Official Title: A Phase II Open-Label Extension Study of Patients Previously Enrolled in Study GA29350 to Evaluate the Long-Term Safety and Efficacy of GDC-0853 in Patients With Moderate to Severe Rheumatoid Arthritis

NCT Number: NCT02983227

Document Date: Protocol Version 2: 08-August-2016

PROTOCOL

TITLE:	**A PHASE II OPEN-LABEL EXTENSION STUDY OF PATIENTS PREVIOUSLY ENROLLED IN STUDY GA29350 TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF GDC-0853 IN PATIENTS WITH MODERATE TO SEVERE RHEUMATOID ARTHRITIS**
PROTOCOL NUMBER:	GA30067
VERSION NUMBER:	2
EUDRACT NUMBER:	2016-000498-19
IND NUMBER:	120,162
TEST PRODUCT:	GDC-0853 (RO7010939)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 18 February 2016
DATE AMENDED:	Version 2: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	08-Aug-2016 17:39:29

PROTOCOL AMENDMENT, VERSION 2
RATIONALE

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

- Background and nonclinical experience with GDC-0853 had been updated to include no observed adverse effect levels from 9-month study in dogs and chronic toxicity findings in rats and dogs that support multiple-dose exposures in patients with rheumatoid arthritis at the proposed clinical doses (Sections 1.2, 1.3, and 5.1.1.1).
- The secondary efficacy objective to assess Boolean- and SDAI-based remission has been clarified.
- Week 2 assessments have been removed throughout the protocol to reduce patient burden.
- The rationale for GDC-0853 dose and schedule has been updated to reflect results from the available clinical and nonclinical data.
- The inclusion criterion for completion of Study GA29350 has been clarified (Section 4.1.1).
- Temperature for GDC-0853 storage has been updated to be between 2°C and 8°C (Section 4.2.1.).
- Dosing for Day 1 has been clarified (Section 4.2.2).
- Labeling of dates on the blister wallets and bottles has been changed to be prepopulated by the sites, with the time of dosing to be recorded by the patient for ease of labeling (Appendix 10).
- The male-specific Informed Consent has been removed now that additional nonclinical toxicology results suggest lower testicular toxicity risk (Section 4.4.1). Upon completion of the nonclinical chronic duration dog toxicity study for GDC-0853, the potential risk of testicular toxicity has been reduced since similar effects were observed in both GDC-0853–treated and vehicle-treated dogs, and the only testicular effects considered GDC-0853 related occurred at a very high dose in rats.
- The method of patient-reported (via electronic device) and clinician-reported outcomes (paper based) has been clarified (Section 4.4.6).
- Updated nonclinical information has been added regarding immune function, hepatotoxicity, and vascular inflammation, and pancreatic effects have been removed on the basis of U.S. Food and Drug Administration agreement that this was a rat species–specific finding (Section 5.1.1).
- Management guidelines have been updated to reflect changes in text, and the hepatotoxicity wording has been clarified (Table 3).

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 2:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

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

SECTION 1.2.1: Bruton's Tyrosine Kinase

…Affected male patients have a primary immune deficiency called X-linked agammaglobulinemia (XLA) and are susceptible to recurrent infections starting shortly after birth. ~~Intravenous immunoglobulin (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.~~ *Patients with XLA can live relatively normal lives on a standard therapy of intravenous (IV) Ig (Kaveri et al. 2011), suggesting that BTK can be safely inhibited especially in people with established immune systems.*

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.

SECTION 1.2.2: Nonclinical Experience with GDC-0853

The GDC-0853 safety profile has been assessed in repeat-dose, general toxicology studies (daily 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 system, and embryo-fetal development (Segment 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 ~~37~~ *36* μM • h). ~~To date, the n~~*N*otable findings identified in nonclinical toxicology studies include ~~effects to the male reproductive organs (≥ 37 μM • h) in dog and rats,~~ vascular inflammation (≥ 56 μM • h) in dogs, ~~and~~ 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.* ~~The projected mean exposure for the highest dose in this clinical study, GA29530, is anticipated to not exceed 10 μM • h area under the concentration time curve from time 0 to 24 hours (AUC_{0-24}) and 0.150 μM unbound C_{max}, which is below the corresponding exposures at which the above adverse effects occurred in dogs, the most sensitive species.~~ Fetal malformations and ossification site changes in rats (≥ 190 μM • h) and fetal malformations in rabbits (≥ 10.6 μM • h) warrant the continued use of highly effective contraception in clinical trials. ~~Additionally, pancreatic findings have been observed in rats administered GDC-0853 (and other BTK inhibitors) and are considered to be a species specific effect (see the GDC-0863 Investigator's Brochure).~~ 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, GA30067.

SECTION 1.2.3: Clinical Experience with GDC-0853

~~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 (U.S.) and Europe for use in patients with mantle cell lymphoma, chronic lymphocytic leukemia (CLL), and Waldenstrom's macroglobulinemia.~~

SECTION 1.3: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

~~In non-clinical studies with GDC-0853, the no observed adverse effect levels (NOAELs) determined in the repeat-dose, 6-month Wistar Han rat (20 mg/kg; 104 μM•h) and 4-week dog (3 mg/kg; 10 μM•h) studies support multiple-dose exposures in healthy subjects and RA patients up to 10 μM•h. The 9-month dog study recovery phase is ongoing, and the final report is expected in May 2016.~~ *The no-observed-adverse-effect levels (NOAELs) determined in the repeat-dose, 6-month Wistar Han rat (20 mg/kg; 104 μM•h) and 9-month dog (10 mg/kg; 36 μM•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):

- *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 μM•h). In dogs, after 4 months of dosing, decreased circulating total lymphocytes were observed at ≥10 mg/kg/day (≥36 μM•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 μM•h); there were no GDC-0853–related effects on total T, helper T, or cytotoxic T cells. Ig isotyping in high-dose dogs (36 μM•h) and rats (104 μM•h) showed decreased IgG concentration; mid- and high-dose rats (≥17 μM•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, 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 ≥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 (≤104 μM•h) and dogs (≤36 μM•h).*
- ~~Effects to the male reproductive organs in rats (observed at 1438 μM•h) and dogs (findings in one animal observed at 37 μM•h) included seminiferous tubule~~

~~degeneration/atrophy and associated hypospermia in the epididymis. These findings did not reverse in the 1-month recovery period in rats. A more robust evaluation of reversibility is ongoing in the recovery phase of the 9-month dog study as well as in a male rat Segment I study. Thus, the informed consent will include male reproductive risks and a mandatory male-specific informed consent.~~

- Pancreatic findings observed in rats administered GDC-0853 (and other BTK inhibitors) are considered to be a~~n on target,~~ species-specific effect supported by a number of investigative studies ~~and the lack of associated findings in humans with X-linked agammaglobulinemia (XLA;~~ (see the GDC-0853 Investigator's Brochure for details).

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 *initially* from Study GA29350 if they have a history of hospitalization due to an infection in the 8 weeks before screening *for Study GA29350*, evidence of active or latent or inadequately treated infection with mycobacterium tuberculosis (TB), any known immunodeficiency, including IgG $<$ 500 mg/dL, or if they have experienced a serious infection or an infection requiring treatment with an IV antimicrobial agent during participation in Study GA29350. *Total Ig, IgG, IgM, IgA, and IgE concentrations will also be measured regularly throughout both studies.* Patients should be carefully monitored throughout both the blinded Study GA29350 and the open-label Study GA30067 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.

Hepatotoxicity

Evidence of hepatobiliary injury was observed in animals administered relatively high doses of GDC-0853 in repeat-dose toxicity studies….

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 before screening will be excluded *initially* from participation in Study GA29350 *(and therefore from Study GA30067),* 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 considered adverse events of special interest with expedited reporting requirements to the Sponsor.

~~**Pancreatic Effects:** No significant changes in amylase, lipase, or serum glucose levels have been observed in patients with cancer or after single-dose and multi-dose administration in healthy subjects. However, as a precautionary safety monitoring measure, amylase, lipase, and serum glucose levels will be monitored in patients during the study.~~

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 *initially* from Study GA29350 *(and therefore from Study GA30067* and complete blood counts (CBCs), creatinine levels, and urinalysis findings will be monitored in all patients during both studies: Studies GA29350 and GA30067. 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.

SECTION 3.1: DESCRIPTION OF THE STUDY

At Week 12, if there has not been at least a 20% improvement in the swollen joint count (SJC) and tender joint count (TJC) relative to the patient's baseline joint counts in the blinded Study GA29350, then therapy should be escalated *or substituted* per the investigator's judgment. Such changes may include an increase in the dose of MTX, addition of other DMARDs (e.g., hydroxychloroquine or sulfasalazine), substitution of MTX with leflunomide, and/or an increase in the dose of corticosteroids (see Section 5.1). The investigator may adjust the therapy (e.g., escalate or reduce) on the basis of his or her overall clinical assessment of the patient. However, certain medications, including but not limited to ~~azathioprine,~~ mycophenolate, biologics, Janus kinase (JAK) inhibitors, and calcineurin inhibitors, are prohibited throughout the OLE Study (see Section 4.3.2). Adjustment of MTX, other DMARDs, or corticosteroids for safety reasons is allowed throughout the trial (see Section 4.3.1.1).

Since patients enrolling in this study may be receiving GDC-0853 for the first time, all patients will be monitored closely with more frequent visits at the beginning of this OLE study (i.e., *more frequent visits* up to Week 12 ~~with a visit frequency similar to Study GA29350~~ and then every 3 months, thereafter). Patients will have safety and clinical efficacy assessments at Weeks 0, ~~2,~~ 4, 8, 12, 24, 36, and 52 (see Figure 1).

SECTION 3.1.1: <u>Internal Monitoring Committee</u>

Periodic safety reviews for this OLE will *also* be performed by the Sponsor's IMC as outlined in the IMC Charter. *If necessary, cumulative unblinded data for patients remaining in the parent study may also be made available to IMC members….*

SECTION 3.3.5.1: Efficacy Measurements

Efficacy based on SJC and TJC will be assessed at Weeks 12 and 24*, and improvement will be calculated using formulas provided in Appendix 9*. If a 20% improvement in

SJC and TJC *(relative to baseline values in the blinded Study GA29350)* is not observed by Week 12, concomitant therapy will be escalated (e.g., adjusting the dose of corticosteroids, MTX, or both as well as the possible addition *or substitution* of other DMARDs; see Section 4.3.1.1.3). If a 20% improvement in SJC and TJC *(relative to baseline values in the blinded Study GA29350)* is not observed by Week 24, the patient will be discontinued from this study because of lack of efficacy. Confirmation of efficacy at these prescribed intervals will help to ensure that patients are not kept on an ineffective treatment for a prolonged period of time.

SECTION 4.1.1: Inclusion Criteria

Patients must meet the following criteria for study entry:

- Completion of treatment *period through Day 84* as specified in Study GA29350~~, including completion of the Day 84 study visit assessments~~
- If receiving oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and/or NSAIDs (up to the maximum recommended dose), doses have remained stable for the duration (i.e., since the first administration of study drug) of Study GA29350. *If a change in dose was needed during Study GA29350, discuss with the Medical Monitor.*
- 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 4)

  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.

SECTION 4.2.1: Formulation, Packaging, and Handling

Tablets will be supplied in bottles, which will be appropriately labeled for this study. GDC-0853 tablets should be stored ~~at or below~~ *between* 2 ℃ and 8°C.

SECTION 4.2.2.1: *GDC-0853 Dose and Administration*

The GDC-0853 dose regimen is oral 200 mg BID. Patients will receive GDC-0853 approximately every 12 hours for 52 weeks. Patients should be directed to take one dose (a total of 4 tablets) BID (total of 8 tablets each day). On clinic visit days during the first 12 weeks of the study, patients should be instructed that the a.m. dose of GDC-0853 will be administered in the clinic*, except for Day 1, since the last dose of GDC-0853 for Study GA29350 is the a.m. dose on Day 84 for all patients. For patients continuing into the OLE Study GA30067, the first open-label dose of GDC-0853 should be the p.m. dose (may be taken at home) on Day 84 (which is Day 1 of Study GA30067).* After Week 12, GDC-0853 administration in the clinic is not required.

Guidelines for dose reduction and treatment interruption or discontinuation are provided in Section 5.1.

GDC-0853 may be orally administered with or without food. The dates and times of the most recent prior meal, last dose of GDC-0853 (prior to clinic visit), and timing of GDC-0853 administration in clinic should be recorded at each clinic visit. In addition, any use of PPIs, H2-receptor antagonists (H2RAs), and/or *other* antacids *(e.g., Maalox®, Pepto-Bismol®, Rolaids®)* should be recorded as concomitant medications, including time and date of last administration. Administration of GDC-0853 should be staggered with antacid use (i.e., GDC-0853 should be taken 2 hours before or 2 hours after the antacid).

At study visits, sufficient GDC-0853 tablets will be dispensed to complete dosing until the next scheduled visit. When GDC-0853 is administered at the site, it will be administered under supervision of study personnel, and the amount of GDC-0853 dispensed must be recorded. ~~Patients will be instructed to return used and unused bottles of GDC-0853 at each clinic visit where GDC-0853 is administered in order to calculate the number of tablets and compliance.~~

SECTION 4.2.2.2: *GDC-0853 Compliance*

The following measure will be taken to assess patient compliance with study drug: patients will be directed to bring any used and unused bottles to each visit.

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 10 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.

~~Guidelines for dosage reduction and treatment interruption or discontinuation are provided in Section 5.1.~~

SECTION 4.3.1.1.3: Other DMARDs

Treatment with certain medications, including but not limited to ~~azathioprine,~~ mycophenolate, calcineurin inhibitors, biologic agents (e.g., anti-TNF, anti-IL-6 or anti-IL6 receptor, anti-IL-1, T-cell costimulation modulator agents, anti-CD20), and JAK inhibitors (e.g., tofacitinib), is prohibited throughout this study (see Section 4.3.2).

SECTION 4.3.1.3: Acid-Reducing Agents

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

SECTION 4.4.1: Informed Consent Forms and Screening Log

Written informed consent for participation in this study must be obtained before performing any study-related procedures. ~~Male patients will be required to sign the "Mandatory Consent for Males Participating in the Study" Informed Consent Form.~~

~~All screening evaluations must be completed and reviewed to confirm that p~~*P*atients *must* meet all eligibility criteria before ~~the~~ *receiving their* first *open-label* dose in this study. 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.

SECTION 4.4.3: Physical Examinations

A complete physical examination should be performed at Day 1 *(which is Day 84 of Study GA29350)* and should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, 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.

SECTION 4.4.5: Efficacy Assessments

The sequence of assessments where efficacy is assessed (see Appendix 1 for Schedule of Assessments) will be standardized as follows:

- Administration of GDC-0853 *in clinic (only at the indicated visits, per* Appendix 1*)*
- ~~Post dose vital signs, post dose PK samples (only at the indicated visits, per Appendix 1), adverse events~~

SECTION 4.4.5.1.1: Swollen and Tender Joint Count (66*/68*)

…A joint assessment training module ~~will~~ *may* be used as a tool to facilitate consistency in performing the joint counts.

SECTION 4.4.5.1.2: Tender/Painful Joint Count (68)

Sixty-eight (68) joints will be assessed by a joint assessor (not blinded), and it is recommended that this assessor be the same as from the blinded Study GA29350 (for consistency), 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/Not Done~~/Not Applicable (to be used for artificial joints)~~.

SECTION 4.4.6: Patient-Reported and Clinician-Reported Outcomes

Patients ~~and clinicians~~ will use an electronic device to capture PRO *data,* and *clinicians will use a paper-based* ClinRO *for* data *collection*….

SECTION 4.4.7: Laboratory, Biomarker, and Other Biological Samples

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

- Quantitative immunoglobulins: *Total Ig,* IgA, IgG, IgM, IgE

Unless the patient gives specific consent for the leftover samples to be stored for optional exploratory research (see Sections 4.4.9 *and 4.4.10*), biological samples will be destroyed when the final clinical study report has been completed, with the following exception:

SECTION 4.4.8: Electrocardiograms

When triplicate ECGs are indicated, three interpretable ECG recordings (e.g., without artifacts) must be obtained. The ~~average of the three readings will be used to determine~~ ECG intervals (e.g., PR, QRS, ~~and~~ QT*, QTc, and RR) and heart rate from these three ECGs (or single ECG, if indicated) will be entered into the eCRF; in addition, these triplicate readings will be stored for future analysis, if needed*.

SECTION 5.1.1: Safety Plan for Potential Risks Associated with GDC-0853

SECTION 5.1.1.1: Infections

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.

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 tuberculosis, and should be evaluated promptly. *Physicians or a health care provider 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 ~~that require treatment~~, 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 as an adverse event of special interest and should be reported to the Sponsor in an expedited manner as outlined in Section 5.2.3.

SECTION 5.1.1.3: Bleeding

~~Bleeding was not~~ *No decrease in platelets, changes in coagulation parameters, or bleeding events were* observed in nonclinical studies with GDC-0853….

SECTION 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 (≥~~37~~*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 GDC-0853 Investigator's Brochure for further details).

~~**SECTION 5.1.1.8: Pancreatic Effects**~~

~~Pancreatic findings have been observed in rats administered GDC-0853 (and other BTK inhibitors) and are considered to be an on-target, species-specific effect on the basis of a number of investigative studies and the lack of associated findings in humans with XLA (see GDC-0853 Investigator's Brochure for details).~~

~~No significant changes in amylase, lipase, and serum glucose have been observed in patients with cancer or after single dose and multi-dose administration in healthy subjects. Patients with a history of non-gall stone pancreatitis will be excluded from study participation and as a precautionary safety monitoring measure, amylase, lipase, and serum glucose will continue to be monitored in patients during the study.~~

~~Guidelines for management of GDC-0853 in the event of pancreatic effects in patients are provided in Table 3. Please refer to the GDC-0853 Investigator's Brochure for further details.~~

SECTION 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.* ~~However, at the terminal necropsy in the ongoing 9-month toxicity study in dogs, no GDC-0853 related vascular inflammation was observed up to the highest dose of 10 mg/kg/day (37 μM•h) (study to be completed~~

~~May 2016; see the GDC 0853 Investigator's Brochure for further details). The risk to human safety based on toxicological findings of vascular inflammation in animal studies is uncertain. 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).

SECTION 5.1.1.9: Malignancy

Discussion of malignancy was moved to later in Section 5.1.1 (previously Section 5.1.1.6). No change has been made to the text of this Malignancy section.

SECTION 5.3.5.6: 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 to be an indicator of severe liver injury (as defined by Hy's law)….

SECTION 5.4.1: Emergency Medical Contacts
Medical Monitor Contact Information

[redacted] Medical Monitor contact information:

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

Alternate Medical Monitor contact information for all sites:

Medical Monitor: [redacted], M.D.

Telephone Nos.: [redacted]

Emergency Telephone Nos. [redacted]

SECTION 7.4: SOURCE DATA DOCUMENTATION

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, patient-reported outcomes, *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.

FIGURE 1: Study Schema

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

TABLE 1: OBJECTIVES AND ENDPOINTS

Secondary Efficacy Objective:

- To assess *ACR/EULAR remission according to the* Boolean-based ~~remission, defined as~~*definition (*tender joint count ≤ 1, swollen joint count ≤ 1, CRP ≤ 1, and patient global assessment ≤ 1*)*
- To assess SDAI-based remission *(defined as ≤3.3 for ACR/EULAR remission)* and CDAI-based remission

Corresponding Endpoint(s) for Exploratory Pharmacokinetic Objectives:

- ~~Presence of genetic polymorphisms and/or genotype(s)~~

TABLE 3: Guidelines for Management of GDC-0853 in Patients Who Experience Specific Adverse Events

Table 3 has been revised to reflect changes in the protocol.

APPENDIX 1: Schedule of Assessments

The schedule of assessments has been revised to reflect the changes to the protocol.

APPENDIX 9: *Joint Count Improvement Formula*

Appendix 9 has been added to the protocol.

APPENDIX 10: *Bottle and Label Configuration for GDC-0853 Administration*

Appendix 10 has been added to the protocol.

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE II OPEN-LABEL EXTENSION STUDY OF PATIENTS PREVIOUSLY ENROLLED IN STUDY GA29350 TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF GDC-0853 IN PATIENTS WITH MODERATE TO SEVERE RHEUMATOID ARTHRITIS**
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EUDRACT NUMBER:	2016-000498-19
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 PHASE II OPEN-LABEL EXTENSION STUDY OF PATIENTS PREVIOUSLY ENROLLED IN STUDY GA29350 TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF GDC-0853 IN PATIENTS WITH MODERATE TO SEVERE RHEUMATOID ARTHRITIS**
PROTOCOL NUMBER:	GA30067
VERSION NUMBER:	2
EUDRACT NUMBER:	2016-000498-19
IND NUMBER:	120,162
TEST PRODUCT:	GDC-0853 (RO7010939)
PHASE:	Phase II
INDICATION:	Rheumatoid Arthritis
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This open-label extension (OLE) study will evaluate the long-term safety and efficacy of GDC-0853 in patients with rheumatoid arthritis (RA). Specific objectives and corresponding endpoints and analyses for the study are outlined below.

Objectives	Corresponding Endpoint(s)
Primary Objective (Safety)	
• To evaluate the long-term safety of GDC-0853 over an extended treatment period of up to 52 weeks	• The nature, frequency, severity, and timing of adverse events • Changes in vital signs, physical findings, ECGs, and clinical laboratory results during and following GDC-0853 administration
Primary Efficacy Objective	
• To evaluate the efficacy of GDC-0853 (analyzed separately for MTX-IR and TNF-IR patients) at Week 52 relative to baseline in Study GA29350	• ACR50 response at Week 52
Secondary Efficacy Objective	
• To determine the improvement in disease activity through 52 weeks of treatment (analyzed separately for MTX-IR and TNF-IR patients) relative to baseline in Study GA29350	• ACR50 response up to Week 12 • ACR20, ACR70, DAS 28-3 (CRP), DAS 28-4 (CRP), DAS 28-3 (ESR), and DAS 28-4 (ESR) response up to Week 52
• To assess DAS28 remission (<2.6) and LDA (<3.2) state	• States up to Week 52

Objectives	Corresponding Endpoint(s)
• 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 status up to Week 52
• To assess SDAI-based remission *(defined as ≤3.3 for ACR/EULAR remission)* and CDAI-based remission	• Remission status up to Week 52
• To assess efficacy based on the individual components of the ACR relative to baseline in Study GA29350	Response status up to Week 52 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 evaluate the effect of GDC-0853 on health-related quality of life	• SF-36, standard, Version 2, questionnaire through 52 weeks
• To evaluate the effect of GDC-0853 on fatigue	• FACIT-Fatigue Scale up to Week 52
Pharmacokinetic Objectives	
• To characterize the pharmacokinetics of GDC-0853 in patients using a population PK approach	• Steady-state PK parameters (AUC_{0-t}, C_{trough}, $t_{1/2}$, apparent CL/F)
Exploratory Pharmacokinetic Objectives:	
• To evaluate the relationship between measures of drug exposure and PD effect(s), efficacy, and safety of GDC-0853	• Exploratory biomarker measures • 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 baseline covariates on measures of GDC-0853 exposure and/or response	• Steady-state PK parameters (AUC_{0-t}, 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_{trough}, $t_{1/2}$, apparent CL/F)

Objectives	Corresponding Endpoint(s)
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 whether 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; AUC_{0-t} = area under the concentration time-curve from time 0 to time t; C_{trough} = minimum observed plasma concentration; C_{max} = maximum 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; EULAR = European League Against Rheumatism; 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; PD = pharmacodynamic; PK = pharmacokinetic; $t_{1/2}$ = half-life; t_{max} = time to maximum concentration; TNF = tumor necrosis factor.

Study Design

Description of Study

This is a Phase II, multicenter, OLE study to evaluate the long-term safety and efficacy of GDC-0853 in patients with RA who have completed 12 weeks of study treatment in Study GA29350. The population for this study consists of patients with RA who have had an inadequate response to previous MTX therapy (Cohort 1 of Study GA29350) or previous TNF and MTX therapy (Cohort 2 of Study GA29350).

This OLE study will be conducted in centers that have participated in the double-blind, Phase II Study GA29350. The maximum number of patients potentially enrolling in this study will be approximately 580 patients. Patients will be assigned the same patient number they had in Study GA29350.

Eligible patients from Study GA29350 who elect to participate will receive treatment with GDC-0853 at 200 mg BID in an open-label fashion for 52 weeks, followed by a safety follow-up period of 8 weeks. Dose reductions of GDC-0853 to 200 mg once daily are allowed for specific safety reasons and may be allowed on the basis of clinical safety concerns of the investigator, only after discussion with the Medical Monitor. Eligible patients will be enrolled directly into Study GA30067 following treatment completion at Week 12 of Study GA29350 (e.g., they will not undergo the 8 weeks of safety follow-up in Study GA29350). The dose and route of administration of methotrexate (MTX) at the end of the blinded Study GA29350 should be continued and held stable for the first 12 weeks of the OLE study. Discontinuation of MTX or alteration of the MTX dose prior to Week 12 is discouraged. Use of additional disease-modifying anti-rheumatic drugs (DMARDs) other than MTX is discouraged prior to Week 12.

At Week 12, if there has not been at least a 20% improvement in the swollen joint count (SJC) and tender joint count (TJC) relative to the patient's baseline joint counts in the blinded Study GA29350, then therapy should be escalated *or substituted* per the investigator's judgment. Such changes may include an increase in the dose of MTX, addition of other DMARDs (e.g., hydroxychloroquine or sulfasalazine), substitution of MTX with leflunomide, and/or an increase in the dose of corticosteroids. The investigator may adjust the therapy (e.g., escalate or reduce) on the basis of his or her overall clinical assessment of the patient. However, certain medications, including but not limited to mycophenolate, biologics, Janus kinase (JAK) inhibitors, and calcineurin inhibitors, are prohibited throughout the OLE Study. Adjustment of MTX, other DMARDs, or corticosteroids for safety reasons is allowed throughout the trial.

At Week 24 in Study GA30067, if there has not been at least a 20% improvement in the SJC and TJC relative to the patient's baseline joint counts in the blinded Study GA29350, the patient should be discontinued from this study due to lack of efficacy of GDC-0853. See the protocol for adverse event reporting in the event of an unanticipated worsening of SJC and TJC.

Patients who are receiving concomitant MTX will also receive a stable dose of folic acid given as either a single dose or divided into daily doses to achieve at least 5 mg of folic acid per week.

Stable oral corticosteroids (i.e., ≤10 mg/day prednisone equivalent) are allowed at entry into the study. Maintaining a stable dose of oral corticosteroids between the time of entry up to Week 12 is encouraged. However, at any time during the study, patients who have worsening RA may receive concomitant therapy with oral or intra-articular corticosteroids at the discretion of the investigator. Starting at Week 12, doses of corticosteroid, MTX, or both may be modified (e.g., increased or tapered) based on the investigator's clinical assessment of the patient. It is strongly encouraged that the corticosteroid dose not exceed 10 mg/day of prednisone or equivalent. Adjustment for safety reasons is allowed throughout the trial.

Since patients enrolling in this study may be receiving GDC-0853 for the first time, all patients will be monitored closely with more frequent visits at the beginning of this OLE study (i.e., *more frequent visits* up to Week 12 and then every 3 months, thereafter). Patients will have safety and clinical efficacy assessments at Weeks 0, 4, 8, 12, 24, 36, and 52.

Following completion of the 52-week treatment period, there will be an 8-week safety follow-up visit.

Throughout this OLE study, patients will be monitored for safety by recording adverse events, ECGs, and clinical laboratory evaluations. Efficacy and safety data will be collected at least every 4 weeks for the first 3 months and then approximately every 12 weeks thereafter until the safety follow-up visit. Safety monitoring will also be performed routinely by the Internal Monitoring Committee.

Number of Subjects

The maximum number of patients potentially enrolling in this study will be approximately 580 patients.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Age 18 to 76 years
- Able and willing to provide written informed consent and to comply with the requirements of the protocol
- Completion of treatment *period through Day 84* as specified in Study GA29350
- Acceptable safety and tolerability during Study GA29350 as determined by the investigator or Medical Monitor
- Have not received any prohibited medications in Study GA29350
- While taking MTX, must be willing to receive oral folic acid (at least 5 mg/week)
- If receiving oral corticosteroids (≤10 mg/day prednisone or equivalent) and/or NSAIDs (up to the maximum recommended dose), doses have remained stable for the duration (i.e., since the first administration of study drug) of Study GA29350. *If a change in dose was needed during Study GA29350, discuss with the Medical Monitor.*
- Women of childbearing potential must test negative for pregnancy prior to enrollment
- 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

  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.

Exclusion Criteria

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

- Met protocol defined treatment stopping criteria during Study GA29350
- Treatment with any investigational agent (i.e., other than study drug) or live/attenuated vaccine during Study GA29350 or since the last administration of study drug in Study GA29350
- Treatment with any of the following prohibited medications during Study GA29350 or since the last administration of study drug in Study GA29350:

  TNF inhibitors (except adalimumab for patients from Cohort 1), anti-IL-6 or anti-IL-6 receptor antagonists, anti-CD20, abatacept, anakinra, all biosimilar agents

  JAK inhibitors

  Azathioprine, chlorambucil, cyclophosphamide, cyclosporine, gold, immunosorbent column, mycophenolate mofetil, mycophenolic acid sodium, penicillamine, sirolimus, tacrolimus

  Oral anticoagulants (including but not limited to warfarin, dabigatran, rivoxaban, apixaban), anti-platelet agents (e.g., clopidogrel; note: non-steroidal anti-inflammatory drugs and aspirin of 162 mg/day or less are acceptable), heparin, low-molecular-weight heparin
- In the opinion of the investigator, any new (since initially enrolling in the Phase II Study GA29350), significant, uncontrolled comorbidity, such as neurological, cardiac (e.g., moderate to severe heart failure New York Heart Association Class III/IV), pulmonary, renal, hepatic, endocrine, or GI disorders (excluding RA) that would increase the risk to the patient in Study GA30067
- Pregnant or lactating or intending to become pregnant during the study
- Any uncontrolled or clinically significant laboratory abnormality that would affect safety, interpretation of study data, or the patient's participation in the study in the opinion of the investigator
- Patients who experienced a de novo or reactivated serious viral infection such as hepatitis B virus, hepatitis C virus, or HIV during the Phase II Study GA29350

- Any major episode of infection requiring hospitalization or treatment with IV antibiotics during the Phase II Study GA29350
- Patients who developed a malignancy (with the exception of non-serious local and resectable basal or squamous cell carcinoma of the skin) during the Phase II Study GA29350
- 12-lead ECG on Day 84 in Study GA29350 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 msec demonstrated by at least two ECGs $>$ 30 minutes apart
- Current treatment with medications that are well known to prolong the QT interval
- Laboratory values from the Day 56 visit of Study GA29350 (which may be repeated once at an unscheduled visit, if necessary) that meet the following criteria:

  Creatinine $> 1.5 \times$ ULN

  ALT or AST $> 1.5 \times$ ULN

  Total bilirubin $>$ ULN

  Hemoglobin < 8.5 g/dL

  ANC $< 1.5 \times 10^9$/L

  Platelet count $< 100 \times 10^9$/L

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur approximately 60 weeks after the last patient is enrolled.

Length of Study

The maximum time in the study for a patient is 60 weeks, including treatment for 52 weeks and an 8-week safety follow-up period after the last dose of GDC-0853.

Investigational Medicinal Product

The investigational medicinal product (IMP) for this study is GDC-0853.

The GDC-0853 dose regimen is oral 200 mg BID. Patients will receive GDC-0853 approximately every 12 hours for 52 weeks. Patients should be directed to take one dose (a total of 4 tablets) BID (total of 8 tablets each day). On clinic visit days during the first 12 weeks of the study, patients should be instructed that the a.m. dose of GDC-0853 will be administered in the clinic*, except for Day 1, since the last dose of GDC-0853 for Study GA29350 is the a.m. dose on Day 84 for all patients. For patients continuing into the OLE Study GA30067, the first open-label dose of GDC-0853 should be the p.m. dose (may be taken at home) on Day 84 (which is Day 1 of Study GA30067).* After Week 12, GDC-0853 administration in the clinic is not required.

Non-Investigational Medicinal Products

From the beginning of the study until Week 12, patients should continue to receive the same dose of MTX that they were receiving at the end of Study GA29350, which should be between 15 and 25 mg/week (doses as low as 7.5 mg/week are allowed only in the case of documented MTX intolerance). Dose reductions for MTX or a change of route of administration are allowed prior to Week 12 only for safety reasons.

After Week 12, patients may change (i.e., increase, decrease, or discontinue) their dose of MTX and/or add other permitted DMARDs as clinically indicated and tolerated by the patient, according to the investigator's judgment.

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

Starting at Week 12, concomitant DMARDs in addition to MTX that may be used during the study include hydroxychloroquine, chloroquine, sulfasalazine, and leflunomide, as clinically indicated and tolerated by the patient, according to the investigator's judgment.

Statistical Methods

Primary Analysis

Patient efficacy data will be summarized separated by treatment cohorts during the blinded study (GA29350). Efficacy summary will be based on the intent-to-treat population, defined as all eligible patients enrolled into this OLE study. Analyses of additional study populations (e.g., completers, and per protocol [excluding major protocol violators]) will be performed as supportive evaluations. Additional subgroup analyses may be conducted on an exploratory basis. Details will be provided in the Data Analysis Plan.

Determination of Sample Size

No formal sample size calculations were performed for this OLE study. The maximum number of patients eligible for enrollment is approximately 580 (i.e., all patients enrolled in Study GA29350).

Interim Analysis

No formal interim analysis is planned. Data cuts may be performed at appropriate time points for inclusion in the submission with the main studies to support the safety profile.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACR	American College of Rheumatology
ALP	alkaline phosphatase
AUC	area under the concentration time-curve
AUC_{0-24}	area under the concentration time-curve from time 0 to 24 hours
AUC_{0-t}	area under the concentration time-curve from time 0 to time t
BCR	B cell–antigen receptor
BID	twice daily
BTK	Bruton's tyrosine kinase
C_{max}	maximum observed plasma concentration
CBC	complete blood count
CDAI	Clinical Disease Activity Index
CIA	collagen-induced arthritis
ClinRO	clinician-reported outcome
CLL	chronic lymphocytic leukemia
CRP	C-reactive protein
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
FACIT	Functional Assessment of Chronic Illness Therapy
FACS	fluorescence activated cell sorting
FDA	U.S. Food and Drug Administration
GI	gastrointestinal
H2RA	H2 receptor antagonist
HAQ-DI	Health Assessment Questionnaire – Disability Index
HIPAA	U.S. Health Insurance Portability and Accountability Act
[redacted]	[redacted]
[redacted]	[redacted]
ICH	International Conference on Harmonisation
IL	Interleukin
IMC	Internal Monitoring Committee

Abbreviation	Definition
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
JAK	Janus kinase
LMWH	low molecular weight heparin
LPLV	last patient, last visit
MAD	multiple-ascending dose
MCP	metacarpophalangeal
MOA	mechanism of action
MTP	metatarsophalangeal
MTX	methotrexate
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no-observed-adverse-effect level
NSAID	non-steroidal anti-inflammatory drug
OLE	open-label extension
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PK	pharmacokinetic
PIP	proximal interphalangeal
PO	orally
PPI	proton pump inhibitor
PRN	as needed
PRO	patient-reported outcome
QD	once daily
QTcF	QT interval corrected using Fridericia's formula
RA	rheumatoid arthritis
RCR	Roche Clinical Repository
SAD	single-ascending dose
SDAI	Simplified Disease Activity Index
SF-36	Short-Form 36 Health Survey
SJC	swollen joint count
TB	tuberculosis
TJC	tender joint count
TLR	toll-like receptor
TNF	tumor necrosis factor

Abbreviation	Definition
ULN	upper limit of normal
VAS	Visual Analog Scale
WGS	whole-genome sequencing
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, 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 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 called 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 (Kaveri et al. 2011), suggesting that BTK can be safely inhibited especially in people with established immune systems.*

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 ≥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 (daily 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 system, and embryo-fetal development (Segment 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). *N*otable findings identified in nonclinical toxicology studies include vascular inflammation (≥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 and ossification site changes in rats (≥190 μM • h) and fetal malformations in rabbits (≥10.6 μM • h) warrant the continued use of highly effective 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, GA30067.

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 or CLL. In this study, 24 patients received study drug at 100, 200, or 400 mg orally (PO) once per day and preliminary analysis shows anti-tumor activity at all dose levels of GD-0853 tested. Nine patients received 400 mg of GDC-0853 PO daily 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 ≥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 to 600 mg) with 53 subjects receiving 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.

Study GP29832 is a Phase Ia, randomized, open-label study investigating the effect of food, rabeprazole, and formulation on the pharmacokinetics of GDC-0853. GDC-0853 was well tolerated when administered to 32 healthy subjects at the 200-mg dose level in Parts 1 and 2 of the study.

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, open-label extension (OLE) Study GA30067 is to evaluate the long-term safety and efficacy of GDC-0853 in combination with methotrexate (MTX) and/or other disease-modifying anti-rheumatic drugs (DMARDs) in patients with active RA. Participation in Study GA30067 is optional and is based on the patient's preference, the investigator's clinical judgment, and meeting the eligibility requirements for this protocol. Eligible patients will have participated in Study GA29350, which comprises of 2 cohorts. In Cohort 1, three doses of GDC-0853 will be compared with placebo and HUMIRA® (adalimumab) in patients with an inadequate response to

MTX). In Cohort 2, one dose of GDC-0853 will be compared with placebo in patients with an inadequate response to TNF inhibitors). Study GA30067 is designed with safeguards in place to optimize clinical efficacy and minimize safety risks. Patients who do not derive clinical benefit from GDC-0853, based on at least a 20% improvement in both SJCs and TJCs, relative to baseline values in the blinded Study GA29350, should not continue in the study past Week 24 of Study GA30067. In addition, safety in both the blinded Study GA29350 and the open-label Study GA30067 will be monitored at regular intervals by the Internal Monitoring Committee (IMC). If there are any concerning safety issues that arise, either as specified in Section 5.1.2 or based on the investigator's judgment and discussion with the Medical Monitor, dose reductions and dose interruptions will be allowed in Study GA30067. The blinded Study GA29350 is designed with an interim analysis at approximately 150 patients (i.e., 30 patients per arm), at which point the IMC will evaluate the unblinded efficacy and safety. If the benefit-risk assessment is not deemed to be favorable, based on safety concerns and/or suboptimal efficacy, then a futility decision will be triggered to minimize patients' exposure to GDC-0853.

Inhibition of BTK offers a promising mechanism for the treatment of autoimmune diseases such as RA and lupus (see 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 μM • h) and 9-month dog (10 mg/kg; 36 μM • 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 μM • h but not in the ongoing 9-month chronic toxicity study at the terminal necropsy (≤37 μM • h).

- *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 μM • h). In dogs, after 4 months of dosing, decreased circulating total lymphocytes were observed at ≥10 mg/kg/day (≥36 μM • 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 μM • h); there were no GDC-0853–related effects on total T, helper T, or cytotoxic T cells. Ig isotyping in high-dose dogs (36 μM • h) and rats (104 μM • h) showed decreased IgG concentration; mid- and high-dose rats (≥17 μM • 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, 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 ≥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 (≤104 μM•h) and dogs (≤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 ≥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) are 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 on the basis 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 *initially* from Study GA29350 if they have a history of hospitalization due to an infection in the

8 weeks before screening *for Study GA29350*, evidence of active or latent or inadequately treated infection with mycobacterium tuberculosis (TB), any known immunodeficiency, including IgG $<$500 mg/dL, or if they have experienced a serious infection or an infection requiring treatment with an IV antimicrobial agent during participation in Study GA29350. *Total Ig, IgG, IgM, IgA, and IgE concentrations will also be measured regularly throughout both studies.* Patients should be carefully monitored throughout both the blinded Study GA29350 and the open-label Study GA30067 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 of patients with XLA. In the GDC-0853 clinical study involving oncology patients, 2 patients experienced Grade $\geq$3 gastrointestinal (GI) bleeding. These events were not dose related and occurred in patients on non-steroidal anti-inflammatory drugs (NSAIDs)/acetylsalicylic acid 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 receiving antiplatelet or anticoagulant therapies. Therefore, the eligibility criteria of the blinded Study GA29350 will 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 to the Sponsor.

Cytopenias

Neutropenia, anemia, and thrombocytopenia have been observed in patients with hematologic malignancies who received GDC-0853. Events have been monitorable and clinically manageable. The eligibility criteria for this study exclude patients with cytopenias (see Section 4.1.2). Cell counts will be monitored regularly throughout this study.

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 daily 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 considered adverse events of special interest with expedited reporting requirements to the Sponsor. The criteria for stopping GDC-0853 in the event of elevated transaminases are presented in Table 3.

Cardiovascular Effects

GDC-0853 is considered to have a low potential to cause QT interval prolongation or to directly affect other cardiovascular parameters at therapeutic exposures. A minimal increase in corrected QT (QTc; 7 msec or 3%) interval was noted at 45 mg/kg in the single-dose, cardiovascular, 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 before screening will be excluded *initially* from participation in Study GA29350 *(and therefore from Study GA30067),* 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 considered 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 *initially* from Study GA29350 *(and therefore from Study GA30067* and complete blood counts (CBCs), creatinine levels, and urinalysis findings will be monitored in all patients during both studies: Studies GA29350 and GA30067. 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 in patients with hematological malignancies. On the basis of the compelling mechanism for BTK inhibition in RA, the risk-benefit ratio for this study is deemed acceptable. The long-term safety profile of GDC-0853 will be further characterized in this open-label 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 OLE study will evaluate the long-term safety and efficacy of GDC-0853 in patients with RA. Specific objectives and corresponding endpoints and analyses for the study are outlined in Table 1.

Table 1 Primary (Safety), Efficacy, Pharmacokinetic, and Exploratory Objectives with Corresponding Endpoints

Objectives	Corresponding Endpoint(s)
Primary Objective (Safety)	
• To evaluate the long-term safety of GDC-0853 over an extended treatment period of up to 52 weeks	• The nature, frequency, severity, and timing of adverse events • Changes in vital signs, physical findings, ECGs, and clinical laboratory results during and following GDC-0853 administration
Primary Efficacy Objective	
• To evaluate the efficacy of GDC-0853 (analyzed separately for MTX-IR and TNF-IR patients) at Week 52 relative to baseline in Study GA29350	• ACR50 response at Week 52
Secondary Efficacy Objective	
• To determine the improvement in disease activity through 52 weeks of treatment (analyzed separately for MTX-IR and TNF-IR patients) relative to baseline in Study GA29350	• ACR50 response up to Week 12 • ACR20, ACR70, DAS 28-3 (CRP), DAS 28-4 (CRP), DAS 28-3 (ESR), and DAS 28-4 (ESR) response up to Week 52
• To assess DAS28 remission (<2.6) and LDA (<3.2) state	• States up to Week 52
• 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 status up to Week 52
• To assess SDAI-based remission *(defined as ≤ 3.3 for ACR/EULAR remission)* and CDAI-based remission	• Remission status up to Week 52
• To assess efficacy based on the individual components of the ACR relative to baseline in Study GA29350	Response status up to Week 52 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

Objectives	Corresponding Endpoint(s)
• To evaluate the effect of GDC-0853 on health-related quality of life	• SF-36, standard, Version 2, questionnaire through 52 weeks
• To evaluate the effect of GDC-0853 on fatigue	• FACIT-Fatigue Scale up to Week 52
Pharmacokinetic Objectives	
• To characterize the pharmacokinetics of GDC-0853 in patients using a population PK approach	• Steady-state PK parameters (AUC_{0-t}, C_{trough}, $t_{1/2}$, apparent CL/F)
Exploratory Pharmacokinetic Objectives:	
• To evaluate the relationship between measures of drug exposure and PD effect(s), efficacy, and safety of GDC-0853	• Exploratory biomarker measures • 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 baseline covariates on measures of GDC-0853 exposure and/or response	• Steady-state PK parameters (AUC_{0-t}, 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_{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 whether 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; AUC_{0-t} = area under the concentration time-curve from time 0 to time t; C_{trough} = minimum observed plasma concentration; C_{max} = maximum 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; EULAR = European League Against Rheumatism; 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; PD = pharmacodynamic; PK = pharmacokinetic; $t_{1/2}$ = half-life; t_{max} = time to maximum concentration; TNF = tumor necrosis factor.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase II, multicenter, OLE study to evaluate the long-term safety and efficacy of GDC-0853 in patients with RA who have completed 12 weeks of study treatment in Study GA29350. The population for this study consists of patients with RA who have had an inadequate response to previous MTX therapy (Cohort 1 of Study GA29350) or previous TNF and MTX therapy (Cohort 2 of Study GA29350).

This OLE study will be conducted in centers that have participated in the double-blind, Phase II Study GA29350. The maximum number of patients potentially enrolling in this study will be approximately 580 patients. Patients will be assigned the same patient number they had in Study GA29350.

Eligible patients from Study GA29350 who elect to participate will receive treatment with GDC-0853 at 200 mg BID in an open-label fashion for 52 weeks, followed by a safety follow-up period of 8 weeks. Dose reductions of GDC-0853 to 200 mg QD are allowed for specific safety reasons (see Section 5.1.2) and may be allowed on the basis of clinical safety concerns of the investigator, only after discussion with the Medical Monitor. Eligible patients will be enrolled directly into Study GA30067 following treatment completion at Week 12 of Study GA29350 (e.g., they will not undergo the 8 weeks of safety follow-up in Study GA29350). The dose and route of administration of MTX at the end of the blinded Study GA29350 should be continued and held stable for the first 12 weeks of the OLE study. Discontinuation of MTX or alteration of the MTX dose prior to Week 12 is discouraged. Use of additional DMARDs other than MTX is discouraged prior to Week 12.

At Week 12, if there has not been at least a 20% improvement in the swollen joint count (SJC) and tender joint count (TJC) relative to the patient's baseline joint counts in the blinded Study GA29350, then therapy should be escalated *or substituted* per the investigator's judgment. Such changes may include an increase in the dose of MTX, addition of other DMARDs (e.g., hydroxychloroquine or sulfasalazine), substitution of MTX with leflunomide, and/or an increase in the dose of corticosteroids (see Section 5.1). The investigator may adjust the therapy (e.g., escalate or reduce) on the basis of his or her overall clinical assessment of the patient. However, certain medications, including but not limited to mycophenolate, biologics, Janus kinase (JAK) inhibitors, and calcineurin inhibitors, are prohibited throughout the OLE Study (see Section 4.3.2). Adjustment of MTX, other DMARDs, or corticosteroids for safety reasons is allowed throughout the trial (see Section 4.3.1.1).

At Week 24 in Study GA30067, if there has not been at least a 20% improvement in the SJC and TJC relative to the patient's baseline joint counts in the blinded Study GA29350, the patient should be discontinued from this study due to lack of efficacy of GDC-0853.

See Section 5.3.5.9 for adverse event reporting in the event of an unanticipated worsening of SJC and TJC.

Patients who are receiving concomitant MTX will also receive a stable dose of folic acid given as either a single dose or divided into daily doses to achieve at least 5 mg of folic acid per week.

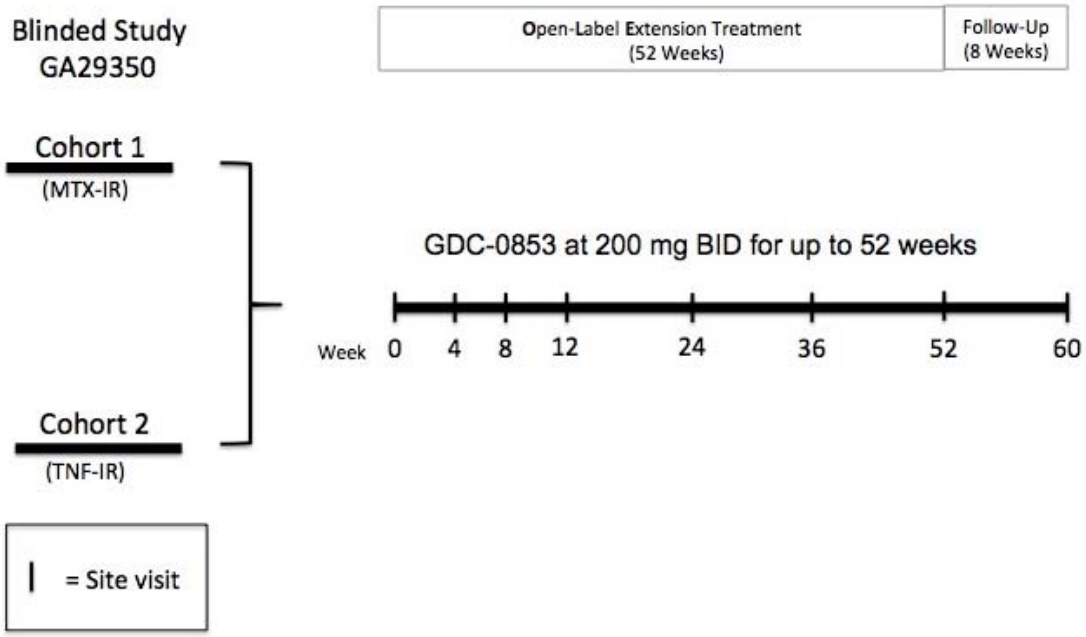
Stable oral corticosteroids (i.e., ≤10 mg/day prednisone equivalent) are allowed at entry into the study. Maintaining a stable dose of oral corticosteroids between the time of entry up to Week 12 is encouraged. However, at any time during the study, patients who have worsening RA may receive concomitant therapy with oral or intra-articular corticosteroids (see Section 4.3.1.1) at the discretion of the investigator. Starting at Week 12, doses of corticosteroid, MTX, or both may be modified (e.g., increased or tapered) based on the investigator's clinical assessment of the patient. It is strongly encouraged that the corticosteroid dose not exceed 10 mg/day of prednisone or equivalent. Adjustment for safety reasons is allowed throughout the trial (see Section 4.3.1.1.4).

Since patients enrolling in this study may be receiving GDC-0853 for the first time, all patients will be monitored closely with more frequent visits at the beginning of this OLE study (i.e., *more frequent visits* up to Week 12 and then every 3 months, thereafter). Patients will have safety and clinical efficacy assessments at Weeks 0, 4, 8, 12, 24, 36, and 52 (see Figure 1).

Following completion of the 52-week treatment period, there will be an 8-week safety follow-up visit.

Throughout this OLE study, patients will be monitored for safety by recording adverse events, ECGs, and clinical laboratory evaluations. Efficacy and safety data will be collected at least every 4 weeks for the first 3 months and then approximately every 12 weeks thereafter until the safety follow-up visit. Safety monitoring will also be performed routinely by the IMC.

Figure 1 Study Schema



BID = twice daily; IR = inadequate response; MTX = methotrexate; OLE = open-label extension; TNF = tumor necrosis factor.

Eligible patients from the blinded study (GA29350) will be enrolled to receive GDC-0853 in this OLE study (GA30067). This study consists of 2 parts: A 52-week open-label treatment period and an 8-week safety follow-up period.

At study visits during the OLE treatment period, the morning dose of oral GDC-0853 will be administered in the clinic on Weeks 0, 4, 8, and 12 after pre-dose study assessments.

3.1.1 Internal Monitoring Committee

Periodic safety reviews for this OLE will *also* be performed by the Sponsor's IMC as outlined in the IMC Charter. *If necessary, cumulative unblinded data for patients remaining in the parent study may also be made available to IMC members.* This committee will be unblinded to treatment assignments from the parent Study GA29350 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 60 weeks, including treatment for 52 weeks and an 8-week safety follow-up period after the last dose of GDC-0853.

3.2.2 End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur approximately 60 weeks after the last patient is enrolled.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for GDC-0853 Dose and Schedule

The GDC-0853 dose of 200 mg BID is the highest dose under evaluation in Study GA29350 and was selected in order to characterize its efficacy, safety, and tolerability profile in a larger patient population and for a longer treatment period. [redacted] This study will be discontinued if Study GA29350 is stopped at the interim analysis.

In the event of a safety issue, dose reduction to 200 mg QD is permitted (see Section 5.1.2). This dose was selected because it is expected to reflect what may be a physician-initiated dose reduction in a real-world clinical setting (i.e., changing the dosing interval from BID to QD). [redacted]

No safety or tolerability issues were identified in healthy subjects receiving GDC-0853 up to 600 mg in the single-dose Study GP29318 (SAD) and up to 250 mg BID and 500 mg QD for 14 days in the multiple-dose study GA29347 (MAD). No maximum tolerated dose was identified, and there were no dose-limiting adverse events; all adverse events were Grade 1 (mild) and transient.

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.

Dose levels in this study are anticipated to result in exposures below 10 μM • h (mean AUC_{0-24}), which is the NOAEL from nonclinical toxicology studies. The NOAEL (10 μM • h) was defined in the 4-week dog study by vasculitis at higher doses (≥ 56 μM • h). In the ongoing 9-month dog study, no vasculitis was observed up to the highest dose tested (37 μM • h); however, 1 of 4 dogs at the highest dose had seminiferous tubule degeneration in the testis; a 4-month recovery phase is in progress. No testicular findings have been observed at lower doses (≤ 10 μM • h). For further details, see the GDC-0853 Investigator's Brochure.

[redacted]

[redacted]

- [redacted]
- [redacted]

3.3.2 Rationale for Open-Label Design

The primary objective of Study GA30067 is to understand the long-term safety of GDC-0853 over an extended treatment period of up to 52 weeks. The open-label study design will allow all eligible patients originating from the blinded Study GA29350 to be treated with GDC-0853.

3.3.3 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.

3.3.4 Rationale for PK Sample Collection Schedule

The PK sampling schedule consists of predose assessments at multiple visits, which will enable the estimation of GDC-0853 exposure as well as an evaluation of intrapatient variability over the 52-week dosing period. In addition, these results will contribute to the understanding of the GDC-0853 exposure-response analysis, which will assist in characterizing how safety and efficacy are impacted by drug exposure.

3.3.5 Rationale for Other Study Design Elements

3.3.5.1 Efficacy Measurements

The American College of Rheumatology (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 Scale [see Appendix 5, Appendix 6, and Appendix 7, 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 this study at regular intervals.

Efficacy based on SJC and TJC will be assessed at Weeks 12 and 24*, and improvement will be calculated using formulas provided in Appendix 9*. If a 20% improvement in SJC and TJC *(relative to baseline values in the blinded Study GA29350)* is not observed by Week 12, concomitant therapy will be escalated (e.g., adjusting the dose of corticosteroids, MTX, or both as well as the possible addition *or substitution* of other DMARDs; see Section 4.3.1.1.3). If a 20% improvement in SJC and TJC *(relative to baseline values in the blinded Study GA29350)* is not observed by Week 24, the patient will be discontinued from this study because of lack of efficacy. Confirmation of efficacy at these prescribed intervals will help to ensure that patients are not kept on an ineffective treatment for a prolonged period of time.

3.3.5.2 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) should be performed after the pain assessment. In cases where this is logistically challenging, potentially painful procedures will be performed at least 15 minutes prior to initiation of the PRO measures.

3.3.5.3 Concomitant Medications

Patients in this study will be able to 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. Stability of MTX and other concomitant medications will be encouraged for the first 12 weeks of this study, in order to assess efficacy at Week 12, which represents a total of 24 weeks of treatment for a proportion of patients coming from the blinded Study GA29350. In addition, there will be more flexibility in the dosing of specified concomitant DMARDs and corticosteroids after Week 12 to optimize patient care, which will also enable a better understanding of the long-term safety and efficacy of GDC-0853 in a real-world context.

4. MATERIALS AND METHODS

4.1 PATIENTS

Up to 580 patients from Study GA29350 will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Age 18 to 76 years
- Able and willing to provide written informed consent and to comply with the requirements of the protocol
- Completion of treatment *period through Day 84* as specified in Study GA29350
- Acceptable safety and tolerability during Study GA29350 as determined by the investigator or Medical Monitor
- Have not received any prohibited medications in Study GA29350
- While taking MTX, must be willing to receive oral folic acid (at least 5 mg/week)
- If receiving oral corticosteroids (≤10 mg/day prednisone or equivalent) and/or NSAIDs (up to the maximum recommended dose), doses have remained stable for the duration (i.e., since the first administration of study drug) of Study GA29350. *If a change in dose was needed during Study GA29350, discuss with the Medical Monitor.*
- Women of childbearing potential must test negative for pregnancy prior to enrollment

- 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 (see Appendix 4)

  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 4)

  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.

4.1.2 Exclusion Criteria

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

- Met protocol-defined treatment-stopping criteria during Study GA29350
- Treatment with any investigational agent (i.e., other than study drug) or live/attenuated vaccine during Study GA29350 or since the last administration of study drug in Study GA29350

- Treatment with any of the following prohibited medications during Study GA29350 or since the last administration of study drug in Study GA29350:

  TNF inhibitors (except adalimumab for patients from Cohort 1), anti-IL-6 or anti-IL-6 receptor antagonists, anti-CD20, abatacept, anakinra, all biosimilar agents

  JAK inhibitors

  Azathioprine, chlorambucil, cyclophosphamide, cyclosporine, gold, immunosorbent column, mycophenolate mofetil, mycophenolic acid sodium, penicillamine, sirolimus, tacrolimus

  Oral anticoagulants (including but not limited to warfarin, dabigatran, rivoxaban, apixaban), anti-platelet agents (e.g., clopidogrel; note: NSAIDs and aspirin of 162 mg/day or less are acceptable), heparin, low-molecular-weight heparin (LMWH)
- In the opinion of the investigator, any new (since initially enrolling in the Phase II Study GA29350), significant, uncontrolled comorbidity, such as neurological, cardiac (e.g., moderate to severe heart failure New York Heart Association Class III/IV), pulmonary, renal, hepatic, endocrine, or GI disorders (excluding RA) that would increase the risk to the patient in Study GA30067
- Pregnant or lactating or intending to become pregnant during the study
- Any uncontrolled or clinically significant laboratory abnormality that would affect safety, interpretation of study data, or the patient's participation in the study in the opinion of the investigator
- Patients who experienced a de novo or reactivated serious viral infection such as hepatitis B virus, hepatitis C virus, or HIV during the Phase II Study GA29350
- Any major episode of infection requiring hospitalization or treatment with IV antibiotics during the Phase II Study GA29350
- Patients who developed a malignancy (with the exception of non-serious local and resectable basal or squamous cell carcinoma of the skin) during the Phase II Study GA29350
- 12-lead ECG on Day 84 in Study GA29350 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 msec demonstrated by at least two ECGs $>$ 30 minutes apart
- Current treatment with medications that are well known to prolong the QT interval
- Laboratory values from the Day 56 visit of Study GA29350 (which may be repeated once at an unscheduled visit, if necessary) that meet the following criteria:

  Creatinine $>$ 1.5 $\times$ ULN

  ALT or AST $>$ 1.5 $\times$ ULN

  Total bilirubin $>$ ULN

Hemoglobin < 8.5 g/dL

ANC $< 1.5 \times 10^9$/L

Platelet count $< 100 \times 10^9$/L

4.2 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is GDC-0853.

4.2.1 Formulation, Packaging, and Handling

GDC-0853 will be provided by the Sponsor as 50-mg dose strength tablets.

Tablets will be supplied in bottles, which will be appropriately labeled for this study. GDC-0853 tablets should be stored *between* 2 ℃ and 8°C.

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

4.2.2 Dosage, Administration, and Compliance

4.2.2.1 *GDC-0853 Dose and Administration*

The GDC-0853 dose regimen is oral 200 mg BID. Patients will receive GDC-0853 approximately every 12 hours for 52 weeks. Patients should be directed to take one dose (a total of 4 tablets) BID (total of 8 tablets each day). On clinic visit days during the first 12 weeks of the study, patients should be instructed that the a.m. dose of GDC-0853 will be administered in the clinic*, except for Day 1, since the last dose of GDC-0853 for Study GA29350 is the a.m. dose on Day 84 for all patients. For patients continuing into the OLE Study GA30067, the first open-label dose of GDC-0853 should be the p.m. dose (may be taken at home) on Day 84 (which is Day 1 of Study GA30067)*. After Week 12, GDC-0853 administration in the clinic is not required.

A dose reduction of GDC-0853 for specific safety events is permitted (see Table 3). For a potential dose reduction for other adverse events not listed in the table, please consult the Medical Monitor. If dose reduction is indicated, the dose of GDC-0853 may be reduced from 200 mg BID to 200 mg QD. In this case, patients should be directed to take one dose (a total of 4 tablets) QD in the morning (total of 4 tablets each day).

Guidelines for dose reduction and treatment interruption or discontinuation are provided in Section 5.1.

GDC-0853 may be orally administered with or without food. The dates and times of the most recent prior meal, last dose of GDC-0853 (prior to clinic visit), and timing of GDC-0853 administration in clinic should be recorded at each clinic visit. In addition, any use of PPIs, H2-receptor antagonists (H2RAs), and/or *other* antacids *(e.g., Maalox®, Pepto-Bismol®, Rolaids®)* should be recorded as concomitant medications, including time and date of last administration. Administration of GDC-0853 should be staggered with antacid use (i.e., GDC-0853 should be taken 2 hours before or 2 hours after the antacid).

At study visits, sufficient GDC-0853 tablets will be dispensed to complete dosing until the next scheduled visit. When GDC-0853 is administered at the site, it will be administered under supervision of study personnel, and the amount of GDC-0853 dispensed must be recorded.

4.2.2.2 *GDC-0853 Compliance*

The following measure will be taken to assess patient compliance with study drug: patients will be directed to bring any used and unused bottles to each visit.

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 10 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 electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If compliance is ≤80%, the investigator or designee is to counsel the patient and ensure steps are taken to improve compliance.

4.2.3 Investigational Medicinal Product Accountability

The IMP required for completion of this study (GDC-0853 tablet) will be provided by the Sponsor. The study site will acknowledge receipt of the IMP using the Interactive Voice/Web Response System (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

The IMP 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.

4.2.4 Post-Trial Access to GDC-0853

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 Study GA30067. The Sponsor may evaluate whether to continue

providing GDC-0853 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

4.3 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 the start of the OLE Study GA30067 (Day 1) until the study completion visit. 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. All concomitant medication taken during the study must be recorded with indication, daily dose, and start and stop dates of administration must be recorded on the appropriate pages of 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.

If possible, it is recommended that patients avoid changing other prescription or non-prescription drugs, vitamins, and dietary supplements during the study.

4.3.1 Permitted Therapy

4.3.1.1 Use of Treatments for Rheumatoid Arthritis

The investigator must use the procedures outlined below in making modifications to these medications and document all changes in the eCRF. If necessary, unscheduled safety laboratory samples may be collected at the discretion of the investigator to monitor for toxicity from concomitant medications (e.g., DMARDs, NSAIDs, steroids).

4.3.1.1.1 Methotrexate

From the beginning of the study until Week 12, patients should continue to receive the same dose of MTX that they were receiving at the end of Study GA29350, which should be between 15 and 25 mg/week (doses as low as 7.5 mg/week are allowed only in the case of documented MTX intolerance). Dose reductions for MTX or a change of route of administration are allowed prior to Week 12 only for safety reasons. If dose reduction of MTX is a result of intolerance, such intolerance must be recorded as an adverse event and the dose modification must be recorded in the eCRF.

After Week 12, patients may change (i.e., increase, decrease, or discontinue) their dose of MTX and/or add other permitted DMARDs as clinically indicated and tolerated by the patient, according to the investigator's judgment (see Section 4.3.1.1.3).

4.3.1.1.2 Folic Acid

To prevent adverse events associated with MTX, patients are required to take folic acid or equivalent (e.g., 1 mg/day) at a stable dose of at least 5 mg/week (or equivalent)

while they are receiving MTX. This can be administered as either a single weekly dose or a daily dose per the discretion of the investigator.

4.3.1.1.3 Other DMARDs

At Week 12, if there has not been at least a 20% improvement in the SJC and TJC relative to the patient's baseline joint counts in the blinded Study GA29350, then therapy should be escalated per the investigator's judgment.

Starting at Week 12, concomitant DMARDs in addition to MTX that may be used during the study include hydroxychloroquine, chloroquine, sulfasalazine, and leflunomide, as clinically indicated and tolerated by the patient, according to the investigator's judgment. Allowable DMARDs can be used alone or in combination, except for the combination of MTX and leflunomide, which is not allowed. Dose reductions or discontinuations of DMARDs may be performed at any time for safety or for clinical improvement, per the investigator's judgment. If a dose reduction is a result of intolerance, such intolerance must be recorded as an adverse event and the dose modification must be recorded in the eCRF.

Treatment with certain medications, including but not limited to mycophenolate, calcineurin inhibitors, biologic agents (e.g., anti-TNF, anti-IL-6 or anti-IL6 receptor, anti-IL-1, T-cell costimulation modulator agents, anti-CD20), and JAK inhibitors (e.g., tofacitinib), is prohibited throughout this study (see Section 4.3.2).

4.3.1.1.4 Corticosteroids

Oral corticosteroids (≤10 mg/day) will be permitted during this study. If a patient was receiving background oral corticosteroids in Study GA29350, he or she should continue this same dose (≤10 mg/day prednisone or equivalent), which should remain stable for the first 12 weeks of the study. Starting at Week 12, corticosteroid doses may be modified (e.g., increased, tapered) on the basis of the investigator's clinical assessment of the patient. It is strongly encouraged that the dose not exceed 10 mg/day of prednisone or equivalent. Adjustment for safety reasons is allowed throughout the trial (see Section 4.3).

The use of IV or intramuscular corticosteroids is not permitted in this study.

Starting at Week 12 of this study, up to 3 intra-articular corticosteroid injections are permitted. No single injection should exceed 40 mg of triamcinolone or equivalent, and the total annual dose of intra-articular corticosteroid should not exceed 80 mg of triamcinolone or equivalent.

4.3.1.1.5 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). Dose adjustments, including discontinuation, are permitted throughout the study. Dose adjustments may be made for

safety reasons at any time and if 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, on the basis of 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 cardiovascular 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).

4.3.1.1.6 Analgesics (Other than NSAIDs)

Analgesics (e.g. acetaminophen, opioids) up to the 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/day, and the total daily dose of opioid must not exceed the potency equivalent of 30 mg of orally administered morphine (see Appendix 2).

4.3.1.2 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 (such as hypervitaminosis). Herbals with pharmaceutical properties are allowed only if there is acceptable evidence of no CYP3A inhibition or induction (refer to Appendix 3 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 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.

4.3.1.3 Acid-Reducing Agents

Patients who use antacids (e.g., Maalox®, Pepto-Bismol®, Rolaids®) for symptomatic relief of heartburn should take GDC-0853 at least 2 hours before or 2 hours after antacid administration because GDC-0853 requires an acidic gastric environment in order to be absorbed.

Patients may be treated with PPIs or H2RAs, but should remain on a stable regimen throughout the study.

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

4.3.2 Prohibited Therapy

A listing of concomitant medications that is prohibited or should be used with caution because of potential drug-drug interactions is provided in Appendix 3.

Intravenous, intra-articular, or intramuscular corticosteroids; biologic response modifiers; tofacitinib or other JAK inhibitors; and medications listed below are not allowed during this study and any use will require discontinuation of GDC-0853.

Use of the following therapies is prohibited during the study, unless otherwise specified below:

- Investigational therapy other than study drug
- Abatacept
- Adalimumab
- Anakinra
- Anti-TNF inhibitors (infliximab, etanercept, golimumab, certolizumab, or biosimilar equivalents)
- Chlorambucil
- Cyclophosphamide
- Cyclosporine
- Immunosorbent column
- Intravenous or intramuscular steroids
- Mycophenolate mofetil
- Mycophenolic acid sodium
- Oral anticoagulants, including but not limited to warfarin, dabigatran, rivaroxaban, apixaban
- Anti-platelet agents, e.g. clopidogrel (Note: NSAIDs and low-dose aspirin are acceptable.)
- Heparin, LMWH
- Penicillamine
- Rituximab (or biosimilar equivalent)
- Sirolimus
- Tacrolimus

- Tocilizumab and other anti-IL6R or anti-IL6 agents
- Tofacitinib and other JAK inhibitors
- All biosimilar agents

4.3.2.1 Live or Attenuated Vaccinations

Immunization with a live or attenuated vaccine is prohibited for the duration of study participation, including the 8-week follow-up period after the administration of the last dose. See Section 5.1.1.1 for further details and precautions around vaccinations.

4.3.2.2 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 below and 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 3 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 4); 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 3) 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 3) 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 3 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

4.3.3 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 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of assessments to be performed during this study.

The following results, collected at the final Day 84 study visit in the blinded Study GA29350, will be used as baseline assessments in Study GA30067:

- Pregnancy test, ECGs, vital signs, physical examination
- Joint counts, Patient Global Assessment of Disease Activity, Patient Assessment of Arthritis Pain, Physician's Global Assessment of Arthritis
- HAQ-DI, FACIT-Fatigue Scale, SF-36v2

- Laboratory tests
- Concomitant medications
- PK/PD assessments

4.4.1 Informed Consent Forms and Screening Log

Patients will be screened on Day 84 of the blinded Study GA29350 to confirm that they meet the entrance criteria for this 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 this 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.

*P*atients *must* meet all eligibility criteria before *receiving their* first *open-label* dose in this study. 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.

4.4.2 Medical History and Demographic Data

Any adverse events that commenced during and are still ongoing at the end of the blinded Study GA29350 will be recorded as "unresolved" and reopened in Study GA30067 with the start date, adverse event term, and initial intensity of the adverse event being identical to those in the Study GA29350. Adverse events that occurred during the core study and resolved before the patient's enrollment into Study GA30067 will be reported in the patient's medical history according to their medical relevance.

4.4.3 Physical Examinations

A complete physical examination should be performed at Day 1 *(which is Day 84 of Study GA29350)* and should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, 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.

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

4.4.4 Vital Signs

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

4.4.5 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, potentially painful procedures will be performed no less than 15 minutes prior to initiation of the PRO measures.

The sequence of assessments where efficacy is assessed (see Appendix 1 for Schedule of Assessments) will be standardized as follows:

- Patient-Reported Outcome Measures:

  Patient's Assessment of Arthritis Pain (see Section 4.4.6.1)

  Patient's Global Assessment of Arthritis (see Section 4.4.6.2)

  HAQ-DI (see Appendix 5)

  SF-36v2 (see Appendix 6)

  FACIT-Fatigue Scale (see Appendix 7)
- Laboratory samples for safety, efficacy, biomarkers, and pharmacokinetics should be drawn after patient self-assessments are completed
- Investigators

  Joint counts

  Physician's Global Assessment of Arthritis Visual Analog Scale (VAS), safety assessments (adverse events, vital signs, concomitant medications, review of laboratory data)
- Administration of GDC-0853 *in clinic (only at the indicated visits, per* Appendix 1*)*

4.4.5.1 ACR Assessments

The ACR's definition for calculating improvement in RA (ACR20) is calculated as a 20% improvement in TJCs and SJCs 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 4.4.5.1.1)
- Swollen Joint Count (66) (see Section 4.4.5.1.2)
- Patient's Assessment of Arthritis Pain (see Section 4.4.6.1)
- Patient's Global Assessment of Arthritis (see Section 4.4.6.2)
- Physician's Global Assessment of Arthritis (see Section 4.4.6.3)

- C-reactive protein (CRP) (see Section 4.4.7)
- HAQ-DI (see Appendix 5)

These clinical assessments will be performed according to the Schedule of Assessments (see Appendix 1) and are detailed in Sections 4.4.5.1.1–4.4.5.1.3.

4.4.5.1.1 Swollen and Tender Joint Count (66/*68*)

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 that 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.
- **Intraarticular injection:** Any joint that has received a steroid intra-articular injection should be documented as "not done" for the following 12 weeks. After this time, the joint may be assessed again.
- **Arthrocentesis:** Any joint that has 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.

4.4.5.1.2 Tender/Painful Joint Count (68)

Sixty-eight (68) joints will be assessed by a joint assessor (not blinded), and it is recommended that this assessor be the same as from the blinded Study GA29350 (for consistency), 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/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 (MCP I, II, III, IV, V), thumb interphalangeal, proximal interphalangeals (PIP II, III, IV, V), distal interphalangeals (DIP II, III, IV, V);
- **Lower extremity:** Hip, knee, ankle, tarsus (includes subtalar, transverse tarsal and tarsometatarsal considered as one unit), metatarsophalangeals (MTP I, II, III, IV, V),

great toe interphalangeal, proximal and distal interphalangeals combined (PIP II, III, IV, V)

4.4.5.1.3 Swollen Joint Count (66)

The joint assessor will also assess joints for swelling using the following scale: Present, Absent, Not Done, or Not Applicable (to be used for artificial joints).

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.

4.4.5.2 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) and the DAS 28-4 (ESR) are presented in Appendix 8.

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

- Tender/Painful Joint Count (28) (see Section 4.4.5.2.1)
- Swollen Joint Count (28) (see Section 4.4.5.2.2)
- CRP or ESR (see Section 4.4.7)
- Patient's Global Assessment of Arthritis (included in the DAS 28-4 only) (see Section 4.4.6.2)

4.4.5.2.1 Tender/Painful Joint Count (28)

Twenty-eight tender/painful joint count includes the following joints: shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and knees. This count will be calculated by the Sponsor from the 68 tender/painful joint count assessed by the joint assessor as described in Section 4.4.5.1.

4.4.5.2.2 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 joint assessor as described in Section 4.4.5.1.

4.4.6 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 5, Appendix 6, and Appendix 7, 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.

4.4.6.1 Patient's Assessment of Arthritis Pain

Patients will assess the severity of their arthritis pain using a 100 mm VAS placing a mark on the scale between 0 (No Pain) and 100 (Most Severe Pain), which corresponds to the magnitude of their RA pain, as follows:

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

No_____Most Severe Pain **Pain**

4.4.6.2 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 (0 = Very well and 100 = Very poorly), as follows:

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

Very well_____Very poorly

4.4.6.3 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, 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 (0 = Very good and 100 = Very poor), as follows:

The patient's rheumatoid arthritis at this time is:

Very good_____Very poor

4.4.6.4 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) on a scale of 0 "without any difficulty" to 3 "unable to do." 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). A lower HAQ-DI score indicates better quality of life. See Appendix 5 for a review copy of the HAQ-DI questions.

4.4.6.5 Short-Form 36 Health Survey Questionnaire, Version 2

The SF-36v2 will be used to assess health-related quality of life (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 quality of life and for economic modeling. See Appendix 6 for a sample version of the SF-36v2 questionnaire.

4.4.6.6 Functional Assessment of Chronic Illness Therapy-Fatigue Scale

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 7 for a list of questions in the FACIT-Fatigue Scale.

4.4.7 Laboratory, Biomarker, and Other Biological Samples

Laboratory assessments will be performed as indicated on the Schedule of Assessments (see Appendix 1). 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 study drug administration, laboratory samples should be drawn before the administration of study drug and after the administration of patient reported PRO assessments (e.g., pain questionnaires).

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 urine pregnancy test at entry into the OLE and at monthly intervals (see Appendix 1). If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test. Should a positive pregnancy result be recorded at any time, the procedures detailed in Section 5.4.3 should be followed.

- ESR: Can be performed at local laboratory or as point-of-care test in the clinic

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, ALP, ALT, AST, uric acid, LDH, amylase, and lipase
- CRP: CRP performed at the central lab
- Urinalysis including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- Coagulation: INR, activated partial thromboplastin time (aPTT), PT
- Lipids (fasting not required): Cholesterol, LDL cholesterol, HDL cholesterol
- Quantitative immunoglobulins: *Total Ig,* IgA, IgG, IgM, IgE
- T, B, and natural killer cells
- Rheumatoid factor
- Anti-cyclic-citrullinated peptide antibody or anti-citrullinated protein/peptide antibody

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

- Serum, plasma, cells, and RNA from blood for exploratory PD markers (lymphoid, myeloid and other inflammatory markers as well as other markers potentially related to disease, drug, or clinical response; see Table 2).
- 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 2. 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 2 Proposed Biomarkers for Exploratory Research

Sample Type	Proposed Biomarkers
Whole blood for FACS	Cells and markers including but not limited to monocytes, B cells, and B cell subsets
Plasma	Markers including but not limited to CCL3, CCL4
Serum	Markers including but not limited to sICAM1, CXCL13, CCL20
Blood for PBMC cell lysate	Markers including but not limited to phosphorylated and total BTK protein
RNA extracted from blood	Markers including but not limited to myeloid RNA markers

BTK = Bruton's tyrosine kinase; FACS = flow cytometry; PBMC = peripheral blood mononuclear cell.

Note: Biomarkers will be assessed 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 4.4.9 *and 4.4.10*), 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.

4.4.8 Electrocardiograms

Triplicate ECG recordings will be obtained at specified timepoints up to Week 12, as outlined in the schedule of assessments. After Week 12, single ECGs will be obtained (see Appendix 1).

When triplicate ECGs are indicated, three interpretable ECG recordings (e.g., without artifacts) must be obtained. The ECG intervals (e.g., PR, QRS, QT*, QTc, and RR) and heart rate from these three ECGs (or single ECG, if indicated) 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 are to 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. 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 a 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 msec and/or 60 msec longer than the baseline value, another triplicate ECG must be recorded, ideally within the next 5 minutes, and triplicate ECG monitoring should continue at least hourly 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 5.1. 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).

4.4.9 Optional Samples for Whole-Genome Sequencing

An optional whole 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/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 4.4.9) 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 are to 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).

4.4.10 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/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.

4.4.10.1 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.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. 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

4.4.10.2 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 blood 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).

4.4.10.3 Confidentiality

4.4.10.3.1 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.

4.4.10.3.2 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.

4.4.10.4 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.

4.4.10.5 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 GA30067 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 GA30067.

4.4.10.6 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.

4.4.11 Assessments at Unscheduled Visits

An unscheduled visit may occur at any time during the study (i.e., due to flare of disease activity or due to an adverse event). Patients who are seen by the investigator or site staff at a timepoint not required by the protocol may undergo any of the assessments indicated (see Appendix 1), based on the reason for the unscheduled visit. These assessments may include collection of PK and PD, to assess drug exposure and/or PD measures of drug activity.

4.5 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.5.1 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 Week 52 treatment completion visit, an early termination visit should be conducted. These patients should return for the 8-week safety follow-up visit in this study (see Appendix 1).

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).

4.5.2 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Pregnancy
- Anaphylaxis or other severe hypersensitivity reaction

- Malignancy (with the exception of non-serious local and resectable basal or squamous cell carcinoma of the skin)
- Any serious infection or infection requiring treatment with an IV antimicrobial agent
- Any prohibited medication as defined in Section 4.3
- Any Grade 3 or greater thrombocytopenia (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE v4.0])
- Any Grade 4 neutropenia (NCI CTCAE v4.0)
- Failure to achieve a 20% improvement in both SJC and TJC (relative to baseline values in Study GA29350) at Week 24

Patients who discontinue study treatment prematurely for the reasons listed above will be asked to return to the clinic for an early termination visit (see Section 4.5.1) 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.

4.5.3 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

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 the patients participating in this study. Eligibility criteria in both the controlled and open-label studies have been designed to exclude patients at a 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, dose reduction, and enhanced safety reporting are provided below.

Dose reduction from 200 mg BID to 200 mg QD for safety events is permitted for specific events as detailed in Table 3 of Section 5.1.2. For adverse events not listed in the table where the investigator thinks a dose reduction may be indicated, please consult with the Medical Monitor.

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.

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 tuberculosis, and should be evaluated promptly. *Physicians or a health care provider 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 as 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 GDC-0853 in the event that infections are observed in patients are provided in Table 3.

Please also 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 2016) or European League Against Rheumatism (EULAR; van Assen 2010) recommendations or local guidelines be up to date before entry into the blinded study. Immunization with a live or attenuated vaccine is prohibited for the duration of study participation, including the 8-week follow-up period after the administration of the last dose of GDC-0853.

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 CTCAE Grade 1 bruising and serious Grade ≥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 in 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 anti-platelet or anti-coagulant therapies. 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 PPIs should be considered (Scheiman 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 ≥60years

  High-dose NSAID use

  Concurrent corticosteroid use

  Dyspepsia or gastroesophageal reflux disease symptoms

Any bleeding event Grade 2 or above 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 GDC-0853 in the event that bleeding is observed in patients are provided in Table 3. 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 GDC-0853 in the event of cytopenias in patients are provided in Table 3. 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 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 effects.

Guidelines for management GDC-0853 in the event of GI side effects in patients are provided in Table 3. 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 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 daily dosing for over 1 year in patients with hematological malignancies, there have been no adverse events of liver enzyme elevations nor 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 Day 56 or Day 84 of Study GA29350 prior to entering Study GA30067 (see Section 4.1.2 for details). 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 AST or ALT elevations of Grade ≥3 (i.e., >5× ULN) are considered 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 GDC-0853 in the event of hepatotoxicity in patients are provided in Table 3. 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 cardiovascular parameters, at therapeutic exposures. A minimal increase in corrected QT (QTc; 7 msec or 3%) interval was noted at 45 mg/kg in the single-dose, cardiovascular, 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-observable-effect level of 15 mg/kg [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 for cardiac interval analysis as outlined in the schedule of assessments, routine safety ECGs, and collection of adverse events (see Appendix 1).

Management of patients with sustained QTcF prolongation (QTcF that is >500 msec and/or >60 msec 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 (see Section 4.4.8).

Guidelines for management of GDC-0853 in the event of cardiovascular effects in patients are provided in Table 3. 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 GDC-0853 in the event of vasculitis in patients are provided in Table 3. 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 blinded Study GA29350. 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 in the blinded study are not exclusionary.

All malignancies are considered 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 GDC-0853 in the event of malignancies in patients are provided in Table 3. Please refer to the GDC-0853 Investigator's Brochure for further details.

5.1.2 Management of GDC-0853 in Patients Who Experience Specific Adverse Events

Guidelines for management of GDC-0853 in patients who experience specific adverse events are provided in Table 3. For a potential dose reduction for other adverse events not listed in the table, please consult the Medical Monitor.

Table 3 Guidelines for Management of GDC-0853 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 GDC-0853 and report event as adverse event of special interest.
Self-limited non-serious infections that require treatment	Withhold GDC-0853 during antimicrobial therapy. GDC-0853 may be resumed 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 or above) bleeding events, withhold GDC-0853 and consult with the Medical Monitor.
Neutropenia [c]	
Grade 2: ANC >1000-1500/mm^3	Maintain GDC-0853 dosing.
Grade 3: ANC 500–1000/mm^3	**For the first occurrence** of a Grade 3 neutrophil count decreased, withhold GDC-0853 and recheck the CBC in 7 days. If the neutrophil count has recovered to Grade 1 ($>1500/mm^3$) or normal range, resume dosing at 200 mg BID. If the Grade 3 neutropenia persists, discontinue GDC-0853. **Second occurrence** of Grade 3 neutrophil count decreased: Withhold GDC-0853, recheck CBC in 7 days. If the neutrophil count has recovered to Grade 1 ($>1500/mm^3$) or normal range, restart GDC-0853 at the lower dose of 200 mg QD. If the Grade 3 neutrophil count decreased persists, discontinue GDC-0853. **Third occurrence** of Grade 3 neutrophil count decreased: Discontinue GDC-0853.
Grade 4: ANC $<500/mm^3$	For Grade 4 neutrophil count decreased: discontinue GDC-0853.
Thrombocytopenia [d]	
Grade 1: PLT $>75{,}000/mm^3$	In the absence of bleeding event(s), maintain GDC-0853 dosing.
Grade 2: PLT 50,000–75,000/mm^3	**First occurrence** of Grade 2 platelet count decreased: withhold GDC-0853, recheck CBC in 7 days. If platelet count has recovered to Grade 1 or has returned to the normal range, and in the absence of bleeding resume dosing at 200 mg BID. **Second occurrence** of Grade 2 platelet count decreased: withhold GDC-0853, recheck CBC in 7 days. If platelet count has recovered to Grade 1 or has returned to the normal range and in the absence of bleeding restart GDC-0853 at the lower dose of 200mg QD. **Third occurrence** of Grade 2 platelet count decreased: Discontinue GDC-0853.

Table 3 Guidelines for Management of GDC-0853 in Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken [a]
Grade ≥ 3: PLT $< 50{,}000/mm^3$	For Grade 3 or greater platelet count decreased: discontinue GDC-0853.
Gastrointestinal effects	
Nausea, vomiting, and/or diarrhea	Manage according to site institutional guidelines. Consider administration of GDC-0853 with food as possible mitigation strategy. Consider reducing GDC-0853 dose to 200 mg QD and discuss with Medical Monitor.
Malignancy	
Any malignancy (with the exception of non-serious local and resectable basal or squamous cell carcinoma of the skin).	Discontinue GDC-0853. Report event as an adverse event of special interest to the Sponsor in an expedited manner.
Hepatotoxicity	
Any AST or ALT $> 3.0\text{-}5.0 \times$ ULN	Withhold GDC-0853 and consult with the Medical Monitor.
AST or ALT elevation $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN, *of which at least 35% is direct bilirubin,* or clinical jaundice	Discontinue GDC-0853. Report event as adverse event of special interest to the Sponsor in an expedited manner.
Any AST or ALT $> 5 \times$ ULN	Discontinue GDC-0853. Elevations of AST or ALT of $> 5 \times$ ULN should be reported as adverse event*(s)* 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 msec and/or > 60 msec longer than the baseline value	Unless there is a clear alternative cause other than study drug, discontinue GDC-0853 [e]

Table 3 Guidelines for Management of GDC-0853 in Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken [a]
Sustained absolute QTcF that is $>$515 msec	Unless there is a clear alternative cause other than study drug, discontinue GDC-0853 [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 GDC-0853 [e]
Vascular Inflammation	
Vasculitis	Consult with the Medical Monitor
Hypersensitivity reactions	
Fever, chills, pruritis, urticaria, angioedema, and skin rash	Treat patient according to the standard of care for management of anaphylaxis/anaphylactoid or a hypersensitivity reaction.
Cardiopulmonary reactions, including chest pain, dyspnea, hypotension, or hypertension	Discontinue GDC-0853.
Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)	

CBC = complete blood count; IV = intravenous; MTX = methotrexate; PLT = platelet count; ULN = upper limit of normal.

[a] Any patient who discontinues GDC-0853 should enter safety follow-up if possible.

[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 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 GDC-0853, provided that any ECG abnormalities have resolved and that the patient is appropriately monitored. Clinical judgment should be applied and discussion with the Medical Monitor should occur.

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 5.3.5.10
- 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 an AST or ALT elevation of Grade ≥ 3 (i.e., AST or ALT $> 5 \times$ ULN)

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 5.3.5.6)
- 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.

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 collections, 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. 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 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4 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 the 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 5):

- 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 5 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 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.

5.3.5.2 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.

5.3.5.3 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.

5.3.5.4 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).

5.3.5.5 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).

5.3.5.6 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 to be an indicator of severe liver injury (as defined by Hy's law)…. Therefore, in addition to the protocol defined adverse events of special interest for GDC-0853 of elevations of AST or ALT of Grade ≥ 3 ($>5\times$ULN), investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN (i.e., Grade ≥ 2) in combination with total bilirubin $>2\times$ULN (of which 35% is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ULN (i.e., Grade ≥ 2) 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 5.3.5.2) 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).

5.3.5.7 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. 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.

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

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening for Study GA29350. 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").

5.3.5.9 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").

5.3.5.10 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.

The following hospitalization scenarios are not considered to be adverse events:

- 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

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

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

5.3.5.11 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.

5.3.5.12 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.*
Argentina: [redacted]
Rest of World: [redacted]
United States: [redacted]

Alternate Medical Monitor contact information for all sites:

Medical Monitor: [redacted], M.D.

Telephone Nos.: [redacted]

Emergency Telephone Nos. [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 patient receives either in Study GA29350 or in this study. 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 in this study. 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).

5.5 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 in this study) 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

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

Because of the non-comparative nature of the study, no statistical tests are planned. All efficacy parameters will be summarized descriptively. Demographic and baseline characteristics will be summarized descriptively.

6.1 DETERMINATION OF SAMPLE SIZE

No formal sample size calculations were performed for this OLE study. The maximum number of patients eligible for enrollment is approximately 580 (i.e., all patients enrolled in Study GA29350).

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

Demographic and baseline characteristics such as age, sex, weight, and disease activity will be summarized using means or medians for continuous variables and proportions for categorical variables. Medical history including diagnoses and treatment will be tabulated.

6.4 SAFETY ANALYSES

The safety analyses will include all patients who received at least one dose of study drug, during this OLE study. Safety will be analyzed on the basis of reported/documented adverse events, laboratory results, and vital signs, including adverse events of special interest, separated by treatment cohorts during the blinded study (GA29350).

6.5 EFFICACY ANALYSES

Patient efficacy data will be summarized separated by treatment cohorts during the blinded study (GA29350). Efficacy summary will be based on the intent-to-treat population, defined as all eligible patients enrolled into this OLE study. Analyses of additional study populations (e.g., completers, and per protocol [excluding major protocol violators]) will be performed as supportive evaluations. Additional subgroup analyses may be conducted on an exploratory basis. Details will be provided in the Data Analysis Plan.

6.6 PHARMACOKINETIC ANALYSES

Systemic GDC-0853 exposures will be evaluated using a population PK approach, and estimates of PK parameters (including total exposure [AUC] and clearance following oral dosing) will be generated and summarized by PK parameter (mean, SD, coefficient of variation, median, minimum, and maximum). The extent of interpatient variability will be evaluated, and potential sources of variability will be assessed. Relationships between exposures, biomarkers, and efficacy endpoints will be characterized.

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

No formal interim analysis is planned. Data cuts may be performed at appropriate time points for inclusion in the submission with the main studies to support the safety profile.

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, using 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

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, patient-reported outcomes, *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 Child's Informed Assent Form or 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., LPLV).

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. 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 healthcare professionals 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).

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Appendix 1
Schedule of Assessments

	Treatment Visits														SC/ SFU [d] (±7)	ET	UV [e]
Week	0 [a]	4	8	12	16 [b]	20 [b]	24	28 [b]	32 [b]	36	40 [b]	44 [b]	48 [b]	52			
Day (±days)	1 [c]	28 (±4)	56 (±4)	84 (±4)	112 (±3)	140 (±3)	168 (±7)	196 (±7)	224 (±7)	252 (±7)	280 (±7)	308 (±7)	336 (±7)	365 (±7)			
Informed consent [f]	x																
General medical history and baseline conditions	x																
Inclusion/exclusion criteria	x																
Concomitant medications	x [g]	x	x	x			x			x				x	x	x	x
Adverse events	x [g]	x	x	x			x			x				x	x	x	x
Vital signs [h]	x [g]	x	x	x			x			x				x	x	x	x
Weight	x [g]														x	x	
Complete physical examination [i]	x [g]																
Limited physical examination [j]		x	x	x			x			x				x	x	x	x
ECG [k]	x [g]	x	x	x			x			x				x	x	x	x
GDC-0853 administration in clinic [l]	x [m]	x	x	x													
Hematology [n]	x [g]	x	x	x			x			x				x	x		x
Chemistry [o]	x [g]	x	x	x			x			x				x	x		x
Coagulation studies PT/PTT																	x
Pregnancy test (urine) women [p]	x [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Drug dispensing	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*				
Urinalysis [q]	x [g]	x	x	x			x			x				x	x	x	x
Quantitative Ig [r]	x [g]			x			x			x				x			x
Lipid panel [s]				x											x	x	
Rheumatoid Factor/anti-CCP				x											x		

Appendix 1
Schedule of Assessments (cont.)

	Treatment Visits														SC/ SFU [d]	ET	UV [e]
Week	0 [a]	4	8	12	16 [b]	20 [b]	24	28 [b]	32 [b]	36	40 [b]	44 [b]	48 [b]	52			
Day (±days)	1 [c]	28 (±4)	56 (±4)	84 (±4)	112 (±3)	140 (±3)	168 (±7)	196 (±7)	224 (±7)	252 (±7)	280 (±7)	308 (±7)	336 (±7)	365 (±7)	*(±7)*		
TBNK	x [g]			x			x							x	x	x	x
ACR/DAS:																	
CRP	x [g]	x	x	x			x			x				x	x	x	x
ESR (on site or at local laboratory)	x [g]	x	x	x			x			x				x	x	x	x
Tender/painful joint count (68), swollen joint count (66)	x [g]	x	x	x [t]			x [t]			x				x	x	x	x
Patient's Assessment of Arthritis Pain (VAS) [u]	x [g]	x	x	x			x			x				x	x	x	x
Patient Global Assessment of Arthritis (VAS) [u]	x [g]	x	x	x			x			x				x	x	x	x
Physician's Global Assessment of Arthritis (VAS) [v]	x [g]	x	x	x			x			x				x	x	x	x
HAQ-DI [u]	x [g]	x	x	x			x			x				x	x	x	x
SF-36v2 [u]	x [g]			x			x							x	x		
FACIT-Fatigue Scale [u]	x [g]			x			x							x	x		
Blood for PK assessment [x]	x [g]			x										x		x	x
PBMC protein lysate [u] *(U.S. sites only)*	x [g]			x										x	*x*		
Blood for FACS (U.S. sites only) [w]	x [g]			x										x	*x*		
*S*erum biomarkers	x [g, x]			*x* [x]										x	*x*		
*P*lasma biomarkers	x [g, x]			x [x]										x	*x*		

Appendix 1
Schedule of Assessments (cont.)

	Treatment Visits														SC/ SFU [d]	ET	UV [e]
Week	0 [a]	4	8	12	16 [b]	20 [b]	24	28 [b]	32 [b]	36	40 [b]	44 [b]	48 [b]	52			
Day (±days)	1 [c]	28 (±4)	56 (±4)	84 (±4)	112 (±3)	140 (±3)	168 (±7)	196 (±7)	224 (±7)	252 (±7)	280 (±7)	308 (±7)	336 (±7)	365 (±7)	*(±7)*		
PAXgene RNA blood	x [g, x]			x [x]										x	*x*		
Optional blood sample for genotyping [y]	x																

ACR = American College of Rheumatology; CCP = cyclic citrullinated protein; CRP = C-reactive protein; DAS = DAS = Disease Activity Score; eCRF = Electronic Case Report Form; ESR = erythrocyte sedimentation rate; ET = early termination; HAQ-DI = Health Assessment Questionnaire—Disability Index; OLE = open-label extension; PD = pharmacodynamics; PK = pharmacokinetic; PPI = proton pump inhibitor; SC = study completion; SFU = safety follow-up; TBNK = T, B, and natural killer cells; UV = unscheduled visit; VAS = visual analog scale.

[a] Day 1 OLE assessments that overlap with Day 84 assessments in the main Study GA29350 do not need to be repeated.

[b] This clinical visit is required only for women of childbearing potential for their monthly urine pregnancy testing.

[c] Day 1 of Study GA30067 should be Day 84 in the blinded Study GA29350.

[d] Safety follow-up should occur 8 weeks (±7 days) after last dose.

[e] An unscheduled visit represents a visit that is not as per Schedule of Assessments and is required for an adverse event or for potential relapse assessment. All indicated assessments do NOT need to be performed at each unscheduled visit. Assessments should be based on the reason for the unscheduled visit. These assessments may include collection of PK and PD, to assess drug exposure and/or PD measures of drug activity. Assessments performed during unscheduled visits should be recorded on the corresponding eCRF(s).

[f] Patients who wish to enroll in this OLE study must complete up to Day 84 of Study GA29350 (but should not take blinded study drug on Day 84) prior to signing OLE Informed Consent Form.

[g] *Day 84 assessments in Study GA29350 should be used as the Day 1 assessments of Study GA30067.*

[h] Includes pulse rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature.

[i] 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. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[j] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Appendix 1
Schedule of Assessments (cont.)

[k] Triplicate digital ECG recordings will be obtained at weeks 0 *(collected on Day 84 of Study GA29350)*, 4, 8 and 12, single ECG recording otherwise. The ECG intervals *(e.g., PR, QRS, QT, QTcF, and RR) and heart rate will be entered into the eCRF; in addition, ECG readings will be stored for future analysis, if needed*. ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for ≥10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in HR. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

[l] Patients will receive oral GDC-0853 200 mg twice daily (unless dose reduction is indicated) approximately every 12 hours starting on Day 1 *(starting with the a.m. dose)* and ending on Day 365 (52 weeks). GDC-0853 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. At the indicated clinic visits during the first 12 weeks of the study, patients should be instructed that the first (a.m.) dose of GDC-0853 will be administered in the clinic. After Week 12, GDC-0853 administration in the clinic is not required.

[m] *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).*

[n] Includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[o] Includes sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, LDH, lipase and amylase

[p] During this study, monthly urine pregnancy testing is required for women of childbearing potential. Tests will be performed locally at specified clinic visits. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test (performed locally).

[q] Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[r] Includes IgM, IgA, IgG, and IgE.

[s] Fasting sample not necessary.

[t] *Tender and Swollen Joint Count improvement should be calculated at Week 12 and 24 of OLE with use of formula provided in Appendix 9.*

[u] 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.

[v] The same clinician should complete the Physician's Global Assessment of Arthritis throughout the study.

[u] Collect prior to drug administration. Blood for PBMCs will be shipped overnight to central laboratory for processing.

[v] *The dates and times of the most recent prior meal and most recent prior dose of PPI, H2-RA, or other 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 (on Days 1 and 84) should be recorded at clinic visits at which PK samples are collected.*

[w] 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 within 24 hours.

[x] Sample to be collected prior to drug administration.

[y] Not applicable if optional WGS sample was collected in Study GA29350. 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
Appropriate Equivalent Morphine Doses of Opioid Analgesics
Common Opioid Analgesics

Drug	Maximum Allowed Total Daily Dose	Relative Potency to Oral Morphine	Half-Life
Morphine	30 mg	1	1.5–4 hours
Hydrocodone (Vicodin, Lortab)	30 mg	1	3.8–4.5 hours
Hydromorphone (Dilaudid)	7.5 mg	4	2.5 hours
Meperidine (Demerol, Pethidine)	300 mg	0.1	3.2–3.7 hours
Methadone (Dolophine, Methadose, Physeptone)	10 mg	3.0	23 hours
Codeine (Paveral, Tylenol #2 and #3)	200 mg	0.15	2.5–3.5 hours
Oxycodone [Roxicodone; Percocet, Tylox]	15 mg	~2	3.2 hours
Tramadol [Ultram, Zydol; Zamadol, Ultracet, Tramal]	300 mg	~0.1	4.7–5.1 hours
Propoxyphene HCl (Darvon, Darvocet, Doloxene)	300 mg propoxyphene HCl	~0.1	6–12 hours; 30–36 hours for active metabolite (norpropoxyphene)
Propoxyphene napsylate (Darvon-N, Darvocet-N 100)	400 mg propoxyphene napsylate		

Note: Sites should contact the project team for acceptable alternative preparations and related data.

Appendix 3
Concomitant Medications (Including Foods and Herbal Products)

Class	Expected Interaction	Recommendation	Examples of Drugs in this Class [a]
Antacids	Decreased GDC-0853 absorption due to increased gastric pH	Take GDC-0853 2 hours before or 2 hours after 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 3
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 4
Childbearing Potential, Pregnancy Testing, and Contraception

For Women

All women of childbearing potential (including those who have had a tubal ligation) will have a urine pregnancy test on Study Day 1 prior to administration of study drug and at monthly intervals throughout the study. 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 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 postovulation 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*
- Contraceptive transdermal patch (estrogen and progestin containing)

  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.
- 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 (i.e., refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

- With female partners of childbearing potential, 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 postovulation methods) and withdrawal are not acceptable methods of contraception.

Appendix 5
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

HAQ – United States/English
HAQ-DI_AU1.0-eng-USori.doc

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	HYGNASST_____
____ Reach	____ Errands and chores	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_____

HAQ – United States/English
HAQ-DI_AU1.0-eng-USori.doc

Appendix 6
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?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

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)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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 7
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 past 7 days.**

	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 starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing 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 8
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] or C-reactive protein [CRP]), 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:

- $\text{DAS 28(4)-ESR} = 0.56 \times \text{SQRT(TJC28)} + 0.28\text{SQRT(SJC28)} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{GH}$
- $\text{DAS 28(4)-CRP} = 0.56 \times \text{SQRT(TJC28)} + 0.28\text{SQRT(SJC28)} + 0.36 \times \ln(\text{CRP} + 1) + 0.014 \times \text{GH} + 0.96$
- 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

GH = general health; ln = natural logarithm; SQRT = square root.

Appendix **9**
Joint Count Improvement Formula

The following formulas should be used to calculate T/S Joint Count Improvement for Weeks 12 and 24 of this study. Refer to Section 3.3.5.1 for details on patient management based on improvement calculation at each timepoint.

Tender Joints

$$\left[1 - \left[\frac{\text{Total \# of Tender Joints @ week 12 or 24 of OLE}}{\text{Total \# of Tender Joints @ baseline (D1) of Blinded Study}}\right]\right] \times 100\% =$$

Swollen Joints

$$\left[1 - \left[\frac{\text{Total \# of Swollen Joints @ week 12 or 24 of OLE}}{\text{Total \# of Swollen Joints @ baseline (D1) of Blinded Study}}\right]\right] \times 100\% =$$

To calculate joint count improvement at Week 12 or 24, follow the steps below:

Step 1: *Begin by calculating the fraction inside the inner most brackets (see below):*

For Tender Joints →

$$\left[\frac{\text{Total \# of Swollen Joints @ week 12 or 24 of OLE}}{\text{Total \# of Swollen Joints @ baseline (D1) of Blinded Study}}\right]$$

For Swollen Joints →

$$\left[\frac{\text{Total \# of Tender Joints @ week 12 or 24 of OLE}}{\text{Total \# of Tender Joints @ baseline (D1) of Blinded Study}}\right]$$

Step 2: *Subtract this result from 1:*

1– (Insert value calculated in Step 1 above.)

Step 3: *Multiply the result you obtained from Step 2 above by 100%:*

(Insert value calculated in Step 2 above) ×100%.)

Appendix 10
Bottle and Label Configuration for GDC-0853 Administration

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.*