Official Title: A Two-Cohort Randomized Phase II, Double-Blind, Parallel Group Study in Patients With Active Rheumatoid Arthritis Evaluating the Efficacy and Safety of GDC-0853 Compared With Placebo and Adalimumab in Patients With an Inadequate Response to Previous Methotrexate Therapy (Cohort 1) and Compared With Placebo in Patients With an Inadequate Response or Intolerance to Previous TNF Therapy (Cohort 2)

NCT Number: NCT02833350

Document Date: Protocol Version 4: 10-March-2017

PROTOCOL

TITLE:	**A TWO-COHORT RANDOMIZED PHASE II, DOUBLE−BLIND, PARALLEL GROUP STUDY IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS EVALUATING THE EFFICACY AND SAFETY OF GDC-0853 COMPARED WITH PLACEBO AND ADALIMUMAB IN PATIENTS WITH AN INADEQUATE RESPONSE TO PREVIOUS METHOTREXATE THERAPY (COHORT 1) AND COMPARED WITH PLACEBO IN PATIENTS WITH AN INADEQUATE RESPONSE *OR INTOLERANCE* TO PREVIOUS TNF THERAPY (COHORT 2)**
PROTOCOL NUMBER:	GA29350
VERSION NUMBER:	4
EUDRACT NUMBER:	2016-000335-40
IND NUMBER:	120,162
TEST PRODUCT:	GDC-0853 (RO7010939)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 29 January 2016
DATES AMENDED:	Version 2 (Korea): 22 July 2016 Version 3: 5 August 2016 Version 4: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory (Clinical)	10-Mar-2017 21:59:20

PROTOCOL AMENDMENT, VERSION 4
RATIONALE

Changes to the protocol, along with a rationale for each change, are summarized as follows and are reflected as applicable in the Schedules of Assessments (Appendices 1–3):

- Clinical Disease Activity Index (CDAI)-based remission has been defined as ≤ 2.8 (Table 1).
- The initiation of Cohort 2 will no longer be gated on the interim analysis. The decision to open Cohort 2 now is based on evidence for activity of BTK inhibition in rheumatoid arthritis patients, as demonstrated by another BTK inhibitor (Section 3.1).
- The population for Cohort 2 has been broadened to also include those who may have had intolerance to 1 or 2 TNF inhibitors and who may have also had exposure to no more than one non-TNF inhibitor biologic (Section 3.1).
- For Cohort 2, the randomization will be stratified by geographic region and prior exposure to a non-TNF inhibitor biologic, in order to balance treatment assignments for the purpose of limiting any potential confounding of efficacy. The Sponsor may choose to limit the percentage of patients enrolled that have had prior exposure to a non-TNF inhibitor biologic in order to minimize heterogeneity of the Cohort 2 population (Section 3.1).
- The size of Cohort 2 has been expanded to include approximately 120 patients who will be randomized to placebo or 200 mg BID GDC-0853 (Figure 1 and Section 3.1)
- The definition of inadequate response to TNF inhibitors has been updated to allow exposure to TNF inhibitors at doses and durations that, in accordance with local clinical practice, are considered acceptable to assess clinical response (Section 4.1.1).
- The eligibility requirement based on high sensitivity C-reactive protein (hsCRP) has been lowered to ≥ 0.400 mg/dL for Cohort 1 at screening in order to broaden the eligible population for Cohort 1. The Sponsor may choose to limit the percentage of patients enrolled who have a screening hsCRP of between 0.400 and 0.649 mg/dL in order to minimize confounding of efficacy, as patients with higher levels of inflammation might be expected to demonstrate an enhanced response to GDC-0853 based on mechanism of action (Section 3.1).
- The protocol has been updated to state that at any time during the study, the Sponsor may choose to inactivate and suspend enrollment and further dosing for a given treatment arm (in Cohort 1) due to safety concerns and as guided by the Internal Monitoring Committee (IMC), and that in Cohort 1, subsequently enrolled patients will be randomly allocated to the remaining active arms (Section 3.1).
- For patients entering the trial on methotrexate (MTX) doses < 15 mg/week, the protocol has been clarified that for patients taking doses as low as 7.5 mg/week, there must be clear documentation that higher doses were not tolerated or that the dose of MTX is the highest acceptable dose based on local clinical practice guidelines (Section 4.1.1).

- Systemic involvement secondary to rheumatoid arthritis (RA) has been clarified, including specific examples (Section 4.1.1).
- Current treatment with medications that are well known to prolong the QT interval has been clarified to specify that this refers to use of medications at doses that have a clinically meaningful effect on the QT interval; a reference website for QT prolonging medications has been included (Section 4.1.2).
- Exclusion criteria of current liver disease and pancreatitis have been clarified (Section 4.1.2).
- Guidance on missed doses has been added (Section 4.3.2.1).
- Language around mandatory morning visits for clinic visits on Days 1, 28, and 84 has been removed and logistics of study drug dosing have been clarified (Section 4.5).
- Grade 3 LFT abnormalities have been added, and use of prohibited medications has been removed from the reasons for permanent discontinuation of study treatment. In addition, patients will be asked to remain in the blinded study (off study treatment) through Week 12, instead of transferring to safety follow-up, in order to minimize missing data (Section 4.6.2).
- The reporting of the term “sudden death” has been clarified (Section 5.3.5.8).
- Event reporting for hospitalization has been clarified (Section 5.3.5.11).
- Language around the interim analysis has been clarified, including the case in which the IMC decides to unblind the study team to enable decision-making and potential interactions with regulatory bodies (Section 6.8.1.1).
- Updated language for the interim analysis includes the possibility of increasing enrollment by up to 20% to obtain greater precision for estimation of treatment differences (Section 6.8.1.1).
- Updated language for an optional interim analysis (for Cohort 2) has been added in order to guide internal decision making around issues such as the adequacy of dose ranging, the adequacy of sample sizes for safety and/or efficacy analyses, or to inform further development decisions (Section 6.8.1.2).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 4:
SUMMARY OF CHANGES

GLOBAL CHANGE

The population for Cohort 2 has been broadened to also include those who may have had intolerance to 1 or 2 TNF inhibitors and who may have also had exposure to no more than one non-TNF inhibitor biologic.

The number of patients has increased from approximately 580 to approximately 600.

Use of antacids has been clarified that the protocol is referencing short-acting antacids.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

TABLE 1: Primary, Secondary, Safety, Pharmacokinetic, and Exploratory Objectives with Corresponding Endpoints

Table 1 has been updated to reflect the broadening of Cohort 2 as well as to define CDAI-based remission.

SECTION 3.1: DESCRIPTION OF THE STUDY

This is a multicenter, Phase II, randomized, double-blind, placebo-controlled, active comparator (Cohort 1 only), parallel-group, dose-ranging study to evaluate the efficacy and safety of GDC-0853 in patients with moderate to severe active RA and an inadequate response to previous MTX therapy (Cohort 1) or MTX and TNF therapy ~~(Cohort 2).~~*who may have also had exposure to no more than one non-TNF inhibitor biologic (Cohort 2).* Moderate to severe active RA is defined by ≥6 tender/painful joints on motion (68 joint count) and ≥6 swollen joints (66 joint count) at both screening and Day 1 (randomization), as well as a *high sensitivity* C-reactive protein (~~CRP~~*hsCRP*) ≥0.~~7~~*400* mg/dL *for Cohort 1 and a hsCRP ≥0.650 mg/dL for Cohort 2* at screening. Improvement in disease activity will be measured using the American College of Rheumatology (ACR) response rate.

This study will enroll approximately ~~580~~ 600 patients. ~~Initially,~~*In* Cohort 1 ~~will be opened and,~~ approximately 480 MTX-IR patients will be randomized to placebo, ADA, or one of 3 doses of GDC-0853 (50 mg QD, 150 mg QD, or 200 mg BID). ~~An interim analysis (IA) of data from the first approximately 150 patients (~30 patients per arm) will evaluate safety and efficacy, including exposure-response relationships. On the basis of the results of the Cohort 1 interim analysis,~~*In* Cohort 2 ~~will be opened and, approximately 100~~ approximately 120 *TNF-IR patients will be randomized to placebo or 200 mg BID* ~~of~~ *GDC-0853*~~; however, the selected dose may be lower than 200 mg BID, depending on the outcome of the IA~~*(see Figure 1).* ~~The randomization will be stratified by geographic region, and patients who withdraw or discontinue will not be replaced.~~

At any time during the study, the Sponsor may choose to inactivate and suspend enrollment and further dosing for a given treatment arm (Cohort 1) or reduce the dose in Arm F (Cohort 2) due to safety concerns, and as guided by the IMC. In Cohort 1, subsequently enrolled patients will be randomly allocated to the remaining arms.

FIGURE 1: Study Schema

Figure 1 has been updated to reflect the changes in the protocol.

SECTION 3.1.1: Cohort 1 (MTX-IR)

Cohort 1 includes patients with active RA who have demonstrated an inadequate response to MTX. An inadequate response to MTX is defined as meeting entry criteria for active disease despite having received MTX for at least 12 weeks immediately prior to randomization, of which the last 8 weeks prior to randomization must have been at a stable dose of between 15 and 25 mg/week (oral or parenteral; *for patients entering the trial on MTX doses <15 mg/week, doses as low as 7.5- mg/week are allowed only if there is clear documentation in the* ~~case~~*medical record that higher doses were not tolerated or that the dose of* ~~documented MTX intolerance~~*MTX is the highest acceptable dose based on local clinical practice guidelines).*

At baseline (Day 1), patients in Cohort 1 will be randomly assigned in a 1:1:1:1:1 fashion to 1 of 5 parallel treatment arms:

- Arm A: 50 mg QD GDC-0853 (BID tablets) + ~~SC~~ placebo injections *SC every 2 weeks (Q2W)* (n = 40)
- Arm B: 150 mg QD GDC-0853 (BID tablets) + ~~SC~~ placebo injections *SC Q2W* (n = 110)
- Arm C: 200 mg BID GDC-0853 (BID tablets) + ~~SC~~ placebo injections *SC Q2W* (n = 110)
- Arm D: placebo (BID tablets) + ~~SC~~ placebo injections *SC Q2W* (n = 110)
- Arm E: placebo (BID tablets) + 40 mg ~~SC~~ ADA injections *SC Q2W* (n = 110)

Once enrollment in Arm A ~~has completed~~*is complete*, patients will be randomized 1:1:1:1 across the 4 remaining treatment arms.

For Cohort 1 the randomization will be stratified by geographic region. The Sponsor may choose to limit the percentage of patients enrolled who have a screening hsCRP of between 0.400 and 0.649 mg/dL.

Patients will be assessed at site visits on Days 1, 7, 14, 28, 42, 56, 70, and 84 during the treatment period and, if the patient does not enroll in OLE Study GA30067, on Day 140 during the follow-up period.

After 150 patients in Cohort 1 (~30 patients/arm) have completed 12 weeks of treatment, an IA ~~and~~*to evaluate* safety ~~assessment~~*and efficacy* will be performed by the IMC~~.~~

~~Cohort 1 will continue to enroll while the IA is being performed. If the IA demonstrates that futility criteria are not met, as defined in the Data Analysis Plan (DAP), and safety data are acceptable, as determined by the IMC and Sponsor, the study will continue. The Sponsor will open enrollment into~~*(see Section 6.8).* ~~at this time, if appropriate. If the IA indicates that one or more dose levels of GDC-0853 in Cohort 1 do not have sufficient efficacy or safety/tolerability, the Sponsor may discontinue the dose arm(s) in this cohort and continue the study. The Sponsor may also elect to amend the protocol to change the dose level of GDC-0853 in Arm F of Cohort 2.~~

SECTION 3.1.2: Cohort 2 (TNF-IR)

Cohort 2 includes patients with active RA who *must* have demonstrated an inadequate response *or intolerance* to one or two TNF inhibitors and MTX and *who may have also had exposure to no more than one non-TNF inhibitor biologic. Cohort 2* is designed to assess the safety and efficacy of GDC-0853, administered orally at 1 dose level, in combination with MTX.

At baseline (Day 1), patients in Cohort 2 will be randomly assigned in a 1:1 fashion to 1 of 2 parallel treatment arms:

- Arm F: 200 mg BID GDC-0853 (BID tablets; *approximately* n=~~50 – 67~~0)
- Arm G: placebo (BID tablet; *approximately* n=~~50 – 70~~60)

~~The dose for Arm F of Cohort 2 may be reduced, depending upon the results of the exposure-response and efficacy analyses from the IA.~~

For Cohort 2, the randomization will be stratified by geographic region and prior exposure to a non-TNF inhibitor biologic. The Sponsor may choose to limit the percentage of patients enrolled who have had prior exposure to a non-TNF inhibitor biologic.

SECTION 3.3.2: Rationale for Patient Population

This Phase II study will evaluate patients with unmet need due to an inadequate response to MTX (Cohort 1) or *inadequate response or intolerance to* TNF inhibitors *and who may have been exposed to one other non-TNF inhibitor biologic agent* (Cohort 2), given the greater unmet need in these populations of patients with RA.

SECTION 3.3.3.2: Active Control Group

ADA is a biologic TNF inhibitor licensed for the treatment of RA *at a dose of 40 mg Q2W* and is considered the SOC in many countries, often in combination with MTX. ~~Refer to local ADA prescribing information and RA treatment guidelines for details.~~ ADA will be used as an ~~internal~~*active* control to assess relative differences in efficacy, safety, and tolerability of GDC-0853. ADA will be provided by the Sponsor. *Refer to local ADA prescribing information and RA treatment guidelines for details.*

SECTION 3.3.6.4: Stratification *and Enrollment Cap*

Patient randomization will be stratified by geographic region~~,~~ because regional variation in the management of RA can manifest as variability in response rates, including differences in placebo *response* rates. The stratification is intended to balance the proportion of patients from different regions across the study arms in order to limit any confounding of the study results. *In Cohort 1, the Sponsor may choose to limit the percentage of patients enrolled who have a screening hsCRP of between 0.400 and 0.649 mg/dL in order to enrich for patients with higher levels of inflammation who might be expected to demonstrate an enhanced response to GDC-0853, based on mechanism of action.*

Patients in Cohort 2 will also be stratified based on whether or not they have had prior exposure to a non-TNF inhibitor biologic, in order to balance treatment assignment for the purpose of limiting any potential confounding of efficacy. The Sponsor may choose to limit the percentage of patients enrolled who have had prior exposure to a non-TNF inhibitor biologic, in order to minimize heterogeneity of the Cohort 2 population.

~~SECTION 3.3.6.5: Interim Analysis~~

~~The IA for Cohort 1, which will be conducted *after 150 patients in Cohort 1 (~30 patients/arm) have completed 12 weeks of treatment*, is intended to minimize the number of patients exposed to GDC 0853, should a safety signal or a lack of meaningful efficacy be observed at one or multiple dose levels of GDC 0853. In addition, the IA will be used to confirm the appropriateness of the dose used in Cohort 2.~~

SECTION 4.1.1: Inclusion Criteria

- *At screening, must have hsCRP as follows:*

  *Cohort 1: ≥*0.~~7~~*400* mg/dL ~~at screening~~*(may be repeated once)*

  Cohort 2: ≥0.650 mg/dL (may be repeated once)

- Have received MTX for at least 12 weeks immediately prior to randomization, of which the last 8 weeks prior to randomization must have been at a stable dose of between ~~15~~*7.5* and 25 mg/week (oral or parenteral~~); doses as low as 7.5 mg/week are allowed only in the case of documented MTX intolerance~~ *)*

  For patients entering the trial on MTX doses <15 mg/week, there must be clear documentation in the medical record that higher doses were not tolerated or that the dose of MTX is the highest acceptable dose based on local clinical practice guidelines.

- *Willing to withdraw all non-biologic disease-modifying anti-rheumatic drugs- (DMARDs), other than MTX and leflunomide, at least 4 weeks prior to randomization~~;~~. Patients previously on leflunomide ~~should be~~ must have either discontinued ≥~~2~~ 8* weeks ~~after standard (e.g., 11 day) cholestyramine or charcoal washout~~ prior to randomization *or discontinued with the following elimination procedure at least 28 days prior randomization:*

Cholestyramine or activated charcoal should be taken at standard doses for a minimum of 6 days but ideally for the standard 11 days (Arava® U.S. Package Insert; Arava® Summary of Product Characteristics)

- Willing to receive treatment at an adequate and stable dose of folic acid (not less than 5 mg *total dose* weekly) during study
- Only for patients currently receiving NSAIDs~~:~~ *on a regular basis (e.g., not as needed):* Treatment must be at a stable dose during the 2 weeks prior to randomization and with a plan to remain at a stable dose for the duration of the study.

To be enrolled into Cohort 2, patients must also meet the following criteria:

- Experienced ~~an~~*an* inadequate response ~~for ≥3 months~~ *or intolerance* to previous treatment **with at least one and no more than 2** ~~of the following~~*biologic TNFα inhibitors (e.g., infliximab, etanercept, adalimumab, golimumab, or certolizumab, or biosimilar equivalent) and in the opinion of the investigator either of the following (which must be documented in the eCRF):*
  - *Experienced insufficient efficacy or loss of efficacy at a dose and duration that, in accordance with local clinical practice, is considered acceptable to adequately assess clinical response*
  - ~~:~~*Experienced intolerance of such treatment*
- *May have also been exposed to **no more than one** non-TNFα inhibitor biologic (e.g., abatacept, tocilizumab, sarilumab, sirukumab, anakinra, or any biologics or ~~or~~ biosimilar equivalents with the same mode of action to the listed agents, including investigational biosimilar agents).* ~~Etanercept (or biosimilar equivalent) at 25 mg twice a week or 50 mg weekly~~

  ~~At least 4 consecutive infusions of infliximab (or biosimilar equivalent) at ≥3 mg/kg~~

  ~~ADA (or biosimilar equivalent) at 40 mg every other week~~

  ~~At least 4 consecutive injections of golimumab ≥50 mg~~

  ~~At least 5 consecutive injections of certolizumab ≥200 mg~~

- ~~Prior to randomization, will have discontinued all biologic anti TNF therapies as follows:~~

  ~~Etanercept for ≥2 weeks~~

  ~~Infliximab, adalimumab, golimumab, or certolizumab for ≥8 weeks~~

SECTION 4.1.2: Exclusion Criteria

Patients who meet any of the following criteria ~~will~~*must* be excluded from study entry:

- ~~Significant systemic~~*Systemic* involvement secondary to RA~~, including but not limited to~~ *leading to clinically significant organ dysfunction or increased risk for participation in the study, in the opinion of the investigator. For example, patients with* known RA vasculitis, pulmonary fibrosis, or Felty's syndrome~~;~~ should be excluded. Exceptions are as follows:~~; NB:~~

- Sjogren's syndrome with RA *is allowable*
- A~~and a~~nemia secondary to RA (if Hgb is greater than or equal to 8.5 mg/dL) is~~are~~ allowable.

– History of treatment with ~~any non-TNF inhibitor biologic DMARD~~ cell-depleting therapy including B cell–depleting therapy (e.g., anti-CD20–directed therapy ~~[e.g.,~~such as rituximab~~], anti-IL6–directed therapy [e.g., tocilizumab], or T cell–directed therapy [e.g., abatacept]) including biosimilar equivalents~~)

– History of treatment with any investigational biologics for the treatment of RA

– ~~*Any*~~RA~~A~~ny condition or medication that precludes the use of or is contraindicated with MTX or folic acid, according to the local prescribing label or the investigator *(e.g., patients with pleural effusion, ascites, or who are on concomitant acitretin)*

~~For Cohort 1 only:~~

– ~~**For Cohort 1 only: For Cohort 1 only: 2:** History of anaphylactic or other serious allergic reaction to ADA~~treatment with anti-CD20-directed therapy [e.g., rituximab]

– History of treatment with tofacitinib or other Janus kinase (JAK) inhibitor(s) *(approved or experimental)*

– Prior to randomization, must have discontinued all biologic ~~anti-TNF~~ therapies as follows:

  Etanercept and etanercept biosimilar agents for ≥2 weeks

  ~~Infliximab, adalimumab, golimumab, or certolizumab~~All other biologic agents (including biosimilars and investigational biosimilars to approved agents) for≥ ~~≥8 weeks~~28 days

– *Previous exposure to any* ~~cell-depleting therapy or~~ investigational agent *(not including investigational biosimilars to approved therapies)* within 12 weeks or 5 half-lives of the investigational agent, whichever is longer, prior to randomization

- *Current treatment with medications that are well known to prolong the QT interval at doses that have a clinically meaningful effect on QT, as determined by the investigator. The investigator may contact the Sponsor for confirmation if needed. The investigator may reference the website: https://www.crediblemeds.org/pdftemp/pdf/CompositeList.pdf.*
- Current liver disease *that is clinically significant, in the opinion of the investigator*
- *History of non–gallstone-related pancreatitis or chronic pancreatitis that is judged to be clinically significant, in the opinion of the investigator (e.g., unexplained upper abdominal pain or malabsorptive diarrhea)*
- Neuropathies or other painful conditions that might interfere with pain evaluation ~~as determined by~~*, in the opinion of* the investigator
- ~~History~~. *Aspirin at doses* of ~~non-gallstone-related pancreatitis or chronic pancreatitis~~*up to 162 mg QD is allowed.*

- History of CV accident (CVA) within 10 years ~~or~~, any history of hemorrhagic CVA, *history of spontaneous intracranial hemorrhage, or history of traumatic intracranial hemorrhage within 10 years*
- ~~History of spontaneous intracranial hemorrhage or history of traumatic intracranial hemorrhage within 10 years~~
- ~~Current treatment with medications that are well known to prolong the QT interval~~

Additionally, patients who meet any of the following criteria will be excluded from Cohort 1:

- History of treatment with *non-TNFα inhibitor biologic for RA, including* anti-IL6–directed therapy (e.g., tocilizumab, sarilumab, sirukumab), anti-IL1-directed therapy (e.g., anakinra), or T cell–directed therapy (e.g., abatacept) including biosimilar equivalents

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT AND BLINDING

The Sponsor will provide the specifications of the randomization algorithm to the interactive voice and Web response system (IxRS) vendor. ~~The~~For Cohort 1 t~~T~~he randomization will be stratified by geographic region. *For Cohort 2, the randomization will be stratified by geographic region and prior exposure to a non-TNF inhibitor biologic.*

SECTION 4.3.2.1: GDC-0853 and Placebo Dose and Administration

The GDC-0853 dose levels are 50 mg QD, 150 mg QD, and 200 mg BID, with matching placebos (see Table 2). Patients will receive GDC-0853/placebo BID, approximately every 12 hours starting on Day 1 and ending on Day ~~84~~*83*. Patients should be directed to take one dose (a total of 4 tablets) BID (a total of 8 tablets each day). On clinic visit days, patients should be instructed that study drug will be administered in the clinic.

If a dose is missed, the patient should resume normal dosing with the next scheduled dose. Missed doses should not be taken, as they result in doubling of the dose. Patients should record on the blister wallet (Cohort 1) or bottle (Cohort 2) the dose that was missed and notify study staff of any missed doses. Doses that are vomited will be considered missed doses.

GDC-0853 or placebo may be orally administered with or without food, except ~~on Days 1, 28, and 84 (see Appendix 1 and Appendix 2), when the morning~~*for the* dose of oral study drug *taken at the clinic visit on Days 1 and 28 (see Appendix 1 and Appendix 2), which* will be administered at the~~ morning (mandatory)~~ clinic visit while fasting. The dates and times of the most recent prior meal, last dose of oral study drug (prior to clinic visit), and timing of oral study drug administration in clinic should be recorded at each clinic visit. In addition, any use of PPIs, H2RAs, and/or ~~*other*~~*short-acting* antacids (e.g., Maalox®, Pepto-Bismol®, Rolaids®) should be recorded as concomitant medications, including date and time of last administration~~.~~ *prior to the clinic visit.* Administration of study drug should be staggered with *short-acting* antacid use (i.e., oral study drug should be taken 2 hours before or 2 hours after the *short-acting* antacid).

SECTION 4.3.2.2: GDC-0853 and Placebo Compliance

The following measures will be taken to assess patient compliance with study drug: patients will *receive Patient Dosing Instructions and* be directed to bring any used and unused blister wallets (Cohort 1) or bottles (Cohort 2) to each visit after randomization.

SECTION 4.3.3.1: Methotrexate

In order to minimize confounding of study assessments, MTX treatment must have been initiated for at least the last 12 weeks immediately before randomization, of which the last 8 weeks before randomization must have been at a stable dose between 15 and 25 mg/week (oral or parenteral). ~~Doses as low as 7.5 mg/week are allowed only in cases of documented MTX intolerance.~~ Patients are required to be on a stable MTX dose of ~~15~~*7.5–*25 mg/week (oral or parenteral) for the duration of their participation in this study. *For patients entering the trial on MTX doses <15 mg/week, there must be clear documentation in the medical record that higher doses were not tolerated or that the dose of MTX is the highest acceptable dose based on local clinical practice guidelines.* ~~(doses as low as 7.5 mg/week are allowed only in cases of documented MTX intolerance).~~

SECTION 4.3.5: Post-Trial Access to GDC-0853

Patients ~~who complete all study assessments~~ may be eligible to screen for and enroll in the OLE Study GA30067, if considered appropriate according to the investigator.

SECTION 4.4.1.2: Non-Steroidal Anti-inflammatory Drugs

Patients may be treated with NSAIDs at up to the maximum recommended dose according to local labeling, including COX-2 inhibitors. ~~The~~*For patients who are receiving NSAID treatment on a regular basis (e.g., not as needed), the* dose should remain stable for at least the 2 weeks before randomization and throughout the study.

SECTION 4.5: STUDY ASSESSMENTS

Morning visits are strongly recommended for the clinic visits on Days 1, 28, and 84, particularly for the Day 28 visit at which post-dose PK blood samples will be collected. Patients should be fasting (≥4–8 hours) prior to these clinic visits. Study drug will be administered at these visits after pre-dose blood samples are collected when applicable. If a morning visit is logistically challenging, then based on the timing of their scheduled visit and scheduled dose, patients may be asked to take their morning dose of study drug as scheduled, then fast (≥4–8 hours) prior to their clinic visit later in the day. At the clinic visit, pre-dose blood samples will be collected and the evening dose of oral study drug will be administered if applicable (e.g., for the Day 28 visit when post-dose blood samples are collected).

SECTION 4.5.1.2: Rescreening

Rescreening refers to repeating the whole screening process. Rescreening is required if a patient has not met all of the eligibility criteria within 28 days after the original screening visit. (Note: patients who have failed two laboratory testing attempts as

described in Section 4.5.1.1 cannot be rescreened~~).~~*, except in cases where eligibility criteria such as hsCRP have been updated).*

SECTION 4.5.2: Medical History and Demographic Data

- Medical history: The *diagnosis of RA should be recorded on the medical history eCRF (and captured as "rheumatoid arthritis"), including the date of diagnosis. The* history must include dates of ~~previous~~*the most recent* vaccinations (specifically influenza, pneumococcus, and zoster~~).~~*) on the eCRF.* All medical history relevant to RA will be collected. The medical history should include CHD risk factors per the National Cholesterol Education Program (NCEP) guidelines (*e.g., smoking, hypertension, low HDL, family history of premature CHD* - see Appendix 6).

  The medical history must also include clinically significant diseases, surgeries, procedures, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse.

  A detailed history of medication used for RA is required. This should include a complete history of all *conventional synthetic DMARDs and biological* DMARDs ever taken (those taken within 5 years before screening should include dose/duration, date of discontinuation, and reason for discontinuation).

SECTION 4.5.3: Physical Examinations

A complete physical examination should be performed at screening and should include an evaluation of the head, eyes, ears, nose, and throat and the CV, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems. ~~-~~Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF~~.~~*, including assessment of rheumatoid nodules and other physical manifestations of RA (to be recorded in the eCRF).*

SECTION 4.5.5: Chest Radiograph ~~(Chest X-Ray)~~

~~Posterior anterior and lateral chest radiographs~~*Chest radiographs of appropriate quality (to adhere to local standards for the exclusion of active TB) and* with formal readings by a radiologist will be obtained at screening. If chest radiographs have been taken within 90 days prior to screening and documented results *(as read by a radiologist)* show no clinically significant abnormality as ~~read~~*determined* by ~~a radiologist~~*the investigator*, the chest radiograph does not need to be repeated.

SECTION 4.5.6: Efficacy Assessments

- The Efficacy Assessor (or designee) should be a rheumatologist or other skilled arthritis assessor. The Efficacy Assessor cannot be the Principal Investigator. The efficacy assessor will be responsible for completing the joint counts and the Physician's Global Assessment of Arthritis VAS. To ensure consistent joint evaluation throughout the trial, individual patients should be evaluated by the same efficacy assessor *whenever possible* for all study visits.

SECTION 4.5.6.1.1: Swollen and Tender Joint Count

For clarification of how to assess joints which have undergone a procedure, please see below:

- **Surgery:** Joints that have been replaced or fused at any time prior to or at any time during the study should be documented as not done for the duration of the study. Any joints which have undergone synovectomy at any time prior to or at any time during the study (including chemical and radiation synovectomy) should be documented as not done for the duration of the study. *Surgery should not occur during the trial except in the case of a documented emergency.*
- **Arthrocentesis:** Any joint that *had* fluid drained (and no steroid injected) will not be assessed at the next scheduled visit and will be graded as not done. After this time, the joint may be assessed again. *If arthrocentesis is necessary at a visit, it should only be performed after the joint assessment at the visit has been completed.*

SECTION 4.5.6.1.2: Tender/Painful Joint Count (68)

The 68 joints to be assessed are as follows:

- Upper body: Temporomandibular, sternoclavicular, acromioclavicular
- Upper extremity: Shoulder, elbow, wrist (includes radiocarpal, carpal, and carpometacarpal considered as one unit), metacarpophalangeals (~~MCP~~*MCPs* I, II, III, IV, V), thumb interphalangeal, proximal interphalangeals (PIPs II, III, IV, V), distal interphalangeals (DIPs II, III, IV, V)
- Lower extremity: Hip, knee, ankle, tarsus (includes subtalar, transverse tarsal and tarsometatarsal considered as one unit), metatarsophalangeals (MTPs I, II, III, IV, V), great toe interphalangeal, ~~PIP and DIP combined~~*PIPs* (PIPs II, III, IV, V)

SECTION 4.5.6.2: DAS Assessments

The DAS assessment is a derived measurement with differential weighting given to each component (Prevoo et al. 1995). The DAS 28-4 (CRP), the DAS 28-3 (CRP), the DAS 28-4 (erythrocyte sedimentation rate [ESR]), and the DAS 28-3 (ESR) will be calculated. The calculations for the DAS 28-4 (CRP)*, DAS 28-3 (CRP), and DAS 28-3 (ESR)* ~~and the~~ DAS 28-4 (ESR) are presented in Appendix 14.

SECTION 4.5.8: Laboratory, Biomarker, and Other Biological Samples

- ESR: ~~Can be~~Should *be* performed ~~at local laboratory or~~ as *a* point-of-care test in clinic *(with kits provided) in accordance with test guidelines*
- PPD (if QFT not available): Should be read locally ~~per local guidelines~~

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- *hsCRP:* performed at the central laboratory will be blinded after the baseline visit.
- Quantiferon *as appropriate*

SECTION 4.5.9: Electrocardiograms

Triplicate ECG recordings will be obtained at specified timepoints *within approximately 2-5 minutes of each other*, as outlined in the Schedule of Assessments (see Appendix 1 and Appendix 2).

Predose ECGs acquired on Day 1 and Day 28 should be as closely time-matched as feasible (morning ~~only, morning visit required~~*visits are strongly recommended*), and the patient should be fasting~~.~~ *(≥4–8 hours).*

All ECGs ~~are to~~*should* be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) ~~and should not be obtained within 3 hours after any meal if possible.~~ *whenever possible.*

SECTION 4.6.1: Patient Discontinuation

These patients are not eligible to enter the OLE Study GA30067 and should return for the 8-week safety follow-up visit in this study (see Appendix 1 and Appendix 2). *If the patient is unable to return for a follow-up visit, the trial site may contact the patient by telephone to determine their clinical status.*

SECTION 4.6.2: Study Treatment Discontinuation

Patients must *permanently* discontinue study treatment ~~(~~with both oral study drug and SC comparator drug~~)~~ *(however patients should be asked to remain in the blinded study through Week 12 even if their study treatment is discontinued in order to minimize missing data that limits study interpretability)* if they experience any of the following:

- ~~Pregnancy~~
- *Pregnancy (the patient may still remain in the blinded study at the investigator's discretion)*
- Anaphylaxis or other severe hypersensitivity reaction
- Malignancy
- Any serious infection or infection requiring treatment with an IV antimicrobial agent
- ~~Any prohibited medication as defined in Section 4.4.2~~
- *Grade >2 AST or ALT elevation: (AST or ALT >3 ×ULN) in combination with total bilirubin >2 ×ULN or clinical jaundice as defined by Hy's law*
- *Grade ≥3 AST or ALT elevation: (AST or ALT >5 ×ULN)*
- Any Grade 3 or greater thrombocytopenia (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE v4.0~~])~~ *]): Platelets <50,000/mm^3*
- Any Grade 4 neutropenia (NCI CTCAE v4.0~~)~~*): ANC <500/mm^3*

Patients who discontinue study treatment ~~prematurely for the reasons listed above will be~~ *and who do not remain in the blinded study will be* asked to return to the clinic for an early termination visit (see Section 4.6.1) followed by 8 weeks of safety follow-up.

SECTION 5.1.3: Management of Study Treatment in Patients Who Experience Specific Adverse Events

If there are any other situations where it seems appropriate to hold and/or discontinue study treatment, please discuss with the Medical Monitor before reinitiating treatment.

TABLE 5: Guidelines for Management of Study Treatment in Patients Who Experience Specific Adverse Events

Table 5 has been updated to clarify study treatment discontinuation.

SECTION 5.3.5.8: Deaths

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. ~~The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.~~ If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

SECTION 5.3.5.11: Hospitalization or Prolonged Hospitalization

~~The following~~ *An event that leads to* hospitalization ~~scenarios are~~*under the following circumstances should* not ~~considered to~~ be *reported as an* adverse ~~events~~*event or a serious adverse event*:

~~The following~~ *An event that leads to* hospitalization ~~scenario~~*under the following circumstances* is not considered to be *a* serious adverse ~~events~~*event,* but should be reported as *an* adverse ~~events~~*event* instead:

SECTION 5.4.1: <u>Emergency Medical Contacts</u>

Medical Monitor Contact Information

[redacted] Medical Monitor contact information:

Medical Monitors: [redacted] Medical Monitor (Primary)
[redacted] M.D.
~~*Argentina:*~~ [redacted]
~~*Rest of World*~~*Office:* [redacted]
Mobile: [redacted]
~~*United States:*~~ [redacted]
Email: [redacted]

Alternate Medical ~~Monitor~~*Monitors* contact information for all sites:

Medical Monitor:	[redacted], M.D.
Telephone No.:	[redacted] *Office:* [redacted]
	Mobile [redacted]
	Email: [redacted]
Emergency Telephone Nos.	[redacted]
Sponsor Medical Monitor:	[redacted], *M.D.*
Telephone *No.:*	*Office:* [redacted]
	Email: [redacted]

SECTION 6.1.1: Cohort 1: MTX-IR (Arms A–E)

~~An IA will be performed after *150 patients* (~30 patients per arm) have completed the 12-week assessment. A sample size of 30 patients per arm has 80% power to detect a difference of 30% between the placebo (Arm D) and a GDC-0853–treated arm for an ACR50 response rate of up to 20% in the placebo arm, with a two-sided type one error rate of 0.2 with use of Fisher's exact test. The minimally detectable difference for superiority at the interim is an improvement of 20%. No adjustment for multiple comparisons will be made.~~

The overall sample-size may be increased by up to 20% depending on the outcome of the IA (see Section 6.8).

SECTION 6.1.2: Cohort 2: TNF-IR (Arms F–G)

The purpose of this cohort is estimation and hypothesis generation regarding the effects of GDC-0853 on ACR50 response relative to placebo. A target of approximately ~~100~~ *120* patients will be enrolled and randomized with a 1:1 ratio to the two treatment groups: 200 mg BID GDC-0853 (Arm F) or placebo (Arm G). The study is designed to detect a significant difference in ACR50 response rates between the active and placebo arms at Day 84. A sample size of ~~50~~approximately ~~50~~60 patients per arm provides 80% power~~, respectively,~~ to detect a difference of 20% for an ACR50 response rate of up to ~~15~~2015~~%~~% in the placebo arm (Arm G) with a two-sided type one error rate of 0.2 with use of Fisher's exact test.

SECTION 6.4.2: Secondary Efficacy Endpoints

The key secondary efficacy analysis for the MTX-IR population will compare the proportion of patients achieving an ACR50 response between each of two higher dose-levels (Arm B and Arm C) of GDC-0853–treated patients and ADA-treated patients (Arm E). *The Cochran-Mantel Haenszel test will be used to assess the difference in the proportion of responders, adjusted for the randomization stratification factor, geographic region.* The key secondary efficacy analysis for the TNF-IR cohort will compare the proportion of patients achieving an ACR50 response between GDC-

0853–treated patients (Arm F) with the placebo-treated arm (Arm G). The Cochran-Mantel Haenszel test will be used to assess the difference in the proportion of responders, adjusted for the randomization stratification ~~factor,~~*factors* geographic region *and prior exposure to a non-TNF inhibitor biologic.* The details for other secondary efficacy analyses will be specified in the DAP.

SECTION 6.8.1.1: Cohort 1: MTX-IR (Arms A–E)

An IA ~~for futility~~ will be performed after *approximately* 150 patients have completed their 12-week evaluation (~30 patients/arm). The purpose of this IA is to assess the efficacy of the GDC-0853–treated arms compared with the placebo-treated arm~~ and to determine whether to terminate the study and whether to open the TNF-IR cohort. The IA for futility will be prepared by an IMC with selected members with no direct contact with investigational staff and monitors.~~ . Summaries of safety and efficacy data by treatment group will be prepared ~~*for review*~~*and reviewed* by members of the IMC~~.~~*; the IMC consists of Sponsor's members who do not have direct contact with investigational staff and monitors.* No unblinded individual patient data will be shared with the *members of the* Sponsor's study team~~,~~ *who have direct contact with investigational staff and monitors* except for the ~~PK scientist, statistician,~~*case in which the IMC decides to unblind the study team to enable decision-making* and ~~the statistical programming analyst~~*potential interactions with regulatory bodies*. Recruitment of patients will continue during the conduct of the IA. Further details of the IA, including the use of the IMC and decision criteria, will be specified in the DAP. No further IAs are planned in Cohort 1; however, given the hypothesis-generating nature of this study, the Sponsor may choose to conduct one subsequent efficacy IA~~. It should be noted that other Sponsor representatives (e.g., governance committee members) who are not associated with the study team may review unblinded interim data to enable decision-making.~~

If the results of the IA yield encouraging evidence of activity in one or more BTK containing treatment groups relative to placebo and is accompanied by an unexpected placebo response rate (for example), the Sponsor may opt to increase enrollment by up to 20% to obtain greater precision for estimation of treatment differences.

SECTION 6.8.1.2: Cohort 2: TNF-IR (Arms F–G)

No IA is planned in Cohort 2; however, given the hypothesis-generating nature of this study, the Sponsor may choose to conduct one ~~efficacy IA.~~*optional efficacy IA in order to guide internal decision making around issues such as the adequacy of dose ranging, the adequacy of sample sizes for safety and/or efficacy analyses, or to inform further development decisions. The IA plan will be detailed in an updated Data Analysis Plan prior to conducting the IA.* The decision to conduct this optional IA and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the IA. ~~The~~*This optional* IA will be performed and interpreted by an IMC~~ with no~~*; the IMC consists of Sponsor's members who do not have* direct contact with investigational staff and monitors. ~~No unblinded individual patient data will be shared with the Sponsor's~~ *IMC may decide to unblind the* study team~~, except for the statistician, the~~

~~statistical programming analyst, and the PK scientist. It should be noted that other Sponsor representatives (e.g., governance committee members) who are not associated with the study team may review unblinded interim data~~ to enable decision~~-~~making~~.~~ *and potential interactions with regulatory bodies.*

APPENDIX 1: SCHEDULE OF ASSESSMENTS (COHORT 1: MTX-IR)

Appendix 1 has been updated to reflect the changes in the main protocol.

APPENDIX 2: SCHEDULE OF ASSESSMENTS (COHORT 2: TNF-IR)

Appendix 2 has been updated to reflect the changes in the main protocol.

APPENDIX 3: SCHEDULE OF PHARMACOKINETIC AND BIOMARKER SAMPLES

Appendix 3 has been updated to reflect the changes in the main protocol.

APPENDIX 14: DISEASE ACTIVITY SCORE 28

Appendix 14 has been updated to reflect the changes in the main protocol.

APPENDIX 15: BLISTER WALLET CONFIGURATION FOR GDC-0853/PLACEBO ADMINISTRATION (COHORT 1 ONLY)

Appendix 15 has been updated to reflect the changes in the main protocol.

APPENDIX 16: BOTTLE AND LABEL CONFIGURATION FOR GDC-0853/PLACEBO ADMINISTRATION (COHORT 2 ONLY)

Appendix 16 has been updated to reflect the changes in the main protocol.

SAMPLE INFORMED CONSENT FORMS

The sample Informed Consent Forms have been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A TWO-COHORT RANDOMIZED PHASE II, DOUBLE−BLIND, PARALLEL GROUP STUDY IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS EVALUATING THE EFFICACY AND SAFETY OF GDC-0853 COMPARED WITH PLACEBO AND ADALIMUMAB IN PATIENTS WITH AN INADEQUATE RESPONSE TO PREVIOUS METHOTREXATE THERAPY (COHORT 1) AND COMPARED WITH PLACEBO IN PATIENTS WITH AN INADEQUATE RESPONSE *OR INTOLERANCE* TO PREVIOUS TNF THERAPY (COHORT 2)**
PROTOCOL NUMBER:	GA29350
VERSION NUMBER:	4
EUDRACT NUMBER:	2016-000335-40
IND NUMBER:	120,162
TEST PRODUCT:	GDC-0853 (RO7010939)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy to the contact provided to the investigator at study start.

PROTOCOL SYNOPSIS

TITLE:	**A TWO-COHORT RANDOMIZED PHASE II, DOUBLE−BLIND, PARALLEL GROUP STUDY IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS EVALUATING THE EFFICACY AND SAFETY OF GDC-0853 COMPARED WITH PLACEBO AND ADALIMUMAB IN PATIENTS WITH AN INADEQUATE RESPONSE TO PREVIOUS METHOTREXATE THERAPY (COHORT 1) AND COMPARED WITH PLACEBO IN PATIENTS WITH AN INADEQUATE RESPONSE *OR INTOLERANCE* TO PREVIOUS TNF THERAPY (COHORT 2)**
PROTOCOL NUMBER:	GA29350
VERSION NUMBER:	4
EUDRACT NUMBER:	2016-000335-40
IND NUMBER:	120,162
TEST PRODUCT:	GDC-0853 (RO7010939)
PHASE:	II
INDICATION:	Rheumatoid Arthritis
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the efficacy and safety of GDC-0853 compared with placebo (Cohorts 1 and 2) and compared with ADA (Cohort 1), each in combination with methotrexate (MTX), in patients with moderate to severe active rheumatoid arthritis (RA). Specific objectives and corresponding endpoints for the study are outlined below.

Objective(s)	Corresponding Endpoint(s)
Primary Efficacy Objective	
• To evaluate the efficacy of GDC-0853 at three dose levels compared with placebo used in combination with stable doses of MTX in patients with active RA who have had an inadequate response to MTX and are naive to TNF therapy (Cohort 1: MTX-IR)	• ACR50 response rates at Day 84
Key Secondary Efficacy Objectives	
• To evaluate the efficacy of GDC-0853 compared with ADA used in combination with stable doses of MTX in patients with active RA who have had an inadequate response to MTX and who are naive to TNF therapy (Cohort 1: MTX-IR)	• ACR50 response rates at Day 84
• To evaluate the efficacy of GDC-0853 compared with placebo used in combination with stable doses of MTX in patients with active RA who have had an inadequate response *or intolerance* to 1 or 2 TNF inhibitors *and may have been previously exposed to no more than one non-TNF biologic* (Cohort 2: TNF-IR)	• ACR50 response rates at Day 84
Secondary Efficacy Objectives	
• To evaluate the efficacy of GDC-0853 over time with multiple standardized assessments	• ACR20, ACR70, DAS 28-3 (CRP), DAS 28-4 (CRP), DAS 28-3 (ESR), and DAS 28-4 (ESR) response rates, change from baseline SDAI, and change from baseline CDAI at Days 7, 14, 28, 56, and 84
• To assess the efficacy of GDC-0853 over time	• ACR50 response rates at Days 7, 14, 28, and 56
• To assess efficacy on the basis of the individual components of the ACR	Response rates at Days 7, 14, 28, 56, and 84 for: • Tender/Painful Joint Count (68) • Swollen Joint Count (66) • Patient's Assessment of Arthritis Pain • Patient's Global Assessment of Arthritis • Physician's Global Assessment of Arthritis • CRP • HAQ-DI
• To assess DAS28 remission (< 2.6) and LDA (< 3.2) state	• States at Days 7, 14, 28, 56, and 84
• To assess ACR/EULAR remission according to the Boolean-based definition (tender joint count ≤ 1, swollen joint count ≤ 1, CRP ≤ 1, and patient global assessment ≤ 1)	• Remission at Days 7, 14, 28, 56, and 84
• To assess SDAI-based remission (defined as ≤ 3.3 for ACR/EULAR remission) and CDAI-based remission *(defined as ≤2.8)*	• Remission at Days 7, 14, 28, 56, and 84
• To evaluate the effect of GDC-0853 compared with placebo on health-related quality of life	• SF-36, standard, Version 2, questionnaire at Day 84
• To evaluate the effect of GDC-0853 compared with placebo on fatigue	• FACIT-Fatigue measure at Day 84

Safety Objective	
• To evaluate the safety of GDC-0853 given in combination with MTX in patients with moderate to severe RA	• The nature, frequency, severity, and timing of adverse events • Changes in vital signs, physical findings, ECGs, and clinical laboratory results following GDC-0853 administration
Pharmacokinetic Objective:	
• To characterize the pharmacokinetics of GDC-0853 in patients using a population PK approach	• Steady-state PK parameters (AUC_{0-t}, C_{max}, T_{max}, C_{trough}, $t_{1/2}$, apparent CL/F)
Exploratory Pharmacokinetic Objectives	
• To evaluate the relationship between measures of drug exposure and pharmacodynamic effect(s), efficacy, and safety of GDC-0853	• Exploratory biomarker measures in Table 4 • ACR50, DAS28, and other measures of efficacy or clinical activity • The nature, frequency, severity, and timing of adverse events • Changes in vital signs, physical findings, ECGs, and clinical laboratory results following GDC-0853 administration
• To evaluate the impact of selected covariates on measures of GDC-0853 exposure and/or response	• Steady-state PK parameters (AUC_{0-t}, C_{max}, T_{max}, C_{trough}, $t_{1/2}$, apparent CL/F) • ACR50, DAS28, and other measures of efficacy or clinical activity
• To evaluate the impact of genetic polymorphisms of on measures of GDC-0853 exposure	• Steady-state PK parameters (AUC_{0-t}, C_{max}, T_{max}, C_{trough}, $t_{1/2}$, apparent CL/F)
Exploratory Biomarker Objectives	
• To evaluate the effect of GDC-0853 on biomarkers to aid in defining the MOA. • To evaluate the relationship between changes in biomarkers and efficacy. • To evaluate if biomarkers, measured at baseline, identify a subset of patients with enhanced clinical benefit to GDC-0853.	• Lymphoid, myeloid, and other potential inflammatory biomarkers (e.g., including but not limited to CXCL13 and sICAM) • ACR50, DAS28, and other measures of efficacy

ACR = American College of Rheumatology; ADA = adalimumab; AUC_{0-t} = area under the concentration time-curve from time 0 to time t; C_{max} = maximum observed plasma concentration; C_{trough} = minimum observed plasma concentration; CDAI = Clinical Disease Activity Index; CL/F = clearance following oral dosing; CRP = C-reactive protein; DAS = Disease Activity Score; ESR = erythrocyte sedimentation rate; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ-DI = Health Assessment Questionnaire–Disability Index; IR = inadequate responder; LDA = low disease activity; MOA = mechanism of action; MTX = methotrexate; PK = pharmacokinetic; RA = rheumatoid arthritis; SDAI = Simplified Disease Activity Index; SF-36 = Short-Form 36 Health Survey; $t_{1/2}$ = half-life; T_{max} = time to maximum concentration; TNF = tumor necrosis factor.

Study Design

Description of Study

This is a multicenter, Phase II, randomized, double-blind, placebo-controlled, active comparator (Cohort 1 only), parallel-group, dose-ranging study to evaluate the efficacy and safety of GDC-0853 in patients with moderate to severe active RA and an inadequate response to previous MTX therapy (Cohort 1) or MTX and TNF therapy *who may have also had exposure to no more than one non-TNF inhibitor biologic (Cohort 2).* Moderate to severe active RA is defined by ≥ 6 tender/painful joints on motion (68 joint count) and ≥ 6 swollen joints (66 joint count) at both screening and Day 1 (randomization), as well as a *high sensitivity* C-reactive protein (*hsCRP*) ≥ 0. *400* mg/dL *for Cohort 1 and a hsCRP ≥ 0.650 mg/dL for Cohort 2* at screening.

Improvement in disease activity will be measured using the American College of Rheumatology (ACR) response rate.

This study will enroll approximately 600 patients. *In* Cohort 1*,* approximately 480 MTX-IR patients will be randomized to placebo, ADA, or one of 3 doses of GDC-0853 (50 mg QD, 150 mg QD, or 200 mg BID). *In* Cohort 2*,* approximately 120 *TNF-IR patients will be randomized to placebo or 200 mg BID GDC-0853 (see Figure 1).*

At any time during the study, the Sponsor may choose to inactivate and suspend enrollment and further dosing for a given treatment arm (Cohort 1) or reduce the dose in Arm F (Cohort 2) due to safety concerns, and as guided by the IMC. In Cohort 1, subsequently enrolled patients will be randomly allocated to the remaining arms.

After the screening period (up to 28 days), patients in both cohorts will receive blinded study drug (oral GDC-0853 or matching placebo) for 12-weeks, after which they will have the option of either entering an 8-week follow-up period or enrolling into an open-label extension (OLE) study (Study GA30067). In addition to study drug, patients in Cohort 1 will also be treated with the subcutaneous (SC) comparator drug (ADA or placebo).

Cohort 1 treatment regimens: Patients in Cohort 1 will be randomly assigned in a 1:1:1:1:1 fashion to 1 of 5 parallel treatment arms; once enrollment in Arm A has completed, patients will be randomized 1:1:1:1 across the 4 remaining treatment arms:

- Arm A: 50 mg QD GDC-0853 (BID tablets) + placebo injections *SC every 2 weeks (Q2W)* (n = 40)
- Arm B: 150 mg QD GDC-0853 (BID tablets) + placebo injections *SC Q2W* (n = 110)
- Arm C: 200 mg BID GDC-0853 (BID tablets) + placebo injections *SC Q2W* (n = 110)
- Arm D: placebo (BID tablets) + placebo injections *SC Q2W* (n = 110)
- Arm E: placebo (BID tablets) + 40 mg ADA injections *SC Q2W* (n = 110)

Cohort 2 treatment regimens: Patients in Cohort 2 will be randomly assigned in a 1:1 fashion to 1 of 2 parallel treatment arms:

- Arm F: 200 mg BID GDC-0853 (BID tablets; *approximately* n = 60)
- Arm G: placebo (BID tablet; *approximately* n = 60)

Patients must enter and remain on stable MTX treatment and a stable dose of folic acid while in the study.

For patients receiving chronic non-steroidal anti-inflammatory drug (NSAIDs) and/or corticosteroids, the continued use of stable (for at least 2 weeks prior to randomization) oral NSAIDs and/or stable (for at least 6 weeks prior to randomization) oral corticosteroid ($\leq$ 10 mg/day prednisone equivalent) doses is allowed and should be continued unchanged throughout the study, unless an adjustment is necessary for safety reasons.

Patients receiving proton pump inhibitors (PPIs) or H2 receptor antagonists (H2RAs) should be stabilized on a regimen beginning at least 2 weeks prior to randomization and continuing throughout the study.

Safety will be assessed at regular intervals by the Sponsor's Internal Monitoring Committee for the duration of the study.

Number of Subjects

This study will enroll approximately *600* patients. Approximately 480 patients will take part in Cohort 1, and approximately *120* patients will take part in Cohort 2.

Target Population

Inclusion Criteria

All patients must meet the following criteria for study entry:

- Age 18 to 75 years at screening
- Able and willing to provide written informed consent and to comply with the requirements of the protocol
- Have a diagnosis of adult-onset RA as defined by the 2010 ACR/European League Against Rheumatism Classification Criteria for RA

- RA disease activity by joint counts and laboratory markers of inflammation:

  ≥6 tender/painful joints on motion (68 joint count) and ≥6 swollen joints (66 joint count) at BOTH screening and Day 1 (randomization)

- *At screening, must have hsCRP as follows:*

  Cohort 1: ≥0.400 mg/dL (may be repeated once)
  Cohort 2: ≥0.650 mg/dL (may be repeated once)

- Positive for anti-cyclic citrullinated protein/peptide antibody (anti-CCP or ACPA), rheumatoid factor, or both (if based on historical data, need documentation of prior positive laboratory value in the electronic Case Report Form)
- Have received MTX for at least 12 weeks immediately prior to randomization, of which the last 8 weeks prior to randomization must have been at a stable dose of between *7.5* and 25 mg/week (oral or parenteral*)*

  For patients entering the trial on MTX doses <15 mg/week, there must be clear documentation in the medical record that higher doses were not tolerated or that the dose of MTX is the highest acceptable dose based on local clinical practice guidelines.

- *Willing to withdraw all non-biologic disease-modifying anti-rheumatic drugs (DMARDs), other than MTX and leflunomide, at least 4 weeks prior to randomization. Patients previously on leflunomide must have either discontinued ≥8 weeks prior to randomization or discontinued with the following elimination procedure at least 28 days prior randomization:*

  Cholestyramine or activated charcoal should be taken at standard doses for a minimum of 6 days but ideally for the standard 11 days (Arava® U.S. Package Insert; Arava® Summary of Product Characteristics)

- Willing to receive treatment at an adequate and stable dose of folic acid (not less than 5 mg *total dose* weekly) during study
- Only for patients currently receiving oral corticosteroids: Treatment must be at a stable dose of ≤10 mg/d prednisone (or equivalent) during the 6 weeks prior to randomization and with a plan to remain at a stable dose for the duration of the study.
- Only for patients currently receiving NSAIDs *on a regular basis (e.g., not as needed):*: Treatment must be at a stable dose during the 2 weeks prior to randomization and with a plan to remain at a stable dose for the duration of the study.
- Only for patients currently receiving PPIs or H2RAs: Treatment must be at a stable dose during the 2 weeks prior to randomization and with a plan to remain at a stable dose for the duration of the study.
- No evidence of active or latent or inadequately treated infection with *Mycobacterium tuberculosis* (TB) as defined by <u>all</u> of the following:

  A negative QuantiFERON TB-Gold® (QFT) or, if QFT unavailable, a Mantoux Purified Protein Derivative (PPD) skin test (performed per Centers for Disease Control and Prevention guidelines with use of 5 tuberculin units per 0.1 mL) result of <5 mm of induration, performed at the screening visit or within the 3 months prior to screening

  Patients with a history of Bacille Calmette-Guérin vaccination should be screened using the QFT test only.

  An indeterminate QFT test should be repeated.

  A positive QFT test or two successive indeterminate QFT results should be considered a positive diagnostic TB test.

  An indeterminate QFT test followed by a negative QFT test should be considered a negative diagnostic TB test.

A chest radiograph taken at the screening visit or documented results within the 3 months prior to screening (must be read by a radiologist), without changes suggestive of active TB infection

If a patient has previously received an adequate documented course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multidrug-resistant TB infection are $<5\%$ or an acceptable alternative regimen, according to local guidelines) or active (acceptable multidrug regimen, according to local guidelines) TB infection, neither a PPD test nor a QFT test need be obtained, but a chest radiograph must still be obtained if not done so within the prior 3 months; this chest radiograph must be without changes suggestive of active TB infection.

- For women of childbearing potential (including those who have had a tubal ligation): Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 60 days after the last dose of study drug or longer if required per the local prescribing label for ADA

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. Women using estrogen-containing hormonal contraceptives as a method of contraception must also use a barrier, such as a male condom, in conjunction with the hormonal contraceptives.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below

  Men with female partners of childbearing potential (including those who have had a tubal ligation) must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period and for at least 120 days (4 months) after the last dose of study treatment. Men must refrain from donating sperm during this same period.

  Men with pregnant female partners must remain abstinent or use a condom during the treatment period and for at least 28 days after the last dose of study treatment to avoid exposing the fetus.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

To be enrolled into Cohort 2, patients must also meet the following criteria:

- Experienced an inadequate response *or intolerance* to previous treatment **with at least one and no more than 2** *biologic TNFα inhibitors (e.g., infliximab, etanercept, adalimumab, golimumab, or certolizumab, or biosimilar equivalent) and in the opinion of the investigator either of the following (which must be documented in the eCRF):*
  - *Experienced insufficient efficacy or loss of efficacy at a dose and duration that, in accordance with local clinical practice, is considered acceptable to adequately assess clinical response*
  - *Experienced intolerance of such treatment*

- *May have also been exposed to no more than one non-TNFa inhibitor biologic (e.g., abatacept, tocilizumab, sarilumab, sirukumab, anakinra, or any biologics or or biosimilar equivalents with the same mode of action to the listed agents, including investigational biosimilar agents).*

Exclusion Criteria

Patients who meet any of the following criteria *must* be excluded from study entry:

- History of or current inflammatory joint disease other than RA (e.g., gout requiring current treatment, reactive arthritis, psoriatic arthritis, seronegative spondyloarthritis, Lyme disease) or other systemic autoimmune disorder (e.g., systemic lupus erythematosus, inflammatory bowel disease, scleroderma, inflammatory myopathy, mixed connective tissue disease, or other overlap syndrome)
- *Systemic* involvement secondary to RA *leading to clinically significant organ dysfunction or increased risk for participation in the study, in the opinion of the investigator. For example, patients with* known RA vasculitis, pulmonary fibrosis, or Felty's syndrome should be excluded. Exceptions are as follows:
  - Sjogren's syndrome with RA *is allowable*
  - Anemia secondary to RA (if Hgb is greater than or equal to 8.5 mg/dL) is allowable.
- Functional Class IV, according to the ACR 1991 Revised Criteria for Global Functional Status in Rheumatoid Arthritis
- Major surgery, including bone/joint surgery (e.g., joint fusion) within 8 weeks prior to screening or joint surgery planned within 12 weeks following randomization
- Previous treatment with GDC-0853 or other BTK inhibitors
- *History of treatment with cell-depleting therapy including B cell–depleting therapy (e.g., anti-CD20–directed therapy such as rituximab)*
- History of treatment with any non-TNF inhibitor biologic DMARD (e.g., anti-CD20–directed therapy [e.g., rituximab], anti-IL6–directed therapy [e.g., tocilizumab], or T cell–directed therapy [e.g., abatacept]) including biosimilar equivalents
- Any condition or medication that precludes the use of or is contraindicated with MTX or folic acid, according to the local prescribing label or the investigator *(e.g., patients with pleural effusion, ascites, or who are on concomitant acitretin)*
- History of treatment with tofacitinib or other Janus kinase (JAK) inhibitor(s) *(approved or experimental)*
- Prior to randomization, must have discontinued all biologic therapies as follows:

  Etanercept and etanercept biosimilar agents for ≥ 2 weeks

  All other biologic agents (including biosimilars and investigational biosimilars to approved agents) for ≥ 28 days
- *Previous exposure to any* investigational agent *(not including investigational biosimilars to approved therapies)* within 12 weeks or 5 half-lives of the investigational agent, whichever is longer, prior to randomization
- Previous treatment within 6 months of randomization with IV gamma globulin or the Prosorba Column
- History of treatment with alkylating agents such as cyclophosphamide or chlorambucil or with total lymphoid irradiation
- Require any prohibited concomitant medications (see Section 4.4.2).
- Current treatment with corticosteroids at doses > 10 mg/d of prednisone (or equivalent)
- Intra-articular or parenteral corticosteroids within 4 weeks prior to and during screening

- History of live attenuated vaccine within 6 weeks prior to randomization or requirement to receive these vaccinations at any time during study drug treatment

  Seasonal influenza and H1N1 vaccinations are permitted if the inactivated vaccine formulations are administered.
- Evidence of serious uncontrolled concomitant cardiac, neurologic, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus), metabolic, or GI disease that, in the investigator's opinion, would preclude patient participation
- Patients meeting the New York Heart Association Class III and Class IV criteria for congestive heart failure:

  Class III: Patients with marked limitation of activity; they are comfortable only at rest

  Class IV: Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest
- Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect patient safety or interpretation of study results, including

  QT interval corrected using Fridericia's formula (QTcF) $>$ 440 ms demonstrated by at least two ECGs $>$ 30 minutes apart
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as long QT syndrome and other genetic risk factors (e.g., Brugada syndrome), structural heart disease (e.g., severe left ventricular systolic dysfunction, severe left ventricular hypertrophy), coronary heart disease (CHD; symptomatic, or with ischemia demonstrated by diagnostic testing, prior coronary artery bypass grafting, or coronary lesions $>$70% diameter stenosis that have not been or cannot be re-vascularized), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or cardiac ion channel mutations (e.g., congenital long QT syndrome)
- *Current treatment with medications that are well known to prolong the QT interval at doses that have a clinically meaningful effect on QT, as determined by the investigator. The investigator may contact the Sponsor for confirmation if needed. The investigator may reference the website: https://www.crediblemeds.org/pdftemp/pdf/CompositeList.pdf.*
- Uncontrolled disease states, such as asthma, psoriasis, or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids
- History of vasculitis
- Current liver disease t*hat is clinically significant, in the opinion of the investigator*
- Evidence of chronic and/or active hepatitis B or C

  Positive hepatitis B surface antigen (HBsAg) or hepatitis C serology (regardless of treatment status)

  Positive hepatitis B core antibody (HBcAb)
- Abnormalities in hepatic synthetic function tests (e.g., prothrombin [PT], INR, PTT, albumin) judged by the investigator to be clinically significant
- History of alcohol, drug, or chemical abuse within the 12 months prior to screening as determined by the investigator
- *History of non–gallstone-related pancreatitis or chronic pancreatitis that is judged to be clinically significant, in the opinion of the investigator (e.g., unexplained upper abdominal pain or malabsorptive diarrhea)*
- Any known active infection (with the exception of fungal nail infections or oral herpes)

- History of recurrent bacterial, viral, mycobacterial or fungal infections (defined as >2 similar episodes requiring anti-microbial treatment within the previous 12 months), with the exception of recurrent oral or genital herpes (HSV1/HSV2)
- Any history of opportunistic infections that, in the Investigator or Sponsor's judgment, would raise safety concerns regarding the patient's participation in the study
- Any major episode of infection requiring hospitalization or treatment with IV anti-microbials within 8 weeks prior to and during screening or treatment with oral anti-microbials within 2 weeks prior to and during screening

  Antimicrobials include antifungal, antibacterial, and antiviral agents.
- History of or currently active primary or secondary immunodeficiency, including known history of HIV infection
- History of cancer, including hematologic malignancy and solid tumors, within 10 years before screening; basal or squamous cell carcinoma of the skin that has been excised and is considered cured and in situ carcinoma of the cervix treated with apparent success by curative therapy >1 year prior to screening are not exclusionary.
- Women who are pregnant, nursing (breastfeeding), or intending to become pregnant during the study or within 60 days after completion of the study
- For women of childbearing potential (including those who have had a tubal ligation): Positive serum pregnancy test result at screening or on Day 1; a serum pregnancy test is needed on Day 1 ONLY if the urine pregnancy test is positive (see Appendix 8 for definition of "childbearing potential").
- Neuropathies or other painful conditions that might interfere with pain evaluation*, in the opinion of* the investigator
- Need for systemic anti-coagulation with warfarin, other oral or injectable anti-coagulants, or anti-platelet agents other than NSAIDs, aspirin, and other salicylates

  Aspirin at doses of *up to 162 mg QD is allowed.*
- History of hospitalizations or transfusion for a GI bleed
- History of CV accident (CVA) within 10 years, any history of hemorrhagic CVA, *history of spontaneous intracranial hemorrhage, or history of traumatic intracranial hemorrhage within 10 years*
- Known bleeding diathesis
- Any condition possibly affecting oral drug absorption (e.g., gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass); procedures such as gastric banding, that simply divide the stomach into separate chambers, are not exclusionary
- Any uncontrolled clinically significant laboratory abnormality that would affect safety, interpretation of study data, or the patient's participation in the study

The following exclusion criteria are based on screening laboratory tests. Laboratory tests may be repeated once during the screening period unless otherwise indicated (see Section 4.5.1.1):

- Creatinine >1.5 times the ULN (may be repeated if $1.5–2\times$ULN)
- ALT or AST >1.5 times ULN (may be repeated if $1.5–3\times$ULN)
- Total bilirubin $>$ULN (may be repeated if $1–3\times$ULN)
- Hemoglobin <8.5 g/dL (may be repeated if 7–8.4 g/dL)
- ANC $<1.5\times10^9$/L (may be repeated if $1.2–1.5\times10^9$/L)
- Platelet count $<100\times10^9$/L (may be repeated if $80–100\times10^9$/L)
- IgG $<$500 mg/dL (should not be repeated)

Additionally, patients who meet any of the following criteria will be excluded from Cohort 1:

- History of treatment with *non-TNFα inhibitor biologic for RA, including* anti-IL6–directed therapy (e.g., tocilizumab, sarilumab, sirukumab), anti-IL1-directed therapy (e.g., anakinra), or T cell–directed therapy (e.g., abatacept) including biosimilar equivalents
- History of treatment with any TNF inhibitor (e.g., infliximab, etanercept, ADA, golimumab, or certolizumab), including biosimilar equivalents and investigational biosimilars to approved agents
- Any condition that is a contraindication for treatment with ADA in accordance with the approved local label
- History of anaphylactic or other serious allergic reaction to ADA

End of Study

The end of study is defined as the last patient, last safety follow-up visit in this protocol or the last patient in this protocol enrolled into the OLE Study GA30067, whichever is later.

Length of Study

The maximum time in the study for a patient is 24 weeks, including screening for up to 28 days, treatment for 12 weeks, and the safety follow-up period for 8 weeks (after the last dose of study drug). Patients enrolling in OLE Study GA30067 for GDC-0853 will not enter the safety follow-up period of Study GA29350.

Investigational Medicinal Products

Test Product (Investigational Drug)

The GDC-0853 dose levels are 50 mg QD, 150 mg QD, and 200 mg BID, with matching placebos. Patients will receive GDC-0853/placebo BID, approximately every 12 hours starting on Day 1 and ending on Day 84. Patients should be directed to take one dose (a total of 4 tablets) BID (a total of 8 tablets each day). On clinic visit days, patients should be instructed that study drug will be administered in the clinic.

		No. of Tablets	
Arm	GDC-0853 Dose (mg)	GDC-0853 (a.m./p.m.)	Placebo (a.m./p.m.)
A	50	1/0	3/4
B	150	3/0	1/4
C	200	4/4	0/0
D	0	0/0	4/4
E	0	0/0	4/4
F	200	4/4	0/0
G	0	0/0	4/4

BID = twice daily.

Note: All patients will take 4 tablets BID (i.e., 8 tablets daily) regardless of assigned GDC-0853 dose regimen; therefore, patients may be receiving some placebo tablets as part of their daily dose in order to maintain the blind.

Comparator

ADA is to be administered at a dose of 40 mg SC every other week (starting on Day 1). In this study, the ADA and ADA placebo are not visually identical. To maintain the ADA blind, all SC comparator drug administration will be administered by the unblinded health-care professional in a manner that prevents the patient from observing which study treatments he or she is receiving.

Non-Investigational Medicinal Products

Patients must enter and remain on stable MTX treatment and a stable dose of folic acid while in the study.

Statistical Methods

Primary Analysis

Efficacy analyses will be conducted for the intent-to-treat population, defined as all randomized patients. Sensitivity analyses of additional study populations (e.g., completers and per protocol [excluding major protocol violators]) will also be performed. Exploratory subgroup analyses (e.g., based on baseline biomarker characteristics) may be also be conducted.

The primary efficacy analysis will compare the proportion of patients achieving an ACR50 response between each of three dose-levels (Arms A to C) of GDC-0853–treated patients and placebo-treated patients (Arm D) at Day 84 for patients who had an inadequate response to MTX and are naive to TNF therapy. Non-responder imputation will be implemented in the event of missing data. The Cochran-Mantel-Haenszel test will be used to assess the difference in the proportion of responders, adjusted for the randomization stratification factor, geographic region.

Determination of Sample Size

Cohort 1

The purpose of this cohort is estimation and hypothesis generation regarding the effects of GDC-0853 on ACR50 response relative to placebo and relative to ADA as the active comparator. Point and interval estimates of the ACR50 response rates will be obtained. A target of approximately 480 patients will be enrolled and randomized. The first 200 patients will be randomly allocated in a 1:1:1:1:1 ratio to the five treatment arms: 50 mg QD GDC-0853 (Arm A), 150 mg QD GDC-0853 (Arm B), 200 mg BID GDC-0853 (Arm C), placebo (Arm D), or ADA (Arm E). The remaining 280 patients will be randomly allocated in a 1:1:1:1 ratio to Arms B–E. The study is designed to estimate differences in ACR50 response rates between the active comparator Arm E and GDC-0853–treated Arms B or C at Day 84. A sample size of 110 patients per arm has 80% power to detect a difference of 15% between Arm E and Arm B or C, for an ACR50 response rate of up to 50% in the active comparator arm (Arm E), with a two-sided type-one error rate of 0.2 with the χ^2 test with continuity correction. No adjustment for multiple comparisons is made.

Cohort 2

The purpose of this cohort is estimation and hypothesis generation regarding the effects of GDC-0853 on ACR50 response relative to placebo. A target of approximately *120* patients will be enrolled and randomized with a 1:1 ratio to the two treatment groups: 200 mg BID GDC-0853 (Arm F) or placebo (Arm G). The study is designed to detect a significant difference in ACR50 response rates between the active and placebo arms at Day 84. A sample size of *approximately 60* patients per arm provides 80% power to detect a difference of 20% for an ACR50 response rate of up to *20*% in the placebo arm (Arm G) with a two-sided type one error rate of 0.2 with use of Fisher's exact test.

Interim Analyses

An IA will be performed after *approximately* 150 patients have completed their 12-week evaluation (~30 patients/arm). The purpose of this IA is to assess the efficacy of the GDC-0853–treated arms compared with the placebo-treated arm. Summaries of safety and efficacy data by treatment group will be prepared *and reviewed* by members of the IMC*; the IMC consists of Sponsor's members who do not have direct contact with investigational staff and monitors.* No unblinded individual patient data will be shared with the *members of the* Sponsor's study team *who have direct contact with investigational staff and monitors* except for the *case in which the IMC decides to unblind the study team to enable decision-making* and *potential interactions with regulatory bodies*. Recruitment of patients will continue during the conduct of the IA. Further details of the IA, including the use of the IMC and decision criteria, will be specified in the DAP. No further IAs are planned in Cohort 1; however, given the hypothesis-generating nature of this study, the Sponsor may choose to conduct one subsequent efficacy IA.

If the results of the IA yield encouraging evidence of activity in one or more BTK containing treatment groups relative to placebo and is accompanied by an unexpected placebo response rate (for example), the Sponsor may opt to increase enrollment by up to 20% to obtain greater precision for estimation of treatment differences.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACPA	anti-citrullinated protein/peptide antibody
ACR	American College of Rheumatology
ADA	adalimumab
ALP	alkaline phosphatase
ASA	acetylsalicylic acid
AUC	area under the concentration time-curve
[redacted]	[redacted]
BCG	Bacille Calmette-Guérin
BCR	B cell–antigen receptor
BID	twice daily
BTK	Bruton's tyrosine kinase
C_{max}	maximum observed plasma concentration
C_{trough}	minimum observed plasma concentration
CBC	complete blood count
CCP	cyclic citrullinated protein
CDAI	Clinical Disease Activity Index
CHD	coronary heart disease
CIA	collagen-induced arthritis
ClinRO	clinician-reported outcome
CLL	chronic lymphocytic leukemia
CRP	C-reactive protein
CV	cardiovascular
CVA	cardiovascular accident
DAP	Data Analysis Plan
DAS	Disease Activity Score
DIP	distal interphalangeal
DLAE	dose-limiting adverse event
DMARD	disease-modifying anti-rheumatic drug
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FACS	fluorescence-activated cell sorting
FDA	U.S. Food and Drug Administration

Abbreviation	Definition
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
GMR	geometric mean ratio
H2RA	H2 receptor antagonist
HAQ-DI	Health Assessment Questionnaire—Disability Index
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCP	health-care professional
HIPAA	U.S. Health Insurance Portability and Accountability Act
HN	home nurse
hsCRP	*high sensitivity C-reactive protein*
IA	interim analysis
[redacted]	[redacted]
[redacted]	[redacted]
ICH	International Conference on Harmonisation
IL	interleukin
IMC	internal monitoring committee
IMP	investigational medicinal product
IND	Investigational New Drug
IR	inadequate response
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IxRS	interactive voice and Web response system
JAK	Janus kinase
MAD	multiple-ascending dose
MCP	metacarpophalangeal
MOA	mechanism of action
MTX	methotrexate
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NOAEL	no-observed-adverse-effect level
NSAID	non-steroidal anti-inflammatory drug
OLE	open-label extension
PD	pharmacodynamic
PFS	prefilled syringe

Abbreviation	Definition
PK	pharmacokinetic
PIP	proximal interphalangeal
PO	orally
PPD	purified protein derivative
PPI	proton pump inhibitor
PRN	as needed
PRO	patient-reported outcome
PT	prothrombin time
Q2W	*every 2 weeks*
QD	once daily
QFT	QuantiFERON TB -Gold®
QoL	quality of life
QTcF	QT interval corrected using Fridericia's formula
RA	rheumatoid arthritis
RCR	Roche Clinical Repository
RF	rheumatoid factor
SAD	single-ascending dose
SC	subcutaneous
SDAI	Simplified Disease Activity Index
SF-36	Short-Form 36 Health Survey
SOC	standard of care
TB	tuberculosis
TBNK	T, B, and natural killer cells
TLR	toll-like receptor
TNF	tumor necrosis factor
ULN	upper limit of normal
VAS	visual analog scale
WGS	whole-genome sequence
XLA	X-linked agammaglobulinemia

1. BACKGROUND

1.1 BACKGROUND ON RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by progressive synovitis, systemic inflammation, and the production of characteristic autoantibodies (e.g., rheumatoid factor, anti-citrullinated peptide antibodies) that can lead to progressive damage to the joints, arthropathy, and impaired joint-dependent movement leading to significant reduction in quality of life (QoL), unemployment, and premature death (Lundkvist et al. 2008). Current hypotheses on the pathogenesis of RA have focused on autoantibody production, immune complex formation in the synovium, pro-inflammatory cytokine production (especially interleukin [IL]-6 and tumor necrosis factor–alpha [TNF-α]), and the role of B cells and myeloid cells in inflamed synovium (Martin and Chan 2004; Looney 2006; Shlomchik 2008; Goronzy and Weyand 2009; Scott et al. 2010). B cell–depletion therapy has provided evidence of the important role of B cells in the pathogenesis of RA and other inflammatory diseases (Eisenberg and Albert 2006; Hauser et al. 2008). Although there are many medications available for the pharmacotherapy of RA, there remains an unmet need for safer therapy with improved efficacy, especially in the signs and symptoms of disease leading to full remission (Kjeken et al. 2006; Montag et al. 2011).

Targeted B-cell treatments have become a focus of development as immunomodulators in autoimmune disorders and for B-cell neoplasms (Swanson et al. 2009; Robak and Robak 2012; Puri et al. 2013; Vargas et al. 2013). One novel class of these immunomodulatory agents is inhibitors of Bruton's tyrosine kinase (BTK) (Kelly and Genovese 2013; Tan et al. 2013). BTK is a member of the TEC family of non-receptor or cytoplasmic tyrosine kinases, with expression restricted largely to the hematopoietic system (Rawlings and Witte 1995). BTK is a key kinase in signaling cascades following B cell–antigen receptor (BCR) activation in B cells, in Fc receptor binding of immune complexes in myeloid cells, and in some toll-like receptor (TLR) signaling events in B cells, myeloid cells, and dendritic cells (Satterthwaite and Witte 2000; Brunner et al. 2005; Sochorová et al. 2007). Autoimmune disorders marked by prominent B-cell and immune complex-mediated activities, such as RA and systemic lupus erythematous, may benefit from targeted antagonism of BTK signaling.

1.2 BACKGROUND ON BRUTON'S TYROSINE KINASE AND GDC-0853

1.2.1 Bruton's Tyrosine Kinase

Discovery of the genetic basis for primary immunodeficiencies has been the source of new therapeutic targets in immunomodulatory therapies (Puri et al. 2013; Bugatti et al. 2014; Whang and Chang 2014). In humans, mutations in the gene for BTK, which is located on the X chromosome, can result in the development of an immunodeficiency state characterized by a significant absence of circulating B cells

(Bruton 1952; Tsukada et al. 1993; Vetrie et al. 1993; Conley et al. 2005) and very low immunoglobulin levels due to a defect in B-cell differentiation at the pro– to pre–B cell stage that precludes assembly of the BCR complex and immunoglobulin gene expression (Reth and Nielsen 2014). Affected male patients have a primary immune deficiency, X-linked agammaglobulinemia (XLA), and are susceptible to recurrent infections starting shortly after birth. Patients with XLA can live relatively normal lives on a standard therapy of intravenous (IV) Ig, which suggests that BTK can be safely inhibited, especially in people with established immune systems. IVIg replacement therapy lowers the rate of infection, reduces hospitalization rates for patients with XLA, and has greatly improved the long-term prognosis of these patients.

BTK is essential for the differentiation and activity of B cells during immune system ontology and normal adaptive immune responses. BTK is activated by phosphatidylinositol 3-kinase–dependent plasma membrane recruitment and phosphorylation on tyrosine Y551 by the Src-family kinase Lyn. Autophosphorylation and activation also occurs on tyrosine Y223 in a BTK-specific manner. Once activated, BTK induces PLCγ2- and $Ca2^{+}$-dependent signaling, which leads to the activation of NF-κB– and NFAT-dependent pathways leading to cellular activation and differentiation (Niiro and Clark 2002).

The therapeutic potential of BTK inhibitors as anti-cancer agents has been established in clinical trials with agents including ibrutinib, a covalent inhibitor of BTK, which has been approved in the United States and Europe for use in patients with mantle-cell lymphoma, chronic lymphocytic leukemia (CLL), and Waldenstrom's macroglobulinemia.

1.2.2 Nonclinical Experience with GDC-0853

GDC-0853 is a highly selective, orally administered, reversible inhibitor of BTK that is being developed by Genentech, Inc. as a potential therapeutic for autoimmune diseases, such as RA. GDC-0853 has undergone extensive investigation in nonclinical in vitro and in vivo studies to characterize its pharmacological, metabolic, and toxicological properties (see the GDC-0853 Investigator's Brochure for further details).

In vitro cell-based experiments suggest that antagonism of BTK leads to inhibition of BCR-dependent cell proliferation and a reduction of inflammatory cytokine production from myeloid cells (including TNF-α, IL-1, and IL-6) by preventing signaling through the FCγRIII receptor (Di Paolo et al. 2011; Liu et al. 2011). GDC-0853 effectively blocks BCR- and CD40-mediated activation and proliferation of B cells. BTK in B cells also plays a role in TLR4-mediated B-cell proliferation and class switching. In monocytes, GDC-0853 inhibits TLR4- and immune complex-mediated inflammatory cytokine production, including TNF-α, which contributes to disease pathogenesis in RA. In dendritic cells, BTK contributes to TLR8-mediated cytokine production (TNF-α and IL-6) (Sochorová et al. 2007). In basophils, BTK-dependent activation of the FcεR leads to activation and up-regulation of CD63.

The efficacy of GDC-0853 on inflammatory arthritis was investigated in female Lewis rats with developing Type II collagen-induced arthritis (CIA). GDC-0853 treatment was well tolerated and resulted in significant and dose-dependent beneficial effects. GDC-0853 was effective at significantly reducing anti-rat collagen II IgG antibodies in the serum (obtained on Day 16) with daily (QD) doses $\geq$0.25 mg/kg/day. However, there was no effect of GDC-0853 treatment on total anti-rat IgG antibodies in the serum. Findings from the histopathology evaluation were consistent with the clinical findings.

The GDC-0853 safety profile has been assessed in repeat-dose, general toxicology studies (QD oral dosing) ranging from 1 week to 9 months in rats and dogs; in vitro and in vivo genetic toxicology studies; in vitro phototoxicity evaluation; in vitro and in vivo safety pharmacology studies of the central nervous, respiratory, and cardiovascular (CV) system; and embryo-fetal development (Seg II) studies in rats and rabbits. Overall, GDC-0853 was well tolerated for 6 months in rats (up to 104 μM•h) and 9 months in dogs (up to 36 μM•h). Notable findings identified in nonclinical toxicology studies include vascular inflammation ($\geq$56 μM•h) in dogs, hepatotoxicity (180 μM•h) in dogs and rats, and a minimal increase in corrected QT interval (QTc; 7 ms or 3%; extrapolated unbound maximum observed concentration [C_{max}] of 3.17 μM) in dogs. Fetal malformations in rats (at 627 μM•h) and rabbits ($\geq$10.6 μM•h) warrant the continued use of contraception in clinical trials. On the basis of the nonclinical and clinical safety data to date, GDC-0853 is expected to be well tolerated at the doses and duration administered in the current study, Study GA29350.

1.2.3 Clinical Experience with GDC-0853

Study GO29089 is a Phase I, open-label study in which GDC-0853 has been evaluated in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma (NHL) or CLL. In that study, 24 patients received study drug at 100, 200, or 400 mg orally (PO) QD. Nine patients received 400 mg of GDC-0853 PO QD for over 12 months. GDC-0853 was well tolerated with no dose-limiting toxicities, and adverse events have been generally non-serious Grade 1 or Grade 2 events that have been clinically manageable. The adverse events regardless of causality reported in $\geq$15% of patients include fatigue, nausea, diarrhea, headache, abdominal pain, dizziness, cough, and thrombocytopenia. Nine serious adverse events have been reported in 5 patients, of whom 2 had a fatal outcome (i.e., complications of H1N1 influenza and influenza pneumonia). Refer to the GDC-0853 Investigator's Brochure for further information on Study GO29089, including long-term safety.

Study GP29318 was a two-part, single-ascending dose (SAD) study to assess the safety, tolerability, and pharmacokinetics of GDC-0853 administered to 93 healthy subjects. In Part 1, the single-dose-escalation portion, 71 subjects were randomized to panels of 8 subjects (6:2 active:placebo ratio) per dose group (0.5–600 mg), 53 subjects received active GDC-0853. In Part 2, 100 mg GDC-0853 was administered to 40 subjects in the open-label food and pilot rabeprazole effect study. There were no serious adverse

events and no withdrawals due to adverse events during the conduct of Study GP29318. In Part 1 of the study, there were no dose-limiting adverse events (DLAEs) at single doses up to 600 mg GDC-0853. All adverse events were mild in intensity (Grade 1; Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials) and transient. No adverse events increased in intensity or frequency with dose escalation. There were two treatment-emergent adverse events of mild self-limited headache reported as related to GDC-0853 administration. There were no trends in safety laboratory findings, vital sign changes, physical examination findings, or ECG changes. There were no trends in hepatic laboratory changes following single doses of GDC-0853 in healthy subjects. Refer to the GDC-0853 Investigator's Brochure for further information on Study GP29318, including pharmacokinetics.

Study GA29347 was a multiple-ascending dose (MAD) study to assess the safety, tolerability, and pharmacokinetics of multiple doses of GDC-0853 administered to 30 healthy subjects for 14 days. Subjects were randomized to panels of 8 subjects (6:2 active:placebo) per dose group, at doses of 20 mg twice daily (BID), 60 mg BID, 150 mg BID, 250 mg BID, or 500 mg QD for 14 days. The study drug was well tolerated. There were no serious adverse events and no withdrawals due to adverse events during the conduct of the study. All adverse events were mild in intensity (Grade 1) and transient, with no relationship to dose. Adverse events included skin reactions (i.e., rash, contact dermatitis, and skin irritation from ECG leads), nausea, headache, insomnia, toothache, tinnitus, and asymptomatic bacteriuria. There were no trends in safety laboratory, vital sign, physical examination, or ECG findings.

In Study GP29832, GDC-0853 was also well tolerated when administered to 32 healthy subjects at the 200-mg dose level. This was a Phase Ia, randomized, open-label study investigating the effect of food, rabeprazole, and formulation on the pharmacokinetics of GDC-0853.

Refer to the GDC-0853 Investigator's Brochure for detailed background information on GDC-0853 as well as for additional details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The results from the Phase I studies, nonclinical toxicology studies, and studies in nonclinical models of RA support further evaluation of GDC-0853 as a potential treatment for RA. The goal of this Phase II study (GA29350) is to evaluate the clinical efficacy and safety of GDC-0853 in combination with methotrexate (MTX) in patients with active RA. In Cohort 1, three dose levels of GDC-0853 will be compared with placebo and HUMIRA® (adalimumab [ADA]) in patients with an inadequate response to methotrexate [MTX-IR]. In Cohort 2, one dose level of GDC-0853 will be compared with placebo in patients with an inadequate response *or intolerance* to *1 or 2* TNF inhibitors [TNF-IR] *and who may have had exposure to no more than one non-TNF inhibitor biologic*. The study is powered to detect a meaningful clinical benefit and includes

multiple safety assessments and monitoring by an unblinded Internal Monitoring Committee (IMC). It is not known whether patients in this study will benefit from GDC-0853 or, instead, whether GDC-0853 will cause harm.

Inhibition of BTK offers a promising mechanism for the treatment of autoimmune diseases such as RA and lupus (Section 1.2); however, data from clinical studies are lacking. Humans with a mutation in the XLA gene and who therefore lack functional BTK can live relatively normal lives on a standard therapy of IVIg (Kaveri et al. 2011), suggesting that BTK can be safely inhibited in patients with RA who have functional immune systems to explore this hypothesis. Clinical experience with GDC-0853 to date has not generated safety concerns that would preclude further evaluation in patients with autoimmune diseases. GDC-0853 has been administered to 179 subjects to date (i.e., 155 healthy subjects and 24 patients with hematological malignancies) at doses from 0.5 to 600 mg and has been well tolerated with no safety signals. In the SAD (Study GP29318), MAD (Study GA29347), relative bioavailability (Study GP29832), and oncology (Study GO29089) studies, GDC-0853 was well tolerated with no DLAEs or dose-limiting toxicities. In the oncology study, there were two deaths due to complications of confirmed influenza (i.e., H1N1 influenza and influenza pneumonia).

The no-observed-adverse-effect levels (NOAELs) determined in the repeat-dose, 6-month Wistar Han rat (20 mg/kg; 104 $\mu M \cdot h$) and 9-month dog (10 mg/kg; 36 $\mu M \cdot h$) studies support multiple-dose exposures in patients with RA at the proposed clinical doses, [redacted] The primary toxicities identified in animals include the following (see Section 5.1 and the GDC-0853 Investigator's Brochure for details):

- Vascular inflammation in dogs, characterized by endothelial necrosis, proliferation and hypertrophy, vascular/perivascular lymphocyte and macrophage infiltrates, and occasional necrosis of the medial smooth-muscle cells, was observed in a 4-week toxicity study at ≥ 56 $\mu M \cdot h$ but not in the ongoing 9-month chronic toxicity study at the terminal necropsy (≤ 37 $\mu M \cdot h$). [redacted]
- Effects on lymphocytes and immunoglobulins in rats and dogs were reversible and considered to be related to pharmacological activity involving BTK inhibition. In rats, after 4 weeks of dosing, elevated circulating total lymphocyte counts were observed at ≥ 20 mg/kg/day (≥ 104 $\mu M \cdot h$). In dogs, after 4 months of dosing, decreased circulating total lymphocytes were observed at ≥ 10 mg/kg/day (≥ 36 $\mu M \cdot h$). Peripheral-blood immunophenotyping showed decreased circulating B-cell counts in male rats at 20 mg/kg/day and in dogs at ≥ 1 mg/kg/day (≥ 2.1 $\mu M \cdot h$); there were no GDC-0853–related effects on total T, helper T, or cytotoxic T cells. Ig isotyping in high-dose dogs (36 $\mu M \cdot h$) and rats (104 $\mu M \cdot h$) showed decreased IgG concentration; mid- and high-dose rats (≥ 17 $\mu M \cdot h$) also had decreased IgM. Histopathology in rats and dogs showed a decrease in the number of lymphocytes

in follicular germinal centers in the spleen, mesenteric and mandibular lymph nodes, and/or Peyer's patches.

- Hepatotoxicity in dogs, consisting of increases in ALT, AST, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), and/or total bilirubin levels correlated with microscopic findings of minimal hepatocyte degeneration/disorganization, Kupffer cell hypertrophy/hyperplasia and pigment, and perivascular mixed cell infiltrates. Serum chemistry and histopathology findings were observed in the 4-week toxicity study at $\geq$56 μM•h and 180 μM•h, respectively (considered monitorable with liver function tests; details below). No adverse liver findings were observed in the chronic toxicity studies in rats ($\leq$104 μM•h) and dogs ($\leq$36 μM•h).
- Fetal malformations were observed in rats (i.e., cleft palate observed at 627 μM•h) and rabbits (i.e., domed-shaped heads with enlarged lateral/third ventricles at $\geq$10.6 μM•h). Thus, highly effective contraception will be mandatory for trial participation, and pregnancy monitoring will be performed at least monthly during the study.
- Pancreatic findings observed in rats administered GDC-0853 (and other BTK inhibitors) were considered to be a species-specific effect, supported by a number of investigative studies (see the GDC-0853 Investigator's Brochure for details).

Several measures will be taken to ensure the safety of patients participating in this study because of potential risks from nonclinical and clinical studies and published literature (see Section 5.1 for details). Eligibility criteria in both the blinded and open-label studies have been designed to exclude patients at higher risk for potential toxicities.

Infections

GDC-0853 is a targeted immunomodulator; however, as a reversible inhibitor, the degree to which GDC-0853 antagonism of BTK signaling may suppress immune activity is unknown. Patients participating in this study may be at risk for infections, including opportunistic infections. Therefore, patients will be excluded from the study if they have a history of hospitalization due to an infection in the 8 weeks before screening, evidence of active or latent or inadequately treated infection with *Mycobacterium tuberculosis* (TB), or any known immunodeficiency, including IgG $<$500 mg/dL. Total Ig, IgM, IgG, IgA, and IgE will be measured regularly throughout the study. Patients should be carefully monitored throughout the study for infections. GDC-0853 will be discontinued in any patient who develops a serious infection or any infection requiring treatment with an IV antimicrobial agent. In addition, any serious infection, any infection requiring IV antimicrobials (i.e., Grade 3 infection), or any opportunistic infection is considered an adverse event of special interest with expedited reporting requirements to the Sponsor.

Bleeding

BTK is expressed in platelets and is involved in platelet function via GPVI/collagen receptor signaling and GP1b receptor signaling. Platelets from patients with XLA demonstrate decreased activation in response to submaximal collagen stimulation but normal response to thrombin; clinically, there is no reported bleeding propensity in

patients with XLA. In the GDC-0853 clinical study involving oncology patients, 2 patients experienced Grade ≥ 3 gastrointestinal (GI) bleeding. These events were not dose related and occurred in patients on non-steroidal anti-inflammatory drugs (NSAIDS)/acetylsalicylic acid (ASA) with a history of gastroesophageal or peptic ulcer disease.

It is unknown whether GDC-0853 will increase the risk of bleeding in patients with RA who receive antiplatelet or anticoagulant therapies. Therefore, the eligibility criteria exclude patients at high risk for bleeding complications, and patients at high risk for NSAID-related GI injury are advised to follow local or recognized guidelines, including concomitant use of proton pump inhibitors (PPIs), if indicated. Any bleeding event of Grade 2 or above is considered an adverse event of special interest with expedited reporting requirements.

Cytopenias

Neutropenia, anemia, and thrombocytopenia have been observed in patients with hematologic malignancies who received GDC-0853. Events have been monitorable and clinically manageable. Cell counts will be monitored regularly throughout Study GA29350.

Hepatotoxicity

Evidence of hepatobiliary injury was observed in animals administered relatively high doses of GDC-0853 in repeat-dose toxicity studies. In clinical studies to date, including single dose and multiple dosing for 14 days in healthy subjects and QD dosing for over 1 year in patients with hematological malignancies, there have been no adverse events of liver enzyme elevations or trends toward elevations in laboratory evaluations. For inclusion in this study, AST and ALT levels should be no more than 1.5 times the upper limit of normal (ULN) and total bilirubin levels should be normal at screening. Baseline and routine evaluations of AST/ALT and total bilirubin will be performed throughout the study. Laboratory results of AST or ALT elevations of Grade ≥ 3 ($> 5 \times$ ULN) are adverse events of special interest with expedited reporting requirements to the Sponsor.

Cardiovascular Effects

GDC-0853 is considered to have a low potential to cause QT interval prolongation or to directly affect other CV parameters at therapeutic exposures. A minimal increase in corrected QT (QTc; 7 ms or 3%) interval was noted at 45 mg/kg in the single-dose CV safety pharmacology study in telemetry-instrumented dogs. Cardiac safety will be evaluated in all patients at baseline and throughout the study, with routine monitoring of vital signs, including heart rate and blood pressure, collection of ECGs, and reporting of cardiac adverse events.

Malignancy

The impact of BTK inhibition on the development of malignancies is not known; however, malignancies are considered a potential concern for all immunomodulatory agents.

Patients with a history of cancer within 10 years of screening will be excluded from study participation, except for basal or squamous cell carcinoma of the skin that has been excised and is considered cured and in situ carcinoma of the cervix treated with apparent success by curative therapy more than 1 year prior to screening. All malignancies are adverse events of special interest with expedited reporting requirements to the Sponsor.

Vasculitis

The risk to human safety based on toxicological findings of vascular inflammation in animal studies is uncertain. As a safety risk-mitigation measure, patients with a history of vasculitis, including RA-associated vasculitis, will be excluded from the study, and complete blood counts (CBC), creatinine levels, and urinalysis findings will be monitored in all patients during the study. Study drug should be discontinued in any patient who develops an adverse event of vasculitis, and the patient should enter the safety follow-up period.

Overall, GDC-0853 has been well tolerated in Phase I healthy subjects and oncology studies. On the basis of the compelling mechanism for BTK inhibition in RA, the risk-benefit ratio for this study is deemed acceptable. The safety profile of GDC-0853 will be further characterized in this Phase II study, and a robust safety monitoring plan that describes the potential risks for GDC-0853 and the risk-mitigation strategies to minimize risks for the patients in this trial is provided in Section 5.1.

Please refer to the most recent GDC-0853 Investigator's Brochure for additional details on clinical and nonclinical studies and additional safety information.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of GDC-0853 compared with placebo (Cohorts 1 and 2) and compared with ADA (Cohort 1), each in combination with MTX, in patients with moderate to severe active RA. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Primary, Secondary, Safety, Pharmacokinetic, and Exploratory Objectives with Corresponding Endpoints

Objective(s)	Corresponding Endpoint(s)
Primary Efficacy Objective	
• To evaluate the efficacy of GDC-0853 at three dose levels compared with placebo used in combination with stable doses of MTX in patients with active RA who have had an inadequate response to MTX and are naive to TNF therapy (Cohort 1: MTX-IR)	• ACR50 response rates at Day 84
Key Secondary Efficacy Objectives	
• To evaluate the efficacy of GDC-0853 compared with ADA used in combination with stable doses of MTX in patients with active RA who have had an inadequate response to MTX and who are naive to TNF therapy (Cohort 1: MTX-IR)	• ACR50 response rates at Day 84
• To evaluate the efficacy of GDC-0853 compared with placebo used in combination with stable doses of MTX in patients with active RA who have had an inadequate response *or intolerance* to 1 or 2 TNF inhibitors *and may have been previously exposed to no more than one non-TNF biologic* (Cohort 2: TNF-IR)	• ACR50 response rates at Day 84
Secondary Efficacy Objectives	
• To evaluate the efficacy of GDC-0853 over time with multiple standardized assessments	• ACR20, ACR70, DAS 28-3 (CRP), DAS 28-4 (CRP), DAS 28-3 (ESR), and DAS 28-4 (ESR) response rates, change from baseline SDAI, and change from baseline CDAI at Days 7, 14, 28, 56, and 84
• To assess the efficacy of GDC-0853 over time	• ACR50 response rates at Days 7, 14, 28, and 56
• To assess efficacy on the basis of the individual components of the ACR	Response rates at Days 7, 14, 28, 56, and 84 for: • Tender/Painful Joint Count (68) • Swollen Joint Count (66) • Patient's Assessment of Arthritis Pain • Patient's Global Assessment of Arthritis • Physician's Global Assessment of Arthritis • CRP • HAQ-DI
• To assess DAS28 remission (< 2.6) and LDA (< 3.2) state	• States at Days 7, 14, 28, 56, and 84
• To assess ACR/EULAR remission according to the Boolean-based definition (tender joint count ≤ 1, swollen joint count ≤ 1, CRP ≤ 1 *mg/dL*, and patient global assessment ≤ 1)	• Remission at Days 7, 14, 28, 56, and 84
• To assess SDAI-based remission (defined as ≤ 3.3 for ACR/EULAR remission) and CDAI-based remission *(defined as ≤ 2.8)*	• Remission at Days 7, 14, 28, 56, and 84
• To evaluate the effect of GDC-0853 compared with placebo on health-related quality of life	• SF-36, standard, Version 2, questionnaire at Day 84
• To evaluate the effect of GDC-0853 compared with placebo on fatigue	• FACIT-Fatigue measure at Day 84

Table 1 Primary, Secondary, Safety, Pharmacokinetic, and Exploratory Objectives with Corresponding Endpoints (cont.)

Safety Objective	
• To evaluate the safety of GDC-0853 given in combination with MTX in patients with moderate to severe RA	• The nature, frequency, severity, and timing of adverse events • Changes in vital signs, physical findings, ECGs, and clinical laboratory results following GDC-0853 administration
Pharmacokinetic Objective:	
• To characterize the pharmacokinetics of GDC-0853 in patients using a population PK approach	• Steady-state PK parameters (AUC_{0-t}, C_{max}, T_{max}, C_{trough}, $t_{1/2}$, apparent CL/F)
Exploratory Pharmacokinetic Objectives	
• To evaluate the relationship between measures of drug exposure and pharmacodynamic effect(s), efficacy, and safety of GDC-0853	• Exploratory biomarker measures in Table 4 • ACR50, DAS28, and other measures of efficacy or clinical activity • The nature, frequency, severity, and timing of adverse events • Changes in vital signs, physical findings, ECGs, and clinical laboratory results following GDC-0853 administration
• To evaluate the impact of selected covariates on measures of GDC-0853 exposure and/or response	• Steady-state PK parameters (AUC_{0-t}, C_{max}, T_{max}, C_{trough}, $t_{1/2}$, apparent CL/F) • ACR50, DAS28, and other measures of efficacy or clinical activity
• To evaluate the impact of genetic polymorphisms of on measures of GDC-0853 exposure	• Steady-state PK parameters (AUC_{0-t}, C_{max}, T_{max}, C_{trough}, $t_{1/2}$, apparent CL/F)
Exploratory Biomarker Objectives	
• To evaluate the effect of GDC-0853 on biomarkers to aid in defining the MOA. • To evaluate the relationship between changes in biomarkers and efficacy. • To evaluate if biomarkers, measured at baseline, identify a subset of patients with enhanced clinical benefit to GDC-0853.	• Lymphoid, myeloid, and other potential inflammatory biomarkers (e.g., including but not limited to CXCL13 and sICAM) • ACR50, DAS28, and other measures of efficacy

ACR = American College of Rheumatology; ADA = adalimumab; AUC_{0-t} = area under the concentration time-curve from time 0 to time t; C_{max} = maximum observed plasma concentration; C_{trough} = minimum observed plasma concentration; CDAI = Clinical Disease Activity Index; CL/F = clearance following oral dosing; CRP = C-reactive protein; DAS = Disease Activity Score; ESR = erythrocyte sedimentation rate; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ-DI = Health Assessment Questionnaire–Disability Index; IR = inadequate responder; LDA = low disease activity; MOA = mechanism of action; MTX = methotrexate; PK = pharmacokinetic; RA = rheumatoid arthritis; SDAI = Simplified Disease Activity Index; SF-36 = Short-Form 36 Health Survey; $t_{1/2}$ = half-life; T_{max} = time to maximum concentration; TNF = tumor necrosis factor.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a multicenter, Phase II, randomized, double-blind, placebo-controlled, active comparator (Cohort 1 only), parallel-group, dose-ranging study to evaluate the efficacy and safety of GDC-0853 in patients with moderate to severe active RA and an inadequate response to previous MTX therapy (Cohort 1) or MTX and TNF therapy *who may have also had exposure to no more than one non-TNF inhibitor biologic (Cohort 2).* Moderate to severe active RA is defined by ≥6 tender/painful joints on motion (68 joint count) and ≥6 swollen joints (66 joint count) at both screening and Day 1 (randomization), as well as a *high sensitivity* C-reactive protein (*hsCRP*) ≥0. *400* mg/dL *for Cohort 1 and a hsCRP ≥0.650 mg/dL for Cohort 2* at screening. Improvement in disease activity will be measured using the American College of Rheumatology (ACR) response rate.

This study will enroll approximately 600 patients. *In* Cohort 1*,* approximately 480 MTX-IR patients will be randomized to placebo, ADA, or one of 3 doses of GDC-0853 (50 mg QD, 150 mg QD, or 200 mg BID). *In* Cohort 2*,* approximately 120 *TNF-IR patients will be randomized to placebo or 200 mg BID GDC-0853 (see Figure 1).*

At any time during the study, the Sponsor may choose to inactivate and suspend enrollment and further dosing for a given treatment arm (Cohort 1) or reduce the dose in Arm F (Cohort 2) due to safety concerns, and as guided by the IMC. In Cohort 1, subsequently enrolled patients will be randomly allocated to the remaining arms.

After the screening period (up to 28 days), patients in both cohorts will receive blinded study drug (oral GDC-0853 or matching placebo) for 12-weeks, after which they will have the option of either entering an 8-week follow-up period or enrolling into an open-label extension (OLE) study (Study GA30067). In addition to study drug, patients in Cohort 1 will also be treated with the subcutaneous (SC) comparator drug (ADA or placebo).

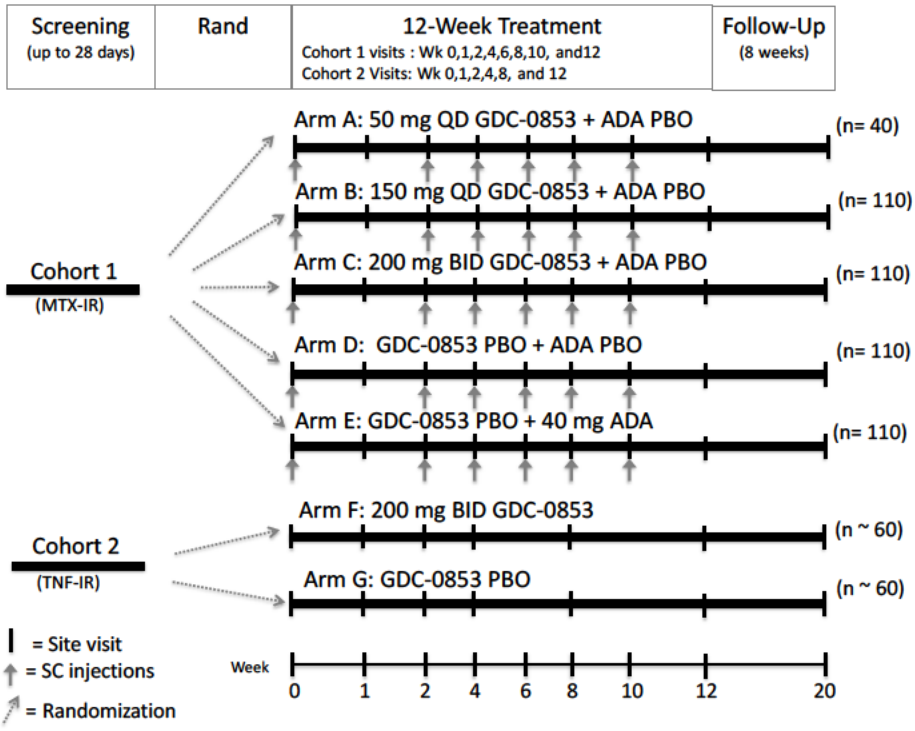
Patients must enter and remain on stable MTX treatment while in the study (see Section 4.3.3.1). In order to prevent adverse events associated with MTX treatment, patients are also required to be on a stable dose of folic acid while in the study (see Section 4.3.3.2).

For patients receiving chronic NSAIDs and/or corticosteroids, the continued use of stable (for at least 2 weeks prior to randomization) oral NSAIDs and/or stable (for at least 6 weeks prior to randomization) oral corticosteroid (≤10 mg/day prednisone equivalent) doses is allowed and should be continued unchanged throughout the study, unless an adjustment is necessary for safety reasons (see Section 4.4.1).

Patients receiving PPIs or H2 receptor antagonists (H2RAs) should be stabilized on a regimen beginning at least 2 weeks prior to randomization and continuing throughout the study (see Section 4.4.1.5).

Safety will be assessed at regular intervals by the Sponsor's IMC for the duration of the study (see Section 3.1.2).

Figure 1 Study Schema



ADA=adalimumab; BID=twice daily; *IMC=Internal Monitoring Committee;* MTX-IR=methotrexate inadequate response patients; PBO=placebo; QD=once daily; Rand=randomization; SC=subcutaneous; TNF-IR=tumor necrosis factor inhibitor inadequate response patients.

This study consists of 3 parts: A screening period of up to 28 days, a 12-week blinded treatment period, and an 8-week safety follow-up period. The treatment for Cohort 1 will consist of study drug (GDC-0853 or matching placebo) and SC comparator drug (ADA or placebo); the treatment for Cohort 2 will consist of study drug only. The above schematic shows all clinic visits. *In Cohort 1,* patients will be randomized 1:1:1:1:1 into Arms A–E. After Arm A is filled (40 patients), subsequent Cohort 1 patients will be randomized 1:1:1:1 into Arms B–E. In Cohort 2, patients will be randomized 1:1 into Arms F and G.

3.1.1 Cohort 1 (MTX-IR)

Cohort 1 includes patients with active RA who have demonstrated an inadequate response to MTX. An inadequate response to MTX is defined as meeting entry criteria for active disease despite having received MTX for at least 12 weeks immediately prior to randomization, of which the last 8 weeks prior to randomization must have been at a

stable dose of between 15 and 25 mg/week (oral or parenteral; *for patients entering the trial on MTX doses <15 mg/week, doses as low as 7.5 mg/week are allowed only if there is clear documentation in the medical record that higher doses were not tolerated or that the dose of MTX is the highest acceptable dose based on local clinical practice guidelines).*

Cohort 1 Arms A–E are designed to assess the safety and efficacy of GDC-0853 administered orally at 3 dose levels in combination with background MTX therapy. Comparisons will be made against placebo and ADA and among the 3 dose levels of GDC-0853. Patients will receive both study drug (GDC-0853 and/or placebo tablets) BID and SC comparator drug (ADA or placebo injection) every 2 weeks in a double-dummy design. No patient will receive both GDC-0853 and ADA.

At baseline (Day 1), patients in Cohort 1 will be randomly assigned in a 1:1:1:1:1 fashion to 1 of 5 parallel treatment arms:

- Arm A: 50 mg QD GDC-0853 (BID tablets)+ placebo injections *SC every 2 weeks (Q2W)* (n=40)
- Arm B: 150 mg QD GDC-0853 (BID tablets) + placebo injections *SC Q2W* (n=110)
- Arm C: 200 mg BID GDC-0853 (BID tablets) + placebo injections *SC Q2W* (n=110)
- Arm D: placebo (BID tablets) +placebo injections *SC Q2W* (n=110)
- Arm E: placebo (BID tablets) +40 mg ADA injections *SC Q2W* (n=110)

Once enrollment in Arm A *is complete*, patients will be randomized 1:1:1:1 across the 4 remaining treatment arms.

For Cohort 1 the randomization will be stratified by geographic region. The Sponsor may choose to limit the percentage of patients enrolled who have a screening hsCRP of between 0.400 and 0.649 mg/dL.

Patients will be assessed at site visits on Days 1, 7, 14, 28, 42, 56, 70, and 84 during the treatment period and, if the patient does not enroll in OLE Study GA30067, on Day 140 during the follow-up period.

After 150 patients in Cohort 1 (~30 patients/arm) have completed 12 weeks of treatment, an IA *to evaluate* safety *and efficacy* will be performed by the IMC *(see Section 6.8)*.
Cohort 2 (TNF-IR)

Cohort 2 includes patients with active RA who *must* have demonstrated an inadequate response *or intolerance* to one or two TNF inhibitors and MTX and *who may have also had exposure to no more than one non-TNF inhibitor biologic. Cohort 2* is designed to assess the safety and efficacy of GDC-0853, administered orally at 1 dose level, in combination with MTX.

At baseline (Day 1), patients in Cohort 2 will be randomly assigned in a 1:1 fashion to 1 of 2 parallel treatment arms:

- Arm F: 200 mg BID GDC-0853 (BID tablets; *approximately* n=60)
- Arm G: placebo (BID tablet; *approximately* n=60)

For Cohort 2, the randomization will be stratified by geographic region and prior exposure to a non-TNF inhibitor biologic. The Sponsor may choose to limit the percentage of patients enrolled who have had prior exposure to a non-TNF inhibitor biologic.

Patients will be assessed at site visits on Days 1, 7, 14, 28, 56, and 84 during the treatment period and, if the patient does not enroll in OLE Study GA30067, on Day 140 during the follow-up period.

3.1.2 Internal Monitoring Committee

Periodic safety reviews and the IA will also be performed by the Sponsor's IMC as outlined in the IMC Charter. This committee will be unblinded to treatment assignments and will include a clinical scientist, drug safety scientist, biostatistician, and statistical programmer from the Sponsor. The IMC members will not have direct contact with investigational staff or site monitors. The IMC may request that additional Sponsor scientists participate in the data analyses and review.

3.2 END OF STUDY AND LENGTH OF STUDY

3.2.1 Length of Study

The maximum time in the study for a patient is 24 weeks, including screening for up to 28 days, treatment for 12 weeks, and the safety follow-up period for 8 weeks (after the last dose of study drug). Patients enrolling in OLE Study GA30067 for GDC-0853 will not enter the safety follow-up period of Study GA29350.

3.2.2 End of Study

The end of study is defined as the last patient, last safety follow-up visit in this protocol or the last patient in this protocol enrolled into the OLE Study GA30067, whichever is later.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for GDC-0853 Dose and Schedule

The range of GDC-0853 dose levels in this study were determined on the basis of data from Phase I studies in healthy subjects and patients with hematologic malignancies as well as nonclinical toxicology studies and arthritis models. Preliminary analysis in Study GO29089 found anti-tumor activity in patients with B-cell malignancies at all doses of GDC-0853 tested (i.e., 100 mg, 200 mg, and 400 mg PO QD). No safety or tolerability issues were identified in healthy subjects receiving GDC-0853 up to 600 mg in the single-ascending-dose Study GP29318 and up to 250 mg BID and 500 mg QD for

14 days in the multiple-ascending-dose Study GA29347. No maximum tolerated dose was identified, and there were no dose-limiting adverse events; all adverse events were Grade 1 (mild) and transient. [redacted]

Data from experiments evaluating the PD effects and anti-inflammatory activity of a tool BTK inhibitor compound (GDC-0834) in the rat model of CIA suggest that the amount of BTK inhibition anticipated in this study may be sufficient to achieve meaningful anti-inflammatory activity. These studies suggest that 70% BTK inhibition, as measured by phospho-BTK inhibition, is required for half-maximal activity (Liu et al. 2011). However, it is not known whether BTK inhibition in the rat CIA model accurately predicts efficacy in human RA.

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

It should be noted that the extent of target engagement required for clinical efficacy is unknown. Consequently, doses were selected to evaluate a wide range of target engagement and to characterize dose response in order to select the optimal dose for further study.

3.3.2 Rationale for Patient Population

Despite many advances in the treatment of RA, including the use of biologic agents, there remain a substantial number of patients with RA who do not achieve an adequate response, who lose response over time, or who cannot tolerate currently available therapies. Given limitations with the current therapeutic options for RA, there remains a need for therapies that provide a higher degree of both efficacy and safety.

This Phase II study will evaluate patients with unmet need due to an inadequate response to MTX (Cohort 1) or *inadequate response or intolerance to* TNF inhibitors *and who may have been exposed to one other non-TNF inhibitor biologic agent* (Cohort 2), given the greater unmet need in these populations of patients with RA. Eligibility criteria for this study are similar to those of many Phase II proof-of-concept RA studies. Following demonstration of acceptable efficacy and safety in this Phase II program, the use of GDC-0853 may be subsequently considered for treatment-naive patients with RA and potentially as a monotherapy option.

No adverse drug reactions for GDC-0853 have been established to date, and no patterns of adverse events have been identified that would preclude testing GDC-0853 in patients with RA. Patients with RA whose medical history or laboratory findings at screening might increase their risk of adverse events will be excluded from the study

(see Section 4.1.2 and Section 5.1.1). Potential risks with GDC-0853, such as infections, will be monitored during the conduct of this study, and the study will be modified or terminated as appropriate to ensure the safety of the patients in the study (see Section 3.1.2).

3.3.3 Rationale for Control Groups

3.3.3.1 Placebo Control Groups

Placebo-treated control groups, Arms D and G, are required for this study to achieve its efficacy and safety objectives. Historical control groups are not sufficiently comparable given changes in RA populations and treatment patterns over time, inherent variability in the subjective assessments comprising the endpoint, and regional differences in the management of patients with RA. Use of an active comparator only (e.g., ADA) could result in an underestimation of the safety or efficacy effects of GDC-0853. Patients in the placebo arms will receive stable standard-of-care (SOC) MTX therapy throughout the study. The placebo treatment period will be limited to 12 weeks, which is typically the minimum time necessary to establish the peak-level efficacy of RA therapeutics. Multiple recent Phase II and Phase III studies incorporate 12-week placebo comparator groups.

Patients in the placebo-treated control groups will enter the study while on their stable background MTX treatment, low-dose corticosteroids (≤10 mg/day), and any other stable background medications (e.g., NSAIDs, PPIs, H2RAs).

3.3.3.2 Active Control Group

ADA is a biologic TNF inhibitor licensed for the treatment of RA *at a dose of 40 mg Q2W* and is considered the SOC in many countries, often in combination with MTX. ADA will be used as an *active* control to assess relative differences in efficacy, safety, and tolerability of GDC-0853. ADA will be provided by the Sponsor. *Refer to local ADA prescribing information and RA treatment guidelines for details.*

3.3.4 Rationale for Biomarker Assessments

Biomarker assessments, before and at various timepoints after treatment, will be used to advance the understanding of the mechanism of action (MOA) of GDC-0853 in patients with RA, define PK/PD relationships, and aid dose regimen selection for future studies. A biomarker that predicts response to GDC-0853 would be valuable to patients and treating physicians as an aid in identifying patients with increased likelihood to achieve clinical benefit, thus guiding treatment decisions.

3.3.5 Rationale for PK Sample Collection Schedule

The sampling schedule is designed to capture data at several timepoints over the dosing interval (i.e., on Day 28) in order to provide information about the absorption, distribution, and elimination of GDC-0853 in patients with RA. In addition, assessments will enable the evaluation of intrapatient variability over a 12-week dosing period. Results will be used to select dosing regimens for future studies of GDC-0853. In addition, these

results will enable a robust exposure-response analysis, which will help characterize how efficacy is impacted by drug exposure and, thus, inform the most appropriate dose for further study.

3.3.6 Rationale for Other Study Design Elements

3.3.6.1 Efficacy Measurements

The ACR response criteria are commonly used in RA studies and accepted by health authorities to measure reduction in RA disease activity; ACR50 has been chosen as the primary efficacy endpoint because it measures a more robust response with a lower placebo response rate than ACR20, which has traditionally been used by most pivotal trials in RA. In addition, several other clinically meaningful aspects of RA will be evaluated, including Disease Activity Score (DAS) 28 remission and low disease activity, Boolean remission, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), and patient-reported outcome (PRO) measures (i.e., Health Assessment Questionnaire—Disability Index [HAQ-DI], Short-Form 36 Health Survey [SF-36] v2, and Functional Assessment of Chronic Illness Therapy [FACIT]—Fatigue [see Appendix 11, Appendix 12, and Appendix 13, respectively]). Each of these measures has been well established and validated in previous studies. The kinetics of response to GDC-0853 will be carefully evaluated throughout the course of the study at regular intervals (at least every month for a period of 12 weeks).

3.3.6.2 Blinding Strategy

To minimize bias in efficacy and safety assessments, this study uses blinded, matching placebos for GDC-0853 and a double-dummy design for the SC comparator drug. Because ADA does not have a matching placebo SC injection, an unblinded health-care professional (HCP) will administer the SC comparator drug to maintain the blind.

To prevent potential blind breaks due to observed efficacy or laboratory changes and to minimize bias in efficacy assessment, the “dual assessor” approach (i.e., an “efficacy assessor” and the treating physician; see Section 4.5.6) will be used to evaluate efficacy and safety. Both efficacy assessor and treating physician will be blinded to treatment assignment. The efficacy assessor, who will not have access to any other patient data, will perform the swollen and tender joint count and the Physician’s Global Assessment of Arthritis. The investigator (treating physician) will have access to both safety and efficacy data and will make all treatment decisions based on the patient’s clinical response and laboratory parameters (see Section 4.5.6 for details). If required for the safety of a patient, the investigator may break the blind and determine the treatment assignment of that patient (see Section 4.2).

3.3.6.3 Clinical Outcomes Assessments

PRO and clinician-reported outcome (ClinRO) data will be collected to more fully characterize the clinical profile of GDC-0853. To minimize the confounding of PRO assessments that evaluate pain, any potentially painful procedures (e.g., blood draws, SC administration of medication) should be performed after the pain assessment. In

cases where this is logistically challenging (e.g., the visit of Day 28 with intensive PK assessments), potentially painful procedures will be performed at least 15 minutes prior to initiation of the PRO measures.

3.3.6.4 Stratification *and Enrollment Cap*

Patient randomization will be stratified by geographic region because regional variation in the management of RA can manifest as variability in response rates, including differences in placebo *response* rates. The stratification is intended to balance the proportion of patients from different regions across the study arms in order to limit any confounding of the study results. *In Cohort 1, the Sponsor may choose to limit the percentage of patients enrolled who have a screening hsCRP of between 0.400 and 0.649 mg/dL in order to enrich for patients with higher levels of inflammation who might be expected to demonstrate an enhanced response to GDC-0853, based on mechanism of action.*

Patients in Cohort 2 will also be stratified based on whether or not they have had prior exposure to a non-TNF inhibitor biologic, in order to balance treatment assignment for the purpose of limiting any potential confounding of efficacy. The Sponsor may choose to limit the percentage of patients enrolled who have had prior exposure to a non-TNF inhibitor biologic, in order to minimize heterogeneity of the Cohort 2 population.

3.3.6.5 Methotrexate Therapy

Patients in this study will continue on their background MTX therapy, because this represents a common treatment paradigm for patients who initiate additional therapies following an inadequate response to MTX and/or TNF inhibitors. In addition, MTX is commonly prescribed with ADA to minimize the potential for immunogenicity with ADA.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 600 patients with moderate to severe active RA will be enrolled in this study.

4.1.1 Inclusion Criteria

All patients must meet the following criteria for study entry:

- Age 18 to 75 years at screening
- Able and willing to provide written informed consent and to comply with the requirements of the protocol
- Have a diagnosis of adult-onset RA as defined by the 2010 ACR/European League Against Rheumatism (EULAR) Classification Criteria for RA (see Appendix 9)
- RA disease activity by joint counts and laboratory markers of inflammation:

  ≥6 tender/painful joints on motion (68 joint count) and ≥6 swollen joints (66 joint count) at BOTH screening and Day 1 (randomization)

- *At screening, must have hsCRP as follows:*

  Cohort 1: ≥0.400 mg/dL *(may be repeated once)*

  Cohort 2: ≥*0.650 mg/dL* (may be repeated once)

- Positive for anti-cyclic citrullinated protein/peptide antibody (anti-CCP or ACPA), rheumatoid factor (RF), or both (if based on historical data, need documentation of prior positive laboratory value in the electronic Case Report Form [eCRF])
- Have received MTX for at least 12 weeks immediately prior to randomization, of which the last 8 weeks prior to randomization must have been at a stable dose of between *7.5* and 25 mg/week (oral or parenteral*)*

  For patients entering the trial on MTX doses <15 mg/week, there must be clear documentation in the medical record that higher doses were not tolerated or that the dose of MTX is the highest acceptable dose based on local clinical practice guidelines.

- *Willing to withdraw all non-biologic disease-modifying anti-rheumatic drugs (DMARDs), other than MTX and leflunomide, at least 4 weeks prior to randomization. Patients previously on leflunomide must have either discontinued ≥8 weeks prior to randomization or discontinued with the following elimination procedure at least 28 days prior randomization:*

  Cholestyramine or activated charcoal should be taken at standard doses for a minimum of 6 days but ideally for the standard 11 days (Arava® U.S. Package Insert; Arava® Summary of Product Characteristics)

- Willing to receive treatment at an adequate and stable dose of folic acid (not less than 5 mg *total dose* weekly) during study
- Only for patients currently receiving oral corticosteroids: Treatment must be at a stable dose of ≤10 mg/d prednisone (or equivalent) during the 6 weeks prior to randomization and with a plan to remain at a stable dose for the duration of the study.
- Only for patients currently receiving NSAIDs *on a regular basis (e.g., not as needed):* Treatment must be at a stable dose during the 2 weeks prior to randomization and with a plan to remain at a stable dose for the duration of the study.
- Only for patients currently receiving PPIs or H2RAs: Treatment must be at a stable dose during the 2 weeks prior to randomization and with a plan to remain at a stable dose for the duration of the study.
- No evidence of active or latent or inadequately treated infection with TB as defined by <u>all</u> of the following:

  A negative QuantiFERON TB-Gold® (QFT) or, if QFT unavailable, a Mantoux Purified Protein Derivative (PPD) skin test (performed per Centers for Disease Control and Prevention guidelines with use of 5 tuberculin units per 0.1 mL) result of <5 mm of induration, performed at the screening visit or within the 3 months prior to screening

Patients with a history of Bacille Calmette-Guérin (BCG) vaccination should be screened using the QFT test only.

An indeterminate QFT test should be repeated.

A positive QFT test or two successive indeterminate QFT results should be considered a positive diagnostic TB test.

An indeterminate QFT test followed by a negative QFT test should be considered a negative diagnostic TB test.

A chest radiograph taken at the screening visit or documented results within the 3 months prior to screening (must be read by a radiologist), without changes suggestive of active TB infection

If a patient has previously received an adequate documented course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multidrug-resistant TB infection are $<5\%$ or an acceptable alternative regimen, according to local guidelines) or active (acceptable multidrug regimen, according to local guidelines) TB infection, neither a PPD test nor a QFT test need be obtained, but a chest radiograph must still be obtained if not done so within the prior 3 months; this chest radiograph must be without changes suggestive of active TB infection.

- For women of childbearing potential (including those who have had a tubal ligation): Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 60 days after the last dose of study drug or longer if required per the local prescribing label for ADA (see Appendix 8)

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. Women using estrogen-containing hormonal contraceptives as a method of contraception must also use a barrier, such as a male condom, in conjunction with the hormonal contraceptives.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below (also see Appendix 8):

  Men with female partners of childbearing potential (including those who have had a tubal ligation) must remain abstinent or use a condom plus an additional

contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period and for at least 120 days (4 months) after the last dose of study treatment. Men must refrain from donating sperm during this same period.

Men with pregnant female partners must remain abstinent or use a condom during the treatment period and for at least 28 days after the last dose of study treatment to avoid exposing the fetus.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

To be enrolled into Cohort 2, patients must also meet the following criteria:

- Experienced *an* inadequate response *or intolerance* to previous treatment **with at least one and no more than 2** *biologic TNFα inhibitors (e.g., infliximab, etanercept, adalimumab, golimumab, or certolizumab, or biosimilar equivalent) and in the opinion of the investigator either of the following (which must be documented in the eCRF):*
  - *Experienced insufficient efficacy or loss of efficacy at a dose and duration that, in accordance with local clinical practice, is considered acceptable to adequately assess clinical response*
  - *Experienced intolerance of such treatment*
- *May have also been exposed to* ***no more than one*** *non-TNFα inhibitor biologic (e.g., abatacept, tocilizumab, sarilumab, sirukumab, anakinra, or any biologics or biosimilar equivalents with the same mode of action to the listed agents, including investigational biosimilar agents).*

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria *must* be excluded from study entry:

- History of or current inflammatory joint disease other than RA (e.g., gout requiring current treatment, reactive arthritis, psoriatic arthritis, seronegative spondyloarthritis, Lyme disease) or other systemic autoimmune disorder (e.g., systemic lupus erythematosus, inflammatory bowel disease, scleroderma, inflammatory myopathy, mixed connective tissue disease, or other overlap syndrome)
- *Systemic* involvement secondary to RA *leading to clinically significant organ dysfunction or increased risk for participation in the study, in the opinion of the investigator. For example, patients with* known RA vasculitis, pulmonary fibrosis, or Felty's syndrome should be excluded. Exceptions are as follows:
  - Sjogren's syndrome with RA *is allowable*
  - Anemia secondary to RA (if Hgb is greater than or equal to 8.5 mg/dL) is allowable.
- Functional Class IV, according to the ACR 1991 Revised Criteria for Global Functional Status in Rheumatoid Arthritis (see Appendix 10)

- Major surgery, including bone/joint surgery (e.g., joint fusion) within 8 weeks prior to screening or joint surgery planned within 12 weeks following randomization
- Previous treatment with GDC-0853 or other BTK inhibitors
- *History of treatment with cell-depleting therapy including B cell–depleting therapy (e.g., anti-CD20–directed therapy such as rituximab)*
- Any condition or medication that precludes the use of or is contraindicated with MTX or folic acid, according to the local prescribing label or the investigator *(e.g., patients with pleural effusion, ascites, or who are on concomitant acitretin)*
- History of treatment with tofacitinib or other Janus kinase (JAK) inhibitor(s) *(approved or experimental)*
- Prior to randomization, must have discontinued all biologic therapies as follows:

  Etanercept and etanercept biosimilar agents for ≥2 weeks

  All other biologic agents (including biosimilars and investigational biosimilars to approved agents) for ≥ 28 days
- *Previous exposure to any* investigational agent *(not including investigational biosimilars to approved therapies)* within 12 weeks or 5 half-lives of the investigational agent, whichever is longer, prior to randomization
- Previous treatment within 6 months of randomization with IV gamma globulin or the Prosorba Column
- History of treatment with alkylating agents such as cyclophosphamide or chlorambucil or with total lymphoid irradiation
- Require any prohibited concomitant medications (see Section 4.4.2).
- Current treatment with corticosteroids at doses >10 mg/d of prednisone (or equivalent)
- Intra-articular or parenteral corticosteroids within 4 weeks prior to and during screening
- History of live attenuated vaccine within 6 weeks prior to randomization or requirement to receive these vaccinations at any time during study drug treatment

  Seasonal influenza and H1N1 vaccinations are permitted if the inactivated vaccine formulations are administered.
- Evidence of serious uncontrolled concomitant cardiac, neurologic, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus), metabolic, or GI disease that, in the investigator's opinion, would preclude patient participation
- Patients meeting the New York Heart Association Class III and Class IV criteria for congestive heart failure:

  Class III: Patients with marked limitation of activity; they are comfortable only at rest

Class IV: Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest

- Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect patient safety or interpretation of study results, including

  QT interval corrected using Fridericia's formula (QTcF) > 440 ms demonstrated by at least two ECGs > 30 minutes apart

- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as long QT syndrome and other genetic risk factors (e.g., Brugada syndrome), structural heart disease (e.g., severe left ventricular systolic dysfunction, severe left ventricular hypertrophy), coronary heart disease (CHD; symptomatic, or with ischemia demonstrated by diagnostic testing, prior coronary artery bypass grafting, or coronary lesions > 70% diameter stenosis that have not been or cannot be re-vascularized), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or cardiac ion channel mutations (e.g., congenital long QT syndrome)
- *Current treatment with medications that are well known to prolong the QT interval at doses that have a clinically meaningful effect on QT, as determined by the investigator. The investigator may contact the Sponsor for confirmation if needed. The investigator may reference the website: https://www.crediblemeds.org/pdftemp/pdf/CompositeList.pdf.*
- Uncontrolled disease states, such as asthma, psoriasis, or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids
- History of vasculitis
- Current liver disease *that is clinically significant, in the opinion of the investigator*
- Evidence of chronic and/or active hepatitis B or C

  Positive hepatitis B surface antigen (HBsAg) or hepatitis C serology (regardless of treatment status)

  Positive hepatitis B core antibody (HBcAb)

- Abnormalities in hepatic synthetic function tests (e.g., prothrombin [PT], INR, PTT, albumin) judged by the investigator to be clinically significant
- History of alcohol, drug, or chemical abuse within the 12 months prior to screening as determined by the investigator
- *History of non–gallstone-related pancreatitis or chronic pancreatitis that is judged to be clinically significant, in the opinion of the investigator (e.g., unexplained upper abdominal pain or malabsorptive diarrhea)*
- Any known active infection (with the exception of fungal nail infections or oral herpes)
- History of recurrent bacterial, viral, mycobacterial or fungal infections (defined as > 2 similar episodes requiring anti-microbial treatment within the previous 12 months), with the exception of recurrent oral or genital herpes (HSV1/HSV2)

- Any history of opportunistic infections that, in the Investigator or Sponsor's judgment, would raise safety concerns regarding the patient's participation in the study
- Any major episode of infection requiring hospitalization or treatment with IV anti-microbials within 8 weeks prior to and during screening or treatment with oral anti-microbials within 2 weeks prior to and during screening

  Antimicrobials include antifungal, antibacterial, and antiviral agents.
- History of or currently active primary or secondary immunodeficiency, including known history of HIV infection
- History of cancer, including hematologic malignancy and solid tumors, within 10 years before screening; basal or squamous cell carcinoma of the skin that has been excised and is considered cured and in situ carcinoma of the cervix treated with apparent success by curative therapy >1 year prior to screening are not exclusionary.
- Women who are pregnant, nursing (breastfeeding), or intending to become pregnant during the study or within 60 days after completion of the study
- For women of childbearing potential (including those who have had a tubal ligation): Positive serum pregnancy test result at screening or on Day 1; a serum pregnancy test is needed on Day 1 ONLY if the urine pregnancy test is positive (see Appendix 8 for definition of "childbearing potential").
- Neuropathies or other painful conditions that might interfere with pain evaluation*, in the opinion of* the investigator
- Need for systemic anti-coagulation with warfarin, other oral or injectable anti-coagulants, or anti-platelet agents other than NSAIDs, aspirin, and other salicylates

  Aspirin at doses of up to 162 mg QD is allowed.
- History of hospitalizations or transfusion for a GI bleed
- History of CV accident (CVA) within 10 years*,* any history of hemorrhagic CVA*, history of spontaneous intracranial hemorrhage, or history of traumatic intracranial hemorrhage within 10 years*
- Known bleeding diathesis
- Any condition possibly affecting oral drug absorption (e.g., gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass); procedures such as gastric banding, that simply divide the stomach into separate chambers, are not exclusionary
- Any uncontrolled clinically significant laboratory abnormality that would affect safety, interpretation of study data, or the patient's participation in the study

The following exclusion criteria are based on screening laboratory tests. Laboratory tests may be repeated once during the screening period unless otherwise indicated (see Section 4.5.1.1):

- Creatinine $>$ 1.5 times the ULN (may be repeated if 1.5–2 $\times$ ULN)
- ALT or AST $>$ 1.5 times ULN (may be repeated if 1.5–3 $\times$ ULN)
- Total bilirubin $>$ ULN (may be repeated if 1–3 $\times$ ULN)
- Hemoglobin $<$ 8.5 g/dL (may be repeated if 7–8.4 g/dL)
- ANC $< 1.5 \times 10^9$/L (may be repeated if 1.2–1.5 $\times 10^9$/L)
- Platelet count $< 100 \times 10^9$/L (may be repeated if 80–100 $\times 10^9$/L)
- IgG $<$500 mg/dL (should not be repeated)

Additionally, patients who meet any of the following criteria will be excluded from Cohort 1:

- History of treatment with *non-TNFα inhibitor biologic for RA, including* anti-IL6–directed therapy (e.g., tocilizumab, sarilumab, sirukumab), anti-IL1-directed therapy (e.g., anakinra), or T cell–directed therapy (e.g., abatacept) including biosimilar equivalents
- History of treatment with any TNF inhibitor (e.g., infliximab, etanercept, ADA, golimumab, or certolizumab), including biosimilar equivalents and investigational biosimilars to approved agents
- Any condition that is a contraindication for treatment with ADA in accordance with the approved local label
- History of anaphylactic or other serious allergic reaction to ADA

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

The Sponsor will provide the specifications of the randomization algorithm to the interactive voice and Web response system (IxRS) vendor. For Cohort 1 the randomization will be stratified by geographic region. *For Cohort 2, the randomization will be stratified by geographic region and prior exposure to a non-TNF inhibitor biologic.*

To prevent potential blind breaks due to observed efficacy or laboratory changes, a dual assessor approach will be used to evaluate efficacy and safety (see Section 4.5.6).

To maintain the blind, after screening, sites will not receive data related to selected laboratory parameters, including but not limited to TBNK (T, B, and natural killer cells) results (including CD19 counts) and CRP levels.

PK samples will be collected from patients assigned to all arms in order to maintain the blinding of the treatment assignments. Since PK assay results for patients in the comparator arms are generally not needed for the safe conduct or proper interpretation

of this trial, samples from patients assigned to the comparator arm will not be analyzed except by request (i.e., to evaluate a possible error in dosing). Sponsor personnel responsible for performing PK assays, which may include contracted laboratory personnel, will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed.

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly to discuss the rationale. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event), without disclosing the treatment assignment in the documentation.

For regulatory reporting purposes and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (SUSARs, see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are GDC-0853 and ADA.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 GDC-0853 and Placebo Tablet

GDC-0853 will be provided by the Sponsor as 50-mg dose strength tablets with corresponding matching placebo tablets, which will be indistinguishable in appearance.

Tablets will be supplied in blister wallets (Cohort 1) and bottles (Cohort 2) as appropriate for the treatment arm to which the patient is randomized. Blister wallets and bottles will be appropriately labeled for this study. GDC-0853 and placebo tablets should be stored between 2°C and 8°C.

For information on the formulation and handling of GDC-0853, see the GDC-0853 Investigator's Brochure.

4.3.1.2 Adalimumab and Adalimumab Placebo

For Cohort 1 only, SC comparator drug will be provided by the Sponsor in two, non-matching prefilled syringes (PFSs): one for ADA and one for placebo. Because of the different appearance of the syringes, they will need to be administered by an unblinded HCP in a manner that does not unblind the patient or blinded study staff.

ADA will be supplied by the Sponsor for use as a single-use, 1-mL, glass PFS with a fixed 27-gauge 1/2-inch needle, providing 40 mg (0.8 mL) of ADA. ADA is supplied as a preservative-free, sterile solution for SC administration.

ADA placebo will be supplied by the Sponsor as a liquid formulation in PFSs to be administered as an SC injection. Each 1-mL PFS will contain 0.7 mL of a solution of 20 mM histidine, 0.2 M arginine succinate, and 0.04% polysorbate 20, pH 5.8. Each syringe is for single-dose SC administration and contains no preservatives.

Study drug packaging will be overseen by the Sponsor's Clinical Trial Supplies Department and bear a label with the identification required by local law, the protocol number, drug identification, and dosage. The packaging and labeling of the SC comparator drug will be in accordance with the Sponsor's standards and local regulations.

Upon arrival of investigational products at the site, the unblinded HCP (e.g., pharmacist or pharmacy staff) should check for damage and verify proper identity, quantity, integrity of seals, and temperature conditions and report any deviations or product complaints to the monitor upon discovery.

The SC comparator drug must be stored according to the details on the product label. The drug label indicates the storage temperature. PFSs of the SC comparator drug should be refrigerated at 2°C–8°C and protected from excessive light and heat. PFSs should not be frozen, shaken, or stored at room temperature.

For further details, see the ADA Summary of Product Characteristics (SmPC) or United States Package Insert (USPI).

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 GDC-0853 and Placebo Dose and Administration

The GDC-0853 dose levels are 50 mg QD, 150 mg QD, and 200 mg BID, with matching placebos (see Table 2). Patients will receive GDC-0853/placebo BID, approximately every 12 hours starting on Day 1 and ending on Day *83*. Patients should be directed to take one dose (a total of 4 tablets) BID (a total of 8 tablets each day). On clinic visit days, patients should be instructed that study drug will be administered in the clinic.

If a dose is missed, the patient should resume normal dosing with the next scheduled dose. Missed doses should not be taken, as they result in doubling of the dose. Patients should record on the blister wallet (Cohort 1) or bottle (Cohort 2) the dose that was missed and notify study staff of any missed doses. Doses that are vomited will be considered missed doses.

GDC-0853 or placebo may be orally administered with or without food, except *for the* dose of oral study drug *taken at the clinic visit on Days 1 and 28 (see Appendix 1 and*

Appendix 2), which will be administered at the clinic visit while fasting. The dates and times of the most recent prior meal, last dose of oral study drug (prior to clinic visit), and timing of oral study drug administration in clinic should be recorded at each clinic visit. In addition, any use of PPIs, H2RAs, and/or *short-acting* antacids (e.g., Maalox®, Pepto-Bismol®, Rolaids®) should be recorded as concomitant medications, including date and time of last administration *prior to the clinic visit.* Administration of study drug should be staggered with *short-acting* antacid use (i.e., oral study drug should be taken 2 hours before or 2 hours after the *short-acting* antacid).

Table 2 GDC-0853 Dosing Regimen by Treatment Arm (Cohorts 1 and 2)

Arm	GDC-0853 Dose (mg)	No. of Tablets	
		GDC-0853 (a.m./p.m.)	Placebo (a.m./p.m.)
A	50	1/0	3/4
B	150	3/0	1/4
C	200	4/4	0/0
D	0	0/0	4/4
E	0	0/0	4/4
F	200	4/4	0/0
G	0	0/0	4/4

BID = twice daily.

Note: All patients will take 4 tablets BID (i.e., 8 tablets daily) regardless of assigned GDC-0853 dose regimen; therefore, patients may be receiving some placebo tablets as part of their daily dose in order to maintain the blind.

At study visits, sufficient study medication tablets will be dispensed to complete dosing until the next scheduled visit. When study medication is administered at the site, it will be administered under supervision of study personnel, and the amount of study medication dispensed must be recorded.

4.3.2.2 GDC-0853 and Placebo Compliance

The following measures will be taken to assess patient compliance with study drug: patients will *receive Patient Dosing Instructions and* be directed to bring any used and unused blister wallets (Cohort 1) or bottles (Cohort 2) to each visit after randomization. For Cohort 1, sites will be responsible for prepopulating the dates on the blister wallets for when patients are scheduled to take study drug. Under the corresponding dates listed, the patients will record the times (a.m. or p.m.) that they take each dose on the blister wallet (refer to Appendix 15 for Blister Wallet configuration). Patients will be instructed to return all blister wallets (used and unused) at each study visit for assessment of compliance and for medication disposal.

For Cohort 2, sites will be responsible for prepopulating the dates on the dosing label (that should be affixed to the bottle) for when patients are scheduled to take study drug. Under the corresponding dates listed, the patients will record the times (a.m. or p.m.) that they take each dose on the affixed label (refer to Appendix 16 for the bottle and label configuration). The number of tablets issued minus the number of tablets returned will be used to calculate the number of tablets taken and compliance.

Compliance will be documented on the source record. Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If compliance is $\leq$80%, the investigator or designee is to counsel the patient and ensure steps are taken to improve compliance.

4.3.2.3 Adalimumab and Placebo Dose and Administration

During this study, the SC comparator drug is intended for use under the guidance and supervision of a physician. The SC comparator drug will be administered by the unblinded HCP using the provided PFS (to be supplied by the Sponsor). Prior to use, the solution in the PFS must be carefully inspected for particulate matter and discoloration. If particulates and discolorations are noted, the product should not be used.

ADA is to be administered at a dose of 40 mg SC every other week (starting on Day 1).

In this study, the ADA and ADA placebo are not visually identical. To maintain the ADA blind, all SC comparator drug administration will be administered by the unblinded HCP in a manner that prevents the patient from observing which study treatments he or she is receiving. The unblinded HCP will not be involved in safety and efficacy assessments and will not be involved with or have access to patient data.

There are two recommended injection sites for the SC comparator drug: the front of the middle thighs and the lower part of the abdomen below the navel except for the 2-inch area directly around the navel.

Injections should never be given into areas where the skin is not intact or is tender, bruised, red, or hard. The injection sites will be inspected by the site personnel at each clinic visit. Local injection-site reactions should be reported as described in Section 5.1.2.2.

For all administrations, the SC comparator drug is to be administered by the unblinded HCP in a setting where medications and resuscitation facilities are available. Following each SC comparator drug administration, patients should be monitored for acute hypersensitivity reactions as indicated in the local label. Epinephrine and parenteral diphenhydramine must be readily available for immediate use if required to treat a

hypersensitivity reaction; site personnel must be able to detect and treat such reactions. Patients with severe hypersensitivity reactions (e.g., stridor, angioedema, life-threatening change in vital signs) must be withdrawn from study treatment and complete the 8-week safety follow-up phase in this study (See Appendix 7 for Sampson's Criteria).

All adverse events of systemic hypersensitivity reactions or anaphylactoid or anaphylaxis reactions must be reported as outlined in Section 5.1.2.1.

If the unblinded HCP cannot administer the SC comparator drug on the scheduled dosing day, the SC comparator drug is to be administered within a window of ±2 days from the scheduled dosing date. If the patient experiences a minor illness (e.g., minor infection), at the discretion of the investigator, the SC comparator drug may be delayed for a maximum period of 1 week. Following the delay, the SC comparator drug dosing is to be resumed in accordance with the original dosing schedule. Any potential deviation from this window is to be discussed with the Medical Monitor for the study.

Any overdose or incorrect administration of SC comparator drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.3 Required Background Treatment for Rheumatoid Arthritis

4.3.3.1 Methotrexate

In order to minimize confounding of study assessments, MTX treatment must have been initiated for at least the last 12 weeks immediately before randomization, of which the last 8 weeks before randomization must have been at a stable dose between 15 and 25 mg/week (oral or parenteral). Patients are required to be on a stable MTX dose of *7.5–*25 mg/week (oral or parenteral) for the duration of their participation in this study. *For patients entering the trial on MTX doses <15 mg/week, there must be clear documentation in the medical record that higher doses were not tolerated or that the dose of MTX is the highest acceptable dose based on local clinical practice guidelines.* Adjustments to this dose or a change in route of administration will not be allowed except in the case of MTX intolerance or toxicity; this must be discussed in advance with the Medical Monitor unless medically emergent. If dose reduction is a result of intolerance, such intolerance must be recorded as an adverse event and the dose modification recorded in the eCRF.

4.3.3.2 Folic Acid

To prevent adverse events associated with MTX, all patients are required to take folic acid or equivalent (e.g., 1 mg/day) at a stable dose of at least 5 mg/week total dose (or equivalent). This can be administered as either a single weekly dose or a QD dose per the discretion of the investigator.

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (i.e., GDC-0853 tablet, GDC-0853 placebo tablet, ADA, and ADA placebo) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.5 Post-Trial Access to GDC-0853

Patients may be eligible to screen for and enroll in the OLE Study GA30067, if considered appropriate according to the investigator.

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide GDC-0853 or any other study treatments or interventions to patients who have completed the study and are not qualified or elect not to enter OLE Study GA30067, in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 12 weeks prior to initiation of study drug through 8 weeks after the last dose of study drug or entrance into the OLE, whichever occurs first. A patient who is receiving an allowed concomitant medication for any reason must be on a locally approved medication and dose that is considered standard of care for the treated indication. The concomitant medication must be documented on the eCRF. Adverse events related to the administration of a concomitant medication or the performance of a procedure must also be documented on the appropriate adverse event page of the eCRF.

A description of the type of medication, the amount, duration, and reason for administration of drug or procedure must also be documented.

It is recommended that patients avoid changing other prescription or non-prescription drugs, vitamins, and dietary supplements within 7 days or 5 half-lives, whichever is longer, prior to the first dose of study medication and throughout the study.

All concomitant medication taken during the study must be recorded along with indication, daily dose, and start and stop dates of administration. Adverse events related to the administration of a concomitant medication or the performance of a procedure must also be documented on the appropriate adverse event page of the eCRF.

4.4.1 Permitted Therapy

4.4.1.1 Corticosteroids

During the study, patients may continue to receive background oral corticosteroids at a dose of ≤ 10 mg/day prednisone (or equivalent) that remains stable for the 6 weeks prior to randomization and throughout the study. If a dose > 10 mg/day prednisone (or equivalent) is needed to manage an adverse event (e.g., a flare of RA disease activity or other clinical condition requiring steroids), this must first be discussed with the Medical Monitor (unless urgent) and the event must be documented on the appropriate eCRF as an adverse event.

4.4.1.2 Non-Steroidal Anti-inflammatory Drugs

Patients may be treated with NSAIDs at up to the maximum recommended dose according to local labeling, including COX-2 inhibitors. *For patients who are receiving NSAID treatment on a regular basis (e.g., not as needed), the* dose should remain stable for at least the 2 weeks before randomization and throughout the study. Dose adjustments may be made for safety reasons and if absolutely required to treat disease flares. If possible, dose adjustments should be avoided within 24 hours before a visit where clinical efficacy assessments are scheduled to be performed and recorded.

Topical NSAIDs are allowed.

Patients should receive NSAIDs only on an as-needed (PRN) basis if absolutely required to treat RA disease flares, based on the investigator's judgment; however, PRN use should be avoided within 24 hours before a visit where clinical efficacy assessments are scheduled to be performed and recorded.

Aspirin can be taken to reduce CV risk, but the dose is not to exceed 162 mg/day.

In order to prevent NSAID-related GI complications in high-risk patients, concomitant agents (e.g., PPIs) should be used according to local guidelines (see Section 5.1.1.3).

4.4.1.3 Analgesics Other than NSAIDs

Analgesics (e.g., acetaminophen, opioids) up to their maximum recommended doses may be used for pain as required. However, patients should not take analgesics within 24 hours prior to a visit where clinical efficacy assessments are to be performed and

recorded. The total daily dose of acetaminophen may not exceed 2.6 g per day, and the total daily dose of opioid must not exceed the potency equivalent of 30 mg of orally administered morphine (see Appendix 4).

4.4.1.4 Dietary Supplements

For the purposes of this protocol, dietary supplements are defined as vitamins, minerals, purified food substances, and herbals with pharmaceutical properties.

Vitamins, minerals, and purified food substances are allowed in amounts not known to be associated with adverse effects (e.g., hypervitaminosis). Herbals with pharmaceutical properties are allowed only if there is acceptable evidence of no CYP3A inhibition or induction (refer to Appendix 5 for a list of prohibited concomitant medications, including herbal products). Otherwise, herbals with pharmaceutical properties must be discontinued for at least 4 weeks prior to the first dose of study medication, unless there are sufficient data available regarding the duration of an herbal medication's PK and PD effects to allow a shorter washout to be specified (e.g., 5 half-lives). Please direct any questions to the Medical Monitor.

4.4.1.5 Acid-Reducing Agents

Patients who use *short-acting* antacids (e.g., Maalox®, Pepto-Bismol®, Rolaids®) for symptomatic relief of heartburn should take GDC-0853 or matching placebo 2 hours before or 2 hours after *short-acting* antacid administration because gastric acid improves GDC-0853 absorption.

Patients may be treated with PPIs or H2RAs at up to the maximum recommended dose according to local labeling. The dose should remain stable for at least the 2 weeks before randomization and throughout the study.

At visits with scheduled PK assessments (see Appendix 1 and Appendix 2), any use of PPIs, H2RAs, and/or other *short-acting* antacids (e.g., Maalox®, Pepto-Bismol®, Rolaids®) should be recorded as concomitant medications, including the date and time of last administration *prior to the clinic visit*.

4.4.2 Prohibited Therapy

A listing of concomitant medications that is prohibited or should be used with caution due to potential drug-drug interactions is provided in Appendix 5.

IV, intra-articular, intramuscular corticosteroids, biologic response modifiers, tofacitinib or other JAK inhibitors, and DMARDs other than MTX are not allowed during this study and any use will require discontinuation of study treatment.

Use of the following therapies is prohibited *while the patient is receiving* study *treatment*, unless otherwise specified below:

- Investigational therapy other than study drug

- Abatacept
- Adalimumab (ADA) (prohibited for Cohort 2)
- Anakinra
- Anti-TNF inhibitors (e.g., infliximab, etanercept, golimumab, certolizumab, or biosimilar equivalents)
- Azathioprine
- Chlorambucil
- Chloroquine
- Cyclophosphamide
- Cyclosporine
- Gold
- Hydroxychloroquine
- Immunosorbent column
- IV, intramuscular, or intra-articular steroids
- Leflunomide
- Mycophenolate mofetil
- Mycophenolic acid sodium
- Oral anticoagulants, including but not limited to warfarin, dabigatran, rivaroxaban, apixaban
- Anti-platelet agents, such as clopidogrel (Note: NSAIDs and low-dose aspirin are acceptable.)
- Heparin, low molecular weight heparin (LMWH)
- Penicillamine
- Rituximab (or biosimilar equivalent)
- Sirolimus
- Sulfasalazine
- Tacrolimus
- Tocilizumab and other anti-IL6R or anti-IL6 agents
- Tofacitinib and other JAK inhibitors
- All biosimilar agents

4.4.2.1 Live or Attenuated Vaccinations

Immunization with a live or attenuated vaccine is prohibited within 6 weeks prior to baseline and for the duration of study participation, including the 8-week follow-up period after the administration of the last dose. See Section 5.1.1.2 for further details and precautions around vaccinations.

4.4.2.2 CYP3A Inhibition

In vitro studies suggest that GDC-0853 is a time-dependent inhibitor of CYP3A with inhibitory constant (K_i) values of approximately 10 μM (Study 13-0384). Although peak plasma concentrations are anticipated to be much lower than 10 μM (preliminary results from Study GA29347 indicate that a BID dose of 250 mg powder in capsule resulted in a mean steady-state C_{max} of approximately 849 nM), it is possible that GDC-0853 inhibition of CYP3A may alter the metabolism of CYP3A substrates, including estrogen derivatives such as ethinylestradiol, subsequently leading to an increase in plasma concentrations of these drugs (see the GDC-0853 Investigator's Brochure). Medications that are sensitive substrates of CYP3A or substrates of CYP3A with a narrow therapeutic window should be used with caution during this study (refer to Appendix 5 for a list of relevant medications).

Ethinylestradiol is metabolized by CYP3A; therefore, plasma concentrations may increase in the presence of GDC-0853. The use of hormone-replacement therapy containing ethinylestradiol or hormonal contraceptives containing ethinylestradiol, with the concomitant use of a barrier method, is permitted during this study (see Appendix 8); however, these agents should be used with caution and patients should be counseled regarding the potential risks and benefit of these medications per the local prescribing information. Any increase in ethinylestradiol plasma concentrations is anticipated to be modest at most because CYP-mediated oxidation appears to be a relatively minor component of orally administered ethinylestradiol (Zhang et al. 2007). Although contraceptive efficacy is not expected to be impacted, increased ethinylestradiol plasma concentrations may lead to an increase in common side effects, such as nausea, breast tenderness, and headaches, and to a theoretical increase in rare dose-related events such as thromboembolism (Inman et al. 1970).

In vitro data suggest that GDC-0853 is metabolized by CYP3A, and there is a moderate to high potential for a drug-drug interaction with any medication that strongly inhibits or induces this enzyme. Therefore, medications in the following categories (listed in detail in Appendix 5) should be avoided for 7 days or 5 half-lives, whichever is longer, prior to the first dose of study drug until the last dose of study drug. If use of one of these medications is necessary, the risks and benefits should be discussed with the Medical Monitor prior to concomitant administration with study drug.

- Moderate or strong CYP3A inhibitors
- Moderate or strong CYP3A inducers

Data also suggest that GDC-0853 inhibits CYP3A, and there is a moderate to high potential for a drug-drug interaction with any medication that is metabolized by CYP3A. Plasma concentrations of the medications in the following categories (listed in detail in Appendix 5) may increase; therefore, they should be used with caution:

- Sensitive CYP3A substrates
- CYP3A substrates with a narrow therapeutic index

The medications listed above and in Appendix 5 are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the Internet references provided below when determining whether a certain medication is metabolized by or strongly inhibits or induces CYP3A. The investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

4.4.3 Prohibited Food

Use of the following foods is prohibited during the study and for at least 7 days prior to initiation of study treatment: furanocoumarin derivatives as found in grapefruit, Seville orange, pomegranate, or star fruit juice or products.

4.4.4 Additional Restrictions

Patients should be fasting for ≥4–8 hours prior to first PK draw at Days 1, 28, and 84. On Day 28, patients should also remain fasting for the 2-hour *post-dose* PK timepoint (see Appendix 3).

4.5 STUDY ASSESSMENTS

Please see Appendix 1 and Appendix 2 for the schedules of assessments to be performed during this study.

The screening visit can occur up to 28 days prior to the first dose of study drug. The Day 1 (baseline and randomization) visit occurs on the first day of study drug administration.

Morning visits are strongly recommended for the clinic visits on Days 1, 28, and 84, particularly for the Day 28 visit at which post-dose PK blood samples will be collected. Patients should be fasting (≥4–8 hours) prior to these clinic visits. Study drug will be administered at these visits after pre-dose blood samples are collected when applicable. If a morning visit is logistically challenging, then based on the timing of their scheduled visit and scheduled dose, patients may be asked to take their morning dose of study drug as scheduled, then fast (≥4–8 hours) prior to their clinic visit later in the day. At the clinic visit, pre-dose blood samples will be collected and the evening dose of oral study drug will be administered if applicable (e.g., for the Day 28 visit when post-dose blood samples are collected).

Patients who complete the treatment period should complete the Day 84 treatment completion visit (see Appendix 1 and Appendix 2). After the Day 84 visit is completed, patients who are eligible and consent are to enroll into the OLE Study GA30067 directly; they will not enter the 8-week safety follow-up phase of this study. Patients not eligible

or who choose not to enroll in the OLE study should return for the 8-week safety follow-up visit in this study.

At applicable sites (U.S. only), if the patient is unable to return to the clinic on Day 28 for the PK blood draw at the 8–10 hour timepoint (see Appendix 3), then this sample may be collected by a home nurse (HN) professional at the patient's home or another suitable location to improve access and convenience for patients participating in the study. If a home visit is needed, the Sponsor will select and provide a health-care company that will be responsible for providing HN services (the HN vendor). The HN vendor is responsible for ensuring that all HN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that HN services are appropriate for a patient and the patient gives written informed consent to participate in HN visits, the HN network will communicate with the patient and the patient's site. HN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the HN professional. The schedule of assessments (see Appendix 3) specifies the assessment that may be performed by an HN professional.

4.5.1 Informed Consent Forms and Screening Log

Patients will be screened within a period of up to 28 days prior to administration of study medication to confirm that they meet the entrance criteria for the study. The study investigator or subinvestigator will discuss with each patient the nature of the study, its requirements, and its restrictions.

Written informed consent for participation in the study must be obtained before performing any study-related procedures.

Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.1.1 Retesting: Laboratory Inclusion/Exclusion

If a patient does not meet certain laboratory inclusion/exclusion criteria at screening, the investigator may repeat the test once within the screening period (see Section 4.1.2 for a list of laboratory tests and levels that can be retested). If the patient meets the laboratory eligibility criteria on the second assessment, he or she will be permitted to enter the study. It will not be considered a retesting if blood samples have to be redrawn because of sample handling problems, breakage, sample integrity, or laboratory error.

4.5.1.2 Rescreening

Rescreening refers to repeating the whole screening process. Rescreening is required if a patient has not met all of the eligibility criteria within 28 days after the original screening visit. (Note: patients who have failed two laboratory testing attempts as described in Section 4.5.1.1 cannot be rescreened*, except in cases where eligibility criteria such as hsCRP have been updated).* Patients are allowed to be rescreened only once. Each patient must be re-consented before rescreening occurs. It will not be considered a rescreening if blood samples have to be redrawn because of sample handling problems, breakage, sample integrity, or laboratory error.

4.5.2 Medical History and Demographic Data

At screening, the following information will be collected:

- Confirmation of rheumatoid arthritis (RA) diagnosis: The patient must have a diagnosis of RA based upon the 2010 ACR/EULAR Criteria for RA Diagnosis (see Appendix 9*)*.
- Medical history: The *diagnosis of RA should be recorded on the medical history eCRF (and captured as "rheumatoid arthritis"), including the date of diagnosis. The* history must include dates of *the most recent* vaccinations (specifically influenza, pneumococcus, and zoster*) on the eCRF.* All medical history relevant to RA will be collected. The medical history should include CHD risk factors per the National Cholesterol Education Program (NCEP) guidelines (*e.g., smoking, hypertension, low HDL, family history of premature CHD* - see Appendix 6).

  The medical history must also include clinically significant diseases, surgeries, procedures, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse.

  A detailed history of medication used for RA is required. This should include a complete history of all *conventional synthetic DMARDs and biological* DMARDs ever taken (those taken within 5 years before screening should include dose/duration, date of discontinuation, and reason for discontinuation).

  All medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, vitamins, and nutritional or dietary supplements) used by the patient within 12 weeks prior to initiation of study drug are to be recorded.
- Demographic data: This data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination should be performed at screening and should include an evaluation of the head, eyes, ears, nose, and throat and the CV, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF*, including assessment of rheumatoid nodules and other physical manifestations of RA (to be recorded in the eCRF).*

At subsequent visits or as clinically indicated, limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressures while the patient is in a seated position for at least 5 minutes.

4.5.5 Chest Radiograph

Chest radiographs of appropriate quality (to adhere to local standards for the exclusion of active TB) and with formal readings by a radiologist will be obtained at screening. If chest radiographs have been taken within 90 days prior to screening and documented results *(as read by a radiologist)* show no clinically significant abnormality as *determined* by *the investigator*, the chest radiograph does not need to be repeated.

4.5.6 Efficacy Assessments

Questionnaires will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment. In cases where this is logistically challenging because of a long visit duration (e.g., the visit on Day 28 with intensive PK assessments), potentially painful procedures will be performed no less than 15 minutes prior to initiation of the PRO measures.

Except for the Day 28 visit, the sequence of assessments where efficacy is assessed (see Appendix 1 and Appendix 2 for Schedules of Assessments) will be standardized as follows:

- PRO Measures:

  Patient's Assessment of Arthritis Pain

  Patient's Global Assessment of Arthritis

  HAQ-DI (see Appendix 11)

  SF-36v2 (see Appendix 12)

  FACIT-Fatigue (see Appendix 13)

- Laboratory samples for safety, efficacy, biomarkers, and pharmacokinetics must be drawn after patient self-assessments are completed (except where specified)
- Investigators

  Efficacy assessor: Joint counts and Physician's Global Assessment of Arthritis visual analog scale (VAS)

  Treating physician: Safety assessments (adverse events, vital signs, concomitant medications, review of laboratory data)

- **For Cohort 1 only:** SC comparator drug injection
- **For Cohorts 1 and 2:** Administration of oral study drug
- Post-dose vital signs, post-dose PK sample (at the indicated visits per Appendix 1 and Appendix 2), adverse events

To prevent potential unblinding due to observed efficacy or laboratory changes, a dual assessor approach (see Section 3.3.6.2) will be used to evaluate efficacy and safety as described below:

- The Efficacy Assessor (or designee) should be a rheumatologist or other skilled arthritis assessor. The Efficacy Assessor cannot be the Principal Investigator. The efficacy assessor will be responsible for completing the joint counts and the Physician's Global Assessment of Arthritis VAS. To ensure consistent joint evaluation throughout the trial, individual patients should be evaluated by the same efficacy assessor *whenever possible* for all study visits.
- The treating physician (or designee) should be a rheumatologist (or other medically qualified physician) and will have access to both safety and efficacy data. The treating physician may be the Principal Investigator. The treating physician will have access to source documents, laboratory results, and the eCRFs and will be responsible for completing safety assessments (e.g., adverse events, vital signs, concomitant medications, and review of laboratory data).

It is essential that assessments completed by the patient and the Efficacy Assessor are made before those by the treating physician so that the treating physician has the data needed for his or her assessment.

Table 3 describes the roles and access to data for specific site personnel.

Table 3 Roles and Data Access for Specific Site Personnel

	Medication Allocation	Efficacy Assessment(s)	Safety Data
Study Coordinator	**No access to SC medication assignment**	Access to patient efficacy data [a]	Access to patient safety data
Treating Physician and Principal Investigator	**No access to SC medication assignment**	Access to patient efficacy data [a]	Access to patient safety data
Efficacy Assessor	**No access to SC medication assignment**	Will perform joint counts and Physician's Global Assessment of Arthritis **but have no access to other patient efficacy data**	**No access to any patient safety data**
Pharmacist or pharmacy staff (if available at the site)	Access to SC medication assignment	**Cannot participate in patient care or data collection from patient**	**Cannot participate in patient care or data collection from patient**
Medication HCP	Access to SC medication assignment and administration of unblinded study medication	**Cannot participate in patient care or data collection from patient**	**Cannot participate in patient care or data collection from patient**

CRP = C-reactive protein; HCP = health-care professional; SC = subcutaneous.
[a] Efficacy data will not include CRP.

4.5.6.1 ACR Assessments

The ACR's definition for calculating improvement in RA (ACR20) is calculated as a 20% improvement in tender and swollen joint counts and a 20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant. Similarly, ACR50 and ACR70 are calculated with the respective percent improvements. The Sponsor, on the basis of the component parts, will calculate the ACR score.

The specific components of the ACR Assessments that will be used in this study are as follows:

- Tender/Painful Joint Count (68) (see Section 4.5.6.1.2)
- Swollen Joint Count (66) (see Section 4.5.6.1.3)
- Patient's Assessment of Arthritis Pain (see Section 4.5.7.1)
- Patient's Global Assessment of Arthritis (see Section 4.5.7.2)
- Physician's Global Assessment of Arthritis (see Section 4.5.7.3)

- CRP (see Section 4.5.8)
- HAQ-DI (see Section 4.5.7.4)

The following clinical assessments will be performed according to the Schedule of Assessments (see Appendix 1 and Appendix 2).

4.5.6.1.1 Swollen and Tender Joint Count

An assessment of 66 joints for swelling and 68 joints for tenderness will be made. Joints will be assessed and classified as swollen/not swollen and tender/not tender by pressure and joint manipulation on physical examination. Joint prosthesis, arthrodesis, or fused joints will not be taken into consideration for swelling or tenderness. A joint assessment training module may be used as a tool to facilitate consistency in performing the joint counts.

For clarification of how to assess joints which have undergone a procedure, please see below:

- **Surgery:** Joints that have been replaced or fused at any time prior to or at any time during the study should be documented as not done for the duration of the study. Any joints which have undergone synovectomy at any time prior to or at any time during the study (including chemical and radiation synovectomy) should be documented as not done for the duration of the study. *Surgery should not occur during the trial except in the case of a documented emergency.*
- **Arthrocentesis:** Any joint that *had* fluid drained (and no steroid injected) will not be assessed at the next scheduled visit and will be graded as not done. After this time, the joint may be assessed again. *If arthrocentesis is necessary at a visit, it should only be performed after the joint assessment at the visit has been completed.*

4.5.6.1.2 Tender/Painful Joint Count (68)

Sixty-eight (68) joints will be assessed by an efficacy assessor who is blinded to the patient's safety data and randomization, to determine the number of joints that are considered tender or painful. The response to pressure/motion on each joint will be assessed using the following scale: Present, Absent, or Not Done.

The 68 joints to be assessed are as follows:

- Upper body: Temporomandibular, sternoclavicular, acromioclavicular
- Upper extremity: Shoulder, elbow, wrist (includes radiocarpal, carpal, and carpometacarpal considered as one unit), metacarpophalangeals (*MCPs* I, II, III, IV, V), thumb interphalangeal, proximal interphalangeals (PIPs II, III, IV, V), distal interphalangeals (DIPs II, III, IV, V)
- Lower extremity: Hip, knee, ankle, tarsus (includes subtalar, transverse tarsal and tarsometatarsal considered as one unit), metatarsophalangeals (MTPs I, II, III, IV, V), great toe interphalangeal, *PIPs* (PIPs II, III, IV, V)

4.5.6.1.3 Swollen Joint Count (66)

The blinded efficacy assessor will also assess joints for swelling using the following scale: Present, Absent, or Not Done.

Sixty-six (66) joints will be assessed for swelling, the same as those listed above for tenderness/pain, except that the right and left hip joints are not included in the swollen joint count. Artificial joints will not be assessed.

4.5.6.2 DAS Assessments

The DAS assessment is a derived measurement with differential weighting given to each component (Prevoo et al. 1995). The DAS 28-4 (CRP), the DAS 28-3 (CRP), the DAS 28-4 (erythrocyte sedimentation rate [ESR]), and the DAS 28-3 (ESR) will be calculated. The calculations for the DAS 28-4 (CRP), DAS 28-4 (ESR), *DAS 28-3 (CRP), and DAS 28-3 (ESR)* are presented in Appendix 14.

The components of the DAS 28 arthritis assessment are as follows:

- Tender/Painful Joint Count (28) (see Section 4.5.6.2.1)
- Swollen Joint Count (28) (see Section 4.5.6.2.2)
- CRP or ESR (see Section 4.5.8)
- Patient's Global Assessment of Arthritis (included in the DAS 28-4 only) (see Section 4.5.7.2)

4.5.6.2.1 Tender/Painful Joint Count (28)

The 28 tender/painful joint count includes the following joints: shoulders, elbows, wrists, MCP joints, PIP joints, and knees. This count will be calculated by the Sponsor from the 68 tender/painful joint count assessed by the blinded efficacy assessor as described in Section 4.5.6.

4.5.6.2.2 Swollen Joint Count (28)

This measurement will include the same joints as described for the Tender/Painful Joint Count and will be calculated by the Sponsor from the 66 swollen joint count assessed by the blinded efficacy assessor as described in Section 4.5.6.

4.5.7 Patient-Reported and Clinician-Reported Outcomes

PRO (Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, HAQ-DI, SF-36v2, and FACIT-Fatigue Scale [see Appendix 11, Appendix 12, and Appendix 13, respectively]) and ClinRO (Physician's Global Assessment of Arthritis) data will be collected via questionnaires to more fully characterize the clinical profile of GDC-0853. The questionnaires, translated into the local language as required, will be completed in their entirety at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered before the patient receives any information on

disease status, prior to the performance of non-PRO and ClinRO assessments, and prior to the administration of study treatment, unless otherwise specified.

Patients will use an electronic device to capture PRO data, and clinicians will use a paper-based ClinRO for data collection. The electronic device and instructions for completing the questionnaires electronically will be provided by the investigator staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

4.5.7.1 Patient's Assessment of Arthritis Pain

Patients will assess the severity of their arthritis pain using a 100-mm VAS by placing a mark on the scale between 0 (no pain) and 100 (most severe pain) that corresponds to the magnitude of their RA pain, as follows:

My pain due to my rheumatoid arthritis at this time is:

No Pain_____**Most Severe Pain**

4.5.7.2 Patient's Global Assessment of Arthritis

Patients will answer the following question: "Considering all the ways your rheumatoid arthritis affects you, how are you feeling today?" The patient's response will be recorded using a 100-mm VAS, as follows:

Considering all the ways your rheumatoid arthritis affects you, how are you feeling today?

Very well_____**Very poorly**

4.5.7.3 Physician's Global Assessment of Arthritis

The investigator will assess how the patient's overall RA appears at the time of the visit. This is an evaluation based on the patient's disease signs, functional capacity (see Appendix 10), and physical examination and should be independent of the Patient's Global Assessment of Arthritis and Patient's Assessment of Arthritis Pain. The investigator's response will be recorded using a 100-mm VAS, as follows:

The patient's rheumatoid arthritis at this time is:

Very good_____**Very poor**

4.5.7.4 Health Assessment Questionnaire—Disability Index

The HAQ-DI will be used to assess patient's physical functioning. The HAQ-DI is a 20-item, validated questionnaire used to assess difficulty in performing activities of daily living (Fries 1983). The HAQ-DI refers to the previous week and assesses eight

domains of physical functioning: Dressing and Grooming (2 items), Hygiene (3 items), Arising (2 items), Reach (2 items), Eating (3 items), Grip (3 items), Walking (2 items), Common Daily Activities (3 items). The questions assess usual abilities ranging from 0 "without any difficulty" to 3 "unable to do." A lower HAQ-DI score indicates better QoL. See Appendix 11 for a review copy of the HAQ-DI questions.

This questionnaire should be completed by the patient prior to any procedures being performed at the visit, if possible.

4.5.7.5 Short-Form 36 Health Survey Questionnaire, Version 2

The SF-36v2 will be used to assess health-related QoL (Ware and Sherbourne 1992). The 36-item questionnaire consists of 8 domains: Physical Functioning (10 items), Role-Physical (4 items), Bodily Pain (2 items), General Health (5 items), Vitality (4 items), Social Functioning (2 items), Role-Emotional (3 items), Mental Health (5 items), and an additional item on reported health transition. The SF-36v2 has a recall specification of 4 weeks and items are assessed on Yes/No and 5- to 6-point Likert scales. A higher score indicates better health. The SF-36v2 health survey will be used in this study to assess health-related QoL and for economic modeling. See Appendix 12 for a sample version of the SF-36v2 questionnaire.

4.5.7.6 Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue)

The FACIT-Fatigue scale will be used to assess patients' fatigue (Cella et al. 2005). The 13-item questionnaire has been validated for use with RA patients and has a 7-day recall period. Items are assessed on a 5-point Likert scale, with responses ranging from 0 "not at all" to 4 "very much" and possible total scores range from 0 to 52. A higher score indicates less fatigue. See Appendix 13 for a list of questions in the FACIT-Fatigue.

4.5.8 Laboratory, Biomarker, and Other Biological Samples

Laboratory assessments will be performed as indicated on the Schedule of Assessments (see Appendix 1, Appendix 2, and Appendix 3). All laboratory tests will be sent to one or more central laboratories for analysis, with the exception of serum and urine pregnancy tests and ESR, which will be conducted locally.

On days of clinic visits at which study drug is administered, laboratory samples should generally be drawn before the administration of study drug (and SC comparator drug for Cohort 1) and after the administration of patient reported PRO assessments (e.g., pain questionnaires). An exception is on Day 28, where indicated PK samples should also be collected at timepoints following study treatment administration (see Appendix 3).

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Pregnancy test

  All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test. Should a positive result be recorded at any time, the procedures detailed in Section 5.4.3 should be followed.

- ESR: Should *be* performed as *a* point-of-care test in clinic *(with kits provided) in accordance with test guidelines*
- PPD (if QFT not available): Should be read locally

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): Sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, LDH, amylase, and lipase
- *hsCRP:* performed at the central laboratory will be blinded after the baseline visit.
- Urinalysis including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- Coagulation: INR, activated PTT, PT
- Viral serology

  Hepatitis B: HBsAg, total HBcAb, and hepatitis B surface antibody

  Hepatitis C antibody
- Fasting lipids: Cholesterol, LDL cholesterol, HDL cholesterol, triglycerides
- Quantitative immunoglobulins: Total Ig, IgA, IgG, IgM, IgE
- TBNKs: Once treatment with study medication begins, TBNK results will be blinded.
- RF
- Anti-CCP antibody (or ACPA)
- Quantiferon *as appropriate*

The following will be sent to the Sponsor or a designee for analysis:

- Serum, plasma, cells, and RNA from blood for exploratory non-inherited PD markers (lymphoid, myeloid, and other inflammatory markers as well as other markers potentially related to disease, drug, or clinical response; see Table 4).
- Plasma samples for PK analysis
- Whole-blood sample for DNA extraction for exploratory research on inherited biomarkers (including but not limited to genes that express proteins that may influence GDC-0853 pharmacokinetics)

Exploratory biomarker research may include but will not be limited to the biomarkers listed in Table 4. Given the complexity and exploratory nature of biomarker analyses, results from the analyses will not be shared with investigators or study participants, unless required by law.

Table 4 Proposed Non-Inherited Biomarkers for Exploratory Research

Sample Type	Proposed Non-Inherited Biomarkers
Whole blood for FACS (United States only)	Cells and markers, including but not limited to basophil CD63, monocytes, B cells, and B cell subsets
Plasma	Markers, including but not limited to CCL3 and CCL4
Serum	Markers, including but not limited to sICAM, CXCL13, CCL20
Blood for PBMC cell lysate (United States only)	Markers including but not limited to phosphorylated and total BTK protein
RNA extracted from blood	Markers including but not limited to myeloid RNA markers

FACS = fluorescence-activated cell sorting; PBMC = peripheral blood mononuclear cell.
Note: The timing for all samples is at baseline and at subsequent timepoints during and after treatment.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for the leftover samples to be stored for optional exploratory research (see Sections 4.5.10 and 4.5.11), biological samples will be destroyed when the final clinical study report has been completed, with the following exception:

- Blood, plasma, and serum samples collected for biomarker analyses will be destroyed no later than 15 years after the final clinical study report has been completed.

4.5.9 Electrocardiograms

Triplicate ECG recordings will be obtained at specified timepoints *within approximately 2-5 minutes of each other*, as outlined in the Schedule of Assessments (see Appendix 1 and Appendix 2).

Predose ECGs acquired on Day 1 and Day 28 should be as closely time-matched as feasible (morning *visits are strongly recommended*), and the patient should be fasting *(≥4–8 hours)*.

The post-dose ECGs on Day 28 should occur 2 hours (±30 minutes) after oral study medication is administered, and the patient should be fasting.

ECGs obtained at all other timepoints can be performed without specific restrictions (e.g., may be any time of day, before or after dosing, fasting or fed).

Three interpretable ECG recordings (e.g., without artifacts) must be obtained. The ECG intervals (e.g., PR, QRS, QT, QTcF, and RR) and heart rate from these three ECGs will be entered into the eCRF; in addition, these triplicate readings will be stored for future analysis, if needed.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECGs for each patient should be obtained from the same machine whenever possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes prior to beginning the first ECG recording. All ECGs *should* be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) *whenever possible.* Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, and conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at central laboratory. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular post-dose timepoint the mean QTcF is >500 ms and/or 60 ms longer than the baseline value, another triplicate ECG must be recorded, ideally within the next 5 minutes, and triplicate ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 4.6.2. The investigator should also evaluate the patient for potential concurrent risk factors

(e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.10 Optional Samples for Whole-Genome Sequencing

An optional blood sample will be collected for DNA extraction to enable whole-genome sequencing (WGS) and may be sent to one or more laboratories for analysis.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

Collection and submission of WGS samples is contingent upon the review and approval of the exploratory research and the WGS portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling, this section of the protocol (i.e., Section 4.5.10) will not be applicable at that site.

WGS data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health research databases for broad sharing with other researchers. Patients will not be identified by name or any other personally identifying information. Given the complexity and exploratory nature of these analyses, WGS data and analyses will not be shared with investigators or patients unless required by law.

WGS samples will be stored until they are no longer needed or until they are exhausted. The storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.11 Samples for Roche Clinical Repository

Genentech is a member of the Roche group and participates in the collection and/or submission of biological samples to the Roche Clinical Repository (RCR). Collection and submission of biological samples to the RCR is contingent upon the review and approval of the RCR portion of the Informed Consent Form by each site's IRB or EC and, if applicable, an appropriate regulatory body. If a site is not granted the necessary approval for RCR sampling, this section of the protocol will not be applicable at that site.

4.5.11.1 Overview of the Roche Clinical Repository

The RCR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will

facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Sample Collection

The following samples will be collected for research purposes, including but not limited to research on biomarkers related to GDC-0853 and RA:

- Leftover plasma samples
- Leftover serum samples
- Leftover blood RNA and/or protein samples
- Leftover DNA samples

For all samples, dates of consent should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.11.3 Confidentiality

Confidentiality for All RCR Specimens

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Additional Confidentiality for Specimens Used for Genetic Research

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens collected for genetic research. Upon receipt by the RCR, specimens for genetic research are "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

4.5.11.4 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.11.5 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Patient Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research

Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GA29350 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study GA29350.

4.5.11.6 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include but are not limited to the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, as per Principal Investigator's discretion

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

If a patient discontinues the study prior to the Day 84 treatment completion visit, an early termination visit should be conducted.

These patients are not eligible to enter the OLE Study GA30067 and should return for the 8-week safety follow-up visit in this study (see Appendix 1 and Appendix 2). *If the patient is unable to return for a follow-up visit, the trial site may contact the patient by telephone to determine their clinical status.*

Patients who discontinue the study during the safety follow-up period but prior to completion of the 8-week safety follow-up will be asked to return to the clinic within

30 days (±7 days) after the last dose of study drug or last scheduled visit for an early termination visit (see Appendix 1 and Appendix 2).

4.6.2 Study Treatment Discontinuation

Patients must *permanently* discontinue study treatment with both oral study drug and SC comparator drug *(however patients should be asked to remain in the blinded study through Week 12 even if their study treatment is discontinued in order to minimize missing data that limits study interpretability)* if they experience any of the following:

- *Pregnancy (the patient may still remain in the blinded study at the investigator's discretion)*
- Anaphylaxis or other severe hypersensitivity reaction
- Malignancy
- Any serious infection or infection requiring treatment with an IV antimicrobial agent
- *Grade >2 AST or ALT elevation: (AST or ALT >3 × ULN) in combination with total bilirubin >2 × ULN or clinical jaundice as defined by Hy's law*
- *Grade ≥3 AST or ALT elevation: (AST or ALT >5 × ULN)*
- Any Grade 3 or greater thrombocytopenia (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE v4.0*]): Platelets <50,000/mm³*
- Any Grade 4 neutropenia (NCI CTCAE v4.0*): ANC <500/mm³*

Patients who discontinue study treatment *and who do not remain in the blinded study will be* asked to return to the clinic for an early termination visit (see Section 4.6.1) followed by 8 weeks of safety follow-up.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include but are not limited to the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include but are not limited to the following:

- Excessively slow recruitment

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

To protect patient safety, an unblinded IMC will monitor safety throughout the study (see Section 3.1.2).

The safety plan for patients in this study is based on nonclinical and clinical experience with GDC-0853 in completed and ongoing studies as well as published literature on other BTK inhibitors. The important potential safety risks for GDC-0853 are outlined below. Please refer to the GDC-0853 Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for potential toxicities. Patients will undergo safety monitoring during the study, including monitoring of vital signs, physical examination, ECGs, and routine laboratory safety assessments (hematology, chemistry, and urinalysis) and assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing potential adverse events, including criteria for treatment interruption or discontinuation, and enhanced safety reporting are provided below.

5.1.1 Safety Plan for Potential Risks Associated with GDC-0853

5.1.1.1 Infections

GDC-0853 is a reversible inhibitor of BTK, and the degree to which GDC-0853 antagonism of BTK signaling may suppress immune activity is unknown. On the basis of patients with XLA, a primary immunodeficiency of B cells and immunoglobulin production, it is anticipated that inhibitors of BTK may raise the risk for certain bacterial infections (Lederman and Winkelstein 1985; Broides et al 2006), enteroviral infections (Misbah et al. 1992; Ziegner et al. 2002), intestinal infections with giardia and *Campylobacter* species (Winkelstein et al. 2006; van den Bruele et al. 2010), or other opportunistic infections, which are cleared primarily by B-cell adaptive immune responses. This risk is likely independent of sex for patients exogenously administered GDC-0853.

Effects on lymphocytes and immunoglobulins in rats and dogs were reversible and considered to be related to pharmacological activity involving BTK inhibition. See

Section 1.2.2 for related primary nonclinical toxicity findings and the GDC-0853 Investigator's Brochure for further details.

To date, no immune-challenge experiments (e.g., T-dependent antigen response test) have been conducted in animals. It is not known whether these effects on B cells and IgG concentrations in animals will translate to humans or whether such changes would have functional or deleterious impact on immune function.

Infections, including pneumonia and fatal influenza infections, have occurred in patients with B-cell malignancies treated with GDC-0853. In studies with healthy subjects with single doses and with dosing for 14 days, self-limited Grade 1 events of nasopharyngitis were reported but did not lead to any change in study drug dosing. One subject had asymptomatic bacteriuria, which resolved while study drug dosing continued.

Patients will be excluded from the study if they have a history of hospitalization due to an infection in the 8 weeks before screening, evidence of active or latent or inadequately treated infection with *Mycobacterium* TB, known active infection (current) or history of recurrent infection, or any known immunodeficiency including IgG $<$500 mg/dL.

Total Ig, IgG, IgM, IgA, and IgE concentrations will be measured regularly throughout the study. All patients in the study should be monitored for fever and potential infectious complications, including opportunistic infections and TB, and should be evaluated promptly. Physicians or an HCP should give patients advice to prevent potential transmission of and exposure to endemic infections according to local or Centers for Disease Control and Prevention guidelines. Patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of an infection. All infections occurring during the study, including but not limited to respiratory infections, cutaneous infections, urinary tract infections, systemic viral infections and episodes of suspicious or febrile diarrhea, should be evaluated using serology or PCR if available and cultured if feasible and any identified organisms noted in the eCRF. Any serious infection, infection requiring IV antimicrobials (i.e., any Grade 3 infection), or any opportunistic infection is considered an adverse event of special interest and should be reported to the Sponsor as outlined in Section 5.2.3.

Guidelines for management of study treatment in the event that infections are observed are provided in Table 5.

Please refer to the GDC-0853 Investigator's Brochure for further details.

5.1.1.2 Vaccinations

The effect of GDC-0853 upon the efficacy of vaccinations is unknown. It is recommended that appropriate vaccinations per ACR (Singh et al. 2016) or EULAR (van Assen et al. 2011) recommendations or local guidelines be up to date before study participation. Patients will be excluded from study participation and will not be dosed

with GDC-0853 if they have been vaccinated with live, attenuated vaccines (e.g., the intranasal live attenuated influenza vaccines, BCG, varicella) within 6 weeks before planned dosing. In addition, immunization with a live or attenuated vaccine is prohibited for the duration of study participation, including the 8-week safety follow-up period after the administration of the last dose.

In addition, current routine household contact with children or others who have been vaccinated with live vaccine components may pose a risk to the patient during study treatment with GDC-0853. Some of these vaccines include varicella ("chickenpox") vaccine, oral polio vaccine, and the inhaled flu vaccine. Following vaccination with live component vaccines, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted to the patient.

General guidelines for immunosuppressed patients suggest that exposure to vaccinated individuals should be avoided following vaccination with these vaccines for the stated time periods:

- Varicella or attenuated typhoid fever vaccination for 4 weeks following vaccination
- Oral polio vaccination for 6 weeks following vaccination
- Attenuated rotavirus vaccine for 10 days following vaccination
- FluMist® (inhaled flu vaccine) for 1 week following vaccination

Please refer to the GDC-0853 Investigator's Brochure for further details.

5.1.1.3 Bleeding

No decrease in platelets, changes in coagulation parameters, or bleeding events were observed in nonclinical studies with GDC-0853. Bleeding events, including non-serious NCI CTCAE Grade 1 bruising and serious Grade $\geq$3 GI bleeding, have been reported in patients with hematological malignancies treated with GDC-0853 in Study GO29089. The GI bleeding events have not been dose related, and the events occurred in patients who were taking concomitant NSAIDs and who had a history of gastroesophageal or peptic ulcer disease. The impact of BTK inhibition as a potential risk factor for bleeding is unknown. BTK is expressed in platelets and is involved in platelet function via GPVI/Collagen receptor signaling and GP1b receptor signaling. Platelets from patients with XLA, a genetic deficiency of BTK, demonstrate decreased activation in response to submaximal collagen stimulation but normal response to thrombin; clinically, there is no reported bleeding propensity of patients with XLA.

Bruising or bleeding events related to GDC-0853 have not been reported in healthy subjects.

It is unknown whether GDC-0853 will increase the risk of bleeding in patients, especially in those receiving antiplatelet or anticoagulant therapies. As a precautionary safety measure, patients will be excluded from study participation if they have a need for

systemic anticoagulation with warfarin or other oral or injectable anti-coagulants or anti-platelet agents (other than NSAIDs, aspirin, and other salicylates), any history of hospitalizations or transfusion for a GI bleed, any history of a hemorrhagic CVA, any history of spontaneous intracranial hemorrhage, traumatic intracranial hemorrhage within 10 years prior to the study, or a known bleeding diathesis. Patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of clinically significant bleeding.

Several risk factors, including patient age, co-morbidities, concurrent medications, prior medical history, and *Helicobacter pylori* infection, have been demonstrated in a variety of studies to increase the risk of NSAID-related GI injury (Lanza et al. 2009). It is unknown whether GDC-0853 will increase the risk of bleeding in patients receiving NSAIDs. Therefore, in order to prevent NSAID-related GI complications in high-risk patients, concomitant use of PPI should be considered (Bhatt et al. 2008) and used according to local or recognized guidelines (e.g., ACCF/ACG/AHA 2008 Expert Consensus Document).

Patients at high risk for NSAID-related GI toxicity include:

- Patients using both aspirin and an NSAID
- Patients with a history of ulcer disease
- Patients with one or more of the following:

  Age ≥60 years

  High-dose NSAID use

  Concurrent corticosteroid use

  Dyspepsia or gastroesophageal reflux disease symptoms

Any bleeding event of Grade ≥2 is considered an adverse event of special interest and should be reported to the Sponsor in an expedited manner as outlined in Section 5.2.3.

Guidelines for management of study treatment in the event that bleeding is observed in patients are provided in Table 5. Please refer to the GDC-0853 Investigator's Brochure for further details.

5.1.1.4 Cytopenias

Cytopenias have been observed in patients with hematological malignancies who received GDC-0853, including neutropenia, anemia, and thrombocytopenia; events have been monitorable and clinically manageable (see the GDC-0853 Investigator's Brochure for further details).

Patients should be monitored regularly with hematology laboratory evaluations as outlined in the schedule of assessments and should receive appropriate supportive care as clinically indicated. Patients should be advised to seek immediate medical attention if

they develop signs and symptoms suggestive of cytopenias (e.g., persistent fever, bruising, bleeding, pallor).

Guidelines for the management of study treatment in the event of cytopenias in patients are provided in Table 5. Please refer to the GDC 0853 Investigator's Brochure for further details.

5.1.1.5 Gastrointestinal Effects

Body weight gain and food consumption changes have been observed in animals, including nonsignificant increases in male Wistar-Han rats administered ≥2 mg/kg/day (4.3 μM•h) for 6 months, and significant reductions in rats administered 100 mg/kg/day (1438 μM•h) and dogs administered 25 mg/kg (180 μM•h) for 4 weeks. These effects on body weight gain and food consumption were reversible following discontinuation of GDC-0853 dosing.

Grade 1 diarrhea, nausea, and abdominal pain have been reported in patients with B-cell malignancies; however, the events have resolved and have not led to study drug discontinuation. Healthy subjects in the MAD Study GA29347 reported events of mild self-limited nausea.

Throughout the study, patients will be monitored for GI side effects.

Guidelines for management of study treatment in the event of GI side effects in patients are provided in Table 5. Please refer to the GDC-0853 Investigator's Brochure for further details.

5.1.1.6 Hepatotoxicity

Evidence of hepatobiliary injury was observed in animals administered relatively high doses of GDC-0853 in repeat-dose toxicity studies. Dose-dependent increases in ALT, AST, and/or bilirubin have been observed in rats administered ≥6 mg/kg/day (≥17 μM•h) and dogs administered ≥10 mg/kg/day (≥36 μM•h), with corresponding microscopic changes in the liver of dogs administered 25 mg/kg/day (180 μM•h). The hepatotoxicity findings in dogs were associated with moribundity in two high-dose animals. The NOAEL for these findings was considered to be 10 mg/kg (36 μM•h) in dogs, the most sensitive species, given the absence of GDC-0853–related hepatotoxicity at this dose when administered for 9 months. These findings were fully reversible and considered monitorable by changes in plasma transaminases and bilirubin that occurred at doses lower than those producing histopathology findings (see the GDC-0853 Investigator's Brochure for further details).

In clinical studies to date, including single dosing and multiple dosing for 14 days in healthy subjects and QD dosing for over 1 year in patients with hematological malignancies, there have been no adverse events of liver enzyme elevations or trends toward elevations in laboratory evaluations.

As a safety risk-mitigation measure, to be eligible for the study, AST and/or ALT levels should be no more than 1.5 × ULN, and total bilirubin levels should be normal at screening. Safety monitoring for potential hepatotoxicity includes baseline and routine evaluations of AST/ALT and total bilirubin levels throughout the study as outlined in the schedule of assessments. The local prescribing information for MTX should also be consulted.

Laboratory results of Grade ≥ 3 (> 5 × ULN) AST or ALT elevation are adverse events of special interest and should be reported to the Sponsor in an expedited manner as outlined in Section 5.2.3.

Guidelines for the management of study treatment in the event of hepatotoxicity in patients are provided in Table 5. Please refer to the GDC-0853 Investigator's Brochure for further details.

5.1.1.7 Cardiovascular Effects

GDC-0853 is considered to have a low potential to cause QT interval prolongation or to directly affect other CV parameters, at therapeutic exposures. A minimal increase in QTc (7 ms or 3%) interval was noted at 45 mg/kg in the single-dose CV safety pharmacology study in telemetry-instrumented dogs. Based on extrapolated/interpolated toxicokinetic data, the unbound C_{max} at 45 mg/kg (considered a NOAEL) and no-observed-effect level of 15 mg/kg were [redacted] There have been no GDC-0853–related changes in ECG parameters in the 4-week or 9-month dog toxicity studies.

Analysis of ECG data from the SAD and MAD studies in healthy subjects did not demonstrate any significant increase in either QRS interval or QTcF intervals. However, cardiac safety will be evaluated in all patients at baseline and throughout the study, with routine monitoring of vital signs (including heart rate and blood pressure), collection of triplicate ECGs with PK-matched timepoints, routine safety ECGs, and collection of adverse events (see Appendix 1 and Appendix 2).

Management of patients with sustained QTcF prolongation (QTcF that is > 500 ms and/or > 60 ms longer than the baseline value on at least two ECG measurements > 30 minutes apart) should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval. Consultation with a cardiologist or electrophysiologist is recommended, to help in the management of such patients. The Medical Monitor should be notified as soon as possible.

Guidelines for management of study treatment in the event in the event of CV effects in patients are provided in Table 5.

Please refer to the GDC-0853 Investigator's Brochure for further details.

5.1.1.8 Vascular Inflammation

Vascular inflammation (vasculitis) was observed in dogs administered GDC-0853 at ≥10 mg/kg/day (≥56 μM • h) in the 4-week toxicity study, and these changes were not completely reversed by the end of the 4-week recovery period. There was no consistent correlation with any clinical biomarkers. However, in the 9-month toxicity study in dogs, no GDC-0853–related vascular inflammation was observed up to the highest dose of 10 mg/kg/day (36 μM•h), which is considered to be the NOAEL (AUC) for the canine vascular inflammation findings. [redacted] The translatability of these findings to humans is unknown; however, Beagle dogs are susceptible to spontaneous development of polyarteritis syndrome (Snyder et al. 1995) and may be more sensitive to any drug-induced effects. Further, there are several examples of approved therapies for which there is no correlation between the finding of vasculitis in dogs or rats at clinically relevant exposures and adverse outcomes in patients (FDA 2011).

As a safety risk-mitigation measure, patients with a history of vasculitis, including RA associated vasculitis, will be excluded from the study, and CBC, creatinine, and urinalysis will be monitored in all patients during the study. Study drug should be discontinued in any patient who develops an adverse event of vasculitis, and the patient should enter safety follow up.

Guidelines for management of study treatment in the event of vasculitis in patients are provided in Table 5.

Please refer to the GDC-0853 Investigator's Brochure for further details.

5.1.1.9 Malignancy

The impact of BTK inhibition on the development of malignancies is not known; however, malignancies have been identified as a potential concern for immunomodulatory agents. Malignancies have been reported in patients with XLA, including lymphoreticular malignancies, gastric and colorectal adenocarcinoma, and squamous cell carcinoma of the lung.

Patients with a history of cancer, including hematologic malignancy and solid tumors, within 10 years before screening will be excluded from the study. Basal or squamous cell carcinoma of the skin that has been excised and is considered cured and in situ carcinoma of the cervix treated with apparent success by curative therapy more than 1 year prior to screening are not exclusionary.

All malignancies are adverse events of special interest and should be reported to the Sponsor in an expedited manner as outlined in Section 5.2.3.

Guidelines for management of study treatment in the event of malignancies in patients are provided in Table 5. Please refer to the GDC-0853 Investigator's Brochure for further details.

5.1.2 Potential Risks with Adalimumab

Investigators should be aware of the risks associated with ADA and their management, including serious infections, injection-site reactions, liver enzyme elevations, headache, and rash (for full details, see the local prescribing information).

5.1.2.1 Hypersensitivity Reactions

Patients with a history of anaphylactic or other serious allergic reaction to ADA are excluded from study participation.

Investigators and HCPs administering study injections should be trained to recognize and manage the signs and symptoms of a potential anaphylactic/anaphylactoid or hypersensitivity reaction and to accurately and appropriately report these events.

HCPs should also instruct patients how to recognize the signs and symptoms of any anaphylactic/anaphylactoid or hypersensitivity reaction and to contact a health-care provider and/or seek emergency care in case of any such symptoms. See Appendix 7 for clinical criteria for diagnosing anaphylaxis (Sampson's criteria).

Guidelines for management of study treatment in the event of hypersensitivity reactions in patients are provided in Table 5.

5.1.2.2 Local Injection-Site Reactions

A local injection-site reaction is any local cutaneous reaction occurring at the site of injection following SC comparator drug administration. In the clinic setting, patients should be monitored for local injection-site reactions in the period immediately following injections and adverse events reported as outlined in Section 5.3.1.

5.1.3 Management of Study Treatment in Patients Who Experience Specific Adverse Events

Guidelines for management of study treatment in patients who experience specific adverse events are provided in Table 5.

If there are any other situations where it seems appropriate to hold and/or discontinue study treatment, please discuss with the Medical Monitor before reinitiating treatment.

Table 5 Guidelines for Management of Study Treatment in Patients Who Experience Specific Adverse Events

Event	Action to Be Taken [a]
Infection [b]	
Serious infection or any infection requiring treatment with an IV antimicrobial agent	Discontinue study treatment and report event as an adverse event of special interest.
Self-limited infections that require treatment	Withhold study treatment during antimicrobial therapy. Study treatment may resume after consultation with the Medical Monitor.
Bleeding	Any Grade ≥ 2 bleeding event is considered an adverse event of special interest and should be reported to the Sponsor in an expedited manner. For serious (Grade ≥ 3) bleeding events, withhold study treatment and consult with the Medical Monitor.
Neutropenia [c]	
Grade 2: ANC $>1000-1500/mm^3$	Maintain study treatment dosing.
Grade 3: ANC $500-1000/mm^3$	For the first event, hold study treatment and recheck CBC in 7 days. If neutrophil count has recovered to Grade 1 ($>1500/mm^3$) or has returned to the normal range, study treatment can be resumed. If Grade 3 neutropenia persists or for recurrent Grade 3 neutropenia, discontinue study treatment.
Grade 4 ANC <500 /mm^3	Discontinue study treatment.
Thrombocytopenia [d]	
Grade 1: PLT $>75,000/mm^3$	In the absence of bleeding event(s), maintain study treatment dosing.
Grade 2: PLT $50,000-75,000/mm^3$	For the first event, hold study treatment and recheck CBC in 7 days. If platelet count has recovered to Grade 1 or has returned to the normal range, study treatment can be resumed. For recurrent Grade 2 thrombocytopenia and in the absence of bleeding events, discuss with the Medical Monitor (or discontinue study treatment).
Grade ≥ 3: PLT $<50,000/mm^3$	Discontinue study treatment.
Gastrointestinal effects	
Nausea, vomiting, and/or diarrhea	Manage according to site institutional guidelines. Consider administration of GDC-0853 with food as a possible mitigation strategy.

Table 5 Guidelines for Management of Study Treatment in Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken [a]
Malignancy	
Any malignancy	Discontinue study treatment with the exception of non-serious local and resectable basal or squamous cell carcinoma of the skin. Report event as an adverse event of special interest to the Sponsor in an expedited manner.
Hepatotoxicity	
AST or ALT $>3.0-5.0\times$ ULN	Withhold study treatment and consult with the Medical Monitor
AST or ALT $>3\times$ ULN in combination with a total bilirubin $>2\times$ ULN, of which at least 35% is direct bilirubin, or clinical jaundice	Discontinue study treatment. Report event(s) as adverse event of special interest to the Sponsor in an expedited manner.
AST or ALT $>5\times$ ULN	Discontinue study treatment. Any elevation of an AST or ALT $>5\times$ ULN should be reported as an adverse event of special interest to the Sponsor in an expedited manner.
Cardiovascular effects	
Sustained (at least two ECG measurements >30 minutes apart) QTcF that is >500 ms and/or >60 ms longer than the baseline value	Unless there is a clear alternative cause other than study drug, discontinue study treatment. [e]
Sustained absolute QTcF that is >515 ms	Unless there is a clear alternative cause other than study drug, discontinue study treatment. [e]
An episode of torsades de pointes or a new ECG finding of clinical concern	Unless there is a clear alternative cause other than study drug, discontinue study treatment. [e]
Vascular inflammation	
Vasculitis	Consult with the Medical Monitor.
Hypersensitivity reactions	
Fever, chills, pruritis, urticaria, angioedema, and skin rash Cardiopulmonary reactions, including chest pain, dyspnea, hypotension, or hypertension Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)	The patient should be treated according to the standard of care for management of anaphylaxis/anaphylactoid or a hypersensitivity reaction. The patient must discontinue study treatment.

Table 5 Guidelines for Management of Study Treatment in Patients Who Experience Specific Adverse Events (cont.)

CBC = complete blood count; IV = intravenous; MTX = methotrexate; PLT = platelet count; QTcF = QT interval corrected using Fridericia's formula ; SC = subcutaneous; ULN = upper limit of normal.

Note: "Study treatment" includes study drug (GDC-0853 or placebo) and SC comparator drug (ADA or placebo, applicable only to Cohort 1).

[a] Any patient who *must* discontinue study treatment *for safety reasons (where specified above)* should be asked to stay in the blinded study through Week 12 *if deemed appropriate by the investigator,* however they *must not receive study treatment.*

[b] Appropriate laboratory investigations, including but not limited to cultures, should be performed to establish the etiology of any serious infection.

[c] Patients withdrawn from the study because of a reduced neutrophil count must be followed closely for signs of infection, with treatment as deemed appropriate by the investigator, including discontinuation of MTX if indicated, and must have a repeat WBC count with differential performed weekly until the ANC is above 1000 cells/mm³ (1.0×10^9/L). If the ANC does not return to above 1000 cells/mm³ (1.0×10^9/L) within 2 months (or sooner if deemed necessary by the investigator), a hematology referral is recommended.

[d] Patients withdrawn from the study because of a reduced platelet count must have a repeat platelet count checked weekly until the count is above 100,000 cells/mm³ (100×10^9/L). Additional management and treatment should be as deemed appropriate by the investigator, including discontinuation of MTX if indicated. If the platelets do not return to above 100,000 cells/mm³ (100×10^9/L) within 2 months (or sooner if deemed necessary by the investigator), a hematology referral is recommended.

[e] In rare circumstances, it may be acceptable to resume study drug, provided that any ECG abnormalities have resolved and that the patient is appropriately monitored. Clinical judgment should be applied.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.11
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Adverse events of special interest for GDC-0853

  Any serious infection, any infections requiring IV antimicrobials (i.e., Grade 3 infection) and any opportunistic infections

  Any bleeding event Grade 2 or above

  All malignancies

  A laboratory result of Grade $\geq$3 AST or ALT elevation

- Adverse events of special interest for general drug development

  Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)

  Suspected transmission of an infectious agent by the study drug, as defined below

    Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent

may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6. The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsy sample collection, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 8 weeks after the last dose of study drug the patients receives, either in this study or the OLE Study GA30067. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding an event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 7):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 7 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection-Site Reaction

Local cutaneous adverse events that occur at or around the injection site during or within 24 hours following study drug injection should be captured as individual signs (e.g., erythema, induration/swelling at injection site) and symptoms (e.g., pain, pruritus at injection site) on the Adverse Event eCRF rather than a diagnosis of allergic reaction or injection-site reaction.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should be recorded only once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should be recorded only once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should be recorded only once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN, of which at least 35% is direct bilirubin) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered an indicator of severe liver injury (as defined by Hy's law). Therefore, in addition to the protocol defined adverse event of special interest of Grade ≥ 3 AST or ALT elevations, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN (of which at least 35% is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or, if a diagnosis cannot be established, the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.3) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of condition being studied.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

If the death is attributed to progression of RA, "Rheumatoid arthritis progression" should be recorded on the Adverse Event eCRF.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept

that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Rheumatoid Arthritis

Medical occurrences or symptoms of deterioration that are anticipated as part of condition being studied should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of RA on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated rheumatoid arthritis").

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization *under the following circumstances should* not be *reported as an* adverse *event or a serious adverse event*:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization *under the following circumstances* is not considered to be *a* serious adverse *event,* but should be reported as *an* adverse *event* instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No safety data related to overdosing of GDC-0853 are available.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

[redacted] Medical Monitor contact information:

Medical Monitors: [redacted] Medical Monitor (Primary)
[redacted] M.D.
Office: [redacted]
Mobile: [redacted]
Email: [redacted]

Alternate Medical *Monitors* contact information for all sites:

Medical Monitor:	[redacted] M.D.
Telephone No.:	*Office:* [redacted]
	Mobile: [redacted]
	Email: [redacted]
Emergency Telephone Nos.	[redacted]
Sponsor Medical Monitor:	[redacted], *M.D.*
Telephone *No.:*	*Office* [redacted]
	Email: [redacted]

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by scanning and emailing the form to [redacted] (U.S. and ex-U.S. sites) or by faxing using the contact information provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 8 weeks after the last dose of study drug the patients receives, either in this study or the OLE Study GA30067. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by scanning and emailing the form to [redacted] (U.S. and ex-U.S. sites) or by faxing using the contact information provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 8 weeks after the last dose of study drug, either in this study or the OLE Study GA30067. A paper Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form to [redacted] (U.S. and ex-U.S. sites) or by faxing using the contact information provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 120 days (4 months) after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see

Section 5.4.2). Any abortion should be reported in the same fashion (because the Sponsor considers abortions to be medically significant).

5.4.4 Reporting Requirements for Medical Device Complaints

In this study, ADA PFS is considered a medical device. The investigator must report all medical device complaints to the Sponsor. The investigator should document as much information as possible on the PD 103 IMP Deviation Form, including the product batch number and expiration date, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; refer to the pharmacy manual for further details). The PD 103 IMP Deviation Form, together with pictures of the defective PFS, should be sent to kaiseraugst.global_impcomplaint_management@roche.com. Where possible, the investigator will retrieve the PFS unit(s) involved in the complaint and attempt to return to the Sponsor for further assessment, if necessary.

If the medical device results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

If the medical device complaint results in an adverse event to an individual rather than the study patient, the device complaint must be reported on the PD 103 IMP Deviation Form and the adverse event must be reported as a spontaneous adverse event to Roche Safety Risk Management via telephone.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 8 weeks after the last dose of study drug the patients receives, either in this study or the OLE Study GA30067), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- GDC-0853 Investigator's Brochure
- Local prescribing information for ADA

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

6.1.1 Cohort 1: MTX-IR (Arms A–E)

The purpose of this cohort is estimation and hypothesis generation regarding the effects of GDC-0853 on ACR50 response relative to placebo and relative to ADA as the active comparator. Point and interval estimates of the ACR50 response rates will be obtained. A target of approximately 480 patients will be enrolled and randomized. The first 200 patients will be randomly allocated in a 1:1:1:1:1 ratio to the five treatment arms: 50 mg QD GDC-0853 (Arm A), 150 mg QD GDC-0853 (Arm B), 200 mg BID GDC-0853 (Arm C), placebo (Arm D), or ADA (Arm E). The remaining 280 patients will be randomly allocated in a 1:1:1:1 ratio to Arms B–E. The study is designed to estimate differences in ACR50 response rates between the active comparator Arm E and GDC-0853–treated

Arms B or C at Day 84. A sample size of 110 patients per arm has 80% power to detect a difference of 15% between Arm E and Arm B or C, for an ACR50 response rate of up to 50% in the active comparator arm (Arm E), with a two-sided type-one error rate of 0.2 with the χ^2 test with continuity correction. No adjustment for multiple comparisons is made.

The overall sample-size may be increased by up to 20% depending on the outcome of the IA (see Section 6.8).

6.1.2 Cohort 2: TNF-IR (Arms F–G)

The purpose of this cohort is estimation and hypothesis generation regarding the effects of GDC-0853 on ACR50 response relative to placebo. A target of approximately *120* patients will be enrolled and randomized with a 1:1 ratio to the two treatment groups: 200 mg BID GDC-0853 (Arm F) or placebo (Arm G). The study is designed to detect a significant difference in ACR50 response rates between the active and placebo arms at Day 84. A sample size of *approximately 60* patients per arm provides 80% power to detect a difference of 20% for an ACR50 response rate of up to *20*% in the placebo arm (Arm G) with a two-sided type one error rate of 0.2 with use of Fisher's exact test.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Treatment group comparability will be analyzed. Demographic and baseline characteristics such as age, sex, weight, and disease activity will be summarized by treatment group with use of means or medians for continuous variables and proportions for categorical variables. Medical history, including diagnoses and treatment, will be tabulated.

6.4 EFFICACY ANALYSES

Efficacy analyses will be conducted for the intent-to-treat (ITT) population, defined as all randomized patients. Sensitivity analyses of additional study populations (e.g., completers and per protocol [excluding major protocol violators]) will also be performed. Exploratory subgroup analyses (e.g., based on baseline biomarker characteristics) may also be conducted.

6.4.1 Primary Efficacy Endpoint

The primary efficacy analysis will compare the proportion of patients achieving an ACR50 response between each of three dose-levels (Arms A to C) of

GDC-0853–treated patients and placebo-treated patients (Arm D) at Day 84 for patients who had an inadequate response to MTX and are naive to TNF therapy. Non-responder imputation will be implemented in the event of missing data. The Cochran-Mantel-Haenszel test will be used to assess the difference in the proportion of responders, adjusted for the randomization stratification factor, geographic region.

6.4.2 Secondary Efficacy Endpoints

The key secondary efficacy analysis for the MTX-IR population will compare the proportion of patients achieving an ACR50 response between each of two higher dose-levels (Arm B and Arm C) of GDC-0853–treated patients and ADA-treated patients (Arm E). *The Cochran-Mantel Haenszel test will be used to assess the difference in the proportion of responders, adjusted for the randomization stratification factor, geographic region.* The key secondary efficacy analysis for the TNF-IR cohort will compare the proportion of patients achieving an ACR50 response between GDC-0853–treated patients (Arm F) with the placebo-treated arm (Arm G). The Cochran-Mantel Haenszel test will be used to assess the difference in the proportion of responders, adjusted for the randomization stratification *factors* geographic region *and prior exposure to a non-TNF inhibitor biologic.* The details for other secondary efficacy analyses will be specified in the DAP.

6.5 SAFETY ANALYSES

The safety analyses will include all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received. Safety will be analyzed on the basis of reported/documented adverse events, laboratory results, and vital signs, including adverse events of special interest.

6.6 PHARMACOKINETIC ANALYSES

The PK analyses will include patients with sufficient data to enable estimation of key parameters (e.g., AUC, predose concentrations [C_{trough}], and half-life), with patients grouped according to treatment received.

Systemic GDC-0853 exposure will be evaluated using a population PK approach, and estimates of PK parameters will be generated. The extent of interpatient variability will be evaluated, and potential sources of variability will be assessed. Relationships between exposure and PD, efficacy, and safety endpoints will be explored.

Additional PK analyses will be conducted during and/or at the end of the study as appropriate.

6.7 BIOMARKER ANALYSES

PD biomarker analyses will include patients with at least one predose and post-dose biomarker assessment. Descriptive statistics in PD biomarkers will be listed by dose, cohort, and response status. Data will be analyzed by absolute levels of the biomarker

as well as normalized to baseline levels. Additional PD analyses will be conducted as appropriate. The ability of biomarkers (e.g. but not limited to CXCL13 and sICAM1) measured at baseline to identify a subset of patients with enhanced clinical benefit to GDC-0853 will also be evaluated.

6.8 INTERIM ANALYSIS

6.8.1 Planned Interim Analysis

6.8.1.1 Cohort 1: MTX-IR (Arms A–E)

An IA will be performed after *approximately* 150 patients have completed their 12-week evaluation (~30 patients/arm). The purpose of this IA is to assess the efficacy of the GDC-0853–treated arms compared with the placebo-treated arm. Summaries of safety and efficacy data by treatment group will be prepared *and reviewed* by members of the IMC*; the IMC consists of Sponsor's members who do not have direct contact with investigational staff and monitors.* No unblinded individual patient data will be shared with the *members of the* Sponsor's study team *who have direct contact with investigational staff and monitors* except for the *case in which the IMC decides to unblind the study team to enable decision-making* and *potential interactions with regulatory bodies*. Recruitment of patients will continue during the conduct of the IA. Further details of the IA, including the use of the IMC and decision criteria, will be specified in the DAP. No further IAs are planned in Cohort 1; however, given the hypothesis-generating nature of this study, the Sponsor may choose to conduct one subsequent efficacy IA.

If the results of the IA yield encouraging evidence of activity in one or more BTK containing treatment groups relative to placebo and is accompanied by an unexpected placebo response rate (for example), the Sponsor may opt to increase enrollment by up to 20% to obtain greater precision for estimation of treatment differences.

6.8.1.2 Cohort 2: TNF-IR (Arms F–G)

No IA is planned in Cohort 2; however, given the hypothesis-generating nature of this study, the Sponsor may choose to conduct one *optional efficacy IA in order to guide internal decision making around issues such as the adequacy of dose ranging, the adequacy of sample sizes for safety and/or efficacy analyses, or to inform further development decisions. The IA plan will be detailed in an updated Data Analysis Plan prior to conducting the IA.* The decision to conduct this optional IA and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the IA. *This optional* IA will be performed and interpreted by an IMC*; the IMC consists of Sponsor's members who do not have* direct contact with investigational staff and monitors. *IMC may decide to unblind the* study team to enable decision-making *and potential interactions with regulatory bodies.*

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and other additional non-eCRF data will be sent directly to the Sponsor, with use of the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected through the use of an electronic device provided by a vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The electronic data are available for view access only via secure access to a Web server. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patients will use an electronic device to capture PRO data. The data will be transmitted wirelessly automatically after entry to a centralized database maintained by the electronic device vendor.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, PROs, ClinROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Home Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports

or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient last safety follow-up visit in this protocol or the last patient in this protocol enrolled into the OLE Study GA30067).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The study will be conducted globally and include approximately 600 patients. The contract research organization [redacted] will be responsible for submission to IRB/ECs for approval of the study protocol, patient recruitment, study conduct, data collection, and reporting.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to HCPs and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

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Appendix 1
Schedule of Assessments (Cohort 1: MTX-IR)

Week	Screening Period	Treatment Period								SFU		
		0	1	2	4	6	8	10	12	8 weeks after last dose		
Day (± days)	−28 to −1	Day 1 [a]	Day 7 (±1)	Day 14 (±1)	Day 28 [a] (±2)	Day 42 (±2)	Day 56 (±2)	Day 70 (±2)	Day 84 [a,b] (±2)	(±4)	ET	UV
Informed consent	x											
Demographic data	x											
General medical history and baseline conditions [c]	x	x										
Inclusion/exclusion criteria	x	x										
Concomitant medications [d]	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x
Vital signs [e]	x	x	x	x	x	x	x	x	x	x	x	x [f]
Height	x											
Weight	x	x			x		x		x	x	x	
Complete physical examination [g]	x								x	x	x	
Limited physical examination [h]		x	x	x	x	x	x	x				x [f]
Triplicate ECG [i]	x [j]	x [k]	x [j]		x [k]		x [j]		x [j]	x [j]	x [j]	x [f, j]
HBsAg, HBsAb, Hep B cAb, HCV Ab	x											
QFT or PPD [l]	x											
Chest radiograph [m]	x											
GDC-0853/placebo administration in clinic [n]		x	x	x	x	x	x	x				
Drug dispensing		x		x	x	x	x	x				
ADA/placebo SC administration [o]		x		x	x	x	x	x				
Hematology [p]	x	x	x		x		x		x	x	x	x [f]

Appendix 1
Schedule of Assessments (Cohort 1: MTX-IR) (cont.)

Week	Screening Period	Treatment Period								SFU		
		0	1	2	4	6	8	10	12	8 weeks after last dose (±4)	ET	UV
Day (± days)	−28 to −1	Day 1 [a]	Day 7 (±1)	Day 14 (±1)	Day 28 [a] (±2)	Day 42 (±2)	Day 56 (±2)	Day 70 (±2)	Day 84 [a,b] (±2)			
Chemistry [q]	x	x	x		x		x		x	x	x	x [f]
Coagulation studies PT/PTT	x											x [f]
Pregnancy test [r]	x	x			x		x		x	x	x	x [f]
Urinalysis [s]	x	x			x		x		x	x	x	x [f]
Quantitative Ig [t]	x	x			x		x		x	x	x	x [f]
Lipid panel		x			x				x	x	x	
Rheumatoid factor and anti-CCP/ACPA	x								x	x	x	
TBNK	x	x	x	x	x		x		x	x	x	x [f]
ACR/DAS:												
CRP	x	x	x	x	x		x		x	x	x	x [f]
ESR (on site or at local laboratory)	x	x	x	x	x		x		x	x	x	x [f]
Tender/painful joint count (68), swollen joint count (66)	x	x	x	x	x		x		x	x	x	x [f]
Patient's Assessment of Arthritis Pain [u]		x	x	x	x		x		x	x	x	x [f]
Patient Global Assessment of Arthritis [u]		x	x	x	x		x		x	x	x	x [f]
Physician's Global Assessment of Arthritis [v]		x	x	x	x		x		x	x	x	x [f]
HAQ-DI [u]		x	x	x	x		x		x	x	x	x [f]
SF-36v2 [u]		x					x		x	x	x	
FACIT-Fatigue [u]		x		x	x		x		x	x	x	
PK assessment [w]		x	x		x		x		x		x	x [f]
PBMC protein lysate [x] (U.S. sites only)	x	x			x				x	x	x	

Appendix 1
Schedule of Assessments (Cohort 1: MTX-IR) (cont.)

Week	Screening Period	Treatment Period								SFU		
		0	1	2	4	6	8	10	12	8 weeks after last dose		
Day (± days)	−28 to −1	Day 1 [a]	Day 7 (±1)	Day 14 (±1)	Day 28 [a] (±2)	Day 42 (±2)	Day 56 (±2)	Day 70 (±2)	Day 84 [a,b] (±2)	(±4)	ET	UV
Blood for FACS (U.S. sites only) [y]	x	x			x				x	x	x	x [f]
PD blood sample for FACS/basophils (U.S. sites only) [z]	x	x	x		x				x		x	x [f]
Serum biomarkers [aa]	x	x	x		x				x	x	x	x [f]
Plasma biomarkers [bb]	x	x	x		x				x	x	x	x [f]
PAXgene RNA blood biomarkers [cc]	x	x	x		x				x	x	x	x
Whole blood PG sample		x										
Whole blood sample for genotyping (optional) [dd]		x										

ACPA = anti-citrullinated protein/peptide antibody; ACR = American College of Rheumatology; ADA = adalimumab; BID = twice daily; CCP = cyclic citrullinated protein; CRP = C-reactive protein; DAS = Disease Activity Score; eCRF = electronic Case Report Form; ESR = erythrocyte sedimentation rate; ET = early termination; FACIT = Functional Assessment of Chronic Illness Therapy; FACS = fluorescence-activated cell sorting; HAQ-DI = Health Assessment Questionnaire–Disability Index; HBsAg = hepatitis B core antibody; HBsAb = hepatitis B surface antigen; HCP = health-care professional; HCV = hepatitis C virus; IRB/EC = Institutional Review Board/Ethics Committee; MTX-IR = patients who had an inadequate response to methotrexate; OLE = open-label extension; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PG = pharmacogenomic; PK = pharmacokinetic; PPD = purified protein derivate; PPI = proton pump inhibitor; PRO = patient reported outcome; QFT = QuantiFERON-TB Gold; RA = rheumatoid arthritis; SC = subcutaneous; SF-36 = Short-Form 36 Health Survey; SFU = safety follow-up; SST = serum separator tube; TB = tuberculosis; TBNK = T, B, and natural killer cells; UV = unscheduled visit; WGS = whole-genome sequencing.

[a] *A morning* clinic visit *(fasting)* is *strongly recommended* for visits on Days 1, 28, and 84*, and particularly on Day 28 (*for *intensive PK sampling). When* morning visits are *strongly* recommended, the patient should be fasting *(≥4–*8 hours) prior to the first PK blood draw and fasting lipid panel.

[b] Day 84 is the last day of the study treatment period (however, no blinded study drug will be given on Day 84*; the last dose of blinded study drug is the PM dose of Day 83).* If eligible, patients may enroll into the OLE Study GA30067 to receive their first open-label dose of GDC-0853 *on Day 1 of Study GA30067 (after a trough PK level is drawn)* or they will proceed to the SFU period and return for the SFU visit on Day 140 (8 weeks after last dose of study drug).

[c] Medical history will include *the diagnosis of rheumatoid arthritis and date of RA diagnosis,* all history relevant to RA, including a detailed history of RA medications taken within 5 years before screening, with dose(s)/duration(s), date(s) of discontinuation, and reason(s) for discontinuation; coronary heart disease risk factors; dates of previous vaccinations, if applicable (including influenza, pneumococcus, zoster); other clinically significant diseases; reproductive status; smoking history; and use of alcohol and drugs of abuse. *The evaluation on Day 1 should only include any updates from screening.*

Appendix 1
Schedule of Assessments (Cohort 1: MTX-IR) (cont.)

[d] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, vitamins, and nutritional or dietary supplements) used by a patient from 12 weeks prior to initiation of study drug until 8 weeks after the last dose of study drug or entrance into the OLE, whichever occurs first. In addition, at each clinic visit, any use of PPIs, H2 receptor antagonists, and/or other *short-acting* antacids (e.g., Maalox®, Pepto-Bismol®, Rolaids®) should be recorded as concomitant medications, including the date and time of last administration *prior to the clinic visit*.

[e] Includes respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressures while the patient is in a seated position for at least 5 minutes.

To be performed only if medically indicated on the basis of the reason for the UV.

[g] Includes evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. *The baseline rheumatoid nodules assessment should be recorded in the Day 1 eCRF.* At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. *After the baseline visit, any* new or worsened clinically significant abnormalities *should be recorded* on the Adverse Event eCRF.

[i] Triplicate interpretable digital ECG recordings (e.g., without artifacts) will be obtained *within approximately 2–5 minutes of each other.* The ECG intervals (e.g., PR, QRS, QT, QTcF, and RR) and heart rate from these three ECGs will be entered into the eCRF; in addition, these triplicate readings will be stored for future analysis, if needed. ECGs for each patient should be obtained from the same machine whenever possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes prior to beginning the first ECG recording. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws*) whenever possible.* Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

ECGs *at these specified timepoints* can be performed without specific restrictions (e.g., can be any time of day, before or after dosing, fasting or fed).

[k] Instructions for ECG collection at the indicated timepoints: before dosing of the *in-clinic* dose on Days 1 and 28 (while patient is fasting) and at 2 hours (±30 minutes) after dosing of the *in-clinic* dose on Day 28 (while patient is fasting).

PPD should be performed only if QFT is not available. *Refer to the requirements for TB testing in Section 4.1.1 (may be performed within 3 months of screening, if indicated).*

[m] Not required if documented results of a chest radiograph (read by a radiologist) taken within the 3 months prior to screening is without changes suggestive of active TB infection.

[n] Patients will receive GDC-0853/placebo BID approximately every 12 hours starting on Day 1 and ending on Day *83*. GDC-0853/placebo should be taken with water by mouth. The dates and times of the most recent prior meal, last dose of oral study drug (prior to clinic visit), and timing of study drug administration in clinic should be recorded at each clinic visit. The last dose of blinded study drug in Study GA29350 is the p.m. dose on the day before the Week 12 (Day 84) visit for all patients. For patients continuing into the OLE Study GA30067, the first open-label dose of GDC-0853 should be the a.m. dose on Day 84 (which is Day 1 of Study GA30067).

Appendix 1
Schedule of Assessments (Cohort 1: MTX-IR) (cont.)

[o] The SC comparator drug will be administered subcutaneously in the thigh region. Alternatively, the injections can be administered subcutaneously in the abdomen. Following each SC comparator drug administration, patients should be monitored for acute hypersensitivity reactions per the local label. If the unblinded HCP cannot administer the SC comparator drug on the scheduled dosing day, the SC comparator drug is to be administered within a window of ±2 days from the scheduled dosing date. If the patient experiences a minor illness (e.g., minor infection), at the discretion of the investigator, the SC comparator drug may be delayed for a maximum period of 1 week. Following the delay, the SC comparator drug dosing is to be resumed in accordance with the original dosing schedule. Any potential deviation from this window is to be discussed with the Medical Monitor for the study.

[p] Includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[q] Includes sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, LDH, lipase, and amylase.

All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed locally at specified subsequent visits. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test (performed locally).

[s] Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

Includes total Ig, IgM, IgA, IgG, and IgE.

[u] Questionnaires will be self-administered on an electronic device ("ePRO"). Patients will complete the ePRO assessments before receiving any information on disease status, prior to the performance of non-PRO assessments and prior to the administration of study treatment. See Appendix 11, Appendix 12, Appendix 13, and Appendix 14 for sample questionnaires for the HAQ-DI, SF-36v2, FACIT-Fatigue, and DAS-28, respectively.

[v] The same clinician who performs the joint counts (Efficacy Assessor, see Section 4.5.6) should complete the Physician's Global Assessment of Arthritis throughout the study.

[w] See Appendix 3 for detailed schedule.

[x] Collect prior to drug administration. Blood for PBMCs will be shipped overnight to a central laboratory for processing.

[y] Collect prior to drug administration. Blood for flow cytometry analysis (e.g., B-cell and monocyte subsets). To be performed at select centers in the United States, where samples can be shipped to FACS laboratory (see Laboratory Manual) within 24 hours.

[z] Collect prior to drug administration. Blood for flow cytometry. To be performed at selected centers in the United States where samples can be shipped to a FACS laboratory (see Laboratory Manual) within 24 hours.

[aa] SST(s). Collect prior to drug administration.

[bb] Citrate plasma tube. Collect prior to drug administration.

[cc] Collection into two PaxGene blood tubes. Collect prior to drug administration.

[dd] Optional WGS is contingent upon the review and approval by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS, this assessment will not be applicable at that site. A single blood sample will be collected for WGS and may be sent to one or more laboratories for analysis.

Appendix 2
Schedule of Assessments (Cohort 2: TNF-IR)

Week	Screening Period	Treatment Period						SFU		
		0	1	2	4	8	12	8 Weeks after Last Dose	ET	UV
Day	−28 to −1	Day 1 [a]	Day 7 (±1)	Day 14 (±1)	Day 28 [a] (±2)	Day 56 (±2)	Day 84 [a, b] (±2)	(±4)		
Informed consent	x									
Demographic data	x									
General medical history and baseline conditions [c]	x	*x*								
Inclusion/exclusion criteria	x	x								
Concomitant medications [d]	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x
Vital signs [e]	x	x	x	x	x	x	x	x	x	x [f]
Height	x									
Weight	x	x			x	x	x	x	x	
Complete physical examination [g]	x						x	x	x	
Limited physical examination [h]		x	x	x	x	x				x [f]
Triplicate ECG [i]	x [j]	x [k]	x [j]		x [k]	x [j]	x [j]	x [j]	x [j]	x [f]
HBsAg, HBsAb, Hep B cAb, HCV Ab	x									
QFT or PPD [l]	x									
Chest radiograph [m]	x									
GDC-0853/placebo administration in clinic [n]		x	x	x	x	x				
Drug dispensing		x		x	x	x				

Appendix 2
Schedule of Assessments (Cohort 2: TNF-IR) (cont.)

Week	Screening Period	Treatment Period						SFU		
		0	1	2	4	8	12	8 Weeks after Last Dose (±4)	ET	UV
Day	−28 to −1	Day 1 [a]	Day 7 (±1)	Day 14 (±1)	Day 28 [a] (±2)	Day 56 (±2)	Day 84 [a, b] (±2)			
Hematology [o]	x	x	x		x	x	x	x	x	x [f]
Chemistry [p]	x	x	x		x	x	x	x	x	x [f]
Coagulation studies PT/PTT	x									x [f]
Pregnancy test [q]	x	x			x	x	x	x	x	x [f]
Urinalysis [r]	x	x			x	x	x	x	x	x [f]
Quantitative Ig [s]	x	x			x	x	x	x	x	x [f]
Lipid panel		x			x		x	x	x	
Rheumatoid factor and anti-CCP/ACPA	x						x	x	x	
TBNK	x	x	x	x	x	x	x	x	x	x [f]
ACR/DAS:										
CRP	x	x	x	x	x	x	x	x	x	x [f]
ESR (on site or at local laboratory)	x	x	x	x	x	x	x	x	x	x [f]
Tender/painful joint count (68), swollen joint count (66)	x	x	x	x	x	x	x	x	x	x [f]
Patient's Assessment of Arthritis Pain (VAS) [t]		x	x	x	x	x	x	x	x	x [f]
Patient Global Assessment of Arthritis (VAS) [t]		x	x	x	x	x	x	x	x	x [f]
Physician's Global Assessment of Arthritis (VAS) [u]		x	x	x	x	x	x	x	x	x [f]
HAQ-DI [t]		x	x	x	x	x	x	x	x	x [f]
SF-36v2 [t]		x				x	x	x	x	
FACIT-Fatigue [t]		x		x	x	x	x	x	x	
PK assessment [v]		x	x		x	x	x		x	x [f]

Appendix 2
Schedule of Assessments (Cohort 2: TNF-IR) (cont.)

Week	Screening Period	Treatment Period						SFU		
		0	1	2	4	8	12	8 Weeks after Last Dose (±4)	ET	UV
Day	−28 to −1	Day 1 [a]	Day 7 (±1)	Day 14 (±1)	Day 28 [a] (±2)	Day 56 (±2)	Day 84 [a, b] (±2)			
PBMC protein lysate [w] (U.S. sites only)	x	x			x		x	x	x	
Blood for FACS (U.S. sites only) [x]	x	x			x		x	x	x	x [f]
PD blood sample for FACS/basophils (U.S. sites only) [y]	x	x	x		x		x		x	x [f]
Serum biomarkers [z]	x	x	x		x		x	x	x	x [f]
Plasma biomarkers [aa]	x	x	x		x		x	x	x	x [f]
PAXgene RNA blood biomarkers [bb]	x	x	x		x		x	x	x	x
Whole blood PG sample		x								
Whole blood sample for genotyping (optional) [cc]		x								

ACPA = anti-citrullinated protein/peptide antibody; ACR = American College of Rheumatology; BID = twice daily; CCP = cyclic citrullinated protein; CRP = C-reactive protein; DAS = Disease Activity Score; eCRF = electronic Case Report Form; ESR = erythrocyte sedimentation rate; ET = early termination; FACIT = Functional Assessment of Chronic Illness Therapy; FACS = fluorescence-activated cell sorting; HAQ-DI = Health Assessment Questionnaire–Disability Index; HBsAg = hepatitis B core antibody; HBsAb = hepatitis B surface antigen; HCV = hepatitis C virus; IRB/EC = Institutional Review Board/Ethics Committee; OLE = open-label extension; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; PPD = purified protein derivate; PPI = proton pump inhibitor; PRO = patient reported outcome; QFT = QuantiFERON-TB Gold; RA = rheumatoid arthritis; SF-36 = Short-Form 36 Health Survey; SFU = safety follow-up; SST = serum separator tube; TB = tuberculosis; TBNK = T, B, and natural killer cells; TNF-IR = patients who had an inadequate response to tissue necrosis factor inhibitors; UV = unscheduled visit; VAS = visual analog scale; WGS = whole-genome sequencing.

[a] *A morning* clinic visit is *strongly recommended* for visits on Days 1, 28, and 84*, and particularly on Day 28 (*for *intensive PK sampling). When* morning visits are *strongly* recommended, the patient should be fasting *(>* 4-8 hours) prior to the first PK blood draw and fasting lipid panel.

[b] Day 84 is the last day of the study treatment period (however, no blinded study drug will be given on Day 84; the last dose of blinded study drug is the PM dose of Day 83). If eligible, patients may enroll into the OLE Study GA30067 to receive their first open-label dose of GDC-0853 *on Day 1 of Study GA30067 (after a trough PK level is drawn),* or they will proceed to the SFU period and return for the SFU visit on Day 140 (8 weeks after last dose of study drug).

Appendix 2
Schedule of Assessments (Cohort 2: TNF-IR) (cont.)

[c] Medical history will include *the diagnosis of rheumatoid arthritis and date of RA diagnosis,* all history relevant to RA, including a detailed history of RA medications taken within 5 years before screening, with dose(s)/duration(s), date(s) of discontinuation, and reason(s) for discontinuation; coronary heart disease risk factors; dates of previous vaccinations, if applicable (including influenza, pneumococcus, zoster); other clinically significant diseases; reproductive status; smoking history; and use of alcohol and drugs of abuse. *The evaluation on Day 1 should only include any updates from screening.*

[d] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, vitamins, and nutritional or dietary supplements) used by a patient from 12 weeks prior to initiation of study drug until 8 weeks after the last dose of study drug or entrance into the OLE, whichever occurs first. In addition, at each clinic visit, any use of PPIs, H2 receptor antagonists, and/or other *short-acting* antacids (e.g., Maalox®, Pepto-Bismol®, Rolaids®) should be recorded as concomitant medications, including the date and time of last administration *prior to the clinic visit*.

[e] Includes respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressures while the patient is in a seated position for at least 5 minutes.

[f] To be performed only if medically indicated on the basis of the reason for the UV.

[g] Includes evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. *The baseline rheumatoid nodules assessment should be recorded in the Day 1 eCRF.* At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. *After the baseline visit, any* new or worsened clinically significant abnormalities *should be recorded* on the Adverse Event eCRF.

[i] Triplicate interpretable digital ECG recordings (e.g., without artifacts) will be obtained *within approximately 2–5 minutes of each other.* The ECG intervals (e.g., PR, QRS, QT, QTcF, and RR) and heart rate from these three ECGs will be entered into the eCRF; in addition, these triplicate readings will be stored for future analysis, if needed. ECGs for each patient should be obtained from the same machine whenever possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes prior to beginning the first ECG recording. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws*) whenever possible.* Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, and conversation) should be avoided during the pre-ECG resting period and during ECG recording.

[j] ECGs *at these specified timepoints* can be performed without specific restrictions (e.g., can be any time of day, before or after dosing, fasting or fed).

[k] Instructions for ECG collection at the following timepoints: screening, before dosing of the *in-clinic* dose on Days 1, 28, and 84 (while patient is fasting) and at 2 hours (±30 minutes) after dosing of the *in-clinic* dose on Day 28 (while patient is fasting).

[l] PPD should be performed only if QFT is not available. *Refer to the requirements for TB testing in Section 4.1.1 (may be performed within 3 months of screening, if indicated).*

Appendix 2
Schedule of Assessments (Cohort 2: TNF-IR) (cont.)

[m] Not required if documented results of a chest radiograph (read by a radiologist) taken within the 3 months prior to screening is without changes suggestive of active TB infection.

[n] Patients will receive GDC-0853/placebo BID approximately every 12 hours starting on Day 1 and ending on Day 83. GDC-0853/placebo should be taken with water by mouth. The dates and times of the most recent prior meal, last dose of oral study drug (prior to clinic visit), and timing of study drug administration in clinic should be recorded at each clinic visit. The last dose of blinded study drug in Study GA29350 is the p.m. dose on the day before the Week 12 (Day 84) visit for all patients. For patients continuing into the OLE Study GA30067, the first open-label dose of GDC-0853 should be the a.m. dose on Day 84 (which is Day 1 of Study GA30067).

[o] Includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[p] Includes sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, LDH, lipase, and amylase.

[q] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed locally at specified subsequent visits. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test (performed locally).

[r] Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[s] Includes total Ig, IgM, IgA, IgG, and IgE.

[t] Questionnaires will be self-administered on an electronic device ("ePRO"). Patients will complete the ePRO assessments before receiving any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment. See Appendix 11, Appendix 12, Appendix 13 and Appendix 14 for sample questionnaires for the HAQ-DI, SF-36v2, FACIT-Fatigue, and DAS-28, respectively.

[u] The same clinician who performs the joint counts (Efficacy Assessor, see Section 4.5.6) should complete the Physician's Global Assessment of Arthritis throughout the study.

[v] See Appendix 3 for detailed schedule.

[w] Collect prior to drug administration: blood for PBMCs will be shipped overnight to a central laboratory for processing.

[x] Collect prior to drug administration: blood for flow cytometry analysis of lymphocytes (e.g., B-cell and monocyte subsets). To be performed at select centers in the United States where samples can be shipped to a FACS laboratory (see Laboratory Manual) within 24 hours.

[y] Collect prior to drug administration. Blood for flow cytometry. To be performed at selected centers in the United States where samples can be shipped to a FACS laboratory (see Laboratory Manual) within 24 hours.

[z] SST(s). Collect prior to drug administration.

Appendix 2
Schedule of Assessments (Cohort 2: TNF-IR) (cont.)

[aa] Citrate plasma tube. Collect prior to drug administration.

[bb] Collection into two PaxGene blood tubes. Collect prior to drug administration.

[cc] Optional WGS is contingent upon the review and approval by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS, this assessment will not be applicable at that site. A single blood sample will be collected for WGS and may be sent to one or more laboratories for analysis.

Appendix 3
Schedule of Pharmacokinetic and Biomarker Samples

Visit	Timepoint	Sample Type
Screening (Day −28 to Day −1)	*No timing restrictions*	PBMC protein lysate (U.S. sites only) Blood for FACS (U.S. sites only)
		Blood sample for FACS/basophils; (U.S. sites only)
		Serum biomarkers
		Plasma biomarkers
		PAXgene RNA blood
Day 1 [a]	Prior to the dose *(to be administered in clinic if applicable)*, fasting	GDC-0853 PK (plasma)
		PBMC protein lysate (U.S. sites only)
		Blood for FACS (U.S. sites only)
		Blood sample for FACS/basophils (U.S. sites only)
		Serum biomarkers
		Plasma biomarkers
		PAXgene RNA blood
		PG sample
		(Optional) WGS
Day 7	Prior to the dose *(to be administered in clinic if applicable)*	GDC-0853 PK (plasma)
		Blood sample for FACS/basophils (U.S. sites only)
		Serum biomarkers
		Plasma biomarkers
		PAXgene RNA blood
Day 28 [a]	Prior to the dose ***(must** be administered in clinic)*, fasting	GDC-0853 PK (plasma)
		PBMC protein lysate (U.S. sites only)
		Blood for FACS (U.S. sites only)
		Blood sample for FACS/basophils (U.S. sites only)
		Serum biomarkers
		Plasma biomarkers
		PAXgene RNA blood
	2 h (±30 min) after dosing, fasting	GDC-0853 PK (plasma)
	4–6 h after dosing	GDC-0853 PK (plasma)
	8–10 h after dosing (U.S. sites only) [c]	GDC-0853 PK (plasma)
Days 56	Prior to the dose *(to be administered in clinic if applicable)*	GDC-0853 PK (plasma)

Appendix 3
Schedule of Pharmacokinetic and Biomarker Samples (cont.)

Visit	Timepoint	Sample Type
Day 84 [a, b]	*No timing restrictions unless the patient is entering Study GA30067, in which case collection should occur prior to first dose on Day 1 of Study GA30067*	*GDC-0853 PK (plasma)*
		PBMC protein lysate (U.S. sites only)
		Blood for FACS (U.S. sites only)
		Blood sample for FACS/basophils (U.S. sites only)
		Serum biomarkers
		Plasma biomarkers
		PAXgene RNA blood
Day 140 *(Safety follow up visit)*	*No timing restrictions*	PBMC protein lysate (U.S. sites only) Blood for FACS (U.S. sites only) Serum biomarkers Plasma biomarkers PAXgene RNA blood
Unscheduled visit	*No timing restrictions*	*PAXgene RNA blood*
	Only collect if medically indicated, based on the reason for the unscheduled visit:	*GDC-0853 PK (plasma)*
		Blood for FACS (U.S. sites only)
		Serum biomarkers
		Plasma biomarkers

Appendix 3
Schedule of Pharmacokinetic and Biomarker Samples (cont.)

Visit	Timepoint	Sample Type
Early termination visit	*No timing restrictions*	GDC-0853 PK (plasma)
		PBMC protein lysate (U.S. sites only)
		Blood for FACS (U.S. sites only)
		Blood sample for FACS/basophils (U.S. sites only)
		Serum biomarkers
		Plasma biomarkers
		PAXgene RNA blood

FACS = fluorescence-activated cell sorting; H2RA = H2 receptor antagonist; PBMC = peripheral blood mononuclear cell; PG = pharmacogenomic; PK = pharmacokinetic; PPI = proton pump inhibitor; WGS = whole-genome sequencing.

Notes: Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

Morning clinic visits are preferred for all visits but are *especially encouraged* on Days 1, 28, and 84. Prior to each clinic visit, patients should be instructed not to take their dose and to bring their study medication with them to their clinic visit. For all PK samples, the dates and times of the most recent prior meal and most recent prior dose of PPI, H2RA, or other *short-acting* antacid (e.g., Maalox®, Pepto-Bismol®, Rolaids®), last dose of oral study drug (prior to clinic visit), and timing of study drug administration in clinic should be recorded at each clinic visit. The procedures for collection, handling, and shipping of PK samples can be found in the study's Laboratory Manual.

[a] Morning visit is *strongly recommended.* Patients must be fasting *(≥4–8 hours)* prior to PK draw *(trough level).*

[b] *The last dose of blinded study drug in GA29350 is the PM dose on Day 83.* For patients enrolling into the open-label Study GA30067, the Day 84 *first* dose will be the first dose (Day 1) of open-label GDC-0853*, which should be administered after the trough PK sample has been obtained.*

[c] **U.S. sites only:** If the patient is unable to stay or return to clinic for the post-dose 8–10-hour timepoint, this sample may be collected by a home nurse visit on Day 28.

Appendix 4
Appropriate Equivalent Morphine Doses of Common Opioid Analgesics

Drug	Maximum Allowed, Total Daily Dose (mg)	Relative Potency to Oral Morphine	Half-Life (hours)
Morphine	30	1	1.5–4
Hydrocodone (Vicodin, Lortab)	30	1	3.8–4.5
Hydromorphone (Dilaudid)	7.5	4	2.5
Meperidine (Demerol, Pethidine)	300	0.1	3.2–3.7
Methadone (Dolophine, Methadose, Physeptone)	10	3.0	23
Codeine (Paveral, Tylenol #2 and #3)	200	0.15	2.5–3.5
Oxycodone (*Roxicodone; Percocet, Tylox)	15	~2	3.2
Tramadol (Ultram, Zydol; Zamadol, Ultracet, Tramal)	300	~0.1	4.7–5.1
Propoxyphene HCl (Darvon, Darvocet, Doloxene) Propoxyphene napsylate (Darvon-N, Darvocet-N 100)	300 (propoxyphene HCl) 400 (propoxyphene napsylate)	~0.1	6–12; 30–36 for active metabolite (norpropoxyphene)

Note: Sites should contact the project team for acceptable alternative preparations and related data.

Appendix 5
Concomitant Medications (Including Foods and Herbal Products)

Class	Expected Interaction	Recommendation	Examples of Drugs in this Class [a]
Short-acting Antacids	Decreased GDC-0853 absorption due to increased gastric pH	Take GDC-0853 2 hours before or 2 hours after *short-acting* antacid	• Maalox®, Pepto-Bismol®, Rolaids®
Moderate or strong CYP3A inhibitors	Increased GDC-0853 plasma concentrations due to inhibition of metabolism	Avoid for 7 days or 5 half-lives (whichever is longer) prior to first dose of study drug and during the treatment period	• Antimicrobials (clarithromycin, erythromycin, itraconazole, ketoconazole, telithromycin, troleandamycin, voriconazole, posaconazole) • Antidepressants (nefazodone) • Antihypertensive/cardiac (verapamil, diltiazem) • Other (grapefruit juice, Seville orange juice, pomegranate, star fruit)
CYP3A inducers	Decreased GDC-0853 plasma concentrations due to increased metabolism	Avoid for 7 days or 5 half-lives (whichever is longer) prior to first dose of study drug and during the treatment period	• Antimicrobials (rifampin, rifapentine, rifabutin) • Antidepressants (St. John's wort, hyperforin) • Antiepileptics (carbamazepine, phenytoin, phenobarbital, hyperforin) • Diabetes (pioglitazone, troglitazone) • Other (modafinil, bosentan)

Appendix 5
Concomitant Medications (Including Foods and Herbal Products) (cont.)

Class	Expected Interaction	Recommendation	Examples of Drugs in this Class [a]
Sensitive and narrow therapeutic window CYP3A substrates	Potential for increased plasma concentrations of CYP3A substrates due to inhibition of metabolism by GDC-0853	Use with caution and monitor for adverse events related to CYP3A substrates as directed by product labeling	• Antiemetic/prokinetic (aprepitant, cisapride) • Anti-histamine (astemizole, terfenadine) • Anti-hypertensive/cardiac (dronedarone, eplerenone, felodipine, nisoldipine, quinidine, ticagrelor, vardenafil) • Benzodiazepines (alprazolam, diazepam, midazolam) • Lipid-lowering (simvastatin, lovastatin) • Migraine (eletriptan, ergotamine) • Steroids (budesonide, fluticasone) • Other (alfentanil, buspirone, conivaptan, darifenacin, dasatinib, dihydroergotamine, fentanyl, lurasidone, pimozide, quetiapine, sildenafil, tolvaptan, triazolam)

[a] The following list is not comprehensive. Please refer to the following Web sites for additional information and consult the Medical Monitor if necessary:

U.S. FDA Table of Substrates, Inhibitors, and Inducers (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm).

Indiana University Department of Medicine P450 Interaction Table (http://medicine.iupui.edu/clinpharm/ddis).

Appendix 6
National Cholesterol Education Program (NCEP) Guidelines

ATP III Guidelines At-A-Glance Quick Desk Reference

1

Step 1

Determine lipoprotein levels–obtain complete lipoprotein profile after 9- to 12-hour fast.

ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

LDL Cholesterol – Primary Target of Therapy	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High

2

Step 2

Identify presence of clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent):

- Clinical CHD
- Symptomatic carotid artery disease
- Peripheral arterial disease
- Abdominal aortic aneurysm.

3

Step 3

Determine presence of major risk factors (other than LDL):

Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals

Cigarette smoking
Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
Low HDL cholesterol (<40 mg/dL)*
Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
Age (men ≥45 years; women ≥55 years)

** HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.*

- Note: in ATP III, diabetes is regarded as a CHD risk equivalent.

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154/Protocol GA29350, Version 4

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Step 4

If 2+ risk factors (other than LDL) are present without CHD or CHD risk equivalent, assess 10-year (short-term) CHD risk (see Framingham tables).
Three levels of 10-year risk:

- >20% — CHD risk equivalent
- 10-20%
- <10%

5

Step 5

Determine risk category:

- Establish LDL goal of therapy
- Determine need for therapeutic lifestyle changes (TLC)
- Determine level for drug consideration

LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

** Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.*

† Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

6

Step 6

Initiate therapeutic lifestyle changes (TLC) if LDL is above goal.

TLC Features

- TLC Diet:
  - Saturated fat <7% of calories, cholesterol <200 mg/day
  - Consider increased viscous (soluble) fiber (10-25 g/day) and plant stanols/sterols (2g/day) as therapeutic options to enhance LDL lowering
- Weight management
- Increased physical activity.

7

Step 7

Consider adding drug therapy if LDL exceeds levels shown in Step 5 table:

- Consider drug simultaneously with TLC for CHD and CHD equivalents
- Consider adding drug to TLC after 3 months for other risk categories.

Drugs Affecting Lipoprotein Metabolism

Drug Class	Agents and Daily Doses	Lipid/Lipoprotein Effects		Side Effects	Contraindications
HMG CoA reductase inhibitors (statins)	Lovastatin (20-80 mg) Pravastatin (20-40 mg) Simvastatin (20-80 mg) Fluvastatin (20-80 mg) Atorvastatin (10-80 mg) Cerivastatin (0.4-0.8 mg)	LDL HDL TG	↓18-55% ↑5-15% ↓7-30%	Myopathy Increased liver enzymes	Absolute: • Active or chronic liver disease Relative: • Concomitant use of certain drugs*
Bile acid sequestrants	Cholestyramine (4-16 g) Colestipol (5-20 g) Colesevelam (2.6-3.8 g)	LDL HDL TG	↓15-30% ↑3-5% No change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	Absolute: • dysbeta-lipoproteinemia • TG >400 mg/dL Relative: • TG >200 mg/dL
Nicotinic acid	Immediate release (crystalline) nicotinic acid (1.5-3 gm), extended release nicotinic acid (Niaspan®) (1-2 g), sustained release nicotinic acid (1-2 g)	LDL HDL TG	↓5-25% ↑15-35% ↓20-50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Absolute: • Chronic liver disease • Severe gout Relative: • Diabetes • Hyperuricemia • Peptic ulcer disease
Fibric acids	Gemfibrozil (600 mg BID) Fenofibrate (200 mg) Clofibrate (1000 mg BID)	LDL *(may be increased in patients with high TG)* HDL TG	↓5-20% ↑10-20% ↓20-50%	Dyspepsia Gallstones Myopathy	Absolute: • Severe renal disease • Severe hepatic disease

* *Cyclosporine, macrolide antibiotics, various anti-fungal agents, and cytochrome P-450 inhibitors (fibrates and niacin should be used with appropriate caution).*

8

Step 8

Identify metabolic syndrome and treat, if present, after 3 months of TLC.

Clinical Identification of the Metabolic Syndrome – Any 3 of the Following:

Risk Factor	Defining Level
Abdominal obesity*	Waist circumference†
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dL

* *Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.*

† *Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94-102 cm (37-39 in). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.*

Treatment of the metabolic syndrome

- Treat underlying causes (overweight/obesity and physical inactivity):
  - Intensify weight management
  - Increase physical activity.

- Treat lipid and non-lipid risk factors if they persist despite these lifestyle therapies:
  - Treat hypertension
  - Use aspirin for CHD patients to reduce prothrombotic state
  - Treat elevated triglycerides and/or low HDL (as shown in Step 9).

9

Step 9

Treat elevated triglycerides.

ATP III Classification of Serum Triglycerides (mg/dL)

<150	Normal
150-199	Borderline high
200-499	High
≥500	Very high

Treatment of elevated triglycerides (≥150 mg/dL)

- Primary aim of therapy is to reach LDL goal
- Intensify weight management
- Increase physical activity
- If triglycerides are ≥200 mg/dL after LDL goal is reached, set secondary goal for non-HDL cholesterol (total – HDL) 30 mg/dL higher than LDL goal.

Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for Three Risk Categories

Risk Category	LDL Goal (mg/dL)	Non-HDL Goal (mg/dL)
CHD and CHD Risk Equivalent (10-year risk for CHD >20%)	<100	<130
Multiple (2+) Risk Factors and 10-year risk ≤20%	<130	<160
0-1 Risk Factor	<160	<190

If triglycerides 200-499 mg/dL after LDL goal is reached, consider adding drug if needed to reach non-HDL goal:

- intensify therapy with LDL-lowering drug, or
- add nicotinic acid or fibrate to further lower VLDL.

If triglycerides ≥500 mg/dL, first lower triglycerides to prevent pancreatitis:

- very low-fat diet (≤15% of calories from fat)
- weight management and physical activity
- fibrate or nicotinic acid
- when triglycerides <500 mg/dL, turn to LDL-lowering therapy.

Treatment of low HDL cholesterol (<40 mg/dL)

- First reach LDL goal, then:
- Intensify weight management and increase physical activity
- If triglycerides 200-499 mg/dL, achieve non-HDL goal
- If triglycerides <200 mg/dL (isolated low HDL) in CHD or CHD equivalent consider nicotinic acid or fibrate.

Men

Estimate of 10-Year Risk for Men

(Framingham Point Scores)

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Point Total	10-Year Risk %
<0	< 1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥ 30

10-Year risk _____%

Women

Estimate of 10-Year Risk for Women

(Framingham Point Scores)

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Point Total	10-Year Risk %
< 9	< 1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥ 30

10-Year risk _____%

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health
National Heart, Lung, and Blood Institute

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May 2001

Appendix 7
Clinical Criteria for Diagnosing Anaphylaxis

These criteria are taken from a summary report from the second symposium on the definition and management of anaphylaxis, conducted by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (Sampson et al. 2006[1]). Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING:

   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms (e.g., hypotonia, syncope, incontinence)
   - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):

   - Infants and children: low systolic blood pressure (age specific)[2] or greater than 30% decrease in systolic blood pressure
   - Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline

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[1] Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–397.

[2] Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 × age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.

Appendix 8
Childbearing Potential, Pregnancy Testing, and Contraception

For Women

All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening and a urine pregnancy test on Study Day 1 prior to administration of study drug and at subsequent clinic visits. If a urine pregnancy test result is positive, study drug will not be administered until pregnancy is ruled out. The result must be confirmed by a serum pregnancy test (conducted by the local laboratory). Refer to Section 5.4.3 of the protocol for management of a patient with a confirmed pregnancy.

All female patients are considered to be of childbearing potential unless they meet one of the following criteria:

- The patient has been postmenopausal (non−therapy-induced amenorrhea) for at least 12 continuous months with no other identified cause
- The patient had a surgical bilateral oophorectomy (with or without hysterectomy) more than 6 weeks prior to enrollment
- The patient had a hysterectomy

Female patients of reproductive or childbearing potential who are unwilling to use a method of contraception that results in a failure rate of <1 % per year or remain abstinent (refrain from heterosexual intercourse) during the treatment period and for at least 60 days after the last dose of study drug or longer if required per the local prescribing label for adalimumab will be excluded from study participation.

Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Examples of contraceptive methods with a failure rate of <1% per year include the following:

- Sterilization, bilateral surgical tubal ligation
- Intrauterine device
- Combined oral contraceptive pill[1]
- Contraceptive transdermal patch (estrogen and progestin containing)[1]

[1] Women using estrogen-containing hormonal contraceptives as a method of contraception must also use a barrier such as a male condom in conjunction with the hormonal contraceptives.

Appendix 8
Childbearing Potential, Pregnancy Testing, and Contraception (cont.)

- Hormonal vaginal device
- Progestogen-only hormonal contraception associated with inhibition of ovulation
- Implants for contraception
- Injections for contraception (with prolonged release)
- Sole sexual partner consisting of surgically sterilized male partner with appropriate postsurgical verification of the absence of spermatozoa in the ejaculate. Patients may provide verbal confirmation that the partner completed appropriate follow-up after vasectomy. Sites are not required to obtain partner medical records.

For Men

All men must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and to refrain from donating sperm, as defined below:

- With female partners of childbearing potential (including those who have had a tubal ligation), men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period and for at least 120 days (4 months) after the last dose of study treatment. Men must refrain from donating sperm during this same period.
- With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 28 days after the last dose of study treatment to avoid exposing the fetus.

For Men and Women

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Appendix 9
2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis

Target population (Who should be tested?):

1. Patients who have at least 1 joint with definite clinical synovitis (swelling) [a]
2. Patients with synovitis not better explained by another disease [b]

Classification criteria for RA) score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA) [c]

Classification Criteria	Score
A. Joint involvement [d]	
1 large joint [e]	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints) [f]	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint) [g]	5
B. Serology (at least 1 test result is needed for classification) [h]	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification) [i]	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms [j]	
<6 weeks	0
≥6 weeks	1

Source: Aletaha D, Neogi T, Silman AJ, et al. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81.

ACPA = anti citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IU = international units; RA = rheumatoid arthritis; RF = rheumatoid factor; ULN = upper limit of normal.

[a] The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of RA with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment), who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

[b] Differential diagnoses vary among patients with different presentations but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

[c] Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

Appendix 9
2010 American College of Rheumatology/European League against Rheumatism Classification Criteria for Rheumatoid Arthritis (cont.)

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[d] Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

[e] "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

[f] "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

[g] In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular).

[h] Negative refers to IU values that are less than or equal to the ULN for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤ 3 times the ULN for the laboratory and assay; high-positive refers to IU values that are > 3 times the ULN for the laboratory and assay. Where RF information is available only as positive or negative, a positive result should be scored as low-positive for RF.

[i] Normal/abnormal is determined by local laboratory standards.

[j] Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

Appendix 10
ACR Classification of Functional Capacity in Rheumatoid Arthritis

Class I	Complete functional capacity with ability to carry on all usual duties without handicaps
Class II	Functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints
Class III	Functional capacity adequate to perform only few or none of the duties of usual occupation or of self-care
Class IV	Largely or whole incapacitated with patient bedridden or confined to wheelchair, permitting little or no self-care

Source: Hochberg MC, Chang RW, Dwosh I, et al. The American College of Rheumatology 1991 Revised Criteria for the Classification of Global Functional Status in Rheumatoid Arthritis. Arthritis Rheum 1992;35:498–502.

Appendix 11
Health Assessment Questionnaire—Disability Index (HAQ-DI)

HEALTH ASSESSMENT QUESTIONNAIRE

Name_____ **Date**_____

PATKEY#_____
QUESTDAT_____
_

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

HAQADMIN_____

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

QUESTYPE_____

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
DRESSING & GROOMING				
Are you able to:				
- Dress yourself, including tying shoelaces and doing buttons?	_____	_____	_____	_____
- Shampoo your hair?	_____	_____	_____	_____
ARISING				
Are you able to:				
- Stand up from a straight chair?	_____	_____	_____	_____
- Get in and out of bed?	_____	_____	_____	_____
EATING				
Are you able to:				
- Cut your meat?	_____	_____	_____	_____
- Lift a full cup or glass to your mouth?	_____	_____	_____	_____
- Open a new milk carton?	_____	_____	_____	_____
WALKING				
Are you able to:				
- Walk outdoors on flat ground?	_____	_____	_____	_____
- Climb up five steps?	_____	_____	_____	_____

PMSVIS_____
RASTUDY_____
QUESTNUM_____
DRESSNEW_____
RISENEW_____
EATNEW_____
WALKNEW_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____ Cane
_____ Walker
_____ Crutches
_____ Wheelchair
_____ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
_____ Built up or special utensils
_____ Special or built up chair
_____ Other (Specify:_____)

DRSGASST_____
_
RISEASST_____
_
EATASST_____
WALKASST
_

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____ Dressing and Grooming
_____ Arising
_____ Eating
_____ Walking

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	
HYGIENE					
Are you able to:					
- Wash and dry your body?	_____	_____	_____	_____	
- Take a tub bath?	_____	_____	_____	_____	
- Get on and off the toilet?	_____	_____	_____	_____	HYGNNEW_____
REACH					
Are you able to:					
- Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?	_____	_____	_____	_____	
- Bend down to pick up clothing from the floor?	_____	_____	_____	_____	REACHNEW_____
GRIP					
Are you able to:					
- Open car doors?	_____	_____	_____	_____	
- Open jars which have been previously opened?	_____	_____	_____	_____	
- Turn faucets on and off?	_____	_____	_____	_____	GRIPNEW_____
ACTIVITIES					
Are you able to:					
- Run errands and shop?	_____	_____	_____	_____	
- Get in and out of a car?	_____	_____	_____	_____	
- Do chores such as vacuuming or yardwork?	_____	_____	_____	_____	ACTIVNEW_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____Raised toilet seat
_____Bathtub bar
_____Bathtub seat
_____Long-handled appliances for reach
_____Jar opener (for jars previously opened)
_____Long-handled appliances in bathroom
_____Other (Specify: _____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____Hygiene
_____Gripping and opening things
_____Reach
_____Errands and chores

HYGNASST_____
RCHASST_____
GRIPASST_____
ACTVASST_____

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (I) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.

NO PAIN 0 _____ SEVERE PAIN 100

PAINSCAL_____

Appendix 12
The Short-Form 36 Version 2 Health Survey (SF-36v2)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking more than a mile	☐ 1	☐ 2	☐ 3
h	Walking several hundred yards	☐ 1	☐ 2	☐ 3
i	Walking one hundred yards	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

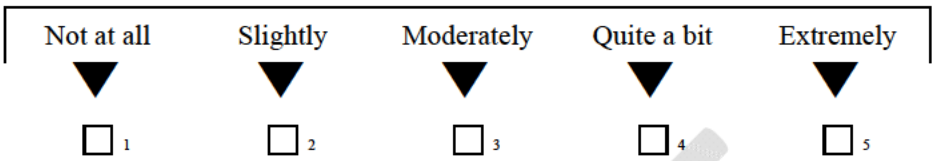
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

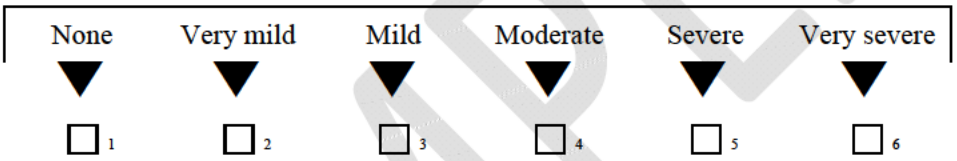
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

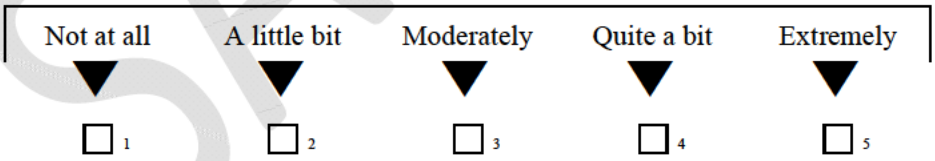
6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**



7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**



8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**



9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 13
Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-Fatigue) Scale

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	FOR REFERENCE ONLY	Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix 14
Disease Activity Score 28

The DAS 28-4 (CRP) and the DAS 28-4 (ESR) will be calculated as follows.

Assessments

- Tender joint count of 28 joints (TJC28), square-root transformed
- Swollen joint count of 28 joints (SJC28), square-root transformed
- Acute-phase reactant (erythrocyte sedimentation rate [ESR mm/hr] or $high\ sensitivity$ C-reactive protein [$hsCRP\ mg/L$]), log transformed
- Patient's global assessment of disease activity on visual analog scale (0–100 mm)

Calculations

The DAS 28 is calculated according to the following formulas:

- DAS 28(4)-ESR $= 0.56 \times \text{SQRT(TJC28)} + 0.28\text{SQRT(SJC28)} + 0.70 \times \ln(\text{ESR}) + 0.014 \times PtGA$
- DAS 28(4)-CRP $= 0.56 \times \text{SQRT(TJC28)} + 0.28\text{SQRT(SJC28)} + 0.36 \times \ln(\text{CRP} + 1) + 0.014 \times PtGA + 0.96$
- Total score: Range, 0.49–9.07

Scoring

- Disease remission ≤ 2.6
- Low disease activity ≤ 3.2
- Moderate disease activity > 3.2 and ≤ 5.1
- High disease activity > 5.1

$PtGA = patient's\ global\ assessment\ of\ disease\ activity$; ln = natural logarithm; SQRT = square root.

The DAS28(3) and DAS28-CRP(3) will be calculated as follows:

Calculations

$$DAS28(3) = [0.56 \times SQRT(TJC28) + 0.28SQRT(SJC28) + 0.70 \times ln(ESR)] \times 1.08 + 0.16$$

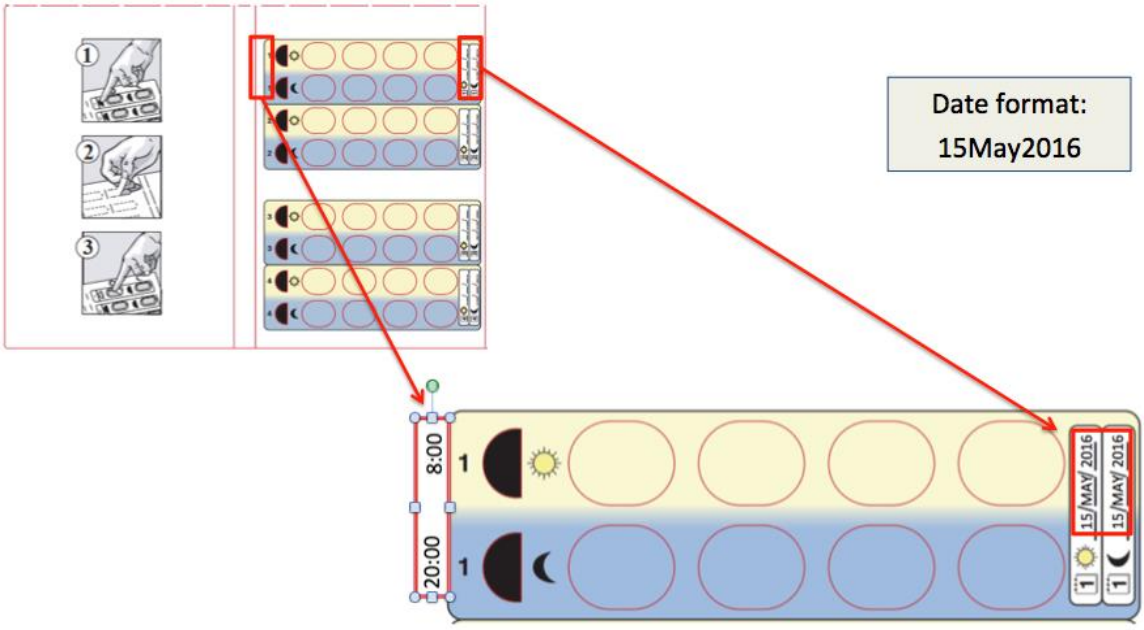
$$DAS28\text{-}CRP(3) = [0.56 \times SQRT(TJC28) + 0.28SQRT(SJC28) + 0.36 \times ln(CRP + 1)] \times 1.10 + 1.15$$

Appendix 15
Blister Wallet Configuration for GDC-0853/Placebo Administration (Cohort 1 Only)

Cohort 1 only: Blister Wallet configuration shown below denotes a.m. (sun) versus p.m. (moon) dose:

Site will be responsible for prepopulating the dates on the blister wallets.

Patients should record time (in military time) of each dose on blister wallets.



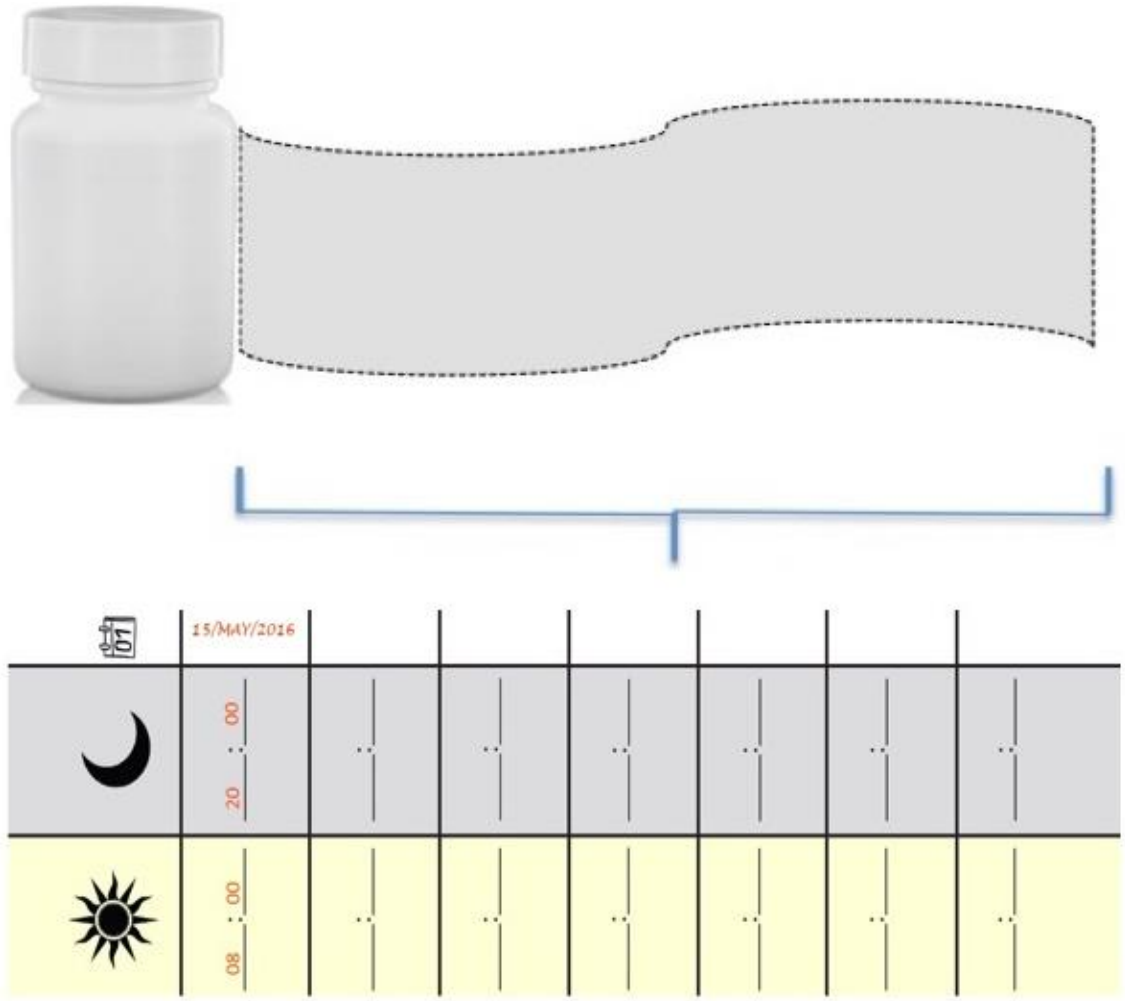
Patient Dosing Instructions will be provided for guidance on dose administration at home, during clinic visits, and in the event if a dose is missed.

Appendix 16
Bottle and Label Configuration for GDC-0853/Placebo Administration (Cohort 2 Only)

Cohort 2 only: Label to be affixed on the study drug bottle shows a.m. (sun) versus p.m. (moon) dose.

Site will be responsible for prepopulating the dates on the label and affixing the label to the bottle.

Patients should record the time (in military time) of each dose on label.



Patient Dosing Instructions will be provided for guidance on dose administration at home, during clinic visits, and in the event if a dose is missed.