered as a protocol deviation.

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Additionally, upon completion of or termination from this study, patients will participate in a 2-year follow-up survey, as described in Section [7.6](#).

5. STUDY POPULATION

5.1 Inclusion Criteria for Rollover Patients

Each rollover patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Voluntarily able to give informed consent.
2. Previous treatment in Study C13004, Study C13006, Study C13007, or Study C13011 that, in the opinion of the investigator, was well tolerated. Patients who participated in Study C13011 must have completed the Week 10 assessments in that study.

Patients who withdrew early from C13006 or C13007 must have withdrawn due to one of the following:

- Sustained Nonresponse for patients with UC in C13006: Failure to achieve a clinical response (2 point and 25% improvement in partial Mayo score) by Week 14 and a minimum partial Mayo score of ≥ 5 points
- Sustained Nonresponse for patients with CD in C13007: Failure to achieve a clinical response (70 point improvement in CDAI score) by Week 14 and a minimum CDAI score of 220 points
- Disease Worsening for patients with UC in C13006: An increase in partial Mayo score of ≥ 3 points on 2 consecutive visits from the Week 6 value (or an increase to 9 points on 2 consecutive visits if the Week 6 value > 6) and a minimum partial Mayo score of ≥ 5 points
- Disease Worsening for patients with CD in C13007: A ≥ 100 point increase in CDAI score on 2 consecutive visits from the Week 6 value at any study visit and a minimum CDAI score of 220 points
- Required rescue medications for patients in C13006 and C13007 at Week 14 or beyond. Requirement for rescue medication is defined as the receipt of or need for any new medication or any increase in dose of a baseline medication required to treat new or unresolved UC or CD symptoms (other than antidiarrheals for control of chronic diarrhea). Patients who experienced treatment failure in Study C13006 or Study C13007 only as a result of receiving rescue medications (and without meeting the definition of Disease

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Worsening) before Week 14 are not eligible for Study C13008.

3. The first dose of MLN0002 in this study (ie, Week 0) should occur no more than 9 weeks after the last dose of study drug in the previous study; the preferable period is within 3 to 5 weeks after the last dose in the previous study.
4. Female patients who:
 - are postmenopausal for at least 1 year before enrollment, **OR**
 - are surgically sterile, **OR**
 - if they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 18 weeks after the last dose of MLN0002, **OR** agree to completely abstain from heterosexual intercourse.

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- agree to practice effective barrier contraception during the entire study treatment period and through 18 weeks after the last dose of MLN0002, **OR**
 - agree to completely abstain from heterosexual intercourse.
5. Patients with extensive colitis or pancolitis of > 8 years duration or limited colitis of > 12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months of enrollment.
 6. Patients with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age > 50 years, or other known risk factor must be up-to-date on colorectal cancer surveillance.
 7. May be receiving a therapeutic dose of the following drugs:
 - a. Oral 5-ASA compounds
 - b. Oral corticosteroid therapy, as described in Section 6.2.3
 - c. Topical (rectal) treatment with 5-ASA or corticosteroid enemas/suppositories
 - d. Probiotics (eg, Culturelle, *Saccharomyces boulardii*)
 - e. Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea
 - f. Antibiotics used for the treatment of IBD (ie, ciprofloxacin, metronidazole)
 - g. Azathioprine, 6-mercaptopurine, or methotrexate (methotrexate for CD only)

5.2 Exclusion Criteria for Rollover Patients

Rollover patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Female patients who are lactating or pregnant.
2. Required major surgical intervention for IBD (eg, bowel resection) during or after participation in a prior MLN0002 study, currently requires major surgical intervention for IBD, or is anticipated to require major surgical intervention for IBD during this study; minor surgical procedures (eg, fistulotomy) are permissible.
3. Any live vaccinations within 30 days prior to MLN0002 administration except for the influenza vaccine.
4. Development of any new, unstable, or uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, neurologic, oncologic, or other medical disorder during or after participation in a prior MLN0002 study that, in the opinion of the investigator, would confound the study results or compromise patient safety.
5. Withdrawal from a previous MLN0002 study due to a study-drug related AE.
6. Active psychiatric or substance abuse problems that, in the investigator's opinion, may interfere with compliance with the study procedures.
7. Unable to attend all the study visits or comply with study procedures.

5.3 Inclusion Criteria for De Novo Ulcerative Colitis Patients

Each de novo UC patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Age 18 to 80.
2. Male or female patient who is voluntarily able to give informed consent.
3. Female patients who:

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- Are postmenopausal for at least 1 year before the Screening visit, **OR**
- Are surgically sterile, **OR**
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 18 weeks after the last dose of study drug, **OR** agree to completely abstain from heterosexual intercourse.

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- Agree to practice effective barrier contraception during the entire study treatment period and through 18 weeks after the last dose of study drug, **OR**
 - Agree to completely abstain from heterosexual intercourse.
4. Diagnosis of ulcerative colitis established at least 3 months prior to enrollment by clinical and endoscopic evidence and corroborated by a histopathology report.
 5. Moderately to severely active ulcerative colitis as determined by a partial Mayo score of 3 to 9 within 7 days prior to the first dose of study drug (see Section 15.1).
 6. Evidence of ulcerative colitis extending proximal to the rectum (≥ 15 cm of involved colon).
 7. Patients with extensive colitis or pancolitis of > 8 years duration or left-sided colitis of > 12 years duration must have documented evidence that a surveillance colonoscopy with random and targeted biopsies was performed within 18 months of the initial Screening visit (may be performed during screening).
 8. Patients with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age > 50 years, or other known risk factor must be up-to-date on colorectal cancer surveillance (may be performed during screening).
 9. Demonstrated, over the previous 5-year period, an inadequate response to, loss of response to, or intolerance of at least 1 of the following agents as defined below:

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- Corticosteroids
 - Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily orally for 2 weeks or intravenously for 1 week **OR**
 - Two failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally **OR**
 - History of intolerance of corticosteroids (including, but not limited to Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection)
 - Immunomodulators
 - Signs and symptoms of persistently active disease despite a history of at least one 8-week regimen of oral azathioprine (≥ 1.5 mg/kg) or 6-mercaptopurine mg/kg (≥ 0.75 mg/kg) **OR**
 - History of intolerance of at least 1 immunomodulator (including, but not limited to nausea/vomiting, abdominal pain, pancreatitis, LFT abnormalities, lymphopenia, *TPMT* genetic mutation, infection)
 - TNF α antagonists
 - Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen of infliximab 5 mg/kg IV, 2 doses at least 2 weeks apart **OR**
 - Recurrence of symptoms during maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify) **OR**
 - History of intolerance of infliximab (including, but not limited to infusion-related reaction, demyelination, congestive heart failure, infection)
10. May be receiving a therapeutic dose of the following drugs:
- a. Oral or topical (rectal) 5-ASA compounds provided that the dose has been stable for the 2 weeks immediately prior to enrollment

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- b. Oral corticosteroid therapy (prednisone at a stable dose \leq 30 mg/day, or equivalent steroid) provided that the dose has been stable for the 4 weeks immediately prior to enrollment if corticosteroids have just been initiated, or for the 2 weeks immediately prior to enrollment if corticosteroids are being tapered
- c. Topical (rectal) corticosteroid enemas/suppositories
- d. Azathioprine or 6-mercaptopurine provided that the dose has been stable for the 8 weeks immediately prior to enrollment
- e. Antibiotics used for the treatment of IBD (ie, ciprofloxacin, metronidazole)
- f. Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea
- g. Probiotics (eg, Culturelle, *S. boulardii*) provided that the dose has been stable for the 2 weeks immediately prior to enrollment

5.4 Inclusion Criteria for De Novo Crohn's Disease Patients

Each de novo CD patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Age 18 to 80.
2. Male or female patient who is voluntarily able to give informed consent.
3. Female patients who:
 - Are postmenopausal for at least 1 year before the Screening visit, **OR**
 - Are surgically sterile, **OR**
 - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 18 weeks after the last dose of study drug, **OR** agree to completely abstain from heterosexual intercourse.

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- Agree to practice effective barrier contraception during the entire study

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treatment period and through 18 weeks after the last dose of study drug, **OR**

- Agree to completely abstain from heterosexual intercourse.
4. Diagnosis of Crohn's disease established at least 3 months prior to enrollment by clinical and endoscopic evidence and corroborated by a histopathology report. Cases of Crohn's disease established at least 6 months prior to enrollment for which a histopathology report is not available will be considered based on the weight of the evidence supporting the diagnosis and excluding other potential diagnoses, and must be discussed with the sponsor on a case-by-case basis prior to enrollment.
 5. Moderately to severely active Crohn's disease as determined by an HBI score of 8 to 18 (see Section 15.2) within 7 days prior to the first dose of study drug **and** 1 of the following:
 - a. CRP level > 2.87 mg/L during the Screening period **OR**
 - b. Ileocolonoscopy with photographic documentation of a minimum of 3 nonanastomotic ulcerations (each > 0.5 cm in diameter) or 10 aphthous ulcerations (involving a minimum of 10 contiguous cm of intestine) consistent with CD, within 4 months prior to randomization **OR**
 - c. Fecal calprotectin > 250 mcg/g stool during the Screening period in conjunction with CT enterography, MR enterography, contrast-enhanced small bowel radiography, or wireless capsule endoscopy revealing Crohn's ulcerations (aphthae not sufficient), within 4 months prior to screening (patients with evidence of fixed stenosis or small bowel stenosis with prestenotic dilation should not be included).
 6. CD involvement of the ileum and/or colon, at a minimum.
 7. Patients with extensive colitis or pancolitis of > 8 years duration or limited colitis of > 12 years duration must have documented evidence that a surveillance colonoscopy with random and targeted biopsies was performed within 18 months of enrollment (may be performed during screening).
 8. Patients with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age > 50 years, or other known risk factor must be up-to-date on colorectal cancer surveillance (may be performed during screening).
 9. Demonstrated, over the previous 5 year period, an inadequate response to, loss of

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response to, or intolerance of at least 1 of the following agents as defined below:

- Corticosteroids
 - Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily orally for 2 weeks or intravenously for 1 week **OR**
 - Two failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally on 2 separate occasions **OR**
 - History of intolerance of corticosteroids (including, but not limited to Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection)

- Immunomodulators
 - Signs and symptoms of persistently active disease despite a history of at least one 8-week regimen of oral azathioprine (≥ 1.5 mg/kg) or 6-mercaptopurine (≥ 0.75 mg/kg) **OR**
 - Signs and symptoms of persistently active disease despite a history of at least one 8-week regimen of methotrexate (≥ 12.5 mg/week) **OR**
 - History of intolerance of at least 1 immunomodulator (including, but not limited to nausea/vomiting, abdominal pain, pancreatitis, LFT abnormalities, lymphopenia, *TPMT* genetic mutation, infection)

- TNF α antagonists
 - Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen of 1 of the following agents:
 - Infliximab: 5 mg/kg IV, 2 doses at least 2 weeks apart
 - Adalimumab: one 80-mg SC dose followed by one 40-mg dose at least 2 weeks apart
 - Certolizumab pegol: 400 mg SC, 2 doses at least 2 weeks apart **OR**

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- Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify) **OR**
- History of intolerance of at least 1 TNF antagonist (including, but not limited to infusion-related reaction, demyelination, congestive heart failure, infection)

10. May be receiving a therapeutic dose of the following drugs:

- a. Oral or topical (rectal) 5-ASA compounds provided that the dose has been stable for the 2 weeks immediately prior to enrollment
- b. Oral corticosteroid therapy (prednisone at a stable dose \leq 30 mg/day, budesonide at a dose \leq 9 mg/day, or equivalent steroid) provided that the dose has been stable for the 4 weeks immediately prior to enrollment if corticosteroids have just been initiated, or for the 2 weeks immediately prior to enrollment if corticosteroids are being tapered
- c. Topical (rectal) corticosteroid enemas/suppositories
- d. Azathioprine or 6-mercaptopurine provided that the dose has been stable for the 8 weeks immediately prior to enrollment
- e. Methotrexate provided that the dose has been stable for the 8 weeks immediately prior to enrollment
- f. Antibiotics used for the treatment of IBD (ie, ciprofloxacin, metronidazole)
- g. Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea
- h. Probiotics (eg, Culturelle, *S. boulardii*) provided that the dose has been stable for the 2 weeks immediately prior to enrollment

5.5 Exclusion Criteria for Ulcerative Colitis and Crohn's Disease De Novo Patients

The exclusion criteria are divided into 3 categories: gastrointestinal exclusion criteria, infectious disease exclusion criteria, and general exclusion criteria. Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

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5.5.1 Gastrointestinal Exclusion Criteria for De Novo Patients

1. Evidence of abdominal abscess at the initial Screening visit
2. Extensive colonic resection, subtotal or total colectomy
3. History of > 3 small bowel resections or diagnosis of short bowel syndrome
4. Have received tube feeding, defined formula diets, or parenteral alimentation within 21 days prior to the administration of the first dose of study drug
5. Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine
6. Within 30 days prior to enrollment, have received any of the following for the treatment of underlying disease:
 - a. Any investigational or approved nonbiologic therapy for IBD (eg, cyclosporine, thalidomide) other than those specifically listed in Section 6.2.1.
 - b. Adalimumab
7. Within 60 days prior to enrollment, have received any of the following:
 - a. Infliximab
 - b. Certolizumab pegol
 - c. Any other investigational or approved biological agent, other than local injections for non IBD conditions (eg intra-ocular injections for the treatment of wet macular degeneration)
8. Any prior exposure to natalizumab, efalizumab, or rituximab
9. Evidence of or treatment for *C. difficile* infection or other intestinal pathogen within 28 days prior to enrollment
10. Currently require or are anticipated to require surgical intervention during the study
11. History or evidence of adenomatous colonic polyps that have not been removed
12. History or evidence of colonic mucosal dysplasia

5.5.2 Infectious Disease Exclusion Criteria for De Novo Patients

1. Chronic hepatitis B or C infection

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2. Active or latent tuberculosis, regardless of treatment history, as evidenced by any of the following:
 - a. History of tuberculosis
 - b. A diagnostic TB test performed within 1 month of enrollment that is positive, as defined by:
 - i. a positive QuantiFERON[®] test or 2 successive indeterminate QuantiFERON[®] tests **OR**
 - ii. a tuberculin skin test reaction ≥ 10 mm (≥ 5 mm in patients receiving the equivalent of > 15 mg/day prednisone).
 - c. Chest X-ray within 3 months of enrollment in which active or latent pulmonary tuberculosis cannot be excluded
3. Any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation)
4. Any live vaccinations within 30 days prior to study drug administration except for the influenza vaccine
5. Clinically significant extra-intestinal infection (eg, pneumonia, pyelonephritis) within 30 days of the initial Screening visit

5.5.3 General Exclusion Criteria for De Novo Patients

1. Previous exposure to MLN0002
2. Female patients who are lactating or have a positive serum pregnancy test during the Screening period or a positive urine pregnancy test on Day 1 prior to study drug administration.
3. Any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise patient safety
4. Had any surgical procedure requiring general anesthesia within 30 prior to enrollment or is planning to undergo major surgery during the study period
5. Any history of malignancy, except for the following: (a) adequately-treated nonmetastatic basal cell skin cancer; (b) squamous cell skin cancer that has been

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adequately treated and that has not recurred for at least 1 year prior to enrollment; and (c) history of cervical carcinoma in situ that has been adequately treated and that has not recurred for at least 3 years prior to enrollment. Patients with remote history of malignancy (eg, > 10 years since completion of curative therapy without recurrence) will be considered based on the nature of the malignancy and the therapy received and must be discussed with the sponsor on a case-by-case basis prior to enrollment.

6. History of any major neurological disorders, including but not limited to stroke, multiple sclerosis, brain tumor, or neurodegenerative disease
7. Positive PML subjective symptom checklist prior to the administration of the first dose of study drug
8. Any of the following laboratory abnormalities during the Screening period:
 - a. Hemoglobin level < 8 g/dL
 - b. White blood cell (WBC) count < $3 \times 10^9/L$
 - c. Lymphocyte count < $0.5 \times 10^9/L$
 - d. Platelet count < $100 \times 10^9/L$ or > $1200 \times 10^9/L$
 - e. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × the upper limit of normal (ULN)
 - f. Alkaline phosphatase > 3 × ULN
 - g. Serum creatinine > 2 × ULN
 - h. Albumin < 2.0 g/dL (< 20 g/L)
9. Current or recent history (within 1 year prior to enrollment) of alcohol dependence or illicit drug use
10. Active psychiatric problems that, in the investigator's opinion, may interfere with compliance with the study procedures
11. Unable to attend all the study visits or comply with study procedures

6. STUDY TREATMENT

6.1 Study Drug Administration

Vedolizumab (MLN0002) will be administered only to eligible patients under the supervision of the investigator or identified designee(s). Female patients of childbearing potential must have a negative urine pregnancy test prior to receiving each dose.

The study pharmacist will obtain study drug kit assignments through the IVRS. Study medication will be prepared according to the procedures outlined in the Pharmacy Manual.

Patients will receive a 300 mg dose of MLN0002 by intravenous (IV) infusion over approximately 30 minutes. Longer infusion times of up to 60 minutes may be used based on study observations. All patients will be observed at the clinical site for at least 1 hour after the completion of each dose in a room where appropriate treatment for infusion-related reactions is available. The patient should be considered clinically stable by the investigator or designee prior to discharge.

Please also refer to the Pharmacy Manual for additional details, and to the following related sections of this protocol:

- [Section 6.7, Preparation, Reconstitution, and Dispensation](#)
- [Section 6.8, Packaging and Labeling](#)

6.2 Concomitant Procedures and Medications

All medications that are administered and all procedures that are performed during the study must be recorded in the patient's electronic case report form (eCRF) and in the source documents. Concomitant medications for medical conditions other than UC or CD are permitted as clinically indicated, subject to specific protocol requirements outlined in Section 6.2.1 and Section 6.2.2. The oral corticosteroid dosing and tapering schedule is described in Section 6.2.3.

The following should be taken into account with regard to concomitant procedures:

- Patients should be encouraged to avoid major elective surgery while enrolled in this study.
- Patients may not donate blood, sperm, or oocytes during the study and for 18 weeks after the last dose of study drug.

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- Patients with extensive colitis or pancolitis of > 8 years duration or limited colitis of > 12 years duration must have a surveillance colonoscopy with random and targeted biopsies within 18 months of their most recent prior examination, and every 18 months thereafter.
- Colorectal cancer screening should also be kept current during the study for patients with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age > 50 years, or other known risk factors.

6.2.1 Permitted Medications for the Treatment of IBD

The following concomitant medications for the treatment of IBD are permitted:

- Oral and topical (rectal) 5-ASA treatment.
- Oral corticosteroids are permitted under the guidelines described in Section 6.2.3.
- Topical (rectal) corticosteroid enemas/suppositories.
- Azathioprine, 6-mercaptopurine, or methotrexate (methotrexate for CD only); stable doses of these medications are encouraged.
- Antibiotics.
- Antidiarrheals for control of chronic diarrhea.
- Probiotics (eg, Culturelle, *S. boulardii*).
- Vedolizumab (Entyvio) will be allowed during the 16-week follow-up where clinically indicated.

6.2.2 Excluded Medications

The following medications are excluded from the study:

- Treatments for UC or CD other than those listed in Section 6.2.1 (either approved or investigational)
- All live vaccines during study treatment and for at least 6 months after the last dose of study drug (except for live influenza vaccine)
- Either approved or investigational biological agents for the treatment of non-IBD conditions, other than localized injections (eg, intra-ocular injections for wet macular degeneration)

6.2.3 Oral Corticosteroid Dosing and Tapering Regimen

The maximum dose of oral corticosteroid for the treatment of IBD that may be co-administered with MLN0002 as a long-term regimen is 30 mg/day prednisone (or equivalent), or 9 mg/day budesonide. Short-term use of higher doses, or corticosteroids that are required for pre-infusion medication (to be given only on the day of infusion), is

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acceptable. However, patients who require consistent doses higher than 30 mg/day prednisone (or equivalent) should be withdrawn from the study. Cases in which the investigator believes the patient should stay on study must be discussed with the Medical Advisor or the Takeda Medical Monitor.

It is strongly recommended that patients receiving oral corticosteroids should begin an oral corticosteroid tapering regimen once they either achieve clinical response or if, in the opinion of the investigator, they have demonstrated sufficient improvement.

The recommended tapering schedule is as follows:

- For prednisone at doses > 10 mg/day (or equivalent), the dose should be reduced at a rate of 5 mg per week until a 10 mg/day dose is reached.
- For prednisone at doses ≤ 10 mg/day (or equivalent) or once a 10 mg/day dose (or equivalent) is achieved by tapering, the dose should be reduced at a rate of 2.5 mg/week until discontinuation.
- For budesonide, the dose should be tapered at a rate of 3 mg every 3 weeks.

Investigators should strongly consider withdrawing patients who require recurrent corticosteroid courses with an inability to taper.

6.3 Precautions and Restrictions

Female patients participating in MLN0002 clinical studies should avoid becoming pregnant and male subjects should avoid impregnating a female partner.

Female patients of childbearing potential must practice 2 effective methods of contraception, at the same time, during from the time of signing the informed consent form through 18 weeks after the last dose of study drug. It is strongly recommended that at least 1 of these 2 methods be highly effective (eg, oral, implantable or injectable contraceptives, contraceptive patches, intrauterine devices). Female patients are exempt from contraception requirements if they are postmenopausal for at least 1 year before enrollment, are surgically sterile (ie, status post effective tubal ligation, or bilateral oophorectomy, or hysterectomy), or completely abstain from heterosexual intercourse.

Male patients, even if surgically sterilized (ie, status postvasectomy), must practice effective barrier contraception during the entire study treatment period and continue contraception for 18 weeks after their last dose of study drug, or completely abstain from heterosexual intercourse.

6.4 Management of Clinical Events

6.4.1 Adverse Event Collection Involving Medically Anticipated Clinical Events (IBD)

UC and CD are associated with certain characteristic signs and symptoms including diarrhea, rectal bleeding, and abdominal pain that may be present at baseline and persist or fluctuate based on the individual patient's disease history during the course of the study. These signs and symptoms are considered medically anticipated clinical events for the condition under study and will not be collected as adverse events. These characteristics of disease activity will be regularly captured in either the partial Mayo score or the HBI and will be reviewed by the DSMB.

Exacerbations of disease activity for UC (eg, increase in the daily amount of rectal bleeding beyond the patient's normal fluctuation) or CD (eg, increase in the daily amount of abdominal pain beyond the patient's normal fluctuation) will be collected as adverse events (AEs) and reported according to regulatory reporting requirements.

Extra-intestinal manifestations of the patient's disease (eg, arthralgias, arthritis, uveitis) that develop or worsen during the study are considered AEs.

6.4.2 Infusion-Related Reactions

Currently, there is no evidence to support the routine prophylactic administration of premedication (eg, antihistamines, corticosteroids) to patients receiving MLN0002; hence, such premedications are unlikely to be necessary or beneficial. At the discretion of the investigator, however, patients may be administered premedication prior to any study drug infusion. Corticosteroids, if given as premedication, should be limited to the day of infusion.

Patients will be monitored for acute infusion-related reactions during infusion and for at least 1 hour after the completion of each administration of MLN0002. Epinephrine and parenteral diphenhydramine must be readily available for immediate use in case an infusion-related reaction occurs. Site personnel must be able to detect and treat infusion-related reactions.

Patients should be instructed to report the development of rash, hives, pruritus, flushing, urticaria, etc. that may represent an infusion-related reaction to MLN0002. If any signs or symptoms of infusion-related reactions are observed during the infusion, administration of

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MLN0002 must be immediately discontinued and the patient treated as medically appropriate. In the case of a mild reaction, MLN0002 infusion may be reinitiated (with appropriate premedication) at the discretion of the investigator. Patients with a severe or serious infusion-related reaction (eg, stridor, angioedema, life-threatening change in vital signs) must be withdrawn from the study.

In all cases of infusion-related reactions, the medical monitor must be informed as soon as is practical (see the Study Manual for contact information). The disposition of patients with less severe infusion-related reactions should be discussed with the medical monitor. All cases of infusion-related reactions that do not meet SAE definitions as specified in Section 10.1.2 will be collected as AEs. The intensity, relationship to study medication, action taken and outcome for all cases of infusion-related reactions, regardless of seriousness, will be recorded on the AE eCRF.

6.4.3 Leukopenia or Lymphopenia

Total WBC and lymphocyte counts will be regularly monitored for all patients. Azathioprine, 6-mercaptopurine, or methotrexate, if applicable, must be discontinued and the dose of MLN0002 held for an absolute lymphocyte count $< 0.5 \times 10^9/L$ at any point during the study. The absolute lymphocyte count must be repeated at appropriate intervals as determined by the investigator. The next dose of MLN0002 can be administered only if the absolute lymphocyte count is $\geq 0.5 \times 10^9/L$. If the absolute lymphocyte count remains $< 0.5 \times 10^9/L$ for greater than 9 weeks, permission for the patient to continue on study must be obtained from the Takeda Medical Monitor.

6.4.4 Infection

Patients will be monitored for signs and symptoms of infection and for lymphopenia during the study. Patients with signs and symptoms suggestive of infection, including GI infections, will be treated as clinically indicated; interventions may include antibiotic treatment, if appropriate, and/or discontinuation of concomitant immunomodulatory medications. Blood, sputum, urine, and/or stool cultures will be obtained as appropriate for detection and diagnosis of infection. Withholding or terminating MLN0002 administration may be considered as described in Section 7.4. Failure to respond to standard therapies for infection will be recorded as part of AE collection.

6.4.5 Malignancy

All cases of malignancies that are detected during the study will be reported as AEs or SAEs as defined in Section 10.1. Local medical practices will apply. Monitoring for colorectal mucosal dysplasia and cancer will be performed during the study as described in Section 6.2.

6.4.6 Hepatotoxicity

Patients will be monitored throughout the study for evidence of hepatotoxicity with regular liver function tests and routine clinical assessments.

6.4.7 Management of Positive Subjective PML Checklist

All patients will be screened for new neurological signs and symptoms potentially consistent with PML at frequent and regular intervals and ad hoc as appropriate using the PML subjective symptom checklist. De novo patients with a positive subjective PML checklist at screening will not be enrolled. Any patient with a positive subjective PML checklist at any time after enrollment will be evaluated according to the PML case evaluation algorithm as described in the Study Manual. The next dose of MLN0002 will be held until the evaluation is completed and results are available. Subsequent doses of MLN0002 will be administered only if the possibility of PML is definitively excluded, as described in the RAMP program (see Section 10.5).

6.4.8 Unscheduled Visits Due to Disease Exacerbation

Patients who are experiencing symptoms of possible disease exacerbation need not wait until their next scheduled visit to be seen; they should be evaluated as deemed appropriate by the treating physician. Patients who are seen by the investigator or site staff at a time point not required by the protocol (ie, an unscheduled visit) due to disease exacerbation should undergo the following:

- Symptom-directed physical examination
- Vital signs assessment
- Patient assessment of disease activity
- Recording of concomitant medications and procedures
- Collection of AEs and SAEs
- Clinical chemistry and hematology as indicated

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- Stool sample, if indicated, may be obtained for culture, ova and parasite evaluation, and *C. difficile* assay
- Partial Mayo score or HBI score
- HAHA sample collection

There is no minimum time for repeat evaluation by unscheduled visit.

6.4.9 Need for Rescue Medications

Administration of a new medication to treat a new or unresolved luminal manifestation of UC or CD, with the exclusion of 5-ASA agents (oral and topical/rectal), oral corticosteroids as outlined in Section 6.2.3, topical (rectal) corticosteroids, azathioprine/6-mercaptopurine/methotrexate (methotrexate for CD only), antibiotics, antidiarrheals for control of chronic diarrhea, and probiotics, is considered a rescue medication, and constitutes long-term treatment failure (Section 6.4.10).

Medications should not be withheld if, in the opinion of the investigator, failure to prescribe them could compromise patient safety. Based on the clinical pharmacology of MLN0002 and the potential for additive toxicities with other immunosuppressive drugs, serious consideration should be given to the administration (as rescue medications) of biologic agents or other therapies with a prolonged pharmacodynamic effect.

6.4.10 Long-term Treatment Failure

As defined in the [Study Definitions](#), there are 3 types of long-term treatment failure: (1) patients who require rescue medications (see Section 6.4.9); (2) patients who require major surgical intervention for the treatment of IBD; and (3) patients who have a study drug-related AE leading to discontinuation from the study. Patients who meet the definition of long-term treatment failure must be withdrawn from the study (Section 7.4).

6.5 Blinding and Unblinding

This is an open-label study, there is no blinding.

6.6 Description of Investigational Agents

MLN0002 drug product is a lyophilized solid formulation at 60 mg/mL in a solution containing CCI histidine, CCI arginine, CCI sucrose, CCI polysorbate 80, CCI

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Each vial will be reconstituted with sterile water for injection according to the instructions in the Pharmacy Manual.

6.7 Preparation, Reconstitution, and Dispensation

The investigational pharmacist will prepare the study treatment under standard aseptic conditions. Each vial will be reconstituted according to the Pharmacy Manual with 4.8 mL sterile water for injection. A 300 mg dose (5.0 mL), will be removed from each vial and diluted into 0.9% sodium chloride to an approximate volume of 250 mL. Additional details on the preparation of MLN0002 are provided in the Pharmacy Manual.

Because MLN0002 is a biological protein and therefore subject to denaturation upon shaking, **reconstituted vials and IV solution bags should not be shaken**. Vials are for single use administration.

6.8 Packaging and Labeling

MLN0002 will be supplied in 20 mL CCI glass vials with 20 mm CCI rubber stoppers and aluminum crimp seals with CCI flip-top covers. The injection vials will be packaged into kits containing one 20 mL vial of active MLN0002. Both the primary and secondary label information will fulfill all requirements specified by local governing regulations. Additional details are provided in the Pharmacy Manual.

6.9 Storage, Handling, and Accountability

MLN0002 will be stored in a secure facility with controlled access. MLN0002 must be stored refrigerated at 2°C to 8°C. Additional storage and handling instructions are provided in the Pharmacy Manual.

6.10 Other Protocol-Specified Materials

The following supplies will also be required for study treatment administration and are to be provided by the clinical study center:

- Bottled sterile water for injection (for MLN0002 reconstitution)
- 250 mL 0.9% sodium chloride for injection in polyvinyl chloride (PVC) IV bag(s) or 250 mL 0.9% sodium chloride in alternative IV bags or bottles listed in the Pharmacy Manual

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- Polyvinyl chloride (PVC) infusion line or alternative infusion line listed in the Pharmacy Manual

7. STUDY CONDUCT

7.1 Study Personnel and Organizations

The contact information for the Takeda medical monitor, the central and any additional clinical laboratories, the IVRS provider and other vendors, the coordinating investigator for each member state/country, and the contract research organization (CRO) team can be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

7.2 Arrangements for Recruitment of Patients

Most patients enrolling in this study will have participated in a previous qualifying MLN0002 study (rollover patients) as detailed in Section 4.1. The remainder (de novo patients) will be recruited from a subset of the same sites.

7.3 Study Procedures

The study procedures are described below. After Week 0, dosing visits must occur within ± 1 week of the specified time. It is anticipated that the total duration of MLN0002 treatment will vary on a patient-by-patient basis, based on continued benefit. Patients who do not transition into the XAP study will return 16 weeks after the last dose of MLN0002 for final safety assessments at the Final Safety visit. All patients will also complete the 2-year follow-up survey (see Section 7.6). Patients who transition into the XAP study are not required to attend the Final Safety Visit. The safety of these patients will be monitored as part of the XAP study. The end-of-study eCRF page must be completed for all patients regardless of whether they transition into the XAP study or not.

7.3.1 Informed Consent

Rollover patients will be required to sign and date an informed consent form prior to enrollment (Week 0), and de novo patient will be required to sign and date an informed consent form prior to performance of any study-related procedures. During the consent process, patients will be made aware of the known and potential risks of MLN0002 treatment (including the hypothetical risk of PML and how to recognize symptoms of

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possible PML), and what to report to their health care professional. All patients will be given an opportunity to ask questions. Patients will be given written information about PML to take home and read prior to their return at Week 0.

7.3.2 Wallet Card

A wallet card specifically for this study that denotes key study information, including signs and symptoms of PML, will be distributed prior to Week 0.

7.3.3 Demographics

Demographics information will be obtained from the MLN0002 study in which the patient previously participated (rollover patients) or during the Screening period (de novo patients).

7.3.4 Tobacco Use

Tobacco use information will be obtained from the MLN0002 study in which the patient previously participated (rollover patients) or during the Screening period (de novo patients).

7.3.5 Medical History

Medical history information will be obtained from the MLN0002 study in which the patient previously participated (rollover patients) or during the Screening period (de novo patients).

7.3.6 Prior Therapies

Information regarding prior therapies for UC or CD will be obtained from the MLN0002 study in which the patient previously participated (rollover patients) or during the Screening period (de novo patients).

7.3.7 Disease History

UC or CD history information will be obtained from the MLN0002 study in which the patient previously participated (rollover patients) or during the Screening period (de novo patients).

7.3.8 Physical Examination

A physical examination, which will include assessments of general appearance, skin, head (eyes, ears, nose, and throat), neck, lungs, heart, abdomen, back, lymph nodes, extremities,

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and neurologic system, will be conducted at the study visits specified in the [Schedule of Events](#). A symptom-directed physical examination will be performed at any unscheduled visit(s) due to disease exacerbation.

Any clinically significant findings on the physical examination will be recorded as AEs.

7.3.9 Neurological Examination

A neurological examination will be performed at the study visits specified in the [Schedule of Events](#). The neurological examination should be performed by the principal investigator or subinvestigator and will include assessments of cranial nerves, motor and sensory function, coordination, and mental status.

Any new clinically significant findings on the neurological examination will be recorded as AEs.

7.3.10 Vital Signs and Weight

Vital signs, including heart rate, respiratory rate, systolic and diastolic blood pressure, and temperature, will be obtained at screening (for de novo patients) and at every study visit, including any unscheduled visit(s) due to disease exacerbation. On dosing days, vital signs will be obtained prior to dosing.

Weight (in kg) will be recorded at screening (for de novo patients) as specified in the [Schedule of Events](#). On dosing days, weight will be recorded prior to dosing.

7.3.11 Progressive Multifocal Leukoencephalopathy (PML) Checklist

The subjective PML symptom checklist will be administered at every study visit to probe for symptoms suggestive of PML. On dosing days, the PML symptom checklist will be administered prior to dosing. De novo patients with a positive subjective checklist during the Screening period will not be enrolled. Any patients reporting or exhibiting suspicious signs and/or symptoms of PML will undergo objective testing and may be referred to a neurologist for a full evaluation, as described in the RAMP algorithm. The PML checklist and the RAMP algorithm and tools are included in the Study Manual. See Section [10.5](#) for additional details regarding RAMP program.

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7.3.12 Patient Assessment of Disease Activity

The patient will be asked to report on components (ie, disease activity) of the partial Mayo score or HBI score at the study visits specified in the [Schedule of Events](#). On dosing days, these reports must be collected prior to dosing.

7.3.13 Concomitant Medications and Procedures

Any medications that are ongoing at the time of enrollment into the C13008 study will be recorded in the eCRF for Study C13008. Concomitant medications and procedures must be reviewed at each study visit (including any unscheduled visit(s) due to disease exacerbation) and recorded in the eCRF. For patients enrolling into the XAP study, concomitant medications will be collected until the patient is consented into the XAP study (this is expected to occur at the final C13008 dosing visit where possible).

7.3.14 Enrollment

Enrollment in this study is defined as the time the patient is entered into the IVRS at Week 0.

7.3.15 Dosing

MLN0002 will be administered as described in Section [6.1](#) at the study visits specified in the [Schedule of Events](#). Female patients of childbearing potential must have a negative urine pregnancy test confirmed prior to receiving each dose of MLN0002.

7.3.16 Partial Mayo Score

A partial Mayo score will be evaluated for patients with UC at the study visits specified in the [Schedule of Events](#). On dosing days, the partial Mayo score will be evaluated prior to dosing.

7.3.17 Harvey-Bradshaw Index (HBI) Score

An HBI score will be evaluated for patients with CD at the study visits specified in the [Schedule of Events](#). On dosing days, data used to derive the HBI score (ie, clinical symptoms and physical exam findings) will be collected prior to dosing.

7.3.18 Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ will be completed at the study visits specified in the [Schedule of Events](#).

7.3.19 Short Form-36 (SF-36)

The SF-36 will be completed at the study visits specified in the [Schedule of Events](#).

7.3.20 EuroQual (EQ-5D)

The EQ-5D will be completed at the study visits specified in the [Schedule of Events](#).

7.3.21 12-Lead ECG

A single 12-lead ECG will be obtained at screening for de novo patients and prior to dosing annually for the first 4 years of the study (as specified in the [Schedule of Events](#)) and at the Final Safety visit for all patients.

Patients will be supine and will have rested for 2 or more minutes before any ECG is recorded. During the course of the study, ECGs will be reviewed by the investigational sites. Any findings from ECGs collected after MLN0002 administration at Week 0 will be captured as AEs if, in the opinion of the investigator, there has been a clinically significant change from baseline.

7.3.22 Tuberculosis Screening and Chest X-ray

All de novo patients will complete TB screening to determine eligibility. All de novo patients who do not report a history of TB must complete a diagnostic TB test within 1 month prior to enrollment and a chest X-ray within 3 months prior to enrollment. Patients will be excluded from the study if they have active or latent TB, regardless of treatment history, as evidenced by any of the following:

- History of TB
- A diagnostic TB test within 1 month of enrollment that is positive, as defined by:
 - A positive QuantiFERON[®] test or 2 successive indeterminate QuantiFERON[®] tests **OR**

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- A tuberculin skin test reaction ≥ 10 mm (≥ 5 mm in patients receiving the equivalent of > 15 mg/day prednisone)
- Chest X-ray within 3 months of enrollment in which active or latent pulmonary TB cannot be excluded.

7.3.23 Collection of Adverse Events and Serious Adverse Events

For rollover patients, AEs and SAEs will be collected from the time the patient enrolls in the study through the Final Safety visit in Study C13008 (16 weeks after the last dose of MLN0002), as applicable.

For de novo patients, AEs will be collected from the time of enrollment, and SAEs will be collected from the time of signing informed consent; as with rollover patients, AEs and SAEs will be collected through the Final Safety visit (16 weeks after the last dose of MLN0002), as applicable.

For patients enrolling into the XAP study, AEs and SAEs will be collected until the patient is consented into the XAP study (this is expected to occur at the final C13008 dosing visit where possible). SAEs that occur after the end of study and are considered to be related to MLN0002 will be collected and forwarded to Takeda Pharmacovigilance (see Section 10.2). Definitions, documentation, and reporting of SAEs are described in detail in Section 10.

7.3.24 Sample Collection

Blood or urine samples will be obtained for the following assessments. On dosing days, samples will be collected prior to dosing. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an adverse event and, if this AE leads to discontinuation of MLN0002, it must be recorded on the AE eCRF.

Pregnancy Testing

A serum pregnancy test will be performed at screening for all females enrolling de novo, and at the Final Safety visit for all females of childbearing potential. A urine pregnancy test will be completed for all females of childbearing potential prior to each dose.

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Clinical Chemistry, Hematology, Coagulation, and Urinalysis

Clinical laboratory evaluations will be performed centrally. Handling and shipment of clinical laboratory samples will be outlined in the Study Manual. Clinical laboratory evaluations will be performed as outlined below:

Blood samples for clinical chemistry assessments, hematology assessments, and coagulation assessments, and urine samples for urinalysis will be collected at the study visits specified in the [Schedule of Events](#).

Blood samples for analysis of the following clinical chemistry, hematological, and coagulation parameters and urine samples for the following urinalysis tests will be obtained:

Clinical Chemistry

- | | | |
|-----------------------------|--------------|------------------------------|
| • Albumin | • Calcium | • Phosphorus |
| • Alkaline phosphatase | • Chloride | • Potassium |
| • ALT and AST | • Creatinine | • Sodium |
| • Amylase | • Glucose | • Total and direct bilirubin |
| • Bicarbonate | • Lipase | • Total protein |
| • Blood urea nitrogen (BUN) | • Magnesium | • Uric acid |

Hematology

- | | | |
|-------------------------|---------------|--------------------------|
| • Basophils | • Lymphocytes | • Platelets |
| • Eosinophils | • Monocytes | • Red blood cells (RBCs) |
| • Hemoglobin/hematocrit | • Neutrophils | • WBCs |

Coagulation

- | | |
|------|-------|
| • PT | • PTT |
|------|-------|

Urinalysis

- | | | |
|-------------|----------------------|---|
| • Bilirubin | • Leukocyte esterase | • Specific gravity |
| • Blood | • Nitrite | • Microscopic (to be obtained in the event of positive leukocyte esterase or blood, will include WBCs, RBCs, and cast[s]) |
| • Glucose | • pH | |
| • Ketones | • Protein | |
-

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Hepatitis B, Hepatitis C, and HIV Screening

Screening for hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus (using an ELISA) will be performed during screening.

C-Reactive Protein Assessment

CRP levels will be measured at the study visits specified in the [Schedule of Events](#). The sample for CRP will be obtained from the blood drawn for the clinical chemistry assessments.

HAHA Assessment

Human anti-human antibody (HAHA) assessments will be performed at the study visits specified in the [Schedule of Events](#). Blood samples for HAHA assessments will be obtained prior to dosing, if applicable. A blood sample for HAHA assessment will also be collected at any unscheduled visit(s) due to disease exacerbation, at any time during the visit. Neutralizing HAHA assessments may be performed for HAHA-positive samples. Drug concentration may be determined as part of the HAHA testing.

Stool Sample

A stool sample for culture, ova and parasite evaluation, and *C. difficile* assay will be obtained (if indicated) at any point during the study when a patient becomes symptomatic, including worsening or return of disease activity.

Fecal Calprotectin

For the de novo patients, a stool sample will be collected during screening for the analysis of fecal calprotectin, a biomarker of intestinal inflammatory activity. Fecal calprotectin will only be analyzed if necessary for eligibility requirements.

7.4 Withdrawal of Patients From Study

Patients who meet the criteria for long-term treatment failure ([Study Definitions](#)) or who, in the opinion of the investigator or patient, are not benefiting from therapy must be withdrawn from the study.

Investigators should strongly consider withdrawing patients who require recurrent corticosteroid courses with an inability to taper.

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Patients who withdraw early will return 16 weeks after the last dose of MLN0002 for final safety assessments at the Final Safety visit. The reason(s) for discontinuation from study treatment is/are listed below and is/are to be recorded in the source documents and on the eCRF.

- Adverse event
- Withdrawal by patient
- Study terminated by sponsor
- Protocol violation(s)
- Lost to follow-up
- Lack of efficacy

Patients who withdraw or are withdrawn from the study will participate in a 2-year follow-up survey, as discussed in Section 7.6. Patients who withdraw or are withdrawn from the study will not be replaced.

7.5 Study Compliance

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the patients, will be maintained at the study site. A drug calculation and reconstitution worksheet, which details specific volumes used for MLN0002 reconstitution, will be completed for each MLN0002 administration and initialed by the pharmacy technician and/or investigational pharmacist or qualified site personnel.

7.6 Post End of Study

Upon completion of or early termination from this study, patients will participate in a 2-year follow-up survey. A specific questionnaire will be administered via telephone at 6, 12, 18, and 24 months after the final dose of study drug. The questionnaire will collect data on events such as pregnancy and infections resulting in hospitalization (6-month telephone call only), colorectal dysplasia or cancer, IBD-related surgeries, and the development of PML.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Determination of Sample Size

This is a phase 3 study to determine the long-term safety of MLN0002 in patients with UC and CD. Most patients enrolled in this study will have participated in a previous qualifying MLN0002 study as detailed in Section 4.1 (rollover patients). Up to 400 additional patients who have not been previously treated with MLN0002 may be enrolled (de novo patients) to supplement the safety database. The current estimate is that approximately 2200 patients total will enter this study.

8.2 Randomization and Stratification

No randomization or stratification is planned for this study.

8.3 Populations for Analysis

There are 2 patient populations in this study for data analyses: the efficacy population and the safety population.

Efficacy Population

The efficacy population consists of all enrolled patients. However, to be included in an analysis at any specific time point, the patient must have had a postbaseline measurement for the time point. Additionally, to be included in a change from baseline analysis, the patient must have had a baseline measurement.

This population will be used for all exploratory efficacy analyses.

Safety Population

The safety population for this study is defined as all patients who receive any amount of MLN0002 in this study. The study safety population will be used for all safety analyses.

8.4 Procedures for Handling Missing, Unused, and Spurious Data

All available safety and efficacy data will be included in data listings and tabulations. No imputation of values for missing data will be performed. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

8.5 General Methodology

Summary tabulations will be presented and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. Statistical analyses will be primarily descriptive in nature. No formal statistical tests will be performed.

A formal statistical analysis plan will be developed and finalized prior to the completion of the study. This plan will define the populations for analysis, outline the data handling conventions, and specify the statistical methods to be used for safety and exploratory efficacy analyses.

8.6 Baseline Comparisons

Demographic and baseline characteristics will be summarized using frequency distributions and summary statistics.

8.7 Safety Analyses

Safety evaluations will be based on incidence, severity and type of AEs, PML checklist responses, vital signs, laboratory results and ECGs. Descriptive statistics will be calculated.

In addition to overall safety summary, subgroup analyses will be performed: 1) by UC patient population and CD patient population; and 2) by concomitant medication.

Treatment emergent AEs (TEAEs) will be tabulated by primary system organ class (SOC), high level term (HLT), and preferred term. The Medical Dictionary for Regulatory Activities (MedDRA) will be used for coding AEs. To summarize the number of patients with AEs, patients reporting the same event more than once will have that event counted only once within each SOC, HLT, and preferred term. Events that are considered related to treatment will also be tabulated. AEs will also be summarized by intensity. Death, patients with SAEs, and events resulting in study discontinuation, if present, will be presented in separate data listings.

The distribution of HAHA across time will be summarized. Whether HAHA is neutralizing may be determined. Furthermore, the results from HAHA and neutralizing HAHA may be used to evaluate the relationships among HAHA and efficacy and safety.

Comprehensive Safety Assessment

Safety data from this study will be reviewed using data including, but not limited to, the following:

- a. Data from both the active and the placebo arms of C13006, C13007 and C13011.
- b. Data from the 2-year follow-up survey after the final dose of study drug in C13006, C13007, and C13011 (for patients who did not enroll in this Long-term Safety Study).
- c. Data from an external administrative database, which includes a broad representation of patients on various therapies for IBD (including biological agents). This database will provide an understanding of the background rates of selected events, such as IBD-related surgeries and hospitalizations that may occur with current therapies for IBD. Additionally, to allow comparison to Study C13008, a sub population of patients who have characteristics similar to those in Study C13008 will be selected from this database. This will allow for some comparison to similar patients who may be on conventional treatment for IBD, including treatment with biological agents.

Patients who previously participated in the phase 2, open-label, long-term safety study (Study C13004) will not be part of the integrated safety analysis for C13008. Data from all patients who previously participated in Study C13004 will be analyzed separately.

Details for the condition and methods of comparison will be discussed in the statistical analysis plan.

8.8 Resource Utilization and Patient Reported Outcomes

Changes in health-related quality of life over time will be assessed using IBDQ, SF-36 and EQ-5D scores. Change from baseline in IBDQ, SF-36 and in EQ-5D will be calculated and 95% confidence intervals will be provided. For these quality of life assessments, the baseline value will be the last measurement from the previous study as applicable (ie, Study C13004, Study C13006, Study C13007, or Study C13011) or the measurement obtained during the Screening period for de novo patients. The proportion of patients who fall into different categories in IBDQ, SF-36, and EQ-5D scores will be summarized and 95% confidence intervals will be provided.

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Time to major IBD-related events (hospitalizations, surgeries and procedures) will be analyzed and 95% confidence intervals will be provided.

8.9 Exploratory (Efficacy) Analyses

This long-term safety study is not sized based on power considerations. Thus, no formal statistical hypothesis testing is to be performed. Furthermore, the lack of a true control arm for comparison purposes limits the use of any formal statistical comparisons that may be made. Therefore, the primary statistical focus for the efficacy analyses will be on descriptive tabulation of efficacy endpoints rather than on formal analysis of the clinical data. Descriptive statistics, including 95% confidence intervals, will be provided for all clinical efficacy variables of interest.

Descriptive statistics will be used in analyses of partial Mayo score (patients with UC) or HBI score (patients with CD), IBDQ score, and SF-36 score.

The change from baseline in CRP level, partial Mayo score or HBI score, and IBDQ score will be summarized by time point, and the means will be plotted over time. The percentage of patients with a clinical response and with clinical remission will be tabulated at each time point. For patients who were not in clinical response or clinical remission at the beginning of the study, the percentage of patients who demonstrate an initial clinical response and go on to maintain a sustained clinical response or clinical remission will be tabulated at each time point.

For definitions of clinical response and clinical remission, refer to the [study definitions](#) Study Definitions. Further details on the statistical analyses, including exploratory evaluations, any sensitivity analyses and data handling details regarding issues such as missing data, will be discussed in the statistical analysis plan.

8.10 Interim Analysis

Interim analyses and reports will be done periodically during the conduct of the study to support regulatory filings and updates.

9. STUDY COMMITTEES

9.1 Data Safety Monitoring Board

A data safety monitoring board (DSMB), independent from the sponsor, will be established to review safety data from this study including, but not limited to, AEs of special interest (eg, infusion-related reactions, infections) on a regular basis and to make appropriate recommendations. With agreement of the DSMB and Takeda, the schedule may be modified based on the rate of patient accrual and findings from reviews. A detailed charter outlines all activities of the DSMB (eg, type of data reviewed, frequency of meetings, location of meetings).

The safety analyses will be generated for the DSMB by an independent statistician.

New neurological signs and symptoms potentially consistent with PML will be reviewed and adjudicated by the IAC per the RAMP algorithm (see Section 9.2).

9.2 Progressive Multifocal Leukoencephalopathy (PML) Independent Adjudication Committee

Takeda's RAMP program includes an independent adjudication committee (IAC) consisting of a panel of leading PML experts, including a neurologist, a neuroradiologist, and a virologist. The RAMP PML evaluation algorithm describes the involvement of the IAC. Descriptions of the RAMP program and the IAC are in the Study Manual. The processes for IAC case review are defined in the IAC Charter. IAC proceedings and recommendations will be promptly communicated to the DSMB.

9.3 Publications Committee

A publications committee will be convened, details of which will be provided in a publications committee charter. Additional details on the use of information are provided in Section 12.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

Refer to Section 6.4.1 for additional details regarding clinical events related to IBD.

10.1.2 Serious Adverse Event Definition

A serious adverse event (SAE) is any AE, occurring at any dose and regardless of causality that:

- Results in **death**
- Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient **hospitalization or prolongation of existing hospitalization** (see Section 10.2)
- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect

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- Is an **important medical event**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.
- Additionally, in this study, any diagnosis of PML will be considered an SAE.

Clarification should be made between the terms “serious” and “severe” because they ARE NOT synonymous. The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as “serious,” which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient’s life or functioning. A severe adverse event does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate page of the eCRF. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an adverse event and must be recorded on the appropriate pages of the eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

All SAEs that occur during the course of the study, as defined in Section 10.1, must be reported by the investigator Takeda Pharmacovigilance, (contact information provided below) by faxing the SAE Form within 1 working day after becoming aware of the event.

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All SAEs and deaths must be reported whether or not considered causally related to the study drug. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE may be requested by Takeda. SAE report information must match the data provided on the eCRF.

SAE Reporting Contact Information

Takeda Pharmacovigilance
Fax: +1 224-554-1052 (North and South America)
Email: TakedaEntyvioCases@cognizant.com (All countries)

Planned hospital admissions or surgical procedures for an illness or disease which existed before the patient was enrolled in the trial or before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial.

Hospital admissions related to a protocol-required procedure (eg, admissions for patient/clinic convenience prior to or following colonoscopy or infusion) will not be considered AEs.

Additionally, any diagnoses of PML will be reported as SAEs.

For both SAEs and AEs, the investigator must determine both the intensity of the event and the relationship of the event to MLN0002 administration.

Intensity for each AE, including any laboratory abnormality, will be defined according to the following criteria:

- Mild* Awareness of sign or symptom, but easily tolerated
- Moderate* Discomfort enough to cause interference with normal daily activities
- Severe* Inability to perform normal daily activities

Relationship to MLN0002 administration will be determined by the investigator responding yes or no to the question: Is there a reasonable possibility that the AE was associated with the study drug?

10.3 Monitoring of Adverse Events and Period of Observation

All AEs and SAEs will be collected from the time of enrollment (for de novo patients, SAE collection will begin after the signing of informed consent) up to 16 weeks (112 days) after the last on-study dose of MLN0002 (as applicable). For patients enrolling into the XAP study, AEs and SAEs will be collected until the patient is consented into the XAP study (this is expected to occur at the final C13008 dosing visit where possible). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Any SAE that occurs at any time after completion of the study period that the investigator considers to be related to study drug must be reported to Takeda Pharmacovigilance.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects she is pregnant while participating in this study, or within 18 weeks after the last dose of study drug, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to Takeda Pharmacovigilance (see Section 10.2). The pregnancy must be followed through for the final pregnancy outcome.

If a female partner of a male study participant becomes pregnant during the male patient's participation in this study, or within 18 weeks after the last dose of study drug, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to Takeda Pharmacovigilance. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Risk Management

Risk minimization, management, and assessment procedures have been implemented in the study to minimize and assess potential risks to patients who participate in clinical studies of MLN0002. Components include: (1) specific study entry and exclusion criteria to ensure that patients who have underlying characteristics that potentially increase their risk for an adverse outcome are excluded; (2) protocol-specific procedures for minimizing and managing certain AEs, such as infusion-related reactions and infections; (3) overview surveillance by 2 independent safety committees (DSMB and IAC; see Section 9.1 and Section 9.2, respectively); (4) a dedicated Risk Minimization Action Plan for PML (the RAMP, see Section 10.5.3) that educates staff and patients on PML and includes an

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algorithm for early detection and evaluation of signs and symptoms suggestive of PML; and (5) long-term, poststudy follow-up (2 years) safety assessment. Specific components are described below, in Section 6.4 and Section 7.6, and in the Study Manual.

10.5.1 Specific Risk Assessment and Minimization Procedures for Identified Risk Associated With MLN0002 Treatment: Infusion-Related Reaction

Site personnel will be trained in rapid detection and standard treatment of infusion-related reactions. Management of infusion-related reactions is detailed in Section 6.4.2.

Immunogenicity

Based on existing data from clinical studies with vedolizumab, there is the possibility of developing HAHA to vedolizumab that may cause infusion-related reactions, other nonspecific AEs, and/or reduced efficacy. Patients will be monitored for AEs and treated as clinically appropriate.

10.5.2 Specific Risk Assessment and Minimization Procedures for Potential Risk of MLN0002 Treatment: Increased Rates of Infections

Patients who have an increased risk of infection (eg, serious comorbidity, immune system dysfunction) will be excluded from the study. Patients on study will be monitored for signs and symptoms of infection and for lymphopenia. Patients with signs and symptoms suggestive of infection will be treated as clinically indicated; interventions may include antibiotic treatment, if appropriate, and/or discontinuation of concomitant immunomodulatory medications. Blood, sputum, urine, and/or stool cultures will be obtained as appropriate for detection and diagnosis of infection. Withholding or terminating study drug administration may be considered, as appropriate. Management of infection is described in Section 6.4.4.

10.5.3 Specific Risk Assessment and Minimization Procedures for Hypothetical Risks of MLN0002 Treatment (Not Observed to Date)

Gastrointestinal Infections

The hypothetical risk that MLN0002 may increase GI infections will be addressed as detailed above (Section 10.5.2) for the potential risk of increased rates of infections.

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Progressive Multifocal Leukoencephalopathy

The cases of PML reported in patients being treated with the pan- α_4 integrin antagonist natalizumab (Tysabri[®]) have focused safety concerns on integrin antagonists. The immunomodulatory mechanism of vedolizumab, as a selective $\alpha_4\beta_7$ integrin antagonist, may not predispose patients to an increased risk of PML. Nevertheless, all ongoing vedolizumab clinical studies will use the RAMP program as a Risk Minimization Action Plan for PML. The RAMP program minimizes the risk of PML by focusing on early clinical detection and management of PML, including discontinuation of study drug, if applicable. An independent adjudication committee (IAC) has been established as part of the RAMP program to review possible cases of PML and will provide input regarding patient evaluation and management as defined in the IAC charter. Additional details of the RAMP program are in the Study Manual. Plasmapheresis and mefloquine have been reported as potentially efficacious treatments for natalizumab-associated PML. ^(25, 26, 27, 28, 29, 30)

Patients are assessed for signs and symptoms of PML before the administration of each dose of study drug using a PML subjective symptom checklist. Patients with a positive PML subjective symptom checklist at any time after enrollment in an MLN0002 clinical study will be evaluated according to a prespecified algorithm (the PML Case Evaluation Algorithm, provided in the Study Manual). The next dose of study drug will be held until the evaluation is complete and results are available. Subsequent doses of study drug will be administered only if the possibility of PML is definitively excluded, as described in the RAMP algorithm. The IAC will review new neurological signs and symptoms potentially consistent with PML and will provide input regarding patient evaluation and management as defined in the IAC charter.

To ensure the success of the RAMP program, site personnel will be trained to recognize the features of PML, and patients will be trained to report specific neurological signs and symptoms without delay. Educational materials for teaching site personnel and patients about PML and the RAMP procedures will be distributed to all sites. Formal teaching and training will be performed for site personnel before the start of the study. Patients will receive training and educational materials before enrollment. The ICF will contain specific information on the hypothetical risk of PML.

The PML IAC will be informed of all new neurological signs and symptoms potentially consistent with PML per the PML Case Evaluation Algorithm and will review the individual patient data. The algorithm and tools are included in the Study Manual.

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All documented cases of PML will be reported as SAEs, regardless of whether hospitalization occurs.

Malignancy

Patients with a history of malignancy (except for specific cancers) or at increased risk for malignancy (eg, patients with identified established immunodeficiencies or colonic mucosal dysplasia) will be excluded from this study (see Section 5.2). It is expected that patients enrolled in the study will be up-to-date on colorectal cancer screening.

10.5.4 Risk Assessment

For patients who do not enroll in Study C13008, the risk assessment part of this study will include a 2-year follow-up survey after the last dose of study drug, as described in Section 7.6, to determine if any patients have been diagnosed with PML or malignancy, or have had bowel surgeries.

11. ADMINISTRATIVE REQUIREMENTS

11.1 Good Clinical Practice

The study will be conducted in accordance with the ICH Guideline for GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of MLN0002 as described in the protocol and the IB.

11.2 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated web-based electronic data capture (EDC) application. Takeda will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

11.3 Electronic Case Report Form Completion

Takeda or designee will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for which they are responsible.

eCRFs will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The audit trail entry will show the user's identification information, and the date and time of the correction. The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she is responsible.

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Takeda, or a designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk or other electronic media will be placed in the investigator's study file.

11.4 Study Monitoring

Monitoring and auditing procedures developed or approved by Takeda will be followed, in order to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

11.5 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, IB, informed consent form, advertisements (if applicable), written information given to the patients (including diary cards and wallet cards, if applicable), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or the sponsor, as allowable by local regulations.

11.6 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent is to comply with ICH-GCP and all applicable regulatory requirement(s).

11.7 Patient Confidentiality

In order to maintain patient privacy, all eCRFs, MLN0002 accountability records, study reports and communications will identify the patient by initials where permitted and/or by

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the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.8 Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by Takeda, and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and Takeda. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. Takeda, or a designee, will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the investigator will contact Takeda, or a designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

11.9 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Takeda may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

11.10 Investigator and Site Responsibility for Drug Accountability

Accountability for the MLN0002 at the trial site is the responsibility of the investigator. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Takeda, or a designee, (or disposal of the drug, if approved by Takeda) will be maintained by the clinical site. Takeda or its designee will review drug accountability at the site on an ongoing basis.

All material containing MLN0002 will be treated and disposed of in accordance with governing regulations.

11.11 Product Complaints

A product complaint is a verbal, written or electronic expression which implies dissatisfaction regarding the identity, strength, purity, quality or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact the CRA or Takeda in accordance with the contact list provided in the Study Manual to report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Takeda quality representative.

11.12 Closure of the Study

Within 90 days of the end of the study, the sponsor will notify the competent authorities and ethics committees where the study is being carried out that the study has ended.

Within 1 year of the end of the study, a summary of the clinical trial results will be submitted to the competent authorities and IECs in all member states involved in the study.

Study participation by individual sites or the entire study may be prematurely terminated, if in the opinion of the investigator or Takeda, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Takeda by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the study drug

Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. In the event that any access devices for the EDC application have been provided, these will be returned to Takeda once the site's participation in the study has concluded.

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Within 15 days of premature closure, Takeda must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.

11.13 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and Takeda notified.

12. USE OF INFORMATION

All information regarding MLN0002 supplied by Takeda to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Takeda. It is understood that there is an obligation to provide Takeda with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of MLN0002 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by Takeda, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. A Publications Group, comprised of Takeda employees and study investigators will be formed to oversee the publication of the study results that will reflect the experience of all participating study centers. Subsequently, individual investigators may publish results from the study in compliance with their agreements with Takeda.

A prepublication manuscript or abstract is to be provided to Takeda a minimum of 30 days prior to the intended submission date of the manuscript or abstract to a publisher. Within 30 days after receipt by Takeda of the notification, Takeda shall inform the study centers whether it has objections to the publication for reasons, including but not limited to, those defined below:

If patentable subject matter is disclosed, the publication shall be delayed for a period not to exceed 90 days from Takeda's receipt of the proposed publication to allow time for the filing of patent applications covering patentable subject matter.

If confidential information is contained in any proposed publication or public disclosure, such confidential information will be removed at Takeda's request.

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13. INVESTIGATOR AGREEMENT

I have read Protocol C13008 Amendment 20: A Phase 3, Open-label Study to Determine the Long-Term Safety and Efficacy of Vedolizumab (MLN0002) in Patients With Ulcerative Colitis and Crohn's Disease.

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

Principal investigator printed name

Principal investigator signature

Date

Investigational site or name of institution and location (printed)

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15. APPENDICES

15.1 Partial Mayo Scoring System for the Assessment of Ulcerative Colitis Activity

Category
Stool frequency ^b 0 = Normal no. of stools for this patient 1 = 1 to 2 stools more than normal 2 = 3 to 4 stools more than normal 3 = 5 or more stools more than normal Sub score, 0 to 3
Rectal bleeding ^c 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passes Sub score, 0 to 3
Physician's global assessment ^d 0 = Normal 1 = Mild disease 2 = Moderate disease 3 = Severe disease Sub score, 0 to 3

Partial Mayo score ranges from 0–9 with higher scores indicating more severe disease.⁽³¹⁾

b Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.

c The daily bleeding score represents the most severe bleeding of the day.

d The physician's global assessment acknowledges the 3 other criteria, the patient's daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

Adapted from: Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987; 317 (26):1625-9

15.2 Harvey-Bradshaw Scoring System for the Assessment of Crohn's Disease Activity

Category	Total
General Wellbeing 0 = Very Well 1 = Slightly Below Par 2 = Poor 3 = Very Poor 4 = Terrible	<input type="checkbox"/>
Abdominal Pain 0 = None 1 = Mild 2 = Moderate 3 = Severe	<input type="checkbox"/>
Number of Liquid Stools Per Day	<input type="checkbox"/>
Abdominal Mass 0 = None 1 = Dubious 2 = Definite 3 = Definite and Tender	<input type="checkbox"/>
Complications (score 1 per item) <input type="checkbox"/> Arthralgia/Arthritis <input type="checkbox"/> Uveitis/Iritis <input type="checkbox"/> Erythema nodosum <input type="checkbox"/> Aphthous ulcers <input type="checkbox"/> Pyoderma gangrenosum <input type="checkbox"/> Anal fissure <input type="checkbox"/> Draining fistula (eg, perianal, enterocutaneous, rectovaginal) <input type="checkbox"/> Perianal Abscess	<input type="checkbox"/>
Final Score (add totals)	<input type="checkbox"/>

Adapted from: Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980; 1 (8167):514.

15.3 Purposes and Rationale for Amendment 1

Rationale for Amendment 1

Since the previous version of the protocol a generic name for MLN0002, vedolizumab, was approved by USAN and has hence been included in key sections of the protocol for reference.

As planned in the original protocol, blood samples collected at regular intervals throughout the study will be assessed for HAHA as a safety endpoint. The decision of whether or not to assess any HAHA-positive samples for neutralizing HAHA will be determined as HAHA and pharmacodynamic data from all ongoing MLN0002 studies are reviewed. A neutralizing HAHA assay will be performed only if the results will contribute to a better understanding of the immunogenicity of MLN0002.

Other changes are corrections of primarily typographical, grammatical, contextual and punctuation errors.

Purposes for Amendment 1

The purposes of this amendment are to:

- Cross-reference the USAN-approved generic name, vedolizumab, which is synonymous with the MLN0002 drug product being investigated in this study
- Clarify that neutralizing HAHA assessment may be performed if necessary to better understand the immunogenicity of MLN0002
- Clarify that recommendations regarding pregnancy begin at the time of signing the informed consent form
- Clarify that the RAMP (Risk Assessment and Minimization for PML) is a RiskMAP
- Clarify in Section 7.3.23 that hematology is not being performed at Week 0
- Clarify in Section 7.6 that all patients will participate in a 2 year follow-up survey
- Correct the value for absolute lymphocyte count in Section 6.4.3
- Clarify that concomitant procedures will be recorded starting at time of enrollment (concomitant procedures from a previous study will not be recorded in the eCRFs for Study C13008)
- Expand the definition of serious adverse event (SAE) to include any event that involves suspected transmission of an infectious agent via a medicinal product
- Correct typographical, grammatical, contextual, and punctuation errors

15.4 Purposes and Rationale for Amendment 2

Rationale for Amendment 2

Revisions and corrections have been made to clarify the initial intent of this protocol as listed below in the purposes. Also, the window for patients to enroll in this study after the last dose of MLN0002 in Study C13004 has been extended from 5 to 9 weeks. This window is consistent with the dosing intervals in Study C13004 and is not expected to affect the patients' clinical progress or the planned statistical analyses. The enrollment window for patients entering this study after Study C13006 or Study C13007 is unchanged.

Purposes for Amendment 2

The purposes of this amendment are to:

- Revise the definition of rescue medications with all applicable exceptions.
- Clarify that data for pre-enrollment quality of life assessments will be obtained from the previous study as applicable.
- Clarify that patients who withdrew from Study C13006 or Study C13007 only as a result of receiving rescue medications before Week 14 are not eligible for Study C13008.
- Extend the window for patients to enroll in this study after the last dose of MLN0002 in Study C13004 from 5 to 9 weeks.
- Revise inclusion criteria by removing the requirement of "stable dose" for patients on corticosteroids at the time of enrollment.
- Clarify the length of required observation at the clinical site based on the completion of dosing.
- Revise the advice regarding prophylactic administration of premedication for better clarity.
- Add language to Section 6.4.8 to clarify the timing of an unscheduled visit as it relates to the criteria for defining disease worsening.
- Remove language in Section 7.3.22 regarding the transfer of AE and SAE information from the previous study to the C13008 eCRFs.
- Clarify that data from patients who previously participated in Study C13004 will not be part of the integrated safety analysis, but will be analyzed separately.
- Correct an incorrect crossreference in Section 10.5.3 and remove an unnecessary statement regarding the reporting of malignancies. Reporting of malignancies is covered in Section 6.4.5 and governed by the definitions and reporting requirements of adverse events (AEs) and serious adverse events (SAEs) as detailed in Section 10.
- Remove statements in the rationale for Amendment 1 (see Section 15.3) regarding pharmacodynamic sampling and objectives. These statements were incorrect because there were no pharmacodynamic objectives or pharmacodynamic samples to be collected in this study at any time.
- Correct typographical, grammatical, contextual, and punctuation errors, as necessary.

15.5 Purposes and Rationale for Amendment 3 (for use only outside of the US)

Rationale for Amendment 3

Recently published data suggest incremental efficacy, acceptable safety, and the potential for decreased long-term immunogenicity with concomitant immunomodulator therapy; therefore, it may be beneficial for patients enrolled in this study to receive concomitant immunomodulators. If deemed appropriate by the investigator, patients will now be allowed to continue azathioprine, 6-mercaptopurine, or methotrexate if they were receiving these medications during prior participation in Study C13006 or Study C13007.

This amendment also allows patients who are unable to complete the corticosteroid taper within the first 6 months of the study to continue in the study, provided they do not exceed a daily oral corticosteroid dose of the equivalent of 5 mg/day of prednisone or 3 mg/day of budesonide. After 6 months, given the long duration of this study, a one-time oral corticosteroid course of up to the equivalent of 30 mg/day of prednisone or 9 mg/day of budesonide is permitted for documented disease flare; however, the dose must be tapered to the equivalent of 5 mg/day of prednisone or 3 mg/day of budesonide within 3 months. Patients who fail to meet these corticosteroid tapering requirements will be withdrawn.

Purposes for Amendment 3

- Allow patients who received azathioprine, 6-mercaptopurine, or methotrexate during prior participation in Study C13006 or Study C13007 to continue these medications in this study
- Allow patients who are unable to complete the corticosteroid taper within the first 6 months of the study to continue in the study
- Correct typographical, grammatical, contextual, and punctuation errors, as necessary.

15.6 Purposes and Rationale for Amendment 4 (for use in Norway and the United Kingdom)

Rationale for Amendment 4

This amendment, which is for use only in Norway and in the United Kingdom (UK), incorporates changes requested by the Norwegian Medicines Agency (NMA) and the Medicines and Healthcare products Regulatory Agency (MHRA).

Purposes for Amendment 4

- Change the study length for patients enrolled in Norway and in the UK, based on a request by the NMA and MHRA, to a maximum of 100 weeks irrespective of marketing authorization.
- Add a requirement, based on a request by the MHRA, that patients enrolling in this study in the UK must have negative hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) tests within 4 months before enrollment.
- Correct typographical, grammatical, contextual, and punctuation errors, as necessary

15.7 Purposes and Rationale for Amendment 5 (for use in all countries except the US, Norway, and the United Kingdom)

Rationale for Amendment 5

With this amendment, the maximum duration of study treatment with MLN0002 is being increased from 100 weeks to 196 weeks (approximately 46 months). This increase accounts for the maximum estimated time from enrollment of the first patient in the trial until approval for MLN0002. Extension of the maximum treatment duration is supported by the accumulated safety data to date, including data from this open-label study. This extension serves the dual purposes of providing patients who are deriving clinical benefit continued access to MLN0002 and increasing our understanding of the long-term safety profile of this compound. Safety assessments, including the predose progressive multifocal leukoencephalopathy (PML) checklists and the Risk Assessment and Minimization for PML (RAMP), will continue during the entire course of the trial. It should be noted that the total duration of study treatment is a maximum duration; if approval is obtained and MLN0002 becomes available in a specific country while the study is still ongoing, the study may be terminated in that country.

This amendment also will allow patients who participated in Study C13011 to continue MLN0002 treatment in this study (C13008). Study C13011, a pivotal phase 3 induction study in patients with Crohn's disease, has been added to the GEMINI program (Millennium's phase 3 pivotal program for vedolizumab [MLN0002] in Crohn's disease and ulcerative colitis). Patients who complete induction therapy and follow-up through Week 10 in Study C13011 may be eligible to enroll in this study.

Additionally, the maximum time allowed from last dose of study drug in the prior qualifying MLN0002 study to first dose of MLN0002 in this study (C13008) has been increased from 5 weeks to 9 weeks to allow more flexibility for patients to enroll in this study. This extension is based on cumulative clinical pharmacology data in the entire vedolizumab program to date, as well as data from a recently completed study (C13004) that showed that patients tolerated an interruption in dosing longer than 5 weeks and were also able to derive therapeutic benefit from subsequent dosing.

Several other modifications have been made to the protocol in light of the increased duration of the study. The observation time after first infusion has been modified from 2 hours to 1 hour. This modification is acceptable based on the considerable increase in accumulated safety experience to date involving first and subsequent doses of MLN0002, since the prior version of this protocol.

Given the long duration of the trial, it is likely that patients may require antibiotics, either for control of symptoms for IBD or for infections, or may undergo surgery during the course of the trial. Antibiotic use (both for IBD and for other conditions) and surgery (non-IBD-related) are now allowed during the course of the study. Similarly, if a patient is otherwise demonstrating benefit from MLN0002, short-term courses of corticosteroids to control occasional and intermittent exacerbations of disease are allowed (up to a maximum daily dose of 30 mg of prednisone or its equivalent) for documented disease exacerbations after 6 months on study (previously, only a single course was allowed after 6 months). This

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modification allows for the treatment of modest disease fluctuations, allowing patients the opportunity to continue receiving long-term MLN0002 treatment.

Patients who undergo or may need to undergo minor surgical procedures in Studies C13006, C13007, or C13011 as a result of their IBD (eg, fistulotomy) are now permitted to enroll. Patients who require or who have undergone major surgery for control of IBD during or after participation in a prior MLN0002 study continue to be excluded.

Finally, the definition of rescue medication in the context of this trial was clarified so that common medications taken for symptoms of disease that are not intestinal anti-inflammatory therapies (such as probiotics) are allowed during the course of the study.

Purposes for Amendment 5

The purposes of this amendment are to:

- Increase maximum on-study MLN0002 treatment from 100 weeks to 46 months or until MLN0002 becomes available in the patient's country, whichever is sooner
- Allow patients who participated in Study C13011 to enroll in this study (Study C13008)
- Increase maximum time allowed from last dose of study drug in the prior qualifying MLN0002 study to first dose of MLN0002 in this study (C13008) from 5 weeks to 9 weeks
- Clarify that the number of study centers is approximately 400 (rather than 550 as originally projected)
- Clarify timing of and requirement for rescue medication in prior study (Study C13006 or Study C13007) as it relates to eligibility for this study (Study C13008)
- Correct reference in inclusion criterion #5 from "left-sided colitis" to the more appropriate term of "limited colitis"
- Permit use of antibiotics and methotrexate for all patients (ie, patients with UC as well as patients with CD)
- Clarify that patients who undergo or may need to undergo minor surgical procedures in Studies C13006, C13007, or C13011 as a result of their IBD (eg, fistulotomy) are permitted to enroll
- Allow for minor IBD-related surgery (eg, fistulotomy) to occur during the study
- Allow for non-IBD-related surgery to occur during the study
- Clarify excluded medications description
- Allow occasional short-term courses of corticosteroids for disease exacerbations throughout the study (previously, only a single course was allowed after 6 months)
- Clarify the definition of rescue medications as those that are used to treat luminal disease
- Update information on clinical experience
- Update information on potential risks
- Revise the term "Long-Term Population" to "Efficacy Population" to be consistent

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with the statistical analysis plan terminology

- Update contact information for serious adverse event (SAE) reporting
- Clarify that drug concentration may be determined as part of the HAHA testing
- Change the post-infusion observation time requirement to at least 1 hour for all infusions, including Week 0 (previously this was approximately 2 hours at Week 0)
- Correct typographical, grammatical, contextual, and punctuation errors, as necessary

15.8 Purposes and Rationale for Amendment 6 (for use in the US only)

Rationale for Amendment 6

With this amendment, the maximum duration of study treatment with MLN0002 is being increased from 100 weeks to 196 weeks (approximately 46 months). This increase accounts for the maximum estimated time from enrollment of the first patient in the trial until approval for MLN0002. Extension of the maximum treatment duration is supported by the accumulated safety data to date, including data from this open-label study. This extension serves the dual purposes of providing patients who are deriving clinical benefit continued access to MLN0002 and increasing our understanding of the long-term safety profile of this compound. Safety assessments, including the predose progressive multifocal leukoencephalopathy (PML) checklists and the Risk Assessment and Minimization for PML (RAMP), will continue during the entire course of the trial. It should be noted that the total duration of study treatment is a maximum duration; if approval is obtained and MLN0002 becomes available in the United States (US) while the study is still ongoing, the study may be terminated in the US.

This amendment also will allow patients who participated in Study C13011 to continue MLN0002 treatment in this study (C13008). Study C13011, a pivotal phase 3 induction study in patients with Crohn's disease, has been added to the GEMINI program (Millennium's phase 3 pivotal program for vedolizumab [MLN0002] in Crohn's disease and ulcerative colitis). Patients who complete induction therapy and follow-up through Week 10 in Study C13011 may be eligible to enroll in this study.

Additionally, the maximum time allowed from last dose of study drug in the prior qualifying MLN0002 study to first dose of MLN0002 in this study (C13008) has been increased from 5 weeks to 9 weeks to allow more flexibility for patients to enroll in this study. This extension is based on cumulative clinical pharmacology data in the entire vedolizumab program to date, as well as data from a recently completed study (C13004) that showed that patients tolerated an interruption in dosing longer than 5 weeks and were also able to derive therapeutic benefit from subsequent dosing.

Several other modifications have been made to the protocol in light of the increased duration of the study. The observation time after first infusion has been modified from 2 hours to 1 hour. This modification is acceptable based on the considerable increase in accumulated safety experience to date involving first and subsequent doses of MLN0002, since the prior version of this protocol.

Given the long duration of the trial, it is likely that patients may require antibiotics, either for control of symptoms for IBD or for infections, or may undergo surgery during the course of the trial. Antibiotic use (both for IBD and for other conditions) and surgery (non-IBD-related) are now allowed during the course of the study.

Patients who undergo or may need to undergo minor surgical procedures in Studies C13006, C13007, or C13011 as a result of their IBD (eg, fistulotomy) are now permitted to enroll. Patients who require or who have undergone major surgery for control of IBD during or after participation in a prior MLN0002 study continue to be excluded.

Finally, the definition of rescue medication in the context of this trial was clarified so that

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common medications taken for symptoms of disease that are not intestinal anti-inflammatory therapies (such as probiotics) are allowed during the course of the study.

Purposes for Amendment 6

The purposes of this amendment are to:

- Increase maximum on-study MLN0002 treatment from 100 weeks to 46 months or until MLN0002 becomes available in the US, whichever is sooner
- Allow patients who participated in Study C13011 to enroll in this study (Study C13008)
- Increase maximum time allowed from last dose of study drug in the prior qualifying MLN0002 study to first dose of MLN0002 in this study (C13008) from 5 weeks to 9 weeks
- Clarify that the number of study centers is approximately 400 (rather than 550 as originally projected)
- Clarify timing of and requirement for rescue medication in prior study (Study C13006 or Study C13007) as it relates to eligibility for this study (Study C13008)
- Correct reference in inclusion criterion #5 from “left-sided colitis” to the more appropriate term of “limited colitis”
- Permit use of antibiotics for all patients (ie, patients with UC as well as patients with CD)
- Clarify that patients who undergo or may need to undergo minor surgical procedures in Studies C13006, C13007, or C13011 as a result of their IBD (eg, fistulotomy) are permitted to enroll
- Allow for minor IBD-related surgery (eg, fistulotomy) to occur during the study
- Allow for non-IBD-related surgery to occur during the study
- Clarify excluded medications description
- Clarify the definition of rescue medications as those that are used to treat luminal disease
- Update information on clinical experience
- Update information on potential risks
- Revise the term “Long-Term Population” to “Efficacy Population” to be consistent with the statistical analysis plan terminology
- Update contact information for serious adverse event (SAE) reporting
- Clarify that drug concentration may be determined as part of the HAHA testing
- Change the post-infusion observation time requirement to at least 1 hour for all infusions, including Week 0 (previously this was approximately 2 hours at Week 0)
- Correct typographical, grammatical, contextual, and punctuation errors, as necessary

15.9 Purposes and Rationale for Amendment 7 (for use in Norway and the United Kingdom only)

Rationale for Amendment 7

With this amendment, the maximum duration of study treatment with MLN0002 is being increased from 100 weeks to 196 weeks (approximately 46 months). This increase accounts for the maximum estimated time from enrollment of the first patient in the trial until approval for MLN0002. Extension of the maximum treatment duration is supported by the accumulated safety data to date, including data from this open-label study. This extension serves the dual purposes of providing patients who are deriving clinical benefit continued access to MLN0002 and increasing our understanding of the long-term safety profile of this compound. Safety assessments, including the predose progressive multifocal leukoencephalopathy (PML) checklists and the Risk Assessment and Minimization for PML (RAMP), will continue during the entire course of the trial.

This amendment also will allow patients who participated in Study C13011 to continue MLN0002 treatment in this study (C13008). Study C13011, a pivotal phase 3 induction study in patients with Crohn's disease, has been added to the GEMINI program (Millennium's phase 3 pivotal program for vedolizumab [MLN0002] in Crohn's disease and ulcerative colitis). Patients who complete induction therapy and follow-up through Week 10 in Study C13011 may be eligible to enroll in this study.

Additionally, the maximum time allowed from last dose of study drug in the prior qualifying MLN0002 study to first dose of MLN0002 in this study (C13008) has been increased from 5 weeks to 9 weeks to allow more flexibility for patients to enroll in this study. This extension is based on cumulative clinical pharmacology data in the entire vedolizumab program to date, as well as data from a recently completed study (C13004) that showed that patients tolerated an interruption in dosing longer than 5 weeks and were also able to derive therapeutic benefit from subsequent dosing.

Several other modifications have been made to the protocol in light of the increased duration of the study. The observation time after first infusion has been modified from 2 hours to 1 hour. This modification is acceptable based on the considerable increase in accumulated safety experience to date involving first and subsequent doses of MLN0002, since the prior version of this protocol.

Given the long duration of the trial, it is likely that patients may require antibiotics, either for control of symptoms for IBD or for infections, or may undergo surgery during the course of the trial. Antibiotic use (both for IBD and for other conditions) and surgery (non-IBD-related) are now allowed during the course of the study. Similarly, if a patient is otherwise demonstrating benefit from MLN0002, short-term courses of corticosteroids to control occasional and intermittent exacerbations of disease are allowed (up to a maximum daily dose of 30 mg of prednisone or its equivalent) for documented disease exacerbations after 6 months on study (previously, only a single course was allowed after 6 months). This modification allows for the treatment of modest disease fluctuations, allowing patients the opportunity to continue receiving long-term MLN0002 treatment.

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Patients who undergo or may need to undergo minor surgical procedures in Studies C13006, C13007, or C13011 as a result of their IBD (eg, fistulotomy) are now permitted to enroll. Patients who require or who have undergone major surgery for control of IBD during or after participation in a prior MLN0002 study continue to be excluded.

Finally, the definition of rescue medication in the context of this trial was clarified so that common medications taken for symptoms of disease that are not intestinal anti-inflammatory therapies (such as probiotics) are allowed during the course of the study.

Purposes for Amendment 7

The purposes of this amendment are to:

- Increase maximum on-study MLN0002 treatment from 100 weeks to 46 months
- Allow patients who participated in Study C13011 to enroll in this study (Study C13008)
- Increase maximum time allowed from last dose of study drug in the prior qualifying MLN0002 study to first dose of MLN0002 in this study (C13008) from 5 weeks to 9 weeks
- Clarify that the number of study centers is approximately 400 (rather than 550 as originally projected)
- Clarify timing of and requirement for rescue medication in prior study (Study C13006 or Study C13007) as it relates to eligibility for this study (Study C13008)
- Correct reference in inclusion criterion #5 from “left-sided colitis” to the more appropriate term of “limited colitis”
- Permit use of antibiotics and methotrexate for all patients (ie, patients with UC as well as patients with CD)
- Clarify that patients who undergo or may need to undergo minor surgical procedures in Studies C13006, C13007, or C13011 as a result of their IBD (eg, fistulotomy) are permitted to enroll
- Allow for minor IBD-related surgery (eg, fistulotomy) to occur during the study
- Allow for non-IBD-related surgery to occur during the study
- Clarify excluded medications description
- Allow occasional short-term courses of corticosteroids for disease exacerbations throughout the study (previously, only a single course was allowed after 6 months)
- Clarify the definition of rescue medications as those that are used to treat luminal disease
- Update information on clinical experience
- Update information on potential risks
- Revise the term “Long-Term Population” to “Efficacy Population” to be consistent with the statistical analysis plan terminology
- Update contact information for serious adverse event (SAE) reporting

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- Clarify that drug concentration may be determined as part of the HAHA testing
- Change the post-infusion observation time requirement to at least 1 hour for all infusions, including Week 0 (previously this was approximately 2 hours at Week 0)
- Correct typographical, grammatical, contextual, and punctuation errors, as necessary

15.10 Purposes and Rationale for Amendment 8 (for use in all countries outside the US)

Rationale for Amendment 8

Amendment 8 is an update to Amendment 5 and Amendment 7 of the C13008 protocol. With this amendment, patients participating in Study C13008 will have access to vedolizumab until March 2016, or until vedolizumab is available in the country in which the patient resides, or until patient withdrawal, whichever comes first (unless the study is terminated early by the sponsor, as described in Section 11.12). Changes in this amendment incorporate or supersede the United Kingdom (UK)/Norway-specific language in Amendment 7.

Another change to the protocol includes removal of JC virus DNA testing. When the vedolizumab pivotal studies were planned in 2008, it was unclear if JC virus DNA testing in the blood might be predictive of progressive multifocal leukoencephalopathy (PML) risk. More recently, controlled studies of natalizumab (which has a proven risk of PML) have conclusively demonstrated that detection of JC virus DNA in the blood is of no clinical utility in minimizing risk of PML.⁽¹⁾ Therefore, monitoring for JC virus DNA in the blood is discontinued with this amendment.

Other changes to the protocol allow for the use of conventional, nonbiological concomitant medications for inflammatory bowel disease (IBD) to be more consistent with standard clinical practice. Thus, patients will now be allowed to start azathioprine, 6-mercaptopurine, methotrexate (methotrexate for Crohn's disease only), or corticosteroids during the course of the study, even if they were not on these medications when enrolled in the study. In addition, oral corticosteroid regimens have been modified to be more consistent with individual patient needs, and the corticosteroid tapering requirement has been changed to a recommendation.

The definition of treatment failure that mandates withdrawal from the study has been modified to "long-term treatment failure" to more accurately reflect true treatment failure that occurs in clinical practice. Given the fluctuating natural history of IBD, patients may be treated for short-term disease worsening with conventional therapies for IBD, as allowed per protocol, without being required to withdraw from the study. Accordingly, one of the criteria for the protocol-defined treatment failure, "disease worsening," that was based on disease activity indices (Harvey-Bradshaw Index and partial Mayo score), has been removed

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from the definition of long-term treatment failure. Importantly, patients are still required to be withdrawn if they require rescue medication or major surgery for the treatment of IBD.

Purposes for Amendment 8

The purposes of this amendment are to:

- Extend the duration of this study to allow all patients access to vedolizumab until March 2016, or until vedolizumab is available in the country in which the patient resides, or until patient withdrawal, whichever comes first (unless the study is terminated early by the sponsor, as described in Section 11.12)
- Increase the maximum number of subjects to 2200
- Discontinue JC virus DNA testing
- Incorporate text from Amendment 7 that required HBV, HCV, and HIV testing for patients in the UK prior to enrolling in Study C13008
- Revise the concomitant medication criteria to make them consistent with the changes allowed in concomitant medications
- Change the requirement for corticosteroid tapering to a recommendation, and clarify the recommended tapering process
- Replace the term “treatment failure” with the term “long-term treatment failure” to be more consistent with clinical practice
- Update the recommendations for unscheduled visits
- Remove the term “disease worsening” from the study definitions and from the definition of “long-term treatment failure”
- Clarify that enrollment for all patients is the time the patient is entered into the IVRS at Week 0.
- Update Inclusion Criterion 7
- Provide updated safety information
- Clarify and update the actions to be taken if a patient experiences leukopenia or lymphopenia
- Align the study withdrawal criteria with the new definition of long-term treatment failure and the changes to the corticosteroid tapering recommendations
- Clarify the inclusion of weight in patient assessments
- Update requirements for 12-lead ECG
- Correct typographical, grammatical, contextual, punctuation, and formatting errors, as necessary

15.11 Purposes and Rationale for Amendment 9 (for use in the US only)

Rationale for Amendment 9

Amendment 9 is an update to Amendment 6 of the C13008 protocol. The primary reason for this amendment is to allow enrollment of up to 400 additional patients with either ulcerative colitis or Crohn's disease who have not been previously treated with vedolizumab ("de novo patients"). The additional patients will increase the number of patients with exposure to vedolizumab and supplement the safety database to detect adverse events resulting from long-term vedolizumab administration that may not be detected in the year-long induction and maintenance studies. The addition of 400 patients will allow for the detection of adverse events that occur at a prevalence of 0.1% to be detected with more than 85% likelihood, and events that occur at a prevalence of 1% to be detected with 99.99% likelihood. Importantly, the inclusion and exclusion criteria for the de novo patients are nearly identical to the criteria for patients who enrolled in Studies C13006, C13007, and C13011; study treatment and assessments will be the same for these de novo patients as for rollover patients (those patients who enrolled in C13008 following participation in C13004, C13006, C13007, or C13011). The additional patients will be enrolled at a subset of existing sites in select countries, including the United States (US).

In addition, with this amendment, both rollover and de novo patients participating in C13008 will have access to vedolizumab until March 2016, or until vedolizumab is available in the US, or until patient withdrawal, whichever comes first (unless the study is terminated early by the sponsor, as described in Section 11.12).

Another change to the protocol includes removal of JC virus DNA testing. When the vedolizumab pivotal studies were planned in 2008, it was unclear if JC virus DNA testing in the blood might be predictive of progressive multifocal leukoencephalopathy (PML) risk. More recently, controlled studies of natalizumab (which has a proven risk of PML) have conclusively demonstrated that detection of JC virus DNA in the blood is of no clinical utility in minimizing risk of PML.⁽¹⁾ Therefore, monitoring for JC virus DNA in the blood is discontinued with this amendment.

The definition of treatment failure that mandates withdrawal from the study has been modified to "long-term treatment failure" to more accurately reflect true treatment failure that occurs in clinical practice. Given the fluctuating natural history of inflammatory bowel disease (IBD), patients may be treated for short-term disease worsening with conventional therapies for IBD, as allowed per protocol, without being required to withdraw from the

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study. Accordingly, one of the criteria for the protocol-defined treatment failure, “disease worsening,” that was based on disease activity indices (Harvey-Bradshaw Index and partial Mayo score), has been removed from the definition of long-term treatment failure.

Importantly, patients are still required to be withdrawn if they require rescue medication or major surgery for the treatment of IBD.

Purposes for Amendment 9

The purposes of this amendment are to:

- Allow up to 400 patients without previous treatment with vedolizumab (de novo patients) to enroll directly into this study
- Extend the duration of this study to allow patients access to vedolizumab until March 2016, or until vedolizumab is available in the US, or until patient withdrawal, whichever comes first (unless the study is terminated early by the sponsor, as described in Section 11.12)
- Discontinue JC virus DNA testing
- Clarify requirements for concomitant medications
- Replace the term “treatment failure” with the term “long-term treatment failure” to be more consistent with clinical practice
- Update the recommendations for unscheduled visits
- Remove the term “disease worsening” from the study definitions and from the definition of “long-term treatment failure”
- Clarify that enrollment for all patients is the time the patient is entered into the IVRS at Week 0.
- Update Inclusion Criterion 7
- Provide updated safety information
- Clarify and update the actions to be taken if a patient experiences leukopenia or lymphopenia
- Align the study withdrawal criteria with the new definition of long-term treatment failure and the changes to the corticosteroid tapering recommendations
- Specify PML checklist requirements for de novo patients at screening
- Clarify the inclusion of weight in patient assessments
- Update requirements for 12-lead ECG
- Correct typographical, grammatical, contextual, punctuation, and formatting errors, as necessary

15.12 Purposes and Rationale for Amendment 10

Rationale for Amendment 10

Amendment 10 is an update to Amendment 5 of the C13008 protocol. The primary reason for this amendment is to allow enrollment of up to 400 additional patients with either ulcerative colitis or Crohn's disease (CD) who have not been previously treated with vedolizumab ("de novo patients"). The additional patients will increase the number of patients with exposure to vedolizumab and supplement the safety database to detect adverse events resulting from long-term vedolizumab administration that may not be detected in the year-long induction and maintenance studies. The addition of 400 patients will allow for the detection of adverse events that occur at a prevalence of 0.1% to be detected with more than 85% likelihood, and events that occur at a prevalence of 1% to be detected with 99.99% likelihood. Importantly, the inclusion and exclusion criteria for the de novo patients are nearly identical to the criteria for patients who enrolled in Studies C13006, C13007, and C13011; study treatment and assessments will be the same for these de novo patients as for rollover patients (those patients who enrolled in C13008 following participation in C13004, C13006, C13007, or C13011). The additional patients will be enrolled at a subset of existing sites in select countries.

In addition, with this amendment, both rollover and de novo patients participating in Study C13008 will have access to vedolizumab until March 2016, or until vedolizumab is available in the country in which the patient resides, or until patient withdrawal, whichever comes first (unless the study is terminated early by the sponsor, as described in Section 11.12).

Another change to the protocol includes removal of JC virus DNA testing. When the vedolizumab pivotal studies were planned in 2008, it was unclear if JC virus DNA testing in the blood might be predictive of progressive multifocal leukoencephalopathy (PML) risk. More recently, controlled studies of natalizumab (which has a proven risk of PML) have conclusively demonstrated that detection of JC virus DNA in the blood is of no clinical utility in minimizing risk of PML.⁽¹⁾ Therefore, monitoring for JC virus DNA in the blood is discontinued with this amendment.

Other changes to the protocol allow for the use of conventional, nonbiological concomitant medications for IBD to be more consistent with standard clinical practice. Thus, patients will now be allowed to start azathioprine, 6-mercaptopurine, methotrexate (methotrexate for CD only), or corticosteroids during the course of the study, even if they were not on these medications when enrolled in the study. In addition, oral corticosteroid regimens have been

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modified to be more consistent with individual patient needs, and the corticosteroid tapering requirement has been changed to a recommendation.

The definition of treatment failure that mandates withdrawal from the study has been modified to “long-term treatment failure” to more accurately reflect true treatment failure that occurs in clinical practice. Given the fluctuating natural history of inflammatory bowel disease (IBD), patients may be treated for short-term disease worsening with conventional therapies for IBD, as allowed per protocol, without being required to withdraw from the study. Accordingly, one of the criteria for the protocol-defined treatment failure, “disease worsening,” that was based on disease activity indices (Harvey-Bradshaw Index and partial Mayo score), has been removed from the definition of long-term treatment failure. Importantly, patients are still required to be withdrawn if they require rescue medication or major surgery for the treatment of IBD.

Purposes for Amendment 10

The purposes of this amendment are to:

- Allow up to 400 patients without previous treatment with vedolizumab (de novo patients) to enroll directly into this study
- Extend the duration of this study to allow patients access to vedolizumab until March 2016, or until vedolizumab is available in the country in which the patient resides, or until patient withdrawal, whichever comes first (unless the study is terminated early by the sponsor, as described in Section 11.12)
- Discontinue JC virus DNA testing
- Revise the concomitant medication criteria to make them consistent with the changes allowed in concomitant medications
- Change the requirement for corticosteroid tapering to a recommendation, and clarify the recommended tapering process
- Replace the term “treatment failure” with the term “long-term treatment failure” to be more consistent with clinical practice
- Update the recommendations for unscheduled visits
- Remove the term “disease worsening” from the study definitions and from the definition of “long-term treatment failure”
- Clarify that enrollment for all patients is the time the patient is entered into the IVRS at Week 0.
- Update Inclusion Criterion 7
- Provide updated safety information
- Clarify and update the actions to be taken if a patient experiences leukopenia or lymphopenia
- Align the study withdrawal criteria with the new definition of long-term treatment

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failure and the changes to the corticosteroid tapering recommendations

- Specify PML checklist requirements for de novo patients at screening
- Clarify the inclusion of weight in patient assessments
- Update requirements for 12-lead ECG
- Correct typographical, grammatical, contextual, punctuation, and formatting errors, as necessary

15.13 Purposes and Rationale for Amendment 16

Rationale for Amendment 16

Amendment 16 is an update to Amendment 10 of the C13008 protocol to be implemented in countries where vedolizumab is either not commercially available or is not reimbursed. With this amendment, patients participating in these countries will have access to vedolizumab in Study C13008 either until December 2016 (at which time patients will be able to transition into an Extended Access Program) or until patient withdrawal, whichever comes first, unless the study is terminated early by the sponsor, as described in Section 11.12. Patients may be transitioned from the C13008 study to an Extended Access Program prior to December 2016, if available.

Purposes for Amendment 16

The purpose of this amendment is to:

- Extend the duration of this study to allow all patients in countries where vedolizumab is either not commercially available or is not reimbursed access to vedolizumab until December 2016 (at which time patients will be able to transition into an Extended Access Program) or until patient withdrawal, whichever comes first, unless the study is terminated early by the sponsor, as described in Section 11.12. Patients may be transitioned from the C13008 study to an Extended Access Program prior to December 2016, if available.
- Remove requirement for women who are not of childbearing potential to perform pregnancy tests prior to each dose of vedolizumab and at the Final Safety Visit as it is not possible for these women to become pregnant.
- Clarify in the Schedule of Events the requirement for sites to obtain a 12-lead ECG from patients at their Final Safety Visit.
- Update the sponsor name and contact details from Millennium to Takeda.
- Update SAE reporting details contact information.
- Clarify that concomitant vedolizumab (Entyvio) taken during the 16-week follow-up period will be recorded as a concomitant medication and will not be considered as a protocol deviation

15.14 Amendment 20 Detailed Summary of Changes

THE PRIMARY SECTIONS OF THE PROTOCOL AFFECTED BY THE CHANGES FROM AMENDMENT 16 ARE INDICATED. THE CORRESPONDING TEXT HAS BEEN REVISED THROUGHOUT THE PROTOCOL.

Purpose: Extend the duration of this study in countries where vedolizumab is not commercially available or is not reimbursed until July 2017, or until an Extended Access Program is available at the site, or until patient withdrawal, or unless the study is terminated early by the sponsor (as described in Section 11.12), whichever comes first.

The primary changes occur in the following sections: [Schedule of Events, 1.3.2](#) (MLN0002 Safety), [1.4](#) (Study Rationale), [1.5.3](#) (Hypothetical Risks of MLN0002 Treatment), [4.1](#) (Overview of Study Design), [4.3](#) (Duration of Study), [5.1](#) (Inclusion Criteria for Rollover Patients), [5.3](#) (Inclusion Criteria for De Novo Ulcerative Patients), [5.4](#) (Inclusion Criteria for De Novo Crohn's Disease Patients), [6.2](#) (Concomitant Procedures and Medications), [6.3](#) (Precautions and Restrictions), [7.3](#) (Study Procedures), [7.3.13](#) (Concomitant Medications and Procedures), [7.3.23](#) (Collection of AEs and SAEs), [10.3](#) (Monitoring of AEs and Period of Observation), and [10.4](#) (Procedures for Reporting Drug Exposure During Pregnancy and Birth Events).

Schedule of Events Pre-enrollment Through Year 2 formerly read:

Note: All patients will return 16 weeks after the last dose of MLN0002 for final safety assessments at the Final Safety visit, as described in the Schedule of Events for Years 5 and beyond.

Now reads:

Note: Patients will return 16 weeks after the last dose of MLN0002 for final safety assessments at the Final Safety visit, as described in the Schedule of Events for Years 5 and beyond. This visit is not required for patients transitioning from Study C13008 into the XAP study.

p If the patient is transitioning from Study C13008 into the XAP study, complete the end-of-study eCRF page at their last dosing visit in C13008. For all other patients, complete the end-of-study page at the Final Safety Visit.

Schedule of Events Year 3 and 4 formerly read:

a All patients will return 16 weeks after the last dose of MLN0002 for final safety assessments at the Final Safety visit, as described in the Schedule of Events for Years 5 and beyond.

Now reads:

a Patients will return 16 weeks after the last dose of MLN0002 for final safety assessments at the Final Safety visit. This visit is not required for patients transitioning from Study C13008 into the XAP study.

g All female subjects of childbearing potential must have a serum pregnancy test at the Final Safety visit (as applicable). A urine pregnancy test will be performed for

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female subjects of childbearing potential prior to each dose of MLN0002.

j If the patient is transitioning from Study C13008 into the XAP study, complete the end-of-study eCRF page at their last dosing visit in C13008. For all other patients, complete the end-of-study page at the Final Safety Visit.

Schedule of
Events
Years 5
and
Beyond
formerly
read:

- a All patients will return 16 weeks after the last dose of MLN0002 for final safety assessments at the Final Safety visit.
- g All female subjects of childbearing potential must have a serum pregnancy test at the Final Safety visit. A urine pregnancy test will be performed for female subjects of childbearing potential prior to each dose of MLN0002.

Now reads:

- a Patients will return 16 weeks after the last dose of MLN0002 for final safety assessments at the Final Safety visit. This visit is not required for patients transitioning from Study C13008 into the XAP study.**
- g All female subjects of childbearing potential must have a serum pregnancy test at the Final Safety visit (as applicable). A urine pregnancy test will be performed for female subjects of childbearing potential prior to each dose of MLN0002.**
- j If the patient is transitioning from Study C13008 into the XAP study, complete the end-of-study eCRF page at their last dosing visit in C13008. For all other patients, complete the end-of-study page at the Final Safety Visit.**

Section
1.3.2
formerly
read:

The phase 3 vedolizumab clinical program is overseen by an independent Data Safety Monitoring Board (DSMB) composed of 2 gastroenterologists, an infectious diseases physician, a physician with training in epidemiology, and a statistician. The DSMB reviews all SAEs monthly and unblinded safety data from all phase 3 trials every 6 months at a minimum. The DSMB last convened on 13 December 2011, and after reviewing unblinded safety data, recommended that the trials proceed without modification.

Now reads:

The phase 3 vedolizumab clinical program is overseen by an independent Data Safety Monitoring Board (DSMB) composed of 2 gastroenterologists, an infectious diseases physician, a physician with training in epidemiology, and a statistician. The DSMB reviews all SAEs monthly and unblinded safety data from all phase 3 trials every 6 months at a minimum. The DSMB convened on 13 December 2011, and after reviewing unblinded safety data, recommended that the trials proceed without modification.

Section 1.4
formerly
read

Although the study was due to complete in March 2016, Takeda has agreed to extend the treatment period until December 2016 to allow access for patients in countries where vedolizumab is either not commercially available or is not reimbursed. For this reason, this amendment is being submitted in all countries currently following Amendment 10 except the following: Austria, France, Germany, Israel, Netherlands, Norway, Serbia, Spain, Sweden, Switzerland and the United Kingdom. Patients may be transitioned from the C13008 study to an Extended Access Program prior to December

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2016, if available. Current safety information is available in the latest version of the Investigator Brochure.

Now reads: **Although the study was due to complete in December 2016, Takeda has agreed to extend the treatment period until July 2017 to allow continued access for patients in countries where vedolizumab is either not commercially available or is not reimbursed. For this reason, this amendment is being submitted in all countries currently following Amendment 16 except the following: Austria, France, Germany, Israel, Netherlands, Norway, Spain, Sweden, Switzerland and the United Kingdom. Current safety information is available in the latest version of the Investigator Brochure.**

Section 1.5.3 formerly read: A number of malignancies have occurred over the duration of the phase 3 program, which remains blinded at the time of the writing of this amendment. At its most recent meeting in December 2011, the DSMB for the phase 3 program reviewed unblinded data, and no modifications to the trial were requested.

Now reads: **A number of malignancies have occurred over the duration of the phase 3 program, which remains blinded at the time of the writing of this amendment. At the meeting in December 2011, the DSMB for the phase 3 program reviewed unblinded data, and no modifications to the trial were requested.**

Section 4.1 formerly read: Following enrollment all patients will be administered 300 mg vedolizomab every 4 weeks for the duration of the study, followed by a 16-week posttreatment observation and safety assessment period. The total duration of MLN0002 treatment will vary by patient based on continued benefit until December 2016 (at which time patients will be able to transition into an Extended Access Program) or until patient withdrawal, whichever is sooner (unless the study is terminated early by the sponsor, as described in Section 11.12). Patients may be transitioned from the C13008 study to an Extended Access Program prior to December 2016, if available.

Now reads: **Following enrollment all patients will be administered 300 mg vedolizumab every 4 weeks for the duration of the study. The total duration of MLN0002 treatment will vary by patient based on continued benefit until July 2017, or until the XAP study is available at the site, or until patient withdrawal, or until vedolizumab is available to the patient through commercial channels (including reimbursement) for the patient's clinical scenario, or unless the study is terminated early by the sponsor, as described in Section 11.12, whichever is sooner.**

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Section 4.1 formerly read: All patients will return 16 weeks after their last dose of MLN0002 for the Final Safety visit.

Now reads: **Patients who do not transition into the XAP study will return 16 weeks after their last dose of MLN0002 for the Final Safety visit. Patients who transition into the XAP study are not required to attend the Final Safety Visit. The safety of these patients will be monitored as part of the XAP study. The end-of-study eCRF page must be completed for all patients regardless of whether they transition into the XAP study or not.**

Section 4.3 formerly read: It is anticipated that the duration of MLN0002 treatment will vary by patient based on continued benefit. Treatment duration may continue until December 2016 (at which time patients will be able to transition into an Extended Access Program) or until patient withdrawal, whichever is sooner (unless the study is terminated early by the sponsor, as described in Section 11.12). Patients may be transitioned from the C13008 study to an Extended Access Program prior to December 2016, if available. After the final dose of MLN0002, patients will complete the 16-week posttreatment observation and safety assessment period. Concomitant vedolizumab (Entyvio) taken during the 16-week follow-up period will be recorded as a concomitant medication and will not be considered as a protocol deviation.

Now reads: **It is anticipated that the duration of MLN0002 treatment will vary by patient based on continued benefit. Treatment duration may continue until July 2017, or until the XAP study is available at the site, or until patient withdrawal, or until vedolizumab is available to the patient through commercial channels (including reimbursement) for the patient's clinical scenario, or unless the study is terminated early by the sponsor, as described in Section 11.12, whichever is sooner. After the final dose of MLN0002, patients who do not transition into the XAP study will complete the 16-week posttreatment observation and safety assessment period (not applicable to patients who transition to the XAP study). Concomitant vedolizumab (Entyvio) taken during the 16-week follow-up period will be recorded as a concomitant medication and will not be considered as a protocol deviation.**

Section 5.1 formerly read: 4. Female patients who:

- are postmenopausal for at least 1 year before enrollment, **OR**
- are surgically sterile, **OR**
- if they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 6 months after the last dose of MLN0002, **OR** agree to completely abstain from heterosexual intercourse.

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Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of MLN0002, **OR**
- agree to completely abstain from heterosexual intercourse.

Now reads:

4. Female patients who:

- **are postmenopausal for at least 1 year before enrollment, OR**
- **are surgically sterile, OR**
- **if they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 18 weeks abstain from heterosexual intercourse.**

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- **agree to practice effective barrier contraception during the entire study treatment period and through 18 weeks after the last dose of MLN0002, OR**
- **agree to completely abstain from heterosexual intercourse.**

Section 5.3
formerly
read:

3. Female patients who:

- Are postmenopausal for at least 1 year before the Screening visit, **OR**
- Are surgically sterile, **OR**
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 6 months after the last dose of study drug, **OR** agree to completely abstain from heterosexual intercourse.

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, **OR**
- Agree to completely abstain from heterosexual intercourse.

Now reads:

3. Female patients who:

- **Are postmenopausal for at least 1 year before the Screening visit, OR**
- **Are surgically sterile, OR**

- **If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 18 weeks after the last dose of study drug, *OR* agree to completely abstain from heterosexual intercourse.**

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- **Agree to practice effective barrier contraception during the entire study treatment period and through 18 weeks after the last dose of study drug, *OR***
 - **Agree to completely abstain from heterosexual intercourse.**
-

Section 5.4
formerly
read:

3. Female patients who:

- Are postmenopausal for at least 1 year before the Screening visit, *OR*
- Are surgically sterile, *OR*
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 6 months after the last dose of study drug, *OR* agree to completely abstain from heterosexual intercourse.

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, *OR*
 - Agree to completely abstain from heterosexual intercourse.
-

Now reads:

3. Female patients who:

- **Are postmenopausal for at least 1 year before the Screening visit, *OR***
- **Are surgically sterile, *OR***
- **If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 18 weeks after the last dose of study drug, *OR* agree to completely abstain from heterosexual intercourse.**

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- **Agree to practice effective barrier contraception during the entire study treatment period and through 18 weeks after the last dose of study drug, *OR***
-

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	<ul style="list-style-type: none">• Agree to completely abstain from heterosexual intercourse.
Section 6.2 formerly read:	<ul style="list-style-type: none">• Patients may not donate blood, sperm, or oocytes during the study and for 6 months after the last dose of study drug.
Now reads:	<ul style="list-style-type: none">• Patients may not donate blood, sperm, or oocytes during the study and for 18 weeks after the last dose of study drug.
Section 6.3 formerly read:	<p>Female patients of childbearing potential must practice 2 effective methods of contraception, <u>at the same time</u>, during from the time of signing the informed consent form through 6 months after the last dose of study drug. It is strongly recommended that at least 1 of these 2 methods be highly effective (eg, oral, implantable or injectable contraceptives, contraceptive patches, intrauterine devices). Female patients are exempt from contraception requirements if they are postmenopausal for at least 1 year before enrollment, are surgically sterile (ie, status post effective tubal ligation, or bilateral oophorectomy, or hysterectomy), or completely abstain from heterosexual intercourse.</p> <p>Male patients, even if surgically sterilized (ie, status postvasectomy), must practice effective barrier contraception during the entire study treatment period and continue contraception for 6 months after their last dose of study drug, or completely abstain from heterosexual intercourse.</p>
Now reads:	<p>Female patients of childbearing potential must practice 2 effective methods of contraception, <u>at the same time</u>, during from the time of signing the informed consent form through 18 weeks after the last dose of study drug. It is strongly recommended that at least 1 of these 2 methods be highly effective (eg, oral, implantable or injectable contraceptives, contraceptive patches, intrauterine devices). Female patients are exempt from contraception requirements if they are postmenopausal for at least 1 year before enrollment, are surgically sterile (ie, status post effective tubal ligation, or bilateral oophorectomy, or hysterectomy), or completely abstain from heterosexual intercourse.</p> <p>Male patients, even if surgically sterilized (ie, status postvasectomy), must practice effective barrier contraception during the entire study treatment period and continue contraception for 18 weeks after their last dose of study drug, or completely abstain from heterosexual intercourse.</p>
Section 7.3 formerly read:	<p>The study procedures are described below. After Week 0, dosing visits must occur within ± 1 week of the specified time. It is anticipated that the total duration of MLN0002 treatment will vary on a patient-by-patient basis, based on continued benefit. All patients will return 16 weeks after the last dose of MLN0002 for final safety assessments at the Final Safety visit. All patients</p>

will also complete the 2-year follow-up survey (see Section 7.6).

Now reads: **The study procedures are described below. After Week 0, dosing visits must occur within ± 1 week of the specified time. It is anticipated that the total duration of MLN0002 treatment will vary on a patient-by-patient basis, based on continued benefit. Patients who do not transition into the XAP study will return 16 weeks after the last dose of MLN0002 for final safety assessments at the Final Safety visit. All patients will also complete the 2-year follow-up survey (see Section 7.6). Patients who transition into the XAP study are not required to attend the Final Safety Visit. The safety of these patients will be monitored as part of the XAP study. The end-of-study eCRF page must be completed for all patients regardless of whether they transition into the XAP study or not.**

Section 7.3.13 formerly read: Any medications that are ongoing at the time of enrollment into the C13008 study will be recorded in the eCRF for Study C13008. Concomitant medications and procedures must be reviewed at each study visit (including any unscheduled visit(s) due to disease exacerbation) and recorded in the eCRF.

Now reads **Any medications that are ongoing at the time of enrollment into the C13008 study will be recorded in the eCRF for Study C13008. Concomitant medications and procedures must be reviewed at each study visit (including any unscheduled visit(s) due to disease exacerbation) and recorded in the eCRF. For patients enrolling into the XAP study, concomitant medications will be collected until the patient is consented into the XAP study (this is expected to occur at the final C13008 dosing visit where possible).**

Section 7.3.23 formerly read: For rollover patients, AEs and SAEs will be collected from the time the patient enrolls in the study through the Final Safety visit in Study C13008 (16 weeks after the last dose of MLN0002).
For de novo patients, AEs will be collected from the time of enrollment, and SAEs will be collected from the time of signing informed consent; as with rollover patients, AEs and SAEs will be collected through the Final Safety visit (16 weeks after the last dose of MLN0002).

Now reads **For rollover patients, AEs and SAEs will be collected from the time the patient enrolls in the study through the Final Safety visit in Study C13008 (16 weeks after the last dose of MLN0002), as applicable.**
For de novo patients, AEs will be collected from the time of enrollment, and SAEs will be collected from the time of signing informed consent; as with rollover patients, AEs and SAEs will be collected through the Final Safety visit (16 weeks after the last dose of MLN0002), as applicable.
For patients enrolling into the XAP study, AEs and SAEs will be

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collected until the patient is consented into the XAP study (this is expected to occur at the final C13008 dosing visit where possible).

Section 10.3 formerly read: All AEs and SAEs will be collected from the time of enrollment (for de novo patients, SAE collection will begin after the signing of informed consent) up to 16 weeks (112 days) after the last on-study dose of MLN0002. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Now reads: **All AEs and SAEs will be collected from the time of enrollment (for de novo patients, SAE collection will begin after the signing of informed consent) up to 16 weeks (112 days) after the last on-study dose of MLN0002 (as applicable). For patients enrolling into the XAP study, AEs and SAEs will be collected until the patient is consented into the XAP study (this is expected to occur at the final C13008 dosing visit where possible). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).**

Section 10.4 formerly read: If a woman becomes pregnant or suspects she is pregnant while participating in this study, or within 6 months after the last dose of study drug, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to Takeda Pharmacovigilance (see Section 10.2). The pregnancy must be followed through for the final pregnancy outcome.

If a female partner of a male study participant becomes pregnant during the male patient's participation in this study, or within 6 months after the last dose of study drug, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to Takeda Pharmacovigilance. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Now reads: **If a woman becomes pregnant or suspects she is pregnant while participating in this study, or within 18 weeks after the last dose of study drug, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to Takeda Pharmacovigilance (see Section 10.2). The pregnancy must be followed through for the final pregnancy outcome.**

If a female partner of a male study participant becomes pregnant during the male patient's participation in this study, or within 18 weeks after the last dose of study drug, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to Takeda Pharmacovigilance. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	31-Aug-2016 17:38 UTC
PPD	Clinical Science Approval	31-Aug-2016 19:34 UTC
PPD	Clinical Science Approval	01-Sep-2016 05:48 UTC