Title: An Open-Label, Phase 1b, Multi-Arm Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of Investigational Treatments in Combination With Standard of Care Immune Checkpoint Inhibitors in Patients With Advanced Melanoma

NCT Number: NCT02723006

Protocol Approve Date: 18 October 2016

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

An Open-Label, Phase 1b, Multi-Arm Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of Investigational Treatments in Combination With Standard of Care Immune Checkpoint Inhibitors in Patients With Advanced Melanoma

Sponsor: Takeda Development Centre Europe Ltd.
Aldwych
London, WC2B 4AE United Kingdom

Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of
Takeda Pharmaceutical Company Limited
40 Landsdowne Street
Cambridge, MA 02139 USA

Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium", "Sponsor", or "Takeda"

Study Number: C28003

IND Number: 129,054 **EudraCT Number:** 2015-005554-35

Compound: TAK-580 (also known as [aka] MLN2480); TAK-202 (aka MLN1202); Vedolizumab

Date: 18 October 2016 **Amendment Number:** 02

Amendment History:

Date	Amendment Number	Amendment Type	Region
11 January 2016	Initial Protocol	Not applicable	Global
26 May 2016	01	Substantial	Global
18 October 2016	02	Substantial	Global

1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	North America	European Union
Serious adverse event and pregnancy reporting	See Section 10.2	See Section 10.2

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (or designee) and other signatories (or their designees) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

Protected Personal Data

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochures, package inserts, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B–Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

1.3 Protocol Amendment No. 02 Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment No. 02.

The primary purpose of this amendment is to incorporate requested changes received from principal investigators (PIs) and by scientific review committees (SRCs) at investigational study sites. In addition, other minor changes in procedures are proposed. Minor grammatical and editorial changes are included for clarification purposes only and are not listed individually. Full details on changes of text are given in Appendix G. The following is a summary of changes made in this amendment:

1. Title page: Updated amendment number and finalization date; added amendment 02 to the Amendment History table and indicated amendment type.
2. Section 1.0: Changed investigational medicinal product (IMP) in header to align with investigational new drug (IND) submission.
3. Section 2.0: Made the following changes/updates:
    a. Added plozalizumab (recommended International Nonproprietary Name [INN]) to TAK-202.
    b. Updated the number (25) and location (North America) of clinical sites on the basis of updated enrollment projections.
    c. Updated standard of care nivolumab dosing to include 240 mg flat dosing as a possible alternative to 3 mg/kg reflecting the recent approval of flat dosing by the Food and Drug Administration (FDA).
    d. Added inclusion that all enrolled patients must be eligible for standard of care melanoma therapy with nivolumab alone or combined with ipilimumab.
    e. Serial tumor biopsies will not be collected from patients enrolled in Arm 3.
    f. Removed ocular melanoma as an exclusion criterion as nivolumab is considered the standard of care for patients with metastatic uveal or conjunctival melanoma.
    g. Removed the exclusion of patients with previous anti-programmed cell death 1 (PD-1), ligands for PD-1 (PD-L1), or anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) treatment as any patient with advanced melanoma for whom nivolumab (Arms 1 and 2) or nivolumab+ipilimumab (Arm 3) are considered standard of care are eligible for this trial.
    h. Changed exclusion criterion with regard to prior therapy: had to be completed more than 2 weeks prior to first dose and all adverse events (AEs) returned to baseline or improved to Grade 1.
4. Section 4.2.2: Added plozalizumab (recommended INN) to TAK-202.
5. Section 4.3.2: Added plozalizumab (recommended INN) to TAK-202.

6. Section 4.4: Clarified that only TAK-580 and TAK-202 will be administered as single agent (SA) therapies for the initial 2-week safety lead-in period.
7. Section 4.4.3: Made the following changes to the rationale for Arm 3:
   a. Deleted effects on the tumor microenvironment due to changed dosing regimen.
   b. Added rationale for the serial assessment of fecal microbiome.
8. Section 4.4.4: Clarified that serial tumor biopsies will be collected from patients enrolled in Arms 1 and 2 only.
9. Section 5.1.3: Clarified the additional objectives:
   a. Company Confidential Information
   b.
10. Section 5.2.3: Clarified the additional endpoints:
   a. Company Confidential Information
   b.
11. Section 6.1.1: The dose-limiting toxicity (DLT) observation period in Arm 3 has been reduced from 8 to 6 weeks to reflect the elimination of the 2-week safety lead-in period of SA vedolizumab.
12. Section 6.1.2: Clarified that the safety profile of combination therapy would be determined in all treatment arms and that the SA and combination treatment effect on the tumor microenvironment would be evaluated in Arms 1 and 2 only because biopsies are restricted to these 2 arms.
13. Section 6.1.3: Made the following changes/updates:
   a. Only patients enrolled in Arms 1 and 2 will receive 2-week SA therapy
   b. Tumor biopsies will be collected from patients enrolled in Arms 1 and 2 only
   c. Clarified progression-free survival follow-up (PFSFU) visits as follows:
      i. PFSFU visits to occur every 12 (±1) weeks
      ii. Progression-free survival (PFS) visits to continue until 2 posttreatment computed tomography (CT) scan evaluations have been performed
   d. Added a 2-week window for the safety long-term follow-up (LTFU) visit after the last dose of vedolizumab: 6 months (± 2 weeks).
   e. Added a 1-week window for the overall survival (OS) visits to occur every 12 (±1) weeks
   f. Disease response assessments using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines to occur:

i. within 7 days prior to the start of Week 15 for patients in Arms 1 and 2 and Week 13 for Arm 3

ii. then every 12 (±1) weeks while on study.

14. Section 6.2: Increased the number of clinical sites and clarified that the first 6 weeks of treatment in Arm 3 constitute the safety lead-in and DLT periods as a consequence of the elimination of the 2-week safety lead-in period of SA vedolizumab in this arm.
15. Section 6.3: Clarified PFSFU visits to provide a range of time for visit occurrences and that they will continue until 2 posttreatment CT scan evaluations are performed.
16. Section 7.1: Clarified that inclusion criterion 8 applies to patients in Arms 1 and 2 only.
17. Section 7.2: Clarified exclusion criterion 4 with regard to prior therapy and related AEs and deletion of the exclusion of patients diagnosed with ocular melanoma (former exclusion criterion number 4). See rationale in Section 2.0.
18. Section 7.2.2: Deleted exclusion of patients previously treated with anti-CTLA-4 therapies in Arm 3. To participate in this arm, ipilimumab+nivolumab should be considered the standard of care.
19. Section 8.1, Figure 8.a: Made the following changes/updates:
    a. IMPs and standard of care drugs are shown in the correct order of administration
    b. IMPs are shown in red, nivolumab in black, and ipilimumab in green
    c. Standard of care (nivolumab+ipilimumab) treatment in Arm 3 starts at Week 1, Day 1 (SA vedolizumab treatment deleted).
20. Section 8.1.2: TAK-202 infusion period includes a range (±5 minutes).
21. Section 8.1.3: Updated vedolizumab dosing times and infusion period.
22. Section 8.1.4: Updated nivolumab administration:
    a. Added the new standard of care FDA-approved flat dosing and updated infusion period.
    b. Clarified specific dosing of the combination of agents in Arm 3: the correct order of administration, the specific dosing days, the specific doses administered on those days, and the infusion period.
23. Section 8.1.5: Ipilimumab infusion period includes a range (±5 minutes).
24. Section 8.2: On the basis of experience from the phase 1 development of TAK-580, Grade 3 asymptomatic hypophosphatemia would not be considered a DLT if it occurred in a patient enrolled in Arm 1.
25. Section 8.3: Updated the DLT period to be the first 6 weeks in Arm 3.
26. Section 8.10.2: Added plozalizumab (recommended INN) to TAK-202.

27. Section 8.10.4.4: Updated nivolumab administration:
    a. Added the new standard of care flat dosing and updated the infusion period.
    b. Clarified the specific dosing of the combination of agents in Arm 3: the correct order of administration, the specific dosing days, the specific doses administered on those days, and the infusion period.
28. Section 8.10.5.3: Updated ipilimumab infusion period and Week1, Day 1 to be the day on which all 3 study drugs in Arm 3 are administered.
29. Section 9.3: Clarified that prior use of a checkpoint inhibitor(s) would be considered when assigning a patient to a treatment arm.
30. Section 9.4.15.2: Corrected footnote (b) that pre-tumor biopsy coagulation testing is conducted for patients in Arms 1 and 2 only.
31. Section 9.4.16.3: Clarified that tumor biopsies will be collected from patients in Arms 1 and 2 only.
32. Section 9.4.18: Added fecal microbiome assessment for patients in Arm 3 only.
33. Section 9.4.19: Added assessment of fecal calprotectin for patients in Arm 3 only.
34. Section 9.10: Clarified posttreatment follow-up assessments (PFSFU and OS).
35. Section 10.3: Clarified collection period of serious pretreatment AEs from consented patients considered screen failures.
36. Section 10.7: Clarified when the safety LTFU will be conducted after the last dose of vedolizumab in Arm 3.
37. Section 13.1.1: Defined the DLT period to be the first 6 weeks of treatment for patients in Arm 3.
38. Section 13.1.5: Clarified that pharmacodynamic effect analyses (tumor biopsies) will be assessed in Arms 1 and 2 only.
39. Section 16.0: Added references to provide rationale for fecal microbiome assessments in Arm 3.
40. Appendix A: Updated schedules of events (SOEs) to be consistent with other changes in the protocol amendment.
41. Appendix F: Added back the footer information to identify the progressive multifocal leukoencephalopathy (PML) Checklists version and date.
42. Correction of inconsistencies within protocol amendment 01.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

<table>
<tr><td>Name of Sponsor(s):
Takeda Development Centre Europe, Ltd
Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited</td><td colspan="2">Compounds:
TAK-580 (MLN2480)
TAK-202 (MLN1202; plozalizumab)
Vedolizumab (Entyvio®)
Nivolumab (Opdivo®)
Ipilimumab (Yervoy®)</td></tr>
<tr><td>Title of Protocol: An open-label, phase 1b, multi-arm study to evaluate the safety, tolerability, and pharmacodynamics of investigational treatments in combination with standard of care immune checkpoint inhibitors in patients with advanced melanoma</td><td>IND No.: 129,054</td><td>EudraCT No.:
2015-005554-35</td></tr>
<tr><td>Study Number: C28003</td><td colspan="2">Phase: 1b</td></tr>
<tr><td colspan="3">Study Design:
Phase 1b, open-label, multi-arm, multi-center, umbrella trial to evaluate the safety and pharmacodynamics of several combinations of approved immune checkpoint inhibitors with investigational drugs in patients with advanced melanoma.</td></tr>
<tr><td colspan="3">Primary Objectives:
Dose escalation and Part 1 limited cohort expansion: To determine the recommended Part 2 expansion dose based on the initial safety profile of the combination treatment arms administered to patients with advanced melanoma.
Part 2 expansion: To determine the initial antitumor activity of each combination arm.</td></tr>
<tr><td colspan="3">Secondary Objectives:
Dose escalation and Part 1 limited cohort expansion: To evaluate preliminary antitumor activity in each combination treatment arm.
Part 2 expansion: To further evaluate the safety in each combination treatment arm in the expanded patient population. For Arm 3 a specific secondary objective is to evaluate the impact of vedolizumab in the frequency and severity of diarrhea and colitis.</td></tr>
<tr><td colspan="3">Subject Population: Subjects, aged ≥18 years, with advanced melanoma.</td></tr>
<tr><td>Number of Subjects:
Up to 52 subjects per arm
Estimated total: up to 156
approximately 12 patients/dose-escalation treatment arm
up to 46 patients/treatment arm in expansion</td><td colspan="2">Number of Sites:
Estimated total: 25 in North America and Europe</td></tr>
<tr><td>Dose Level(s):
TAK-580 (MLN2480): 300 (Dose level −1), 400, or 600 mg QW
TAK-202 (MLN1202): 2 (Dose level −1), 4, or 8 mg/kg at weeks 1, 3, 5, and Q4W thereafter
Vedolizumab: 200 or 450 mg at week 1, 3, 5, and 13
Nivolumab:
3 mg/kg or 240 mg flat dose Q2W (standard of care)
Nivolumab (Nivo) + Ipilimumab (Ipi) (standard of care):
Nivo (1 mg/kg) + Ipi (3 mg/kg) Q3W for 4 doses; then Nivo without Ipi (3 mg/kg or 240 mg flat dose) Q2W until disease progression or unacceptable toxicity</td><td colspan="2">Route of Administration:
TAK-580 (MLN2480) oral
TAK-202 (MLN1202) intravenous (IV)
Vedolizumab IV
Nivolumab IV
Ipilimumab IV</td></tr>
</table>

Duration of Treatment:	**Period of Evaluation:**
up to 50 weeks	12 months

Main Criteria for Inclusion:

- Adult male or female patients ≥18 years old.
- Histologically confirmed, unresectable Stage III or Stage IV melanoma per the American Joint Committee on Cancer (AJCC) staging system.
- Patients must be eligible for treatment with nivolumab or nivolumab+ipilimumab at the dose(s) and schedule(s) recommended as standard of care.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
- Adequate bone marrow reserve and renal and hepatic function within 28 days before the first dose of study drug on the basis of the following laboratory parameters:
  - Absolute neutrophil count (ANC) ≥1000/mm^3, platelet count ≥75,000/mm^3, and hemoglobin ≥8 g/dL (with or without transfusion support).
  - Total bilirubin ≤1.5 × the institutional upper limit of normal (ULN) or <3.0 × ULN in subjects with Gilbert's syndrome.
  - Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤3.0 × the institutional ULN (<5 × ULN if liver enzyme elevations are due to liver metastases).
  - Creatinine <1.5 × the institutional ULN or estimated creatinine clearance using the Cockcroft-Gault formula ≥ 50 mL/minute/1.73 m^2 for patients with serum creatinine concentrations above institutional limits.
- Suitable venous access for the collection of study-required blood sampling, including pharmacokinetic (PK) and pharmacodynamic blood samples.
- Recovered from all toxic effects of previous therapy or at new baseline (patients with ongoing Grade 1 events from prior therapies will be eligible).
  - Prior radiotherapy must have been completed at least 2 weeks prior to study drug administration.
  - Prior systemic antitumor therapy >2 weeks or >5 times the half-life, whichever is shorter.
- For Arms 1 and 2 only: Disease accessible for repeat biopsy and willingness to undergo serial tumor biopsies.

Additional Requirements for ARM 1 ONLY (Nivolumab + TAK-580)

- *BRAF* V600 mutation-positive or *NRAS* mutation-positive disease previously untreated with RAF, MEK, or other inhibitors of the MAPK pathway

Additional Requirements for EXPANSION ARMS ONLY

Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.

Main Criteria for Exclusion:

- Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for high doses of systemic corticosteroids that could result in immunosuppression (>10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.
- Subjects who completed a prior therapy <2 weeks prior to first dose and for whom AEs related to prior therapy had not returned to baseline or improved to Grade 1.
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are

permitted to enroll.

- Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- Subjects with history of pneumonitis requiring treatment with steroids; history of idiopathic pulmonary fibrosis (including pneumonitis), interstitial lung disease, drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest computed tomography (CT) scan; history of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Subjects with a diagnosis of immunodeficiency, ie, any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation).
- Known, previously diagnosed human immunodeficiency virus infection or active chronic hepatitis B or C. Specific screening for chronic viral illness is at the discretion of the site or local institutional review board (IRB).
- Systemic infection requiring IV antibiotic therapy or other serious infection within 14 days before the first dose of study drug. Patients are specifically excluded if they have active, severe infections such as tuberculosis (screening per local practice and epidemiology), sepsis, cytomegalovirus (including CMV colitis), listeriosis, and opportunistic infections (including *C. difficile*) until the infections are controlled.
- Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

Additional Exclusion Requirements for ARM 1 ONLY (Nivolumab + TAK-580)

- Concomitant use or administration of clinically significant enzyme inducers ≤14 days before the first dose of TAK-580.
- Treatment with gemfibrozil (or other strong CYP2C8 inhibitor) within 14 days before the first dose of TAK-580.
- Left ventricular ejection fraction (LVEF) <50% as measured by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan within 4 weeks before receiving the first dose of study drug.
- Known gastrointestinal (GI) disease or prior GI procedure that could interfere with the oral absorption of or tolerance to TAK-580.

Additional Exclusion Requirements for ARM 3 ONLY (Nivolumab + Ipilimumab +Vedolizumab)

- The patient has an abnormal progressive multifocal leukoencephalopathy (PML) objective checklist.
- The patient had prior exposure to rituximab, natalizumab, vedolizumab, or alemtuzumab.
- The patient has a history of any major neurological disorders, including stroke, multiple sclerosis, or neurodegenerative disease.
- Any live vaccinations within 30 days before study drug administration except for the influenza vaccine.

Main Criteria for Evaluation and Analyses:

The primary endpoint for the dose escalation and Part 1 limited cohort expansion phase is the frequency of dose-limiting toxicities (DLTs) as defined in Section 8.2.

The primary endpoint for the Part 2 expansion phase is objective response rate (ORR) as measured by RECIST Version 1.1 as assessed by the investigator in the different combination arms.

Secondary safety endpoints for this study are DLT frequency (Part 2), the frequency and severity of treatment-emergent adverse events (TEAEs) including serious TEAEs, treatment discontinuation rate, and dose modifications. In Arm 3 specific safety secondary endpoints are the frequency and severity of diarrhea and colitis per definitions in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03.

Secondary efficacy endpoints are duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Statistical Considerations:

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. Demographic and baseline characteristics data which include age, gender, race, weight, baseline disease characteristics, histology and genotype status will be summarized descriptively.

Pharmacokinetics:

Descriptive statistics will be presented for plasma concentrations by time.

Safety:

Treatment-emergent AEs will be presented in listings and summarized. Individual results (baseline, postdose, and change from baseline to postdose) of laboratory tests (hematology, chemistry, urinalysis, and immune safety tests) will be listed and summarized. Individual results and changes from baseline in vital signs, electrocardiogram (ECG) results, and ECOG performance status will be presented. Exposure to study treatment and reasons for discontinuation will be tabulated.

Efficacy:

In the dose expansion portion of the study, ORR, defined as complete response (CR) + partial response (PR), in each treatment arm will be estimated and presented with a 2-sided 95% Exact Binomial confidence interval (CI). The number and percentage of patients in each response category will be tabulated for each treatment arm based on RECIST, Version 1.1. The Kaplan-Meier method will be used to analyze PFS, DOR, and overall survival (OS). Descriptive statistics, graphical methods and statistical modeling, whichever are appropriate, may be used to explore the relationship between clinical activity and immune cell infiltration and /or other biomarkers.

Sample Size Justification:

The number of patients enrolled in this study will be driven initially by the dose escalation part and then by the dose expansion part. A 3+3 dose-escalation design will be used with 3 possible dose levels (DL1, DL2, and provision for a DL−1 in case the DL1 is not tolerable) for a sample size of up to 12 patients per arm during dose escalation. The expansion phase will consist of 2 parts. Part 1 will consist of a limited cohort of 15 patients (inclusive of patients in dose escalation at the tolerated dose) for assessment of initial safety and clinical activity in each arm; if ORR >30% is observed in any treatment arm, that arm may be expanded up to a total of 46 patients (inclusive of the 15 patients from Part 1). This will constitute Part 2. Up to 52 patients may be enrolled in each treatment arm for a total enrollment of up to 156 patients.

A sample size of 46 patients yields a power of 80% with a 1-sided test at the significance level of α=0.05 for a null hypothesis of response rate ≤30% versus an alternative hypothesis of response rate ≥50%. Based on a Simon's optimal 2-stage design, 15 evaluable patients will need to be enrolled in the first stage. If there are more than 5 responses (CR or PR) out of these initial 15 patients, an additional 31 patients will be enrolled.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Clinical Study Supplier List or equivalent. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Signatory Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

ADA	anti-drug antibody
ADL	activities of daily living
ADR	adverse reaction
AE	adverse event
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the [plasma/blood/serum] concentration-time curve
BCRP	breast cancer resistance protein
BIM	protein biomarker; involved in coordination of programmed cell death
BSA	body surface area
BUN	blood urea nitrogen
CCR2	cysteine-cysteine chemokine receptor type 2
CD	Crohn's disease
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CL	total clearance
C_{max}	maximum observed {plasma/blood/serum} concentration
CMV	cytomegalovirus
CR	complete response
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
C_{ss}	plasma concentration at steady state
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
CYP	cytochrome P-450
DDI	drug-drug interaction
DL1, DL2,DL−1	dose levels 1, 2, and −1
DLT	dose-limiting toxicity
DOR	duration of response
DTIC	dacarbazine
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMA	European Medicines Agency

EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HIV	human immunodeficiency virus
HR	hazard ratio
IA	interim analysis
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
Ig	immunoglobulin
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	investigational new drug [application]
irAE	immune-related adverse event
INN	International Nonproprietary Name
IRB	institutional review board
IRR	immune-related reaction
IV	intravenous
JCV	John Cunningham virus
LDH	lactate dehydrogenase
LFT	liver function test
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MAPK	mitogen-activated protein kinase
MCP-1	monocyte chemoatrractant protein-1, also known as CCL2
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition [scan]
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death 1
PD-L1, PD-L2	ligands for PD-1
PFS	progression-free survival

PFSFU	progression-free survival follow-up
PI	principal investigator
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PO	oral
PR	partial response
PT	Preferred Term
PTE	pretreatment events
Q2W	[dosing] every 2 weeks
QOD	[dosing] every other day
QW	[dosing] once weekly
RA	rheumatoid arthritis
RAMP	Risk Assessment and Minimization for PML
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
RR	relative risk
RRMS	relapsing-remitting multiple sclerosis
SA	single agent
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOE	Schedule of Events
SRC	scientific review committee
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal elimination half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF-α	tumor-necrosis factor alpha
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
USPI	US prescribing information
VCAM-1	vascular cell adhesion molecule-1
V_{ss}	volume of distribution at steady state
WHO	World Health Organization

3.4 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.
TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

Programmed cell death 1 (PD-1) is a negative costimulatory receptor expressed primarily on the surface of activated T-cells. PD-1, when engaged by the ligand PD-L1, triggers inhibitory signaling in T-cells. PD-L1 can be constitutively expressed on the surface of cancer cells or can be expressed in response to T cells producing immune-stimulating cytokines such as interferons. Nivolumab is an anti-PD-1 monoclonal antibody (mAb) that disrupts the PD-1 / PD-L1 interaction with resultant tumor recognition by cytotoxic T cells. Nivolumab has demonstrated long term benefit to a clinically significant but infrequent number of patients with treatment naïve and relapsed/refractory metastatic melanoma. While tumor PD-L1 expression is associated with improved outcomes, benefit was also observed in a subset of patients whose disease was PD-L1 negative/indeterminate. Preliminary studies would indicate that the tumor microenvironment plays a significant role in determining resistance, response, and duration of response to immune checkpoint inhibitor monotherapy.

A strategy to therefore increase the long term benefit of immunotherapy to a majority of melanoma patients would be to focus on the tumor microenvironment role in 1) blocking effector functions (such as antigen specific T-cell recognition and homing to tumor) and 2) reducing T-cell killing capacity. To augment T-cell killing capacity, nivolumab has been combined with ipilimumab, a mAb that targets cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), another negative costimulatory receptor also expressed on T-cells.

4.1.1 Disease Under Treatment

4.1.1.1 Overview of Melanoma

Melanoma is the most serious form of skin cancer and strikes adults of all ages. In the United States (US) in 2014, approximately 76,100 patients were estimated to be diagnosed with malignant melanoma and 9,710 deaths due to malignant melanoma were anticipated [1]. The incidence of melanoma varies considerably with geography, as would be expected since sun exposure (both the intensity of individual episodes of sun exposure and cumulative ultraviolet light exposure) is the dominant etiologic risk factor. Data from the majority of countries show that at a time when the incidence of many tumor types is decreasing, melanoma incidence continues to increase. In the US, melanoma incidence rates have been increasing for at least 30 years with increases occurring in both females (1.7% average annual increase between 2006-2010) and in males (2.4% average annual increase).

About 80% of malignant melanomas are diagnosed at a localized stage. However, melanoma is more likely than other skin tumors to spread to other parts of the body and the degree of spread greatly impacts survival. Patients with regional or distant stage diseases have 5-year survival rates of 62% and 16%, respectively.

4.1.1.2 Current Therapies for Metastatic Melanoma

Historically, once malignant melanoma became metastatic and beyond the scope of surgical resection, it represented one of the most treatment-refractory malignancies. However, new therapies that inhibit dysregulation of the mitogen-activated protein kinase (MAPK) signaling pathway or activate endogenous anti-cancer immune surveillance via T-cell checkpoint blockade have substantially improved the outcomes for patients with metastic melanoma.

Single-agent (SA) chemotherapeutic agents, including dacarbazine (DTIC) and temozolomide, produce responses in 10% to 20% of patients, with a median survival of approximately 9 months and a 2-year survival rate of 13% [2]. Combination chemotherapy regimens, including cisplatin-vinblastine-DTIC and cisplatin-DTIC-carmustine-tamoxifen (Dartmouth regimen), result in improved response rates of 30% to 50%. However, these superior response rates failed to translate into an improvement in median survival and the negative impact on tolerability was significant [3].

BRAF inhibitors as SA or in combination with MEK inhibitors can induce a very rapid response in patients with malignant melanoma whose tumors harbor a V600 mutation of the *BRAF* gene. In *BRAF* V600 mutation-positive patients, both BRAF inhibitors vemurafenib and dabrafenib as SA demonstrated superior survival benefit when compared to DTIC. In the interim analysis (IA) for overall survival (OS) and final analysis for progression-free survival (PFS) in the phase 3 registration trial, vemurafenib was associated with a relative reduction of 63% in the risk of death and of 74% in the risk of either death or disease progression, as compared with DTIC ($p<0.001$ for both comparisons) [4]. Median PFS was 5.1 months for dabrafenib and 2.7 months for DTIC, with a hazard ratio (HR) of 0.30 (95% confidence interval [CI]: 0.18-0.51; $p<0.0001$) [5]. The combination of dabrafenib and the MEK inhibitor trametinib demonstrated improved response and survival compared to dabrafenib alone. In the pivotal trial, median OS was 25.1 months (95% CI: 19.2-not reached) in the dabrafenib + trametinib group versus 18.7 months (15.2-23.7) in the dabrafenib only group (HR of 0.71, 95% CI: 0.55-0.92; $p=0.0107$) [6]. However, the tolerability of this combination has led to the recommendation in compendium guidelines [7,8] of combination therapy over SA therapy in patients who are able to tolerate it.

Ipilimumab, a humanized mAb that inhibits activation of CTLA-4, a negative regulator of T-cell activity, was first approved in the treatment of previously-treated advanced melanoma after demonstrating a survival benefit over an experimental vaccine (gp100) [9]. In treatment-naïve malignant melanoma patients, ipilimumab plus DTIC demonstrated a median OS significantly longer in previously untreated patients receiving ipilimumab plus DTIC than those receiving DTIC plus placebo (11.2 months vs 9.1 months; HR: 0.72, $p<0.001$), with higher survival rates in the ipilimumab plus DTIC group at 1 year (47.3% vs 36.3%), 2 years (28.5% vs 17.9%) and 3 years (20.8% vs 12.2%) [10]. However, ipilimumab has demonstrated the potential for significant immune-related adverse events (irAEs) that primarily involve the gastrointestinal (GI) tract and skin, and less frequently, the liver, endocrine glands, and nervous system.

Pembrolizumab and nivolumab, humanized mAbs that inhibit activation of PD-1 were approved in 2014 for the treatment of advanced melanoma in patients who have progressed after ipilimumab and if *BRAF* V600 mutation-positive after progressing to a BRAF inhibitor. Both of

these mAbs received accelerated approval on the basis of tumor response and duration of response (DOR) in uncontrolled studies. Results from a randomized phase III trial with previously untreated patients without *BRAF* mutations randomized to nivolumab or cytotoxic chemotherapy (dacarbazine) showed that nivolumab was markedly superior in terms of response rate (40% vs. 13.9%), median PFS (5.1 months vs. 2.2 months), and 1-year OS (72.9% vs. 42.1%; all comparisons $p<0.001$) [10].

In a phase 3 study in treatment-naïve advanced melanoma patients stratified for *BRAF* mutation, nivolumab alone or in combination with ipilimumab demonstrated significantly longer PFS and higher overall response rate (ORR) compared with ipilimumab alone. These results were independent of PD-L1 (the ligand for PD-1) tumor status or *BRAF* mutation status. While the study did not include a formal comparison between the nivolumab monotherapy group and the nivolumab-plus-ipilimumab group, the combination resulted in numerically longer and higher rate of response in the overall population compared to nivolumab treatment alone. Furthermore, in *BRAF* mutation-positive patients, the combination appeared to have a similar PFS rate to what has been reported in similar *BRAF* mutation-positive patients receiving dabrafenib plus trametinib. The data is not sufficiently mature to provide OS evidence for the nivolumab plus ipilimumab combination relative to SA treatments (or to previously reported BRAF/MEK inhibitor combinations). However, the tolerability of this combination in which >1/3 of patients discontinued treatment due to treatment-related adverse events (AEs) (compared to 8% and 15% for nivolumab and ipilumab monotherapy, respectively), would indicate that like the BRAF inhibitor plus MEK inhibitor experience, the use of this combination may be restricted to those most likely to tolerate it and more likely to benefit over SA PD-1 therapy (such as patients with PD-L1 negative tumors) [11].

In summary, given the continued rise in the incidence of malignant melanoma and despite a growing number of treatments for metastatic melanoma, there remains an unmet medical need to improve the efficacy and the tolerability of anti-cancer treatments in advanced melanoma. The evaluation of novel treatment strategies, to include novel targeted therapies in combination with T-cell checkpoint inhibitors is warranted.

4.2 Study Drugs

Unless otherwise noted, this study will investigate 3 separate combinations (ie, TAK-580 + nivolumab, TAK-202 + nivolumab, and vedolizumab + nivolumab + ipilimumab). Properties of each of the individual agents are briefly described in the following sections.

4.2.1 TAK-580 (MLN2480)

TAK-580 is a potent, small molecule pan-RAF kinase inhibitor being developed for the treatment of solid tumors, both as SA and in combination with other agents. As a combination therapy, TAK-580 has the potential to support the inhibition of tumor cell signaling at multiple nodes. The RAF kinases (A-, B-, and C-RAF) are key components of the MAPK pathway that controls cell proliferation and survival signaling. The MAPK pathway, which is composed of RAS, RAF, MAPK kinase (MEK), and extracellular signal-regulated kinase (ERK), integrates signals from receptors on the cell surface including cancer-related receptor tyrosine kinases such

as the epidermal growth factor receptor (EGFR), mesenchymal epithelial transition factor (MET), and the vascular endothelial growth factor receptor (VEGFR). The MAPK pathway is frequently activated in human cancer by mutation of *BRAF*, *NRAS*, *KRAS*, or other pathway components. Recent approvals of BRAF and MEK small molecule inhibitors in melanoma have confirmed the importance of this pathway in cancer patients.

The ability of TAK-580 to inhibit both RAF monomer- and dimer-mediated signaling is a key feature that distinguishes it from approved BRAF inhibitors (vemurafenib and dabrafenib). TAK-580 is a potential first-in-class molecule with clinical attributes of both a RAF and MEK inhibitor. A weekly dosing schedule of TAK-580 is expected to achieve higher unit doses, which may allow achievement of higher TAK-580 peak concentrations with a higher degree of MAPK pathway inhibition for a window of time within the dosing interval, without compromising overall dose density. On the basis of nonclinical and preliminary clinical data to date, TAK-580 given once weekly (QW) would have an acceptable safety profile enabling a combination approach with a SA immune checkpoint inhibitor (Section 4.3.1).

Further details regarding the nonclinical and clinical experience with TAK-580 is provided in the TAK-580 Investigator's Brochure (IB).

4.2.2 TAK-202 (MLN1202; plozalizumab)

TAK-202 is a genetically engineered humanized mAb of the immunoglobulin (IgG1) class that is a potent specific antagonist of cysteine-cysteine chemokine receptor type 2 (CCR2). As a combination therapy, TAK-202 has the potential to block circulating myeloid derived suppressor cells that overexpress the CCR2-receptor from trafficking to the tumor microenvironment where they suppress T-cell responsiveness. TAK-202 blocks all CCR2 ligands (MCP-1 thru -4) with a high degree of receptor occupancy (90% or higher) thought necessary to block chemokine activity sufficiently to produce a pharmacodynamic effect (based on an increase in monocyte chemoattractant protein 1 [MCP-1], decrease in circulating monocytes, and reduction in C-reactive protein [CRP]).

On the basis of nonclinical and preliminary clinical data to date, TAK-202 has an acceptable safety profile enabling a variety of combination approaches (Section 4.3.2).

Further details regarding the nonclinical and clinical experience with TAK-202 is provided in the TAK-202 IB.

4.2.3 Vedolizumab (Entyvio®)

Vedolizumab (also known as MLN0002, Entyvio®, or Kynteles®) is a recombinant humanized mAb that binds specifically to the human lymphocyte integrin α4β7. The α4β7 integrin is a pivotal mediator of gut immunity and inflammation due to its unique role in mediating the migration of lymphocytes into gut-associated lymphoid tissue (GALT) and lamina propria, via binding to mucosal addressin cell adhesion molecule-1 (MAdCAM-1). Thus, vedolizumab acts as a gut-selective immunomodulator.

Vedolizumab has been developed as a treatment for ulcerative colitis (UC) and Crohn's disease (CD), which are characterized by inflammation of the GI tract. Marketing approval has been granted in the US, European Union, and multiple other countries for the treatment of adult patients with moderately to severely active UC or CD who have failed conventional therapy (ie, corticosteroids or immunomodulators) or have failed or are intolerant to tumor necrosis factor alpha (TNF-α) antagonists.

Further details regarding the nonclinical and clinical experience with vedolizumab is provided in the vedolizumab IB.

4.2.4 Nivolumab (Opdivo®)

Nivolumab (Opdivo®; Bristol-Myers Squibb) is a human IgG4 mAb that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is approved as a monotherapy in *BRAF* wild type advanced melanoma after failing ipilimumab and in *BRAF* V600 mutation-positive advanced melanoma after failing a BRAF inhibitor. Nivolumab in combination with ipilimumab is approved in *BRAF* wild type advanced melanoma with or without prior therapies. Furthermore, compendium guidelines [7,8] have recommended monotherapy with an anti-PD-1 could be considered in 1st or 2nd line treatment of advanced melanoma patients irrespective of *BRAF* V600 mutation status due to the efficacy (ORR and median PFS) observed in randomized clinical trials involving *BRAF* V600 mutation-positive advanced melanoma patients. On the basis of the established clinical profile of SA nivolumab in advanced melanoma, nivolumab has an acceptable safety profile enabling a combination approach with novel anti-cancer therapies.

Further details regarding the clinical experience with nivolumab may be found in the current version of the approved Opdivo® label.

4.2.5 Ipilimumab (Yervoy®)

Ipilimumab (Yervoy®; Bristol-Myers Squibb) is a human mAb that binds to the CTLA-4, a negative regulator of T-cell activity. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor immune response. Combined nivolumab- (anti-PD-1) and ipilimumab-mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumor responses in metastatic melanoma.

Ipilimumab is approved in the treatment of advanced melanoma as a monotherapy (irrespective of *BRAF* V600 mutation status) and in combination with nivolumab in patients with *BRAF* wild type disease. Taken together, the approved indication for ipilimumab monotherapy and the

compendium guidelines noted above, use of the combination of nivolumab and ipilimumab in advanced melanoma could be recommended irrespective of *BRAF* V600 mutation status (and especially after failure of a BRAF inhibitor). On the basis of the established clinical profile of the combination of nivolumab and ipilimumab, combining these agents with targeted therapies intended to reduce the toxicity associated with this combination is warranted.

Further details regarding the clinical experience with ipilimumab as SA and in combination with nivolumab may be found in the current version of the approved Yervoy® and Opdivo® labels, respectively.

4.3 Clinical Experience

4.3.1 TAK-580 (MLN2480)

The clinical activity, safety, pharmacokinetics (PK), and pharmacodynamics of oral SA TAK-580 has been evaluated in a phase 1, multicenter, open-label dose-escalation trial in patients focusing on specific melanoma tumor genotypes in the dose expansion phase. The maximum tolerable doses (MTDs) for an every other day (QOD) continuous dosing schedule and for a once weekly (QW) dosing schedule was determined to be 200 mg QOD and 600 mg QW, respectively. In the dose expansion phase of the QOD schedule, clinical activity was observed in BRAF mutation-positive patients with prior exposure to MAP kinase inhibitor therapy (17% ORR, n=6) or naïve to prior MAP kinase inhibitor therapy (54% ORR, n=14). Clinical activity was also observed in *NRAS* mutation-positive patients naïve to prior MAP kinase inhibitor therapy (7% ORR, n=14) consistent with single agent activity reported with MEK inhibitor therapy. As of 13 October 2015, an expansion cohort examining the QW schedule in *NRAS* mutation-positive melanoma is open and enrolling patients. No clinical data is available from the expansion cohort; however, clinical activity has been reported in the dose escalation phase in 3 patients with *BRAF* mutation-positive thyroid carcinoma.

As of 13 October 2015, the most commonly reported AEs in patients receiving 200 mg QOD (n=79) were rash (combined terms), followed by anemia and fatigue; constipation and nausea were also noted. The majority of these AEs were grade 1 or 2 with grade 3 or 4 AEs of rash and anemia each reported in 14% of patients and grade 3 or 4 elevation of blood creatine kinase (CK) reported in 6% of patients. In patients receiving 600 mg QW dose (n=13) the most commonly reported AEs were also fatigue, nausea, constipation, and anemia. The frequency of grade 3 or 4 AEs appears lower with no grade 3 or 4 rash or elevation of blood CK reported and grade 3 or 4 AEs of anemia or fatigue reported in 8% of patients. However, grade 3 or 4 dyspnea has been reported in 25% patients (with lung metastases) receiving the QW dose schedule.

As of 13 October 2015, preliminary PK data from are available from 45 patients who received 20 to 280 mg QOD and from 17 patients who received 400 mg to 800 mg QW in Study C28001. Following administration of multiple oral doses of TAK-580, peak TAK-580 concentration (C_{max}) was observed at 3 hours postdose (range: 1-8 hours) on Day 21 (QOD). Steady state exposures ($AUC_{0\text{-}48hrs}$) increased in an approximately proportional manner over the 20 to 280 mg dose range based on preliminary assessment of dose proportionality using a power model analysis. Overall mean accumulation following 21 days of QOD dosing was 2.5 fold (coefficient

of variation [CV]: 25%, range: 33–81 hours). Once weekly (QW) administration demonstrates a dose-related increase in C_{max} and AUC following dose escalation from 400 to 800 mg. Minimal to no apparent accumulation has been observed after repeated QW dosing, consistent with the longer 1-week duration between doses.

As of 13 October 2015, 107 serious adverse events (SAEs) were reported in approximately 50% of patients (74 out of 152) who received at least 1 dose of TAK-580. Twenty-five SAEs considered related to TAK-580 were reported in 11% of patients (17 out of 152). The most frequent TAK-580-related SAEs were reported in skin in 8 patients, including 7 rashes and 1 psoriasis. Other TAK-580-related SAEs by System Organ Class (SOC) that occurred in 2 or more patients included Cardiac (3 patients, 1 each of cardiac failure, ejection fraction decrease, and atrial fibrillation), Respiratory (3 patients, 2 with acute respiratory failure and 1 dyspnea), Hepatobiliary (3 patients, 2 hyperbilirubinemia and 1 elevated AST), Blood (2 anemia), Renal (2 acute renal injury), and Gastrointestinal (2 constipation).

Exposure-AE analysis of QOD dosing supported a greater incidence of 2 AEs (acneiform rash and CK elevation associated with MAPK pathway inhibition at higher TAK-580 exposures), suggesting increased MAPK pathway inhibition at higher exposures, which would be consistent with pan-RAF inhibition. Simulations of QW dosing regimen indicated that TAK-580 dosing to 700 mg QW could be expected to offer the same total cycle dose/exposure of TAK-580 as the 200 mg QOD dosing. The initial experience with the 600 mg QW MTD schedule confirms >48 hours continuous exposure above a plasma concentration at steady state (C_{ss}) for pan-RAF inhibition and exposure >C_{ss} required for *BRAF* mutation-positive inhibition throughout the QW dosing interval.

Tumor biopsies pre- and post-TAK-580 treatment from 18 evaluable patients who were enrolled into the QOD melanoma expansion cohorts were evaluated for pERK and BIM. Patients with *BRAF* mutation-positive melanoma (N=6) and patients with *NRAS* mutation-positive melanoma (N=5) showed evidence of on-target MAPK pathway inhibition with decreases of more than 40% of pERK in a majority of samples compared to baseline. BIM was upregulated in both *BRAF* mutation-positive melanoma and in *NRAS* mutation-positive melanoma, indicating that TAK-580 induces pro-apoptotic signaling in MAP kinase dysregulated disease. Similar studies are ongoing in which tumor biopsies are obtained from *NRAS* mutation-positive melanoma patients receiving QW dosing of TAK-580.

On the basis of nonclinical and preliminary clinical data to date, the demonstrated safety of TAK-580 QW enables combination with a SA immune checkpoint inhibitor. Patients should be monitored for the TAK-580-associated AEs of rash and anemia for which treatment interruption and supportive care may be indicated. Furthermore, cardiac AEs (cardiac failure, ejection fraction decrease, and atrial fibrillation) have been reported with TAK-580, warranting careful cardiac assessment during screening and cardiac monitoring while receiving TAK-580 in this study.

Further details regarding the clinical experience with TAK-580 may be found in the current edition of the TAK-580 IB.

4.3.2 TAK-202 (MLN1202; plozalizumab)

TAK-202 has been tested in 5 completed clinical studies that included 2 phase 1 trials and 3 phase 2 trials. A total of 187 subjects were treated with TAK-202, including 60 healthy subjects, 23 subjects with rheumatoid arthritis (RA), 54 subjects with atherosclerotic cardiovascular disease (ASCVD), and 50 subjects with relapsing-remitting multiple sclerosis (RRMS). TAK-202 has been tested in humans up to 10 mg/kg IV infusion as a single dose and up to 8 mg/kg in multiple doses. In a multiple dose study, patients with RA received 3 IV doses ranging from 0.5 to 4 mg/kg dosed Q2W. In another multiple dose study, patients with RRMS received 5 IV doses of either 4 or 8 mg/kg (first 3 doses Q15D and last 2 doses Q30D). This is the dose schedule selected for this oncology trial based on targeting a continuous CCR2 occupation >90% during the whole treatment period.

On the basis of data from CCR2 knockout mice, prolonged CCR2 inhibition could result in increased vulnerability to infections and/or difficulty in resolving an infection, particularly those infections that involve a granulomatous response. Overall, generally mild treatment-emergent adverse events (TEAEs) and at comparable frequencies have been noted in both TAK-202- and placebo-treated subjects, and without evidence of dose-related trends in type or frequency. AEs that led to study drug discontinuation were reported in 2 subjects administered TAK-202 for dermatitis allergic and erythema, rash, and rash maculo-papular.

The clinical data in these 5 studies suggest that TAK-202 is well tolerated at all evaluated doses and when given as multiple infusions. No MTD has been defined due to the absence of dose-limiting toxicities (DLTs). Based on the heterogeneous pool of subjects evaluated to date, the following events in subjects treated with TAK-202 are considered expected events: rash, headache, influenza-like illness, and monocyte count decreased. There has been no evidence of serious infections or cell depletion; however, administration of TAK-202 has been associated with mild reductions in blood monocyte count, which were stable during dosing and returned to normal after discontinuation of study drug. The incidence of any infusion or allergic reactions has been low. Upon administration of TAK-202, serum levels of MCP-1, the ligand for CCR2, increased in a dose-dependent manner in both healthy subjects and patients with RA. MCP-1 levels returned to baseline as TAK-202 was cleared and CCR2 became desaturated. Levels of other serum inflammatory proteins were measured and did not change, and there were no safety consequences of the temporary elevation of serum MCP-1.

In general, TAK-202 exhibited typical nonlinear characteristics of mAb PK with decreasing clearance (CL) as dose increased, suggesting a saturable CL process, and a small constant apparent volume of distribution at steady state (V_{ss}).

Further details regarding the clinical experience with TAK-202 may be found in the current edition of the TAK-202 IB.

4.3.3 Vedolizumab (Entyvio®)

Vedolizumab IV has demonstrated statistically significant and clinically relevant evidence of effectiveness in multiple completed clinical studies in subjects with moderately to severely active UC or CD. Efficacy has been demonstrated in a broad population of patients with UC or CD,

including subjects who have failed previous therapies such as corticosteroids, immunomodulators, and TNF-α antagonists, as well as in subjects who were primary failures of TNF-α antagonist treatment.

In subjects with moderately to severely active UC (GEMINI I), vedolizumab 300 mg administered as an IV infusion at Weeks 0 and 2 (induction) followed by either Q4W or Q8W administration from Week 6 through Week 52 (maintenance) induced a statistically-significant increase in rates of clinical response at Week 6 and clinical remission at Week 52 in induction responders randomized to vedolizumab compared with those randomized to placebo.

In subjects with moderately to severely active CD (GEMINI II), vedolizumab 300 mg administered as an IV infusion at Weeks 0 and 2 (induction) followed by either Q4W or Q8W administration from Week 6 through Week 52 (maintenance) demonstrated statistically significant differences in efficacy compared with placebo for both the induction phase and maintenance phase.

In GEMINI III, vedolizumab (300 mg at Weeks 0, 2, and 6) was administered IV as induction therapy to subjects with moderately or severely active CD who had failed conventional therapies, including TNF-α antagonists. Treatment differences favoring vedolizumab IV were observed for the overall population and in the subgroup of subjects who were TNF-α antagonist naïve although these were not statistically significant.

In phase 1 and 2 clinical studies, there was no consistent evidence of any dose-toxicity relationships, and vedolizumab IV was well tolerated. The majority of the safety data is from 3 placebo-controlled, phase 3 clinical studies that evaluated the safety of vedolizumab IV for up to 12 months in subjects with UC. In addition, an interim safety assessment was conducted for an ongoing, long-term open-label extension study in which subjects are administered vedolizumab IV Q4W. A similar safety profile was observed in subjects who received vedolizumab IV Q4W or Q8W.

In the pivotal phase 3 studies, the most common (≥5% and at a higher incidence than placebo) adverse reactions (ADRs) in subjects administered vedolizumab IV were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache, and cough. Most SAEs were related to exacerbations or complications of the underlying UC or CD. For those infections that were reported more frequently in vedolizumab-treated subjects, the sites of these infections correlate with the known tissue distribution of MAdCAM-1 binding sites. Anal abscess, abdominal abscess, and gastroenteritis were the most frequently reported serious infections. Extraintestinal infections (bronchitis, pneumonia, urinary tract infection, sepsis) occurred at low frequency (<1%). Results from the clinical program to date do not suggest an increased risk for malignancy with vedolizumab IV treatment. No cases of progressive multifocal leukoencephalopathy (PML) were reported in these studies (Section 10.7 for further information on PML).

Overall, 4% of subjects treated with vedolizumab IV and 3% of subjects treated with placebo experienced a TEAE defined by the investigator as an infusion-related reaction (IRR). The majority of IRRs were mild or moderate in intensity, and few resulted in discontinuation of study

treatment. Observed IRRs generally resolved with no or minimal intervention following the infusion.

In summary, precaution should be exerted with the possibility of the following AEs: hypersensitivity reactions (including anaphylaxis) for which treatment with vedolizumab IV may be delayed or discontinued; infections: treatment with vedolizumab IV is not recommended in patients with active, severe infections until the infections are controlled; ≥ Grade 2 colitis/diarrhea for which treatment with vedolizumab IV should be delayed (or discontinued) with serial cultures of stool performed to rule out infectious causes. Finally, although no cases of PML have been observed with vedolizumab IV in clinical trials, John Cunningham virus (JCV) infection resulting in PML and death have occurred in patients treated with another integrin receptor antagonist. A risk for PML cannot be ruled out and therefore patients should be monitored for any new or worsening signs or symptoms.

Further details regarding the clinical experience with vedolizumab may be found in the current edition of the vedolizumab IB.

4.4 Rationale for the Proposed Study

This study seeks to advance the hypothesis that an anti-PD-1 mAb (nivolumab) in combination with other therapies that either 1) target the immunosuppressive tumor microenvironment (beyond additive/synergistic activation of cytotoxic T-cells) or 2) prevent/ameliorate GI irAEs associated with checkpoint inhibition, achieving (or exceeding) the clinical activity observed with combination T-cell checkpoint inhibition (anti-PD-1 + anti-CTLA-4) but with an improved safety profile. Further, this study will evaluate whether novel SA therapies (TAK-580 and TAK-202) influence the tumor microenvironment prior to T-cell checkpoint inhibition and whether changes observed (by immunohistochemistry [IHC], gene expression and cytokine/chemokine profiling) to the tumor microenvironment may be predictive for antitumor efficacy with the novel combination therapy. The novel targeted therapies to be evaluated in combination with either SA T-cell checkpoint inhibition (nivolumab) or combination T-cell checkpoint inhibition (nivolumab + ipilimumab) include:

4.4.1 Arm 1: Nivolumab plus TAK-580 (MLN2480), an oral pan-RAF inhibitor

MAPK pathway dysregulation is common in advanced melanoma. Up to 50% of melanoma harbor the V600 mutation in *BRAF* with another 15% with *NRAS* mutations. Preclinical in vivo studies in *BRAF* mutant melanoma show treatment with MAPK pathway inhibitors (BRAFi ± MEKi) results in immunosensitization (increased melanoma antigen and MHC expression) with tumor-specific effector cell activation [12]. PD-L1 expression was found to be increased suggesting an adaptive immune resistance mechanism induced by the presence of T-effector cells. Clinical studies are now ongoing to evaluate the combination of MAPK pathway inhibition with anti-PD-1 therapy not only in *BRAF* mutant disease but in melanoma harboring mutations or activation in *NRAS*. However, there are limitations to this strategy of combining BRAF + MEK inhibitor or using MEK inhibition alone. The overlapping/additive toxicities as well as drug-mediated CRAF re-activation of the MAPK pathway, may reduce the therapeutic benefit of

an anti-PD-1 + MEKi combination [13]. As a pan-RAF inhibitor with a long half-life, TAK-580 could overcome the potential biological and pharmacological limitations of MEK inhibition in melanoma. TAK-580 QW may result in greater MAPK pathway inhibition than MEK inhibitors with better tolerability and without the potential for drug-induced CRAF re-activation of the MAPK pathway.

BRAF inhibitor or the combination of BRAF and MEK inhibitors were shown to increase CD8+ T cell infiltration in the tumor in a mouse melanoma model and in posttreatment melanoma biopsies in a clinical study [14,15]. Therefore the effects of TAK-580 on the tumor microenvironment (including immune cell infiltration), as a monotherapy and in combination with anti-PD-1 will be evaluated in Arm 1. The hypothesis is that through increasing cytotoxic T cell infiltration, TAK-580 in combination with the anti-PD-1 mAb nivolumab will demonstrate superior clinical benefit (in both PD-L1 positive and negative tumors) compared to either TAK-580 or nivolumab SA, with a better safety profile (relative to other combinations of checkpoint inhibitors + MAPK inhibitors) in patients with melanoma whose disease has MAPK pathway dysregulation.

4.4.1.1 Rationale for TAK-580 Starting Dose and Schedule

There are no readily apparent risks for clinically meaningful mutual PK drug-drug interactions (DDIs) between TAK-580 and nivolumab on the basis of in vitro metabolism data and physiologically relevant exposures achieved at clinical SA doses. Therefore, dose escalation up to the TAK-580 SA MTD of 600 mg once-weekly (QW) will proceed, as tolerated. During the safety lead-in dose-escalation phase, the starting dose of TAK-580 will be 400 mg QW. This starting dose, 33% below the unit dose of TAK-580 SA MTD (600 mg QW continuous) as determined in Study C28001, is predicted to have pan-RAF inhibitory activity at C_{max} and *BRAF* positive-mutation inhibition throughout the dosing interval. TAK-580 administration may be changed to a lower starting dose (ie, 300 mg QW) if a TAK-580 dose (≥400 mg QW) administered continuously is not tolerated.

4.4.2 Arm 2: Nivolumab plus TAK-202 (MLN1202), an anti-CCR2 monoclonal antibody

CCR2 is expressed primarily on monocytes as well as a subset of memory T cells, basophils, immature dendritic cells, and some macrophages. In the setting of normal immune surveillance, through interaction with the primary CCR2 ligand MCP-1 (also known as CCL2), $CCR2^+$ cells from the peripheral blood are recruited to sites of active inflammation and are primed to release proinflammatory cytokines, tissue-damaging proteolytic enzymes and reactive oxygen radicals. However, as part of the immune escape mechanism of cancer, tumors secrete factors such as MCP-1 that cause an imbalance in the homing mechanisms of myeloid precursors. Circulating myeloid derived suppressor cells (MDSCs) overexpress the CCR2 receptor and are preferentially recruited to the tumor microenvironment where they suppress T cell-mediated production of interferon gamma (IFNγ) and effector T-cell proliferation (so called M2-polarization) [16,17].

Arm 2 will evaluate the effects of TAK-202 on the tumor microenvironment as monotherapy and in combination with anti-PD-1 nivolumab. The hypothesis is that TAK-202 will augment the

clinical benefit of nivolumab in patients with melanoma by reducing the immunosuppressive M2 macrophage population, including those at higher risk (based on pretreatment biopsy) for a sub-optimal response to SA anti-PD-1 therapy.

4.4.2.1 Rationale for TAK-202 Starting Dose and Schedule

There are no readily apparent risks for clinically meaningful mutual PK DDIs between TAK-202 and nivolumab on the basis of in vitro metabolism data and physiologically relevant exposures achieved at clinical SA doses. Therefore, dosing of nivolumab will be at the recommended dose and schedule of 3 mg/kg IV Q2W until toxicity, disease progression, or any other discontinuation criterion is met. Dose-escalation of TAK-202 will proceed up to 8 mg/kg, the highest multiple dose evaluated in the clinic in patients with multiple sclerosis, as tolerated.

The reference study M120204-063 evaluated the safety and efficacy of TAK-202 in subjects with RRMS who were administered 5 IV infusions of TAK-202 at 4 or 8 mg/kg/dose. TAK-202 at the assigned dose was administered Q15D for the first 3 doses and Q30D for the remaining 2 doses. Results of the PK-PD modeling (based on sparse PK and PD samples) suggest that nearly complete (at least 90%) CCR2 saturation occurred at serum TAK-202 concentrations of approximately 15 μg/mL or higher. On average, TAK-202 at the 8 mg/kg dose achieved the target concentration (15 μg/mL) and receptor saturation (90%) for the entire treatment period whereas trough concentrations of TAK-202 in the group dosed at 4 mg/kg fell below the target at the end of the treatment period. Increases in serum MCP-1 levels and reversible reductions in circulating monocytes were also observed in each dose group. No DLT or safety concerns were detected in patients treated at 8 mg/kg.

During the safety lead-in dose-escalation phase, the starting dose of TAK-202 will be 4 mg/kg per infusion. This starting dose is 50% below the maximum multi-dosing of SA TAK-202 evaluated clinically. TAK-202 administration may be changed to a lower starting dose (ie, 2 mg/kg) if the 4 mg/kg TAK-202 dose is not tolerated.

4.4.3 Arm 3: Nivolumab plus Ipilimumab plus Vedolizumab, an anti-α4β7 monoclonal antibody

The α4β7 integrin is expressed on the surface of a discrete subset of memory T-lymphocytes that preferentially migrate into the GI tract. MAdCAM-1 is mainly expressed on gut endothelial cells and plays a critical role in the homing of T-lymphocytes to gut lymph tissue. The interaction of the α4β7 integrin with MAdCAM-1 has been implicated as an important contributor to the chronic inflammation that is a hallmark of UC and CD. Vedolizumab is a humanized mAb that specifically binds to the α4β7 integrin and blocks the interaction of α4β7 integrin with MAdCAM-1 and inhibits the migration of memory T-lymphocytes across the endothelium into inflamed GI parenchymal tissue. Vedolizumab does not bind to or inhibit function of the α4β1 and αEβ7 integrins and does not antagonize the interaction of α4 integrins with vascular cell adhesion molecule-1 (VCAM-1).

Immune-related AEs associated with checkpoint inhibition reflect non-specific immune activation resulting in a pattern of tissue-specific inflammation. Target organs of this activation are lungs, colon, kidney, thyroid, pituitary gland and others (Section 8.8).

In a recent meta-analysis with 2774 patients receiving checkpoint inhibitors (CTLA-4 and/or PD-1), diarrhea frequency was 11% to 51% and colitis 1% to 16%. The relative risk (RR) of all-grade diarrhea was 1.64 (95% CI: 1.19–2.26; p=0.002). For colitis, it was 10.35 (95% CI: 5.78–18.53; p<0.00001)[18]. In another meta-analysis (N=1571) assessing ipilimumab-associated diarrhea, the overall incidence of all-grade diarrhea was 41.6% (95% CI: 33.6%– 50.0%). In this analysis, the overall incidence of Grade ≥3 diarrhea was 8.4% (95% CI: 5.5%–12.7%). Ipilimumab RR for all-grade diarrhea is 1.63 (95% CI: 1.37–1.97; p<0.001) and for Grade ≥3 diarrhea is 2.19 (95% CI: 1.11–4.34; p=0.025) [19]. The median time for the occurrence of Grade 2/3 colitis with ipilimumab is 6.5 weeks. In a recent phase 3 trial in patients with melanoma who were treated with the combination of nivolumab plus ipilimumab, the incidence of diarrhea was 44% with 9% Grade 3/4. Colitis was diagnosed in 12% of patients with 8% Grade 3/4 [11]. Enterocolitis is more frequently associated with CTLA-4 inhibition than with PD-1 inhibitors.

Irrespective of grade, nearly half of the patients with irAEs receiving ipilimumab (monotherapy or in combination) required treatment interruption and immune modulatory medication (systemic steroids ± infliximab). Half of these irAEs leading to treatment interruption/discontinuation are diarrhea/colitis [20]. Current guidelines for the management of colitis/diarrhea indicates treatment interruption if it is ≥Grade 2 and starting prednisone if continues at Grade 2 longer than 5 days or immediately if ≥Grade 3. Treatment can only be re-started after symptom improvement and steroids tapering over 1 month. All this creates major difficulties in treatment compliance. Currently systemic steroids at 1-2 mg/kg and infliximab are used empirically without clinical trial supportive evidence. Only budesonide –a corticosteroid indicated to treat inflammatory bowel disease (IBD)- has been evaluated in a randomized clinical trial to prevent ipilimumab-induced colitis with negative results [21]. Despite this treatment algorithm, AEs resulting in treatment discontinuation occurred in 36% of patients receiving combination therapy including 17% of patients experiencing toxicity-associated treatment discontinuation due to GI irAEs [20].

In this study, Arm 3 will evaluate the safety and activity of vedolizumab in combination with the anti-PD-1 mAb nivolumab and the anti-CTLA-4 mAb ipilimumab. The combination of nivolumab plus ipilimumab is now approved for the treatment of patients with metastatic melanoma, with the combination showing greater activity than either drug alone. However, it also displays a higher rate of irAEs and treatment discontinuations. The hypothesis for Arm 3 of this study is that the specificity of vedolizumab restricts its activity to the GI tract and gut lymph tissue and its use in the prevention of GI irAEs will reduce treatment-associated GI irAEs resulting in clinical benefit with a better safety profile in patients with advanced melanoma receiving checkpoint inhibitor combination therapy.

Recent research suggests a novel inter-relationship among the colonic microbiome, anti-tumor immunity, and the efficacy of anti-CTLA-4 or anti-PD-1 inhibitors [22-25]. Furthermore, the

composition of fecal microbiota correlates with susceptibility to anti-CTLA-4 induced colitis [26]. Therefore, the stool microbiome of patients enrolled in Arm 3 will be analyzed pre- and post-treatment to assess whether changes in the microbiome correlates with safety (diarrhea/colitis and other irAEs) and/or antitumor activity.

4.4.3.1 Rationale for Vedolizumab Starting Dose and Schedule

Diarrhea and colitis with checkpoint inhibitors is an acute event that is limited to the time of treatment, therefore the goal for the addition of vedolizumab is to prevent enterocolitis without decreasing antitumor effect. Contrary to IBD, where the treatment goal is to achieve long-term control in a chronic life-time condition in drug-induced immune colitis, the objective is to achieve the pharmacodynamic target as soon as possible. For this reason in this trial vedolizumab will be administered with a loading dose/schedule different from that approved for IBD, using instead a higher dose, increased frequency, but with reduced treatment duration to 4 infusions covering the period when nivolumab and ipilimumab are administered together.

In a randomized phase 2 study of vedolizumab versus placebo in patients with UC, 37 patients received vedolizumab at doses of 2, 6, and 10 mg/kg (approximately equivalent to 140, 420, and 700 mg per dose, respectively), on Days 1, 15, 29, and 85. The treatment was safe and well tolerated at all doses tested. In this study, serum trough concentration at Week 4 for 10 mg/kg was 93 µg/mL, and receptor saturation as measured by MAdCAM-1 FC assay showed that it was maintained throughout the treatment. The lower dose of 2 mg/kg showed loss of receptor saturation after Day 150 whereas higher doses maintained receptor saturation until Day 197. In the phase 3 IBD trial, during induction, vedolizumab was administered at 300 mg on Weeks 0 and 2. PK analysis indicated that for the Q8W regimen at Week 6 mean serum trough concentration was greater than 35 µg/mL and this was associated with increased efficacy during the induction phase. During maintenance treatment, vedolizumab serum trough concentrations above 13 µg/mL were associated with clinical remission.

The target dose level (DL2) in this trial consists of a loading dose that, according to modeling, can achieve target PK and pharmacodynamic steady state early in treatment for this patient population. A loading dose of vedolizumab IV at 450 mg (equivalent to 6.5 mg/kg) will be administered on Weeks 1, 3, and 5. A fourth dose of vedolizumab IV at 450 mg on Week 13 will be administered to maintain serum trough concentrations above 15 µg/mL through Week 21. To evaluate potential DLTs with the combination of ipilimumab, nivolumab, and vedolizumab during the safety lead-in dose-escalation phase, the planned DL1 (starting dose) of vedolizumab IV is 200 mg administered on the Weeks previously indicated.

4.4.4 Rationale for Tumor Characterization

Fresh tumor biopsies, pre- and post-SA treatment and post-combination treatment with checkpoint inhibitors will be requested from patients participating in Arms 1 and 2 with the goal of broadly characterizing the factors underlying each patient's sensitivity/resistance to the respective treatment combination. In addition, an optional biopsy will be requested from patients who initially respond to study treatment and then relapse to identify the mechanism underlying the development of resistance.

Putative biomarkers of sensitivity to checkpoint inhibitors have been identified using IHC that include PD-L1 expression on tumor cells and the presence of tumor infiltrating lymphocytes. Association between specific biomarkers and PD-1 checkpoint blockade has been identified [27,28]. Patient tumor samples will be tested to determine whether the combination agents only demonstrate increased efficacy within those patients whose tumors would already predispose them to sensitivity to checkpoint inhibition or in patients not predicted to benefit from SA PD-1 inhibition. Results of these analyses will contribute to the development of patient selection hypotheses for these combinations.

One of the exploratory objectives proposed for this study is to Company Confidential Information [redacted]

4.5 Potential Overlapping Toxicities and Risk of Drug-Drug Interactions

4.5.1 TAK-580 plus Nivolumab

Based on review of preliminary SA clinical data, no major safety concerns were identified for the combination of TAK-580 + nivolumab. Potential overlapping toxicities of the combination include rash, and pruritus. Rash is reported as the most common ADR (21%) described in patients with melanoma treated with nivolumab, with Grade 3/4 incidence of only 0.4% [29]. Rash (all terms) has been reported in 47% of the 78 patients receiving TAK-580 200 mg QOD, with Grade 3/4 incidence of 17% [30]. Rash (all terms) led to discontinuation of TAK-580 in 4 of 103 patients who had received at least 1 dose of TAK-580 (TAK-580 IB Edition 5 Table 5-16). In patients with melanoma, pruritus was reported in 19% of patients (all Grade 1/2) treated nivolumab and in 16% of patients who received TAK-580 200 mg QOD (all Grade 1/2). Cutaneous toxicity is readily identifiable and manageable with standard supportive care along with treatment interruptions and dose modifications in the setting of Grade 2 or higher toxicity (TAK-580 IB Edition 5 Table 5-11). Refer to Section 8.4.3.1 for interruption/modification guidelines for TAK-580 and management guidelines for potential immune-mediated skin AEs as outlined in Section 8.8.6.

In vitro, TAK-580 is metabolized by aldehyde oxidase and multiple cytochrome P-450 (CYP) enzymes. Based on in vitro and clinical PK data, TAK-580 is not expected to produce clinically meaningful inhibition or induction of major CYP enzymes at clinical doses. Similarly, nivolumab is not a clinically meaningful perpetrator of metabolic/transporter-based DDIs. Therefore, when TAK-580 and nivolumab are administered in combination, the risk for clinically meaningful DDIs is considered low.

4.5.2 TAK-202 plus Nivolumab

Based on review of preliminary SA clinical data, no major safety concerns were identified for the combination of TAK-202 and nivolumab. The main potential overlapping toxicity is rash, reported as the most common ADR (21%) described in patients with melanoma treated with nivolumab, with Grade 3/4 incidence of only 0.4%. Dermatitis allergic and erythema, rash, and rash maculo-papular, AEs leading to discontinuation of TAK-202, were reported in 2 subjects. Cutaneous toxicity is readily identifiable and manageable with standard supportive care.

Infusion-related reactions are another potential overlapping toxicity as both TAK-202 and nivolumab are mAbs; however, because both drugs are humanized, the likelihood of IRRs is considered rare. Depending on the severity, IRRs can manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. Infusions of TAK-202 and nivolumab are to be administered sequentially to reduce the likelihood of IRRs. Grading and management of IRRs are detailed in Section 8.8.1.

Nonclinical PK drug interaction studies have not been performed. Based upon its pharmaceutical properties, there is a low likelihood of DDIs with TAK-202. No clinical studies have been conducted with TAK-202 to evaluate DDIs.

4.5.3 Vedolizumab Plus Nivolumab Plus Ipilimumab

Based on review of SA clinical data with vedolizumab, and the published safety information with the combination nivolumab + ipilimumab, no major safety concerns were identified for the triple combination of vedolizumab + nivolumab + ipilimumab. There is potential for hypersensitivity reactions when combining these 3 mAbs; however, they have rarely been described for any of these 3 humanized mAbs as SA or with the combination of nivolumab plus ipilimumab. Depending on the severity, IRRs can manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. Vedolizumab, nivolumab, and ipilimumab infusions are to be administered sequentially and only if there are no symptoms of infusional reactions at the end of the previous infusion. Grading and management of IRRs are detailed in Section 8.8.1.

Nonclinical PK DDI studies of the combination of the 3 mAbs are planned, but have not yet been performed. However, on the basis of their pharmaceutical properties, there is a low likelihood of DDIs among them.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objective in the dose escalation phase plus Part 1 limited cohort expansion phase is to determine the recommended Part 2 expansion phase dose based on the initial safety profile of the combination treatments in each arm when administered to patients with advanced melanoma.

The primary objective in the Part 2 expansion phase is to determine the initial antitumor activity of each combination arm.

5.1.2 Secondary Objectives

The secondary objective in the dose escalation phase plus Part 1 limited cohort expansion phase is to evaluate preliminary antitumor activity in each combination treatment arm.

The secondary objective in the Part 2 expansion phase is to further evaluate the safety in each combination treatment arm in the expanded patient population. For Arm 3 a specific secondary objective is to evaluate the impact of vedolizumab in frequency and severity of diarrhea and colitis.

5.1.3 Additional Objectives

The additional objectives are:

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-
-
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5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoint in the dose escalation phase plus Part 1 limited cohort expansion phase is the frequency of DLTs as defined in the protocol (Section 8.2). This will be the primary endpoint

to define the recommended Part 2 expansion dose; however secondary safety endpoints will be considered for the final dose definition.

The primary endpoint for the Part 2 expansion phase is ORR as measured by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as assessed by the investigator in the different combination arms.

5.2.2 Secondary Endpoints

In the dose escalation phase plus Part 1 limited cohort expansion phase, the secondary efficacy endpoints are ORR, DOR, PFS, and OS. The secondary safety endpoints to define the recommended Part 2 expansion dose are the frequency and severity of TEAEs per National Cancer Institute Common Terminology Criteria (NCI CTCAE) Version 4.03, serious TEAEs, TEAEs meeting DLT definition but happening outside the dose escalation phase, treatment discontinuation rate, and dose modifications.

The secondary efficacy endpoints in Part 2 are time-to-event measures such as DOR, PFS, and OS. The secondary safety endpoints in Part 2 are the frequency and severity of TEAEs, frequency of serious TEAEs, the rates of treatment discontinuation and dose modifications, and the frequency of TEAEs meeting the DLT definition. In Arm 3, specific safety secondary endpoints are the frequency and severity of diarrhea and colitis per definitions in NCI CTCAE Version 4.03.

5.2.3 Additional Endpoints

The additional endpoints are:

[redacted]

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6.0 STUDY DESIGN

6.1 Overview of Study Design

This is an open-label, multicenter, phase 1b umbrella study (currently with 3 arms) in patients with advanced/metastatic melanoma who are eligible to receive either anti-PD-1 or anti-PD-1 plus anti-CTLA-4 therapy. Standard of care treatment is combined with 1 of the following investigational agents: TAK-580 (pan-RAF inhibitor, previously known as MLN2480) in Arm 1, TAK-202 (anti-CCR2 monoclonal antibody, previously known as MLN1202) in Arm 2, and vedolizumab (anti-α4β7 integrin monoclonal antibody, Entyvio®) in Arm 3. Routes of administration, schedules, and dosing regimens are described in Section 8.1.

The trial will enroll in 3 stages:

6.1.1 Dose-Escalation Safety Lead-in Phase

3 + 3 safety lead-in of novel therapy with starting dose level 1 (DL1) below the recommended phase 2 dose (RP2D) as SA for TAK-580 or TAK-202 and below the prescribed dose for vedolizumab in treatment of IBD; in combination with the approved dose and schedule of checkpoint inhibitor therapy (either nivolumab or nivolumab plus ipilimumab). Each combination will be evaluated for DLTs (Section 8.2) through the 1st 8 weeks (6 weeks for Arm 3) of study treatment. If DL1 is tolerable, dose escalation to a second cohort of patients to the SA RP2D (DL2) for TAK-580 and TAK-202 will occur. For vedolizumab, the rationale for DL2 dose selection is detailed in Section 4.4.3.1. Provision for a DL–1 for TAK-580 and TAK-202 is included in case DL1 is not tolerable.

6.1.2 Part 1: Limited Expansion to Further Characterize Safety of the Combination and Obtain Preliminary Clinical Activity

A total of 15 patients (inclusive of dose-escalation safety lead-in patients treated with the same dose) will be enrolled in each arm at the dose and schedule identified to be tolerable in the initial dose-escalation safety lead-in phase. From this population, a safety profile of the combination will be developed (all arms) and initial observations relative to clinical activity and effects of SA versus combination therapy on the tumor microenvironment will be evaluated (Arms 1 and 2 only).

The additional 9 to 12 patients enrolled into the Part 1 expansion phase will continue to be monitored for DLTs similarly to the patients in dose escalation, through regularly scheduled safety review calls with study investigators and regularly scheduled internal safety reviews by the sponsor.

For selection of the Part 2 expansion recommended dose, all available safety (DLTs and other TEAEs defined per NCI CTCAE Version 4.03), dose modifications, and PK information from all patients participating in the dose escalation and the Part 1 limited cohort expansion will be considered.

6.1.3 Part 2: Additional Expansion Based on Initial Clinical Activity

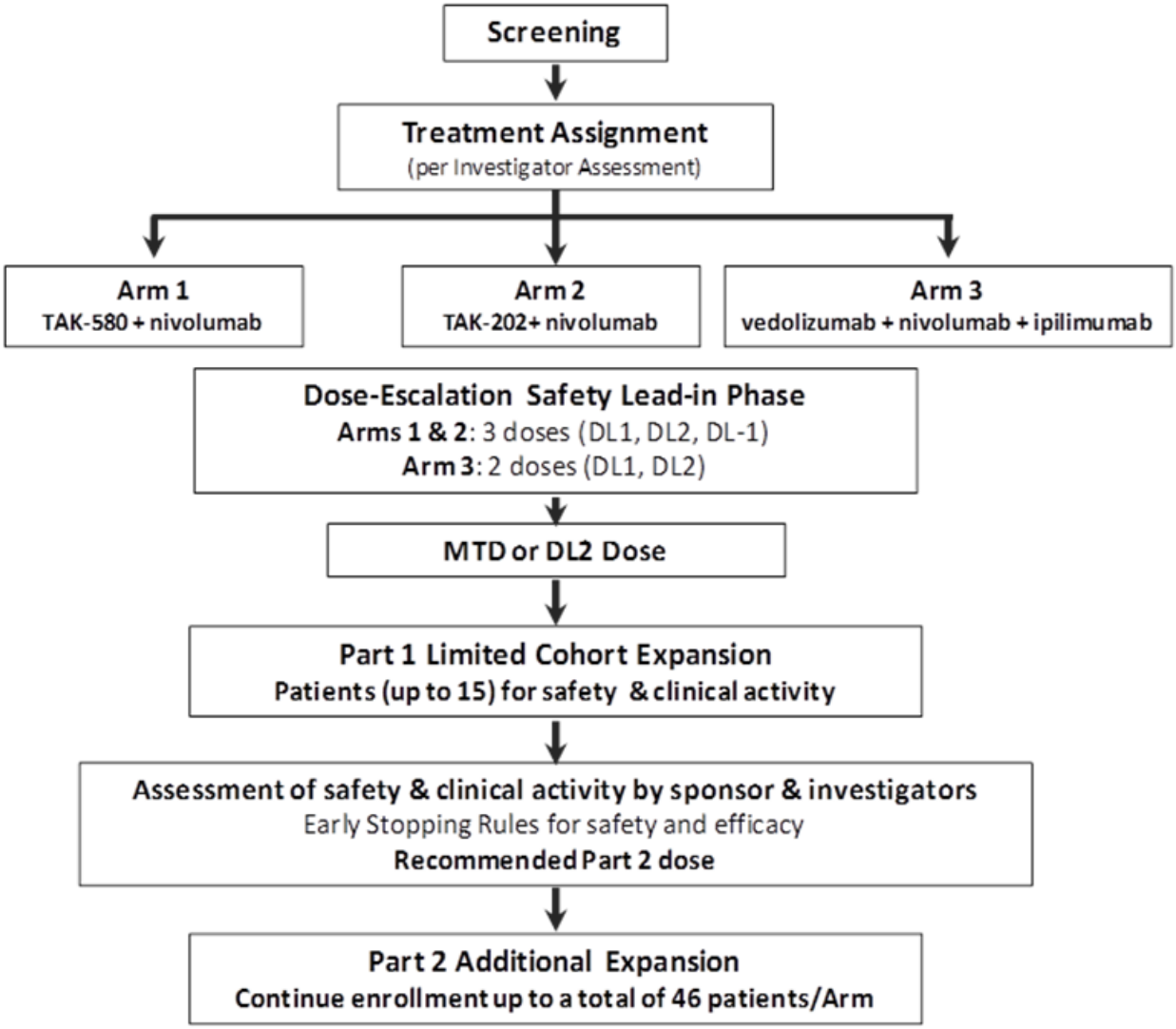
After a minimum of 15 patients have been enrolled in the Part 1 expansion (inclusive of those treated with the same dose in the safety lead-in phase), available safety and efficacy will be evaluated by the sponsor's clinical team and study investigators. If the DLT rate is <33% (ie, fewer than 5 patients with DLT), the cumulative toxicity (including the post-DLT assessment period) is determined to be monitorable and manageable, and if >30% of the evaluable patients present with a partial response (PR) or complete response (CR) at the time of 1st response assessment (12-14 weeks on treatment), enrollment may continue in that arm until a total of 46 patients are treated to further evaluate the safety profile and clinical benefit of the treatment combination.

Additionally for Arm 3, if 2 or more patients present with Grade ≥3 diarrhea or colitis and/or more than 7 patients present with diarrhea/colitis of any grade, Part 2 enrollment will not be initiated.

The trial is not randomized. Patient allocation will be decided by the clinical team. Two main criteria will be followed (1) medical characteristics of the candidate patient that may favor the enrollment in a specific arm (ie, previous treatments, *BRAF* mutation status, suitability for nivolumab plus ipilimumab combination); (2) enrollment efficiency to complete cohorts during dose escalation.

The study will enroll adult patients with advanced melanoma who, in the opinion of the treating physician, are eligible for treatment with either anti-PD-1 monotherapy or with anti-PD-1 plus anti-CTLA-4 therapies. Figure 6.a shows the overall study design.

Figure 6.a Study Design for Study C28003



A total of approximately 156 patients are expected to enroll in this study. Once enrolled, patients in Arms 1 and 2 will be administered a single investigational agent for 2 weeks after which a second biopsy will be performed to assess the pharmacodynamic effects of the investigational agent in the tumor (Section 9.4.16.3). Then, standard-of-care checkpoint inhibitor(s) will be administered (nivolumab in Arms 1 and 2 or nivolumab + ipilimumab in Arm 3). For patients assigned to Arms 1 and 2, a third tumor biopsy will be performed at the end of the initial 8-week period to investigate the effects of the combination treatment in the tumor.

DLTs (defined in Section 8.2 of the protocol) will also be monitored during the Part 2 expansion phase. If the overall DLT rate among patients treated at the same dose is >40% in any arm,

enrollment to this arm will be halted until a thorough analysis of available data allows for a final informed decision.

Patients will receive their assigned SA / study drug combination until they experience disease progression or any other discontinuation criteria (Section 8.4.4). Based on previous experience at assessing response with immune-oncology drugs, subjects experiencing investigator-assessed clinical benefit and tolerating study therapy may continue treatment beyond initial investigator-assessed RECIST Version 1.1-defined progression. To ensure that these patients are not exposed to unreasonable risks by continued use of the investigational agents continuation on treatment is only allowed in the absence of clinical symptoms or signs indicating clinically significant progressive disease (PD), if there is no decline in Eastern Cooperative Oncology Group (ECOG) performance status, and in the absence of rapid PD or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention. Patients for whom there is an approved standard of care still available who continue to receive investigational treatment until confirmation of PD in a subsequent tumor response assessment should be re-consented at the time of the initial documentation of PD to ensure that they are aware of all available alternative effective therapies. Overall, study drug will be discontinued early if there is a negative risk/benefit balance. Treatment will be considered completed at 50 weeks. However, patients who, in the opinion of the investigator, tolerate treatment and have evidence of clinical benefit after 50 weeks may continue treatment with continued monitoring upon prior review and approval by the sponsor project clinician.

Patients will attend the first End-of-Treatment (EOT) visit (EOT 1) 30 days (+10 days) after receiving their last dose of study drug, or prior to the start of subsequent systemic anticancer therapy, whichever occurs first, to permit the detection of any delayed treatment-related AE and the resolution of the ongoing ones. Patients with unresolved treatment-related AEs will continue the periodic safety follow-up until complete resolution or stabilization occurs. Due to the possibility that irAEs can appear more than 30 days after the last dose, patients who have not initiated a subsequent systemic anticancer therapy are scheduled for 2 additional safety visits 60 (±10) days (EOT 2) and 90 (±10) days (EOT 3) after the last dose of study treatment.

Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 12 (±1) weeks from the EOT 1 visit until the occurrence of PD, the start of subsequent systemic anticancer therapy, until 2 posttreatment CT scan evaluations are performed, or the trial (or arm) final cutoff date, whichever occurs first. In addition, patients treated with vedolizumab IV will be specifically evaluated 6 months (±2 weeks) after their last dose of vedolizumab for safety (PML long-term follow-up [LTFU]; in Study Manual) to be compliant with a postapproval regulatory commitment.

After the occurrence of PD or the start of subsequent systemic anticancer therapy, patients will continue to have OS follow-up visits. The OS visits should be conducted every 12 (±1) weeks after documented PD or a new systemic treatment is initiated, until death, until 1 year after the last dose of study drug, or the trial (or arm) final cutoff date, whichever occurs first. The final cutoff date for the clinical study report (CSR) may be conducted after prespecified events (PD

and death) have occurred for the event-driven PFS analysis conducted after all patients enrolled in the study have had the opportunity to complete 50 weeks of treatment. Each treatment arm can be assessed separately if enrollment is completed or is discontinued.

Toxicity will be evaluated according to NCI CTCAE, Version 4.03 [31]. DLTs are pre-specified AEs defined in Section 8.2 that are at least possibly related to the study drugs and happen during the first 8 weeks. DLTs will be assessed throughout all parts of the trial.

AEs will be assessed clinically, and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of each investigational agent alone and in combination with standard of care immunotherapy in each arm.

Company Confidential Information [redacted] lood samples will be obtained at regular times to assess ADA against TAK-202 (Arm 2) and vedolizumab (Arm 3).

Radiological evaluations (computed tomography [CT] scan or magnetic resonance imaging [MRI] as clinically indicated) and clinical measures (using calipers and photographs for visible/palpable lesions) will be employed to assess the status of the patient's underlying disease, and serial blood samples will be collected for tumor-specific markers (if applicable). An evaluation of disease response using RECIST guidelines (Version 1.1) will be performed within 7 days of the start of Week 15 for patients assigned to Arms 1 or 2 or Week 13 for Arm 3 of Study Treatment and then every 12 (±1) weeks while on study.

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6.2 Number of Patients

Approximately 156 patients will be enrolled in this study from approximately 25 study centers in North America and Europe. A patient is considered to be enrolled in the study after receiving 1 dose (even incomplete) of any study drug. Procedures for completion of the enrollment information are described in the Study Manual.

Patients participating in the dose-escalation safety lead-in and Part 1 limited cohort expansion who are withdrawn from treatment during the 1st 8 weeks of treatment (6 weeks for patients assigned to Arm 3) for reasons other than DLTs will be replaced. The DLT-evaluable population consists of all patients in the dose-escalation safety lead-in phase and Part 1 of the expansion phase of the study who either experience DLT during the first 8 weeks of treatment (6 weeks for patients assigned to Arm 3) or who have received at least 6 doses of TAK-580 (Arm 1), 3 doses of the TAK-202 (Arm 2), or 3 doses of vedolizumab (Arm 3), and 3 doses of nivolumab (alone or in combination with ipilimumab), and have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred. Patients discontinued during the Part 2 cohort expansion phase will not be replaced.

6.3 Duration of Study

Patient eligibility for the study will be determined within 28 days before Week 1, Day 1 of dosing.

Patients, including those who achieve a clinical response, may receive combination therapy until they experience disease progression, an unacceptable toxicity occurs, or any other discontinuation criterion is met. Treatment will be considered complete at 50 weeks. After 50 weeks, patients with evidence of clinical benefit in the opinion of the investigator may continue treatment with continued monitoring upon prior review and approval by the sponsor project clinician.

Patients will attend the EOT 1 visit 30 (+10) days after the last dose of study drug or the start of subsequent systemic anticancer therapy, whichever comes first, to permit the detection of any delayed treatment-related AEs and to complete the follow-up of the ongoing ones. Due to the possibility that irAEs can appear more than 30 days after the last dose, patients who have not initiated a subsequent systemic anticancer treatment will attend 2 additional safety visits 60 (±10) days (EOT 2) and 90 (±10) days (EOT 3) after the last dose of study treatment.

PFS follow-up will also be conducted at the site every 12 (±1) weeks from the EOT 1 visit until the occurrence of PD, the start of subsequent systemic anticancer therapy, until 2 posttreatment CT scan evaluations are performed, or the final cutoff date, whichever occurs first. Patients who experience PD on or off study treatment will be followed every 3 months or until final cutoff to assess for OS and for subsequent systemic anticancer therapy. The final data cutoff for the CSR may proceed after prespecified events (PD and death) have occurred for the event-driven PFS analysis conducted after all patients enrolled in the study have had the opportunity to complete 50 weeks of treatment. It will be possible to perform final cutoffs and data analysis for each arm independently in case of premature closure or uneven enrollment.

This study is expected to continue for approximately 36 months.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

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

1. Male or female patients 18 years or older.
2. Histologically confirmed, unresectable Stage III or Stage IV melanoma per the American Joint Committee on Cancer (AJCC) staging system.
3. Patients must be eligible for treatment with nivolumab or nivolumab + ipilimumab at the dose(s) and schedule(s) recommended as standard of care.
4. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (see Appendix D).
5. Adequate bone marrow reserve and renal and hepatic function within 28 days before the first dose of study drug on the basis of the following laboratory parameters:
   - Absolute neutrophil count (ANC) $\geq 1000/mm^3$, platelet count $\geq 75{,}000/mm^3$, and hemoglobin ≥ 8 g/dL (with or without transfusion support).
   - Total bilirubin $\leq 1.5 \times$ the institutional upper limit of normal (ULN) or $< 3.0 \times$ ULN in subjects with Gilbert's syndrome.
   - Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq 3.0 \times$ the institutional ULN ($< 5 \times$ ULN if liver enzyme elevations are due to liver metastases).
   - Creatinine $< 1.5 \times$ the institutional ULN or estimated creatinine clearance using the Cockcroft-Gault formula ≥ 50 mL/minute/1.73 m^2 (Section 9.4.15.3) for patients with serum creatinine concentrations above institutional limits.
6. Suitable venous access for the collection of study-required blood sampling, including PK and pharmacodynamic blood samples.
7. Participation in a previous clinical study will require a washout period before 1st study drug administration:
   - >2 weeks or >5 times the half-life, whichever is shorter, for prior antitumor therapy (chemotherapy, targeted agents, immunotherapy, and radiotherapy) or any investigational treatment.
   - Recovered from all toxic effects of previous therapy or at new baseline (patients with ongoing Grade 1 events from prior therapies will be eligible).
   - Prior radiotherapy must have been completed at least 2 weeks before the first dose of study drug.
8. For Arms 1 and 2 only: Disease accessible for repeat nonsignificant risk biopsies (those occurring outside the brain, lung/mediastinum, and pancreas, or obtained with endoscopic procedures extending beyond the esophagus, stomach or bowel) and willingness to undergo serial tumor biopsies.

9. 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 1 highly effective method of contraception and 1 additional effective (barrier) method of contraception at the same time, from the time of signing the informed consent form (ICF) through 18 weeks after the last dose of TAK-580, TAK-202, or vedolizumab, or for as long as mandated by local labeling for nivolumab or ipilimumab, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
10. 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 TAK-580, TAK-202, or vedolizumab, or for as long as mandated by local labeling for nivolumab or ipilimumab, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject, during the entire study treatment period and through 18 weeks after the last dose of TAK-580, TAK-202, or vedolizumab, or for as long as mandated by local labeling for nivolumab and ipilimumab. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)
11. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

7.1.1 Additional Inclusion Requirements for ARM 1 ONLY (Nivolumab Plus TAK-580)

12. *BRAF* V600 mutation-positive or *NRAS* mutation-positive disease previously untreated with RAF, MEK, or other inhibitors of the MAPK pathway. Patients who have progressed on these agents can still be enrolled in Arms 2 or 3.

7.1.2 Additional Inclusion Requirements for EXPANSION COHORTS ONLY

13. Measurable disease per RECIST guidelines (Version 1.1) and at least 1 nonsignificant risk, non-target lesion accessible for biopsy per the guidelines above.

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

1. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before first dose of study drug, unless the positive pregnancy test is proven to be a false positive.
2. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
3. Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no MRI evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for high doses of systemic corticosteroids that could result in immunosuppression (>10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.
4. Subjects who completed a prior therapy <2 weeks prior to first dose and for whom AEs related to prior therapy had not returned to baseline or improved to Grade 1.
5. Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
6. Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
7. Subjects with history of pneumonitis requiring treatment with steroids; history of idiopathic pulmonary fibrosis (including pneumonitis), interstitial lung disease, drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan; history of radiation pneumonitis in the radiation field (fibrosis) is permitted.
8. Subjects with a diagnosis of immunodeficiency, ie, any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation).
9. Systemic infection requiring IV antibiotic therapy or other serious infection within 14 days before the first dose of study drug. Patients are specifically excluded if they have active, severe infections such as tuberculosis (screening per local practice and epidemiology), sepsis, cytomegalovirus (including CMV colitis), listeriosis, and opportunistic infections (including *C. difficile*) until the infections are controlled.
10. Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the

ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

11. Known, previously diagnosed HIV infection or active hepatitis B or C. Specific screening for chronic viral illness is at the discretion of the site or local institutional review board (IRB).
12. The patient has a history of known serious or severe hypersensitivity reaction to any of the study drugs or its excipients (exclusion criterion for each specific agent/Arm).

7.2.1 Additional Exclusion Requirements for ARM 1 ONLY (Nivolumab Plus TAK-580)

13. Concomitant use or administration of clinically significant enzyme inducers ≤14 days before the first dose of TAK-580 (see Appendix E).
14. Treatment with gemfibrozil (or other strong CYP2C8 inhibitor) within 14 days before the first dose of TAK-580.
15. Left ventricular ejection fraction (LVEF) <50% as measured by echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) within 4 weeks before receiving the first dose of study drug
16. Known GI disease or prior GI procedure that could interfere with the oral absorption or tolerance of the TAK-580.

7.2.2 Additional Exclusion Requirements for ARM 3 ONLY (Vedolizumab Plus Nivolumab Plus Ipilimumab)

17. The patient has an abnormal objective PML checklist (Appendix F).
18. The patient had prior exposure to rituximab, natalizumab, vedolizumab, or alemtuzumab.
19. The patient has a history of any major neurological disorders, including stroke, multiple sclerosis, or neurodegenerative disease.
20. Any live vaccinations within 30 days before study drug administration except for the influenza vaccine.

8.0 STUDY DRUG

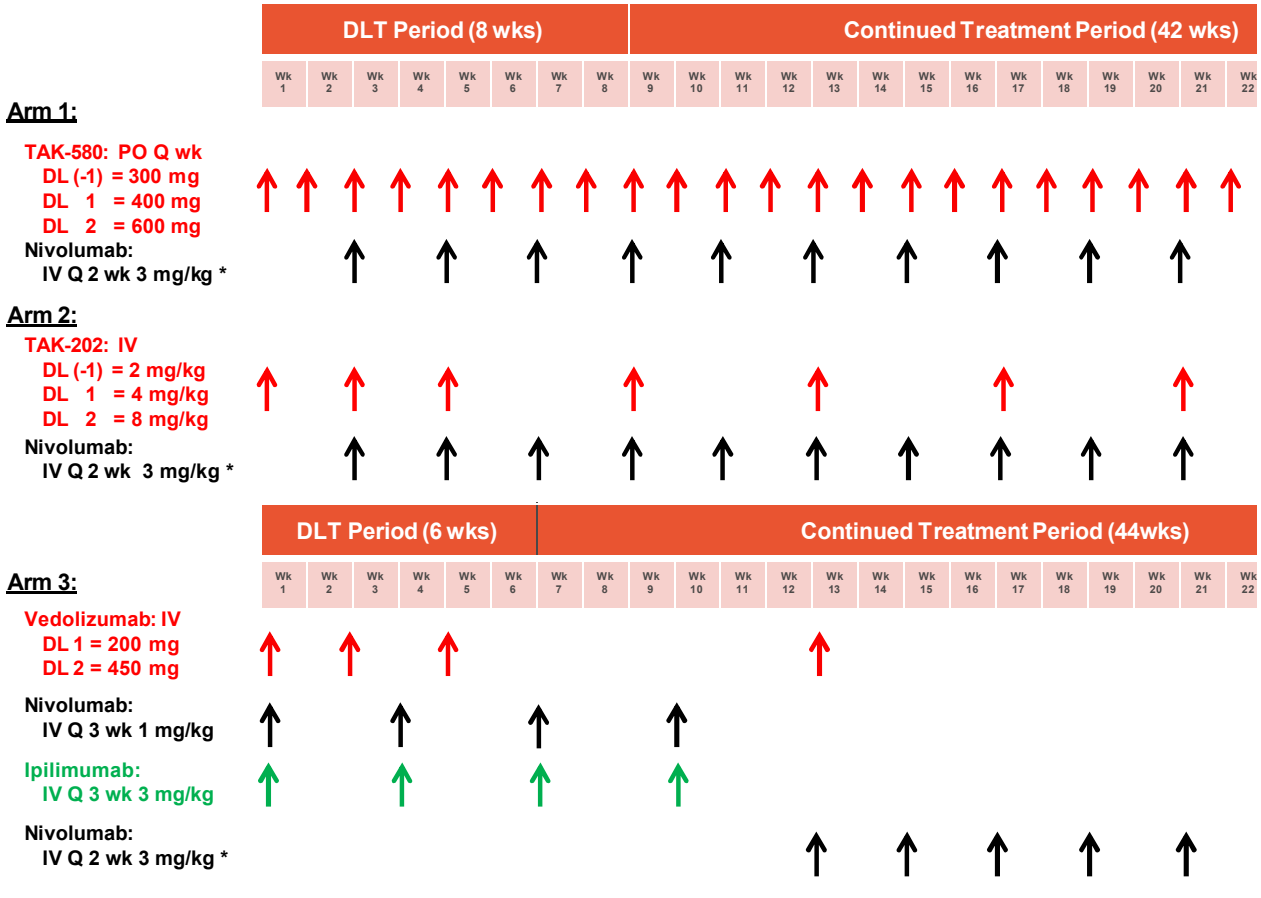
8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented prior to drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

Millennium-sponsored drug products will be provided to the study sites. Commercially available nivolumab (Opdivo®) and ipilimumab (Yervoy®) will be procured or distributed according to the Pharmacy Manual.

Study drugs will be administered according to the schedules outlined in the SOE and shown in Figure 8.a, but may be changed to less frequent dosing should the initial schedule not be tolerated.

Figure 8.a Study C28003 Dosing Regimens in Treatment Arms 1, 2, and 3



* Nivolumab standard of care dose may be 3 mg/kg or 240 mg flat dose

8.1.1 TAK-580 (MLN2480) Administration

TAK-580 (300 [DL−1], 400 [DL], 600 [DL2] mg) will be administered orally (PO) once weekly (QW) starting Week 1, Day 1. No dose escalation above DL2 is planned.

TAK-580 will be given on an empty stomach with patients remaining NPO (nothing by mouth) except for water and prescribed medications for 2 hours before and 1 hour after each dose. If the patient forgets to take TAK-580 on the scheduled day, it is allowed to take the dose within the next 24 hours without re-adjusting the schedule of administration. Beyond this time point it is necessary for the treating physician to consult with the sponsor representative. Patients should take their TAK-580 tablets with approximately 8 ounces (1 cup, 240 mL) of water on dosing days. If emesis occurs after taking study drug, symptoms should be managed with standard antiemetic therapy; a repeat (replacement) dose of study drug should not be taken. Patients should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. Patients should record the time of the emesis in their dosing diary (see the Study Manual).

Patients should swallow the study medication whole and not chew it, open it, or manipulate it in any way before swallowing.

8.1.2 TAK-202 (MLN1202) Administration

Patients allocated to Arm 2 will receive the first infusion of TAK-202 on Week 1, Day 1 and then every 2 weeks on Week 3, Day 15, and Week 5, Day 29 for 2 additional doses. From the 4th dose onwards, the drug is administered every 4 weeks starting on Week 9, Day 57, until any other discontinuation criterion applies.

The 250 mL bag of saline with TAK-202 will be administered IV over 30 (±5) minutes. On the days of concomitant nivolumab dosing, (Week 3, Day 15 and forward), administer TAK-202 prior to nivolumab dosing and separate both infusions by at least 30 minutes.

The initial dose level (DL1) is 4 mg/kg. If this dose proves to be safe, DL2 will be 8 mg/kg. No further escalation is planned. If the DL1 is considered non-feasible, it will be possible to enroll patients to receive 2 mg/kg of TAK-202.

8.1.3 Vedolizumab (Entyvio®) Administration

Patients allocated to Arm 3 will receive 4 doses of vedolizumab starting on Week 1, Day 1. The remaining doses will be administered on Week 3, Day 15, Week 5, Day 29, and Week 13, Day 85.

Administer vedolizumab as an IV infusion over 30 (±5) minutes. Do not administer as an IV push or bolus. On Week 1, Day 1 administer vedolizumab IV prior to nivolumab and ipilimumab dosing. Each infusion needs to be separated from the previous by at least 30 minutes and the patient should not have evidence of infusional reactions to the precedent one. The initial dose level (DL1) is 200 mg flat dose. If this dose proves to be safe, DL2 will be 450 mg flat dose. No escalation above DL2 is planned.

8.1.4 Nivolumab (Opdivo®) Administration

The recommended dose of nivolumab administered in Arms 1 and 2 is 3 mg/kg (or 240 mg flat dose) as an IV infusion over 60 (±5) minutes every 2 weeks (Q2W) until disease progression (PD) or any other discontinuation criterion is met starting on Week 3, Day 15 after the second biopsy has been performed. Nivolumab is to be administered at least 1 hour after TAK-580 oral dosing (Arm 1) and at least 30 minutes after TAK-202 dosing (Arm 2) and if there is no evidence of infusional reaction.

The dose of nivolumab in combination with ipilimumab and vedolizumab (Arm 3) is 1 mg/kg administered as an IV infusion over 60 (±5) minutes, every 3 weeks (Q3W) for 4 doses. Nivolumab is to be administered at least 30 minutes after vedolizumab dosing (Week 1, Day 1) and before ipilimumab dosing (drug order administration: vedolizumab→nivolumab→ipilimumab). The subsequent doses of nivolumab in Arm 3 (without ipilimumab), are 3 mg/kg (or 240 mg flat dose) as an IV infusion over 60 (±5) minutes Q2W starting on Week 13, Day 85 until PD or any other discontinuation criterion is met. When nivolumab and vedolizumab are administered on the same day (eg, Week 13, Day 85), the order of infusion is vedolizumab→nivolumab.

8.1.5 Ipilimumab (Yervoy®)Administration

The dose of ipilimumab to be administered in combination with nivolumab and vedolizumab in Arm 3 is 3 mg/kg as an IV infusion over 90 (±5) minutes every 3 weeks for a total of 4 doses. Ipilimumab is to be infused more than 30 minutes after nivolumab and if there is no evidence of infusional reaction to the previous administration.

8.2 Definitions of Dose-Limiting Toxicity

Toxicity will be evaluated according to the NCI CTCAE, Version 4.03 [32]. These criteria are provided in the Study Manual. A DLT will be defined as any of the following events that are considered by the investigator to be at least possibly related to study treatment: TAK-580, TAK-202, and/or vedolizumab either as SA or in combination with nivolumab or nivolumab plus ipilimumab, and that are observed before treatment administration due on Week 9. DLTs observed during the dose-escalation safety lead-in will be primarily considered for dose-escalation purposes. The overall incidence of TEAEs meeting DLT definitions will be continuously monitored during the study:

- Delay in the administration of the scheduled treatment of ≥3 weeks due to a lack of adequate recovery from treatment-related toxicity (recovery to ≤Grade 1 or to the patient's baseline, or to a level considered acceptable by the investigator after discussion with the sponsor project clinician).
- Other treatment-related nonhematologic toxicities Grade 2 that, in the opinion of the investigator, should also be considered as dose-limiting.

- Any AE Grade 3 or higher that is assessed as at least possibly related to study drug with the exceptions outlined below. Note, while not considered a DLT, the AE Grade 3 or higher may require dose delay until improvement/resolution (see Section 8.4.1).

Exceptions:

Hematologic toxicities that will not be considered a DLT include:

- Grade 4 neutropenia (ANC <500 cells/mm^3) lasting <7 days in duration in the absence of fever >38.5°C sustained for >1 hour.
- Grade 3 neutropenia of any duration in the absence of fever >38.5°C sustained for >1 hour.
- Grade 3 anemia in patients with history of transfusion supportive care or in patients participating in treatment arm 1 (TAK-580 + nivolumab).
- Grade 3 thrombocytopenia without bleeding.

Non-hematologic toxicities:

- Nausea and vomiting will not be considered DLTs if they persist at Grade 3 for ≤3 days after instituting supportive care measures including oral/IV antiemetic medications. At the investigator's discretion, patients who experience nausea and vomiting after taking study drug may receive antiemetic medication before subsequent doses of study drug.
- Isolated ≥Grade 3 laboratory abnormalities will not be considered a DLT if it is asymptomatic and resolves to ≤Grade 2 or baseline levels in ≤7 days.
- Grade 3 asymptomatic hypophosphatemia (Arm 1 only).
- Grade 3 arthralgia/myalgia that responds to NSAID use will not be considered a DLT.
- Grade 3 fatigue will not be considered a DLT.
- Grade 3 rash lasting ≤7 days after treatment that includes topical steroid treatment, PO antihistamines, and pulse PO steroids (if necessary) will not be considered a DLT.
- For ≥Grade 3 irAEs, see specific consideration in Section 8.3.

The dose-escalation safety lead-in phase will be the principle means of determining the recommended dose for cohort expansion; however, ongoing safety surveillance during the Part 1 limited cohort expansion phase will take into account all TEAEs meeting DLT criteria and all emergent ≥Grade 3 AEs to be used to decide Part 2 implementation and/or any requirement in dose/schedule modification (Section 8.3). The frequency of DLTs in Part 2 will be monitored to ensure it is maintained at ≤40% in all patients exposed at the same dose of the investigational agents.

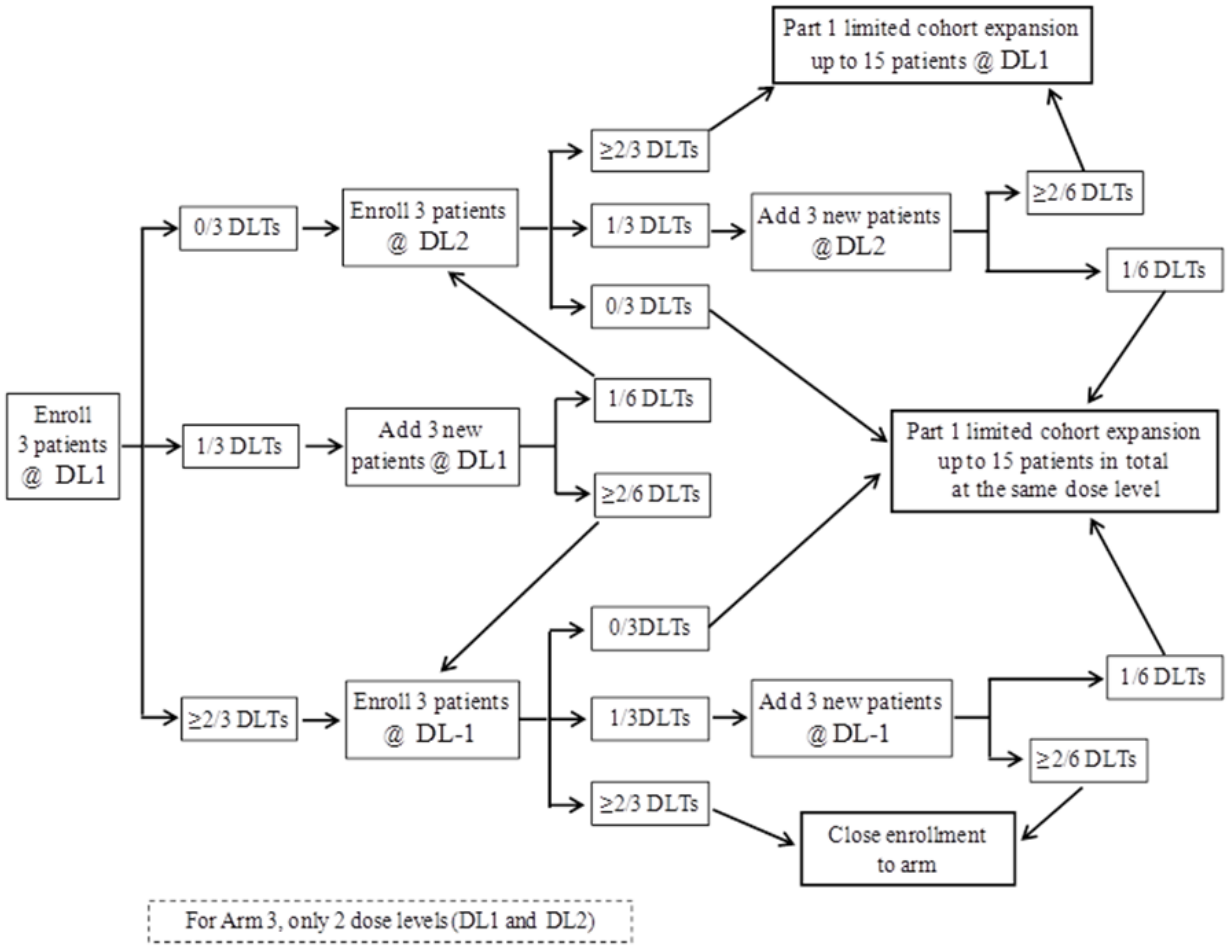
8.3 Dose Escalation Rules

The dose intervals will follow 3+3 escalation rules, starting with the treatment of 3 patients at planned dose level 1 (DL1):

1. If 0 of 3 patients experiences DLT, the dose will be escalated to the next dose level, designated DL2 at which 3 patients will be enrolled.
2. If 1 of 3 patients experiences DLT, 3 more patients will be enrolled at that same dose level (DL1 or DL2).
3. If ≥2 of 6 (or ≥2/3) patients at DL1 experience DLT, then the dose will be de-escalated to the lower dose level, designated DL−1 at which 3 patients will be enrolled (Arms 1 and 2). In this situation, Arm 3 will be closed.
4. If 1 of 3 patients experiences DLT at DL−1, 3 more patients will be enrolled at that dose level (DL−1). If another DLT is found, enrollment will stop in this arm. If no other DLT occurs, DL−1 will be considered the MTD and enrollment at DL−1 will expand up to a total of 15 patients.
5. If ≥2 of 6 (or ≥2/3) patients at DL2 experience DLT, then DL1 will be considered the MTD and enrollment at DL1 will expand up to a total of 15 patients.
6. If 1 of 6 (or 0/3) patients experiences DLT at DL2 or at the MTD defined by the rules above (ie, at DL1 or DL−1), enrollment at that dose level will expand up to a total of 15 patients.

Figure 8.b is a diagrammatical representation of these rules.

Figure 8.b Dose Escalation Overview



However, irAEs observed with checkpoint inhibitors constitute the majority of Grade 3 or higher treatment-emergent AEs (TEAEs) reported frequently in melanoma patients treated with nivolumab monotherapy, ipilimumab monotherapy or the nivolumab + ipilimumab combination at different doses without a clear dose-AE relationship. Therefore, isolated Grade 3 or higher irAEs that may be observed in dose-escalation cannot properly be considered as dose-related and additional modifications of the aforementioned dose-escalation rules are incorporated:

- If 1 patient out of the first 3 enrolled patients needs to withhold nivolumab (± ipilimumab) dosing due to an irAE DLT of Grade 2 (or due to >3 weeks delay in treatment) or higher, 3 more patients will be enrolled in the same dose level. If no other patient in the cohort presents the same irAE event ≥Grade 2, the first event will not be considered as DLT. If a second patient presents the same irAE then dose escalation will be stopped and the 2 events will be considered DLTs as the expected frequency for any specific irAEs ≥Grade 3 (eg, diarrhea) is <10%.

- If in a cohort of 6 patients there is 1 irAE event ≥Grade 2 and 1 non-immune-related DLT, it will be possible to escalate to the next dose level.

The DLT-evaluable population consists of all patients who either experience DLT during the first 8 weeks (6 weeks for patients assigned to Arm 3) of treatment or who have received at least 6 doses of TAK-580 (Arm 1), 3 doses of the TAK-202 (Arm 2), or 3 doses of vedolizumab (Arm 3), and 3 doses of nivolumab (alone or in combination with ipilimumab), and have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred.

More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, or pharmacodynamics.

The above rules applicable to the safety lead-in dose-escalation phase will be the principle means for the initial determination of the dose to be used in the cohort expansion. However, the safety of the selected dose will be confirmed during the Part 1 limited cohort expansion. During Part 1 up to 15 patients (including those from the safety lead-in treated with the same dose) will be observed for emergent DLTs during the first 8 weeks (6 weeks for Arm 3) of treatment and any other ≥Grade 3 TEAEs that may occurred after the DLT observation window. If the overall DLT rate is <33% (ie, fewer than 5 patients experience DLT), the cumulative toxicity is monitorable and manageable, and >30% of the evaluable patients present PR or CR at the time of 1st response assessment (12-14 weeks on treatment), enrollment may continue in that arm with the same dose until a total of 46 patients are treated to further evaluate the safety profile and clinical benefit of the treatment combination. Additionally for Arm 3, if 2 or more patients present with Grade ≥3 diarrhea or colitis and/or more than 7 patients present with diarrhea/colitis of any grade, Part 2 enrollment will not be initiated. Each treatment arm will be evaluated independently. DLTs will also be monitored during the Part 2 expansion phase. If the overall DLT rate among patients treated at the same dose is >40% in any arm, enrollment to this arm will be halted until a thorough analysis of available data allows for a final informed decision.

8.4 Dose Modification Guidelines

Dose reductions or dose escalations are not allowed for ipilimumab, nivolumab, vedolizumab or TAK-202. Only treatment interruptions or discontinuations are allowed. Dose reductions criteria for TAK-580 are described in Section 8.4.3.1.

8.4.1 Criteria for a Delay in Dosing

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to TAK-202, TAK-580, vedolizumab, nivolumab, ipilimumab, or the combinations). All study drugs must be delayed until treatment can resume. Treatment administration (all drugs) should be delayed for the following drug-related AEs (see also Section 8.4.4 for the criteria for permanent discontinuation):

- Grade ≥2 drug-related uveitis or eye pain or blurred vision.
- Grade ≥2 diarrhea or colitis.
- Grade ≥2 pneumonitis.
- Grade ≥2 hypophysitis.
- Grade ≥2 adrenal insufficiency.
- Grade ≥2 AST, ALT, or total bilirubin (only for patients without liver metastases at baseline).
- Grade ≥3 AST or ALT for patients with liver metastases and Grade 2 baseline AST or ALT.
- Grade ≥2 serum creatinine.
- Any Grade ≥3, drug-related AE not listed above or any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Because of the potential for clinically immune- related AEs requiring early recognition and prompt intervention, management algorithms are provided in Section 8.8.1.

8.4.2 Criteria to Resume Treatment

Subjects may resume treatment administration when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- If treatment is delayed >6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 8.4.4.
- If the patient has received steroids, they have to be tapered down to 10 mg/day of prednisone equivalent or less before treatment can be re-initiated. Adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

If the criteria to resume treatment is met and >4 days past a scheduled time point, the subject should restart treatment at the next scheduled timepoint per protocol.

8.4.3 Criteria for Dose Reduction

No dose reduction or dose escalation is allowed for TAK-202, vedolizumab, nivolumab, or ipilimumab.

8.4.3.1 Specific dose reduction criteria for TAK-580 (Arm 1)

During DLT Observation Phase

Any patient in the dose-escalation safety lead-in phase whose toxicity meets a criterion of a DLT will have study treatment of TAK-580 and nivolumab held. If the observed toxicity meets criteria for discontinuation of treatment (see Section 8.4.4 below) but is attributable to TAK-580, it will be possible, after approval by the sponsor representative, to resume nivolumab treatment. In the setting of dose delays that don't meet criteria for discontinuation of treatment, both TAK-580 and nivolumab may resume when criteria are met (See Section 8.4.2). However, dose modification of TAK-580 should be considered in the following circumstances:

- ≥Grade 3 fatigue. The patient may resume taking the original dose of TAK-580 if the fatigue resolves to ≤Grade 1 within 7 days or reduce the dose by 200 mg QW. Fatigue that is Grade 2 after >7 days requires a reduction in TAK-580 dose by 200 mg QW. During the DLT assessment period, TAK-580 should be permanently discontinued if ≥Grade 3 fatigue recurs after a single dose reduction.
- Laboratory abnormality requiring dose delay. The patient may resume taking the original dose of TAK-580 if the laboratory abnormality resolves to ≤Grade 1within 7 days or reduce the dose by 200 mg QW. Laboratory abnormalities that resolve ≤Grade 1 in >7 days requires a reduction in TAK-580 dose by 200 mg QW. During the DLT assessment period, TAK-580 should be permanently discontinued if the laboratory abnormality requiring dose delay recurs after a single dose reduction.
- Other ≥Grade 3 non-laboratory AE requiring dose delays. If the AE resolves to ≤Grade 1 in ≤3 weeks, the patient can resume taking TAK-580 with the dose reduced by 200 mg QW. If the AE does not resolve to ≤Grade 1 after 3 weeks, the patient must discontinue study treatment.

Outside the DLT Observation Period

Any patient outside the DLT window who experiences a toxicity that meets a criterion for dose delay should have study treatment of TAK-580 and nivolumab held. If the observed toxicity meets criteria for discontinuation of treatment (see Section 8.4.4 below) but is mainly attributable to TAK-580, it will be possible after approval by the sponsor representative to resume nivolumab treatment. In the setting of dose delays that don't meet criteria for discontinuation of treatment, both TAK-580 and nivolumab may resume when criteria are met (See Section 8.4.2). However, dose modification of TAK-580 should be considered in the circumstances described above, with the exception that 2 dose reductions of TAK-580 by 200 mg are allowed before permanent discontinuation of TAK-580 is required.

The sponsor must be notified of any TAK-580 dose modification.

When a dose reduction of TAK-580 is required due to DLT, no re-escalation of dose will be permitted. For all other dose reduction events, re-escalation of TAK-580 (to starting dose) is

allowed if patient toxicity does not recur on the reduced dose of TAK-580 for a minimum of 4 weeks.

8.4.4 Criteria for Discontinuation of Treatment

Treatment should be permanently discontinued for the following (See also Section 8.8 for management):

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period or requires systemic treatment.
- Grade ≥3 drug-related uveitis, pneumonitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
- Grade ≥3 colitis or diarrhea in Arm 3 patients that still have pending doses of vedolizumab, should be permanently discontinued from vedolizumab (See details in Section 8.8.3).
- Grade 4 (or Grade 3 that persists or worsens over 3-5 days) colitis or diarrhea requires permanent discontinuation of all study treatments.
- Any Grade 4 laboratory abnormality requires discontinuation with the exception of:
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to <Grade 4 within 1 week of onset.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical symptoms and are corrected with supplementation/appropriate management within 72 hours of their onset.
- Grade 3 drug-related laboratory abnormalities that require treatment discontinuation include:
  - Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation.
  - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    - AST or ALT >5 × ULN (Grade 3) in patients without liver metastases at baseline.
    - Total bilirubin >3 × ULN (Grade 3).
    - Concurrent AST or ALT >3 × ULN and total bilirubin >2 × ULN.
- Any other Grade ≥3 non-skin, non-laboratory abnormalities considered drug-related AEs not defined above lasting >7 days.
- Any Grade ≥3 skin drug-related AEs irrespective of duration with life-threatening consequences.
- Any dosing interruption lasting >6 weeks with the following exceptions:

  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting >6 weeks, the medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions >6 weeks that occur for non-drug-related reasons may be allowed if approved by the medical monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting >6 weeks, the medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued treatment dosing.
- In Arm 1, if more than 2 dose reductions by 200 mg of TAK-580 are required, treatment should be discontinued. When a dose reduction of TAK-580 is required, re-escalation of dose will be permitted if patient tolerates the dose for 4 weeks without recurrence of toxicity.
- In Arm 3, any patient reporting signs or symptoms of PML will undergo objective testing prior to further dosing with vedolizumab. If a patient demonstrates a neurologic deficit related to PML upon administration of the specific test(s) on the PML Checklist (available in Appendix F), no further doses of vedolizumab should be administered to that patient. The patient should be referred to the study neurologist for further testing and the sponsor must be notified of this action. Subsequent doses of vedolizumab will be administered only if the possibility of PML is definitively excluded, as described in the Risk Assessment and Minimization for PML (RAMP) algorithm (available in the Study Manual).

If the patient has to discontinue the standard of care treatment (nivolumab or nivolumab plus ipilimumab) for drug-related toxicity, then the companion investigational drug must also be discontinued and the patient removed from the trial. If the observed toxicity is clearly related to the investigational companion drug, it can be permanently stopped and the patient can continue only with standard of care nivolumab (Arms 1 and 2) or nivolumab plus ipilimumab (Arm 3).

8.5 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related AE).
- Systemic corticosteroids >10 mg daily prednisone equivalent (except as stated in Section 8.8 or to treat a drug-related AE). Inhaled or topical steroids and adrenal replacements doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy), or standard or investigational agents for treatment of cancer).

- The following medications are prohibited for patients enrolled in Arm 1 (receiving TAK-580): the strong CYP2C8 inhibitor gemfibrozil, and the clinically significant enzyme inducers carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, and St. Johns Wort (see Appendix E).

Palliative (limited-field) radiation therapy is permitted, but only for pain control to sites of bone disease present at baseline and only if all of the following criteria are met:

- Repeat imaging demonstrates no new sites of bone metastases or PD.
- The lesion being considered for palliative radiation is not a target lesion (Part 2 expansion phase only).
- The case is discussed with the medical monitor, and the medical monitor agrees that the conditions required to receive palliative radiation are met.

Subjects must be instructed not to take any medications, including over-the-counter products or herbal treatments without first consulting with the investigator. It is also recommended that concomitant medications needed to treat concurrent diseases or co-morbidities (including blood pressure, antidiabetes, and lipid-modifying medications) should be maintained at a stable dose and regimen from the Screening throughout the study (as long as consistent with optimal medical care).

Patients who require administration of prohibited medications to treat intercurrent illnesses will be withdrawn from the study.

8.6 Permitted Concomitant Medications and Procedures

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy or prevention of infusional reactions) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

Supportive care for disease-related symptoms may be offered to all subjects on the trial.

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the electronic case report form (eCRF). All medications (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the eCRF.

8.7 Precautions and Restrictions

TAK-580 is an in vitro inhibitor of the efflux transporter Breast Cancer Resistance Protein (BCRP). On the basis of clinical exposure observed to date, there is a potential risk for TAK-580 to inhibit transport of co-administered drugs that are substrates of BCRP. Although currently there are limited examples of clinically meaningful DDIs related to BCRP inhibition,

information on BCRP-mediated drug interactions continues to evolve. Consequently, caution should be exercised when TAK-580 is administered concurrently with substrates of BCRP. These include, but are not limited to, HMG-CoA reductase inhibitors (rosuvastatin, pitavastatin, cerivastatin), antibiotics (ciprofloxacin, norfloxacin, ofloxacin erythromycin, nitrofurantoin), calcium channel blockers (dipyridamole, nitrendipene, azidopine), sulfasalazine, cimetidine, methotrexate, and glyburide.

TAK-580 did not inhibit P-gp in vitro at concentrations up to 30 μM. A clinically meaningful interaction with co-administered P-gp substrates is not anticipated at systemic sites of transport (liver, kidney, blood-brain barrier). However, as the possibility of inhibition of intestinal P-gp transport by clinical doses of TAK-580 cannot be ruled out due to potentially higher concentrations in the intestinal lumen (>30 μM), cautious use and close monitoring of patients is advised as a precautionary measure when an orally administered P-gp substrate with a narrow therapeutic index (eg, digoxin and cyclosporine) is taken concomitantly with TAK-580.

It is not known what effects TAK-580, TAK-202, vedolizumab, nivolumab, or ipilimumab have on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the ICF through 18 weeks after the last dose of TAK-580, TAK-202, or vedolizumab, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 18 weeks after the last dose of TAK-580, TAK-202, or vedolizumab, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

8.8 Management of Clinical Events

As noted, nivolumab and ipilimumab are associated with irAEs which may be managed per clinical judgement / institutional guidelines. Additional treatment algorithms for use in conjunction with clinical judgement are provided below. If dose alterations are necessary as a result of the events detailed below, please refer to Section 8.4.

8.8.1 Treatment of Infusion Reactions Related to TAK-202, Vedolizumab, Nivolumab, or Ipilimumab Therapy

Since TAK-202 and vedolizumab are humanized mAbs and both nivolumab and ipilimumab are human immunoglobulins, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (Version 4.03) guidelines.

As there is potential for life-threatening anaphylactic reactions, parenteral drugs must be administered by trained and experienced professionals in the management of infusion reactions. Resuscitation equipment should be immediately available at the location where the products are being infused.

Blood pressure, heart rate, temperature, and respiration rate should be monitored before starting the infusion, 10 minutes after the start of the infusion, at the end of the infusion, and before removing the IV line before patient discharge. Vital signs must be obtained if the patient complains of the symptoms listed above. A minimum period of 30 minutes should elapse between the end of the infusion and patient discharge. Patients can only be discharged if they are asymptomatic and if vital signs are Grade 0 or have returned to baseline values.

Specific monitoring and treatment recommendations are given below categorized by NCI CTCAE grading of the reaction.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate.

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated).

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≥24 hours).

Stop TAK-202, vedolizumab, nivolumab, or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further responsible antibody will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the eCRF. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before any antibody administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life-threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of the treatment. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. The patient will be will be permanently discontinued from the trial (Section 8.4.4). Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

8.8.2 Immune-Mediated Pneumonitis

Monitor patients for immune-mediated pneumonitis. Oxygen saturation to be monitored and recorded at the frequency specified in the SOE (Appendix A).

For Grade 1 (radiographic changes only): consider withholding treatment, monitor every 2 to 3 days. If improved, resume treatment at the same doses.

For Grade 2 (mild-to-moderate symptoms; worsening from baseline): withhold treatment until resolution, monitor daily, consider bronchoscopy and lung biopsy. Administer corticosteroids at a dose of 1 mg/kg/day prednisone equivalents. Consider prophylactic antibiotics. When symptoms return to near baseline, taper steroids over at least 1 month and then resume study treatment. If not improving after 2 weeks or worsening treat as Grade 3-4.

For Grade 3 (severe symptoms; new/worsening hypoxia) or **Grade 4** (life-threatening): Permanently discontinue treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents and add antibiotics for opportunistic infections. Consider bronchoscopy and lung biopsy. If improves to baseline, taper steroids over at least 1 month. If persisting or worsening after 2 days, add non-corticosteroid immunosuppressive medication.

8.8.3 Immune-Mediated Colitis

Monitor patients for immune-mediated colitis.

For Grade 1 (Diarrhea <4 stools per day over baseline. Colitis: asymptomatic; clinical or diagnostic observations only). Continue treatment. Administer antidiarrheals and other symptomatic treatment as needed. Educate patient to report worsening immediately.

For Grade 2 (Diarrhea: 4-6 stools/day over base line; IV fluids indicated <24 hours; not interfering with activities of daily living [ADL]. Colitis: abdominal pain, blood in stool). Withhold treatment. Serial stool cultures to rule out bacterial (*Salmonella* and *Listeria*) and viral (cytomegalovirus) infections (Arm 3 patients only). Administer symptomatic antidiarrheal treatment. If symptoms persist >5 days or recur, initiate 0.5 to 1 mg/kg/day prednisone equivalents. When symptoms improve to ≤Grade 1, taper steroids over at least 1 month. Consider adding prophylactic antibiotics for opportunistic infections, and resume treatment. If symptoms persist >3 to 5 days after initiating steroids, treat as Grade 3/4.

For Grade 3 (Diarrhea: ≥7 stools/day over baseline; IV fluids ≥24 hours; interfering with ADL. Colitis: severe abdominal pain, medical intervention indicated, peritoneal signs): withhold treatment and collect serial stool cultures (Arm 3 patients only). In Arm 3, if the patient still has pending doses of vedolizumab, discontinue it. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents, add prophylactic antibiotics for opportunistic infections and consider lower endoscopy. If recovers to ≤Grade 1, begin steroid taper over at least 1 month and resume treatment. If Grade 3 persists for >3-5 days or recurs, permanently discontinue treatment and add non-corticosteroid immunosuppressive medication.

For Grade 4 (colitis: life-threatening, perforation): Permanently discontinue treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents, add prophylactic antibiotics for opportunistic infections, and consider lower endoscopy. If recovers to ≤Grade 1, begin steroid taper over at least 1 month. If Grade 4 persists for >3 to 5 days or recurs, add non-corticosteroid immunosuppressive medication (**note**: avoid use of anti-TNF-α therapies in setting of perforation or sepsis).

8.8.4 Immune-Mediated Hepatitis

Monitor patients for abnormal liver tests prior to and periodically during treatment.

For Grade 1 (AST or ALT >ULN to 3 × ULN and/or total bilirubin >ULN to 1.5 × ULN). Continue treatment. Monitor LFTs per protocol.

For Grade 2 (AST or ALT >3 to ≤5 × ULN and/or bilirubin >1.5 to 3 × ULN). Withhold treatment. Monitor LFTs every 3 days. If persists, >5-7 days or worsens, administer

corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents. If improved to ≤Grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and then resume treatment.

For Grade 3/4 (AST or ALT >5 × ULN and/or bilirubin >3 × ULN). Permanently discontinue treatment. Increase frequency of monitoring to every 1 or 2 days. Administer 1 to 2 mg/kg/day prednisone equivalents and add prophylactic antibiotics for opportunistic infections. If improved to <Grade 2, taper steroids over at least 1 month. If LFTs persist >3 to 5 days, worsen or rebound, add non-corticosteroid immunosuppressive medication.

8.8.5 Immune-Mediated Nephritis

Monitor patients for elevated serum creatinine prior to and periodically during treatment. Exclude other causes for elevated creatinine.

For Grade 1 (creatinine >ULN and > baseline but ≤1.5 × baseline). Continue treatment, monitor creatinine weekly.

For Grade 2 (moderate; creatinine >1.5 to 3 × baseline; >1.5 to 3 × ULN) or **Grade 3** (severe creatinine >3.0 baseline; >3 to 6 × ULN) serum creatinine elevation. Withhold treatment and administer 0.5 to 1 mg/kg/day prednisone equivalents. Consider renal biopsy. If returns to ≤Grade 1, taper steroids over at least 1 month, consider antibiotics for opportunistic infections, and resume treatment. If no improvement occurs >7 days or worsens, treat as Grade 4.

For Grade 4 (creatinine >6 × ULN) serum creatinine elevation. Discontinue study treatment. Administer 1 to 2 mg/kg/day prednisone equivalents and add prophylactic antibiotics for opportunistic infections. Consider renal biopsy.

8.8.6 Immune-Mediated Dermatitis

Monitor patients for immune-mediated dermatitis. Rashes (maculopapular, dermatitis acneiform, and pruritus) have been observed with administration of TAK-580, TAK-202, vedolizumab, ipilimumab, and nivolumab. Patients should avoid excess exposure to sunlight and use broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with an SPF >15. Should a Grade 2 or 3 rash occur, photographic documentation is recommended.

For Grade 1 (mild) or **Grade 2** (moderate) dermatitis, such as rash (covering ≤30% of body surface area [BSA]) and pruritus, treat symptomatically with antihistamines and topical steroids. If persists >1-2 weeks or recurs, withhold study treatment and consider 0.5 to 1 mg/kg/day prednisone equivalents. Once improved, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume study treatment.

For Grade 3-4 dermatitis covering >30% of BSA and other life-threatening consequences such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations: Withhold or permanently discontinue study treatment. Consider skin biopsy. Administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone equivalents. If improves to ≤Grade 1, taper steroids over at

least 1 month and add prophylactic antibiotics for opportunistic infections. For patients with moderate signs and symptoms (non-life threatening) that improve to ≤Grade 1, resume study treatment.

8.8.7 Immune-Mediated Neuropathies

In one study with ipilimumab, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported. Across the clinical development program of ipilimumab, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported.

Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia.

For Grade 1 (asymptomatic or mild symptoms): Continue study treatment and monitor patient. If worsens treat as Grade 2 or Grade 3-4.

For Grade 2 (moderate symptoms; limiting instrumental ADLs): Withhold treatment and treat symptoms per local guidelines. Consider 0.5 to 1 mg/kg/day prednisone equivalents. If improves to baseline, resume study treatment. If worsens, treat as Grade 3-4.

For Grade 3-4 (severe symptoms limiting self-care, life-threatening like Guillain-Barré-like syndromes.): Permanently discontinue treatment. Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for severe neuropathies. Add prophylactic antibiotics for opportunistic infections. If improves to ≤Grade 2, taper steroids over at least 1 month. If worsens or atypical presentation, consider other immunosuppressive therapies per local guidelines.

8.8.8 Immune-Mediated Hypothyroidism and Hyperthyroidism

Monitor thyroid function prior to and periodically during treatment. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. There are no recommended dose adjustments of the treatment for hypothyroidism or hyperthyroidism.

8.8.9 Immune-Related Uveitis

Administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue treatment for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

8.8.10 Other Immune-Mediated Adverse Reactions

Across clinical trials of checkpoint inhibitors, additional clinically significant, immune-mediated adverse reactions were identified: hypophysitis, diabetic ketoacidosis, and hypopituitarism.

For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, withhold treatment, administer high-dose corticosteroids, and if

appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting treatment after completion of corticosteroid taper based on the severity of the event.

8.8.11 Nausea and/or Vomiting

Although this study will not initially employ prophylactic antiemetics, there is no prohibition against their use in the management of a patient who develops nausea and/or vomiting. As in the prophylactic setting, 5-HT3 receptor antagonists and corticosteroids should be tried first.

8.9 Blinding and Unblinding

This is an open-label study.

8.10 Description of Investigational Agents

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.10.1 TAK-580 (MLN2480)

8.10.1.1 Investigational Drug Product

TAK-580 is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling TAK-580.

TAK-580 (MLN2480) drug product consists of MLN2480 active substance and other commonly used, compendial excipients that include microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, vinylpyrrolidone-vinyl acetate copolymer (copovidone), sodium croscarmellose and Opadry®.

TAK-580 drug product is formulated as an immediate-release tablet for oral administration. Only the 100 mg dosage strength tablets will be used in this study.

8.10.1.2 Packaging and Labeling

The drug product, labeled TAK-580 (MLN2480), are constituted as tablets of 100 mg dosage strength that are packaged with desiccant and cotton in 40 cc, white, wide-mouth, round, high-density polyethylene bottles equipped with 33 mm polypropylene child-resistant caps and induction sealed.

There are 16 100-mg tablets in each bottle.

Each bottle of TAK-580 (MLN2480) study medication will be labeled with a multi-panel booklet label containing pertinent study information and a regulatory caution statement. The study drug

is labeled to be used across protocols within the TAK-580 (MLN2480) program. The site is responsible to add the last digit of the study number as "C28003". In addition, if the investigational pharmacy is participating in multiple TAK-580 studies, it is mandatory that the study drug is segregated based on the protocol number.

8.10.1.3 Storage

Investigational drug tablets must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Investigational drug tablets must be stored at 20°C to 25°C under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day. Please refer to the C28003 Pharmacy Manual for more information.

8.10.2 TAK-202 (MLN1202; plozalizumab)

TAK-202 should be administered by a healthcare professional prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate use. Observe patients during infusion and until the infusion is complete.

8.10.2.1 Investigational Drug Product

TAK-202 (MLN1202) will be supplied in a 10 mL 20-mm USP type 1 tubing vial with a 20-mm butyl stopper with a 20-mm flip-off cap. Each lyophilized injection vial will be packaged into individual kits. Both the primary and secondary label information will fulfill all requirements specified by local governing regulations.

Each active vial contains approximately 180 mg TAK-202 (MLN1202) Powder for Concentrate drug product in a lyophilized formulation. Each vial, when reconstituted will contain 150 mg/mL of TAK-202, formulated with 3% sucrose, 0.9% mannitol, in a 30 mM citrate buffer. A 20% overage is included in the formulation to ensure that 1 mL of reconstituted solution can be withdrawn from each vial accounting for losses to the vial, syringe, and needle.

The Pharmacist will dilute the drug into 250 mL of sodium chloride for IV administration. Details regarding the preparation of TAK-202 in saline are contained in the C28003 Pharmacy Manual.

8.10.2.2 Storage

Investigational drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Investigational drug must be stored at 2°C to 8°C under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.10.3 Vedolizumab

Vedolizumab should be administered by a healthcare professional prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate use. Observe patients during infusion and until the infusion is complete.

8.10.3.1 Packaging and Labeling

The sponsor will supply the study sites with vedolizumab IV (300 mg/vial) in 20 mL vials for single use. The study medication will be provided in a glass vial as a lyophilized solid for reconstitution. Each vial will be packaged in an appropriately labeled single vial carton.

Each carton will have a single-panel or multilingual booklet label that will contain, but will not be limited to the following: sponsor's name and address, protocol number, lot number, name and strength of product, medication identification number, subject information, caution statement, directions for use, and storage conditions.

8.10.3.2 Reconstitution Instructions

Entyvio® for injection is presented as 300 mg of vedolizumab as a lyophilized cake in single dose 20 mL vials for reconstitution. Vedolizumab lyophilized powder must be reconstituted with Sterile Water for injection and diluted in 250 mL of sterile 0.9% Sodium Chloride injection prior to administration. Reconstitute vedolizumab at room temperature. Vedolizumab should be reconstituted and prepared by a trained medical professional using the procedure found in the C28003 Pharmacy Manual.

8.10.3.3 Storage

Vedolizumab must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Lyophilized vials of vedolizumab must be stored at 2°C to 8°C under the conditions specified on the label, and remain in the original container until resuspended for administration.

If necessary, the infusion solution may be stored for up to 4 hours at 2° to 8°C (36º to 46ºF).

Additional reference information and administration instructions can be found in the Pharmacy Manual.

8.10.4 Nivolumab

Nivolumab should be administered by a healthcare professional prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate use. Observe patients during infusion and until the infusion is complete.

8.10.4.1 Preparation and Administration

- Do not shake product.

- Inspect parenteral drug product visually for particulate matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, is discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles.

8.10.4.2 Preparation of Solution

- Withdraw the required volume of nivolumab and transfer into an intravenous container.
- Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of nivolumab.

8.10.4.3 Storage of Infusion

The product does not contain a preservative. After preparation, store the nivolumab infusion either:

- at room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F-46°F) for no more than 24 hours from the time of infusion preparation. Do not freeze.

8.10.4.4 Administration

Administer the infusion over 60 (±5) minutes through an intravenous line containing a sterile, nonpyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not coadminister other drugs through the same intravenous line. Flush the IV line at end of infusion.

The dose of nivolumab to be administered is 3 mg/kg (or 240 mg flat dose) as an IV infusion over 60 (±5) minutes every 2 weeks (Q2W) until disease progression (PD) or any other discontinuation criterion is met.

The dose of nivolumab in combination with ipilimumab (Arm 3) is 1 mg/kg administered as an IV infusion over 60 (±5) minutes, followed by ipilimumab on the same day, every 3 weeks (Q3W) for 4 doses in a 90 (±5) minute infusion. The subsequent doses of nivolumab are 3 mg/kg (or 240 mg flat dose) as an IV infusion over 60 (±5) minutes Q2W until PD or any other discontinuation criterion is met.

Further information on nivolumab can be found in the US prescribing information (USPI) or the Summary of Product Characteristics (SmPC).

8.10.5 Ipilimumab

Ipilimumab should be administered by a healthcare professional prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate use. Observe patients during infusion and until the infusion is complete.

8.10.5.1 Preparation and Administration

- Do not shake product.
- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale-yellow color), or there is foreign particulate matter other than translucent-to white, amorphous particles.

8.10.5.2 Preparation of Solution

- Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of ipilimumab and transfer into an IV bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.
- Store the diluted solution for no more than 24 hours under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature (20°C to 25°C, 68°F to 77°F).
- Discard partially used vials or empty vials of ipilimumab.

8.10.5.3 Administration Instructions

- Do not mix ipilimumab with, or administer as an infusion with, other medicinal products.
- Flush the IV line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.
- Administer diluted solution over 90 (±5) minutes through an IV line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

When both nivolumab and ipilimumab are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the IV line of nivolumab before starting the ipilimumab infusion. At least 30 minutes should separate the 2 infusions. When the 3 drugs have to be administered on the same day (Week 1, Day 1), the order of administration is vedolizumab → nivolumab → ipilimumab. At least 30 minutes should

elapse between each infusion and before starting a new infusion, the patient has to be free of IRR symptoms.

Further information on ipilimumab can be found in the USPI or the SmPC.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

9.1 Study Personnel and Organizations

The contact information for the Takeda project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country (where applicable), and the contract research organization (CRO) team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

9.2 Enrollment

A patient is considered to be enrolled in the study when the patient receives the first dose of any study drug. Procedures for completion of the enrollment information are described in the Study Manual.

9.3 Treatment Group Assignments

Investigators should consider first which standard of care checkpoint inhibitor therapy is most suitable for each candidate patient (nivolumab alone versus combination of nivolumab plus ipilimumab). Tumor biology (*BRAF* V600 mutation-positive or *NRAS* mutation-positive disease) and other medical aspects (previous treatment with RAF, MEK, or other inhibitors of the MAPK pathway, or previous use of checkpoint inhibitors) will be considered before allocating the patient to a particular treatment arm. If there is no specific medical rationale to choose 1 arm over others, patients will be allocated maximizing enrollment strategy.

9.4 Study Procedures

Refer to the SOE (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow.

9.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

Patients for whom there is an approved standard of care still available who continue to receive investigational treatment until confirmation of PD in a subsequent tumor response assessment should be re-consented at the time of the initial documentation of PD to ensure that they are aware of all available alternative effective therapies.

9.4.2 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria will be assessed during screening (within 28 days before the first dose of any study drug on Week 1, Day 1).

9.4.3 Patient Demographics

The date of birth (outside the European Economic Area) or age (European Economic Area), race, ethnicity, and sex of the patient are to be recorded during screening.

9.4.4 Medical History

During the Screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 9.4.13.

9.4.5 Physical Examination

A physical examination (complete or targeted) will be completed per standard of care at the times specified in the SOE (Appendix A). Any clinically relevant findings at baseline will be documented.

A "complete" physical examination will include examination of general appearance, skin, head, eyes, ears, nose, throat, neck, lungs, abdomen (including liver and spleen), lymph nodes, extremities, cardiovascular system, genitourinary system, musculoskeletal system, neurological system, body weight, and height.

A "targeted" physical examination will include examination of lungs, abdomen, skin, cardiovascular system and weight.

Any physical examination finding that is assessed by the investigator as a clinically significant change (worsening) compared to a baseline value will be considered an AE and will be recorded and monitored as described in Section 10.2.

9.4.6 Patient Height

Height will be measured only during screening (within 28 days before the first dose of treatment).

9.4.7 Vital Signs

Vital sign measurements include blood pressure (resting for 5 minutes), heart rate, respiration rate, and body temperature to be determined at the times specified in the SOE (Appendix A). Oxygen saturation is also to be assessed at each visit.

9.4.8 Progressive Multifocal Leukoencephalopathy Checklist (Arm 3 Subjects Only)

Clinic staff will administer the subjective PML checklist (Appendix F) during screening to have a baseline reference and a focused evaluation of patients to be enrolled to Arm 3. The subjective PML checklist will be administered before dosing at the time points specified in the SOEs for Arm 3 to probe for symptoms suggestive of PML. The checklist must be administered by appropriate clinic staff as it is not designed as a patient questionnaire. A patient who reports a new and persistent change(s) per the subjective checklist must have the corresponding objective

test(s) (Appendix F) administered and may be referred to a neurologist for a full evaluation, as described in the RAMP algorithm (available in the Study Manual). See Section 10.7 for additional details regarding the RAMP program.

9.4.9 Eastern Cooperative Oncology Group Performance Status

The ECOG performance status will be assessed at the time points specified in the SOE (Appendix A).

9.4.10 Echocardiogram or Multiple Gated Acquisition Scan (Arm 1 Subjects only)

An ECHO or MUGA scan will be administered at the time points specified in the SOE for patients in Arm 1 (Appendix A).

9.4.11 Electrocardiogram

A 12-lead ECG will be administered at the time points specified in the SOE (Appendix A).

9.4.12 Disease Assessments (including skin)

Patients will undergo scanning procedures (CT with contrast, MRI, X-ray and/or bone scanning) and/or caliper and photographs according to RECIST Version 1.1, at screening and at time points as clinically indicated, to monitor and assess disease progression.

At screening, contrast CT scans of the chest, abdominal cavity, and pelvis will be obtained; specific disease sites that cannot be adequately imaged by CT may be documented by MRI. Visible lesions are considered measurable if, in clinical exam, they measure ≥10 mm in the longer diameter using a caliper; lesions that cannot be accurately measured with calipers should be recorded as non-measurable. Investigators are encouraged to take and store photographs of visible lesions. Anatomical measurements (summed across target lesions) will be collected at baseline and each subsequent evaluation using an imaging modality consistent with that used at screening. Objective assessments will be performed at each time point as described in the SOE (Appendix A).

When possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the site, and test results and physicians' findings will be filed in patient source documents.

Investigators should take into consideration some specific characteristics of the tumor response to immunotherapy especially what refers to pseudoprogression. The following concepts should be considered before discontinuing a patient due to PD: (a) the appearance of measurable antitumor activity may take longer for immune therapies than for cytotoxic therapies; (b) responses to immune therapies may occur after conventional PD; (c) discontinuation of immune therapy may not be appropriate in some cases, unless PD is confirmed (as is usually done for response); (d) allowance for "clinically insignificant" PD (eg, small new lesions in the presence of other responsive lesions) is recommended; and (e) durable stable disease (SD) may represent antitumor activity. Unless clinically indicated (rapid deterioration), it is advisable for PD

declaration to demonstrate at least 25% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart [33].

In the event of antitumor response, the sponsor may request electronic images for those patients who demonstrate tumor reduction.

9.4.13 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from the first dose of study drug through 30 days after the last dose of study drug. See Section 8.5 and Section 8.6 for a list of medications and therapies that are prohibited and/or allowed during the study.

9.4.14 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the SOE (Appendix A). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), AEs, and SAEs.

9.4.15 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Handling of clinical laboratory samples will be outlined in the Study Manual. Decisions regarding eligibility for this study will be made using local laboratory determinations. For dosing decisions, local hematology and chemistry laboratory results will be used.

9.4.15.1 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening and within 3 days prior to the first dose of study drug. The results from these tests must be available and negative before the first dose of study drug is administered. All other pregnancy tests may be assessed by urine or serum samples.

9.4.15.2 Clinical Hematology, Coagulation, Chemistry, and Liver Function Testing

Clinical hematology, coagulation testing, blood chemistry, and LFTs will be performed locally. Blood samples for analysis of the hematological and clinical chemistry parameters shown in Table 9.a will be obtained at the time points specified in the SOEs (Appendix A).

Creatine kinase will be assessed with blood chemistry every 4th week (eg, Week 1, Day 1, Week 5, Day 29, etc) for patients receiving TAK-580 treatment (Arm 1).

Table 9.a Clinical Hematology, Coagulation, Chemistry and Liver Function Tests

Hematology	**Serum Chemistry**	
Hematocrit	Albumin	Chloride
Hemoglobin	Amylase	Glucose
Red blood cells (RBC)	Bicarbonate (HCO_3)	Lipase
Leukocytes with differential including neutrophils and monocytes	Blood urea nitrogen (BUN)	Phosphate
	Calcium	Potassium
Platelets	Creatinine	Sodium
	Creatine kinase (CK) (a)	Urate
Coagulation (b)	**Liver Functions**	
Prothrombin (PT)/International normalized ratio (INR)	Alkaline phosphatase (ALP)	Bilirubin (total and indirect)
	ALT	Lactate dehydrogenase (LDH)
Activated partial thromboplastin time (aPTT)	AST	

(a) Performed in patients receiving TAK-580 treatment (Arm 1) as specified in the SOE (Appendix A).
(b) Performed in patients enrolled in Arms 1 and 2 at screening, Week 3, Day 15, and Week 9, Day 99 to confirm normal range before biopsy procedure.

9.4.15.3 Urinalysis

Urine samples will be analyzed locally. Urinalysis will include the parameters shown in Table 9.b and urine samples will be obtained at the time points specified in the SOEs (Appendix A).

Table 9.b Clinical Urinalysis Tests

Urinalysis	
Bilirubin	pH
Glucose	Protein
Ketones	Specific gravity
Leukocytes	Turbidity and color
Nitrite	Urobilinogen
Occult blood	

If creatinine clearance is to be estimated, the Cockroft-Gault formula will be employed as follows:

Estimated creatinine clearance

$$= [(140 - Age) * Mass\ (kg)] / [72 * serum\ creatinine\ (mg/dL)]$$

For female patients, the result of the formula above should be multiplied by 0.85.

9.4.15.4 Immune Safety Tests

Blood samples will be analyzed locally for the immune safety parameters shown in Table 9.c. Blood samples for immune safety tests will be obtained at the time points specified in the SOEs (Appendix A). Serum for additional immune safety testing (if needed) will be obtained and sent

to the study sponsor. Refer to the Laboratory Manual for details on collecting, processing, storage, and shipment of serum samples to the study sponsor.

Table 9.c Immune Safety Tests

Immune Safety Tests	
Adrenocorticotropic hormone (ACTH)	Free T4 level
Antinuclear antibody (ANA)	Rheumatoid factor (RF)
C-reactive protein (CRP)	Thyroid-stimulating hormone (TSH)

Additional tests to evaluate abnormal immunologic or endocrine results may be obtained at the investigator's discretion. Additional endocrine testing may require an endocrine consult.

9.4.16 Exploratory Studies

9.4.16.1 Company Confidential Information

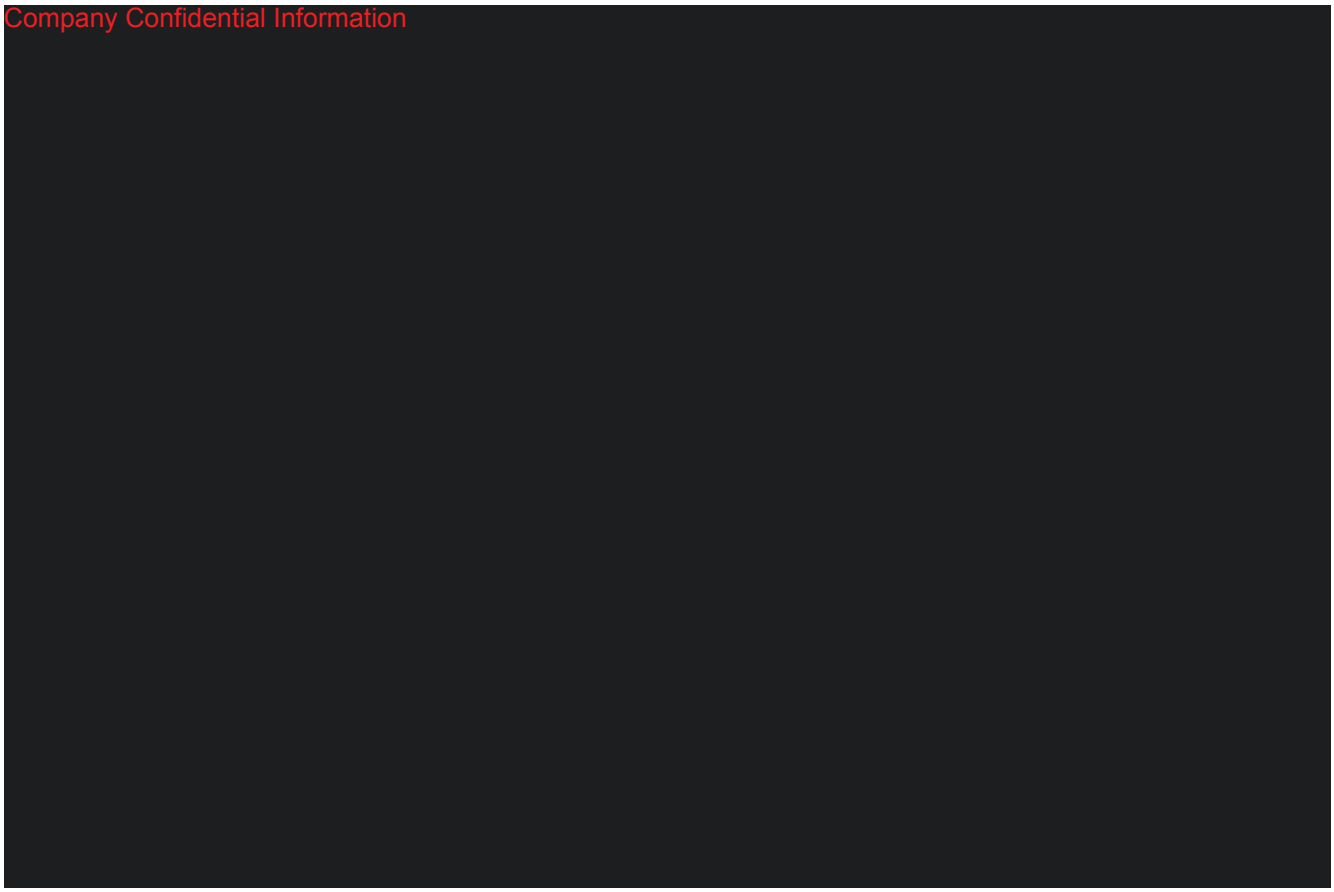
Company Confidential Information

9.4.16.2 Company Confidential Information

Company Confidential Information

9.4.16.3 Company Confidential Information

Company Confidential Information



No patient will be discontinued from the trial if a biopsy is not obtained due to clinical considerations or if the patient does not consent to it.

Refer to the Laboratory Manual for details on collecting, processing, storage, and shipment of tumor biopsies to the study sponsor.

9.4.17 Immunogenicity Assessment

Blood samples to determine the immunogenicity of TAK-202 (Arm 2) and vedolizumab (Arm 3) will be collected at time points specified in the SOEs (Appendix A). Blood samples will be processed to obtain serum, which will be evaluated using immunoassays for detection of ADAs to TAK-202 and vedolizumab. Refer to the Laboratory Manual for details on collecting, processing, storage, and shipment of serum samples to the study sponsor.

9.4.18 Microbiome Assessment

For patients enrolled in Arm 3 only, stool samples will be collected at time points specified in the SOEs (Appendix A). 16S rRNA sequencing and/or metagenomic sequencing will be conducted on DNA extracted from these stool samples. Refer to the Laboratory Manual for details on collecting, processing, storage, and shipment of stool samples to the study sponsor.

9.4.19 Fecal Calprotectin Sample Collection

For patients enrolled in Arm 3 only, stool samples will be collected at the time points specified in the SOE (Appendix A) for analysis of fecal calprotectin, a biomarker of intestinal inflammatory activity. Refer to the Laboratory Manual for details on collecting, processing, storage, and shipment of stool samples to the study sponsor.

9.4.20 Pharmacokinetic Measurements

Pharmacokinetic samples will be obtained to evaluate TAK-580, TAK-202, or vedolizumab pre- and post-dose at the time points specified in the SOEs (Appendix A). Refer to the Laboratory Manual for details on collecting, processing, storage, and shipment of serum samples to the study sponsor.

9.5 Completion of Study Treatment

Patients will be considered to have completed study treatment if they discontinue study drug for any of the reasons outlined in Section 9.7. Treatment will be considered completed at 50 weeks. However, patients who, in the opinion of the investigator, tolerate treatment and have evidence of clinical benefit after 50 weeks may continue treatment with continued monitoring upon prior review and approval by the sponsor project clinician.

9.6 Completion of Study

Study completion will occur once all study procedures (including PFS and OS) are completed as specified in the appropriate SOEs. The primary reason for completion of study will be recorded in the eCRF (Section 6.3).

9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

Study drug must be permanently discontinued for patients meeting any of the criteria presented in Section 8.4.4.

Treatment with study drug may also be discontinued for any of the following reasons:

- Adverse event.
- Major protocol deviation (as evaluated by the sponsor).
- Progressive disease. Treatment beyond initial investigator-assessed RECIST Version 1.1-defined progression is acceptable in subjects experiencing investigator-assessed clinical benefit and tolerating study therapy. Such subjects must discontinue therapy when further progression is documented [33]. To ensure that these patients are not exposed to unreasonable risks by continued use of the investigational agents continuation on treatment is only allowed in the absence of clinical symptoms or signs indicating clinically significant PD, if there is no decline in ECOG performance status and in the absence of rapid PD or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent

alternative medical intervention. Patients in these situations with available standard-of-care options need to be re-consented at the time of the first evidence of PD (Section 9.4.1).

- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.

Once study drug has been discontinued, all study procedures outlined for the EOT 1 visit will be completed as specified in the SOEs (Appendix A). The primary reason for study drug discontinuation will be recorded on the eCRF.

Patients who are withdrawn from treatment during the dose-escalation safety lead-in phase and the Part 1 limited cohort expansion phase for reasons other than DLT will be replaced (Section 6.2).

Note that some patients may discontinue study drug for reasons other than progressive disease before completing the full treatment course; these patients will remain in the study for posttreatment assessments as outlined in the SOEs until disease progression occurs or a new anticancer treatment starts, whichever comes first.

9.8 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Study (or study arm) terminated by sponsor.
- Withdrawal by subject.

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database after the end of treatment visit 30 days after last dose is completed.

9.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

Patients will receive a sufficient quantity of TAK-580 for each treatment period and a diary in which to record their dosing. The study center staff will check the patient's diary versus the patient's supply of remaining study drug at each study visit to ensure proper compliance with dosing. Patients who are not compliant with the dosing schedule may be withdrawn from the study.

TAK-202, nivolumab, ipilimumab and vedolizumab are administered IV at the site.

9.10 Posttreatment Follow-up Assessments (Progression-free Survival and Overall Survival)

Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 12 (±1) weeks from the EOT 1 visit until the occurrence of PD, the start of subsequent systemic anticancer therapy, until 2 posttreatment CT scan evaluations are performed, or study (treatment arm) final cutoff date, whichever occurs first. Patients who experience PD on or off study treatment will be followed every 12 (±1) weeks to assess for OS and for subsequent systemic anticancer therapy. In addition, patients who have not initiated a subsequent systemic anticancer therapy will have safety visits 60 (±10) days (EOT 2) and 90 (±10) days (EOT 3) after the last dose of study treatment.

After the occurrence of PD or the start of subsequent systemic anticancer therapy, patients will continue to have OS follow-up visits. The OS visits should be conducted every 12 (±1) weeks after documented PD or new systemic treatment is initiated, until death, until 1 year after the last dose of study drug, or study (or treatment arm) final cutoff date, whichever occurs first. The final analyses for the CSR may be conducted after prespecified events (PD and death) have occurred for the event-driven PFS analysis conducted after all patients enrolled in the study have had the opportunity to complete 50 weeks of treatment. Each treatment arm can be assessed separately if enrollment is completed or is discontinued.

Survivor information may be collected by methods that include telephone, e-mail, mail, or retrieved from online or other databases (eg, social security indexes). In addition, information on the start of another anticancer therapy will be collected. The EOT 1 visit (and EOT 2 and EOT 3 visits, if applicable) is to be completed at the time the patient withdraws from the study during the follow-up period. See the SOEs (Appendix A) for appropriate assessments during follow-up.

NOTE: Related SAEs must be reported at any time point during the trial to the Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug and that occur during the posttreatment follow-up. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 Adverse Event Definition

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

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 Serious Adverse Event Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, 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.

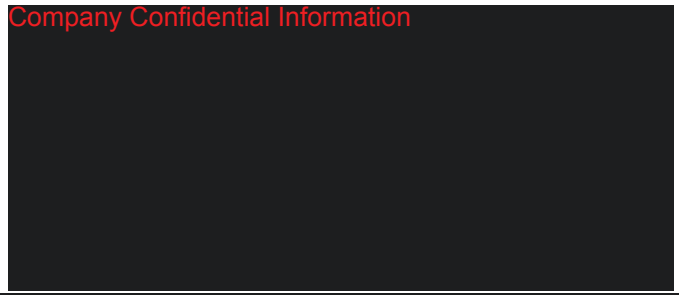
In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03 effective date 14 June 2010 [32]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) 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 (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. 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 or serious pretreatment event may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information*



Planned hospital admissions or surgical procedures for an illness or disease that existed *before study drug was given* are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the toxicity grade of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the toxicity grade of the event and the causality of the event in relation to study procedures.

Toxicity grade for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [32]. The criteria are provided in the Study Manual.

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: "Is there a reasonable possibility that the AE is associated with the study drug?"

10.3 Monitoring of Adverse Events and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the first dose of study drug through 30 days after the last dose of study drug and recorded in the eCRFs.
- Serious pretreatment AEs will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to first dose of study drug, and will also be recorded in the eCRF. For consented patients who do not meet inclusion criteria (ie, are considered screen failures), serious pretreatment AEs will be reported as above for 30 days from the date of screen failure.
- Related and unrelated SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug through *30* days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. 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).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, 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 the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or email addresses below:

Product	Call center	Phone number	E-mail	Fax
TAK-580 **TAK-202** **Entyvio®**	Company Confidential Information			

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Company Confidential Information (refer to Section 10.2)

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency (EMA), investigators and IRBs or independent ethics committees (IECs), as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

10.7 Risk Assessment and Minimization for PML (RAMP Program for Subjects Administered Vedolizumab [Arm 3])

Natalizumab (Tysabri®), another integrin receptor antagonist, has been associated with PML, a rare and often fatal opportunistic infection of the central nervous system. PML is caused by JCV and typically only occurs in patients who are immunocompromised [34,35]. MAdCAM-1 is mainly expressed on gut endothelial cells and plays a critical role in the homing of T lymphocytes to tissues within the GI tract, while VCAM-1 mediates trafficking to the central nervous system. Natalizumab is a pan-α4 integrin antagonist that binds to both the α4β1 and α4β7 integrins and inhibits cellular adhesion to VCAM-1 and MAdCAM-1 [36,37]. In contrast, vedolizumab binds to the α4β7 integrin only [38] and inhibits adhesion to MAdCAM-1, but not VCAM-1. Although no cases of PML have been reported in clinical trials with vedolizumab to date, a risk of PML cannot be ruled out.

To address the theoretical risk of the development of PML in patients treated with vedolizumab, the sponsor, with input from PML experts, has developed a Risk Minimization Action Plan for PML, the RAMP. The complete description of the RAMP program, including materials and instructions for its implementation and monitoring, is included in the Study Manual.

The RAMP is focused on early clinical detection and management of that specific safety risk, including the discontinuation of study drug, if applicable. Patients are assessed for signs and symptoms of PML prior to the administration of each dose of study drug using a PML checklist (available in Appendix F and in the Study Manual). Patients with a positive PML subjective symptom checklist at any time after enrollment in a vedolizumab clinical study will be evaluated according to a prespecified algorithm (the PML Case Evaluation Algorithm). 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. All patients receiving vedolizumab will have a LTFU assessment 6 months (±2 weeks) after their last dose of vedolizumab irrespective of study participation status. The specific form is located in the Study Manual.

To ensure success of the RAMP program, site personnel will be trained to recognize the features of PML. Educational materials for teaching site personnel about PML and the RAMP procedures will be distributed to all sites and are included in the Study Manual. Patients will also receive a PML Patient Brochure that provides detailed information about PML (beyond that which is described in the ICF). This document is also included in the Study Manual. Formal teaching and training will be performed for site personnel prior to the start of the study. Any documented case of PML will be reported as an SAE, regardless of whether hospitalization occurs.

Patients treated with vedolizumab IV in Arm 3 will be followed for 6 months after their last dose of vedolizumab to assess for PML to be compliant with a postapproval regulatory commitment.

11.0 STUDY-SPECIFIC COMMITTEES

For the dose-escalation safety lead-in and Part 1 limited cohort expansion phases, no separate steering committee, data safety monitoring committee, or clinical endpoint committee is planned. Patient safety will be discussed in weekly or biweekly meetings with investigators, other site personnel and sponsor representatives. The main outcomes of these meetings will be DLT determination/confirmation, dose-escalation decision, determinations of MTD or recommended dose for the Part 1 and Part 2 expansion, and confirmation of the safety profile and antitumor activity for each treatment Arm throughout the enrollment period of the Part 1 expansion phase before making the decision of opening Part 2 for enrollment. Meetings will be documented in minutes that need to be approved by the voting members. For more details, refer to Cohort Management Plan.

Patient safety during the Part 2 expansion phase will continue to be monitored by the sponsor along with participating investigators with periodic (monthly) review of enrollment and ongoing clinical data. These meetings will be documented in minutes that will be approved by the voting members and distributed to all participating investigators. This meeting can issue recommendations about the conduct of the study and the need for changes in the protocol and/or the ICF to address new findings/safety concerns.

In addition to the safety review processes described above, the sponsor will conduct internal quarterly safety reviews of the aggregate safety data of this study derived from the clinical database through the independent pharmacovigilance safety reporting mechanism (SAE/EOI reporting) and review of the literature/CSRs that may provide new insights into safety signals associated with non-clinical/clinical studies evaluating similar treatment combinations. This internal safety review can issue recommendations about the conduct of the study and changes in the protocol and/or informed consent to address new finding/safety concerns.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 eCRFs

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing

application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% CIs for time-to-event data.

Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report.

13.1.1 Analysis Sets

The populations used for analysis will include the following:

- **Safety population**: The Safety population is defined as all patients who receive at least 1 dose, even if incomplete, of study treatment (TAK-580, TAK-202, or vedolizumab). Patients will be analyzed according to the treatment actually received.
- **Response-Evaluable population**: The Response-Evaluable population is defined as all patients with advanced melanoma, with measurable disease at baseline, who receive at least 1 dose of study treatment and have at least 1 postbaseline response assessment.
- **DLT-Evaluable population**: The DLT-Evaluable population, defined as all patients in the study who either experience DLT during the 1st 8 weeks (6 weeks for patients assigned to Arm 3) of treatment or have received at least 6 doses of TAK-580 (Arm 1), 3 doses of TAK-202 (Arm 2), or 3 doses of vedolizumab (Arm 3) and 3 doses of nivolumab (plus ipilimumab), and have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred, will be used for the analysis of DLT.
- **PK-Evaluable populations**: The populations of patients evaluable for the determination of the PK of TAK-580, TAK-202 and vedolizumab are defined as all patients in the study for whom there are sufficient dosing and TAK-580, TAK-202, and vedolizumab concentration-time data.

13.1.2 Analysis of Demographics and Other Baseline Disease Characteristics:

The demographic and baseline characteristics will be summarized in a descriptive fashion. Data to be evaluated will include age, gender, race, weight, baseline disease characteristics, histology, and genotype status.

13.1.3 Efficacy Analysis

The primary efficacy endpoint is ORR, defined as CR+PR. The estimate of the RR will be presented with 2-sided 95% exact binomial CIs for each treatment arm. The number and percentage of patients in each response category will be tabulated for each treatment arm based on RECIST, Version 1.1. The secondary efficacy endpoints include PFS, DOR, and OS. PFS is defined as the time from the date of first dose of treatment to the date of first documentation of PD or death due to any cause, whichever occurs first. The censoring method will be described in the SAP. DOR is defined as the time from the date of first documentation of a response to the date of first documentation of PD. Patients without documentation of PD at the time of analysis will be censored at the date of their last response assessment that is SD or better.

OS is defined as the time from the date of first dose of treatment to the date of death.

PFS, DOR, and OS will be analyzed using the Kaplan-Meier method. DOR will be analyzed based on the responders in the Response-Evaluable population. PFS and OS will be analyzed using the Safety population.

13.1.4 Pharmacokinetic Analysis

Individual and mean TAK-580, TAK-202, and vedolizumab plasma concentration data collected at the time points indicated in the SOEs (Appendix A) will be plotted over time. Descriptive statistics will be presented for plasma concentrations of TAK-580, TAK-202, and vedolizumab by time.

13.1.5 Pharmacodynamic Effect Analysis (Arms 1 and 2)

Company Confidential Information

[redacted]

13.1.6 Safety Analysis

The incidence of DLT will be tabulated for each dose group. The preferred term of individual toxicities will be summarized by their frequency and intensity for each dose group. The DLT-evaluable population will be used for the analysis of DLT.

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the Safety population. Exposure to study treatment and reasons for discontinuation will be tabulated.

TEAEs that occur after administration of the first dose of study treatment and through 30 days after the last dose of study treatment will be tabulated.

Adverse events will be tabulated according to MedDRA and will include the following categories:

- TEAEs.

- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher, drug-related, TEAEs.
- The most commonly reported TEAEs (ie, those events reported by ≥10% of all patients).
- SAEs.
- Drug-related SAEs.

A listing of TEAEs resulting in study drug discontinuation will be provided.

Descriptive statistics for actual values of clinical laboratory parameters (and/or change from baseline) will be presented for all scheduled measurements over time. Mean laboratory values over time may be plotted for key laboratory parameters. Creatinine clearance, derived by the sponsor using Cockcroft-Gault equation (Section 9.4.15.3), will also be assessed as a laboratory parameter.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight over time will be tabulated by scheduled time point. Shift tables for laboratory parameters may be generated on the basis of changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values and/or e-dish plots, may be used to understand the safety profiles of the treatments.

All concomitant medications collected from the first dose throughout the study period will be summarized by preferred term according to the WHO drug dictionary.

Descriptive statistics for the actual values and changes from baseline in ECGs will be tabulated by time point including any unscheduled measurements.

ECOG performance status and change from baseline will be summarized. Shifts from baseline to the worst postbaseline score may be tabulated by treatment arm.

13.2 Interim Analysis and Criteria for Early Termination

No formal IA is planned for this study. However, before entering the Part 2 cohort expansion, a thorough evaluation will be performed of the safety and efficacy in the first 15 patients treated at the MTD/recommended expansion phase dose. Safety and activity stopping rules will be applied (See Section 6.1.3). Each treatment Arm can be terminated independently. The frequency of DLTs in Part 2 will be monitored to ensure it is below 40% (Section 8.2).

13.3 Determination of Sample Size

The number of patients enrolled in this study will be driven initially by the dose escalation part and then by the dose expansion part. A 3+3 dose escalation design will be used with 3 possible dose levels (DL1, DL2, and provision for a DL-1 in case the DL1 is not tolerable) for a sample size of up to 12 patients per arm during dose escalation. The expansion phase will consist of 2

parts. Part 1 will consist of a limited cohort of 15 patients (inclusive of patients in dose escalation at the tolerated dose) for assessment of initial safety and clinical activity in each arm. Among this cohort of 15 patients, if ORR >30% is observed in any treatment arm, that arm may be expanded up to a total of 46 patients (inclusive of the 15 patients from Part 1). This will constitute Part 2. Up to 52 patients may be enrolled in each treatment arm for a total enrollment of up to 156 patients.

A sample size of 46 patients yields a power of 80% with a 1-sided test at the significance level of α=0.05 for a null hypothesis of response rate ≤30% versus an alternative hypothesis of response rate ≥50%. Based on a Simon's optimal 2-stage design, 15 patients will need to be enrolled in the first stage. If there are more than 5 responses (CR or PR) out of these initial 15 patients, an additional 31 patients will be enrolled.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution

guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochures for the investigational agents, a copy of each ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, each ICF) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to ICFs, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICFs, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. Each ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. Each ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICFs and if applicable, the subject authorization form. The ICFs, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The ICFs, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICFs, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, EMA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Events

Schedule of Events Until 1st Disease Response Assessment: Arm 1 (TAK-580 [MLN2480])

	Screening (a)	Week 1	Week 3	Week 5	Week 7	Week 9	Week 11	Week 13	Week 15
		Day 1	Day 15 ±3d	Day 29 ±3d	Day 43 ±3d	Day 57 ±3d	Day 71 ±4d	Day 85 ±4d	Day 99 ±4d
Informed consent	X								
Inclusion/exclusion criteria	X								
Demographics/Medical History	X								
Complete physical examination, height, and body weight measurement	X	X (a)							
Targeted PE (b)			X	X	X	X	X	X	X
Vital signs (c) and oxygen saturation	X	X	X	X	X	X	X	X	X
ECOG performance status	X					X			X
ECHO or MUGA Scan	X					X			
12-lead ECG (d)	X	X				X			X
Disease assessment including CT or MRI (e)	X								X (f)
Disease assessment skin (g)	X					X			X
Monitoring of concomitant medications and procedures (h)	Recorded from the signing of informed consent through 30 days after the last dose of study drug or the start of subsequent anticancer therapy whichever comes first								
Adverse event reporting		Recorded from the 1st dose of study drug through 30 days after the last dose of study drug or the start of subsequent anticancer therapy whichever comes first							
	Serious adverse events will be reported from signing of the informed consent form through 30 days after the last dose of study drug.								

Footnotes are on last table page.

Schedule of Events Until 1st Disease Response Assessment: Arm 1 (TAK-580) (continued)

	Screening (a)	Week 1	Week 3	Week 5	Week 7	Week 9	Week 11	Week 13	Week 15
		Day 1	Day 15 ±3d	Day 29 ±3d	Day 43 ±3d	Day 57 ±3d	Day 71 ±4d	Day 85 ±4d	Day 99 ±4d
Laboratory Assessments									
HIV, Hepatitis B, Hepatitis C, and tuberculosis Screening history (i)	X								
Pregnancy test (j)	X	X (a)		X		X			X
Hematology (k)	X (l)	X (a)	X (l)	X	X	X (l)	X	X	X
Chemistry (m)	X	X (a,n)	X	X (n)	X	X (n)	X	X (n)	X
Liver Function (o)	X	X (a)	X	X	X	X	X	X	X
Urinalysis (p)	X	X (a)	X	X	X	X			X
Immune safety (q)	X	X (a)	X	X	X	X	X		X
Exploratory Studies									
Company Confidential Information									
Company Confidential Information									
Company Confidential Information									
Company Confidential Information									
Study Treatment									
TAK-580 QW dosing PO (v)		X X (w)	X X	X X	X X	X X	X X	X X	X X
Nivolumab Q2W dosing IV (x)			X	X	X	X	X	X	X

Footnotes are on last table page.

Abbreviations: ACTH = adrenocorticotropic hormone; AE = adverse event; ALT = alanine aminotransferase; ANA = antinuclear antibody; ANC = Absolute Neutrophil Count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C_{max} = maximum (peak) concentration; CRF = Case Report Form; CRP = C-reactive protein; CT = computed tomography; DLT = dose-limiting toxicity; ECG = Electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; ICF = informed consent form; INR = international normalized ratio; IRB = institutional review board; IV = intravenous; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition [scan]; PD = progressive disease; PE = physical examination; PK = pharmacokinetic; PO = oral; PT = prothrombin time; QW = once weekly; RBC = red blood cell; RECIST = Response Evaluation Criteria in Solid Tumors; RF = rheumatoid factor; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WBC = white blood cell.

AEs that occur during the Screening period will be recorded as part of the patient's medical history.

For the patients enrolled in the dose-escalation safety lead-in phase and Part 1 limited cohort expansion part of the study, the 1st 8 weeks of study treatment will be the DLT observation period (ie Day 1 to Day 57). An End-of-Cohort meeting scheduled by the sponsor will occur after the last patient in each cohort in the dose-escalation safety lead-in phase has completed the DLT observation period. DLTs will be monitored continuously in patients participating in Part 2.

a Assessments need not be repeated if Screening assessments were performed within 72 hours before TAK-580 dosing, unless otherwise specified. Height is to be collected at Screening only.

b Targeted PE = focused examination including lungs, abdomen, skin, cardiovascular system, and weight.

c Measured vital signs to include blood pressure, heart rate, respiration rate, body temperature, and oxygen saturation. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

d A 12-lead ECG performed in triplicate should be completed after a 5-minute rest period in a supine position and will be recorded at 2 to 5 minute intervals. During active treatment with TAK-580, triplicate ECG should be performed 1-2 hours afterTAK-580 dosing (C_{max}).

e Contrast CT or MRI of chest, abdomen, pelvis and brain, and all known sites of disease should be assessed at baseline screening. Subjects with brain metastases at screening or neurological symptoms should have documentation of prior treatment and no evidence by CT or MRI for active disease.

f Contrast CT or MRI of chest, abdomen, pelvis and brain, and all known sites of disease should be assessed ≤7 days before the Week 15, Day 99 assessment visit using the same modality (contrast CT or MRI) used at baseline screening assessments. Patients with PD based on RECIST v1.1 criteria who are otherwise stable, may remain on treatment until PD is confirmed by a repeat CT or MRI assessment at least 4 weeks from the last assessment.

g Skin lesions should be documented by color photography including a ruler to estimate the size of the lesion at baseline screening. Clinical lesions that can be evaluated by both clinical exam and imaging should have imaging performed at baseline screening.

h Refer to Section 8.5 for prohibited medications and therapies and Section 8.6 for medications or procedures that are restricted or should be used cautiously.

i HIV, hepatitis B surface antigen (HBSAg), hepatitis C antibody (HCV Ab) or hepatitis C RNA (HCV RNA), and tuberculosis screening performed locally according to local practice or IRB requirements.

j Women of childbearing potential only. A negative serum pregnancy test performed locally is required within 72 hours of start of TAK-580 dosing. Serum or urine pregnancy testing performed locally is allowed for all other time points.

k Hematology performed locally and includes hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts only for patients who experience recurrent anemia with hemoglobin <8 g/dL despite blood transfusion, absolute differential, and ANC. Refer to Section 9.4.15.2 for further information.

l Company Confidential Information

m Blood chemistry performed locally and will include glucose, BUN, creatinine, sodium, phosphate, potassium, chloride, HCO_3, uric acid, albumin, lipase, amylase, and calcium.

n Creatine kinase performed locally with blood chemistry every 4th week (eg. Week 1, Day 1, Week 5, Day 29, etc) while on TAK-580 treatment.

o Liver functions performed locally and include LDH, AST, ALT, bilirubin (total and indirect), and alkaline phosphatase.

p Urinalysis performed locally and includes dipstick for blood, protein, pH, specific gravity, ketones, bilirubin, nitrite, urobilinogen, leukocytes and glucose (microscopic examination, if abnormal).

q Immune safety labs performed locally to include: RF, TSH, free T4, ACTH, CRP, and ANA. A serum sample will also be collected and sent to study sponsor for additional safety testing (if needed). Refer to Section 9.4.15.4 for further information. Refer to the Laboratory Manual for details on collection, processing, storage, and shipment of serum samples.

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u Company Confidential Information

v TAK-580 (MLN2480) should be administered in the clinic on PK study days (eg, Week 1, Day 1, Week 3, Day 15, Week 9, Day 57, Week 15, Day 99). On nivolumab dosing days that are not TAK-580 PK study days, the patient may take TAK-580 before the study clinic visit.

w "X X" denotes TAK-580 is taken QW for 2 weeks between study visits.

x Administer nivolumab infusion at least 1 hour after TAK-580 administration.

Schedule of Events After 1st Disease Response Assessment: Arm 1 (TAK-580)

	Wk 17	**Wk 19**	**Wk 21**	**Wk 23**	**Wk 25**	**Wk 27**	**Wk 29**	**Wk 31**	**Wk 33**	**Wk 35**	**Wk 37**	**Wk 39**	**Wk 41**	**Wk 43**	**Wk 45**	**Wk 47**	**Wk 49**	**EOT 1**	**EOT 2**	**EOT 3**	**PFSFU/ OSFU**
	Day 113 ±4d	**Day 127 ±4d**	**Day 141 ±4d**	**Day 155 ±4d**	**Day 169 ±4d**	**Day 183 ±4d**	**Day 197 ±4d**	**Day 211 ±4d**	**Day 225 ±4d**	**Day 239 ±4d**	**Day 253 ±4d**	**Day 267 ±4d**	**Day 281 ±4d**	**Day 295 ±4d**	**Day 309 ±4d**	**Day 323 ±4d**	**Day 337 ±4d**	**30+10d (a)**	**60±10d (a)**	**90±10d (a)**	**Q12W ±1W (§)**
Targeted PE (b) and body weight		X		X		X		X		X		X		X		X		X	X	X	
Vital signs (c) and oxygen saturation		X		X		X		X		X		X		X		X		X			
ECOG performance status						X						X						X			
ECHO or MUGA Scan		X				X						X						X			
12-lead ECG (d)						X						X						X			
Disease assessment including CT or MRI (e)						X(f)						X(f)						X			X
Disease assessment skin (g)						X						X						X			X
Monitoring of concomitant medications and procedures (h)	Recorded from the signing of informed consent through 30 days after the last dose of study drug or the start of subsequent anticancer therapy whichever comes first																				
Adverse event reporting	Recorded from the 1st dose of study drug through 30 days after the last dose of study drug or the start of subsequent anticancer therapy whichever comes first																				
	Serious adverse events will be reported from signing of the informed consent form through 30 days after the last dose of study drug.																				

Footnotes are on last table page.

Schedule of Events After 1st Disease Response Assessment: Arm 1 (TAK-580) (continued)

	Wk 17	Wk 19	Wk 21	Wk 23	Wk 25	Wk 27	Wk 29	Wk 31	Wk 33	Wk 35	Wk 37	Wk 39	Wk 41	Wk 43	Wk 45	Wk 47	Wk 49	EOT 1	EOT 2	EOT 3	PFSFU/ OSFU
	Day 113 ±4d	Day 127 ±4d	Day 141 ±4d	Day 155 ±4d	Day 169 ±4d	Day 183 ±4d	Day 197 ±4d	Day 211 ±4d	Day 225 ±4d	Day 239 ±4d	Day 253 ±4d	Day 267 ±4d	Day 281 ±4d	Day 295 ±4d	Day 309 ±4d	Day 323 ±4d	Day 337 ±4d	30+10d (a)	60±10d (a)	90±10d (a)	Q12W ±1W (§)
Laboratory Assessments																					
Pregnancy test (i)		X		X		X		X		X		X		X		X					
Hematology (j)	X	X	X	X	X	X	X(k)	X	X(k)	X	X(k)	X	X(k)	X	X(k)	X	X(k)	X	X	X	
Chemistry (l)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X	X	X	
Liver Function (n)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X			
Urinalysis (o)						X						X						X			
Immune safety (p)		X		X		X		X				X		X		X		X	X	X	
Exploratory Studies																					
Company Confidential Information																					
Company Confidential Information																					
Company Confidential Information																					
Study Treatment																					
TAK-580 QW dosing PO (u)	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 X	X X	X X				
Nivolumab Q2W dosing IV (v)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Footnotes are on last table page.

Abbreviations: ACTH = adrenocorticotropic hormone; AE =adverse event; ALT = alanine aminotransferase; ANA = antinuclear antibody; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C_{max} = maximum (peak) concentration; CRF = case report form; CRP = C-reactive protein; CT = computed tomography; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ICF = informed consent form; IV = intravenous; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition [scan]; PD = progressive disease; PE = physical examination; PK = pharmacokinetic; PO = by mouth (orally); PT = prothrombin time; Q2W = [dosing] every 2 weeks; QW = once weekly [dosing]; RBC = red blood cell; RECIST = Response Evaluation Criteria for Solid Tumors; RF = rheumatoid factor; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WBC = white blood cell.

a EOT 1 should be conducted 30 (+10) days after the last dose of study drug. Discontinued patients who have not initiated another systemic anticancer treatment will also have additional safety visits at 60 (±10) days (EOT 2) and 90 (±10) days (EOT 3) after the last dose.

b Targeted PE = focused examination including lungs, abdomen, skin, cardiovascular system, and weight.

c Measured vital signs to include blood pressure, heart rate, respiration rate, body temperature, and oxygen saturation. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

d A 12-lead ECG performed in triplicate should be completed after a 5-minute rest period in a supine position and will be recorded at 2 to 5 minute intervals. During active treatment with TAK-580, triplicate ECGs should be performed 1-2 hours after TAK-580 dosing (C_{max}) and before nivolumab treatment.

e Contrast CT or MRI of chest, abdomen, pelvis and brain, and all known sites of disease should be assessed ≤7 days before the scheduled assessment visit using the same modality (Contrast CT or MRI) used at baseline screening assessments. Similar assessments should be performed every 12 weeks until disease progression or completion of 50 weeks of study participation (whichever comes first). Patients who continue on study treatment beyond the 50-week planned treatment period should continue undergoing disease response assessments every 12 weeks.

f Patients with PD based on RECIST Version 1.1 criteria who are otherwise stable, may remain on treatment until PD is confirmed by a repeat CT or MRI assessment at least 4 weeks from last assessment.

g Skin lesions should be documented by color photography including a ruler to estimate the size of the lesion at each assessment. Clinical lesions that can be evaluated by both clinical examination and imaging should have imaging performed at each assessment.

h Refer to Section 8.5 for prohibited medications and therapies and Section 8.6 for medications or procedures that are restricted or should be used cautiously.

i Women of childbearing potential only. Serum or urine pregnancy testing performed locally.

j Hematology performed locally every 2 weeks and includes hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts only for patients who experience recurrent anemia with hemoglobin <8 g/dL, despite blood transfusion, absolute differential, and ANC. Refer to Section 9.4.15.2 for further information.

k Hematology only for patients with previous abnormal values that were considered either AEs or for patients who in the opinion of the investigator warrant closer scrutiny.

l Blood chemistry performed locally every 4 weeks and includes creatine kinase (while on TAK-580 treatment), glucose, BUN, creatinine, sodium, phosphate, potassium, chloride, HCO_3, uric acid, albumin, lipase, amylase, and calcium.

m Biochemistry and liver function tests only for patients with previous abnormal values that were considered either AEs or who in the opinion of the investigator warrant closer scrutiny.

n Liver function tests performed locally include LDH, AST, ALT, bilirubin (total and indirect) and alkaline phosphatase.

o Urinalysis performed locally includes dipstick for blood, protein, pH, specific gravity, ketones, bilirubin, nitrite, urobilinogen, leukocytes and glucose (microscopic examination, if abnormal).

p Immune safety labs performed locally to include: RF, TSH, free T4, ACTH, CRP, and ANA. A serum sample will also be collected and sent to the study sponsor for additional safety testing (if needed). Refer to Section 9.4.15.4 for further information. Refer to the Laboratory Manual for details on collection, processing, storage, and shipment of serum samples.

q Company Confidential Information [redacted]

r Company Confidential Information [redacted]

s Company Confidential Information [redacted]

t In addition to the scheduled PK sample collections, a blood sample to measure TAK-580 plasma concentrations should be obtained, if clinically feasible, at the time of a serious or unusual AE that is judged by the investigator to be treatment-related, irrespective of the week or day of occurrence of the AE. See Section 9.4.20.

u TAK-580 (MLN2480) should be administered in the clinic on PK study days (eg, Week 15, Day 99, Week 27, Day 183, and Week 39, Day 267). On nivolumab dosing days that are not TAK-580 PK study days, the patient may take TAK-580 before the study clinic visit.

v Administer nivolumab infusion at least 1 hour after TAK-580 administration.

§ Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 12 (±1) weeks from the EOT 1 visit until the occurrence of PD, the start of subsequent systemic anticancer therapy, until 2 posttreatment CT scan evaluations are performed, or study (treatment arm) final cut off date, whichever occurs first. Patients who experience PD on or off study treatment will be followed every 12 (±1) weeks to assess for OS and for subsequent systemic anticancer therapy. The OS visits should be conducted every 12 (±1) weeks after documented PD until death, until 1 year after the last dose of study drug, or study (treatment arm) final cut off, whichever occurs first.

Schedule of Events Until 1st Disease Response Assessment: Arm 2 (TAK-202 [MLN1202])

	Screening (a)	**Week 1**	**Week 3**	**Week 5**	**Week 7**	**Week 9**	**Week 11**	**Week 13**	**Week 15**
		Day 1	**Day 15 ±3d**	**Day 29 ±3d**	**Day 43 ±3d**	**Day 57 ±3d**	**Day 71 ±4d**	**Day 85 ±4d**	**Day 99 ±4d**
Informed consent	X								
Inclusion/exclusion criteria	X								
Demographics/Medical History	X								
Complete physical examination, height, and body weight measurement	X	X (a)							
Targeted PE (b)			X	X	X	X	X	X	X
Vital signs (c) and oxygen saturation	X	X	X	X	X	X	X	X	X
ECOG performance status	X					X			X
12-lead ECG (d)	X	X				X			
Disease assessment including CT or MRI (e)	X								X (f)
Disease assessment skin (g)	X					X			X
Monitoring of concomitant medications and procedures (h)	Recorded from the signing of informed consent through 30 days after the last dose of study drug or the start of subsequent anticancer therapy whichever comes first								
Adverse event reporting		Recorded from the 1st dose of study drug through 30 days after the last dose of study drug or the start of subsequent anticancer therapy whichever comes first							
	Serious adverse events will be reported from signing of the informed consent form through 30 days after the last dose of study drug.								

Footnotes are on last table page.

Schedule of Events Until 1st Disease Response Assessment: Arm 2 (TAK-202 [MLN1202]) (continued)

	Screening (a)	Week 1	Week 3	Week 5	Week 7	Week 9	Week 11	Week 13	Week 15
		Day 1	Day 15 ±3d	Day 29 ±3d	Day 43 ±3d	Day 57 ±3d	Day 71 ±4d	Day 85 ±4d	Day 99 ±4d
Laboratory Assessments									
HIV, Hepatitis B, Hepatitis C, and tuberculosis Screening history (i)	X								
Pregnancy test (j)	X	X (a)		X		X			X
Hematology (k)	X (l)	X (a)	X (l)	X	X	X (l)	X	X	X
Chemistry (m)	X	X (a)	X	X	X	X	X	X	X
Liver Function (n)	X	X (a)	X	X	X	X	X	X	X
Urinalysis (o)	X	X (a)	X	X		X			X
Immune safety (p)	X	X (a)	X	X	X	X	X		X
Exploratory Studies									
Company Confidential Information									
Company Confidential Information									
Company Confidential Information									
Company Confidential Information									
Company Confidential Information									
Study Treatment									
TAK-202 dosing IV		X	X	X		X		X	
Nivolumab Q2W dosing IV (u)			X	X	X	X	X	X	X

Footnotes are on last table page.

Abbreviations: ACTH = adrenocorticotropic hormone; AE = adverse event; ALT = alanine aminotransferase; ANA = antinuclear antibody; ANC = Absolute Neutrophil Count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C_{max} = maximum (peak) concentration; CRF = Case Report Form; CRP = C-reactive protein; CT = computed tomography; DLT = dose-limiting toxicity; ECG = Electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; ICF = informed consent form; INR = international normalized ratio; IRB = institutional review board; IV = intravenous; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition [scan]; PD = progressive disease; PE = physical examination; PK = pharmacokinetic; PT = prothrombin time; Q2W = [dosing] every 2 weeks; RBC = red blood cell; RECIST = Response Evaluation Criteria for Solid Tumors; RF = rheumatoid factor; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WBC = white blood cell.

For the patients enrolled in the dose-escalation safety lead-in phase and Part 1 limited cohort expansion phase of the study, the 1st 8 weeks of study treatment will be the DLT observation period (ie, Day 1 to Day 57). An End-of-Cohort meeting scheduled by the sponsor will occur after the last patient in each cohort in the dose-escalation safety lead-in phase has completed the DLT observation period. DLTs will be monitored continuously in patients participating in Part 2.

AEs that occur during the Screening period will be recorded as part of the patient's medical history.

a Assessments need not be repeated if Screening assessments were performed within 72 hours before TAK-202 dosing, unless otherwise specified. Height is to be collected at Screening only.

b Targeted PE = focused examination including lungs, abdomen, skin, cardiovascular system, and weight.

c Measured vital signs to include blood pressure, heart rate, respiration rate, body temperature, and oxygen saturation. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

d Single 12-lead ECG after the administration of TAK-202.

e Contrast CT or MRI of chest, abdomen, pelvis and brain, and all known sites of disease should be assessed at baseline screening. Subjects with brain metastases at screening should have documentation of prior treatment and no evidence by CT or MRI for active disease.

f Contrast CT or MRI of chest, abdomen, pelvis and brain, and all known sites of disease should be assessed ≤7 days before the Week 15, Day 99 assessment visit using the same modality (contrast CT or MRI) used at baseline screening assessments. Patients with PD based on RECIST v1.1 criteria who are otherwise stable, may remain on treatment until PD is confirmed by a repeat CT or MRI assessment at least 4 weeks from last assessment.

g Skin lesions should be documented by color photography including a ruler to estimate the size of the lesion at baseline screening. Clinical lesions that can be evaluated by both clinical examination and imaging should have imaging performed at baseline screening.

h Refer to Section 8.5 for prohibited medications and therapies and Section 8.6 for medications or procedures that are restricted or should be used cautiously.

i HIV, hepatitis B surface antigen (HBSAg), hepatitis C antibody (HCV Ab) or hepatitis C RNA (HCV RNA), and tuberculosis screening performed locally per local practice or IRB requirements.

j Women of childbearing potential only. A negative serum pregnancy test performed locally is required within 72 hours before the start of TAK-202 dosing. Serum or urine pregnancy testing performed locally is allowed for all other time points.

k Hematology performed locally and includes hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts only for patients who experience recurrent anemia with hemoglobin <8 g/dL, despite blood transfusion, absolute differential, and ANC. Refer to Section 9.4.15.2 for further information.

l [redacted]

m Blood chemistry performed locally will include glucose, BUN, creatinine, sodium, phosphate, potassium, chloride, HCO_3, uric acid, albumin, lipase, amylase, and calcium.

n Liver function tests performed locally include LDH, AST, ALT, bilirubin (total and indirect) and alkaline phosphatase.

o Urinalysis performed locally includes dipstick for blood, protein, pH, specific gravity, ketones, bilirubin, nitrite, urobilinogen, leukocytes and glucose (microscopic examination, if abnormal).

p Immune safety labs performed locally to include: RF, TSH, free T4, ACTH, CRP, and ANA. A serum sample will also be collected and sent to the study sponsor for additional safety testing (if needed). Refer to Section 9.4.15.4 for further information. Refer to the Laboratory Manual for details on collection, processing, storage, and shipment of serum samples.

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u Administer nivolumab infusion at least 30 minutes after TAK-202 administration and if patient does not present symptoms of infusional reaction.

Schedule of Events After 1st Disease Response Assessment: Arm 2 (TAK-202 [MLN1202])

	Wk 17	**Wk 19**	**Wk 21**	**Wk 23**	**Wk 25**	**Wk 27**	**Wk 29**	**Wk 31**	**Wk 33**	**Wk 35**	**Wk 37**	**Wk 39**	**Wk 41**	**Wk 43**	**Wk 45**	**Wk 47**	**Wk 49**	**EOT 1**	**EOT 2**	**EOT 3**	**PFSFU/ OSFU**
	Day 113 ±4d	**Day 127 ±4d**	**Day 141 ±4d**	**Day 155 ±4d**	**Day 169 ±4d**	**Day 183 ±4d**	**Day 197 ±4d**	**Day 211 ±4d**	**Day 225 ±4d**	**Day 239 ±4d**	**Day 253 ±4d**	**Day 267 ±4d**	**Day 281 ±4d**	**Day 295 ±4d**	**Day 309 ±4d**	**Day 323 ±4d**	**Day 337 ±4d**	**30+10d (a)**	**60±10d (a)**	**90±10d (a)**	**Q12W ±1W (§)**
Targeted PE (b) and body weight		X		X		X		X		X		X		X		X		X	X	X	
Vital signs (c) and oxygen saturation		X		X		X		X		X		X		X		X		X			
ECOG performance status						X						X						X			
12-lead ECG (d)																		X			
Disease assessment including CT or MRI (e)						X (f)						X (f)						X			X
Disease assessment skin (g)						X						X						X			X
Monitoring of concomitant medications and procedures (h)	Recorded from the signing of informed consent through 30 days after the last dose of study drug or the start of subsequent anticancer therapy whichever comes first																				
Adverse event reporting	Recorded from the 1st dose of study drug through 30 days after the last dose of study drug or the start of subsequent anticancer therapy whichever comes first																				
	Serious adverse events will be reported from signing of the informed consent form through 30 days after the last dose of study drug.																				

Footnotes are on last table page.

Schedule of Events After 1st Disease Response Assessment: Arm 2 (TAK-202 [MLN1202]) (continued)

	Wk 17	Wk 19	Wk 21	Wk 23	Wk 25	Wk 27	Wk 29	Wk 31	Wk 33	Wk 35	Wk 37	Wk 39	Wk 41	Wk 43	Wk 45	Wk 47	Wk 49	EOT 1	EOT 2	EOT 3	PFSFU/ OSFU
	Day 113 ±4d	Day 127 ±4d	Day 141 ±4d	Day 155 ±4d	Day 169 ±4d	Day 183 ±4d	Day 197 ±4d	Day 211 ±4d	Day 225 ±4d	Day 239 ±4d	Day 253 ±4d	Day 267 ±4d	Day 281 ±4d	Day 295 ±4d	Day 309 ±4d	Day 323 ±4d	Day 337 ±4d	30+10d (a)	60±10d (a)	90±10d (a)	Q12W ±1W (§)
Laboratory Assessments																					
Pregnancy test (i)		X		X		X		X		X		X		X		X					
Hematology (j)	X(k)	X	X(k)	X	X(k)	X	X(k)	X	X(k)	X	X(k)	X	X(k)	X	X(k)	X	X(k)	X	X	X	
Chemistry (l)	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X	X	
Liver Function (n)	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X			
Urinalysis (o)						X						X						X			
Immune safety (p)		X		X		X		X		X		X		X		X		X	X	X	
Exploratory Studies																					
Company Confidential Information																					
Company Confidential Information																					
Company Confidential Information																					
Company Confidential Information																					
Study Treatment																					
TAK-202 Q4W Dosing IV	X		X		X		X		X		X		X		X		X				
Nivolumab Q2W Dosing IV (u)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Footnotes are on last table page.

Abbreviations: ACTH = adrenocorticotropic hormone; AE = adverse event; ALT = alanine aminotransferase; ANA = antinuclear antibody; ANC = Absolute Neutrophil Count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C_{max} = maximum (peak) concentration; CRF = Case Report Form; CRP =C-reactive protein; CT = computed tomography; DLT = dose-limiting toxicity; ECG = Electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ICF = informed consent form; IV = intravenous; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition [scan]; PD = progressive disease; PE = physical examination; PK = pharmacokinetic; PT = prothrombin time; Q2W = [dosing] every 2 weeks; Q4W = [dosing] every 4 weeks; RBC = red blood cell; RECIST = Response Evaluation Criteria for Solid Tumors; RF = rheumatoid factor; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WBC = white blood cell.

a EOT 1 should be conducted 30 (+10) days after the last dose of study drug. Discontinued patients who have not initiated another systemic anticancer treatment will also have additional safety visits at 60 (±10) days (EOT 2) and 90 (±10) days (EOT 3) after the last dose.

b Targeted PE = focused examination including lungs, abdomen, skin, cardiovascular system, and weight.

c Measured vital signs to include blood pressure, heart rate, respiration rate, body temperature, and oxygen saturation. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

d Single 12-lead ECG after the administration of TAK-202.

e Contrast CT or MRI of chest, abdomen, pelvis and brain, and all known sites of disease should be assessed ≤7 days before the scheduled assessment visit using the same modality (Contrast CT or MRI) used at baseline screening assessments. Similar assessments should be performed every 12 weeks until disease progression or completion of 50 weeks of study participation (whichever comes first). Patients who continue on study treatment beyond the 50 week planned treatment period should continue undergoing disease response assessments every 12 weeks.

f Patients with PD based on RECIST Version 1.1 criteria who are otherwise stable, may remain on treatment until PD is confirmed by a repeat CT or MRI assessment at least 4 weeks from the last assessment.

g Skin lesions should be documented by color photography including a ruler to estimate the size of the lesion at each assessment. Clinical lesions that can be evaluated by both clinical examination and imaging should have imaging performed at each assessment.

h Refer to Section 8.5 for prohibited medications and therapies and Section 8.6 for medications or procedures that are restricted or should be used cautiously.

i Women of childbearing potential only. Serum or urine pregnancy testing performed locally.

j Hematology performed locally every 2 weeks includes hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts only for patients who experience recurrent anemia with hemoglobin <8 g/dL despite blood transfusion, absolute differential, and ANC. Refer to Section 9.4.15.2 for further information.

k Hematology only for patients with previous abnormal values that were considered either AEs or for patients who in the opinion of the investigator warrant closer scrutiny.

l Blood chemistry performed locally every 4 weeks will include glucose, BUN, creatinine, sodium, phosphate, potassium, chloride, HCO_3, uric acid, albumin, lipase, amylase, and calcium.

m Biochemistry and liver function tests only for patients with previous abnormal values that were considered either AEs or for patients who in the opinion of the investigator warrant closer scrutiny.

n Liver function tests performed locally include LDH, AST, ALT, bilirubin (total and indirect) and alkaline phosphatase.

o Urinalysis performed locally includes dipstick for blood, protein, pH, specific gravity, ketones, bilirubin, nitrite, urobilinogen, leukocytes and glucose (microscopic examination, if abnormal).

p Immune safety labs performed locally include: RF, TSH, free T4, ACTH, CRP, and ANA. A serum sample will also be collected and sent to the study sponsor for additional safety testing (if needed). Refer to Section 9.4.15.4 for further information. Refer to the Laboratory Manual for details on collection, processing, storage, and shipment of serum samples.

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t Company Confidential Information

u Administer nivolumab infusion at least 30 minutes after TAK-202 administration and if patient does not present symptoms of infusional reaction.

§ Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 12 (±1) weeks from the EOT 1 visit, until the occurrence of PD, the start of subsequent systemic anticancer therapy, until 2 posttreatment CT scan evaluations are performed, or study (treatment arm) final cut off date, whichever occurs first. Patients who experience PD on or off study treatment will be followed every 12 (±1) weeks to assess for OS and for subsequent systemic anticancer therapy. The OS visits should be conducted every 12 (±1) weeks after documented PD until death, until 1 year after the last dose of study drug, or study (treatment arm) final cut off, whichever occurs first.

Schedule of Events Until 1st Disease Response Assessment: Arm 3 (Vedolizumab plus Nivolumab plus Ipilimumab)

	Screening (a)	Week 1	Week 3	Week 4	Week 5	Week 7	Week 10	Week 13	Week 15
		Day 1	Day 15 ±3d	Day 22 ±3d	Day 29 ±3d	Day 43 ±3d	Day 64 ±3d	Day 85 ±4d	Day 99 ±4d
Informed consent	X								
Inclusion/exclusion criteria	X								
Demographics/Medical History	X								
Complete physical examination, height, and body weight measurement	X	X (a)							
Targeted PE (b)			X	X	X	X	X	X	X
Vital signs (c) and oxygen saturation	X	X	X	X	X	X	X	X	X
ECOG performance status	X						X		X
12-lead ECG (d)	X	X							
Disease assessment including CT or MRI (e)	X							X(f)	
Disease assessment skin (g)	X						X	X	
PML checklist (h)	X	X	X		X			X	
Monitoring of concomitant medications and procedures (i)	Recorded from the signing of informed consent through 30 days after the last dose of study drug or the start of subsequent anticancer therapy whichever comes first								
Adverse event reporting		Recorded from the 1st dose of study drug through 30 days after the last dose of study drug or the start of subsequent anticancer therapy whichever comes first							
	Serious adverse events will be reported from signing of the informed consent form through 30 days after the last dose of study drug.								

Footnotes are on last table page.

Schedule of Events Until 1st Disease Response Assessment: Arm 3 (Vedolizumab plus Nivolumab plus Ipilimumab) (continued)

	Screening (a)	Week 1	Week 3	Week 4	Week 5	Week 7	Week 10	Week 13	Week 15
		Day 1	Day 15 ± 3d	Day 22 ±3d	Day 29 ±3d	Day 43 ±3d	Day 64 ±3d	Day 85 ±4d	Day 99 ±4d
Laboratory Assessments									
HIV, Hepatitis B, Hepatitis C, and tuberculosis screening history (j)	X								
Pregnancy test (k)	X	X (a)					X	X	X
Hematology (l)	X	X (a)		X		X	X	X	X
Chemistry (m)	X	X (a)		X		X	X	X	X
Liver Function (n)	X	X (a)		X		X	X	X	X
Urinalysis (o)	X	X (a)		X		X	X	X	X
Immune safety (p)	X	X (a)		X		X	X	X	X
Exploratory Studies									
Company Confidential Information									
Company Confidential Information									
Company Confidential Information									
Company Confidential Information									
Company Confidential Information									
Study Treatment									
Vedolizumab dosing IV		X	X		X			X	
Nivolumab Q3W dosing IV (u)		X		X		X	X		
Ipilimumab Q3W dosing IV (v)		X		X		X	X		
Nivolumab Q2W dosing IV (w)								X	X

Footnotes are on last table page.

Abbreviations: ACTH = adrenocorticotropic hormone; AE = adverse event; ALT = alanine aminotransferase; ANA = antinuclear antibody; ANC = Absolute Neutrophil Count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C_{max} = maximum (peak) concentration; CRF = Case Report Form; CRP = C-reactive protein; CT = computed tomography; DLT = dose-limiting toxicity; ECG = Electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; ICF = informed consent form; INR = international normalized ratio; IRB = institutional review board; IV = intravenous; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition [scan]; PD = progressive disease; PE =physical examination; PK = pharmacokinetic; PT = prothrombin time; Q2W = [dosing] every 2 weeks; Q3W = [dosing] every 3 weeks; RBC = red blood cell; RF = rheumatoid factor; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WBC = white blood cell.

For the patients enrolled in the dose-escalation safety lead-in phase and Part 1 of the limited cohort expansion part of study, the 1st 8 weeks of study treatment will be the DLT observation period (ie, Day 1 to Day 57). An End-of-Cohort meeting scheduled by the sponsor will occur after the last patient in each cohort in the dose-escalation safety lead-in phase has completed the DLT observation period. DLTs will be monitored continuously in patients participating in Part 2.
AEs that occur during the Screening period will be recorded as part of the patient's medical history.

a Assessments need not be repeated if Screening assessments were performed within 72 hours before vedolizumab dosing, unless otherwise specified. Height is to be collected at Screening only.

b Targeted PE = focused examination including lungs, abdomen, skin, cardiovascular system, and weight.

c Measured vital signs to include blood pressure, heart rate, respiration rate, body temperature, and oxygen saturation. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

d Single 12-lead ECG after treatment administration.

e Contrast CT or MRI of chest, abdomen, pelvis and brain, and all known sites of disease should be assessed at baseline screening. Subjects with brain metastases at screening should have documentation of prior treatment and no evidence by CT or MRI for active disease.

f Contrast CT or MRI of chest, abdomen, pelvis and brain, and all known sites of disease should be assessed ≤7 days before the Week 13, Day 85 assessment visit using the same modality (contrast CT or MRI) used at baseline screening assessments. Patients with PD based on RECIST Version 1.1 criteria who are otherwise stable, may remain on treatment until PD is confirmed by a repeat CT or MRI assessment at least 4 weeks from last assessment.

g Skin lesions should be documented by color photography including a ruler to estimate the size of the lesion at baseline screening. Clinical lesions that can be evaluated by both clinical exam and imaging should have imaging performed at baseline screening.

h During scheduled clinic visits, trained site personnel will complete the PML subjective checklist for each patient to assess for signs and symptoms of PML at screening and before the administration of each dose of vedolizumab. Refer to Section 10.7 for further details. The PML checklists are provided in Appendix F and the Risk Assessment and Minimization for PML (RAMP) and other related information are contained in the Study Manual.

i Refer to Section 8.5 for prohibited medications and therapies and Section 8.6 for medications or procedures that are restricted or should be used cautiously.

j HIV, hepatitis B surface antigen (HBSAg), hepatitis C antibody (HCV Ab) or hepatitis C RNA (HCV RNA), and tuberculosis screening performed locally per local practice or IRB requirements.

k Women of childbearing potential only. A negative serum pregnancy test performed locally is required within 72 hours of start of vedolizumab dosing. Serum or urine pregnancy testing performed locally is allowed for all other time points.

l Hematology performed locally includes hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts only for patients who experience recurrent anemia with hemoglobin <8 g/dL despite blood transfusion, absolute differential, and ANC. Refer to Section 9.4.15.2 for further information.

m Blood chemistry performed locally will include glucose, BUN, creatinine, sodium, phosphate, potassium, chloride, HCO_3, uric acid, albumin, lipase, amylase, and calcium.

n Liver function tests performed locally include LDH, AST, ALT, bilirubin (total and indirect) and alkaline phosphatase.

o Urinalysis performed locally includes dipstick for blood, protein, pH, specific gravity, ketones, bilirubin, nitrite, urobilinogen, leukocytes and glucose (microscopic examination, if abnormal).

p Immune safety labs performed locally to include: RF, TSH, free T4, ACTH, CRP, and ANA. A serum sample will also be collected and sent to the study sponsor for additional safety testing (if needed). Refer to Section 9.4.15.4 for further information. Refer to the Laboratory Manual for details on collection, processing, storage, and shipment of serum samples.

q Company Confidential Information .

r Company Confidential Information

s Company Confidential Information

t Company Confidential Information

u When administered on the same day, administer nivolumab infusion at least 30 minutes after vedolizumab administration.

v Administer ipilimumab infusion at least 30 minutes after nivolumab administration.

w Note: nivolumab dosing is 3 mg/kg (or 240 mg flat dose) IV every 2 weeks starting Week 13, Day 85.

Schedule of Events After 1st Disease Response Assessment: Arm 3 (Vedolizumab plus Nivolumab plus Ipilimumab)

	Wk 17	**Wk 19**	**Wk 21**	**Wk 23**	**Wk 25**	**Wk 27**	**Wk 29**	**Wk 31**	**Wk 33**	**Wk 35**	**Wk 37**	**Wk 39**	**Wk 41**	**Wk 43**	**Wk 45**	**Wk 47**	**Wk 49**	**EOT 1**	**EOT 2**	**EOT 3**	**PFSFU/ OSFU**
	Day 113 ±4d	**Day 127 ±4d**	**Day 141 ±4d**	**Day 155 ±4d**	**Day 169 ±4d**	**Day 183 ±4d**	**Day 197 ±4d**	**Day 211 ±4d**	**Day 225 ±4d**	**Day 239 ±4d**	**Day 253 ±4d**	**Day 267 ±4d**	**Day 281 ±4d**	**Day 295 ±4d**	**Day 309 ±4d**	**Day 323 ±4d**	**Day 337 ±4d**	**30+10d (a)**	**60±10d (a)**	**90±10d (a)**	**Q12W ±1W (§)**
Targeted PE (b)	X	X		X		X		X		X		X		X		X		X	X	X	
Vital signs (c) and oxygen saturation	X	X		X		X		X		X		X		X		X		X			
ECOG performance status	X					X						X						X			
PML LTFU (d)												X									
Disease assessment including CT or MRI (e)						X (f)						X (f)						X			X
Disease assessment skin (g)						X						X						X			X
Monitoring of concomitant medications and procedures (h)	Recorded from the signing of informed consent through 30 days after the last dose of study drug or the start of subsequent anticancer therapy whichever comes first																				
Adverse event reporting	Recorded from the 1st dose of study drug through 30 days after the last dose of study drug or the start of subsequent anticancer therapy whichever comes first																				
	Serious adverse events will be reported from signing of the informed consent form through 30 days after the last dose of study drug.																				

Footnotes are on last table page.

Schedule of Events After 1st Disease Response Assessment: Arm 3 (Vedolizumab plus Nivolumab plus Ipilimumab) (continued)

	Wk 17	Wk 19	Wk 21	Wk 23	Wk 25	Wk 27	Wk 29	Wk 31	Wk 33	Wk 35	Wk 37	Wk 39	Wk 41	Wk 43	Wk 45	Wk 47	Wk 49	EOT 1	EOT 2	EOT 3	PFSFU/ OSFU
	Day 113 ±4d	Day 127 ±4d	Day 141 ±4d	Day 155 ±4d	Day 169 ±4d	Day 183 ±4d	Day 197 ±4d	Day 211 ±4d	Day 225 ±4d	Day 239 ±4d	Day 253 ±4d	Day 267 ±4d	Day 281 ±4d	Day 295 ±4d	Day 309 ±4d	Day 323 ±4d	Day 337 ±4d	30 +10d (a)	60 ±10d (a)	90 ±10d (a)	Q12W ±1W (§)
Laboratory Assessments																					
Pregnancy test (i)		X		X		X		X		X		X		X		X					
Hematology (j)	X(k)	X	X(k)	X	X(k)	X	X(k)	X	X(k)	X	X(k)	X	X(k)	X	X(k)	X	X(k)	X	X	X	
Chemistry (l)	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X	X	
Liver Function (n)	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X	X(m)	X			
Urinalysis (o)		X				X				X				X				X			
Immune safety (p)		X				X				X				X				X	X	X	
Exploratory Studies																					
Company Confidential Information																					
I Company Confidential Information (																					
Company Confidential Information																					
Company Confidential Information																					
Company Confidential Information																					
Study Treatment																					
Vedolizumab dosing IV (u)																					
Nivolumab Q2W dosing IV	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Footnotes are on last table page.

Abbreviations: ACTH = adrenocorticotropic hormone; AE = adverse event; ALT = alanine aminotransferase; ANA = antinuclear antibody; ANC = Absolute Neutrophil Count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C_{max} = maximum (peak) concentration; CRF = Case Report Form; CRP = C-reactive protein; CT = computed tomography; DLT = dose-limiting toxicity; ECG = Electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ICF = informed consent form; IV = intravenous; LTFU=long-term follow-up; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition [scan]; PD = progressive disease; PE = physical examination; PK = pharmacokinetic; PT = prothrombin time; Q2W = [dosing] every 2 weeks; RBC = red blood cell; RECIST = Response Evaluation Criteria for Solid Tumors; RF = rheumatoid factor; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WBC = white blood cell.

a EOT 1 should be conducted 30 (+10) days after the last dose of study drug. Discontinued patients who have not initiated another systemic anticancer treatment will also have additional safety visits at 60 (±10) days (EOT 2) and 90 (±10) days (EOT 3) after the last dose.

b Targeted PE = focused examination including lungs, abdomen, skin, cardiovascular system, and weight.

c Measured vital signs to include blood pressure, heart rate, respiration rate, body temperature, and oxygen saturation. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

d PML long-term follow-up (LTFU) questionnaire administered by site personnel to each patient (whether on active treatment or discontinued) 6 months (±2 weeks) after the last dose of vedolizumab. Refer to Section 10.7 for further details.

e Contrast CT or MRI of chest, abdomen, pelvis and brain, and all known sites of disease should be assessed ≤7 days before the scheduled assessment visit using the same modality (Contrast CT or MRI) used at baseline screening assessments. Similar assessments should be performed every 12 weeks until disease progression or completion of 50 weeks of study participation (whichever comes first). Patients who continue on study treatment beyond the 50 week planned treatment period should continue undergoing disease response assessments every 12 weeks.

f Patients with PD based on RECIST Version 1.1 criteria who are otherwise stable, may remain on treatment until PD is confirmed by a repeat CT or MRI assessment at least 4 weeks from the last assessment.

g Skin lesions should be documented by color photography including a ruler to estimate the size of the lesion at each assessment. Clinical lesions that can be evaluated by both clinical examination and imaging should have imaging performed at each assessment.

h Refer to Section 8.5 for prohibited medications and therapies and Section 8.6 for medications or procedures that are restricted or should be used cautiously.

i Women of childbearing potential only. Serum or urine pregnancy testing performed locally.

j Hematology performed locally every 2 weeks includes hemoglobin, hematocrit, platelet counts, RBC, WBC, absolute reticulocyte counts only for patients who experience recurrent anemia with hemoglobin <8 g/dL despite blood transfusion, absolute differential, and ANC. Refer to Section 9.4.15.2 for further information.

k Hematology only for patients with previous abnormal values that were considered either AEs or for patients who in the opinion of the investigator warrant closer scrutiny.

l Blood chemistry performed locally every 4 weeks and will include glucose, BUN, creatinine, sodium, phosphate, potassium, chloride, HCO_3, uric acid, albumin, lipase, amylase, and calcium.

m Biochemistry and liver function tests only for patients with previous abnormal values that were considered either AEs or for patients who in the opinion of the investigator warrant closer scrutiny.

n Liver function tests performed locally include LDH, AST, ALT, bilirubin (total and indirect) and alkaline phosphatase.

o Urinalysis performed locally includes dipstick for blood, protein, pH, specific gravity, ketones, bilirubin, nitrite, urobilinogen, leukocytes and glucose (microscopic examination, if abnormal).

p Immune safety labs performed locally include: RF, TSH, free T4, ACTH, CRP, and ANA. A serum sample will also be collected and sent to the study sponsor for additional safety testing (if needed). Refer to Section 9.4.15.4 for further information. Refer to the Laboratory Manual for details on collection, processing, storage, and shipment of serum samples.

q Company Confidential Information [redacted]

r Company Confidential Information [redacted].

s Company Confidential Information [redacted]

t Company Confidential Information [redacted]

u Additional vedolizumab dosing allowed for patients with ≥Grade 2 diarrhea or colitis (nivolumab dosing should be held).

§ Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 12 (±1) weeks from the EOT 1 visit until the occurrence of PD, the start of subsequent systemic anticancer therapy, until 2 posttreatment CT scan evaluations are performed, or study (treatment arm) final cut off date, whichever occurs first. Patients who experience PD on or off study treatment will be followed every 12 (±1) weeks to assess for OS and for subsequent systemic anticancer therapy. The OS visits should be conducted every 12 (±1) weeks after documented PD until death, until 1 year after the last dose of study drug, or study (treatment arm) final cut off, whichever occurs first.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572).

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.

12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55.

Appendix E List of Relevant Cytochrome P450 Inhibitors and Clinically Significant Enzyme Inducers

Strong CYP2C8 Inhibitors	
gemfibrozil	
Clinically Significant Enzyme Inducers	
carbamazepine	rifampin
phenobarbital	rifapentine
phenytoin	St. Johns Wort
rifabutin	

Note that these lists are not exhaustive.
Source: fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

a The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a strong CYP3A inhibitor when a certain preparation was used (eg, high dose, double strength) or as a moderate CYP3A inhibitor when another preparation was used (eg, low dose, single strength).

b Withdrawn from the United States market because of safety reasons.

Appendix F PML Checklist

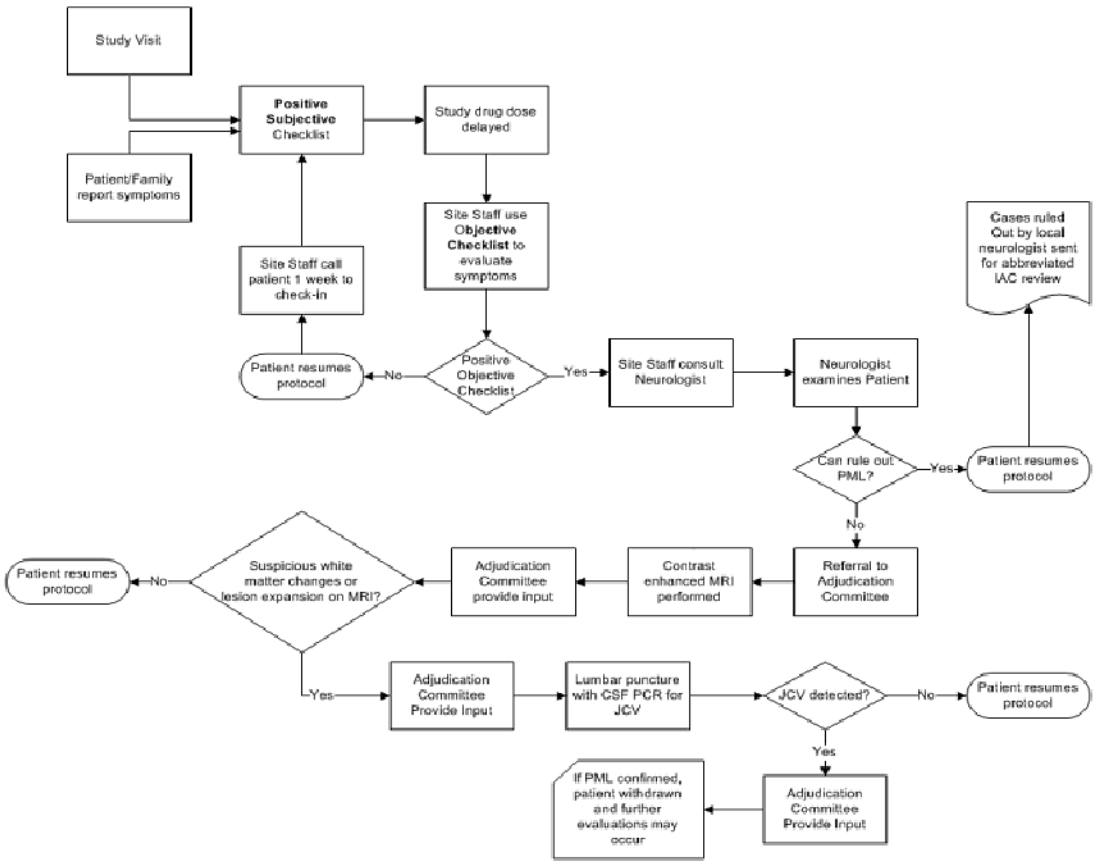
Center ID	Subject ID	Subject Initials
— — —	— — —	— — —

PML Checklists

Instructions

- Administer at specified visits and phone calls as outlined in the schedule of events in the protocol and ad hoc for patient reported symptoms.
- The purpose of this checklist is to identify a definite change in the patient's neurological status from the previous evaluation.
- For all positive subjective findings that are identified, the corresponding objective test must be performed. Please record all positive subjective findings as an adverse event.
- Refer to a Neurologist when there is a definite change in neurological status. Where possible, use the proposed objective tests to confirm a change that warrants referral.
- Any positive subjective or objective findings should be communicated immediately to your CRA and Takeda.

Case Evaluation Algorithm



Center ID	Subject ID	Subject Initials
— — —	— — —	— — —

Subjective PML Checklist

Symptoms	"Compared to how you usually feel, have you had a significant change in any of the following?"		If the answer is "Yes", obtain a description of the symptom(s) with examples.	Applicable Objective Test(s): Document results on PML Objective Checklist
	Yes	No		
1. Have you been experiencing any persistent difficulty with your vision such as loss of vision or double vision? Have you been having trouble with reading?				Test visual fields and ocular motility.
2. Have you been experiencing any persistent difficulty speaking or having your speech understood by others?				Casual observation of speech output for dysarthria or aphasia. Ask patient to name a few objects and repeat a multipart phrase.
3. Have you been experiencing any persistent weakness in an arm or a leg?				Test for pronator drift (Barré maneuver) and/or fixation on arm roll. Assess the ability to hop on either foot; foot and finger tapping. Test symmetric muscle strength.
4. Have you noticed yourself regularly bumping into things or having difficulty writing?				Ask for spontaneous writing sample and observe finger to nose, heel to shin, and tandem gait.
5. Have you regularly been experiencing difficulty understanding others?				Ability to follow serial commands (Close your eyes, stick out your tongue, and touch your left finger to your left ear)
6. Have you had persistent problems with your memory or thinking?				Recall of 3 objects over 1 minute with distraction; ability to follow commands.
7. Have you been experiencing any persistent numbness or other loss of sensation?				Test sensation side to side with pinprick.

_____ _____ _____ _____

Printed Name Date Signature Date
Checklist Administrator Checklist Administrator

Objective PML Checklist – To be completed for patients with positive subjective finding

Perform the objective test(s) that correspond to the subjective checklist finding

Positive Symptom(s)	Applicable Objective Test(s)	Test Result(s)		If test result is abnormal, briefly describe result
		Normal	Abnormal	
1. Difficulty with vision or reading	Test visual fields and ocular motility			
2. Difficulty with speaking	Casual observation of speech output for dysarthria or aphasia. Ask patient to name a few objects and repeat a multipart phrase.			
3. Weakness in an arm or a leg	Test for pronator drift and/or fixation on arm roll. Assess the ability to hop on either foot; foot and finger tapping. Test muscle strength.			
4. Bumping into things or difficulty writing	Ask for spontaneous written sample and observe finger to nose, heel to shin, and tandem gait			
5. Difficulty understanding others	Ability to follow serial commands (Close your eyes, stick out your tongue, and touch your left finger to your left ear)			
6. Problems with memory or thinking	Recall of 3 objects over 1 minute with distraction; ability to follow commands.			
7. Problems with numbness	Test sensation side to side with pinprick.			

- If the objective test corroborates the reported symptom, refer the subject for a Neurology consult. Otherwise, please follow-up with the subject one week after the objective checklist was administered to ensure symptoms are not recurring.
- Please notify your CRA and Takeda of any positive objective checklist findings.

_____ _____ _____ _____

Printed Name Date Signature Date

Checklist Administrator Checklist Administrator

_____ _____

PI Signature Date

Appendix G Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment No. 02. In Existing Text, changed or deleted text is *italicized* and underscored. In Revised Text, newly added or changed text is **bolded**.

Page 1, Title Page

Added Text

Date	Amendment Number	Amendment Type	Region
11 January 2016	Initial Protocol	Not applicable	Global
26 May 2016	01	Substantial	Global
18 October 2016	**02**	**Substantial**	**Global**

Rationale for Amendment

Updated Amendment History table.

Page 2, Section 1.0, Administrative

Existing Text [in header]

TAK-580

Revised Text

TAK-202

Rationale for Amendment

To improve alignment between IND submission and investigational medicinal product (IMP).

Page 5, Section 1.3, Protocol Amendment No. 02 Summary of Changes

Rationale for Amendment

Updated Section 1.3 to highlight changes made in Amendment 02; consistent with Appendix G (Detailed Description of Amendments to Text).

Page 15, Section 2.0, Study Summary, Compounds

Existing Text

TAK-202 (MLN1202)

Revised Text

TAK-202 (MLN1202**; plozalizumab**)

Rationale for Amendment

Updated TAK-202 nomenclature to include the recommended International Nonproprietary Name (INN) designation. This change also appears in Section 4.2.2, Section 4.3.2, and Section 8.10.2.

Page 15, Section 2.0, Study Summary, Number of Sites

Existing Text

Estimated total: *2-15* in *the United States* and Europe

Revised Text

Estimated total: **25** in **North America** and Europe

Rationale for Amendment

Updated the number and location of sites on the basis of updated enrollment projections. These changes also appear in Section 6.2.

Page 15, Section 2.0, Study Summary, Dose Levels

Existing Text

Nivolumab: 3 mg/kg Q2W (standard of care)

Nivolumab + Ipilimumab (standard of care):

Nivo*lumab* (1 mg/kg) + Ipi*limumab* (3 mg/kg) Q3W for 4 doses; then Nivo*lumab* (3 mg/kg) Q2W until disease progression or unacceptable toxicity

Revised Text

Nivolumab: 3 mg/kg **or 240 mg flat dose** Q2W (standard of care)

Nivolumab **(Nivo)** *+ Ipilimumab* **(Ipi)** (standard of care):

Nivo (1 mg/kg) + **Ipi** (3 mg/kg) Q3W for 4 doses; then **Nivo without Ipi** (3 mg/kg **or 240 mg flat dose**) Q2W until disease progression or unacceptable toxicity

Rationale for Amendment

Updated standard of care nivolumab dosing to include 240 mg flat dosing as a possible alternative to 3 mg/kg reflecting the recent FDA-approval of flat dosing; consistent with similar changes in Section 8.1, Figure 8.a, Section 8.1.4, and Section 8.10.4.4.

Page 16, Section 2.0, Study Summary, Main Criteria for Inclusion

Existing Text

- *In lieu of participating in this study, the* patient *would receive* nivolumab or nivolumab + ipilimumab at the dose(s) and schedule(s) *proposed as a* recommended standard of care *treatment*

Revised Text

- **Patients must be eligible for treatment with** nivolumab or nivolumab+ipilimumab at the dose(s) and schedule(s) recommended **as** standard of care.

Rationale for Amendment

All enrolled patients must be eligible for standard of care melanoma therapy. This change also appears in Section 7.1.

Page 16, Section 2.0, Study Summary, Main Criteria for Inclusion

Existing Text

Disease accessible for repeat biopsy and willingness to undergo serial tumor biopsies.

Revised Text

For Arms 1 and 2 only: Disease accessible for repeat biopsy and willingness to undergo serial tumor biopsies.

Rationale for Amendment

Clarification that only patients enrolled in Arms 1 or 2 will undergo serial tumor biopsies. Serial tumor biopsies will not be collected from patients enrolled in Arm 3 due to the elimination of the 2-week SA vedolizumab dosing in this arm. This change also appears in Section 4.4.4, Section 5.1.3, Section 6.1.2, Section 6.1.3, Section 7.1, Section 9.4.16.3, and Section 13.1.5.

Page 16, Section 2.0, Study Summary, Main Criteria for Exclusion

Existing Text

- *Ocular melanoma.*
- *Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2 antibodies. Previous anti-CTLA-4 therapies are excluded only for patients to be enrolled in Arm 3.*
  - *Note that* prior *non-immunotherapy systemic, adjuvant or neoadjuvant melanoma* therapy *is permitted if it was completed at least* 2 weeks prior to first dose, and *all* related *adverse events (AEs) have either* returned to baseline or *stabilized.*

Revised Text

- **Subjects who completed a** prior therapy **<**2 weeks prior to first dose and **for whom AEs** related **to prior therapy had not** returned to baseline or **improved to Grade 1**.

Rationale for Amendment

Due to the many rapid changes in the treatment of melanoma, it is necessary to widen the target population of this trial. Regardless of these modifications, the main inclusion criterion of this study is that all enrolled patients are eligible for standard of care nivolumab (or nivolumab+ ipilimumab), which now includes patients diagnosed with ocular melanoma. The same changes were made in Section 7.2.

Page 27, Section 4.2.2, TAK-202 (MLN1202; plozalizumab)

Added Text

4.2.2 TAK-202 (MLN1202; **plozalizumab**)

Rationale for Amendment

Updated the header to include the recommended INN assigned to TAK-202. The same change was made to Section 2.0, Section 4.3.2 and Section 8.10.2.

Page 31, Section 4.3.2, TAK-202 (MLN1202; plozalizumab)

Added Text

4.3.2 TAK-202 (MLN1202; **plozalizumab**)

Rationale for Amendment

Updated the header to include the recommended INN assigned to TAK-202. The same change was made to Section 2.0, Section 4.2.2, and Section 8.10.2.

Page 33, Section 4.4, Rationale for the Proposed Study

Existing Text

Further, this study will evaluate whether novel SA therapies influence the tumor microenvironment prior to T-cell checkpoint inhibition and whether changes observed (by immunohistochemistry [IHC], gene expression and cytokine/chemokine profiling) to the tumor microenvironment may be predictive for antitumor efficacy with the novel combination therapy.

Revised Text

Further, this study will evaluate whether novel SA therapies **(TAK-580 and TAK-202)** influence the tumor microenvironment prior to T-cell checkpoint inhibition and whether changes observed (by immunohistochemistry [IHC], gene expression and cytokine/chemokine profiling) to the tumor microenvironment may be predictive for antitumor efficacy with the novel combination therapy.

Rationale for Amendment

Clarification that only TAK-580 and TAK-202 will be administered during the 2-week lead-in period as single-agent therapy. This change also appears in Section 6.1.1, Section 6.1.3, and Section 8.1, Figure 8.a.

Page 36, Section 4.4.3, Arm 3: Nivolumab plus Ipilimumab plus Vedolizumab, as anti-α4β7 monoclonal antibody

Existing Text

In this study, Arm 3 will evaluate the safety, activity, *and the effects* of vedolizumab *on the tumor microenvironment as a monotherapy and* in combination with the anti-PD-1 mAb nivolumab and the anti-CTLA-4 mAb ipilimumab. The combination of nivolumab plus ipilimumab is now approved for the treatment of patients with metastatic melanoma, with the combination showing greater activity than either drug alone. However, it also displays a higher rate of irAEs and treatment discontinuations. The hypothesis for Arm 3 of this study is that the specificity of vedolizumab restricts its activity to the GI tract and gut lymph tissue and its use in the prevention of GI irAEs will *1) have no negative impact on T-cell trafficking to tumor or T-cell subpopulations within the tumor microenvironment, and 2)* reduce treatment-associated GI

irAEs resulting in clinical benefit with a better safety profile in patients with advanced melanoma receiving checkpoint inhibitor combination therapy.

Revised Text

In this study, Arm 3 will evaluate the safety **and** activity of vedolizumab in combination with the anti-PD-1 mAb nivolumab and the anti-CTLA-4 mAb ipilimumab. The combination of nivolumab plus ipilimumab is now approved for the treatment of patients with metastatic melanoma, with the combination showing greater activity than either drug alone. However, it also displays a higher rate of irAEs and treatment discontinuations. The hypothesis for Arm 3 of this study is that the specificity of vedolizumab restricts its activity to the GI tract and gut lymph tissue and its use in the prevention of GI irAEs will reduce treatment-associated GI irAEs resulting in clinical benefit with a better safety profile in patients with advanced melanoma receiving checkpoint inhibitor combination therapy.

Rationale for Amendment

Patients enrolled in Arm 3 will not have the 2-week lead-in period of dosing with vedolizumab only. Due to its mechanism of action, vedolizumab is not expected to impact the tumor microenvironment or have any SA activity. Therefore, standard of care antimelanoma treatment will begin on Week 1, Day 1, concurrent with the first dose of vedolizumab. As a consequence, collection of serial tumor biopsies from these patients is not necessary.

Page 36, Section 4.4.3, Arm 3: Nivolumab plus Ipilimumab plus Vedolizumab, as anti-α4β7 monoclonal antibody

Added Text

Recent research suggests a novel inter-relationship among the colonic microbiome, antitumor immunity, and the efficacy of anti-CTLA-4 or anti-PD-1 inhibitors [22-25]. Furthermore, the composition of fecal microbiota correlates with susceptibility to anti-CTL4-A induced colitis [26]. Therefore, the stool microbiome of patients enrolled in Arm 3 will be analyzed pre- and post-treatment to assess whether changes in the microbiome correlate with safety (diarrhea/colitis and other irAEs) and/or antitumor activity.

Rationale for Amendment

To provide rationale for serial stool collection for fecal microbiome assessments in patients enrolled in Arm 3. Similar changes appear in Section 5.1.3, Section 5.2.3, Section 9.4.18, and Section 9.4.19.

Page 37, Section 4.4.4, Rationale for Tumor Characterization

Existing Text

Fresh tumor biopsies, pre- and post-SA treatment and post-combination treatment with checkpoint inhibitors will be requested from *all* patients with the goal of broadly characterizing the factors underlying each patient's sensitivity/resistance to the respective treatment combination. In addition, an optional biopsy will be requested from patients who initially respond to study treatment and then relapse to identify the mechanism underlying the development of resistance.

Revised Text

Fresh tumor biopsies, pre- and post-SA treatment and post-combination treatment with checkpoint inhibitors will be requested from patients **participating in Arms 1 and 2** with the goal of broadly characterizing the factors underlying each patient's sensitivity/resistance to the respective treatment combination. In addition, an optional biopsy will be requested from patients who initially respond to study treatment and then relapse to identify the mechanism underlying the development of resistance.

Rationale for Amendment

To be consistent with elimination of tumor biopsies in patients in Arm 3 (Section 4.4.3), specification that tumor biopsy samples will be collected from patients in Arms 1 and 2 only. Similar changes appear in Section 5.1.3, Section 5.2.3, Section 6.1.2, Section 6.1.3, Section 7.1, Section 9.4.16.3, and Section 13.1.5.

Page 40, Section 5.1.3, Additional Objectives

Existing Text

The additional objectives are:

- Company Confidential Information
- [redacted]
- [redacted]
- [redacted]

Revised Text

The additional objectives are:

- Company Confidential Information
- [redacted]
- [redacted]
- [redacted]

- Company Confidential Information [redacted]

Rationale for Amendment

Clarified which additional objective was relevant to each treatment arm(s). Inclusion of 1 more additional objective for Arm 3 to assess GI-specific characteristics. Related changes were made in Section 5.2.3.

Page 41, Section 5.2.3, Additional Endpoints

Existing Text

- Company Confidential Information [redacted]

Revised Text

- Company Confidential Information [redacted]

Rationale for Amendment

Clarification of assessments of exploratory endpoints to be consistent with changes made to Section 4.4.3 and Section 5.1.3. Similar changes also appear in related study procedures including Section 9.4.15.4, Section 9.4.16.1, Section 9.4.16.3, Section 9.4.17, Section 9.4.18, and Section 9.4.19.

Page 42, Section 6.1.1, Dose-Escalation Safety Lead-in Phase

Existing Text

Each combination will be evaluated for DLTs (Section 8.2) through the 1st 8 weeks of study treatment.

Revised Text

Each combination will be evaluated for DLTs (Section 8.2) through the 1st 8 weeks **(6 weeks for Arm 3)** of study treatment.

Rationale for Amendment

As a consequence of the elimination of the 2-week SA vedolizumab lead-in, the DLT observation period in Arm 3 is reduced to 6 weeks consistent with changes made in Section 6.2, Section 8.1, Figure 8.a, Section 8.3, and Section 13.1.1.

Page 43, Section 6.1.2, Part 1: Limited Expansion To Further Characterize Safety of the Combination and Obtain Preliminary Clinical Activity

Existing Text

A total of 15 patients (inclusive of dose-escalation safety lead-in patients treated with the same dose) will be enrolled in each arm at the dose and schedule identified to be tolerable in the initial dose-escalation safety lead-in phase. From this population, a safety profile of the combination will be developed and initial observations relative to clinical activity and effects of SA versus combination therapy on the tumor microenvironment will be evaluated.

Revised Text

A total of 15 patients (inclusive of dose-escalation safety lead-in patients treated with the same dose) will be enrolled in each arm at the dose and schedule identified to be tolerable in the initial dose-escalation safety lead-in phase. From this population, a safety profile of the combination will be developed **(all arms)** and initial observations relative to clinical activity and effects of SA versus combination therapy on the tumor microenvironment will be evaluated **(Arms 1 and 2 only)**.

Rationale for Amendment

Added distinction that safety will be examined in all arms; however, only Arms 1 and 2 will be evaluated for effects on the tumor environment. Consistent with changes in Section 2.0, Section 4.4.4, Section 5.1.3, Section 5.2.3, Section 6.1.3, Section 7.1, Section 9.4.16.3, and Section 13.1.5.

Page 45, Section 6.1.3, Part 2: Additional Expansion Based on the Initial Clinical Activity

Existing Text

A total of approximately 156 patients are expected to enroll in this study. Once enrolled, patients will be administered a single investigational agent for 2 weeks after which a second biopsy will be performed to assess the pharmacodynamic effects of the investigational agent in the tumor (Section 9.4.16.3). Then, standard-of-care checkpoint inhibitor(s) will be administered (nivolumab in Arms 1 and 2 or nivolumab + ipilimumab in Arm 3). A third tumor biopsy will be performed at the end of the initial 8-week period to investigate the effects of the combination treatment in the tumor.

Revised Text

A total of approximately 156 patients are expected to enroll in this study. Once enrolled, patients **in Arms 1 and 2** will be administered a single investigational agent for 2 weeks after which a second biopsy will be performed to assess the pharmacodynamic effects of the investigational agent in the tumor (Section 9.4.16.3). Then, standard-of-care checkpoint inhibitor(s) will be administered (nivolumab in Arms 1 and 2 or nivolumab + ipilimumab in Arm 3). **For patients assigned to Arms 1 and 2, a** third tumor biopsy will be performed at the end of the initial 8-week period to investigate the effects of the combination treatment in the tumor.

Rationale for Amendment

Added specification that only patients in Arms 1 and 2 would undergo tumor biopsies; consistent with changes made to Section 5.1.3, Section 6.1.2, Section 7.1, Section 9.4.16.3, and Section 13.1.5.

Page 46, Section 6.1.3, Part 2: Additional Expansion Based on the Initial Clinical Activity

Existing Text

Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 12 weeks from the EOT 1 visit until the occurrence of PD, the start of subsequent systemic anticancer therapy, until *6 months after the patient discontinued treatment*, or the trial (or arm) final cutoff date, whichever occurs first. In addition, patients treated with vedolizumab IV will be specifically evaluated 6 months after their last dose of vedolizumab for safety (PML long-term follow-up LTFU; in Study Manual) to be compliant with a postapproval regulatory commitment.

Revised Text

Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 12 **(±1)** weeks from the EOT 1 visit until the occurrence of PD, the start of subsequent systemic anticancer therapy, until **2 posttreatment CT scan evaluations are performed**, or the trial (or arm) final cutoff date, whichever occurs first. In addition, patients treated with vedolizumab IV will be specifically evaluated 6 months **(±2 weeks)** after their last dose of vedolizumab for safety (PML long-term follow-up **[**LTFU**]**; in Study Manual) to be compliant with a postapproval regulatory commitment.

Rationale for Amendment

To adjust the SOE during the follow-up period to avoid inconsistencies in the timing of the evaluations. The same change appears in Section 6.3, Section 9.10, and Appendix A.

Page 46, Section 6.1.3, Part 2: Additional Expansion Based on the Initial Clinical Activity

Existing Text

After the occurrence of PD or the start of subsequent systemic anticancer therapy, patients will continue to have OS follow-up visits. The OS visits should be conducted every 12 weeks after documented PD or a new systemic treatment is initiated, until death, until 1 year after the last dose of study drug, or the trial (or arm) final cutoff date, whichever occurs first.

Revised Text

After the occurrence of PD or the start of subsequent systemic anticancer therapy, patients will continue to have OS follow-up visits. The OS visits should be conducted every 12 **(±1)** weeks after documented PD or a new systemic treatment is initiated, until death, until 1 year after the last dose of study drug, or the trial (or arm) final cutoff date, whichever occurs first.

Rationale for Amendment

To incorporate some flexibility in the timing of follow-up evaluations. The same change appears in Section 9.10 and Appendix A.

Page 47, Section 6.1.3, Part 2: Additional Expansion Based on the Initial Clinical Activity

Existing Text

Company Confidential Information

[redacted]

Revised Text

Radiological evaluations (computed tomography [CT] scan or magnetic resonance imaging [MRI] as clinically indicated) and clinical measures (using calipers and photographs for visible/palpable lesions) will be employed to assess the status of the patient's underlying disease, and serial blood samples will be collected for tumor-specific markers (if applicable). An evaluation of disease response using RECIST guidelines (Version 1.1) will be performed within

7 days of the start of Week 15 **for patients assigned to Arms 1 or 2 or Week 13 for Arm 3** of Study Treatment and then every 12 **(±1)** weeks while on study.

Company Confidential Information

[redacted]

Rationale for Amendment

Clarification of the timing for disease response assessment in each study arm and specification that only patients in Arms 1 and 2 undergo tumor biopsies; consistent with changes made in Section 5.1.3, Section 7.1, and Appendix A.

Page 47, Section 6.2, Number of Patients

Existing Text

Approximately 156 patients will be enrolled in this study from approximately *2 to 15* study centers in North America and Europe. A patient is considered to be enrolled in the study after receiving 1 dose (even incomplete) of any study drug. Procedures for completion of the enrollment information are described in the Study Manual.

Patients participating in the dose-escalation safety lead-in and part 1 limited cohort expansion who are withdrawn from treatment during the 1st 8 weeks of treatment for reasons other than DLTs will be replaced. The DLT-evaluable population consists of all patients in the dose-escalation safety lead-in phase and part 1 of the expansion phase of the study who either experience DLT during the first 8 weeks of treatment or who have received at least 6 doses of TAK-580 (Arm 1), 3 doses of the TAK-202 (Arm 2), or 3 doses of vedolizumab (Arm 3), and 3 doses of nivolumab (alone or in combination with ipilimumab), and have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred. Patients discontinued during the part 2 cohort expansion phase will not be replaced.

Revised Text

Approximately 156 patients will be enrolled in this study from approximately **25** study centers in North America and Europe. A patient is considered to be enrolled in the study after receiving 1 dose (even incomplete) of any study drug. Procedures for completion of the enrollment information are described in the Study Manual.

Patients participating in the dose-escalation safety lead-in and Part 1 limited cohort expansion who are withdrawn from treatment during the 1st 8 weeks of treatment **(6 weeks for patients assigned to Arm 3)** for reasons other than DLTs will be replaced. The DLT-evaluable population consists of all patients in the dose-escalation safety lead-in phase and Part 1 of the expansion phase of the study who either experience DLT during the first 8 weeks of treatment **(6 weeks for patients assigned to Arm 3)** or who have received at least 6 doses of TAK-580 (Arm 1), 3 doses of the TAK-202 (Arm 2), or 3 doses of vedolizumab (Arm 3), and 3 doses of nivolumab (alone or in combination with ipilimumab), and have sufficient follow-up data to

allow the investigators and sponsor to determine whether DLT occurred. Patients discontinued during the Part 2 cohort expansion phase will not be replaced.

Rationale for Amendment

Updated the number of study sites and corrected the text to be consistent with changed dosing schedule in Arm 3 as shown in Section 8.1, Figure 8.a. Similar changes appear in Section 6.1.1, Section 8.3, and Section 13.1.1.

Page 48, Section 6.3, Duration of Study

Existing Text

PFS follow-up will also be conducted at the site every 12 weeks from the EOT 1 visit until the occurrence of PD, the start of subsequent systemic anticancer therapy, until 6 months after the patient discontinued treatment, or the final cutoff date, whichever occurs first. Patients who experience PD on or off study treatment will be followed every 3 months or until final cutoff to assess for OS and for subsequent systemic anticancer therapy. The final data cutoff for the CSR may proceed after prespecified events (PD and death) have occurred for the event-driven PFS analysis conducted after all patients enrolled in the study have had the opportunity to complete 50 weeks of treatment. It will be possible to perform final cutoffs and data analysis for each arm independently in case of premature closure or uneven enrollment.

Revised Text

PFS follow-up will also be conducted at the site every 12 **(±1)** weeks from the EOT 1 visit until the occurrence of PD, the start of subsequent systemic anticancer therapy, until **2 posttreatment CT scan evaluations are performed**, or the final cutoff date, whichever occurs first. Patients who experience PD on or off study treatment will be followed every 3 months or until final cutoff to assess for OS and for subsequent systemic anticancer therapy. The final data cutoff for the CSR may proceed after prespecified events (PD and death) have occurred for the event-driven PFS analysis conducted after all patients enrolled in the study have had the opportunity to complete 50 weeks of treatment. It will be possible to perform final cutoffs and data analysis for each arm independently in case of premature closure or uneven enrollment.

Rationale for Amendment

To incorporate some flexibility in the timing of follow-up evaluations and to be consistent with changes made in Section 6.1.3, Section 9.10, and Appendix A.

Page 49, Section 7.1, Inclusion Criteria

Existing Text

3. *In lieu of participating in this study, the* patient *would receive* nivolumab or nivolumab + ipilimumab at the dose(s) and schedule(s) *proposed as a* recommended standard of care *treatment*.
8. Disease accessible for repeat nonsignificant risk biopsies (those occurring outside the brain, lung/mediastinum, and pancreas, or obtained with endoscopic procedures extending beyond the esophagus, stomach or bowel) and willingness to undergo serial tumor biopsies.

Revised Text

3. Patients **must be eligible for treatment with** nivolumab or nivolumab+ipilimumab at the doses(s) and schedule(s) recommended **as** standard of care.
8. **For Arms 1 and 2 only:** Disease accessible for repeat nonsignificant risk biopsies (those occurring outside the brain, lung/mediastinum, and pancreas, or obtained with endoscopic procedures extending beyond the esophagus, stomach or bowel) and willingness to undergo serial tumor biopsies.

Rationale for Amendment

Clarification that all enrolled patients must be eligible for standard of care melanoma therapy and that serial tumor biopsies will be obtained from patients enrolled in Arms 1 and 2 only. Similar changes appear in Section 2.0, Section 4.4.4, Section 5.1.3, Section 5.2.3, Section 6.1.2, Section 6.1.3, Section 9.4.16.3, and Section 13.1.5.

Page 51, Section 7.2, Exclusion Criteria

Existing Text

4. *Ocular melanoma*.
5. *Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2.*
    - *Note that prior non-immunotherapy systemic, adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 2 weeks prior to first dose, and all related adverse events have either returned to baseline or stabilized.*

Revised Text

4. **Subjects who completed a prior therapy <2 weeks prior to first dose and for whom AEs related to prior therapy had not returned to baseline or improved to Grade 1.**

Rationale for Amendment

Due to the many rapid changes in the treatment of melanoma, it is necessary to widen the target population of this trial. Regardless of this modification, the main inclusion criterion of this trial is that the patient is eligible for standard of care nivolumab (or nivolumab + ipilimumab), which now includes patients diagnosed with ocular melanoma. These same changes were made in Section 2.0.

Page 52, Section 7.2.2, Additional Exclusion Requirements for ARM 3 ONLY (Vedolizumab Plus Nivolumab Plus Ipilimumab)

Existing Text

22. Previous anti-CTLA-4 therapies.

Revised Text

Deleted former exclusion criterion #22 as being too restrictive of enrollment.

Rationale for Amendment

Current standard of care treatment for metastatic melanoma makes this exclusion criterion too restrictive. All patients must be eligible for standard of care treatment with nivolumab and ipilimumab. The same change was made in Section 2.0.

Page 53, Section 8.1, Figure 8.a, Study C28003 Dosing Regimens in Treatment Arms 1, 2, and 3

Modified Figure 8.a in Amendment 02

- IMPs (in red) and standard of care drugs (nivolumab in black; ipilimumab in green) are shown in their designated order of administration in each arm.
- Added the FDA-approved nivolumab standard of care option 240 mg flat dose as an alternative to 3 mg/kg; noted that the 240 mg flat dose is ***not*** used in combination with ipilimumab (in Arm 3 only)
- Changed Arm 3 regimen to show that standard of care treatment (nivolumab+ipilimumab) starts on Week 1, Day 1 in combination with vedolizumab (deleted the 2-week safety lead-in SA vedolizumab treatment period).

Rationale for Amendment

Rearranged the study figure to show the correct order of administration of IMPs and standard of care therapies, updated the FDA-approved standard of care nivolumab dosing to include flat dosing, and removed SA vedolizumab treatment in Arm 3. Similar changes appear in Section 8.1.4, Section 8.10.4.4, and Appendix A.

Page 54, Section 8.1.2, TAK-202 (MLN1202) Administration

Existing Text

The 250 mL *of* bag of saline with TAK-202 will be administered IV over 30 minutes. On the days of concomitant nivolumab dosing, (Week 3, Day 15 and forward), administer TAK-202 prior to nivolumab dosing and separate both infusions by at least 30 minutes.

Revised Text

The 250 mL bag of saline with TAK-202 will be administered IV over 30 **(±5)** minutes. On the days of concomitant nivolumab dosing, (Week 3, Day 15 and forward), administer TAK-202 prior to nivolumab dosing and separate both infusions by at least 30 minutes.

Rationale for Amendment

To incorporate some flexibility in the timing of the infusion.

Page 54, Section 8.1.3, Vedolizumab (Entyvio®) Administration

Existing Text

Administer vedolizumab as an IV infusion over 30 minutes. Do not administer as an IV push or bolus. On Week *3*, Day *15* administer vedolizumab IV prior to nivolumab and ipilimumab dosing. Each infusion needs to be separated from the previous by at least 30 minutes and the

patient should not have evidence of infusional reactions to the precedent one. The initial dose level (DL1) is 200 mg flat dose. If this dose proves to be safe, DL2 will be 450 mg flat dose. No escalation above DL2 is planned.

Revised Text

Administer vedolizumab as an IV infusion over 30 **(±5)** minutes. Do not administer as an IV push or bolus. On Week **1**, Day **1** administer vedolizumab IV prior to nivolumab and ipilimumab dosing. Each infusion needs to be separated from the previous by at least 30 minutes and the patient should not have evidence of infusional reactions to the precedent one. The initial dose level (DL1) is 200 mg flat dose. If this dose proves to be safe, DL2 will be 450 mg flat dose. No escalation above DL2 is planned.

Rationale for Amendment

Removed SA vedolizumab treatment from Arm 3 to allow patients with malignant melanoma to receive the current standard of care therapy of nivolumab plus ipilimumab without delay. The same change was made in Section 8.1, Figure 8.a.

Page 55, Section 8.1.4, Nivolumab (Opdivo®) Administration

Existing Text

The recommended dose of nivolumab administered in Arms 1 and 2 is 3 mg/kg as an IV infusion over 60 minutes every 2 weeks (Q2W) until disease progression (PD) or any other discontinuation criterion is met starting on Week 3, Day 15 after the second biopsy has been performed. Nivolumab is to be administered at least 1 hour after TAK-580 oral dosing (Arm 1) and at least 30 minutes after TAK-202 dosing (Arm 2) and if there is no evidence of infusional reaction.

The dose of nivolumab in combination with ipilimumab and vedolizumab (Arm 3) is 1 mg/kg administered as an IV infusion over 60 minutes, every 3 weeks (Q3W) for 4 doses. Nivolumab is to be administered 30 minutes after vedolizumab dosing (Week *3*, Day *15*) and before ipilimumab dosing (drug order administration: vedolizumab→nivolumab→ipilimumab). The subsequent doses of nivolumab in Arm 3 (without ipilimumab), *is* 3 mg/kg as an IV infusion over 60 minutes Q2W starting on Week *15*, Day *99* until PD or any other discontinuation criterion is met.

Revised Text

The recommended dose of nivolumab administered in Arms 1 and 2 is 3 mg/kg **(or 240 mg flat dose)** as an IV infusion over 60 **(±5)** minutes every 2 weeks (Q2W) until disease progression (PD) or any other discontinuation criterion is met starting on Week 3, Day 15 after the second biopsy has been performed. Nivolumab is to be administered at least 1 hour after TAK-580 oral dosing (Arm 1) and at least 30 minutes after TAK-202 dosing (Arm 2) and if there is no evidence of infusional reaction.

The dose of nivolumab in combination with ipilimumab and vedolizumab (Arm 3) is 1 mg/kg administered as an IV infusion over 60 **(±5)** minutes, every 3 weeks (Q3W) for 4 doses. Nivolumab is to be administered **at least** 30 minutes after vedolizumab dosing (Week **1**, Day **1**)

and before ipilimumab dosing (drug order administration: vedolizumab→nivolumab→ ipilimumab). The subsequent doses of nivolumab in Arm 3 (without ipilimumab), **are** 3 mg/kg **(or 240 mg flat dose)** as an IV infusion over 60 **(±5)** minutes Q2W starting on Week **13**, Day **85** until PD or any other discontinuation criterion is met. **When nivolumab and vedolizumab are administered on the same day (eg, Week 13, Day 85), the order of administration is vedolizumab→nivolumab.**

Rationale for Amendment

Updated nivolumab dosing to include the FDA-approved standard of care flat dosing and corrected the timing of nivolumab dosing in Arm 3 and confirmed the order of administration when >1 study drug is administered on the same day. Similar changes appear in Section 8.1, Figure 8.a and in Section 8.10.4.4.

Page 55, Section 8.1.5, Ipilimumab (Yervoy®) Administration

Existing Text

The dose of ipilimumab to be administered in combination with nivolumab and vedolizumab in Arm 3 is 3 mg/kg as an IV infusion over 90 minutes every 3 weeks for a total of 4 doses. Ipilimumab is to be infused more than 30 minutes after nivolumab and if there is no evidence of infusional reaction to the previous administration.

Revised Text

The dose of ipilimumab to be administered in combination with nivolumab and vedolizumab in Arm 3 is 3 mg/kg as an IV infusion over 90 **(±5)** minutes every 3 weeks for a total of 4 doses. Ipilimumab is to be infused more than 30 minutes after nivolumab and if there is no evidence of infusional reaction to the previous administration.

Rationale for Amendment

To incorporate some flexibility in the timing of the infusion. The same change appears in Section 8.10.5.3.

Page 56, Section 8.2, Definitions of Dose-Limiting Toxicity (Non-hematologic toxicities)

Added Text

- **Grade 3 asymptomatic hypophosphatemia (Arm 1 only).**

Rationale for Amendment

In other phase 1 trials with TAK-580, asymptomatic Grade 3 hypophosphatemia has been frequently observed. No correlation has been made with any clinical symptom. For this reason, Grade 3 asymptomatic hypophosphatemia was removed as a DLT criterion in this and the other trials.

Page 59, Section 8.3, Dose Escalation Rules

Existing Text

The DLT-evaluable population consists of all patients who either experience DLT during the first 8 weeks of treatment or who have received at least 6 doses of TAK-580 (Arm 1), 3 doses of the TAK-202 (Arm 2), or 3 doses of vedolizumab (Arm 3), and 3 doses of nivolumab (alone or in combination with ipilimumab), and have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred.

Revised Text

The DLT-evaluable population consists of all patients who either experience DLT during the first 8 weeks **(6 weeks for patients assigned to Arm 3)** of treatment or who have received at least 6 doses of TAK-580 (Arm 1), 3 doses of the TAK-202 (Arm 2), or 3 doses of vedolizumab (Arm 3), and 3 doses of nivolumab (alone or in combination with ipilimumab), and have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred.

Rationale for Amendment

Clarification of the DLT-evaluable population to be consistent with changes made in Section 6.1.1, Section 6.2, Section 8.1, Figure 8.a, and Section 13.1.1.

Page 59, Section 8.3, Dose Escalation Rules

Existing Text

The above rules applicable to the safety lead-in dose-escalation phase will be the principle means for the initial determination of the dose to be used in the cohort expansion. However, the safety of the selected dose will be confirmed during the Part 1 limited cohort expansion. During Part 1 up to 15 patients (including those from the safety lead-in treated with the same dose) will be observed for emergent DLTs during the first 8 weeks of treatment and any other ≥Grade 3 TEAEs that may occur*red* after the DLT observation window.

Revised Text

The above rules applicable to the safety lead-in dose-escalation phase will be the principle means for the initial determination of the dose to be used in the cohort expansion. However, the safety of the selected dose will be confirmed during the Part 1 limited cohort expansion. During Part 1 up to 15 patients (including those from the safety lead-in treated with the same dose) will be observed for emergent DLTs during the first 8 weeks **(6 weeks for Arm 3)** of treatment and any other ≥Grade 3 TEAEs that may occur after the DLT observation window.

Rationale for Amendment

Clarification of the DLT-evaluable population to be consistent with changes made in Section 6.1.1, Section 6.2, Section 8.1, Figure 8.a, and Section 13.1.1.

Page 72, Section 8.10.2, TAK-202 (MLN1202; plozalizumab)

Added Text

TAK-202 (MLN1202; **plozalizumab**)

Rationale for Amendment

Updated the TAK-202 nomenclature to include the recommended INN designation. The same change was made to Section 2.0, Section 4.2.2 and Section 4.3.2.

Page 74, Section 8.10.4.4, Administration [Nivolumab]

Existing Text

Administer the infusion over 60 minutes through an intravenous line containing a sterile, nonpyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not coadminister other drugs through the same intravenous line. Flush the IV line at end of infusion.

The dose of nivolumab to be administered is 3 mg/kg as an IV infusion over 60 minutes every 2 weeks (Q2W) until disease progression (PD) or any other discontinuation criterion is met.

The dose of nivolumab in combination with ipilimumab (Arm 3) is 1 mg/kg administered as an IV infusion over 60 minutes, followed by ipilimumab on the same day, every 3 weeks (Q3W) for 4 doses in a 90 minute infusion. The subsequent dose of nivolumab*, as a SA, is* 3 mg/kg as an IV infusion over 60 minutes Q2W until PD or any other discontinuation criterion is met.

Revised Text

Administer the infusion over 60 **(±5)** minutes through an intravenous line containing a sterile, nonpyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not coadminister other drugs through the same intravenous line. Flush the IV line at end of infusion.

The dose of nivolumab to be administered is 3 mg/kg **(or 240 mg flat dose)** as an IV infusion over 60 **(±5)** minutes every 2 weeks (Q2W) until disease progression (PD) or any other discontinuation criterion is met.

The dose of nivolumab in combination with ipilimumab (Arm 3) is 1 mg/kg administered as an IV infusion over 60 **(±5)** minutes, followed by ipilimumab on the same day, every 3 weeks (Q3W) for 4 doses in a 90 **(±5)** minute infusion. The subsequent dose**s** of nivolumab **are** 3 mg/kg **(or 240 mg flat dose)** as an IV infusion over 60 **(±5)** minutes Q2W until PD or any other discontinuation criterion is met.

Rationale for Amendment

Updated nivolumab dosing to include FDA-approved standard of care flat dosing and corrected the timing of nivolumab dosing in Arm 3 to be consistent with changes shown in Section 8.1, Figure 8.a, and Section 8.1.4.

Page 75, Section 8.10.5.3, Administration Instructions [Ipilimumab]

Existing Text

- Administer diluted solution over 90 minutes through an IV line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

When both nivolumab and ipilimumab are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the IV line of nivolumab before starting the ipilimumab infusion. At least 30 minutes should separate the 2 infusions. When the 3 drugs have to be administered on the same day (Week *3,* Day *15*), the order of administration is vedolizumab → nivolumab → ipilimumab. At least 30 minutes should elapse between each infusion and before starting a new infusion, the patient has to be free of IRR symptoms.

Revised Text

- Administer diluted solution over 90 **(±5)** minutes through an IV line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

When both nivolumab and ipilimumab are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the IV line of nivolumab before starting the ipilimumab infusion. At least 30 minutes should separate the 2 infusions. When the 3 drugs have to be administered on the same day (Week **1,** Day **1**), the order of administration is vedolizumab → nivolumab → ipilimumab. At least 30 minutes should elapse between each infusion and before starting a new infusion, the patient has to be free of IRR symptoms.

Rationale for Amendment

To incorporate some flexibility in the timing of the infusion consistent with the change in Section 8.1.5. Updated the day on which all 3 drugs are administered to reflect changes in the Arm 3 dosing regimen as shown in Section 8.1, Figure 8.a and Appendix A.

Page 77, Section 9.3, Treatment Group Assignments

Existing Text

Investigators should consider first which standard of care checkpoint inhibitor therapy is most suitable for each candidate patient (nivolumab alone versus combination of nivolumab plus ipilimumab). Tumor biology (*BRAF* V600 mutation-positive or *NRAS* mutation-positive disease) and other medical aspects (previous treatment with RAF, MEK, or other inhibitors of the MAPK pathway, or *anti-CTL4 treatment*) will be considered before allocating the patient to a particular treatment arm. If there is no specific medical rationale to choose 1 arm over others, patients will be allocated maximizing enrollment strategy.

Revised Text

Investigators should consider first which standard of care checkpoint inhibitor therapy is most suitable for each candidate patient (nivolumab alone versus combination of nivolumab plus ipilimumab). Tumor biology (*BRAF* V600 mutation-positive or *NRAS* mutation-positive disease) and other medical aspects (previous treatment with RAF, MEK, or other inhibitors of the MAPK pathway, or **previous use of checkpoint inhibitors**) will be considered before allocating the patient to a particular treatment arm. If there is no specific medical rationale to choose 1 arm over others, patients will be allocated maximizing enrollment strategy.

Rationale for Amendment

Updated the text that due to the many rapid changes in the treatment of melanoma, the target population may have received prior standard of care treatment with checkpoint inhibitors.

Page 81, Section 9.4.15.2, Clinical Hematology, Coagulation, Chemistry, and Liver Function Testing

Existing Text

(b) Performed in *all* patients *in* screening, Week 3, Day 15, and Week 9, Day 99 to confirm normal range before biopsy procedure.

Revised Text

(b) Performed in patients **enrolled in Arms 1 and 2 at** screening, Week 3, Day 15, and Week 9, Day 99 to confirm normal range before biopsy procedure.

Rationale for Amendment

Modification of footnote (b) to indicate that coagulation testing is required only in patients in Arms 1 and 2 who undergo collection of serial tumor biopsies.

Page 82, Section 9.4.16.3, Tumor Biopsies

Added Text [to header]

9.4.16.3 Tumor Biopsies ***(in Patients Assigned to Arms 1 and 2)***

Rationale for Amendment

Clarification that tumor biopsies will be collected only from patients assigned to Arms 1 and 2 to be consistent with changes made to Section 2.0, Section 4.4.4, Section 5.1.3, Section 5.2.3, Section 6.1.2, Section 6.1.3, and Section 7.1.

Page 83, Section 9.4.18, Microbiome Assessment

Inserted New Text

9.4.18 Microbiome Assessment

For patients enrolled in Arm 3 only, stool samples will be collected at time points specified in the SOEs (Appendix A). 16S rRNA sequencing and/or metagenomic sequencing will be conducted on DNA extracted from these stool samples. Refer to the Laboratory Manual for

details on collecting, processing, storage, and shipment of stool samples to the study sponsor.

Rationale for Amendment

To monitor changes in microbiome before and after combination therapy consistent with changes made to Section 4.4.3, Section 5.1.3, and Section 5.2.3.

Page 84, Section 9.4.19, Fecal Calprotectin Sample Collection

Inserted New Text

9.4.19 Fecal Calprotectin Sample Collection

For patients enrolled in Arm 3, stool samples will be collected at the time points specified in the SOEs (Appendix A) for analysis of fecal calprotectin, a biomarker of intestinal inflammatory activity. Refer to the Laboratory Manual for details on collecting, processing, storage, and shipment of stool samples to the study sponsor.

Rationale for Amendment

To test calprotectin as a marker of colitis in patients enrolled in Arm 3 before and after combination therapy; consistent with changes made to Section 4.4.3, Section 5.1.3, and Section 5.2.3.

Page 86, Section 9.10, Posttreatment Follow-up Assessments (Progression-free Survival and Overall Survival)

Existing Text

Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 12 weeks from the EOT 1 visit until the occurrence of PD, the start of subsequent systemic anticancer therapy, until *6 months after the patient discontinued treatment*, or study (treatment arm) final cutoff date, whichever occurs first. Patients who experience PD on or off study treatment will be followed every 3 months to assess for OS and for subsequent systemic anticancer therapy. In addition, patients who have not initiated a subsequent systemic anticancer therapy will have safety visits 60 (±10) days (EOT 2) and 90 (±10) days (EOT 3) after the last dose of study treatment.

After the occurrence of PD or the start of subsequent anticancer therapy, patients will continue to have OS follow-up visits. The OS visits should be conducted every 12 weeks after documented PD until death, until 1 year after the last dose of study drug, or study (treatment arm) final cutoff date, whichever occurs first. The final analyses for the CSR may be conducted after prespecified events (PD and death) have occurred for the event-driven PFS analysis conducted after all patients enrolled in the study have had the opportunity to complete 50 weeks of treatment. Each treatment arm can be assessed separately if enrollment is completed or is discontinued.

Revised Text

Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 12 **(±1)** weeks from the EOT 1 visit until the occurrence of PD, the start of subsequent systemic anticancer therapy, until

2 posttreatment CT scan evaluations are performed, or study (treatment arm) final cutoff date, whichever occurs first. Patients who experience PD on or off study treatment will be followed every **12 (±1) weeks** to assess for OS and for subsequent systemic anticancer therapy. In addition, patients who have not initiated a subsequent systemic anticancer therapy will have safety visits 60 (±10) days (EOT 2) and 90 (±10) days (EOT 3) after the last dose of study treatment.

After the occurrence of PD or the start of subsequent systemic anticancer therapy, patients will continue to have OS follow-up visits. The OS visits should be conducted every 12 **(±1)** weeks after documented PD or new systemic treatment is initiated, until death, until 1 year after the last dose of study drug, or study (or treatment arm) final cutoff date, whichever occurs first. The final analyses for the CSR may be conducted after prespecified events (PD and death) have occurred for the event-driven PFS analysis conducted after all patients enrolled in the study have had the opportunity to complete 50 weeks of treatment. Each treatment arm can be assessed separately if enrollment is completed or is discontinued.

Rationale for Amendment

Clarification of text to be consistent with changes made in Section 6.1.3 and Appendix A.

Page 89, Section 10.3, Monitoring of Adverse Events and Period of Observation

Existing Text

- Serious pretreatment *events* will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to first dose of study drug, and will also be recorded in the eCRF.

Revised Text

- Serious pretreatment **AEs** will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to first dose of study drug, and will also be recorded in the eCRF. **For consented patients who do not meet inclusion criteria (ie, are considered screen failures), serious pretreatment AEs will be reported as above for 30 days from the date of screen failure.**

Rationale for Amendment

To have consistent reporting of serious pretreatment AEs for consented patients who are considered screen failures.

Page 91, Section 10.7, Risk Assessment and Minimization for PML (RAMP Program for Subjects Administered Vedolizumab [Arm 3])

Existing Text

The RAMP is focused on early clinical detection and management of that specific safety risk, including the discontinuation of study drug, if applicable. Patients are assessed for signs and symptoms of PML prior to the administration of each dose of study drug using a PML checklist (available in Appendix F and in the Study Manual). Patients with a positive PML subjective symptom checklist at any time after enrollment in a vedolizumab clinical study will be evaluated

according to a prespecified algorithm (the PML Case Evaluation Algorithm). 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. All patients receiving vedolizumab will have a LTFU assessment *approximately* 6 months after their last dose of vedolizumab irrespective of study participation status. The specific form is located in the Study Manual.

Revised Text

The RAMP is focused on early clinical detection and management of that specific safety risk, including the discontinuation of study drug, if applicable. Patients are assessed for signs and symptoms of PML prior to the administration of each dose of study drug using a PML checklist (available in Appendix F and in the Study Manual). Patients with a positive PML subjective symptom checklist at any time after enrollment in a vedolizumab clinical study will be evaluated according to a prespecified algorithm (the PML Case Evaluation Algorithm). 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. All patients receiving vedolizumab will have a LTFU assessment 6 months **(±2 weeks)** after their last dose of vedolizumab irrespective of study participation status. The specific form is located in the Study Manual.

Rationale for Amendment

To provide more specific timing for the LTFU of patients treated with vedolizumab. This change also appears in Section 6.1.3.

Page 95, Section 13.1.1, Analysis Sets

Existing Text

- **DLT-Evaluable population**: The DLT-Evaluable population, defined as all patients in the study who either experience DLT during the 1st 8 weeks of treatment or have received at least 6 doses of TAK-580 (Arm 1), 3 doses of TAK-202 (Arm 2), or 3 doses of vedolizumab (Arm 3) and 3 doses of nivolumab (plus ipilimumab), and have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred, will be used for the analysis of DLT.

Revised Text

- **DLT-Evaluable population**: The DLT-Evaluable population, defined as all patients in the study who either experience DLT during the 1st 8 weeks **(6 weeks for patients assigned to Arm 3)** of treatment or have received at least 6 doses of TAK-580 (Arm 1), 3 doses of TAK-202 (Arm 2), or 3 doses of vedolizumab (Arm 3) and 3 doses of nivolumab (plus ipilimumab), and have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred, will be used for the analysis of DLT.

Rationale for Amendment

Corrections made to the description of the DLT-evaluable population to be consistent with changes made in Section 6.1.1, Section 6.2, and Section 8.3.

Page 96, Section 13.1.5, Pharmacodynamic Effect Analysis

Added Text [in header]

13.1.5 Pharmacodynamic Effect Analysis (Arms 1 and 2)

Rationale for Amendment

Clarification that exploratory pharmacodynamic endpoints (changes of tumor and serum biomarkers) will be evaluated only for samples collected from patients assigned to Arms 1 and 2 to be consistent with changes made to Section 2.0, Section 4.4.4, Section 5.1.3, Section 5.2.3, Section 6.1.2, Section 6.1.3, and Section 7.1.

Page 105, Section 16.0, REFERENCES

Added Text

Reference citations were added in Section 4.4.3 with regard to microbiome assessments in patients treated with the combination of vedolizumab+nivolumab+ipilimumab in Arm 3. Citations appearing in the protocol after this section have been renumbered.

Page 108, Appendix A, Schedules of Events

Rationale for Amendments to Appendix A (Schedules of Events)

Alterations in Appendix A Schedule of Events were made to be consistent with changes in various sections of the protocol amendment and include:

- In all treatment arms, weight is included in the targeted PE both until and after 1st disease response assessment SOEs.
- For all treatment arms, the timing and study evaluations to be conducted at EOT (1, 2, and 3) and PFSFU/OSFU, were standardized in the after 1st disease response assessment SOEs and the associated footnotes were corrected to align with the protocol Section 9.10 and Section 6.3.
- In Arm 1 (TAK-580), in the after the 1st disease response assessment SOE, the collection of samples for blood chemistries and LFTs were corrected to align with the protocol Section 9.4.15.2.
- In Arm 3 (vedolizumab+nivolumab+ipilimumab), the following changes were made to the until 1st disease response assessment SOE because the 2-week lead-in SA vedolizumab dosing was eliminated:
  - Modified the sample collection times leading to the 1st disease response assessment due to changes in the vedolizumab dosing schedule as shown in the protocol Section 8.1, Figure 8.a.
  - Deleted the collection of tumor biopsies and pre-tumor biopsy coagulation testing from these patients due to the change in the vedolizumab dosing schedule
  - Added the collection of stool samples for microbiome and fecal calprotectin assessments to align with the protocol Section 9.4.18 and Section 9.4.19

- In Arm 3 (vedolizumab+nivolumab+ipilimumab), added 1 stool sample collection for microbiome and fecal calprotectin assessment in the after 1st disease response assessment SOE.

Page 137, Appendix F, PML Checklists

Added Footers on each page of Appendix F

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Rationale for Amendments to Appendix F

The PML Checklists, an independent document, can be updated and/or modified, as needed. The footnote is necessary to correctly identify which version of the checklists is being used.

Amendment 02 to An Open-Label, Phase 1b, Multi-Arm Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of Investigational Treatments in Combination With Standard of Care Immune Checkpoint Inhibitors in Patients With Advanced Melanoma

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Protected Personal Data	Statistical Approval	20-Oct-2016 12:08 UTC
	Clinical Pharmacology Approval	20-Oct-2016 12:19 UTC
	Clinical VP Approval	20-Oct-2016 12:30 UTC
	Clinical VP Approval	20-Oct-2016 13:43 UTC