A PHASE 2A, DOUBLE -BLIND, RANDOMIZED, PLACEBO -CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ORAL PF-06651600 AND PF-06700841 AS INDUCTION AND OPEN LABEL EXTENSION TREATMENT IN SUBJECTS WITH MODERATE TO SEVERE CROHN'S DISEASE

Investigational Product Number:	PF-06651600, PF-06700841
Investigational Product Name:	ritlecitinib, brepocitinib
United States (US) Investigational New Drug (IND) Number:	136177 PF-06651600 136173 PF-06700841
European Clinical Trials Database (EudraCT) Number:	2017-003359-43
Protocol Number:	B7981007
Phase:	2a

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 5	27 July 2021	• Sections Summary, 1, 1.3.2, 1.4.2, 1.5.3, 1.6, 1.6.2.2, 2.1, 3.1, 4.3, 5.4.1: updated to eliminate the PF-06700841 (brepocitinib) active and corresponding (brepocitinib) placebo arms. Section 9.1: updated to provide power for comparison of PF-06651600 (ritlecitinib) to combined placebo only. Rationale: A strategic decision on the part of the sponsor to prioritize future development of PF-06651600 (ritlecitinib), a JAK3/TEC inhibitor currently in development for a number of additional autoimmune diseases namely ulcerative colitis, alopecia areata and vitiligo. The decision to eliminate the PF-06700841 (brepocitinib) cohort from this study B7981007 is not due to any specific safety, efficacy or quality concerns that would negatively affect the overall benefit/risk for patients in this trial or in other trials. • Protocol Summary, Section 2, 9.1 and 9.2.1 and 9.2.2: updated to change the primary endpoint during induction from CMEI to SES-CD 50. Rationale: to enable efficient comparison with contemporary and emerging trials in Crohn's disease. • Section 1.5.1: updated the clinical overview summary. Rationale: to align with the PF-06651600 (ritlecitinib) Dec 2020 Investigator's Brochure.

		• Section 4.4.1: deleted "injectable" from contraception highly effective methods that are user dependent. Rationale: to align with Pfizer May 2020 protocol template updates. • Sections 7.2.5: added clarification when the investigator should assess CDAI parameters in the clinic. Rationale: procedure clarification. • Appendix 3, CDAI sub-component 2 text: updated to replace "Sum of the number of liquid or very soft stools" with the "sum of the abdominal pain ratings". Also added "0 = none, 1 = mild, 2 = moderate, 3 = severe". Rationale: text clarification. • Appendix 4 and section 7.1.10: added elbow circumference measurement. Rationale: to allow frame determination (for the weight item in Crohn's Disease Activity Index [CDAI] for only randomized male subjects with height ≤163 cm (only 1 subject at the time of this amendment). This does not impact the CDAI calculation for subjects with height >163 cm. • All protocol sections updated: added Investigational product names (brepocitinib, ritlecitinib) and replaced JAK3 with JAK3/TEC. Rationale: Generic names assigned to Investigational products and PF-06651600 (ritlecitinib) is a potent inhibitor of JAK3/TEC not JAK3.

Amendment 4	20 November 2020	• Title Page, Protocol Summary and Sections 1 and 1.1: Investigational product names (brepocitinib, ritlecitinib) added. Rationale: Generic names assigned to Investigational products. • Schedule of Activities, Section 5.5, Section 6, Section 7 and Section 7.2.6: Reference to Appendix 12 regarding Alternative Measures during Public Emergencies added. Rationale: To provide guidance on study conduct during public emergencies including COVID-19. • Schedule of Activities Footnote "g" (Induction Period), "d" (Open label period) and Section 7.1.10 are updated to clarify that breast and external genitalia examination as a part of physical exam are optional, but skin examination should include a visual examination of the breast and external genitalia to assess rashes. Rationale: To ensure that rashes are detected and evaluated early. • Schedule of Activities footnote "bb" (Induction Period), "p" (Open label period) and Section 7.3.2 are updated to add the timing of IP-10 sample collection. Rationale: To clarify that IP-10 samples must be collected prior to dosing (PACL 16 Oct 2019). • Section 1.4: Non-clinical safety studies updated to include rat fertility studies. Rationale: To align with Investigator Brochure update.

		• Section 1.5: Summary of Clinical Experience with PF-06651600 and PF-06700841 is updated. Rationale: To align with the updated Investigator Brochure. • Section 4.1 Inclusion criterion #6 and Section 5.9.2 are updated to reference Summary of corticosteroid Equivalents table in Appendix 11. Rationale: To provide guidance on steroid conversions. • Section 4.2 and 7.1.5 are updated to allow central lab to replace QuantiFERON®TB Gold test (QFTG), QuantiFERON®TB Gold InTube test (QFTGIT) and TSPOT® TB test with other acceptable QFT tests. Rationale: To permit central lab to replace the above tests with new ones (PACL 16 Oct 2019). • Section 4.2, exclusion #37 is added to exclude subjects with history of thrombotic event(s) including DVT and known inherited conditions that predispose to hypercoagulability. Rationale: Per regulatory request. • Section 4.4.1 is revised to include "tubal ligation" to the list of highly effective methods of contraception. Rationale: To clarify that tubal occlusion or tubal ligation are both highly effective methods of contraception. • Section 4.4.1 is updated to indicate that the protocol specified contraception language is in alignment with the recommendations received from European regulatory authorities for the B7981018 study.

		Rationale: To align with the Investigator Brochure update. • Section 6.4 is updated to replace Week "52" with Week "68". Rationale: To correct a discrepancy in the protocol (PACL 16 Oct 2019). • Section 6.5 is updated to add Lymphocytes $<800/mm^3$; $<0.8 \times 10^9/L$ and CK > 3x ULN as additional labs to monitor. Rationale: To ensure decreased lymphocytes $<0.8 \times 10^9$ /L or increased CK >3x ULN are followed up in a timely manner and appropriate actions taken (PACL 04 March 2020). • Section 6.5 is updated to clarify the definition of serious infections by referencing Section 7.1.7. Rationale: To clarify definition of serious infections. • Section 6.5: Guidelines for monitoring and discontinuations are updated to include discontinuation of study drug for thrombotic or thromboembolic events. Rationale: Per regulatory request. • Section 7.2.2 is updated to clarify that in South Africa, 18 tissue samples will be collected instead of the protocol defined 19 samples. Rationale: Due to the rejection of the Import License for the Fetal Bovine Serum required for the processing of 1 tissue sample for cytometry, this sample will not be collected for subjects in South Africa (PACL 17 May 2019).

		• Section 7.1.11 is updated to indicate that audiogram results maybe reviewed by an external audiologist. Rationale: To provide clarification on the review of the audiology results. • Sections 7.2.4 and 7.2.5 are updated to add the following sentence: for any visit that has an endoscopy, stool frequency (SF) and abdominal pain (AP) must be collected prior to administration of any bowel prep for endoscopy. Rationale: Clarification of text regarding endoscopies (PACL 16 Oct 2019). • Sections 7.3.5 and 7.3.6 are updated to clarify that during Screening period, collection of stool MUST be prior to administration of any bowel prep for endoscopy. Rationale: To clarify that during Screening, stool samples must be collected prior to the start of diet change for bowel preparation and endoscopy PACL 11 Nov 2018). • Section 9.1: The power has been updated. Rationale: The power was updated to take into account the frequentist rule for futility and also incorporation of the frequentist stopping rule for efficacy. • Section 9.2.1: The alpha adjustment statement has been removed. There is no alpha adjustment for primary and secondary endpoints described in the SAP, hence this statement has been removed. • Section 9.6: Interim Analysis section has been updated to incorporate possibility of additional interims.

		Rationale: The sponsor would like to have the possibility of additional interims including the possibility of stopping the study early due to efficacy. • Section 9.7 is updated to include an internal review committee (IRC) to assess the interim analyses. Rationale: They will be assessing the IA. • Section 9.8: added adjudication committees for opportunistic infections, cardiovascular and neuroaudiometry events. Rationale: three adjudication committees added based on known mechanism of action of JAK inhibitors. • Appendix 11 is added to include steroid conversion table. Rationale: to provide guidance on steroid conversions. • Appendix 12 is added to include Alternative Measures During Public Emergencies. Rationale: To provide guidance on study conduct during public emergencies including COVID-19. • Appendix 1 is updated to include the abbreviation for brainstem auditory evoked potential (BAEP). • Section 16 References are updated to add a new reference.
Amendment 3	24 August 2018	• Protocol summary, Section 1.2, Section 1.3.1, Section 1.4.1, Section 1.5.1.1, Section 1.5.2, Section 1.5.3.1, Section 1.5.3.2 and Section 1.6.3 are being updated to align with PF0665100 Investigator Brochure updated in 2018.

		• SoA footnote "n" is being updated to align the OLE 0.5 hr post dose PK sample collection window with the induction phase 0.5 hr post dose PK collection window (±15 min). • Section 4.2, exclusion criteria 11 is being updated to clarify that subjects with adenomatous polyps finding at screening will be eligible if the polyps have been completely removed and subjects are free of polyps at baseline. • Section 4.2, Exclusion criterion 14 and Section 7.1.6 Screening for Clostridium Difficile are revised to permit treatment and re-testing or re-screening of subjects and to allow subjects with appropriately resolved infection to enter the study. • Section 4.2, Exclusion criterion 16 is revised to allow subjects adequately treated for latent and/or active tuberculosis infection to enter the study. • Section 4.2, Exclusion criterion 33 is revised to lower the eGFR requirement from <80 mL/min/1.73m^2 to <60 mL/min/1.73m^2 because there is no increased risk to include subjects with eGFR >60 and <80 based on the available nonclinical and clinical data to date. The exclusion of subjects with serum creatinine levels > ULN has also been removed form Exclusion criterion 33. Reference to subjects with serum creatinine > ULN has also been removed from Section 7.1.2 Creatinine and Cystatin C and Section 8.4.3 Potential Cases of Decreased eGFR. • Section 4.2, Exclusion criterion 33 is revised to correct that "ALT or AST ≥1.5 times > ULN" not "ALT and AST ≥1.5 times ULN "will be exclusionary.

		• Section 4.4.1 and Exclusion criterion 27 are being updated to align with the Clinical Trials Facilitation Group (CTFG) European guidance of the Heads of Medicines Agencies (HMA) and TransCelerate initiative across Pharma. • Section 5.9.3, is updated to clarify the timeframe in which the listed medications are not permitted for those for which the information is not already stated. • Section 11 Data Handling and Record Keeping and Section 12.3 Subject Information and Consent have been updated to comply with the European Union General Data Protection Regulation (GDPR) which became effective on 25th May 2018.
Amendment 2	15 March 2018	• The SOA is revised to reflect the wrist measurement at the screening visit that will be used to determine frame size as it relates to question 8 of the CDAI. • To address the VHP (Voluntary Harmonization Procedure) request, the protocol summary, Section 2.2, and Section 9.5.2 are updated to add a secondary objective and endpoint to assess the proportion of patients who maintain response after the induction period. • To address the VHP request, Section 4.1 is updated to clarify that inclusion criterion number 5 should be met only after the usual clinical practice in each center has been fulfilled, which may involve administration of more than one line of previous treatment. • To address the VHP request, Section 4.2 is updated to exclude subjects with heart failure (NYHA III, NYHA IV). • To address the VHP request, Section 5.9.2 is updated to clarify that subjects requiring a

		second step up in corticosteroid usage will be required to discontinue the study. • Section 4.1, 4.2 and 5.9.3 are revised to correct a discrepancy and remove Golimumab from the list of antiTNF inhibitors, as Golimumab is not approved for Crohn's disease. • To address the VHP request, Section 4.4.1 is updated to add that male subject must refrain from donating sperm during the study and for 90 days after the last dose of investigational product. • To address the VHP request, Section 5.9.2 is updated to add that subjects requiring a second step up in corticosteroid usage will be required to discontinue the study. • Section 7.2.5 is updated to correct a discrepancy that the wrist measurement value will be recorded on the appropriate CRF page instead of the source document. • Section 7.2.5 is revised to clarify that Hct test will only be performed by the central and not the local lab. • To address VHP request, Section 9.1 is revised to clarify the sample size rationale. • Section 9.2.1 is revised to update the term remission to CMEI response.
Amendment 1	27 November 2017	• (EudraCT) Number added. • To address the FDA request for additional auditory testing, the induction and OLE SOAs are revised to add an auditory testing at Week 48 and to shift the auditory testing from Week 12 to Week 16. These changes together result in audiograms being

		conducted at screening and at Weeks 16, 32, 48, 64 and Early Termination. • The induction and OLE SOAs are revised to add weight measurements at baseline, Weeks 2, 4, 8, 16 and 32 to facilitate CDAI calculation (which is also collected at these time points). • The OLE SOA is being updated to add ECG monitoring at Weeks 32, 48 and 64. This update is to ensure subject safety during the study. • The induction SOA is being revised to clarify that PGIS will be collected continuously for 12 weeks throughout the induction phase (including at Week 2). • The induction SOA, footnote j, is being revised to clarify that fasting lipid profile will be assessed from Baseline visit. • The OLE SOA, footnote m, is being revised to clarify that SF and AP will be collected continuously for 12 weeks throughout the induction phase. • The OLE SOA, footnote n, is being revised to add a window of ±30 min to post dose PK sample collection. • The induction and OLE SOAs are being updated to add: Review and report to the Sponsor of any incidental endoscopic findings reported by Robarts that are deemed clinically significatby the PI/sites. • Section 2.2 and protocol summary are being updated to correct a discrepancy that during the OLE period the proportion of subjects achieving IBDQ symptom domain is being analyzed at Weeks 16, 32 and 64 instead of Weeks 4, 8 and 12.

		• Section 4.1 is being revised to correct a discrepancy and remove Golimumab from the list of antiTNF inhibitors, as Golimumab is not approved for Crohn's disease. • Section 4.2, exclusion criteria 33 and Section 7.1.1 are being updated to add the exclusion of subjects with CK >3 x ULN and positive urine myoglobin. This update is to ensure subject safety is fully evaluated prior to study entry. • Section 4.3 is being updated to clarify that the baseline SES CD stratification factor reflects the isolated ileal disease as a separate strata. • Section 4.4, Lifestyle Requirements, is being updated to add the requirement for subjects to avoid excessive exercise during the study, and maintain adequate hydration, if possible. This update is to ensure subject safety during the study. • Section 4.4.1 is being revised to clarify that male or female condom used with a separate spermicide product is not appropriate or accepted in the EU Union. • Section 5.9.2 is being revised to clarify that steroid tapering is allowed in the OLE period. • Section 7.1.4 and the induction SOA are being revised to delete the requirement of doing a second pregnancy test within 5 days after the first day of the menstrual period (counting the first day of the menstrual period as Day 1). This requirement is not required by any EU or FDA guidance and two highly sensitive negative pregnancy tests at screening and at randomization are sufficient to ensure that the subject is not pregnant prior to first dose of study drug.

		• Section 7.2.1, induction SOA (footnote t) and OLE SOA (footnote l) are being revised to clarify that ET colonoscopy should be performed unless the previous colonoscopy is less than 8 weeks prior. • Section 7.2.3 is being revised to correct a discrepancy that study drug administration will not be reported in the subject Diary and will not be reconciled against the drug accountability inventory form.
Original protocol	26 July 2017	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Background and Rationale:

The Janus kinase (JAK) family of kinases mediates signal transduction via interactions with type I and type II cytokine receptors. Upon binding of the cytokine to its receptor, the associated JAKs are activated and phosphorylate each other and the receptor. The phosphorylated receptors serve as docking sites for the signal transducers and activators of transcription (STAT) family (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) of transcription factors. The STATs are then phosphorylated by the co-localized JAKs, which stabilize homo- or heterodimeric STAT complexes that translocate to the nucleus where they bind to specific gene promoters and activate transcription of a range of target genes.

PF-06651600 (ritlecitinib) is a potent, selective, covalent inhibitor of JAK3/TEC. It is an orally bioavailable small molecule that selectively inhibits JAK3/TEC by irreversibly blocking the adenosine triphosphate (ATP) binding site, without significantly inhibiting the other three JAK isoforms (JAK1, JAK2, and tyrosine-protein kinase 2 (TYK2)). PF-06651600 (ritlecitinib) also inhibits irreversibly the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family (BTK, bone marrow tyrosine kinase on chromosome X (BMX), ITK (IL-2 inducible T-cell kinase), TEC, and tyrosine kinase expressed in T cells (TXK)), with high selectivity over the broader kinome. The selective inhibition of JAK3/TEC will lead to modulation of γ-common chain cytokine pathways, such as interleukin-7 (IL-7), IL-9, IL-15 and IL-21, which have been implicated in the pathophysiology of Crohn's disease (CD). Furthermore, in vivo PF-06651600 (ritlecitinib) will spare signaling of key immunoregulatory cytokines, such as IL-10, IL-27 and IL-35, which have been shown to be critical to maintain immune homeostasis in the gastrointestinal tract. Finally, TEC kinase inhibition will impact CD8+ T and natural killer (NK) cells cytotoxic functions, which play a role in the pathogenesis of intestinal bowel disorder (IBD). Taken together, it is hypothesized that selective inhibition of JAK3/TEC could be efficacious in treatment of CD.

PF-06700841 (brepocitinib) is an orally bioavailable, small molecule, potent dual inhibitor of human TYK2 and JAK1. JAK1 inhibition will impact the signaling of pro-inflammatory cytokines such as Interferon (IFN)-gamma and cytokines signaling through the γ-common chain receptor such as IL-7, IL-9, IL-15 and IL-21, while the inhibition of TYK2 will block the production of pro-inflammatory cytokines such as IFN and IL-17 through upstream inhibition of the IL-12/T helper 1 (Th1) and IL-23/Th17 pathways. Taken together, it is hypothesized that selective and combined inhibition of TYK2 and JAK1 could be efficacious in treatment of CD.

Both PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) are under development as induction and long-term therapy for the treatment of CD.

The original objectives of this study were to evaluate the efficacy [(based on clinically meaningful endoscopic improvement (reduction of ≥3 points from baseline in SES-CD score) at Week 12 as assessed by central reading], safety, tolerability, PK, and PD of 200 mg for 8 weeks followed by 50 mg for 4 weeks of PF-06651600 (ritlecitinib) dosed once daily and 60 mg of PF-06700841 (brepocitinib) dosed once daily during an induction period of 12 weeks, followed by an open label extension period at doses of 50 mg and 30 mg of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib), respectively, for 52 weeks.

Amendment 5 of Protocol B7981007 revises the original design to eliminate the PF-06700841 (brepocitinib) and placebo arms and to change the primary endpoint during induction from CMEI to SES-CD 50 (to enable efficient comparison with contemporary and emerging trials in Crohn's disease). Therefore, upon approval of Amendment 5 by regional Regulatory Authorities and Ethics Committees, Protocol B7981007 will be conducted as a Phase 2a, randomized, double-blind, placebo-controlled, parallel group study focused on the evaluation of the efficacy and safety profile of the PF-06651600 (ritlecitinib) in subjects with moderate to severe active CD. All eligible participants that have been randomized to PF-06700841 (brepocitinib)/PF-06700841 (brepocitinib) placebo or currently actively receiving PF-06700841 (brepocitinib)/PF-06700841 (brepocitinib) placebo under previous protocol amendments will continue to receive PF 06700841 (brepocitinib) through to completion. This study modification is solely a strategic decision on the part of the sponsor to prioritize future development of PF-06651600 (ritlecitinib), a JAK3/TEC inhibitor currently in development for a of number of additional autoimmune diseases namely ulcerative colitis, alopecia areata and vitiligo. The decision to eliminate the PF-06700841 (brepocitinib) cohort from this study B7981007 is not due to any specific safety, efficacy or quality concerns that would negatively affect the overall benefit/risk for patients in this trial or in other trials.

OBJECTIVES AND ENDPOINTS

Objectives and Endpoints during the Induction Period

Primary Objective(s):	**Primary Endpoint(s):**
• To evaluate the efficacy of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo at Week 12 in subjects with moderate to severe CD.	• Proportion of subjects achieving SES-CD 50 (≥50% reduction in SES-CD from baseline) at Week 12.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the safety and tolerability of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo in subjects with moderate to severe CD over 12 weeks.	• Incidence and severity of laboratory abnormalities, vital signs, 12lead ECG, adverse events, serious adverse events and withdrawals due to adverse events. • Incidence of serious infections.
• To evaluate the efficacy of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo during induction of	• Proportion of subjects achieving clinically meaningful endoscopic improvement

additional endoscopic endpoints in subjects with moderate to severe CD.	(reduction of ≥3 points from baseline in SES-CD score) at Week 12. • Mean change from baseline in SES-CD score at Week 12. • Proportion of subjects achieving SES-CD 25 (≥25% reduction in SES-CD from baseline) at Week 12. • Proportion of subjects achieving endoscopic remission (SES-CD ≤2) at Week 12. • Proportion of subjects achieving mucosal healing (complete absence of ulcers) at Week 12.
Tertiary/Exploratory Objective(s):	**Tertiary/Exploratory Endpoint(s):**
• To evaluate the effect of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo on outcomes based on additional clinical criteria.	• Proportion of subjects achieving clinical response and remission using stool frequency (SF), and abdominal pain (AP) measures at Weeks 2, 4, 6, 8, 10 and 12. • Proportion of subjects achieving deep remission (endoscopic remission by SES-CD and clinical remission by SF and AP) at Week 12. • Proportion of subjects with a Crohn's Disease Activity Index (CDAI)100 response (defined by a decrease in CDAI score of at least 100 points from baseline) and proportion of subjects who are remitters (defined as CDAI <150) at Weeks 2, 4, 8 and 12. • The scores and change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) total score and domains (Bowel Symptoms, Systemic Symptoms, Emotional Function and Social Function) at Weeks 4, 8, and 12. • The proportion of subjects with IBDQ total score ≥170 at Weeks 4, 8, and 12. • The proportion of subjects with ≥16 point increase in IBDQ total score from baseline at Weeks 4, 8, and 12. • Proportion of subjects achieving IBDQ symptom domain response at Weeks 4, 8, and 12. • The scores and change from baseline in Euro Quality of Life Questionnaire 5 Dimensions 3

	Levels (EQ5D3L) + Visual Analog Scale (VAS) at Weeks 4, 8, and 12. • The scores and change from baseline in Short Form-36, Version 2 Acute (SF-36 v2): physical and mental component summary scores (PCS & MCS), and 8 domain scores at Weeks 4, 8, and 12. • Mean change from baseline in Patient Global Impression of Severity (PGIS) score at Weeks 4, 8 and 12.
• To evaluate the effect of PF06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo on histopathology score.	• Change from baseline in Global Histologic Disease Activity (GHAS) score at Week 12. • Proportion of subjects achieving histologic remission at Week 12 (defined as GHAS score ≤4).
• To assess the effect of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo on disease and mechanistic biomarkers over time.	• Change from baseline in serum high sensitivity C-reactive protein (hsCRP) levels over time. • Change from baseline in fecal calprotectin over time. • Change from baseline in serum interferon gamma-induced protein 10 (IP-10) levels over time. • Change from baseline in (B-cell lymphoma 2) *BCL-2* gene expression. • Change from baseline in hematological values including reticulocytes, hemoglobin, neutrophils, platelets, and T, B and NK (TBNK) cells.
• To describe the PK of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo in subjects with moderate to severe CD.	• PF-06651600 (ritlecitinib) concentrations at Weeks 2, 4, 8 and 12. • PF-06700841 (brepocitinib) concentrations at Weeks 2, 4, 8 and 12.
• To collect non-banked samples (eg, intestinal biopsies, stool for microbiome analysis, serum and plasma for analysis of proteins and a whole blood tube for RNA analysis) for exploratory research, unless prohibited by local regulations or ethics committee decision. • To collect banked biospecimens samples for exploratory research, unless prohibited by local regulations or ethics committee decision.	• Collection of non-banked exploratory samples unless prohibited by local regulations or ethics committee decision. • Collection of banked biospecimens unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in the Banked Biospecimens section.

Objectives and Endpoints during the Open Label Extension Period

Primary Objective(s):	Primary Endpoint(s):
• To assess the safety and tolerability of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) therapy during open label extension period for subjects with moderate to severe CD.	• Incidence and severity of laboratory abnormalities, vital signs, 12-lead ECG, adverse events, serious adverse events and withdrawals due to adverse events.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the efficacy of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) as maintenance therapy in subjects with moderate to severe CD.	• Proportion of subjects achieving clinically meaningful endoscopic improvement (CMEI response) at Week 64 among subjects who achieved CMEI response at Week 12. • Proportion of subjects achieving SES-CD 25 and SES-CD 50 at Week 64 among subjects who achieved SES-CD 25 and SES-CD 50 at week 12 respectively.
Exploratory Objective(s):	**Exploratory Endpoint(s):**
• To evaluate the efficacy of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) therapy during the open label extension period for subjects with moderate to severe CD.	• Proportion of subjects achieving clinically meaningful endoscopic improvement (reduction of ≥3 points from baseline in SES-CD) at Week 64. • Proportion of subjects achieving SES-CD 25 and SES-CD 50 (≥25% and ≥50% reduction in SES-CD from baseline) at Week 64. • Proportion of subjects achieving endoscopic remission (SES-CD ≤2) at Week 64. • Proportion of subjects achieving mucosal healing (complete absence of ulcers) at Week 64.
• To evaluate the effect of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) on outcomes based on additional clinical criteria.	• Proportion of subjects achieving clinical response and remission as defined by SF and AP endpoints at Weeks 16, 20, 24, 32, 40, 48, 56 and 64. • Proportion of subjects achieving deep remission (endoscopic remission by SES-CD and clinical remission by SF, AP) at Week 64. • Proportion of subjects with a CDAI100 response or CDAI remission (CDAI <150) at Weeks 16, 32 and 64. • The scores and change from baseline in IBDQ Total score and domains (Bowel Symptoms, Systemic Symptoms, Emotional Function and Social Function) at Weeks 16, 32 and 64.

	• The proportion of subjects with IBDQ total score ≥170 at Weeks 16, 32 and 64. • The proportion of subjects with ≥16 point increase in IBDQ total score from baseline at Weeks 16, 32 and 64. • Proportion of subjects achieving IBDQ symptom domain response at Weeks 16, 32 and 64. • The scores and change from baseline in EQ5D3L + VAS at Weeks 16, 32 and 64. • The scores and change from baseline in SF-36 v2: PCS & MCS, and 8 domain scores at Weeks 16, 32 and 64. • Mean change from baseline in PGIS score at Weeks 16, 32 and 64.
• To evaluate the effect of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo on histopathology score.	• Change from baseline in GHAS score at Week 64. • Proportion of subjects achieving histologic remission (GHAS ≤4) at Week 64.
• To describe the PK of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) in subjects with moderate to severe CD.	• PF-06651600 (ritlecitinib) concentrations at Weeks 16, 20, 32, 56 and 64. • PF-06700841 (brepocitinib) concentrations at Weeks 16, 20, 32, 56 and 64.
• To explore the relationship between PK, PD, and clinical endpoints.	• Change from baseline in serum hsCRP levels over time. • Change from baseline in fecal calprotectin. • Change from baseline in serum IP-10 levels over time. • Change in baseline in *BCL-2* gene expression. • Change from baseline in hematological values including reticulocytes, hemoglobin, neutrophils, platelets, and TBNK cells.
• To collect non-banked samples (eg, intestinal biopsies, stool for microbiome analysis, serum and plasma for analysis of proteins and a whole blood tube for RNA analysis) for exploratory research, unless prohibited by local regulations or ethics committee decision. • To collect banked biospecimens samples for exploratory research, unless prohibited by local regulations or ethics committee decision.	• Collection of non-banked exploratory samples unless prohibited by local regulations or ethics committee decision. • Collection of banked biospecimens unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in the Banked Biospecimens section.

Study Design and Treatments:

This is a Phase 2a, randomized, double-blind, placebo-controlled, parallel group, multicenter study in subjects with moderate to severe active CD. The entire study consists of: 1) a screening period of up to 6-weeks, 2) a 12-week induction period, 3) a 52-week open label extension (OLE) period, and 4) a 4-week follow up period. Approximately 230-250 subjects in total will be randomized into the study.

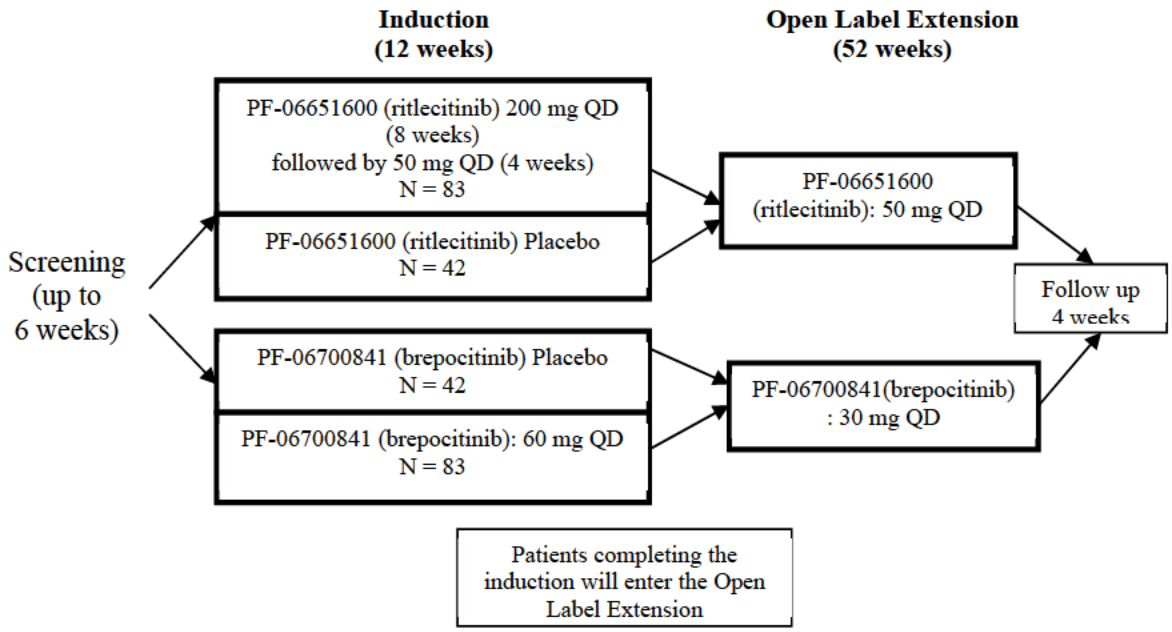
The 12-week induction period will be placebo-controlled and double-blind within each investigational product. Subjects who meet the eligibility criteria at the baseline visit will be randomly assigned to receive either active or placebo treatments. In the induction period, 200 mg QD (one a day) for 8 weeks followed by 50 mg QD for 4 weeks of PF-06651600 (ritlecitinib) and matching placebo in a 2:1 ratio and for subjects enrolled prior to implementation of PA5, 60 mg QD for 12 weeks of PF-06700841 (brepocitinib) and matching placebo in a 2:1 ratio will be investigated. The hybrid dosing regimen for PF-06651600 (ritlecitinib) during the 12-week induction period is a consequence of available nonclinical long-term toxicity data supporting 200 mg treatment for only up to 8 weeks. For analysis, placebo groups will be combined.

After the completion of the induction period, subjects will enter the 52-week OLE period. There will be no re-randomization at the beginning of the OLE period. Subjects will receive the same study drug that they were randomized to receive during the induction period, and there will be no placebo arms. Placebo subjects from the induction period will also receive active drug in the OLE period. The matching placebo subjects from the double-blind PF-06651600 (ritlecitinib) treatment/placebo induction period will receive 50 mg of PF-06651600 (ritlecitinib), while the corresponding placebos from the double-blind PF-06700841 (brepocitinib)/placebo induction period will receive 30 mg of PF-06700841 (brepocitinib) for 52 weeks.

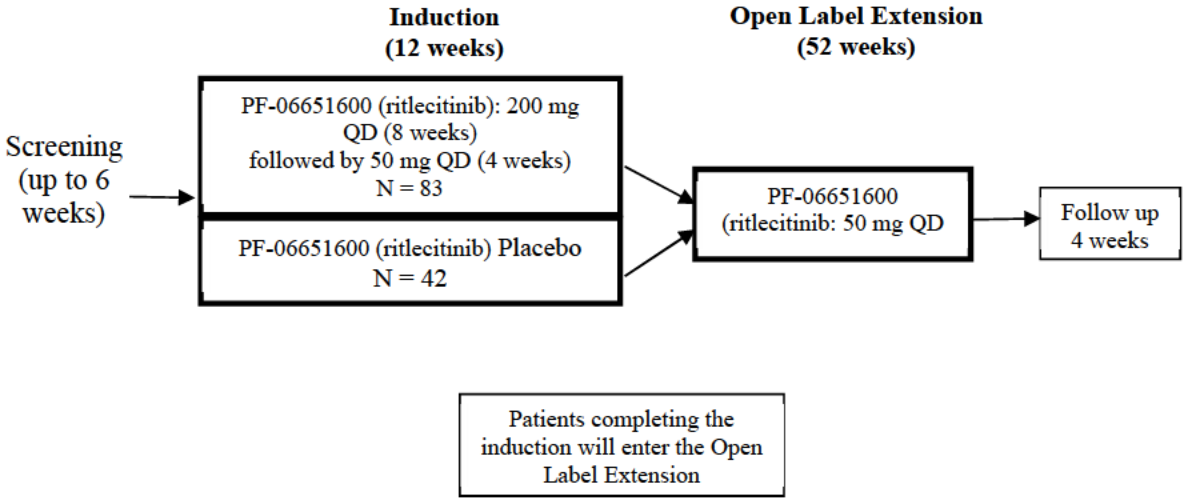
After completion of the OLE period, subjects will enter the 4-week follow up period. Any subjects, who discontinues early from the double-blind period prior to theWeek 12 visit, should undergo the procedures for an Early Termination (Induction) visit on the last day the subject takes the investigational product or as soon as possible thereafter. For subjects who discontinue early from the OLE period (after the Week 12 visit, but prior to the Week 52 visit), the procedures scheduled for an Early Termination (OLE) visit will be performed on the last day the subject takes the investigational product or as soon as possible thereafter.

These early withdrawal subjects, along with subjects who complete the induction period but are not willing to participate in the OLE period, will be asked to complete the Follow-up visit approximately 4 weeks after the last dose of study drug.

Original Study Schematic



Study Schematic Post Implementation of Protocol Amendment 5



Statistical Methods:

A comprehensive overall Statistical Analysis Plan (SAP) will be provided prior to the un-blinding of the trial. The sample size is based on the primary efficacy endpoint, SES-CD 50 at Week 12. All subjects who receive at least one dose of randomized study medication and have a baseline and at least one post-baseline measurement (after taking randomized study medication) will be included in the efficacy data analyses.

The primary efficacy endpoint is the proportion of subjects achieving SES-CD 50 defined as ≥50%reduction from baseline in SES-CD score at Week 12, as assessed by central reading. The safety analysis set will include all subjects who have received at least one dose of the study drug or placebo. Pharmacokinetic (PK) concentrations in treatment period will be summarized and presented with summary statistics. Details regarding the analysis procedures to be used for the interim analysis may be provided in the interim analysis plan (IAP). An interim analysis will be performed when approximately 60% of planned subjects have completed or had the chance to complete the Week 12 visit for possible futility or early efficacy. In case the study fails to stop at this interim, another interim analysis may be performed when approximately 80% of the subjects have completed or had the chance to complete Week 12 visit.

Efficacy endpoints are exploratory in the extension period. Details of the analysis are described in Section 9 and in the SAP.

This study will use an external data monitoring committee (E-DMC). The E-DMC will be responsible for ongoing monitoring of safety of subjects in the study according to the charter. The E-DMC will also be responsible for any interim analysis as specified in the protocol and interim analysis plan.

SCHEDULE OF ACTIVITIES (INDUCTION PERIOD)

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject. Refer to Appendix 12 for Alternative Measures During Public Emergencies if applicable.

Study Procedure	Screening	Baseline	Induction Period (Weeks 0 -12)				Early Term (Induction)[b]
Visit Identifier[a]	**Week -1 to -6**	**Week 0 /Day 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**[c]	
Study Day/Visit Window	**Day -42 -0**	**1**	**15 ±2**	**29 ±2**	**57 ±2**	**85 ±2**	
Informed consent	X						
Medical history[d]	X						
History of Alcohol, Smoking and Drug Abuse	X						
Weight[e]	X	X	X	X	X	X	X
Height[e]	X						
Wrist measurement	X						
Chest radiograph[f]	X						
Complete physical examination[g]	X	X				X	X
Targeted physical examination[g]			X	X	X		
Vital signs & temperature[h]	X	X	X	X	X	X	X
12-Lead ECG[h]	X					X	X
Audiogram[i]	X						X
Laboratory							
Hematology	X	X	X	X	X	X	X
Serum chemistry[j]	X	X	X	X	X	X	X
Fasting Lipid Panel[j]	X	X	X	X	X	X	X
Cystatin C (and eGFR)	X	X	X	X	X	X	X
Urinalysis[k]	X[l]	X	X	X	X	X	X
Urine Myoglobin[z]	X						
HbA1c	X						
Stool microbiology[m]	X						
HBsAg, HBcAb, HCV Ab, HCV RNA PCR if HCV Ab positive[n]	X						

Study Procedure	Screening	Baseline	Induction Period (Weeks 0 -12)				Early Term (Induction)[b]
Visit Identifier[a]	**Week -1 to -6**	**Week 0 /Day 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**[c]	
Study Day/Visit Window	**Day -42 -0**	**1**	**15 ±2**	**29 ±2**	**57 ±2**	**85 ±2**	
HIV serology	X						
Tuberculosis screening[o]	X						
FSH[p]	X						
Serum β-hCG[q]	X						
Urine β-hCG[q]		X	X	X	X	X	X
hsCRP	X	X		X	X	X	X
Fecal calprotectin[r]	X			X	X	X	X
IP-10[bb]		X		X	X	X	X
FACS TBNK Cells		X		X	X	X	X
Stool Sample (Microbiome)[r]	X					X	X
Blood for gene expression profiling (exploratory biomarker)		X			X	X	X
Serum protein profiling (exploratory biomarker)		X			X	X	X
Viral Surveillance[s]		X	X	X	X	X	X
Contraception check	X	X	X	X	X	X	X
Eligibility assessment	X	X					
Randomization		X					
Study treatment							
Investigational product dispensing		X	X	X	X	X	
Investigational product dosing (at site)		X	X	X	X	X	
Investigational product accountability			X	X	X	X	X
Assessments							
Colonoscopy and intestinal tissue biopsies[t]	X[u]					X	X
SES-CD	X					X	X
SF and AP[v]	X	X	X	X	X	X	X
CDAI		X	X	X	X	X	X
PGIS[w]	X	X	X	X	X	X	X
IBDQ		X		X	X	X	X
EQ-5D-3L + VAS		X		X	X	X	X
SF-36 v.2, acute		X		X	X	X	X
Pharmacokinetic blood sampling[x]		X	X	X	X	X	X
Genomic banked biospecimens Prep D1[y]		X					
Other exploratory/banked biospecimens (Prep B1.5, Prep B2.5, Prep R1)		X	X	X	X	X	X

Study Procedure	Screening	Baseline	Induction Period (Weeks 0 -12)				Early Term (Induction)[b]
Visit Identifier[a]	Week -1 to -6	Week 0 /Day 1	Week 2	Week 4	Week 8	Week 12[c]	
Study Day/Visit Window	Day -42 -0	1	15 ±2	29 ±2	57 ±2	85 ±2	
Assess clinical significance of incidental endoscopic findings reported from Robarts[aa]	X					X	X
Prior/Concomitant Treatment(s)	X	→	→	→	→	→	→
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→

Abbreviations: →= ongoing/continuous event; β-hCG = beta human chorionic gonadotropin; CDAI = Crohn's Disease Activity Index; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EQ-5D-3L = Euro quality of life questionnaire 5 dimensions 3 levels; ET= Early Term; FACS TBNK = fluorescent activated cell sorting T-cell B-cell NK cell; FSH = follicle stimulating hormone; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C antibody; HCV RNA PCR = hepatitis C virus ribonucleic acid polymerase chain reaction; HIV = human immunodeficiency virus; hsCRP = high sensitivity C-reactive protein; IBDQ = inflammatory bowel disease questionnaire; Ig = immunoglobulin; IP-10 = interferon gamma induced protein 10; mRNA = messenger ribonucleic acid; PGIS = patient global impression of severity; PRO = Patient reported outcome; SES-CD = Simplified Endoscopic Score for Crohn's Disease; SF-36 v.2, acute = short form 36 version 2 acute.

a. Day relative to start of study treatment (Day 1).

b. For subjects who discontinue early from the double-blind period prior to the Week 12 visit, the procedures scheduled for Early Term (Induction) will be performed on the last day the subject takes the investigational product or as soon as possible thereafter and will be asked to complete the Follow-up visit approximately 4 weeks after the last dose of study drug.

c. Subject not entering the OLE period will proceed to the ET (Induction) visit.

d. Medical history includes detailed histories of conditions specified in Study Procedures Section 6.1.

e. Height and weight will be measured without shoes.

f. Chest radiograph (posterior-anterior and lateral views are recommended, however local guidelines should be followed) is required at Screening. A chest X-ray or other appropriate diagnostic imaging modality (ie, Computerized Tomography (CT) with or without IV contrast or Magnetic Resonance Imaging (MRI)) performed within 12 weeks prior to screening and read by a qualified radiologist with no evidence of current, active TB or previous inactive TB, general infections, heart failure or malignancy may substitute for the chest X-ray taken at Screening. Documentation of the official negative reading must be located and available in the source documentation prior to Baseline (Day 1) randomization.

g. Additional brief PE may be performed during the study at the investigator's discretion. Full and targeted physical examinations must include a full body skin examination. Skin examinations should include visual inspection of the breasts and external genitalia to assess for rashes, even if a subject does not want to have an examination of breast and/or external genitalia (these are optional) done as a part of the physical examination.

h. Vital signs (including temperature) and ECG should be performed before laboratory blood collection and endoscopic procedure.

i. Audiograms may be performed within a ±2 week window relative to study visit.

j. Subjects are required to fast (no food or drink except water) for at least 8 hours prior to study visit (starting from baseline visit), as required for fasting lipid profile and fasting glucose sample collection.

k. Dipstick in all cases; microscopy analysis is indicated if urinalysis is positive for blood, nitrite, leukocyte esterase and/or protein. Urine culture is performed if urinalysis is positive for nitrite and/or leukocyte esterase or if clinically indicated.

l. Screening urinalysis will include spot urine albumin/creatinine ratio.

m. Stool microbiology (stool culture for enteric pathogens, ova and parasites, and Clostridium difficile toxin test), if not performed within 6 weeks prior to screening.

n. Subjects who are HBsAg negative and HBcAb positive must have further testing for HBsAb. Subjects who are HCV Ab positive require further testing with HCV RNA PCR.

o. If not performed within 12 weeks prior to screening (see Assessments Section 7.1.5 for details).

p. To be done in postmenopausal females only (females who are amenorrheic for at least 12 consecutive months).

q. Only for women of childbearing potential.

r. Collection of stool for microbiome and fecal calprotectin analyses MUST be prior (within 1 week) to administration of any bowel prep for endoscopy.

s. Viral surveillance to include analysis of viral load for CMV, EBV, HSV1, HSV2 and VZV. In addition to time points specified, a plasma sample for viral surveillance may also be taken at the time of an adverse event, as clinically appropriate.

t. At each biopsy collection time point 19 biopsies should be taken for the analyses described: 12 biopsies spanning six segments (rectum, sigmoid, left colon, transverse colon, right colon, and ileum), 6 biopsies from inflamed colonic mucosa in the most affected segment, and 1 biopsy from normal adjacent mucosa. See Section 7.2.2 for additional details. ET colonoscopy should be performed unless the previous colonoscopy is less than 8 weeks prior.

u. Endoscopy should be performed within 10 days prior to baseline visit, preferably within 5 to 7 days prior to baseline. The centrally read endoscopic subscore will be used to determine eligibility.

v. Stool frequency (SF) and abdominal pain (AP) diary will be provided at screening.

w. The PGIS will be assessed daily beginning approximately 2 weeks prior to screening endoscopy.

x. PK (PF-06651600 (ritlecitinib) or PF-06700841 (brepocitinib) samples will be collected pre-dose at Weeks 0, 2, 8. On Week 4, PK (PF-06651600 (ritlecitinib) or PF-06700841 (brepocitinib) samples will be collected prior to dosing, and 0.5 hour (±15 min) post dose. On Week 12 PK (PF-06651600 (ritlecitinib) or PF-06700841 (brepocitinib) samples will be collected prior to dosing, and 0.5 hour (±15 min), 1 hour (±30 min), 2 hour (±30 min) and 4 hour (±30 min) post dose.

y. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a subject visit.

z. Urine myoglobin will be measured at Screening and in case of CK >3x ULN during the study (up to week 68). Additional tests may be performed during the study at the investigator's discretion, as indicated by signs and symptoms of ongoing AEs.

aa. Incidental endoscopic findings reported by Robarts that are deemed clinically significant by the principal investigator must be reported as an AE or SAE, as appropriate.

bb. IP-10 samples will be collected prior to dosing.

SCHEDULE OF ACTIVITIES (OPEN LABEL EXTENSION PERIOD)

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject. Refer to Appendix 12 for Alternative Measures During Public Emergencies if applicable.

Study Procedure	Open Label Extension Period(Weeks 12-64)								Follow up	Early Term[b] (OLE)
Visit Identifier[a]	**Week 16[a]**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 48**	**Week 56**	**Week 64**	**Week 68**	
Visit Window	**±7 days based on baseline visit**									
Weight[c]	X			X				X	X	X
Complete physical examination[d]								X		X
Targeted physical examination[d]	X	X	X	X	X	X	X		X	
Vital signs & temperature[e]	X	X	X	X	X	X	X	X	X	X
12-Lead ECG				X		X		X		
Audiogram[f]	X			X		X		X		X
Laboratory										
Hematology	X	X	X	X	X	X	X	X	X	X
Serum chemistry[g]	X	X	X	X	X	X	X	X	X	X
Fasting Lipid Panel[g]	X	X	X	X	X	X	X	X	X	X
Cystatin C (and eGFR)	X	X	X	X	X	X	X	X	X	X
Urinalysis[h]	X	X	X	X	X	X	X	X	X	X
Urine β-hCG[i]	X	X	X	X	X	X	X	X	X	X
hsCRP	X			X				X	X	X
Fecal calprotectin[j]	X			X				X[j]	X	X
IP-10[p]	X			X				X	X	X
FACS TBNK Cells	X			X				X		X
Stool Sample (Microbiome)[j]				X				X		X
Blood for gene expression profiling (exploratory biomarker)				X				X		X
Serum protein profiling (exploratory biomarker)				X				X		X

Study Procedure	Open Label Extension Period(Weeks 12-64)								Follow up	Early Term[b] (OLE)
Visit Identifier[a]	**Week 16[a]**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 48**	**Week 56**	**Week 64**	**Week 68**	
Visit Window	**±7 days based on baseline visit**									
Viral Surveillance[k]	X	X	X	X	X	X	X	X	X	X
Contraception check	X	X	X	X	X	X	X	X	X	X
Randomization										
Study treatment										
Investigational product dispensing	X	X	X	X	X	X	X			
Investigational product dosing (at site)	X	X	X	X	X	X	X	X		
Investigational product accountability	X	X	X	X	X	X	X	X		X
Assessments										
Colonoscopy and intestinal tissue biopsies[l]								X		X
SES-CD								X		X
SF and AP[m]	X			X				X		X
CDAI	X			X				X		X
PGIS[m]	X			X				X		X
IBDQ	X			X				X		X
EQ-5D-3L + VAS	X			X				X		X
SF-36 v.2, acute	X			X				X		X
Pharmacokinetic blood sampling[n]	X	X		X			X	X		X
Other exploratory/banked biospecimens (Prep B1.5, Prep B2.5, Prep R1)	X			X				X		X
Assess clinical significance of incidental endoscopic findings reported from Robarts[o]								X		X
Prior/Concomitant Treatment(s)	→	→	→	→	→	→	→	→	→	X
Serious and non-serious adverse event monitoring	→	→	→	→	→	→	→	→	→	X

Abbreviations: →= ongoing/continuous event; β-HCG = beta human chorionic gonadotropin; CDAI = Crohn's Disease Activity Index; eGFR = estimated glomerular filtration rate; EQ-5D-3L = Euro quality of life questionnaire 5 dimensions 3 levels; FACS TBNK = fluorescent activated cell sorting T-cell B-cell NK cell; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C antibody; HCV RNA PCR = hepatitis C virus ribonucleic acid polymerase chain reaction; hsCRP = high sensitivity C-reactive protein; IBDQ = inflammatory bowel disease questionnaire; Ig = immunoglobulin; IP-10 = interferon gamma induced protein 10; OLE= open label extension; mRNA = messenger ribonucleic acid; PGIS = patient global impression of severity; PRO = Patient reported outcome; SES-CD = Simplified Endoscopic Score for Crohn's Disease; SF-36 v.2, acute = short form 36 version 2 acute.

a. Day relative to start of study treatment (Day 1). Subjects who complete the 12-week induction period will enter the second part of the study which is a 52 week OLE period and will be asked to complete the Follow-up visit approximately 4 weeks after the last dose of study drug.

b. For subjects who discontinue early from OLE period (after the Week 12 visit, but prior to the Week 52 visit), the procedures scheduled for Early Term (OLE) will be performed on the last day the subject takes the investigational product or as soon as possible thereafter and will be asked to complete the Follow-up visit approximately 4 weeks after the last dose of study drug.

c. Weight will be measured without shoes.

d. Additional targeted PE may be performed during the study at the investigator's discretion. Complete and targeted physical examinations must include a full body skin examination. Skin examinations should include visual inspection of the breasts and external genitalia to assess for rashes, even if a subject does not want to have an examination of breast and/or external genitalia (these are optional) done as a part of the physical examination.

e. Vital signs (including blood pressure, pulse rate and temperature) should be performed before laboratory blood collection and endoscopic procedure.

f. Audiograms may be performed within a ±2 week window relative to study visit.

g. Subjects are required to fast (no food or drink except water) for at least 8 hours prior to study visit, as required for fasting lipid profile and fasting glucose sample collection.

h. Dipstick in all cases; microscopy analysis is indicated if urinalysis is positive for blood, nitrite, leukocyte esterase and/or protein. Urine culture is performed if urinalysis is positive for nitrite and/or leukocyte esterase or if clinically indicated.

i. Only for women of childbearing potential.

j. During screening period collection of stool for microbiome and fecal calprotectin sample collection MUST be prior (within 1 week) to administration of any bowel prep for endoscopy. For example, subject can collect their sample one week prior to bowel prep. One week is not a set time period; subject may collect the stool sample sooner than 1 week too.

k. Viral surveillance to include analysis of viral load for CMV, EBV, HSV1, HSV2 and VZV. In addition to time points specified, a plasma sample for viral surveillance may also be taken at the time of an adverse event, as clinically appropriate.

l. At each biopsy collection time point 19 biopsies should be taken for the analyses described: 12 biopsies spanning six segments (rectum, sigmoid, left colon, transverse colon, right colon, and ileum), 6 biopsies from inflamed colonic mucosa in the most affected segment, and 1 biopsy from normal adjacent mucosa. See Section 7.2.2 for additional details. ET colonoscopy should be performed unless the previous colonoscopy is less than 8 weeks prior.

m. The PGIS, SF and AP will be assessed daily from Visit 12 to 16, Visit 24 to 32 and from Visit 56 to 64.

n. PK (PF-06651600 (ritlecitinib) or PF-06700841 (brepocitinib) samples will be collected pre-dose at Weeks 16, 20, 56. On Week 32 and 64 PK (PF-06651600 (ritlecitinib) or PF-06700841 (brepocitinib) samples will be collected at predose and 0.5 hour (±15 min) post dose.

o. Incidental endoscopic findings reported by Robarts that are deemed clinically significant by the principal investigator must be reported as an AE or SAE, as appropriate.

p. IP-10 samples will be collected prior to dosing.

1. INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract that affects five million people worldwide. IBD presents as one of two major forms, ulcerative colitis (UC) or Crohn's disease (CD). UC is characterized by continuous inflammation that is localized to the colon. CD is characterized by discontinuous inflammation that can affect the entire gastrointestinal tract from mouth to anus and may be associated with long-term debilitating sequelae, such as fistulae and intestinal strictures.

Despite multiple therapies being available, there still remains a significant unmet medical need, as subjects can suffer from primary or secondary non-responses, as well as, development of intolerance to treatment regimens. Because of the significantly reduced risk for immunogenicity and the potential for oral administration, small molecule inhibitors have emerged as an attractive therapeutic modality. Tofacitinib is a JAK inhibitor with broad specificity, mainly targeting JAK1 and JAK3/TEC, with lesser effects on JAK2, and therefore affects multiple cytokine signaling pathways. Tofacitinib has been approved for use in rheumatoid arthritis and has demonstrated significant differences in clinical response and remission between tofacitinib and placebo in subjects with UC (NEJM, 2017).[1] Pfizer plans to test multiple selective kinase inhibitor assets simultaneously in the CD setting, which in this trial will include a JAK3/TEC-sp ecific inhibitor and a TYK2/JAK1-specific inhibitor (enrollment into the TYK2/JAK1 arm will conclude upon implementation of PA5) in the context of a single clinical study. Each arm of the study will address a biologically distinct question. The JAK3/TEC -specific arm will address the involvement of cytokines that signal through JAK3/TEC in CD, and the TYK2/JAK1-specific arm address the involvement of cytokines that signal through TYK2 and JAK1 in CD.

Both PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) avoid specific targeting of JAK2, thus reducing the risks of undesired side effects, such as anemia.

1.1. Mechanism of Action/Indication

PF-06651600 (ritlecitinib) is a potent, selective, covalent inhibitor of JAK3/TEC that is currently being investigated in patients with rheumatoid arthritis, alopecia areata, UC, and CD.

PF-06700841 (brepocitinib) is a potent dual inhibitor of human TYK2 and JAK1 that is currently being investigated in patients with psoriasis, alopecia areata, UC, and CD.

1.2. Background and Rationale

The JAK family of kinases mediates signal transduction via interactions with type I and type II cytokine receptors. Upon binding of the cytokine to its receptor, the associated JAKs are activated, and phosphorylate each other and the receptor. The phosphorylated receptors serve as docking sites for the STAT family (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) of transcription factors. The STATs are then phosphorylated by the co-localized JAKs, which stabilize homo- or heterodimeric STAT complexes that translocate to the nucleus where they bind to specific gene promoters and activate transcription of a range of target genes.

PF-06651600 (ritlecitinib) is a potent, selective, covalent inhibitor of JAK3/TEC. It is an orally bioavailable small molecule that selectively inhibits JAK3/TEC by irreversibly blocking the ATP binding site without significantly inhibiting the other three JAK isoforms (JAK1, JAK2, and TYK2). PF-06651600 (ritlecitinib) also inhibits irreversibly the TEC kinase family (BTK, bone marrow tyrosine kinase on chromosome X (BMX), ITK, TEC, and tyrosine kinase expressed in T cells (TXK)), with high selectivity over the broader kinome. The selective inhibition of JAK3/TEC will lead to modulation of γ-common chain cytokine pathways, such as IL-7, IL-9, IL-15 and IL-21, which have been implicated in the pathophysiology of CD. Furthermore, in vivo PF-06651600 (ritlecitinib) will spare signaling of key immunoregulatory cytokines, such as IL-10, IL-27 and IL-35, which have been shown to be critical to maintain immune homeostasis in the gastrointestinal tract. Finally, TEC kinase inhibition will impact CD8+ T and NK cells cytotoxic functions, which play a role in the pathogenesis of IBD. Taken together, it is hypothesized that selective inhibition of JAK3/TEC could be efficacious in treatment of CD.

PF-06700841 (brepocitinib) is an orally bioavailable, small molecule, potent dual inhibitor of human TYK2 and JAK1. JAK1 inhibition will impact the signaling of pro-inflammatory cytokines such as IFN-gamma and cytokines signaling through the γ-common chain receptor such as IL-7, IL-9, IL-15 and IL-21, while the inhibition of TYK2 will block the production of pro-inflammatory cytokines such as interferon-gamma and IL-17 through upstream inhibition of the IL-12/Th1 and IL-23/Th17 pathways. Taken together, it is hypothesized that selective and combined inhibition of TYK2 and JAK1 could be efficacious in treatment of CD.

Both PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) are under development as induction and long-term therapy for the treatment of CD.

Additional information for these compounds may be found in the single reference safety document (SRSD), which for this study is the individual Investigational Brochure (IB) for each compound.

Banked biospecimens will be collected for the purpose of conducting research; specific uses are described in the Banked Biospecimens section. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/genomic/biomarker analyses and retaining them in the Biospecimen Banking System (BBS) make it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

Banked biospecimens retained in the BBS also can be used in research on IBD and other inflammatory diseases.

Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited by local regulations or ethics committee (EC) decision.

1.3. Non-Clinical Pharmacokinetics and Metabolism

1.3.1. Non-Clinical Pharmacokinetics and Metabolism of PF-06651600 (ritlecitinib)

Single dose pharmacokinetic (PK) studies with PF-06651600 (ritlecitinib) were conducted after intravenous (IV) and oral (PO) administration to mice, rats, and dogs. Absorption was rapid and bioavailability ranged from 61-100%. PF-06651600 (ritlecitinib) exhibited a clearance (CL) of 45 mL/min/kg in mice, 69 mL/min/kg in rats, and 13 mL/min/kg in dogs. The steady-state volume of distribution (V_{ss}) was 0.8 L/kg in mice, 1.4 L/kg in rats, and 1.1 L/kg in dogs, resulting in terminal half-lives ($t_{½}$) of 1.3, 0.3, and 1.1 hours, respectively. Systemic exposures of PF-06651600 (ritlecitinib) as measured by maximum concentration (C_{max}) and area under the concentration-time curve (AUC_{24}) in repeat dose oral pivotal toxicology studies increased with dose in rats, rabbits, and dogs. No sex-related differences and no significant accumulation was observed. In vitro, PF-06651600 (ritlecitinib) showed high apparent passive permeability and preliminary studies indicated that PF-06651600 (ritlecitinib) was a substrate for P-glycoprotein (P-gp; also known as multidrug resistance (MDR)1) and breast cancer resistant protein (BCRP) efflux transporters. However, oral bioavailability was high in rat and dog and a dose proportional C_{max} was observed in clinical studies (between 5 and 800 mg) indicating minimal influence of efflux transporters on intestinal absorption.

Fraction unbound of PF-06651600 (ritlecitinib) to plasma proteins was 0.22 (mouse), 0.67 (rat), 0.29 (rabbit), 0.82 (dog), and 0.86 (human) across species. Given the species-related differences in plasma protein binding, in vivo exposure-based safety margins were calculated using unbound concentrations. Following an oral dose of [^{14}C]PF-06651600 (ritlecitinib) to rats, radioactivity was widely distributed throughout the body with the highest concentrations in the uveal tract of the eyes, blood, and aorta. The brain to plasma AUC from zero to the last timepoint (AUC_t) ratio of [^{14}C]PF-06651600 (ritlecitinib) was 0.04, indicating minimal distribution of [^{14}C]PF-06651600 (ritlecitinib) -related radioactivity to the brain, consistent with the drug being a substrate for P-gp/BCRP. Elimination of radioactivity was nearly complete, since the majority of tissues were below the limit of quantitation at 332 or 672 hours post-dose. [^{14}C]PF-06651600 (ritlecitinib) showed high recovery (98.4%) when incubated for 4 hours with human hepatocytes in vitro, indicating limited nonspecific interaction.

In vitro and in vivo metabolite profiling indicated that the primary clearance mechanisms for PF-06651600 (ritlecitinib) were glutathione related conjugation and cytochrome (CYP) 450-mediated oxidation. Renal excretion of parent PF-06651600 (ritlecitinib) was limited in the rat and dog. Biliary excretion of parent PF-06651600 (ritlecitinib) was limited in the rat. No unique human metabolites were observed clinically compared to metabolite profiles in mouse, rat, and dog. Initial metabolite profiling in steady-state first in human (FIH) human samples based on ultraviolet (UV) absorption indicated PF-06651600 (ritlecitinib) as the major circulating species at ~64%, with 3 glutathione remnant metabolites detected (~21% cysteine-, ~9.1% N-acetyl cysteine-, and ~6.3% N-acetyl cysteine

sulfoxide-conjugates), indicating glutathione conjugation as the primary clearance mechanism. The respective ratio of circulating cysteine, N-acetylcysteine, and N-acetylcysteine sulfoxide in rat:human was estimated at ~28:1, 22:1, and 0.74:1 comparing the 6-month good laboratory practice (GLP) toxicity study no-observed-adverse effect (NOAEL) level of 200 mg/kg/day to a top human daily dose of 200 mg. The respective urinary rat:human ratios of excreted cysteine, N-acetylcysteine, and N-acetylcysteine sulfoxide were ~2.7:1, 19:1, and 6.4:1 indicating exposures of these metabolites in rats exceeded those in humans. No evidence of chiral inversion of PF-06651600 (ritlecitinib) was detected in human plasma following oral administration. Reaction phenotyping in recombinant enzyme systems identified CYP3A4 as the predominant CYP450 isoform responsible for the oxidative metabolism of PF-06651600 (ritlecitinib), with minor contributions from CYP2C19 and CYP3A5. In addition, Glutathione-S-Transferase (GST)-conjugate was formed in a time dependent manner in Recombinant Glutatione-S-Transferase (rGST) Mu 1-1 (M1-1) and Pi 1-1 (P1-1) incubations.

PF-06651600 (ritlecitinib) showed a low risk of causing a drug-drug interaction (DDI) due to reversible inhibition of the major CYP450 enzymes (unbound C_{max}/50% inhibitive concentration [IC_{50}] ≤0.04) as well as the major uridine 5'-diphospho-glucuronosyltransferase (UDP)-glucuronosyltransferase (UGT) enzymes (unbound C_{max}/IC_{50} ≤0.07) at a maximum clinical daily dose of 200 mg (unbound C_{max} 3.8 μM). However, in the presence of nicotinamide adenine dinucleotide phosphate (NADPH), PF-06651600 (ritlecitinib) showed evidence of weak time-dependent inhibition of CYP3A4. PF-06651600 (ritlecitinib) (caused >4-fold induction of CYP3A4 messenger ribonucleic acid (mRNA) levels and >2-fold induction of CYP2B6 mRNA levels at 50 to 100 μM, while no CYP1A2 induction was noted. Clinically, PF-06651600 (ritlecitinib) showed no significant changes in 4β-hydroxycholesterol/cholesterol ratio relative to baseline controls following 14 days of dosing up to 400 mg once daily (QD), indicating the lack of potent CYP3A modulation. Further clinical studies are planned to better understand DDI risk.

Based on in vitro transporter DDI assessments compared to exposure following a maximum clinical dose of 200 mg daily, PF-06651600 (ritlecitinib) showed a low potential to inhibit organic anion transporting polypeptide (OATP)1B1, OATP1B3, bile salt export pump (BSEP), organic cation transporter (OCT)2, organic anion transporter (OAT)1, and OAT3 at clinically relative concentrations. However, PF-06651600 (ritlecitinib) has the potential to inhibit P-glycoprotein (P-gp) (systemically and in the gastrointestinal (GI) tract), breast cancer resistance protein (BCRP) (systemically and in the GI tract), organic cation transporter (OCT)1, multidrug and toxin extrusion (MATE)1, and MATE2K at clinically relative concentrations. Clinically, no significant changes in creatinine clearance (OCT2/MATE1/2K) from baseline were noted in multiple dose studies at doses up to 800 mg. PF-06651600 (ritlecitinib) is not a substrate for OATP1B1 or OATP1B3.

Please refer to the Investigator's Brochure (IB) for more details on the non-clinical PK and metabolism of PF-06651600 (ritlecitinib).

1.3.2. Non-Clinical Pharmacokinetics and Metabolism of PF-06700841 (brepocitinib)

This Section is no longer applicable to newly enrolled participants under PA5.

A single-dose PK study with PF-06700841 (brepocitinib) was conducted after per os (PO) and intravenous (IV) administration to male rats. PF-06700841 (brepocitinib) was rapidly absorbed with high oral bioavailability (approximately 100%). After IV administration, PF-06700841 (brepocitinib) demonstrated a steady state volume of distribution (V_{ss}) of approximately 1.7 L/kg and a moderate plasma CL (approximately 31 mL/min/kg), relative to rat liver blood flow. Systemic exposures (C_{max} and AUC_{24}) of PF-06700841 (brepocitinib) after repeat oral dosing in the pivotal toxicity studies increased with increasing dose. In vitro, PF-06700841 (brepocitinib) showed high apparent passive permeability and preliminary studies indicated that PF-06700841 (brepocitinib) was a substrate for MDR1. The mean fraction unbound values in plasma for PF-06700841 (brepocitinib) were 0.51 in mouse, 0.69 in rat, 0.36 in rabbit, 0.73 in monkey, and 0.61 in human.

In vitro and in vivo metabolite profiling suggested that the primary clearance mechanisms for PF-06700841 (brepocitinib) were through CYP450-mediated oxidation. Renal and biliary excretion of parent drug was limited in the rat. No unique human metabolites were observed in vitro compared to metabolite profiles in rat and monkey. In vitro studies using human recombinant CYP450 enzymes suggested that CYP3A4 was the primary enzyme responsible for clearance of PF-06700841 (brepocitinib), with minor contributions from CYP1A2, 2C19, and 2D6. PF-06700841 (brepocitinib) did not significantly inhibit the major CYP450 enzymes by competitive inhibition or time-dependent inhibition in the presence or absence of NADPH (IC_{50} values >100 μM). PF-06700841 (brepocitinib) did not cause significant induction of CYP1A2, 2B6, or 3A4 enzyme activity or mRNA expression at concentrations up to 100 μM. PF-06700841 (brepocitinib) also did not inhibit the major UDP-glucuronosyltransferase (UGT) enzymes (IC_{50} values >100 μM). These results indicated that the risk of PF-06700841 (brepocitinib) to mediate a CYP450 and/or UGT drug interaction at clinically relevant exposures was low (steady state C_{max}, u 722 nM at 60 mg QD). PF-06700841 (brepocitinib) did not significantly inhibit the organic anion transporting polypeptide (OATP) 1B1 (IC_{50} 159 μM) or OATP1B3 (IC_{50} >300 μM). However, PF-06700841 (brepocitinib) did inhibit MDR1 (IC_{50} 7.8 μM), organic cation transporter (OCT) 2 (IC_{50} 1.1 μM), multidrug and toxin extrusion (MATE) 1 (IC_{50} 7.7 μM) and MATE2K (IC_{50} 17 μM). SimCYP® modeling indicated a low/small risk of a transporter mediated drug interaction with digoxin (MDR1; C_{max}/AUC ratios: 1.17/1.08) or metformin (OCT/MATE1; C_{max}/AUC ratios: 1.19/1.21) following a top dose of 60 mg PF-06700841 (brepocitinib) QD at steady state.

1.4. Non-Clinical Safety Studies

1.4.1. Non-Clinical Safety Studies with PF-06651600 (ritlecitinib)

In nonclinical toxicity studies following once daily oral administration of PF-06651600 (ritlecitinib) in rats and dogs up to 6 and 9-months duration respectively, key target organs included effects in bone marrow, and the immune and hematolymphopoietic systems (pharmacology-related effects) in both species and axonal dystrophy (swelling) in the nervous system along with auditory threshold and brainstem auditory evoked potential

(BAEP) waveform deficits in dogs only. The NOAELs in the pivotal toxicity studies were 200 mg/kg/day in rats (mean unbound C_{max} of 16,800 ng/mL and AUC_{24} of 53,700 ng•h/mL) and 10 mg/kg/day in dogs (mean unbound C_{max} of 1910 ng/mL and unbound AUC_{24} of 7940 ng•h/mL). In embryofetal development studies, fetal skeletal and visceral malformations, skeletal variations, and decreased fetal weights were observed in rats and rabbits; the developmental NOAEL in rats was 75 mg/kg (unbound C_{max} of 7770 ng/mL; unbound AUC_{24} of 17,000 ng•h/mL) and in rabbits was 25 mg/kg/day (unbound C_{max} of 4470 ng/mL; AUC_{24} of 13,200 ng•h/mL). PF-06651600 (ritlecitinib) was not mutagenic or clastogenic, but was aneugenic in vitro. In vitro aneugenicity is a common observation with kinase inhibitors. PF-06651600 (ritlecitinib) did not induce micronuclei in vivo in rats. There was no evidence of cutaneous or ocular phototoxicity following once daily oral administration of PF-06651600 (ritlecitinib) in rats.

In the rat fertility study, adverse effects were limited to higher preimplantation loss and lower implantation sites in naïve untreated female rats mated with male rats administered 200 mg/kg/day. These effects occurred in the absence of any effects on spermatogenesis (sperm counts, sperm motility, sperm production rate, or sperm morphology). There were no adverse effects in females at 200 mg/kg/day (mean unbound C_{max} of 17,800 ng/mL and AUC_{24} of 58,600 ng•h/mL) or in males at the NOAEL of 60 mg/kg/day (mean unbound C_{max} of 7,240 ng/mL and AUC_{24} of 14,700 ng•h/mL).

Details of the nonclinical safety program are provided in the current Investigator's Brochure.

1.4.2. Non-Clinical Safety Studies with PF-06700841 (brepocitinib)

This Section is no longer applicable to newly enrolled participants under PA5.

No adverse findings were observed in oral repeat-dose toxicity studies with PF-06700841 (brepocitinib) in rats and monkeys up to 6 and 9 months in duration, respectively. Test article-related, nonadverse, target organs identified include the immune and hemolymphatic systems (thymus, spleen, lymph nodes, and bone marrow), gastrointestinal tract (body weight and weight gain effects), and adrenal gland (vacuolation). The findings in the thymus, spleen, lymph nodes, and bone marrow are consistent with the pharmacological activity of PF-06700841 (brepocitinib). The NOAELs in the pivotal 6-and 9-month toxicity studies were 45 mg/kg/day in rats (unbound C_{max} of 8280 ng/mL and AUC_{24} of 69,700 ng•h/mL) and 20 mg/kg/day in monkeys (unbound C_{max} of 2260 ng/mL and AUC_{24} of 10,700 ng•h/mL). Adverse findings in the central nervous system (decreased activity, mortality, prostration, convulsions) were observed at high exposures in pregnant, but not nonpregnant, rabbits. In pivotal embryo-fetal development studies adverse PF-06700841 (brepocitinib)-related developmental effects occurred (lower embryo-fetal viability and mean fetal body weights, fetal skeletal malformations, external malformations).

The developmental NOAEL in rats and rabbits was 1.5 or 1 mg/kg/day with unbound AUC_{24} exposure of 1820 or 608 ng•h/mL), respectively. In oral rat fertility studies PF-06700841 (brepocitinib)-related adverse effects in females (lower number of viable embryos due to higher early resorptions) occurred. There were no adverse findings in males. The NOAEL for male fertility or female fertility and early embryonic development was 55 or 3 mg/kg/day,

resulting in unbound AUC_{24} exposures of 70,400 or 2890 ng•h/mL, respectively. No effects on female reproductive organs, as assessed by histopathologic examination, were noted in either the rat or monkey repeat-dose toxicity studies.

PF-06700841 (brepocitinib) is not mutagenic in bacterial reverse mutation assays. Although PF-06700841 (brepocitinib) was positive for micronuclei formation in vitro (through an aneugenic mechanism), it did not induce micronuclei in vivo in rats at 55 mg/kg/day (unbound C_{max} = 7730 ng/mL and AUC_{24} = 88,300 ng•h/mL), the highest dose tested in the 1-month oral toxicity study.

Please refer to Section 4.4.1 for the contraception requirements for participation in this study.

Further details of the nonclinical safety program are provided in the current Investigator's Brochure.

1.5. Summary of Clinical Experience

1.5.1. Summary of Clinical Experience with PF-06651600 (ritlecitinib)

PF-06651600 (ritlecitinib) has been explored in 7 completed Phase 1 trials in healthy subjects and in 3 Phase 2 trials in subjects with RA (B7981006), AA (B7931005) and vitiligo (B7981019). There are 3 ongoing studies in AA (B7981015, B7981032, B7981037), and 1 each in CD (B7981007), and RA (B7921023).

As of 31 August 2020, PF-06651600 (ritlecitinib) has been explored in 3 Phase 1 trials in healthy participants, and in 2 completed Phase 2 trials, in participants with RA and AA. There are ongoing Phase 2 studies in ulcerative colitis, Crohn's disease, alopecia areata, and vitiligo; a Phase 2b/3 study in alopecia areata, and a Phase 3 study in alopecia areata.

Based on the current clinical and nonclinical experience with PF-06651600 (ritlecitinib) and other information from other JAK inhibitors (eg, Xeljanz® [tofacitinib], Jakafi® [ruxolitinib], baricitinib, GLPG0634, and VX-509), the potential risks for PF-06651600 (ritlecitinib) include: (1) viral reactivation; (2) serious infections and opportunistic infections; (3) malignancy and lymphoproliferative disorders; (4) decreased lymphocyte counts; (5) change in neutrophil counts; (6) decreased platelet count; (7) alterations in the lipid profile; and (8) dermatologic effects (rash/acne); and (9) thromboembolism. Increased incidences of deep vein thrombosis (DVT) and pulmonary embolism (PE) have recently been identified as potential risks for these other JAK inhibitors. To date, no adverse drug reactions for PF-06651600 (ritlecitinib) have been identified.

Additional information on the safety, tolerability, and efficacy of PF-06651600 (ritlecitinib), including information about ongoing Phase 2/3 studies in other indications may be found in the current version of the PF-06651600 (ritlecitinib) IB.

1.5.1.1. Summary of Clinical Safety of PF-06651600 (ritlecitinib)

1.5.1.1.1. Study B7981001

B7981001 was a Phase 1, randomized, double-blind, third-party open, placebo-controlled, single- and multiple-dose escalation, parallel group study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of PF-06651600 (ritlecitinib) in healthy subjects. This single ascending dose (SAD) and multiple ascending dose (MAD) study was the first evaluation of PF-06651600 (ritlecitinib), a JAK3/TEC inhibitor, in humans. During the SAD period, a total of 64 subjects were randomized and received doses of 5, 20, 50, 100, 200, 400 or 800 mg of PF-06651600 (ritlecitinib) or placebo in a dose escalation format. During the MAD period, a total of 51 subjects were randomized and received doses of 50 mg QD, 100 mg BID (twice a day), 200 mg QD, 400 mg QD, or 200 mg BID or placebo for 14 days.

1.5.1.1.1.1. Brief Summary of Adverse Events

1.5.1.1.1.1.1. SAD Period

During the SAD period, 31 subjects had a total of 42 treatment-emergent adverse events (TEAEs), 30 of which were considered to be treatment-related. There were no deaths, severe adverse events (AEs), temporary discontinuations, or dose reductions due to AEs reported in this study.

1.5.1.1.1.1.2. MAD Period

During the MAD period, 35 subjects had a total of 90 TEAEs, 75 of which were considered to be treatment-related. The treatment groups with the most AEs were the PF-06651600 (ritlecitinib) 400-mg QD (39 AEs in 17 subjects), 200-mg BID (16 AEs in 6 subjects), and 100-mg BID treatment groups (14 AEs in 4 subjects). There were no deaths, temporary discontinuations, or dose reductions due to AEs reported in the study.

1.5.1.1.1.2. Incidence of Adverse Events

1.5.1.1.1.2.1. SAD Period

The System Organ Classes (SOC) with the greatest number of subjects reporting AEs in the SAD period were Infections and infestations (8 subjects); Nervous system disorders (7 subjects); Gastrointestinal disorders (5 subjects); Musculoskeletal and connective tissue disorders (5 subjects); and Respiratory, thoracic, and mediastinal disorders (5 subjects). Most TEAEs reported in the SOCs of Gastrointestinal disorders, Musculoskeletal and connective tissue disorders, and Nervous system disorders were treatment-related.

There were generally few TEAEs in the SAD period, most of which occurred in a single subject, with the exception of headache and nasopharyngitis (experienced by 5 subjects each) and oropharyngeal pain (experienced by 4 subjects). Most of the TEAEs were mild in severity, except for the following AEs that were moderate in severity: 1 adverse event (AE) each in the PF-06651600 (ritlecitinib) 5-mg (oropharyngeal pain), 20-mg (musculoskeletal pain), and 200-mg (subcutaneous abscess) treatment groups, respectively; 2 AEs in the placebo group (dry skin and limb injury); 3 AEs in the PF-06651600 (ritlecitinib) 400-mg treatment group (nasopharyngitis, pilonidal cyst, and headache); and 5 AEs in the

PF-06651600 (ritlecitinib) 100-mg treatment group (abdominal pain, arthralgia, rash maculo-papular, and 2 AEs of headache).

1.5.1.1.1.2.2. MAD Period

The SOCs with the greatest number of subjects reporting AEs in the MAD period were Skin and subcutaneous tissue disorders (21 subjects); Gastrointestinal disorders (18 subjects); Nervous system disorders (12 subjects); Musculoskeletal and connective tissue disorders (6 subjects); and Respiratory, thoracic, and mediastinal disorders (5 subjects). Most TEAEs reported in the SOCs of Skin and subcutaneous tissue disorders, Gastrointestinal disorders, and Nervous system disorders were treatment-related. The most frequently reported TEAEs across all treatment groups were diarrhea and headache, which were experienced by 8 and 7 subjects, respectively.

1.5.1.1.1.3. Analysis of Adverse Events

All TEAEs reported in the SAD period were mild except for the following AEs that were moderate in severity: 1 AE each in the PF-06651600 (ritlecitinib) 5-, 20-, and 200-mg treatment groups; 2 AEs each in the placebo group; 3 AEs in the PF-06651600 (ritlecitinib) 400-mg treatment group; and 5 AEs in the PF-06651600 (ritlecitinib) 100-mg treatment group.

All TEAEs reported in the MAD period were mild or moderate in intensity, except for 1 AE each in the PF-06651600 (ritlecitinib) 400-mg QD and 200-mg BID treatment groups, which were severe in intensity.

1.5.1.1.1.4. Permanent Discontinuations Due to Adverse Events

1.5.1.1.1.4.1. SAD Period

Four (4) subjects discontinued from the study due to AEs, including 1 subject each in the placebo and PF-06651600 (ritlecitinib) 100-, 200-, and 400-mg treatment groups. Subject PPD experienced an AE of erythema after receiving placebo; the AE was considered to be treatment-related by the investigator and mild in severity. Subject PPD experienced an AE of rash maculo-papular after receiving PF-06651600 (ritlecitinib) 100 mg; the AE was considered to be treatment-related by the investigator and moderate in severity. Subject PPD experienced an Serious Adverse Event (SAE) of subcutaneous abscess after receiving PF-06651600 (ritlecitinib) 200 mg; the SAE was considered to be treatment-related by the investigator and moderate in severity. Subject PPD experienced an SAE of pilonidal cyst after receiving PF-06651600 (ritlecitinib) 400 mg; the AE was considered to be treatment-related by the investigator and moderate in severity.

1.5.1.1.1.4.2. MAD Period

Two (2) subjects discontinued from the study due to AEs, including 1 subject each in the PF-06651600 (ritlecitinib) 200-mg BID and 400-mg QD treatment groups. Subject PPD experienced an AE of rash maculo-papular after receiving PF-06651600 (ritlecitinib) 200 mg BID; the AE was considered to be treatment-related by the investigator

and severe in severity. Subject PPD experienced an AE of herpes zoster after receiving PF-06651600 (ritlecitinib) 400-mg QD; the AE was considered to be treatment-related by the investigator and moderate in severity.

1.5.1.1.1.5. Deaths

There were no deaths among subjects who participated in Study B7981001.

1.5.1.1.1.6. Serious Adverse Events

1.5.1.1.1.6.1. SAD Period

Two (2) treatment-emergent SAEs occurred in 2 subjects in the SAD period; both were considered to be treatment-related by the investigator.

1.5.1.1.1.6.2. MAD Period

A treatment-emergent SAE occurred in 1 subject in the PF-06651600 (ritlecitinib) 400-mg QD treatment group. The SAE, naïve varicella, was considered to be treatment-related by the investigator.

1.5.1.1.1.7. Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths occurred during the conduct of this study. Six (6) subjects discontinued from the study due to AEs, while 3 subjects experienced SAEs. Other significant non-serious AEs included rash maculo-papular, erythema, and rash pruritic; these events were considered to be moderate in severity.

1.5.1.1.1.8. Clinical Laboratory Evaluation

None of the laboratory abnormalities (without regard to baseline abnormality) were reported as AEs, and none were considered clinically significant. There was little median % change in neutrophil count (1% increase). Four (4) subjects (doses >200 mg daily) in the PF-06651600 (ritlecitinib) treatment developed a lymphocyte count <500 cells/mm^3. Overall, 36 and 42 subjects had laboratory abnormalities during the SAD and MAD periods, respectively. The most frequently reported laboratory abnormalities in the SAD period were high low-density lipoprotein (LDL) cholesterol concentrations (12 subjects), high numbers of absolute monocytes (11 subjects), and positive urine blood tests (8 subjects). The most frequently reported laboratory abnormalities in the MAD period were high LDL cholesterol concentrations (20 subjects), low lymphocyte percentages (10 subjects), and high numbers of absolute monocytes (10 subjects).

1.5.1.2. Study B7981003

B7981003 was a Phase 1, open-label, single-dose, 3-way crossover study to evaluate the bioavailability (BA) of a solid dose formulation of PF-06651600 (ritlecitinib) relative to an oral solution formulation under fasting conditions and the effect of a high fat meal on the BA of the solid dosage formulation of PF-06651600 (ritlecitinib) in healthy subjects. A total of

14 subjects were randomized to study treatment and treated with 50 mg PF-06651600 (ritlecitinib) solution/tablets under fasted and fed conditions completed the study.

No temporary discontinuations were reported in the study.

1.5.1.2.1. Analysis of Adverse Events

A total of 20 TEAEs were reported in the study of which 14 were reported as treatment-related. All AEs were mild or moderate in severity.

1.5.1.2.2. Permanent Discontinuations Due to Adverse Events

Subject PPD, while having treatment with 50 mg PF-06651600 (ritlecitinib) oral solution under fasted condition, permanently discontinued from treatment due to an AE (urethritis) that was considered unrelated to study treatment. The AE was moderate in severity and resolved.

1.5.1.2.3. Deaths

There were no deaths among subjects who participated in Study B7981003.

1.5.1.2.4. Serious Adverse Events

There were no serious adverse events in subjects who participated in Study B7981003.

1.5.1.2.5. Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths occurred during the conduct of this study. One (1) subject discontinued from the study due to an AE. There were no SAEs or other significant non-serious AEs in subjects who participated in Study B7981003.

1.5.1.2.6. Clinical Laboratory Evaluation

None of the laboratory abnormalities were considered to be clinically significant or reported as AEs by the Investigator.

1.5.1.3. Study B7981008

Study B7981008 is a completed Phase 1, randomized, double-blind, third-party open, placebo-controlled study to evaluate the safety, tolerability, PK and pharmacodynamics after multiple oral doses of PF-06651600 (ritlecitinib) in healthy Japanese adult subjects. Four subjects received oral PF-06651600 (ritlecitinib) 200 mg QD for 10 days, and 2 subjects received the matched placebo.

1.5.1.3.1. Safety Data

One (1) TEAE was reported by 1 subject treated with placebo. This AE was mild in severity and was considered treatment-related. A total of 2 TEAEs were reported by 1 subject treated with PF-06651600 (ritlecitinib). Both AEs were mild in severity, of which 1 AE was considered treatment-related.

No death, SAEs, severe AEs, permanent or temporary discontinuations or dose reductions due to AE were reported during this study.

In the placebo treatment group, dry skin was reported by 1 subject and was considered treatment-related by the investigator. In the PF-06651600 (ritlecitinib) treatment group, musculoskeletal stiffness and oropharyngeal pain were experienced by 1 subject, with musculoskeletal stiffness considered treatment-related. None of the AEs were considered clinically significant.

1.5.1.3.2. Analysis of Adverse Events

There were generally few TEAEs in both treatment groups, with a total of 3 TEAEs reported in this study. All TEAEs were mild in severity. There were no deaths or SAEs in this study and no subjects discontinued from the study.

1.5.1.3.3. Permanent Discontinuations Due to Adverse Events (None)

There were no permanent discontinuations due to AEs reported in this study.

1.5.1.3.4. Dose Reductions or Temporary Discontinuations Due to Adverse Events (None)

There were no dose reductions or temporary discontinuations due to AEs.

1.5.1.3.5. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events (None)

There were no deaths among subjects who participated in this study.

1.5.1.3.6. Other Serious Adverse Events (None)

There were no other SAEs in this study.

1.5.1.3.7. Clinical Laboratory Evaluation

No subjects had laboratory abnormalities in the placebo treatment group. Two (2) subjects in the PF-06651600 (ritlecitinib) 200 mg treatment group were reported to have laboratory abnormalities). One (1) subject met abnormal criterion of lymphocytes/leukocytes (<0.8 × Lower Limit of Normal (LLN)) and 1 subject met abnormal criteria of lymphocytes/leukocytes (<0.8 × LLN) and monocytes (>1.2 × Upper Limit of Normal (ULN)). None of laboratory abnormalities were reported as AEs or considered to be clinically significant by the investigator.

1.5.1.3.8. Electrocardiogram (ECG)

Only 1 subject treated with placebo was reported to meet the maximum QT interval >450 msec and <480 msec and maximum QT interval increase from baseline ≥30 msec and <60 msec in this study. Additionally, there were no subjects meeting the criteria of QT values >500 msec. No ECG values and changes from baseline were considered clinically significant and none of them were reported as AEs.

1.5.1.3.9. Vital Signs

No absolute values or change from baseline in vital signs were considered to be clinically significant and reported as AEs by the investigator.

1.5.1.4. Study B7981016

Study B7981016 was a non-randomized, open-label, multiple-dose, parallel-cohort study to investigate the effect of hepatic impairment on the plasma PK, safety and tolerability of PF-06651600 (ritlecitinib). According to the protocol, 2 parts (Part 1 and Part 2) were planned, and Part 2 was to be conducted only if PF-06651600 (ritlecitinib) AUC_{24} geometric mean ratio for moderate hepatic impairment group compared to normal group was ≥2.0 (the decision criterion to proceed to Part 2). This study was completed after Part 1 since the criterion to proceed to Part 2 was not met. Starting on Day 1, participants received PF-06651600 (ritlecitinib) 30 mg once daily (QD) up to Day 9. On Day 10 the participants received PF-06651600 (ritlecitinib) 30 mg QD after an 8-hour fast.

1.5.1.4.1. Safety Data

Overall, 7 all-causality AEs were reported in 6 (33.3%) participants, of whom 5 (27.8%) participants experienced treatment-related AEs (severe, moderate, and mild treatment-related AEs were reported in 1, 1, and 3 participants, respectively), 1 (5.6%) participant experienced an SAE, and 2 (11.1%) participants discontinued the study drug due to AEs (1 due to thrombocytopenia and the other due to hepatic enzyme increased). In participants with moderate hepatic impairment and in participants with normal hepatic function, all-causality AEs were reported in 4 (40.0%) and 2 (25.0%) participants, respectively, and treatment-related AEs were reported in 4 (40.0%) and 1 (12.5%) participant, respectively. Among all-causality AEs, thrombocytopenia, diarrhoea, cholestasis, arthropod bite, and hepatic enzyme increased were reported in 1 participant each, and there were 2 participants who developed headache.

The SAE, severe AE, and discontinuations from study drug due to AEs were reported only in participants with moderate hepatic impairment while there were none in participants with normal hepatic function (1 [10.0%] versus 0, 1 [10.0%] versus 0, and 2 [20.0% vs 0], respectively).

One participant with moderate hepatic impairment developed an SAE of cholestasis (total bilirubin, ALT, AST, and alkaline phosphatase were 22.8 mg/dL, 51 U/L, 74 U/L, and 267 U/L relative to 1.6 mg/dL, 45 U/L, 60 U/L, and 215 U/L at Baseline, respectively) 29 days after the last dose of PF-06651600 (ritlecitinib). The event was considered as treatment related by the investigator. The event was reported as resolved on Day 111.

There were 2 AEs resulting in permanent discontinuation from study drug, both of which were reported in participants with moderate hepatic impairment. One participant experienced thrombocytopenia (platelet count 95×10^9 /L relative to 124×10^9 /L at Baseline), which was considered mild in severity and treatment related by the investigator. The second participant experienced hepatic enzyme increased (ALT and AST: 204 U/L and 126 U/L, relative to 69 U/L and 51 U/L at Baseline, respectively), which was considered moderate in severity and

treatment related by the investigator. In both cases the study drug was permanently discontinued due to those events and the events were later reported as resolved.

1.5.1.5. Study B7981017

This was a Phase 1, randomized, 2-way cross-over, multiple dose, open-label study of the effect of PF-06651600 (ritlecitinib) on midazolam and efavirenz pharmacokinetics (PKs) in healthy participants. Participants were planned to be randomized to 1 of 2 treatment sequences. A total of approximately 12 healthy male and/or female participants were planned to be enrolled in the study so that approximately 6 participants were enrolled in each treatment sequence. Each treatment sequence consisted of 2 periods in a single fixed sequence.

1.5.1.5.1. Safety Data

PF-06651600 (ritlecitinib), midazolam and efavirenz were safe and well-tolerated in the healthy participants evaluated in this study, when midazolam and efavirenz administered alone and coadministered with multiple doses of PF-06651600 (ritlecitinib). There were no deaths in the study. No SAEs or severe AEs were reported. No participants discontinued from study or study drug due to an AE. No dose reduction or temporary discontinuation due to an AE was reported.

1.5.1.6. Study B7981018

B7981018 was a Phase 1, randomized, 2-way cross-over, multiple dose, open-label study of the effect of multiple dose PF-06651600 (ritlecitinib) (200 mg QD) on single dose OC PK in healthy post-menopausal female volunteers. The OC evaluated was levonorgestrel (LN) and ethinyl estradiol (EE) at doses of 150 µg and 30 µg, respectively.

1.5.1.6.1. Safety Data

A total of 4 participants reported at least 1 AE during the treatment. Six all-causalities TEAEs by preferred term were reported. None of these TEAEs were considered treatment related. All the TEAEs were mild in severity. The most commonly reported TEAE by preferred term was constipation, which was reported by 4 participants administered with multiple doses of PF-06651600 (ritlecitinib) 200 mg QD, and by 1 participant administered with multiple doses of PF-06651600 (ritlecitinib) 200 mg QD and single-dose OC. All the participants with TEAE of constipation were treated with prune juice. TEAE of arthralgia was reported by 1 participant administered with multiple doses of PF-06651600 (ritlecitinib) 200 mg QD and single-dose OC.

No deaths, SAEs, severe AEs, discontinuations from the study due to AEs, temporary discontinuations or dose reduction due to AEs, or medication errors were reported in any treatments. None of laboratory abnormalities were reported as an AE. None of the laboratory abnormalities were considered to be clinically significant by the investigator.

1.5.1.7. Study B7981021

B7981021 was a single-blind, randomized, 5-period, cross-over study in healthy male and/or female adult participants to assess the sensory characteristics, overall palatability and preference of different prototype active formulations of PF-06651600 (ritlecitinib) to support the selection of an age appropriate dosage form for PF-06651600 (ritlecitinib).

1.5.1.7.1. Safety Data

There were no deaths, SAEs, severe AEs, temporary discontinuations or dose reductions due to AEs reported in this study. One all-causality TEAE of gingival bleeding was reported by 1 participant following Treatment A (API in water), which resulted in permanent discontinuation from the study. The event was mild in severity and not considered as treatment related. No abnormalities or clinically significant findings of the laboratory data, vital signs values and ECG data were reported in this study.

1.5.1.8. Study B7981022

Study B7981022 was a Phase 1, open-label, single dose, randomized, 4-period, cross-over design in a single cohort of approximately 12 healthy male or female participants at a single center.

1.5.1.8.1. Safety Data

For each PF-06651600 (ritlecitinib) treatment (Tablet, Capsule, Large API particle size capsule, and Overencapsulated capsule), all 12 participants were evaluated for AEs. The greatest number of AEs was reported for PF-06651600 (ritlecitinib) treatment with Over-encapsulated capsule. Two participants reported 2 TEAEs for PF-06651600 (ritlecitinib) treatment with Tablet, of which none was determined by the investigator as treatment related. One participant reported 1 TEAE for PF-06651600 (ritlecitinib) treatment with Capsule, which was determined by the investigator as treatment related. No TEAEs were reported for PF-06651600 (ritlecitinib) treatment with Large API particle size capsule. Four participants reported 5 TEAEs for PF-06651600 (ritlecitinib) treatment with Overencapsulated capsule, of which 2 TEAEs reported by 1 participant were determined by the investigator as treatment related.

There were no deaths in the study. No SAEs or severe AEs were reported. No participants discontinued from study or study drug due to an AE. No dose reduction or temporary discontinuation due to an AE was reported.

1.5.1.9. Study B7981023

Study B7981023 was a Phase 1, open-label, fixed sequence 2-period study to investigate the effect of multiple doses of itraconazole on the pharmacokinetic of a single dose of PF-06651600 (ritlecitinib) in healthy participants.

1.5.1.9.1. Safety Data

Seven participants reported 11 TEAEs, 6 participants reported 15 TEAEs, and 4 participants reported 5 TEAEs after receiving PF-06651600 (ritlecitinib) 30 mg, itraconazole 200 mg, and co-administration of PF-06651600 (ritlecitinib) and itraconazole, respectively. Among these TEAEs, 7, 14, 2 were considered as treatment-related, respectively. The majority of the TEAEs (8/11, 15/15 and 4/5 after receiving PF-06651600 (ritlecitinib) 30 mg, itraconazole 200 mg, and co-administration of PF-06651600 (ritlecitinib) and itraconazole, respectively) were mild. In general, each TEAE was reported by single participants. The most commonly reported TEAEs by system organ class (SOC) across 3 treatments was Gastrointestinal Disorders, reported by 3, 5, and 2 participants after receiving PF-06651600 (ritlecitinib) 30 mg, itraconazole 200 mg, and co-administration of PF-06651600 (ritlecitinib) and itraconazole, respectively. All the TEAEs under "Gastrointestinal Disorders" were considered as treatment-related. No death, SAEs, severe AEs, permanent or temporary discontinuations or dose reductions due to AE were reported during this study. None of the laboratory findings were considered as clinically significant.

1.5.1.10. Study B7981024

B7981024 was a Phase 1, 2-period fixed sequence, multiple dose, open-label study to estimate the effect of PF-06651600 (ritlecitinib) on rosuvastatin pharmacokinetics in healthy participants. A total of 12 participants were treated with PF-06651600 (ritlecitinib) multiple dose of 200 mg QD for 10 days.

1.5.1.10.1. Safety Data

Single oral dose of rosuvastatin when administered alone or concomitantly with multiple doses of PF-06651600 (ritlecitinib) was safe and well-tolerated in healthy participants. All of TEAEs were mild in severity with the exception of a single AE of moderate back pain in the rosuvastatin 10 mg treatment group, considered as treatment-related by the investigator. There were no SAEs, severe AEs, dose reductions or discontinuations due to AEs during the study. None of the laboratory abnormalities were reported as adverse events or considered to be clinically significant by investigator.

Study B7981028

B7981028 was a Phase 1, open-label, fixed sequence study to evaluate the steady state pharmacokinetic drug-drug interaction between PF-06650833 and PF-06651600) ritlecitinib in healthy adult participants. A total of 15 participants were treated with multiple doses of PF-06650833 400 mg QD and multiple doses of PF-06651600 (ritlecitinib) 100 mg.

1.5.1.10.2. Safety Data

Five TEAEs were reported in 5 (33.3%) participants following administration of PF-06650833 400 mg QD alone. Two (2) of these TEAEs reported in 2 (13.3%) participants were considered treatment related. Fourteen TEAEs were reported in 8 (53.3%) participants following the administration of PF-06651600 (ritlecitinib) 100 mg QD as monotherapy. Four of these TEAEs reported in 4 (26.7%) participants were considered treatment related.

Eleven TEAEs were reported in 4 (26.7%) participants following the co-administration of PF-06650833 400 mg QD and PF-06651600 (ritlecitinib) 100 mg QD. One of these TEAEs was considered treatment related. The most frequently reported all-causality TEAEs by SOC were Nervous System Disorders after receiving PF-06651600 (ritlecitinib) 100 mg QD monotherapy, which were reported in 4 (26.7%) participants. Regardless of SOC, the most commonly reported TEAE by preferred term (PT) was somnolence after receiving PF-06651600 (ritlecitinib) 100 mg QD monotherapy, which was reported in 3 (20%) participants. All TEAEs were considered mild in severity. All treatment-related TEAEs occurred in 1 participant each except for nausea (after receiving PF-06651600 (ritlecitinib) 100 mg QD monotherapy), which occurred in 2 participants. There were no SAEs, severe AEs, discontinuations due to AEs, or dose reductions or temporary discontinuations from treatment due to the AEs. None of the laboratory abnormalities were considered clinically significant.

1.5.1.11. Study B7981035

B7981035 was a Phase 1, randomized, 2-way cross-over, multiple-dose, open-label study of the effect of multiple doses PF-06651600 (ritlecitinib) on single dose combination OC pharmacokinetics (PK) in healthy female participants. Twenty-eight participants were treated with both Treatments A (single dose of combination OC in the form of 1 Portia (ethinyl estradiol [EE] and levonorgestrel [LN] or equivalent oral tablet, containing EE 30 µg and LN 150 µg) and B (single dose of combination OC in the form of 1 Portia (EE and LN) or equivalent oral tablet, containing of EE 30 µg and LN 150 µg on the morning of Day 10 following 9 days of PF-06651600 (ritlecitinib) dosed at 50 mg po QD. On Day 10, the morning dose of PF-06651600 (ritlecitinib) and the single OC dose were administered simultaneously. Dosing with PF-06651600 (ritlecitinib) at 50 mg po QD continued through until Day 13). One participant was only treated with Treatment B.

1.5.1.11.1. Safety Data

All AEs occurred during the treatment period of repeated doses of PF-06651600 (ritlecitinib) (before coadministration of PF-06651600 (ritlecitinib) and OC), except 1 AE of headache which occurred following the single dose of OC. The incidence of TEAEs was low and the severity of TEAEs was mild or moderate in this study. Two participants permanently discontinued from study treatment due to AE(s) following repeated doses of PF-06651600 (ritlecitinib) (before co-administration of PF-06651600 (ritlecitinib) and OC). There were no temporary discontinuations and dose reductions resulting from AEs. There were no SAEs or severe AEs reported in this study. No laboratory abnormalities, vital signs observations or physical findings were clinically significant.

1.5.1.12. Study B7981006

B7981006 was a Phase 2a, randomized, double-blind, parallel group, placebo-controlled, multi-center study to assess the efficacy and safety profile of PF-06651600 (ritlecitinib) in seropositive subjects with moderate to severe active Rheumatoid Arthritis (RA) with an inadequate response to methotrexate. A total of 70 subjects were randomized to study treatment, 28 subjects received placebo and 42 subjects received PF-06651600 (ritlecitinib).

1.5.1.12.1. Analysis of Adverse Events

The majority of all causality TEAEs (28 out of 36) were mild in severity. Overall, the most frequently reported TEAEs were:

- Influenza (3 [4.3%] subjects in total: 3 [7.1%] subjects in the PF-06651600 (ritlecitinib) group and 0 subjects in the placebo group);
- Pruritus (3 [4.3%] subjects in total: 2 [4.8%] subjects in the PF-06651600 (ritlecitinib) group and 1 [3.6%] subject in the placebo group);
- Lymphopenia (3 [4.3%] subjects in total: 3 [7.1%] subjects in the PF-06651600 (ritlecitinib) group and 0 subjects in the placebo group);
- Headache (3 [4.3%] subjects in total: 0 subjects in the PF-06651600 (ritlecitinib) group and 3 [10.7%] subjects in the placebo group).

The majority of all treatment-related TEAEs (9 out of 11) were mild in severity. Overall, the most frequently reported treatment-related TEAE was Lymphopenia (2 [2.9%] subjects in total: 2 [4.8%] subjects in the PF-06651600 (ritlecitinib) group and 0 subjects in the placebo group).

1.5.1.12.2. Permanent Discontinuations due to Adverse Events

A total of 3 subjects (7.1%) in the PF-06651600 (ritlecitinib) group and 0 subjects in the placebo group permanently discontinued due to TEAEs. One (1) subject discontinued due to suicidal ideation, 1 subject discontinued due to lymphopenia, and the third subject discontinued due to hepatotoxicity.

1.5.1.12.3. Deaths

There were no deaths among subjects who participated in Study B7981006.

1.5.1.12.4. Serious Adverse Events

There were no SAE in subjects who participated in study B7981006.

1.5.1.12.5. Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

No deaths occurred in this study. No SAEs were reported in this study. A total of 3 subjects experienced TEAEs that led to permanent discontinuation due to TEAEs during the study. No clinically meaningful differences between the PF-06651600 (ritlecitinib) treatment group and placebo were observed with regard to AEs of special interest.

1.5.1.12.6. Clinical Laboratory Evaluation

Without regard to baseline abnormality, 70 (100%) of the 70 treated subjects experienced laboratory abnormalities. Overall, the most frequently occurring laboratory abnormality was erythrocyte sedimentation rate, reported by 68 (97.1%) subjects.

Three (3) subjects (7.1%) in the PF-06651600 (ritlecitinib) treatment group met the discontinuation criterion of hemoglobin <8 g/dL. One (1) subject (2.4%) in the PF-06651600 (ritlecitinib) treatment group met the discontinuation criterion of lymphocytes (absolute) $<0.5 \times 10^3/mm^3$.

By the Week 8 time point (as early as 2 weeks), in the PF-06651600 (ritlecitinib) group, there were decreases in the median platelet counts (25% change from baseline), lymphocyte counts (21% change from baseline), neutrophil counts (24% change from baseline), and hemoglobin (3% change from baseline). None of these were deemed to be clinically relevant by the investigator and values returned to near baseline by the 12-week follow-up visit.

1.5.1.13. Study B7931005

B7931005 was a Phase 2a, randomized, double-blind, parallel-group, multicenter study to investigate the safety and efficacy of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo in adult participants with AA with scalp hair loss of more than 50%. The study consisted of 3 periods: a 24-week double-blind treatment period, an up to 48-week SBE period, and a 24-week COE period. The study included 2 drug holiday periods of 4 weeks each, and 2 follow-up periods of 4 weeks each. A total of 142 participants were randomized to study treatment: 47 participants received placebo, 48 received PF-06651600 (ritlecitinib) for an induction dose of 200 mg QD for 4 weeks followed by maintenance dosing of 50 mg QD for 20 weeks, and 47 received PF-06700841 (brepocitinib) for an induction dose of 60 mg QD for 4 weeks followed by maintenance dosing of 30 mg QD for 20 weeks during the first 24-week treatment period.

1.5.1.13.1. Safety Data

The most frequently (≥5%) reported all causalities TEAEs were Nasopharyngitis and Headache (12.5% each), Acne (10.4%), Diarrhoea and Upper respiratory tract infection (8.3% each), Dermatitis atopic, Folliculitis, and Nausea (6.3% each). The majority of treatment-related TEAEs (67 out of 84) were mild. The most commonly reported treatment related- TEAEs for PF-06651600 (ritlecitinib) by preferred term were upper respiratory tract infection (6.3%), and acne, nausea, and headache (each at 4.2%).

Two participants discontinued PF-06651600 (ritlecitinib) due to AEs and continued in the study; the AEs were angioedema and blood creatine phosphokinase increased. A total of 5 participants had a temporary discontinuation of study drug due to AEs: due to diarrhoea and due to gastroenteritis in PF-06651600 (ritlecitinib) treatment group; and due to increased transaminases, due to headache, and due to abdominal discomfort in PF-06700841 (brepocitinib) treatment group. All these AEs resolved and were mild in severity. Only abdominal discomfort was considered treatment-related by the investigator. There were no clinically significant auditory changes in the active treatment groups. A mild TEAE of deafness neurosensory was reported in 1 participant in placebo group. There were no SAEs or deaths reported with PF-06651600 (ritlecitinib) in Study B7931005.

The most frequently laboratory abnormality which met retest criterion was total neutrophils (absolute)<2 ×10³/mm³ in 20 (14.2%) participants: 9 (19.6%) participants in placebo group and 3 (6.3%) participants in PF-06651600 (ritlecitinib) treatment group. One participant in PF-06651600 (ritlecitinib) treatment group experienced Grade 3 decreased lymphocyte count. There were no clinically relevant changes in lipid profile. Elevated CK levels of at least 3 × ULN were reported in 1 participant in PF-06651600 (ritlecitinib) treatment group.

During the induction period, when participants received PF-06651600 (ritlecitinib) 200 mg QD for 4 weeks, decreases in mean platelet and lymphocyte counts (-17.89% and -17.30% mean CFB, respectively) were observed in the PF-06651600 (ritlecitinib) group at Week 2. During the maintenance period, when participants received 50 mg QD for 20 weeks, there was improvement in the platelet and lymphocyte counts in the PF-06651600 (ritlecitinib) group. In both groups, hemoglobin level remained comparable to baseline value throughout the Initial 24-Week Treatment Period. No participants met the laboratory abnormality criterion of hemoglobin <0. .8 × LLN.

There were no clinically significant findings in ECG and vital signs except one increased diastolic BP in PF-06651600 (ritlecitinib) treatment group and one in placebo group.

1.5.1.14. Study B7981005

B7981005 is an ongoing Phase 2b, randomized, double-blind, placebo-controlled (in the induction period and not in the chronic dosing period), parallel group, multicenter study examining the efficacy of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) in participants with moderate to severe active UC. The first part of the study is a Screening period of up to 6 weeks followed by an 8-week double-blind induction period. The study is not be blinded across the PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) cohorts, but is placebo-controlled during the induction phase, and double-blinded within each investigational product. At Week 8, all participants are re-randomized within their respective treatment cohort (PF-06651600 (ritlecitinib) or PF-06700841 (brepocitinib) into an additional 24-week active chronic dosing period followed by a 4 week follow-up period after the last dose of investigational product for a total of 36 weeks. The chronic dosing period is in effect open-label, with both participants and Investigators aware that they have been assigned to PF-06651600 (ritlecitinib) or PF-06700841 (brepocitinib), and that there is no placebo control.

1.5.1.14.1. Safety Data

As of 31 August 2020, a total of 316 patients were evaluable for AEs, of whom 197 have reported 562 AEs. The most frequently (≥5%) reported AEs were Colitis ulcerative (10.1%), Nasopharyngitis (7.9%), Anaemia (5.4%), Arthralgia, and Headache (5.1% each).

As of 31 August 2020, a total of 35 SAEs have been reported in 33 participants. Thirteen SAEs were reported pre-randomization in 13 participants. Twenty-two treatment emergent SAEs (TE-SAEs) were reported in 21 participants, of which 6 events were considered treatment related and 16 events were not considered treatment related by the investigator.

The events considered treatment-related (blinded study treatment) by the Investigator are Urticaria (1 participant) and Colitis ulcerative (4 events in 4 participants). The event of acne occurred in a participant receiving blinded therapy with PF-06651600 (ritlecitinib)/placebo and the outcome for the events of Urticaria and Colitis ulcerative (worsening of ulcerative colitis [UC]/UC flare) was recovered/recovering.

The remaining treatment-emergent SAEs (blinded study treatment) assessed as not related to study treatment by the Investigator are as follows (all single events unless otherwise specified): Peripheral artery thrombosis, Thrombocytosis, Pyrexia, Anaemia, Interstitial lung disease, Large intestinal perforation, Colitis ulcerative (4 events), Condition aggravated (exacerbation of UC), Viral infection, Pneumonia, Haemorrhoid operation, Femur fracture, Myocardial ischaemia (post-procedural myocardial ischaemia), Myocardial infarction, Ankle fracture, Ligament injury, Listeria encephalitis, Pneumonia viral and COVID-19.

One death has been reported in the study; a PPD-year-old PPD participant receiving blinded therapy (PF-06651600 (ritlecitinib)/placebo group) experienced a SAE of myocardial infarction on study Day 49 (post-randomization) which resulted in death. Relevant medical history included ongoing PPD . The Investigator considered there was not a reasonable possibility that the event of myocardial infarction was related to the study drug, a concomitant drug or to a clinical trial procedure. The sponsor considered that the ongoing chronic obstructive pulmonary disease and the ongoing hypertension in this participant could provide alternate explanations for the reported event.

Efficacy Results

The study is blinded and ongoing.

1.5.1.15. Study B7981015

B7981015 is an ongoing Phase 2b/3, randomized, double-blind, placebo-controlled, dose-ranging study to investigate PF-06651600 (ritlecitinib) in Alopecia Areata (AA). The study has a maximum duration of approximately 57 weeks. This includes an up to 5-week Screening period, a 48-week treatment period, and a 4-week follow-up period (for subjects who do not roll over into the open-label, long-term study B7981032). The treatment period is comprised of a placebo-controlled period that includes a 4-week loading phase and a 20-week maintenance phase, followed by a 24-week extension phase. The study will enroll a total of approximately 718 subjects. The study will be conducted at approximately 120 sites.

To be eligible to enroll in this study, adolescent (≥12 to <18 years of age) and adult subjects must have moderate to severe AA with >50% hair loss of the scalp (Severity of Alopecia Tool [SALT] score >50) at both Screening and baseline visits, without evidence of terminal hair regrowth within the previous 6 months and with the current episode of hair loss <10 years.

Eligible subjects are randomized to blinded PF-06651600 (ritlecitinib) and matching placebo in a 2:2:2:2:1:1:1 (200 mg/50 mg; 200 mg/30 mg; 50 mg; 30 mg; 10 mg; placebo/200 mg/50 mg; placebo/50 mg) manner for a total of 7 treatment sequences. All subjects begin dosing during the loading phase according to their assigned sequence. Following the 4-week loading phase, subjects continue dosing according to their assigned sequence in the 20-week maintenance phase. At the end of the maintenance phase, placebo-treated subjects are advanced in a prespecified, blinded manner to 1 of 2 active treatment sequences for the remainder of the study (through Week 48). Investigators, subjects, and the sponsor study team are blinded to treatment throughout the duration of the study. Following the last dose of study intervention, both discontinued and completed subjects enter into a 4-week follow-up period for safety monitoring. Subjects who complete treatment may be eligible for enrollment in an open-label, long-term study (Phase 3 study B7981032). Subjects who enroll immediately into the B7981032 study are not required to complete the 4-week follow-up period in this study.

1.5.1.15.1. Safety Results

1.5.1.15.1.1. Discontinuations

As of 31 August 2020, 14 subjects discontinued due to a TEAE.

1.5.1.15.2. Adverse Events

SAEs were reported for 11 subjects in the B7981015 study as of 31 August 2020; 2 of these 11 cases were subsequently determined to be not serious by the investigator (while these cases were updated in the safety database prior to 31 August 2020, this change was not reflected in the clinical database until after 31 August 2020). The remaining 9 cases were: sepsis and empyema, conversion disorder, infected eczema, invasive lobular breast carcinoma, spontaneous abortion, diverticulitis, menorrhagia, pulmonary embolism, and breast cancer.

There were no deaths reported.

Of 701 subjects evaluable for AEs, 506 (72.2%) experienced TEAEs. The total number of TEAEs reported were 1443. Twenty-four subjects experienced severe AEs (3.4%).

The most frequently reported (≥5% of subjects) by MedDRA preferred terms were Nasopharyngitis (12.8%), Headache (10.1%), Upper Respiratory Tract Infection (7.0%), Acne (5.8%), and Nausea (5.3%).

1.5.1.16. Study B7981019

B7981019 is an ongoing Phase 2b, randomized, double-blind, parallel group, multicenter, placebo-controlled, dose-ranging study to investigate different dose/dose regimens of PF-06651600 (ritlecitinib) in active non-segmental vitiligo with a partially blinded extension period. The study includes an up to 4-week Screening period, a 24-week dose ranging period, an up to 24-week extension period, and an 8-week follow-up period. The 24-week dose ranging period is comprised of a placebo-controlled period that includes a 4-week loading phase and a 20-week maintenance phase. An induction dose of 200 mg QD of

PF-06651600 (ritlecitinib) for 4 weeks followed by maintenance dosing of 50 mg QD of PF-06651600 (ritlecitinib) for 20 weeks (n=60), an induction dose of 100 mg QD of PF-06651600 (ritlecitinib) for 4 weeks followed by maintenance dosing of 50 mg QD of PF-06651600 (ritlecitinib) for 20 weeks (n=60), a dose of 50 mg QD of PF-06651600 (ritlecitinib) for 24 weeks (n=60), a dose of 30 mg QD of PF-06651600 (ritlecitinib) for 24 weeks (n=45), a dose of 10 mg QD of PF-06651600 (ritlecitinib) for 24 weeks (n=45), and matching placebo for 24 weeks (n=60) will be investigated during the 24-week dose ranging period.

1.5.1.16.1. Safety Results

1.5.1.16.1.1. Safety Data

As of 31 August 2020, 269 (73.9%) of the 364 evaluable participants experienced at least 1 AE. There were a total of 743 AEs (all causalities). The most frequently (≥5%) reported AEs were Nasopharyngitis (15.9%), Upper respiratory tract infection (10.2%), Headache (8.5%), and Urinary tract infection (5.2%). There were 4 participants with SAEs reported in B7981019 study as of 31 August 2020. SAEs reported were Migraine in 2 participants, Neurogenic bladder, and Oesophageal spasm and Complication associated with device in 1 participant each. There were no deaths reported in B7981019 study

1.5.1.17. Study B7981032

Study B7981032 is an ongoing 2-year Phase 3 open-label, multicenter study to evaluate the safety and efficacy of PF-06651600 (ritlecitinib) in adult and adolescent subjects ≥12 years of age with AA. The study will have a maximum duration of approximately 26 months. This includes up to a 5-week screening period, a 24-month open-label treatment period, and a 4-week follow-up period. Study B7981032 includes eligible subjects who are given the opportunity to enroll from the index studies B7931005 and B7981015, as well as de novo subjects (ie, those who have not previously received study intervention in Study B7931005 or B7981015).

To be eligible to enroll in this study, subjects enrolling from Study B7931005 or B7981015 must not have had any events meeting the B7981032 discontinuation criteria or discontinued for safety-related events. In addition, subjects enrolling from Study B7931005 must have taken their last dose of PF-06700841 (brepocitinib) (a TYK2/JAK1 inhibitor) in Study B7931005 >12 weeks prior to the B7981032 Day 1 visit. There is no necessary washout period for participants who took PF-06651600 (ritlecitinib) in Study B7931005 or B7981015. Participants enrolling from B7981015 must have completed ≥34 weeks of study intervention. De novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the last dose in Study B7931005 or B7981015 and their first visit in Study B7981032 must have a clinical diagnosis of AA with no other etiology of hair loss other than androgenetic alopecia, with ≥25% hair loss of the scalp due to AA at both the screening and Day 1 visits which, in the opinion of the investigator, is appropriate for systemic therapy.

Subjects enrolling from B7931005 and B7981015 studies, receive open-label 50 mg PF-06651600 (ritlecitinib) QD and de novo subjects receive open-label 200 mg PF-06651600 (ritlecitinib) QD for 4 weeks followed by open-label 50 mg PF-06651600 (ritlecitinib) QD. Following the last dose of study drug, both discontinued and completed subjects enter into a 4 week follow-up period for safety monitoring.

1.5.1.17.1. Safety Results

As of 31 August 2020, a total of 369 participants were evaluable for AEs, of whom 127 had reported 246 TEAEs. The most frequently (≥2% of participants) reported TEAEs were headache (4.3%), acne (3.8%), nasopharyngitis (2.7%), and urticaria (2.2%). No TEAEs were reported in ≥5% of participants.

As of 31 August 2020, 1 participant discontinued due to a TEAE.

As of 31 August 2020, SAEs were reported for 2 participants. Please refer to the IB for more details on the clinical safety information with PF-06651600 (ritlecitinib).

1.5.2. Pharmacokinetics of PF-06651600 (ritlecitinib)

The PK parameters from the 5, 20, 50, 100, 200, 400 and 800 mg single dose levels are summarized below in Table 1. PF-06651600 (ritlecitinib) was absorbed rapidly following single doses of 5 mg to 200 mg with median T_{max} values ≤0.75 hours, and more slowly at the higher doses with a median T_{max} of 1.0 and 1.5 hours for the 400 mg and 800 mg doses, respectively.

Table 1. Summary of Plasma PF-06651600 (ritlecitinib) Pharmacokinetic Parameters Following Single Oral Doses, Study B7981001

	PF-06651600 (ritlecitinib) Parameter Summary Statistics[a] by Treatment						
Parameter, units	5 mg	20 mg	50 mg	100 mg	200 mg	400 mg	800 mg
N, n	6,6	6,6	6,6	6,6	6,6	12,12	6,6
AUC_{inf}, ng.hr/mL	43.86 (26)	211.7 (39)	384.1 (47)	1085 (23)	2464 (42)	7824 (34)	16760 (18)
AUC_{last}, ng.hr/mL	42.42 (26)	209.3 (40)	382.6 (47)	1081 (23)	2461 (42)	7821 (34)	16760 (18)
C_{max}, ng/mL	27.02 (29)	120.9 (54)	253. 3 (45)	647.7 (24)	1039 (40))	2691 (26)	4992 (11)
T_{max}, hr	0.5 (0.5-0.5)	0.5 (0.5-1)	0.5 (0.5-1)	0.5 (0.5-0.6)	0.75 (0.5-2)	1(0.5-2)	1.5 (1-2)
t½, hr	1.20 (0.107)	1.2 (0.174)	1.13 (0.166)	1.48 (0.176)	1.75 (0.434)	2.18 (0.337)	2.48 (0.460)

[a] Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for t½.
N = Number of subjects in the treatment group and contributing to the mean; n= number of subjects where t½, AUC_{inf} were determined.

Following attainment of C_{max}, the disposition of PF-06651600 (ritlecitinib) generally showed a monophasic decline at the lower doses of 5 to 200 mg (mean $t_{½}$ of 1.1 to 1.8 hours) while a biphasic decline was observed at doses of 400 and 800 mg (mean $t_{½}$ of 2.2 and 2.5 hours, respectively). An apparent trend toward longer $t_{½}$ values at higher doses (400 and 800 mg) is probably due to concentrations remaining above the quantifiable limit for a longer period of time at the higher doses and defining a later terminal phase. In general, PF-06651600 (ritlecitinib) AUC_{inf} increased in a dose related manner over the 5 to 800 mg dose range with a slightly greater than proportional increase observed over the 200 mg to 400 mg dose range. C_{max} increased with dose in an apparent dose proportional manner.

The PK parameters following administration of 50, 200 and 400 QD and 100 mg and 200 mg BID for 14 days are summarized below in Table 2.

On Day 14 of multiple-dose administration, PF-06651600 (ritlecitinib) was absorbed rapidly with median T_{max} values of 1 hour or less across the entire range of doses, from a total daily dose of 50 mg (50 mg QD) up to 400 mg (200 mg BID or 400 mg QD). Following attainment of C_{max}, the disposition of PF-06651600 (ritlecitinib) was consistent with that observed following single-dose administration, showing a monophasic decline for the lowest doses and a biphasic decline following the 200 mg BID and 400 mg QD dosing regimens and a mean terminal $t_{½}$ of about approximately 1.3 to 2.3 hours. In general, plasma PF-06651600 (ritlecitinib) AUC_{τ} and C_{max} increased with dose across the 50 mg to 400 mg total daily dose range in a dose related manner based on visual comparison of individual and dose normalized geometric mean C_{max} and AUC_{τ} values. Steady-state generally appears to have been reached by Day 4 for the QD regimens and Day 6 for the BID regimens based on similar median trough (predose) concentrations on Days 6, 8, 10, 12 and 14.

Table 2. Summary of Steady State Plasma and Urine PF-06651600 (ritlecitinib) Pharmacokinetic Parameters Following Multiple Dose Administration for 14 Days, Study B7981001

	PF-06651600 (ritlecitinib) Parameter Summary Statistics[a] by Treatment				
Parameter, units	50 mg (QD)	100 mg (BID)	200 mg (QD)	400 mg (QD)	200 mg (BID)
N, n	6, 6	4,4	5, 5	15, 14	5, 5
AUC_{τ}, ng.hr/mL	540.1(38)	1984 (15)	4069 (22)	10040 (19)	5207 (24)
C_{max}, ng/mL	315.2 (38)	663.0 (35)	1422 (28)	3136 (26)	1903 (27)
T_{max}, hr	0.5 (0.5- 1)	0.75 (0.5- 2)	1 (0.5- 1)	1 (0.5- 2)	1 (0.5- 1)
CL/F, L/hr	92.56 (38)	50.43 (15)	49.14 (22)	39.85 (19)	30.41 (24)
t½, hr	1.3 (0.241)	2.11 (0.341)	1.84 (0.409)	2.16 (0.100)	2.27 (0.212)
V_z/F, L	170.6 (26)	151.4 (27)	128.0 (29)	126.1 (18)	125.3(18)
Ae_{τ}%	4.09 (23)	6.46 (4)	5.47 (31)	6.46 (19)	7.04 (20)
CLr, mL/min	63.06 (28)	54.33 (12)	44.76 (38)	42.90 (18)	45.46 (17)

a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for t½; N = Number of subjects in the treatment group and contributing to the mean; n= number of subjects where t½ was determined.

AUC_{τ}, = Area under the concentration-time curve from zero to 24 hours (QD) or zero to 12 hours (BID) postdose at steady state; QD = Once daily; BID = Twice daily; C_{max} = Peak plasma concentration; CL/F = apparent total body clearance; V_z/F = apparent volume of distribution; Ae_{τ}% = Percent of dose recovered unchanged in urine over the dosing interval τ; CLr = Renal clearance.

Urinary recovery of PF-06651600 (ritlecitinib) was low, with approximately <8% of the dose recovered unchanged in urine on Day 14 across all doses (geometric mean Ae_{τ}% of 4.1% to 7.0%). Renal clearance ranged from 42.9 mL/min to 63.1 mL/min.

The relative bioavailability of 50 mg PF-06651600 (ritlecitinib) tablets was compared to 50 mg oral suspension in Study B7981003. The ratio (90% CI) of adjusted geometric mean was 93.4% (87.8, 100) for AUC_{inf} and 90.4% (72.2, 113) for C_{max} under fasted conditions. When the 50 mg tablets were administered under fed conditions, T_{max} was slightly delayed with a median value of 1.0 hours, compared to a median T_{max} 0.5 hours under fasted conditions. For the 50 mg tablets fed vs. fasted, the ratio of adjusted geometric means for AUC_{inf} and C_{max} was 102% (95.2, 109) and 61.5% (48.5, 77.8), respectively.

Pharmacodynamic biomarkers response was best described by an indirect response PK/PD model indicating that AUC rather than C_{max} is the important parameter to modulate disease response hence the recommendation is to administer the IP with no requirement regarding food in the current study.

Following the first morning oral dose of PF-06651600 (ritlecitinib) 200 mg to healthy Japanese subjects (B7981008) under fasted conditions on Day 1, PF-06651600 (ritlecitinib) absorption was rapid with a median Time at which C_{max} occurred (T_{max}) of 0.525 hours and a range of 0.500-1.00 hours. Overall, exposures as measured by Area under the concentration-time profile from time 0 to time tau (AUC_{tau}) based on geometric mean were 3779 ng•hr/mL and for C_{max} of 1803 ng/mL on Day 1 after a single dose. Mean $t_{½}$ was 1.69 hours and it was calculated based on a 24-hour sampling. Mean appearanT clearance (CL/F) was 53.0 L/hr and apparent volume of distribution (V_z/F) was 129 L.

Trough (predose) concentrations on Days 4, 6, 8 and 10 for all subjects were below the lower limit of quantification (LLOQ) (<1.00 ng/mL).

Following multiple oral dosing on Day 10, AUC_{tau} increased slightly while C_{max} was similar to Day 1. The geometric mean values for AUC_{tau} and C_{max} were 4983 ng•hr/mL and 1790 ng/mL, respectively. Median T_{max} was similar to Day 1 with a value of 0.500 hours with no range for Day 10. Following the attainment of C_{max}, concentrations appeared to decline in monophasic fashion. A short mean $t_{½}$ was observed with an estimate of 1.8 hours. Based on AUC_{tau} calculation, mean CL/F was 40.1 L/hr and mean V_z/F was 103 L.

Plasma PF-06651600 (ritlecitinib) accumulation was 1.3–fold for AUC_{tau} (observed accumulation ratio (R_{ac})) and 0.99–fold for C_{max} (observed accumulation ratio for C_{max} [$R_{ac,}C_{max}$]). The steady state accumumation ratio (R_{ss}) compares AUC_{tau} for multiple-dose administration to AUC_{inf} for single-dose administration. The geometric mean R_{ss} was 1.3 (close to 1), suggesting linear increases in PF-06651600 (ritlecitinib) exposure with multiple-dose administration.

Between-subject variability in plasma PF-06651600 (ritlecitinib) exposure on Day 1 and Day 10 based on geometric percent coefficient of variation (%CV), ranged from 35% to 43% for C_{max} and from 23% to 25% for AUC_{tau}.

Urinary recovery of PF-06651600 (ritlecitinib) was low, with <7% of the dose recovered unchanged in urine on Day 10 (geometric mean percent of dose recovered unchanged in urine up to 24 hours [cumulative amount of drug recovered unchanged in urine up to 24 hours (Ae_{tau}%)] of 6.89%). Renal clearance was approximately 46.1 mL/min.

Study B7981017 is a Phase 1, randomized, open label, 2-way crossover study to estimate the effect of multiple dose PF-06651600 (ritlecitinib) on the pharmacokinetics of single dose midazolam and efavirenz in healthy participants. Co-administration of multiple doses of PF-06651600 (ritlecitinib) increased midazolam exposure (AUC_{inf}) and peak exposure (C_{max}) by 2.7 and 1.8 fold, respectively. Efavirenz exposure (AUC_{0-72}) and peak exposure (C_{max}) were similar following coadministration with multiple doses of PF-06651600 (ritlecitinib) and single dose of midazolam and when administered with midazolam only.

Study B7981018 is a Phase 1, randomized, 2-way crossover, multiple dose, open-label study of the effect of multiple dose PF-06651600 (ritlecitinib) (200 mg QD) on single dose OC PK in healthy post-menopausal female volunteers. PF-06651600 (ritlecitinib) decreased the adjusted geometric mean AUC and C_{max} of ethinyl estradiol around 18% and 12%, respectively. Systemic exposure of levonorgestrel did not show any clinically significant changes. The clinical significance of this decrease in ethinyl estradiol is unknown; however, efficacy of estrogen-containing contraceptives may be decreased, and the concurrent use of an additional barrier method of contraception is required. Female subjects who participate in clinical studies with PF-06651600 (ritlecitinib) must agree to use contraception as defined in each protocol (Section 4.4.1).

Study B7981023 is a Phase 1, open-label, fixed sequence 2-period study to investigate the effect of multiple doses of itraconazole on the pharmacokinetics of a single dose of PF-06651600 (ritlecitinib) in healthy participants. Co-administration of multiple 200 mg doses of itraconazole increased PF-06651600 (ritlecitinib) total exposure (AUC_{inf}) by approximately 15% while peak exposure (C_{max}) was similar relative to a single 30 mg PF-06651600 (ritlecitinib) dose given alone.

1.5.3. Summary of Clinical Experience with PF-06700841 (brepocitinib)

This Section is no longer applicable to newly enrolled participants under PA5.

1.5.3.1. Summary of Clinical Safety of PF-06700841 (brepocitinib)

This section consists of safety and efficacy information for PF-06700841 (brepocitinib) in 7 completed Phase 1 studies (Studies B7931001, B7931009, B7931010, B7931014 and B7931029), and 2 completed Phase 2 studies (B7931004 and B7931005). Two Phase 1 studies (B7931019 and B7931033) have completed enrollment and draft data from these small studies are included in the IB. Data have not been pooled for the studies conducted with PF-06700841 (brepocitinib). Safety and efficacy data are presented separately for each study.

Adverse events (AE) may be reported as all-causality or treatment-related. Treatment-related adverse events are those events considered related to the study treatment, at least by the Investigator. See the IB for adverse events that have been further evaluated and determined by the sponsor to be expected adverse reactions (ie, events for which there is a reason to conclude that the drug caused the event[s]).

1.5.3.1.1. Study B7931001

The B7931001 study was a Phase 1, within cohort, randomized, double-blind, third party open, placebo-controlled, parallel group study with single and multiple dose escalation in healthy adult subjects, and multiple dosing in subjects with chronic plaque psoriasis. In addition, the bioavailability (BA) of a tablet formulation relative to the first in human (FIH) solution/suspension formulation, as well as the effect of a high fat meal on the BA of the tablet formulation, was determined in a 3 -way crossover study design.

Of the 96 subjects randomized into study B7931001, 74 subjects have received at least 1 active dose of oral PF-06700841 (brepocitinib),41 healthy subjects in the single and multiple ascending dose period of the trial, 12 healthy subjects in BA and 21 subjects with chronic plaque psoriasis.

In the SAD/MAD period, 41 healthy subjects received doses of 1, 3, 10, 30, 100, or 200 mg of PF-during the SAD period, and doses of 10, 30, 100, or 175 mg QD for 10 days during the MAD period. Subjects participating in the 100 mg multiple dose cohort returned for a third period to receive 50 mg PF-06700841 (brepocitinib) BID for 10 days. Thirty subjects with moderate to severe chronic plaque psoriasis were also randomized into study B7931001 to receive once daily placebo (n=9), 30 mg (n=14), or 100 mg (n=7) PF-06700841 (brepocitinib) for 28 days. In the BA period, 12 healthy subjects were randomized and received PF-06700841 (brepocitinib).

Whereas additional studies with PF-06700841 brepocitinib are underway, none of these studies have been completed to date and the data remain blinded.

1.5.3.1.1.1. Adverse Events

PF-06700841 (brepocitinib) was generally safe and well tolerated in all cohorts in the Phase 1 clinical study B7931001. There were no deaths in the study. Subjects reported 11 TEAEs in the SAD phase, 22 TEAEs in the MAD phase, 39 TEAEs in the psoriasis phase, and 3 TEAEs in the BA phase. All AEs were mild or moderate in severity; there were no severe or serious adverse events, or serious infections in any of the 4 study groups cohorts. Of the 7 healthy volunteers who prematurely discontinued the MAD cohort, 3 discontinuations were due to AEs. Of the 13 patients in the psoriasis cohort who discontinued prematurely, 7 of the discontinuations were due to AEs. There were no discontinuations due to AEs in the SAD or BA cohorts.

1.5.3.1.1.2. Common Adverse Events in Study B7931001

In the SAD cohort, the most commonly reported AEs by System Organ Classes (SOCs) were Investigations, reported by 2 participants, and Nervous System Disorders, reported by 3 participants. The most frequently reported AEs were Blood creatinine increased and Headache, each of which was experienced by 2 participants. All TEAEs were mild in severity.

In the MAD cohort, the most commonly reported AEs by SOCs were Investigations, reported by 13 participants, and Nervous System Disorders, reported by 3 participants. The most frequently reported AEs were blood creatinine increased, experienced by 11 participants, and neutrophil count decreased, experienced by 3 participants. All TEAEs were mild or moderate in severity.

In the psoriasis cohort, the most commonly reported AEs by SOCs were gastrointestinal disorders, reported by 7 participants, investigations, reported by 15 participants, and nervous system disorders, reported by 4 participants. The most frequently reported AEs were constipation, experienced by 6 participants and blood creatinine increased, experienced by 14 participants. All TEAEs were mild in severity.

In the BA cohort, the most commonly reported AEs by SOCs were gastrointestinal disorders, injury, poisoning, and procedural complications, and nervous system disorders, each reported by 1 participant. The most frequently reported AEs were nausea, confusion, and headache, each of which was experienced by 1 participant. All TEAEs were mild in severity.

1.5.3.1.1.3. Other Significant Adverse Events in Study B7931001

One participant in the study B7931001 experienced an AE of herpes zoster after completing 28-day treatment (Psoriasis period of the study) with PF-06700841 (brepocitinib) 100 mg QD. The participant presented with non-disseminated, herpetiform rash on the upper left side of the back and left arm on Day 30. The AE was mild in severity, had a reported duration of 13 days, and was treated with acyclovir and vicodin by the Investigator.

1.5.3.1.1.4. Clinical Laboratory Evaluations

In the SAD and MAD cohorts, 40 participants (7 in the placebo; 4 each in the 1 and 3 mg; 6 each in the 10, 30 and 100 mg; and 7 in the 200 mg treatment groups) in the SAD group and 32 participants (6 in the placebo; 5 each in the 10 and 50 mg; 4 in the 30 mg; and 6 each in the 100 and 175 mg treatment groups) in the MAD group had laboratory abnormalities.

The most frequently reported laboratory abnormalities were elevations of low-density lipoprotein (LDL) >1.2 × upper limits of normal (ULN), 26 participants during SAD and 22 participants during MAD.

Serum creatinine ≥1.5 × ULN occurred in 1 participant in the PF-06700841 (brepocitinib) 100 mg group during SAD, 4 participants (1, 2, and 1 participants in the PF-06700841 (brepocitinib) 10 mg QD, 100 mg QD, and 50 mg BID groups, respectively) in the MAD period. Participants in the MAD and psoriasis cohorts that had increased SCr ≥0.3 mg/dL did demonstrate a change in S Cystatin-C based estimated glomerular filtration rate (eGFR).

Abnormally low neutrophil counts were observed in 3 participants (1 participant each in the 1 mg, 200 mg, and placebo groups) in the SAD cohort and 14 participants in the MAD cohort (1, 3, 3, 5, and 2 participants in the 10 mg QD, 100 mg QD, 50 mg BID, 175 mg QD, and placebo QD groups, respectively). There were no clinically meaningful changes from baseline in other hematology parameters during SAD and MAD.

In the SAD group, there was a slight increase in alanine amino transferase (ALT) in the 30 mg group on Day 8. Overall there were no clinically significant abnormalities in aspartate amino transferase (AST), ALT and total bilirubin during SAD and MAD.

In the psoriasis cohort, 27 participants (7 in the Placebo, 13 in the 30 mg and 7 in the 100 mg PF-06700841 (brepocitinib) treatment groups) had laboratory abnormalities.

The most frequently reported laboratory abnormalities during the psoriasis period were LDL >1.2 × ULN (16 participants: 5 in Placebo, 7 in the 30 mg and 4 in the 100 mg PF-06700841 (brepocitinib) treatment groups and uric acid >1.2 × ULN (10 participants: 4 in Placebo, 4 in the 30 mg and 2 in the 100 mg PF-06700841 (brepocitinib) treatment groups).

In the psoriasis group, 6 participants (1 and 5 participants in the 30 mg QD and 100 mg QD groups, respectively) had neutrophil counts meeting the criteria for abnormally low levels. Overall there were no clinical meaningful changes from baseline in other hematology parameters during psoriasis period.

In the BA cohort, there were 9 participants that had laboratory abnormalities. The most frequently reported laboratory abnormalities during the BA period were total neutrophils <0.8 × LLN (4 participants) and lymphocytes <0.8 × LLN (3 participants). There were no other clinically significant abnormalities during BA period.

There were no participants with clinically significant laboratory abnormalities during the study.

1.5.3.1.1.5. Vital Signs, Physical Findings, Electrocardiogram (ECG) and Other Observations Related to Safety

There were no clinically meaningful findings in vital signs, and ECG in any of the 4 groups.

1.5.3.1.2. Study B7931009

This study was a Phase 1 randomized, double-blind, third-party open, placebo-controlled, multiple dose study in healthy Japanese adult participants.

1.5.3.1.2.1. Safety Summary of Phase 1 Study B7931009

Eight (8) male Japanese participants were assigned to the study treatment with PF-06700841 (brepocitinib) and all participants completed the study. Of the 8 participants, 6 participants received treatment with 100 mg of PF-06700841 (brepocitinib) and 2 participants received matching placebo.

A total of 7 AEs were reported by 3 participants following oral administration of 100mg of PF-06700841 (brepocitinib), including flatulence, fatigue, viral upper respiratory tract infection, headache, somnolence, nocturia, and hematoma. Among these, flatulence, headache, somnolence, and nocturia were considered treatment-related by the investigator. One AE of abdominal pain in the placebo treatment group was moderate and the others were considered mild in severity.

No laboratory abnormalities were identified in the placebo group. Four participants experienced laboratory abnormalities following the administration of 100 mg of PF-06700841 (brepocitinib). None of the laboratory abnormalities were considered clinically significant or reported as AEs by the investigator.

Oral administration of PF-06700841 (brepocitinib) at multiple doses of 100 mg QD was well-tolerated in healthy Japanese participants investigated in this study. There were no deaths, SAEs, severe AEs, discontinuations due to AEs, or dose reductions or temporary discontinuations due to AEs during this study. There were no clinically significant findings observed in laboratory parameters, vital signs, ECG parameters.

1.5.3.1.3. Study B7931014

This study is a Phase 1, open-label, non-randomized, 2-period, fixed sequence, single-dose study of PF-06700841 (brepocitinib) in healthy male participants to characterize the absorption, distribution, metabolism, and excretion (ADME) of 14C PF-06700841 (brepocitinib); and to evaluate the absolute oral bioavailability (F) and fraction absorbed (Fa) of PF-06700841 (brepocitinib) following oral administration of unlabeled PF-06700841 (brepocitinib) and IV and oral administration of 14C- PF-06700841 (brepocitinib) to healthy male participants. A 2-period design will be used to minimize variability and enable within-subject comparison of the urinary excretion of radioactivity with both routes for the estimation of Fa. Fa will be estimated by comparing total 14C urine recovery following IV and oral administration of 14C- PF-06700841 (brepocitinib). There was a 10- to 17-day washout between the 2 treatment periods.

1.5.3.1.3.1. Safety Summary of Phase 1 Study B7931014

Six participants were assigned to open-label study treatment, and all were treated and completed the study. All participants received 2 regimens (A and B). Regimen A is an oral dose of 60 mg radiolabeled PF-06700841 (brepocitinib) containing approximately 300 nCi 14C. Regimen B is an oral dose of 60 mg unlabeled PF-06700841 (brepocitinib) followed by an IV dose of radiolabeled PF-06700841 (brepocitinib).

Seventeen AEs were reported by 5 participants during the study, including dizziness, headache, nasopharyngitis, cough, epistaxis, flatulence, dry skin, diarrhea, dyspepsia and respiratory tract irritation. Two events of headache were considered treatment related by the investigator. All AEs were considered mild except 3 events in 1 participant graded as moderate (headache (2) and common cold). No laboratory abnormalities were considered clinically significant.

Oral administration of PF-06700841 (brepocitinib) was well-tolerated in this ADME study. There were no deaths, SAEs, severe AEs, discontinuations due to AEs, or dose reductions or temporary discontinuations due to AEs during this study. There were no clinically significant findings observed in laboratory parameters, vital signs, or ECG parameters.

1.5.3.1.4. Study B7931019

This study was designed to determine the effect of PF-06700841 (brepocitinib) on QTc interval in healthy participants. This was a Phase 1, 3-way crossover, 3-treatment, 6-sequence, sponsor-open study, in which, each participant received single oral doses of PF-06700841 (brepocitinib) 200 mg, placebo and moxifloxacin 400 mg, according to 1 of the treatment sequences they were randomly assigned. Treatment assignments to PF-06700841 (brepocitinib) and placebo were blinded to the participants and investigator but moxifloxacin treatment was unblinded.

1.5.3.1.4.1. Safety Summary of Phase 1 Study B7931019

In this study, 33 participants were enrolled in the study with 32 completers. Overall PF-06700841 (brepocitinib) 200 mg and moxifloxacin 400 mg were well tolerated with no deaths, SAE, severe AEs, discontinuation due to AE, or clinically significant findings in laboratory parameters, vital signs or ECG parameters. A total of 24 TEAE (all causalities) were reported in 15 participants after PF-06700841 (brepocitinib) treatment. There were 11 and 12 TEAEs reported in 10 and 8 participants after moxifloxacin and placebo treatment respectively. All AEs were mild to moderate in severity. Despite QTc increases observed after single doses of PF-06700841 (brepocitinib) 200 mg and moxifloxacin 400 mg, there were no clinically significant findings in ECG categorical analyses including no changes in QTcF>60 msec or an absolute value >500 msec.

1.5.3.1.5. Study B7931029

This is a Phase 1, single center, randomized, vehicle and white petrolatum controlled, evaluator blinded study to assess the skin irritation potential with a range of concentrations of PF-06700841 (brepocitinib) cream including vehicle and empty patch with white petrolatum under occlusive conditions in adult Japanese healthy participants.

Six investigational products PF-06700841 (brepocitinib) cream 0% [vehicle], 0.1%, 0.3%, 1%, 3%, and empty patch with white petrolatum) were applied topically once using occlusive patches to the infrascapular area of the back on Day 1 and remained under occlusive conditions for 48 hours at which time the patches were removed. The skin irritancy was evaluated approximately 30 minutes after removal of the patches and 24 hours after removal of the patches.

All participants had 6 application sites on the back where 6 patches of investigational products were randomly assigned to determine irritation potential. Dermal reactions at the application sites were assessed using a visual grade rating for erythema, edema, and other signs of skin irritation. One participant experienced a total of 3 TEAEs including nasopharyngitis, asthma and upper-airway cough syndrome; all of which were of moderate intensity, which were not considered treatment-related.

1.5.3.1.5.1. Disposition, and Demographic Characteristics Treatment-Emergent Adverse Events (All-causality and Treatment Related) and Laboratory Values

Twenty Japanese male participants were enrolled into the study and 20 participants completed treatment and safety follow-up. None of the participants discontinued the study. No patients had skin irritation grade equal to or greater than 2 plus (≥++) were 0% on either Day 3 or Day 4 and on both assessment days for any of the 6 treatment groups.

One participant experienced a total of 3 TEAEs including nasopharyngitis, asthma and upper-airway cough syndrome; all of which were of moderate intensity, which were not considered treatment-related.

There were no deaths, SAEs or discontinuations in the study. There were no clinically significant changes in laboratory values, vital signs or ECG.

1.5.3.1.6. Study B7931033

This was a Phase 1, open-label, fixed-sequence, 2-period study to investigate the effect of multiple oral doses of itraconazole on a single oral dose of PF-06700841 (brepocitinib) PK in healthy participants at a single center. Approximately 12 healthy participants were enrolled in the study. The study has completed enrollment; however, the clinical study report was not been finalized as of the time of this IB update, and these summarized results are in draft stage.

1.5.3.1.6.1. Safety Summary of Phase 1 Study B7931033

In this study, 12 healthy participants were enrolled in the study with 12 completers. In Period 1, a single oral dose of 30 mg PF-06700841 (brepocitinib) tablets was given alone, in Period 2, itraconazole 200 mg was administered as oral solution QD on Days 1-7 and 30 mg PF-06700841 (brepocitinib) co-administered on Day 4. There was no required washout between the last dose of PF-06700841 (brepocitinib) in Period 1 and the first dose of itraconazole in Period 2. Overall PF-06700841 (brepocitinib) 30 mg and itraconazole 200 mg were well tolerated with no deaths, SAE, severe AEs, discontinuation due to AE, or clinically significant findings in laboratory parameters, vital signs or ECG parameters.

1.5.3.1.7. Study B7931010

This was an open-label, single dose, 2-period, 2-sequence crossover study in 8 healthy participants to characterize the PF-06700841 (brepocitinib) pharmacokinetic (PK) profile and bioavailability following single oral dose formulation of immediate release (IR) tablets and modified release (MR) tablets each administered as 30 mg dose in the fasted state.

1.5.3.1.7.1. Safety Summary of Phase 1 Study B7931010

All 8 participants received at least 1 dose of study medication and were included in the safety analysis. Two participants reported 2 TEAEs when receiving PF-06700841 (brepocitinib) 30 mg IR and 2 participants reported 3 TEAEs when receiving PF-06700841 (brepocitinib) 30 mg MR. One participant experienced a treatment-related TEAE of headache and 1 participant experienced throat irritation following the administration of PF-06700841 (brepocitinib) 30 mg IR. In the MR treatment group, 1 participant experienced treatment related TEAEs of dry mouth and abdominal pain and 1 participant experienced a TEAE of dizziness.

All the TEAEs were of mild severity. There were no deaths, SAEs, severe AEs, permanent discontinuations, dose reductions or temporary discontinuations due to AEs during the study.

1.5.3.1.8. Study B7931004

This was a Phase 2a, randomized, double-blind, placebo-controlled, parallel group, multicenter study in adult participants with moderate to severe plaque psoriasis. Following a screening period (up to 6 weeks), the study consisted of a 4-week induction treatment period with double-blind daily treatment (PF-06700841 (brepocitinib) 30 mg QD, 60 mg QD or matched placebo). At the end of Week 4, all participants switched to their predefined double-blind maintenance treatment regimen (PF-06700841 (brepocitinib) 10 mg QD, 30 mg QD, 100 mg once weekly (QW) or matched placebo) for Week 5 through Week 12. Subsequent to the induction and maintenance periods, the study had an 8-week follow up period.

1.5.3.1.8.1. Disposition and Demographic Characteristics of Phase 2 Study B7931004

A total of 212 participants were randomized and received at least 1 dose of study treatment. All treated participants were analyzed for efficacy and safety. Participants randomized to treatment received either PF-06700841 (brepocitinib) 60 mg QD or PF-06700841 (brepocitinib) 30 mg QD for the first 4 weeks of treatment (induction) after which those on 60 mg QD were switched to either 30 mg QD, 10 mg QD, 100 mg QW or placebo in the maintenance period. Those who received 30 mg QD during the first 4 weeks of induction were switched to either 30 mg, 10 mg QD, or 100 mg QW in the maintenance period.

Overall, 164 of 212 (77.4%) participants completed the study. The majority of the treated participants were male (69.8%) and white (89.2%). The mean age was 46.0 years (median: 48.0, range: 18 to 75). The mean weight was 94.7 kg (median: 91.6, range: 45.1 to 204.3), and mean body mass index (BMI) was 31.9 kg/m2 (median: 30.9, range: 18.9 to 64.7). The mean duration of psoriasis since first diagnosis was 17.9 years, with a mean baseline PASI score of 20.8, which was comparable for participants in all treatment groups.

1.5.3.1.8.2. Treatment-Emergent Adverse Events (All-causality and Treatment Related) in Phase 2 Study B7931004

The proportion of participants with all-causality TEAEs was comparable across all treatment groups but numerically higher in the active treatment groups (64.0% to 76.7%) than the placebo group (56.5%). The majority of participants in all the treatment groups experienced mild or moderate all-causality TEAEs, and only 11 (5.2%) out of 212 participants experienced severe all-causality TEAEs. Overall, there were no dose dependent increases in the all-causality TEAEs. The most reported non-serious TEAEs were in the SOC of Infections and Infestations with 25.9% of participants. There were more participants experiencing mild to moderate infections and infestations, such as nasopharyngitis, upper respiratory tract infection, bronchitis, sinusitis, or urinary tract infection in the active treatment groups relative to the placebo group. Other non-serious TEAEs in SOCs occurring >5% of participants were Gastrointestinal Disorders, Musculoskeletal and Connective Tissue Disorders, Skin and Subcutaneous Tissue Disorders, and Nervous System Disorders. Incidence occurring in other SOCs except Infections and Infestations was comparable between all treatment groups.

A total of 13 participants discontinued from the study due to TEAEs.

One participant in the 30 to 10 mg group was found to have a positive urine human chorionic gonadotropin test at the Week 6 (Day 42) visit after which confirmation with serum pregnancy test led to permanent discontinuation from study on Day 53. On Day 165, an obstetrical ultrasound demonstrated a right-sided cleft lip with a gap of 10 millimeters in the fetus, with no definite cleft palate. The Day 176 obstetrical ultrasound confirmed presence of cleft lip in the fetus, with all other findings appearing within normal limits. This event of fetal cleft lip was unexpected in the single reference safety document for the study drug and was assessed as related per sponsor.

1.5.3.1.8.3. Serious Adverse Events in Phase 2 Study B7931004

Five participants experienced a total of 6 SAEs during the study; 3 of the SAEs were considered to be related to study drug by the investigator, of which 2 SAEs (pneumonia and sepsis) reported by 1 participant in the 60 mg QD to 100 mg QW group were considered not related to study drug by the sponsor. This participant had 1 dose of PF-06700841 (brepocitinib) 60 mg on Day 1 and had 2 SAEs of pneumonia and sepsis on Day 2 before dosing and was permanently discontinued from study due to the SAE of pneumonia.

One post-therapy death occurred due to gunshot wound after the participant was discontinued from the study due to noncompliance with study drug, which was considered unrelated to the study treatment by the investigator.

1.5.3.1.8.4. Laboratory Evaluation, Vital Signs, and ECG in Phase 2 Study B7931004

There were no clinically meaningful dose dependent neutropenia, lymphopenia, thrombocytopenia, and anemia among the active treatment groups, except for 1 SAE of anemia reported by 1 participant in the 60 to 10 mg QD group.

No participants met the laboratory test discontinuation criteria (laboratory test abnormalities confirmed through re-testing within 48 hours) during study treatment. There was no potential Hy's Law case reported during the study.

1.5.3.1.8.4.1. Hematology

During the induction period, there was a dose-dependent decrease of in reticulocyte count in the active treatment groups compared to the placebo group. During the 8-week maintenance period, the reticulocytes levels appeared to rebound for all the active treatment groups, except for the 30 to 10 mg QD group. There were no clinically meaningful changes from baseline observed in hemoglobin across treatment groups during the study, except for 1 SAE of anemia reported by 1 participant in the 60 to 10 mg QD group.

During the induction period, dose-dependent decreases from baseline in neutrophils were observed for the 60 mg QD induction dose group, compared to the 30 mg QD induction dose group and the placebo group at Week 4. During the maintenance period at Week 12, the neutrophils levels for all the treatment groups were similar to placebo.

During the induction period and maintenance periods, lymphocyte levels in all active treatment groups were similar to placebo at Week 4 and Week 12. A total of 6 participants (3 participants in the 60 mg QD to 100 mg QW group and 1 participant each in the 60 to 10 mg QD group, the 60 mg QD to placebo group, and the placebo group, respectively) had lymphocyte values meeting the criteria for low levels. There were no clinically meaningful changes from baseline observed in lymphocytes across treatment groups during the study.

During the induction period and maintenance periods, platelet levels in all active treatment groups were similar to placebo at Week 4 and Week 12.

1.5.3.1.8.4.2. Liver Function Tests

There were no clinically meaningful changes from baseline observed in AST and ALT across treatment groups during the study. Two participants (1 participant each in the 30 mg QD group and the 30 mg QD to 100 mg QW group) had AST meeting the criteria of AST >3.0 × ULN. One participant in the 30 to 10 mg QD group had ALT meeting the criteria for high levels. The participant was permanently discontinued from the study due to a moderate AE of liver function test (LFT) abnormal.

1.5.3.1.8.4.3. Creatine Kinase

There were no clinically meaningful changes from baseline observed in creatine kinase (CK) during the study. A total of 24 participants (5 participants each in the 60 mg QD to 100 mg QW and 30 to 10 mg QD groups; 4 participants each in the 60 to 30 QD and 30 QD groups; and 3 participants each in the 60 to 10 mg QD and 60 mg QD to placebo groups) had CK meeting the criteria of CK >2 ×ULN. CK levels >10 × ULN were observed in 2 participants without AE. One moderate AE of CK-MB increased reported by 1 participant in the 30 to 10 mg QD group during the induction period, which was considered to be related to the study drug by the investigator. No participant was discontinued from the study due to CK elevation.

1.5.3.1.8.4.4. Serum Creatinine, Serum Cystatin-C, and eGFR (Serum Cystatin C Based)

During the induction period, increases from baseline in SCr were observed in all the active treatment groups (range from 10.9% to 25.0%), compared to the placebo group (1.8%) at Week 4. During the maintenance period, the SCr levels returned close to baseline for all the active treatment groups, except for the 60 to 30 mg QD, 60 to 10 mg QD, and 30 mg QD groups. A total of 4 participants (1 participant each in the 60 to 30 mg QD, 60 to 10 mg QD, 30 mg QD and 30 to 10 mg QD groups) had SCr meeting the criteria of SCr 1.3 × ULN.

There were no clinically meaningful changes from baseline observed in serum cystatin C across treatment groups during the study. Two participants (1 participant each in the 60 to 30 mg QD and 60 to 10 mg QD groups) had elevated serum cystatin C meeting the criteria of serum cystatin C >1.3 × ULN.

There were no clinically meaningful changes from baseline observed in serum cystatin-C based eGFR across treatment groups during the study.

1.5.3.1.8.4.5. Lipids

During the induction period, dose-dependent increases from baseline in LDL were observed in the active treatment groups (13.5% for the 60 mg QD induction dose group, 5.1% for the 30 mg QD induction dose group), compared to placebo (-6.0%) at Week 4.

During the induction period, dose-dependent increases from baseline in HDL were observed in the active treatment groups (22.5% for the 60 mg QD induction dose group, 15.6% for the 30 mg QD induction dose group), compared to placebo (-1.44%) at Week 4.

There were no clinically meaningful changes from baseline observed in LDL/High density lipoprotein (HDL) ratio across treatment groups during the study.

1.5.3.1.8.5. Vital Signs, ECG, and Suicidal Behavior or Ideation

There were no clinically meaningful findings in vital signs, ECG, and suicidal behavior or ideation during the study.

1.5.3.1.9. Study B7931005

This was a Phase 2a, randomized, double-blind, placebo-controlled, parallel group, multicenter study to investigate the efficacy and safety of both PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) in treatment of alopecia areata. The study was to have a maximum duration of approximately 113 weeks, consisting of 3 periods: a 24-week double-blind treatment period, an up to 48-week SBE period, and a 24-week COE period. The study included 2 drug holiday periods of 4 weeks each, and 2 follow-up periods of 4 weeks each.

1.5.3.1.9.1. Summary of Adverse Events

There were no deaths reported. During initial 24 weeks, 2 participants (PPD) experienced SAEs of rhabdomyolysis when receiving PF-06700841 (brepocitinib) 30 mg which resulted in permanent discontinuation from the study. Both SAEs were considered unrelated to the study drug.

There was 1 SAE during SBE period. One retreated PF-06700841 (brepocitinib) responder (Participant PPD) permanently discontinued from PF-06700841 (brepocitinib) and discontinued from study due to a severe SAE of lower limb fracture in the Retreatment Segment, which was caused by an accident and was determined by the investigator and sponsor as not treatment-related.

One participant in PF-06700841 (brepocitinib) cross-over (CO) treatment group (Participant PPD) experienced an SAE of gastroenteritis salmonella which was considered not related to study drug and did not result in discontinuation from study or from study drug.

In the Initial 24 weeks Treatment Period; There were no deaths during the Initial 24-Week Treatment Period. A total of 4 participants discontinued from the study due to TEAEs and 5 participants discontinued study drug due to TEAEs and continued in the study. Two participants in PF-06700841 (brepocitinib) treatment group experienced an SAE of rhabdomyolysis which resulted in permanent discontinuation from the study. The most frequently laboratory abnormality which met retest criterion was total neutrophils (absolute) $<2 \times 10^3/mm^3$ in 20 (14.2%) participants: 9 (19.6%) participants in placebo group and 8 (17.0%) participants in PF-06700841 (brepocitinib) treatment group. Two participants in PF-06700841 (brepocitinib) treatment group experienced Grade 3 decreased neutrophil count. There were 2 participants in placebo group and 13 participants in PF-06700841 (brepocitinib) treatment group experienced a decline of ≥30% from baseline in SCr-based eGFR during the Initial 24-Week Treatment Period but none of these declines were accompanied by a concomitant decline of ≥30% in serum cystatin C-based eGFR. Elevated CK levels of at least 3 × ULN were reported in 9 participants in PF-06700841 (brepocitinib) treatment group. There were no clinically significant findings in ECG and vital signs except increased diastolic BP in 3 participants (one in each group). There were no clinically significant auditory changes in the active treatment groups. A mild TEAE of deafness neurosensory was reported in 1 participant in placebo group.

In the SBE Period; There were no deaths during the SBE Period. Two participants discontinued from the study due to TEAEs (abnormal liver function test in 1 active non-responder on PF-06651600 (ritlecitinib) and lower limb fracture in 1 retreated PF-06700841 (brepocitinib) responder). One active non-responder on PF-06700841 (brepocitinib) discontinued from PF-06700841 (brepocitinib) due to AE of proteinuria but completed the study. Five participants (2 placebo non-responders on PF-06700841 (brepocitinib), 1 non-retreated PF-06651600 (ritlecitinib) responder, 1 non-retreated PF-06700841 (brepocitinib) responder, and 1 retreated PF-06700841 (brepocitinib) responder) had temporary discontinuation due to TEAEs (increased blood creatine phosphokinase in 2 participants, increased blood creatinine and decreased glomerular

filtration rate in 1 participant, palpitations in 1 participant, and rhabdomyolysis in 1 participant). One retreated PF-06700841 (brepocitinib) responder experienced a treatment-emergent SAE of lower limb fracture which was considered not related to study drug. The most frequently met retest criterion was total neutrophils (absolute) $<2 \times 10^3/mm^3$ which was reported in 11 participants receiving PF-06700841 (brepocitinib) and 3 participants receiving placebo. There were no clinically relevant changes in lipid profile. Elevated CK levels of at least 3 × ULN were reported in 2 participants receiving PF-06700841 (brepocitinib) and 3 participants receiving placebo. TEAEs of increased blood creatine phosphokinase were reported in placebo non-responder on PF-06700841 (brepocitinib), and 1 retreated PF-06700841 (brepocitinib) responder; none of these TEAEs were considered as treatment-related by the investigator. There were no clinically significant findings in ECG and vital signs except increased diastolic BP in participants. There were no clinically significant changes from baseline in auditory tests. There were no increased risks with re-exposure to PF-06700841 (brepocitinib).

In the CO period: There were no deaths during the CO Period. No participants discontinued from the study or discontinued study drug due to TEAEs. Two participants (1 participant in each treatment group) had temporary discontinuation due to TEAEs (moderate bronchitis in the PF-06700841 (brepocitinib) CO treatment group; moderate influenza like illness and moderate torticollis in the PF-06651600 (ritlecitinib) CO treatment group). One participant in the PF-06700841 (brepocitinib) CO treatment group experienced a treatment-emergent SAE of gastroenteritis salmonella which was considered not related to study drug. The most frequently met retest criterion was total neutrophils (absolute) $<2 \times 10^3/mm^3$ which was reported by 6 (26.1%) participants: 5 (27.8%) participants in the PF-06700841 (brepocitinib) CO treatment group. One participant in the PF-06700841 (brepocitinib) CO treatment group experienced Grade 3 decreased neutrophil count. There were no clinically relevant changes in lipid profile. Elevated CK levels of at least 3 × ULN were reported in 1 participant in PF-06700841 (brepocitinib) CO treatment group. There were no clinically significant findings in ECG and vital signs except increased diastolic BP in 1 participant. There were no clinically significant changes from baseline in auditory tests. There were no increased risks observed after cross-over to treatment with PF-06700841 (brepocitinib).

1.5.3.1.10. Study B7931028

This is a Phase 2b, double-blind, randomized, placebo controlled, parallel design, multicenter, dose ranging study to assess the efficacy and safety of PF-06700841 (brepocitinib) in participants with active, moderate to severe generalized SLE. This is the first study of PF-06700841 (brepocitinib) in participants with moderate to severe active, generalized SLE that have inadequate response to standard of care. After an up to 5 week screening period, eligible participants will be randomized in a 1:2:2:2 ratio such that participants will receive either 1 of 3 PF-06700841 (brepocitinib) QD dose levels (15 mg, 30 mg and 45 mg) or placebo every day for 52 weeks. All participants will receive blinded dosing throughout the study treatment period in order to maintain the study blind.

1.5.3.1.10.1. Serious Adverse Events

As of 20 August 2020, an SAE of Cerebrovascular accident (assessed by the Investigator as related to study drug) has been reported in the ongoing blinded Study B7931028. The SAE of Cerebrovascular accident is discussed further below. There have been no deaths on this study to date.

A SAE of cerebrovascular accident (right thalamic stroke, blurry vision) was reported in a PPD-year-old PPD participant 99 days after randomization to blinded study treatment.

Relevant ongoing medical history included anemia, and prior medical history included PPD. The participant had no known prior history of either antiphospholipid syndrome, thrombotic disorders or fetal wastage, but had PPD at screening and had been receiving PPD. At the time of the event the participant's laboratory assessments showed a negative MRA, a low protein S, normal protein C, normal AT3, and elevated factor 5 and 8; anticardiolipin antibody IgG and IgM and beta 2 glycoprotein antibody IgG and IgM were negative, but during hospitalization, the participant was noted to have a positive anticardiolipin antibody IgA. In response to the events, the action taken with blinded study treatment was permanently withdrawn. The outcome for the event was recovering; the participant continued to have blurry vision and was discharged on PPD. The investigator considered that the event was related to blinded study treatment.

1.5.3.1.11. Study B7931030

This is a Phase 2B, randomized, double blind, placebo-controlled, dose range, parallel group study of PF-06700841 (brepocitinib) to evaluate the efficacy of PF-06700841 (brepocitinib) at 16 weeks and to evaluate the safety and efficacy up to 1 year in participants with active psoriatic arthritis.

As of 20 August 2020, 8 cases reporting a total of 9 treatment emergent SAEs have been reported in the ongoing blinded Study B7931030. Six of these SAEs are assessed by the investigator as not related to treatment. The SAEs are Appendicitis, Duodenal ulcer, Cholecystitis chronic, Psoriasis, Synovitis, and Varicella.

There were 2 cases reporting 3 SAEs assessed by the investigator as treatment related; A PPD year old PPD experienced Otitis media acute (bilateral acute otitis media with right ear effusion). The outcome is recovered. In the second case, a PPD-year-old PPD experienced Pneumonia and Coronavirus infection [Bilateral (S6-9 on the right and S8-9 on the left) pneumonia. Coronavirus infection]. The outcome is recovered.

Please refer to the IB for more details on the clinical safety information with PF-06700841 (brepocitinib).

1.5.3.1.12. Study B7931022

Study B7931022 was a Phase 2b, POC, randomized, double-blind, vehicle-controlled, parallel group, dose ranging study to assess the efficacy, safety and PK of PF-06700841 (brepocitinib) cream applied topically once or twice daily in participants with mild or moderate atopic dermatitis. Participation in this study was for approximately 16 weeks which included up to a 6-week screening period, a 6-week treatment period, and a 4-week follow-up period. Blood for determination of PF-06700841 (brepocitinib) plasma concentrations was collected prior to dosing at each visit. In order to observe at least 224 participants with 6 weeks of data, 292 participants were randomized and treated at 70 sites across 10 countries.

The safety population included 292 participants with atopic dermatitis involving ≤20% BSA. 73 participants were treated with vehicle and 219 participants were treated with PF-06700841 (brepocitinib).

Treatment-Emergent AEs by 5 Most Common System Organ Class Categories

The 5 most common AEs by SOC were Infections and Infestations, Skin and Subcutaneous tissue disorders, General disorders and Administration site conditions, Investigations, and Respiratory, Thoracic and Mediastinal disorders. The most common reported AE in the study was in the SOC Skin and Subcutaneous disorders and was worsening of atopic dermatitis. The majority of the AEs were mild.

Summary of Safety Results in Adolescent Population

Six male adolescents were enrolled in the study. Two were in the vehicle QD group and 1 each in the vehicle BID, 0.1% QD, 0.3% QD and 1% QD groups.

Out of 6 adolescents that were enrolled in the study, 3 developed AE's, which were all mild in severity. One adolescent participant developed neutropenia of 890/mL absolute neutrophil count at Day 64 in 0.3% QD active group. The neutrophil count, which was borderline low at baseline level consistent with presumed diagnosis of benign ethnic neutropenia, subsequently returned to the previous level. Two participants in vehicle QD group had AEs, one of worsening atopic dermatitis from D12 to D19 requiring use of concomitant medication, and one burning with application of IP from D1 to D27, which spontaneously resolved.

There were no deaths in the study.

There were no cases of malignancies.

Hematological disorders and other clinical lab results

Except for 1 adolescent participant who experienced decrease in neutrophil count to less than 1000/mm^3, there were no other hematologic abnormalities reaching discontinuation criteria.

Two participants in active groups reached >3 x ULN for alanine aminotransferase; one had 131 U/L (in 0.3% QD group, and the other 106 U/L in 1% BID dosing group (ref range 9-34 U/L). Eight participants (5 in active and 3 in vehicle treatment groups) had mild Creatine Kinase (CK) elevation >3 X ULN and <10 ULN, except for one participant in vehicle treatment group who had CK >10 X ULN. Abnormal CK results were sporadic, did not persist, and there was no temporal or dose dependent trend. There were no clinically significant trends in platelet, lymphocyte, neutrophil counts, or hemoglobin, bilirubin, aspartate, alanine transaminase and creatine kinase levels.

Skin tolerability

Overall, the drug was well tolerated. The skin tolerability is based on analysis of AEs and skin tolerability assessments. The study assessments were performed by principal investigator or qualified medical individual at each office visit, immediately before and after IP application. Reported AEs are presented in Results section above (SOC category: General disorders and application site reactions). The assessment of tolerability at site of IP applications before and after the treatment showed that majority of the participants had no evidence of local intolerability after IP application, with small number of participants having mild or moderate intolerability. The numbers of participants with mild and moderate intolerability are comparable through different dosing groups.

There were 3 participants that have documented severe intolerability to IP application that led to early termination. One participant in vehicle QD group developed severe intolerability to IP application on Day 1, 1 in 3% QD group on Day 4 and 1 participant in 1% QD group.

The study met the primary efficacy endpoint. At Week 6 the percentage change from baseline based on the EASI score was statistically significant compared to vehicle with multiplicity adjustment in 1 of 4 active QD treatment groups (1% QD) and in 1 of 2 active BID treatment groups (1% BID). The highest percentage change from baseline (75.0%) was observed in the 1% BID treatment group. Key secondary endpoint results for the response rates based on IGA (clear [0] or almost clear [1] and a reduction from baseline of ≥2 points) were statistically significant in all 4 QD treatment groups (0.1% QD, 0.3% QD, 1% QD and 3% QD) and in 1 of 2 BID treatment groups (0.3% BID).

1.5.3.1.13. Study B7931023

Study B7931023 is a Phase 2b, randomized, double-blind, vehicle-controlled, parallel-group, dose ranging study to assess efficacy, safety, tolerability and pharmacokinetics of PF-06700841 (brepocitinib) topical cream applied once or twice daily for 12 weeks in participants with mild to moderate chronic plaque psoriasis.

As of 20 August 2020, 8 cases reporting a total of 11 treatment emergent SAEs have been reported in the ongoing blinded Study B7931023. There are no SAEs assessed as related to blinded study treatment by the investigator. The SAEs are Pulmonary embolism, Urinary tract infection, Lethargy, Nervous system disorder, Skin laceration and Bursa injury, Cardiac failure and Respiratory failure, Sepsis and Thrombophlebitis, and Bacteremia.

The case with SAEs of Cardiac failure and Respiratory failure resulted in death of the PPD year old PPD participant with ongoing medical history of PPD

Please refer to the IB for more details on the clinical safety information with PF-06700841 (brepocitinib).

1.5.3.2. Pharmacokinetics of PF-06700841 (brepocitinib)

PK data from single doses of 1, 3, 10, 30, 100 and 200 mg and multiple doses of 10, 30, 100 and 175 mg QD and 50 mg BID mg administered for 10 days are summarized in Table 3 and Table 4, respectively. Following single oral doses of 1 mg to 200 mg under fasted conditions, PF-06700841 (brepocitinib) was absorbed rapidly with median T_{max} of 1 hour or less. Following the attainment of C_{max}, concentrations appeared to decline in monophasic fashion. Mean terminal $t_{½}$ ranged from 3.8 to 7.5 hours. In general, both AUC_{inf} and C_{max} appeared to increase proportionally with dose from 1 mg to 100 mg, and there appeared to be a trend toward more than proportional increases from 100 mg to 200 mg for AUC_{inf} and C_{max}.

Table 3. Summary of Plasma PF-06700841 (brepocitinib) Pharmacokinetic Parameters Following Single Oral Doses, Study B7931001

	PF-06700841 (Brepocitinib) Parameter Summary Statistics[a] by Treatment					
Parameter, units	1 mg	3 mg	10 mg	30 mg	100 mg	200 mg
N, n	7, 2	6, 5	6, 6	6, 6	8, 7	8, 8
AUC_{inf}, ng.hr/mL	NR	145.8 (61)	353.8 (31)	1439 (65)	4797 (62)	18410 (46)
AUC_{last}, ng.hr/mL	17.71 (114)	79.18 (239)	340.4 (30)	1431 (65)	5041 (59)	18400 (46)
C_{max}, ng/mL	5.138 (52)	18.21 (92)	79.30 (35)	271.3 (21)	748.4 (35)	2460 (37)
T_{max}, hr	1.00 (0.500-2.00)	1.00 (0.500-1.00)	0.500 (0.500-1.00)	1.00 (0.500-1.02)	1.00 (0.500-2.00)	1.00 (0.500-2.00)
$t_{½}$, hr	NR	4.55 ± 1.81	3.85 ± 1.16	4.36 ± 2.41	7.52 ± 2.82	6.81 ± 1.99

[a] Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for $t_{½}$.

N = Number of subjects in the treatment group and contributing to the mean; n= number of subjects where $t_{½}$, AUC_{inf} were determined.

NR = Not reported. Summary statistics are not presented if fewer than 3 subjects have reportable parameter values.

On Day 10 of multiple-dose administration, PF-06700841 (brepocitinib) was absorbed rapidly with median T_{max} of 1.5 hours or less across the entire range of doses, from a total daily dose of 30 mg up to 175 mg. Following attainment of C_{max}, the disposition of PF-06700841 (brepocitinib) was similar with that observed following single-dose administration. Mean terminal $t_{½}$ ranged from 4.9 to 10.7 hours. In general, both AUC_{tau} and C_{max} appeared to increase proportionally with dose from 10 mg to 175 mg. The mean apparent clearance (CL/F) was 10.8 L/hr to 23.7 L/hr, and the mean apparent volume of distribution (Vz/F) was 106.2 L to 249.4 L.

Table 4. Summary of Steady State Plasma and Urine PF-06700841 (brepocitinib) Pharmacokinetic Parameters Following Multiple Dose Administration (10 Days), Study B7931001

	PF-06700841 (brepocitinib) Parameter Summary Statistics[a] by Treatment				
Parameter, units	10 mg (QD)	30 mg (QD)	100 mg (QD)	50 mg (BID)	175 mg (QD)
N, n	5, 5	3, 3	6, 6	4, 4	4, 4
AUC_{τ}, ng.hr/mL	422.8 (41)	1880 (52)	6089 (38)	3560 (35)	16180 (15)
C_{max}, ng/mL	63.4 (11)	286.6 (17)	734.1 (29)	522.0 (31)	2091 (28)
T_{max}, hr	1.0 (1.0-1.0)	1.00 (1.00-1.00)	1.5 (1.0-2.0)	1.0 (1.0-2.0)	0.98 (0.50-2.0)
CL/F, L/hr	23.7 (41)	16.0 (51)	16.4 (38)	14.0 (35)	10.8 (16)
t½, hr	5.93 ± 3.33	4.86 ± 1.93	10.67 ± 1.84	9.13 ± 2.26	7.46 ± 2.16
V_z/F, L	177.6 (30)	106.2 (12)	249.4 (45)	180.9 (30)	112.4 (18)
Ae_{τ}%	11.1 (45)	9.3 (57)	NR	15.5 (57)	8.9 (44)
CLr, L/hr	2.619 (18)	1.486 (15)	NR	2.179 (31)	0.9629 (58)

[a] Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for t½.

N = Number of subjects in the treatment group and contributing to the mean; n= number of subjects where t½ was determined; NR = Not reported.

AUC_{τ}, = Area under the concentration-time curve from zero to 24 hours (QD) or zero to 12 hours (BID) postdose at steady state; QD = Once daily; BID = Twice daily; C_{max} = Peak plasma concentration; CL/F = apparent total body clearance; V_z/F = apparent volume of distribution; Ae_{τ}% = Percent of dose recovered unchanged in urine over the dosing interval τ; CLr = Renal clearance.

Urinary recovery of PF-06700841 (brepocitinib) was low, with approximately <16% of the dose recovered unchanged in urine on Day 10 across all doses (geometric mean Ae_{τ}% of 8.9% to 15.5%). Renal clearance ranged from 0.96 L/hr to 2.62 L/hr.

The relative BA (B7931001) of 100 mg PF-06700841 (brepocitinib) tablets compared to 100 mg oral suspension was 96.2% for AUC_{inf} and 94.3% for C_{max}. Both of the 90% CIs for the ratio were within the 80% to 125% equivalence interval. When the 100 mg tablets were administered under fed conditions, T_{max} was delayed with a median value of 4.0 hours, compared to a median T_{max} 0.5 hours under fasted conditions. For 100 mg tablets fed vs. fasted, the ratio (90% CI) of adjusted geometric means for AUC_{inf} and C_{max} was 82.3% (73.5%, 92.3%) and 64.3% (56.0%, 73.8%), respectively. Pharmacodynamic biomarkers response was best described by an indirect response PK/PD model indicating that AUC rather than C_{max} is the important parameter to modulate disease response hence the recommendation is to administer the IP with no requirement regarding food in the current study.

Listed in Table 5 are the PK parameters following multiple-dose administration of PF-06700841 (brepocitinib) to psoriasis subjects. PF-06700841 (brepocitinib) was absorbed rapidly with median T_{max} of 1 hour to 2 hours post dose. Mean terminal t½ was 16 hours in the 30 mg group and 6 hours in the 100 mg group. The mean t½ value in the 30 mg group included a reported t½ value of 87.5 hours for one subject with an anomalous data point at

216 hours postdose: all other subjects in the dose group had concentrations below the lower limit of quantitation (LLOQ) after 24 hours, and t½ values of 6.48 hours or less.

Table 5. Summary of Plasma Steady State PF-06700841 (brepocitinib) Pharmacokinetic Parameters Following Multiple Dose Administration (28 Days) in Psoriasis Subjects, Study B7931001

Parameter, units	Parameter Summary Statistics[a] by Treatment	
	PF-06700841 (brepocitinib) 30 mg QD (P)	PF-06700841 (brepocitinib) 100 mg QD (P)
N, n	7, 7	5, 5
AUC_{τ}, ng.hr/mL	990.0 (103)	7672 (43)
C_{max}, ng/mL	204.7 (43)	924.2 (13)
T_{max}, hr	1.00 (0.983-2.00)	2.00 (1.00-2.00)
CL/F, L/hr	30.30 (103)	13.04 (43)
MRT, hr	6.072 (92)	8.534 (36)
PTF	3.414 (44)[b]	2.654 (42)
$t_{½}$, hr	16.01 ± 31.58	6.032 ± 1.712
V_z/F, L	245.4 (206)	109.6 (18)

[a] Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for t½.
[b] 4 subjects contributing to the mean in this group.
N = Number of subjects in the treatment group and contributing to the mean; n= number of subjects where t½, Vz/F and MRT were determined; P= patients with psoriasis.

In general, dose normalized exposure was higher in the 100 mg group than in the 30 mg group although the highest individual dose normalized values for both AUC_{τ} and C_{max} were observed in one subject in the 30 mg group. Note that the subject in the 30 mg group with the highest C_{max} and AUC_{τ} values was not the same subject with the anomalous 87.5 hour t½ value.

1.6. Rationale

1.6.1. Study Rationale

This multicenter, multiple-arm, placebo-controlled study will be the first determination of safety and efficacy of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) in subjects with moderate to severe CD. The original objectives of this study were to evaluate the efficacy (based on clinically meaningful endoscopic improvement), safety, tolerability, PK, and PD of 200 mg for 8 weeks followed by 50 mg for 4 weeks of PF-06651600 (ritlecitinib) dosed once daily and 60 mg of PF-06700841 (brepocitinib) dosed once daily during an induction period of 12 weeks, followed by an open label extension period at doses of 50 mg and 30 mg of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib), respectively, for 52 weeks.

With the implementation of PA5, the aim of the study is revised. The study modifications are based on:

1. A strategic decision the part of the sponsor to prioritize future development of PF-06651600 (ritlecitinib), a JAK3/TEC inhibitor currently in development for a number of additional autoimmune diseases namely ulcerative colitis, alopecia areata and vitiligo; and

2. A desire to enable efficient comparison with contemporary and emerging trials in Crohn's disease.

The decision to eliminate the PF-06700841 (brepocitinib) cohort from this study B7981007 is not due to any specific safety, efficacy or quality concerns that would negatively affect the overall benefit/risk for patients in this trial or in other trials.

The total induction period for both assets is 12 weeks. The 12-week PF-06651600 (ritlecitinib) hybrid induction dosing is a consequence of available nonclinical long-term toxicity data supporting higher 200 mg treatment for only 8 weeks (a lower 50 mg dose is being used for the remainder of the 12 week induction period).

Dermatologic rashes have been observed in the Phase 1 PF-06651600 (ritlecitinib) studies. As the more severe rashes were associated with twice a day administration, dosing has been limited to once a day in this study. The availability of dermatology consultation in this study is purely a precautionary measure.

Increases in serum creatinine have been observed in the Phase 1 PF-06700841 (brepocitinib) studies. However, nonclinical data suggest that this could be due to inhibition of a creatinine transporter in the proximal tubule rather than an indication of renal toxicity. Parallel cystatin C assessments in the Phase 1 studies were consistent with this hypothesis. The availability of nephrology consultation in this study is purely a precautionary measure.

Histologic findings that could impact auditory function were observed in the chronic dog toxicology studies with PF-06651600 (ritlecitinib). As the translation of this finding to humans is unknown at this time, a dose of PF-06651600 (ritlecitinib) is being used for treatment after 8 weeks that is 7.8 times lower than the dose level for which these histologic findings were NOT observed in dogs. Periodic audiogram monitoring is being implemented to detect any clinically-meaningful changes in hearing that might occur. The availability of audiology consultation in this study is purely a precautionary measure.

Changes in lipid profile linked to IL-6 inhibition have been observed with drugs that inhibit IL-6 signaling. Therefore, lipid profiles will be assessed in the clinical programs.

Simvastatin is highly metabolized in the gut and modeling based on in vitro data suggests that PF-06651600 (ritlecitinib) time dependent inhibition of CYP3A may result in a clinically relevant increase in simvastatin plasma levels. Thus, simvastatin use with PF-06651600 (ritlecitinib) is currently prohibited. Since PF-06651600 (ritlecitinib) is metabolized by CYP3A moderate to potent inhibitors and inducers of CYP3A are prohibited (Appendix 10).

In vitro characterization of PF-06700841 (brepocitinib) ability to inhibit drug transporters indicates that it is likely to inhibit drug transporters OCT2, MATE and MDR1. Based on these results, drugs with a low therapeutic index that are transported by (MDR1) (digoxin) or OCT2/MATE (dofetilide) are prohibited.

Since PF-06700841 (brepocitinib) is metabolized by CYP3A moderate to potent inhibitors and inducers of CYP3A are prohibited (Appendix 10).

All endoscopies will be read by a central reader who will be blinded to study treatment. During the endoscopic evaluations, intestinal biopsies will be obtained and subsequently interrogated to provide evidence for pharmacological modulation of the JAK pathways and to define parameters that might be used to enable a precision medicine strategy in future clinical trials. Furthermore, the peripheral blood and stool may be profiled to provide correlative peripheral biomarkers that could complement the precision medicine discovery in intestinal biopsies.

By including two investigational drugs in a single study, the respective placebo groups can be combined, resulting in fewer subjects being exposed to placebo and a smaller overall study size. The inclusion of these two investigational drugs is appropriate as the target population and efficacy outcome measures are identical for both.

1.6.2. Dose Rationale

The dose selection strategy was designed to balance pharmacology and safety for this study with a 12 week induction period followed by a 52 week OLE in subjects with moderate to severe CD. PK was assumed to be similar between healthy subjects and subjects with moderate to severe CD. The activity of the JAK inhibitors was assessed by measurement of various PD markers and markers of safety that were collected in the FIH studies and analyzed using indirect response modeling. The magnitude of change in these markers required for efficacy and/or safety is poorly understood.

1.6.2.1. PF-06651600 (ritlecitinib) Dose Rationale

A 2-compartment PK model with clearance and volume modeled as a function of dose described the concentration profiles at each dose level from the first-in-human study in healthy subjects (B7981001) and under fasted and fed conditions (B7981003). The predicted PK parameters for PF-06651600 (ritlecitinib) based on simulations using the PK model are provided in Table 6.

Table 6. Summary of Predicted Geometric Mean Steady State Total Plasma PF-06651600 (ritlecitinib) Pharmacokinetic and Pharmacodynamic Parameters During the Induction and Chronic Periods of Multiple Dose Administration

Dose mg QD	Total C_{max} ng/mL	Predicted Margins[a] C_{max}[a]	Total AUC_{tau} ng.hr/mL	Predicted Margins[a] AUC[a]	IP-10 % Reduction from Baseline
Induction					
200	1254 (2.1)	12	3712 (14)	14	42 (19)
Induction/Chronic Dosing					
50	259.5 (3.4)	5[b]	662.0 (20)	7[b]	18 (39)

AUC_{tau} = Area under the concentration-time curve from zero to 24 hours postdose at steady state; C_{max} = Peak plasma concentration; QD = Once daily; ( ) = Coefficient of variation expressed as a percent; human unbound fraction (fu) = 0.86; 1 ng/mL= 3.504 nM.

a. Induction: NOAEL-highest dose in dogs, 45 mg/kg/day; Week 8 mean male and female C_{max} (free) = 12,000 ng/mL; C_{max} (total) = 14,634 ng/mL; AUC_{tau} (free) = 44,100 ng•h/mL; AUC_{tau} (total) = 53,780 ng•h/mL.

b. Chronic Dosing: 9 month oral dog NOAEL-5 mg/kg; mean male and female C_{max} (free) = 1115 ng/mL; C_{max} (total) = 1297 ng/mL; AUC_{tau} (free) = 4018 ng•h/mL; AUC_{tau} (total) = 4672 ng•h/mL, dog (fu) = 0.82.

The predicted exposure during the induction period at the top dose of 200 mg QD for 8 weeks is projected to maintain 12- and 14-fold safety margins for C_{max} and AUC_{tau}, respectively. During the remaining 4 weeks of the induction period at 50 mg QD and the OLE for 52 weeks the 50 mg dose is projected to maintain a safety margin for C_{max} and AUC_{tau} of 5- and 7-fold, respectively.

In human whole blood lymphocytes, PF-06651600 (ritlecitinib) inhibited JAK1/JAK3/TEC dependent STAT5 and STAT3 phosphorylation by IL-15 and IL-21 respectively, with IC_{50} values of 56.5 ng/mL and 103 ng/mL, respectively. All other pathways were inhibited at IC_{50} values >571 ng/mL. The inhibition (18-42%) of IP-10 is indicative of modulation of interferon gamma. The predicted mean percent (%) inhibition of IL-15 was 44 and 81, respectively for the 50 mg and 200 mg. The corresponding values for IL-21 mean percent inhibition were 30 and 71, respectively for the 50 and 200 mg.

Pharmacological modulation of the target can be inferred from the predicted inhibition of IL-15 and IL-21.

1.6.2.2. PF-06700841 (Brepocitinib) Dose Rationale

This Section is no longer applicable to newly enrolled participants under PA5.

A 2-compartment PK model with clearance and volume modeled as a function of dose described the concentration profiles at each dose level from the first-in-human study in healthy subjects, subjects with psoriasis and under fasted and fed conditions (B7931001). The predicted PK parameters for PF-06700841 (brepocitinib) based on simulations using the PK model are provided in Table 7.

Table 7. Summary of Predicted Steady State Total Plasma PF-06700841 (brepocitinib) Pharmacokinetic and Pharmacodynamic Parameters

Dose mg QD	Total C_{max} ng/mL	Predicted C_{max} Margins	Total AUC_{tau} ng·hr/mL	Predicted AUC Margins[a]	Percent Reduction from Baseline			
					hsCRP	IP-10	Neutrophils	Reticulocytes
Induction Treatment Period								
60	433.3 (27)	7.2	3797 (43)	3.9	84 (6.4)	51 (21)	32 (70)	50 (34)
Maintenance Treatment Period								
30	201 (29)	15	1575 (43)	9.3	82 (7.7)	47 (26)	30 (45)	36 (35)

AUC_{tau} = Area under the concentration-time curve from zero to 24 hours postdose at steady state; C_{max} = Peak plasma concentration; QD = Once daily; ( ) = Coefficient of variation expressed as a percentage;

[a] 9 month oral monkey NOAEL-20 mg/kg; mean male and female C_{max} (free) = 2263 ng/mL; C_{max} (total) = 3100 ng/mL; AUC_{tau} (free) = 10741 ng•h/mL; AUC_{tau} (total) = 14700 ng•h/mL, monkey (fu) = 0.73; human fu = 0.61

The predicted exposure during the induction period at the top dose of 60 mg QD for 12 weeks is projected to maintain 7.2- and 3.9-fold safety margins for C_{max} and AUC_{tau}, respectively. During the chronic dosing period the 30 mg dose administered QD for 52 weeks is projected to maintain safety margins for C_{max} and AUC_{tau} of 15- and 9.8-fold, respectively.

In study B7931001, mechanistic biomarkers of efficacy, hsCRP and interferon gamma-induced protein 10 (IP-10) related to IL-6 and IFN-gamma, respectively, were measured in healthy subjects. Based on indirect response modeling, the predicted mean percent reductions in the hsCRP levels ranged between 69% and 84% over the dose range 10-60 mg. Similarly, the mean reduction of IP-10 levels ranged between 30% and 51% over the same dose range. Modeling and simulations predicted maximum reductions during the induction period in neutrophils and reticulocytes of 32% and 50%, respectively.

Subjects with moderate to severe psoriasis received doses of 30 mg or 100 mg QD or placebo for 28 days (B7931001). Efficacy was measured by placebo adjusted psoriasis area and severity index (PASI) change from baseline. Significant psoriasis disease modification (change >-9) at 30 mg and 100 mg was observed in the patients.

Overall, the doses selected for this study are expected to demonstrate clinically relevant efficacy in subjects with moderate to severe CD.

1.6.3. Summary of Benefits and Risks

IBD is a serious disease with potentially life-threatening sequelae.

The completed Phase 1 study B7981001 was a randomized, double blind, third party open, placebo controlled, single and multiple dose escalation, parallel group study in healthy adult subjects. Based on this study, PF-06651600 (ritlecitinib) appeared to be generally safe and well-tolerated. No clinically significant changes in vital signs, electrocardiogram or laboratory data were observed. No dose limiting adverse events (AEs) were reported and no subjects met the protocol prescribed individual stopping rules. There were no deaths in the study.

The completed RA Phase 2a study was a randomized double-blind, parallel group, placebo controlled, multi-center study to assess the efficacy and safety profile of 200 mg QD dose of PF-06651600 (ritlecitinib) compared to placebo after 8 week treatment in seropositive subjects with moderate to severe active RA and an inadequate response to methotrexate. PF-06651600 (ritlecitinib) appeared to be generally safe and well tolerated in this study. No deaths or SAEs were reported. TEAEs were numerically higher in the active group compared to placebo and were generally mild in severity. The most common TEAEs by SOC were Infections and Infestations, Skin and Subcutaneous Tissue Disorders, Blood and Lymphatic System Disorders and Gastrointestinal Disorders. There was one mild case of herpes simplex in the PF-06651600 (ritlecitinib) group that was considered to be treatment related with no cases in the placebo group.

The Phase 2a study in subjects with AA is ongoing. However, draft data from an interim analysis at 24 weeks has been reported in this IB. The study is a Phase 2a, randomized, double-blind, placebo-controlled, multi-center study with an extension period to evaluate the efficacy and safety profile of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) in subjects with moderate to severe active AA. PF-06651600 (ritlecitinib) appeared generally safe and well tolerated. There were no deaths in the study. There were no subjects with SAEs in the PF-06651600 (ritlecitinib) group. The number of AEs was higher in the placebo group relative to the PF-06651600 (ritlecitinib) group. The most common AEs were in the Infections and Infestations, Gastrointestinal Disorders, and Skin and Subcutaneous Tissue Disorders categories, and the majority of events were mild. No serious infections or cases of herpes zoster were reported in the study. Hematological changes were observed in both active groups during the induction and maintenance periods, but were not associated with clinically relevant adverse events.

The safety profile observed during the Phase 1 program for PF-06700841 (brepocitinib) appears to be acceptable at dosages up to 175 mg administered orally as multiple doses over 10 days in healthy volunteers. A 28 day dosing duration was explored in psoriasis patients, who received the maximum PF-06700841 (brepocitinib) dose level of 100 mg daily. No serious or severe AEs were reported in the Phase 1 study. However, there was one AE of herpes zoster infection in a psoriasis subject treated with 100 mg PF-06700841 (brepocitinib) for 4 weeks. As with other immunomodulators, the risk of infection is potential concern due to the immunosuppressive effects of PF-06700841 (brepocitinib). To limit this risk, a maximum daily dose of 60 mg will be used in this Phase 2 trial. A chronic therapy dose of 30 mg was selected since this dose has demonstrated anti-inflammatory activity resulting in clinical efficacy in patients with psoriasis.

Additional information for these compounds may be found in the single reference safety document (SRSD), which for this study is the individual IB for each compound.

Banked biospecimens will be collected for the purpose of conducting research; specific uses are described in the Banked Biospecimens section. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting biospecimens

for exploratory pharmacogenomic/genomic/biomarker analyses and retaining them in the Biospecimen Banking System (BBS) make it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

Banked biospecimens retained in the BBS also can be used in research on IBD and other inflammatory diseases.

Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited by local regulations or ethics committee (EC) decision.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives and Endpoints during the Induction Period

Primary Objective(s):	**Primary Endpoint(s):**
• To evaluate the efficacy of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo at Week 12 in subjects with moderate to severe CD.	• Proportion of subjects achieving SES-CD 50 (≥50% reduction in SES-CD from baseline) at Week 12.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the safety and tolerability of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo in subjects with moderate to severe CD over 12 weeks.	• Incidence and severity of laboratory abnormalities, vital signs, 12-lead ECG, adverse events, serious adverse events and withdrawals due to adverse events. • Incidence of serious infections.
• To evaluate the efficacy of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo during induction of additional endoscopic endpoints in subjects with moderate to severe CD.	• Proportion of subjects achieving clinically meaningful endoscopic improvement (reduction of ≥3 points from baseline in SES-CD score) at Week 12. • Mean change from baseline in SES-CD score at Week 12. • Proportion of subjects achieving SES-CD 25 (≥25% reduction in SES-CD from baseline) at Week 12. • Proportion of subjects achieving endoscopic remission (SES-CD ≤2) at Week 12. • Proportion of subjects achieving mucosal healing (complete absence of ulcers) at Week 12.

Tertiary/Exploratory Objective(s):	Tertiary/Exploratory Endpoint(s):
• To evaluate the effect of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo on outcomes based on additional clinical criteria.	• Proportion of subjects achieving clinical response and remission using SF, and AP measures at Weeks 2, 4, 6, 8, 10 and 12. • Proportion of subjects achieving deep remission (endoscopic remission by SES-CD and clinical remission by SF and AP) at Week 12. • Proportion of subjects with a CDAI-100 response (defined by a decrease in CDAI score of at least 100 points from baseline) and proportion of subjects who are remitters (defined as CDAI <150) at Weeks 2, 4, 8 and 12. • The scores and change from baseline in IBDQ total score and domains (Bowel Symptoms, Systemic Symptoms, Emotional Function and Social Function) at Weeks 4, 8, and 12. • The proportion of subjects with IBDQ total score ≥170 at Weeks 4, 8, and 12. • The proportion of subjects with ≥16 point increase in IBDQ total score from baseline at Weeks 4, 8, and 12. • Proportion of subjects achieving IBDQ symptom domain response at Weeks 4, 8, and 12. • The scores and change from baseline in EQ-5D-3L + VAS at Weeks 4, 8, and 12. • The scores and change from baseline in SF-36 v2 acute: PCS & MCS, and 8 domain scores at Weeks 4, 8, and 12. • Mean change from baseline in PGIS score at Weeks 4, 8 and 12.
• To evaluate the effect of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo on histopathology score.	• Change from baseline in Global Histologic Disease Activity (GHAS) score at Week 12. • Proportion of subjects achieving histologic remission at Week 12 (defined as GHAS score ≤4).
• To assess the effect of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo on disease and mechanistic biomarkers over time.	• Change from baseline in serum high sensitivity C-reactive protein (hsCRP) levels over time. • Change from baseline in fecal calprotectin over time. • Change from baseline in serum IP-10 levels over time.

	• Change from baseline in *BCL-2* gene expression. • Change from baseline in hematological values including reticulocytes, hemoglobin, neutrophils, platelets, and TBNK cells.
• To describe the PK of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo in subjects with moderate to severe CD.	• PF-06651600 (ritlecitinib) concentrations at Weeks 2, 4, 8 and 12. • PF-06700841 (brepocitinib) concentrations at Weeks 2, 4, 8 and 12.
• To collect non-banked samples (eg, intestinal biopsies, stool for microbiome analysis, serum and plasma for analysis of proteins and a whole blood tube for RNA analysis) for exploratory research, unless prohibited by local regulations or ethics committee decision. • To collect banked biospecimens samples for exploratory research, unless prohibited by local regulations or ethics committee decision.	• Collection of non-banked exploratory samples unless prohibited by local regulations or ethics committee decision. • Collection of banked biospecimens unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in the Banked Biospecimens section.

2.2. Objectives and Endpoints during the Open Label Extension Period

Primary Objective(s):	**Primary Endpoint(s):**
• To assess the safety and tolerability of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) therapy during open label extension period for subjects with moderate to severe CD.	• Incidence and severity of laboratory abnormalities, vital signs, 12-lead ECG, adverse events, serious adverse events and withdrawals due to adverse events.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the efficacy of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) as maintenance therapy in subjects with moderate to severe CD.	• Proportion of subjects achieving clinically meaningful endoscopic improvement (CMEI response) at Week 64 among subjects who achieved CMEI response at Week 12. • Proportion of subjects achieving SES-CD 25 and SES-CD 50 at Week 64 among subjects who achieved SES-CD 25 and SES-CD 50 at Week 12 respectively.
Exploratory Objective(s):	**Exploratory Endpoint(s):**
• To evaluate the efficacy of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) therapy during the open label extension period for subjects with moderate to severe CD.	• Proportion of subjects achieving clinically meaningful endoscopic improvement (reduction of ≥3 points from baseline in SES-CD) at Week 64. • Proportion of subjects achieving SES-CD 25 and SES-CD 50 (≥25% and ≥50% reduction in SES-CD from baseline) at Week 64.

	• Proportion of subjects achieving endoscopic remission (SES-CD ≤2) at Week 64. • Proportion of subjects achieving mucosal healing (complete absence of ulcers) at Week 64.
• To evaluate the effect of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) on outcomes based on additional clinical criteria.	• Proportion of subjects achieving clinical response and remission as defined by SF and AP endpoints at Weeks 16, 20, 24, 32, 40, 48, 56 and 64. • Proportion of subjects achieving deep remission (endoscopic remission by SES-CD and clinical remission by SF, AP) at Week 64. • Proportion of subjects with a CDAI-100 response or CDAI remission (CDAI <150) at Weeks 16, 32 and 64. The scores and change from baseline in IBDQ Total score and domains (Bowel Symptoms, Systemic Symptoms, Emotional Function and Social Function) at Weeks 16, 32 and 64. • The proportion of subjects with IBDQ total score ≥170 at Weeks 16, 32 and 64. • The proportion of subjects with ≥16 point increase in IBDQ total score from baseline at Weeks 16, 32 and 64. • Proportion of subjects achieving IBDQ symptom domain response at Weeks 16, 32 and 64. • The scores and change from baseline in EQ-5D-3L + VAS at Weeks 16, 32 and 64. • The scores and change from baseline in SF-36 v2: PCS & MCS, and 8 domain scores at Weeks 16, 32 and 64. • Mean change from baseline in PGIS score at Weeks 16, 32 and 64.
• To evaluate the effect of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) compared to placebo on histopathology score.	• Change from baseline in GHAS score at Week 64. • Proportion of subjects achieving histologic remission (GHAS ≤4) at Week 64.
• To describe the PK of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) in subjects with moderate to severe CD.	• PF-06651600 (ritlecitinib) concentrations at Weeks 16, 20, 32, 56 and 64. • PF-06700841 (brepocitinib) concentrations at Weeks 16, 20, 32, 56 and 64.
• To explore the relationship between PK, PD, and clinical endpoints.	• Change from baseline in serum hsCRP levels over time.

	• Change from baseline in fecal calprotectin. • Change from baseline in serum IP-10 levels over time. • Change in baseline in *BCL-2* gene expression. • Change from baseline in hematological values including reticulocytes, hemoglobin, neutrophils, platelets, and TBNK cells.
• To collect non-banked samples (eg, intestinal biopsies, stool for microbiome analysis, serum and plasma for analysis of proteins and a whole blood tube for RNA analysis) for exploratory research, unless prohibited by local regulations or ethics committee decision. • To collect banked biospecimens samples for exploratory research, unless prohibited by local regulations or ethics committee decision.	• Collection of non-banked exploratory samples unless prohibited by local regulations or ethics committee decision. • Collection of banked biospecimens unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in the Banked Biospecimens section.

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 2a, randomized, double-blind, placebo-controlled, parallel group, multicenter study in subjects with moderate to severe active CD. The entire study consists of: 1) a screening period of up to 6-weeks, 2) a 12-week induction period, 3) a 52-week open label extension (OLE) period, and 4) a 4-week follow up period. Approximately 230-250 subjects in total will be randomized into the study.

The 12-week induction period will be placebo-controlled and double-blind within each investigational product. Subjects who meet the eligibility criteria at the baseline visit will be randomly assigned to receive either active or placebo treatments. In the induction period, 200 mg QD for 8 weeks followed by 50 mg QD for 4 weeks of PF-06651600 (ritlecitinib) and matching placebo in a 2:1 ratio and for subjects enrolled prior to implementation of PA5, 60 mg QD for 12 weeks of PF-06700841 (brepocitinib) and matching placebo in a 2:1 ratio will be investigated. The hybrid dosing regimen for PF-06651600 (ritlecitinib) during the 12-week induction period is a consequence of available nonclinical long-term toxicity data supporting 200 mg treatment for only up to 8 weeks. For analysis, placebo groups will be combined.

After the completion of the induction period, subjects will enter the 52-week OLE period. There will be no re-randomization at the beginning of the OLE period. Subjects will receive the same study drug that they were randomized to receive during the induction period, and there will be no placebo arms. Placebo subjects from the induction period will also receive active drug in the OLE period. The matching placebo subjects from the double-blind PF-06651600 (ritlecitinib) treatment/placebo induction period will receive 50 mg of PF-06651600 (ritlecitinib), while the corresponding placebos from the double-blind PF-06700841 (brepocitinib)/placebo induction period will receive 30 mg of PF-06700841 (brepocitinib) for 52 weeks.

After completion of the OLE period, subjects will enter the 4-week follow up period. Any subjects, who discontinues early from the double-blind period prior to the Week 12 visit, should undergo the procedures for an Early Termination (Induction) visit on the last day the subject takes the investigational product or as soon as possible thereafter. For subjects who discontinue early from OLE period (after the Week 12 visit, but prior to the Week 52 visit), the procedures scheduled for an Early Termination (OLE) visit will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. These early withdrawal subjects, along with subjects who complete the induction period but are not willing to participate in the OLE period, will be asked to complete the Follow-up visit approximately 4 weeks after the last dose of study drug.

The original objectives of this study were to evaluate the efficacy [based on clinically meaningful endoscopic improvement (reduction of ≥3 points from baseline in SES-CD score) at Week 12 as assessed by central reading], safety, tolerability, PK, and PD of 200 mg for 8 weeks followed by 50 mg for 4 weeks of PF-06651600 (ritlecitinib) dosed once daily and 60 mg of PF-06700841 (brepocitinib) dosed once daily during an induction period of 12 weeks, followed by an open label extension period at doses of 50 mg and 30 mg of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib), respectively, for 52 weeks.

Amendment 5 of Protocol B7981007 revises the original design to eliminate the PF-06700841 (brepocitinib) and placebo arms and to change the primary endpoint during induction from CMEI to SES-CD 50 (to enable efficient comparison with contemporary and emerging trials in Crohn's disease). Therefore, upon approval of Amendment 5 by regional Regulatory Authorities and Ethics Committees, Protocol B7981007 will be conducted as a Phase 2a, randomized, double-blind, placebo-controlled, parallel group study focused on the evaluation of the efficacy and safety profile of the PF-06651600 (ritlecitinib) in subjects with moderate to severe active CD. All eligible participants that have been randomized to PF-06700841 (brepocitinib)/PF-06700841 (brepocitinib) placebo or currently actively receiving PF-06700841 (brepocitinib)/PF-06700841 (brepocitinib) placebo under previous protocol amendments will continue to receive PF 06700841 (brepocitinib) through to completion. This study modification is solely a strategic decision on the part of the sponsor to prioritize future development of PF-06651600 (ritlecitinib), a JAK3/TEC inhibitor currently in development for a of number of additional autoimmune diseases namely ulcerative colitis, alopecia areata and vitiligo. The decision to eliminate the PF-06700841 (brepocitinib) cohort from this study B7981007 is not due to any specific safety, efficacy or quality concerns that would negatively affect the overall benefit/risk for patients in this trial or in other trials.

Figure 1. Original Study Schematic

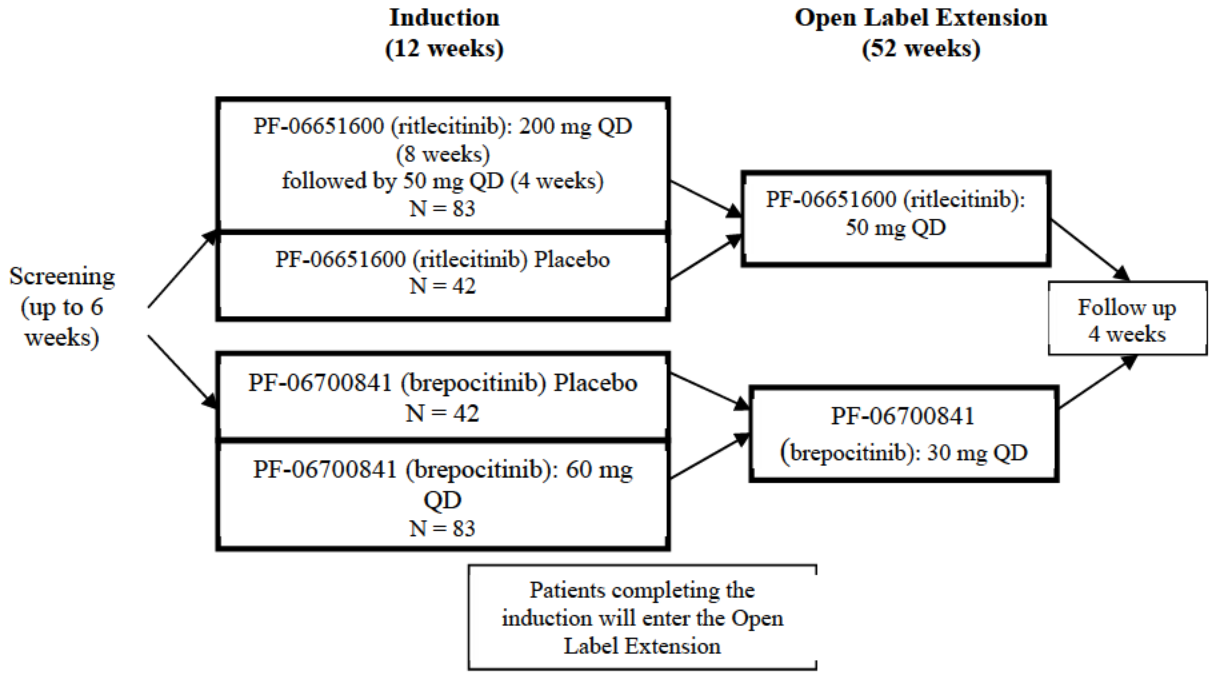
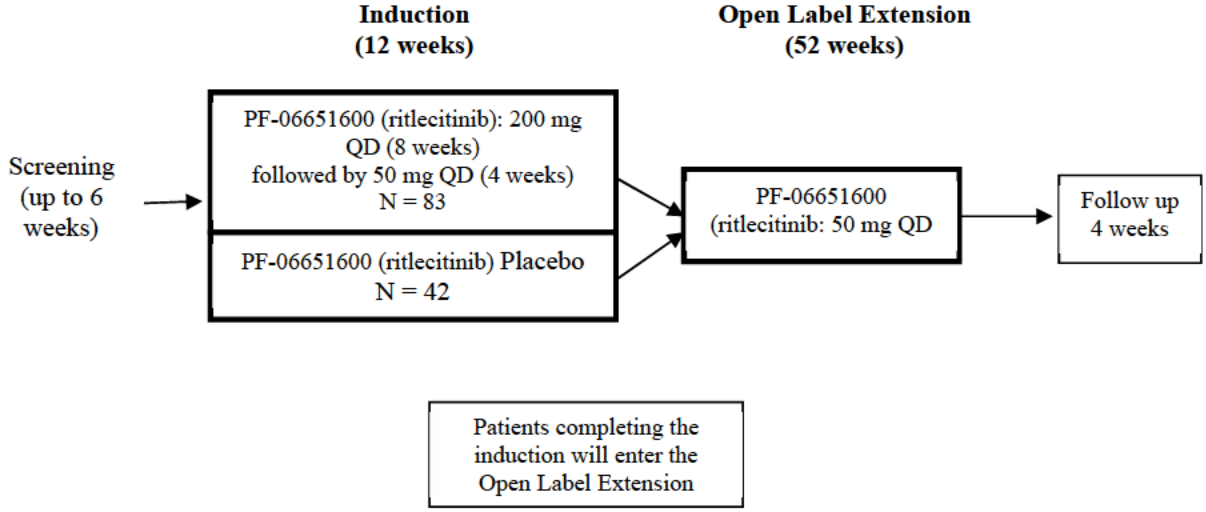


Figure 2. Study Schematic Post Implementation of Protocol Amendment 5



3.2. Duration of Subject Participation

The duration of participation for eligible subjects will be approximately 74 weeks. This includes a screening period of up to 6 weeks, followed by a 12 week double-blind induction period. All subjects who complete the induction period will enter the second part of the study which is a 52-week OLE period.

After completion of the OLE period, subjects will enter the 4-week follow up period.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Male and/or female subjects (including Women of Child Bearing Potential (WOCBP)) ≥18 years to ≤75 years of age at the time of informed consent. **For subjects in Korea:** Male and/or female subjects ≥19 years to ≤75 years of age at the time of informed consent.

2. Documented diagnosis of ileal, ileocolonic, or colonic CD with a minimum disease duration of 3 months, as determined by endoscopic and histopathology assessment.

3. Endoscopic (central reading) confirmation of active disease with total SES-CD total score of at least 7 (≥7)). For isolated ileal disease, SES-CD total score should be at least 4 (≥4).

4. An average daily liquid/soft stool frequency (SF) ≥2.5 or daily abdominal pain (AP) score ≥2.0.

5. Must have inadequate response to, loss of response to, or intolerance to at least one conventional therapy for CD:

   - Steroids;
   - Immunosuppressants (azathioprine [AZA], 6-MP, or methotrexate [MTX]);
   - Anti-TNF inhibitors (infliximab, adalimumab, or certolizumab);
   - Anti-integrin inhibitors (eg, vedolizumab);
   - Anti-IL-12/23 inhibitor (ustekinumab).

   However, this inclusion should be met only after the usual clinical practice in each center has been fulfilled, which may involve administration of more than one line of previous treatment.

   Note: The information below is provided for guidance only. Local standards of care, as well as investigator assessment should be considered in any assessment.

Inadequate response to, loss of response to, or intolerance to corticosteroid treatment may be defined as one or more of the following:

- Steroid refractory: Persistent symptoms of active disease despite treatment with at least one 4-week induction regimen that included a dose of ≥30 mg prednisone (oral) daily for at least 2 weeks or IV for at least 1 week within the previous 5 years;

- Steroid dependent: Two failed attempts to taper steroids below a dose equivalent to 10 mg prednisone (oral) daily;

- Steroid intolerant: History of intolerance to corticosteroids (including but not limited to Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection) within the previous 5 years.

Inadequate response to, loss of response to, or intolerance to prior immunosuppressant treatment is defined by one or more of the following:

- Persistent signs and symptoms of active disease despite a history of at least one 12-week regimen of oral AZA (≥2-2.5 mg/kg/day) or 6-MP (≥1-1.5 mg/kg/day) and/or MTX (≥25 mg/week) within the previous 5 years;

- History of intolerance to AZA, 6-MP, or MTX (including but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver function testing (LFT) abnormalities, lymphopenia, TPMP [thiopurine methyltransferase] genetic mutation, infection) within the previous 5 years.

Inadequate response to, loss of response to, or intolerance to prior anti-TNF inhibitors anti-integrin inhibitors, or ustekinumab (within the previous 5 years) is defined as one or more of the following:

- Persistent signs and symptoms of active disease despite at least one 8-week regimen of adalimumab (subcutaneous doses of 160 mg at Week 0 and 80 mg at Week 2 followed by a dose of ≥40 mg every 2 weeks), or one 14-week regimen of infliximab (3 intravenous doses ≥5 mg/kg), or one 10-week regimen of vedolizumab (intravenous doses of 300 mg at Weeks 0, 2, and 6)), or one 8 week regimen of at least one IV weight-based loading dose infusion and one 90 mg maintenance dose of ustekinumab.

- Intolerance is defined as: Clinically significant side effect(s) [including hypersensitivity (eg, signs/symptoms including rash, flushing, anaphylaxis, serum sickness) and development of anti-drug antibodies] to at least 1 treatment regimen with an anti-TNF inhibitor.

6. Subjects currently receiving the following treatment for CD are eligible providing they have been on stable doses as described below:

   - Oral corticosteroids (prednisone or equivalent up to 25 mg/day; budesonide up to 9 mg/day; See Appendix 11). Stable dose for at least 2 weeks prior to baseline. If oral corticosteroids have been recently discontinued, they must have been stopped at least 2 weeks prior to baseline. Decreases in steroid use due to AEs are allowed.

   - Oral 5-ASA or sulfasalazine are allowed providing that the dose is stable for at least 4 weeks prior to baseline.

   - Crohn's disease-related antibiotics are allowed providing that the dose is stable for at least 4 weeks prior to baseline. If antibiotics are stopped prior to baseline, they must be discontinued at least 4 days prior to baseline.

7. Female subjects of childbearing potential must test negative for pregnancy at screening visit and baseline visit.

8. Female subjects considered to be of non-childbearing potential must meet at least 1 of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   c. Have medically confirmed ovarian failure.

   All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

9. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

10. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Diagnosis of indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, radiation colitis, diverticular disease, ulcerative colitis (UC), or clinical findings suggestive of UC.

2. Presence of active (draining) fistulae or intra-abdominal or perineal abscesses.

3. Strictures with obstructive symptoms.

4. Short bowel syndrome.

5. History of bowel perforation requiring surgical intervention within the past 12 months.

6. Previous bowel surgery resulting in an existing stoma. Subjects who have a j-pouch are excluded, as a j-pouch can result in a stoma.

7. History of bowel surgery within 6 months prior to baseline.

8. Subjects considered in imminent need for surgery or with elective surgery scheduled to occur during the study.

9. Subjects displaying clinical signs of fulminant colitis or toxic megacolon.

10. Subjects with primary sclerosing cholangitis.

11. Subjects with evidence of colonic adenomas, dysplasia or neoplasia. However, subjects with prior history of adenomatous polyps or any adenomatous polyps identified on screening will be eligible if the polyps have been completely removed and the subjects are free of polyps at baseline per the assessment of the investigator based on the screening colonoscopy.

12. Subjects receiving the following therapies within the time period described below or expected to receive any of these therapies during the study period:

    a. >9 mg/day of oral budesonide or >25 mg/day of prednisone or equivalent oral systemic corticosteroid dose within 2 weeks prior to baseline.

    b. IV, IM (parenteral), or topical (rectal) treatment of 5-ASA or corticosteroid enemas/suppositories within 2 weeks prior to baseline.

    c. Azathioprine, 6-mercaptopurine, or methotrexate within 2 weeks prior to baseline.

    d. Anti-TNF inhibitors (or biosimilars thereof) as described below:

        - Infliximab within 8 weeks prior to baseline;
        - Adalimumab within 8 weeks prior to baseline;
        - Certolizumab within 8 weeks prior to baseline;

    e. Anti-integrin inhibitors (eg, vedolizumab) within 8 weeks prior to baseline.

f. Ustekinumab within 8 weeks prior to baseline.

g. Interferon therapy within 8 weeks prior to baseline.

h. Subjects with prior treatment with lymphocyte-depleting agents/therapies within 1 year prior to baseline (eg, CamPath® [alemtuzumab], alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation, etc).

i. Subjects who have received rituximab or other selective B lymphocyte-depleting agents within 1 year prior to baseline.

j. Subjects previously receiving leukocyte apheresis, including selective lymphocyte, monocyte, or granulocyte apheresis, or plasma exchange within 6 months prior to baseline.

k. Other marketed immunosuppressants or biologics with immunomodulatory properties within 3 months prior to baseline.

l. Subjects who have received other JAK inhibitors within 3 months prior to baseline.

m. Subjects who have not responded to or have been intolerant of other JAK inhibitors.

n. Other investigational procedures(s) or product(s), such as immunosuppressants used in transplantation (eg, mycophenolate mofetil, cyclosporine, rapamycin, or tacrolimus) or live (attenuated) vaccine within 30 days prior to baseline.

13. Participation in other studies involving investigational drug(s) within 30 days, or 5 half-lives of investigational product (IP) (whichever is greater), prior to study entry and/or during study participation.

14. Presence of active enteric infections (positive stool culture and sensitivity). *Clostridium difficile* infection (reference C. diff section) or pseudomembranous colitis, or Known active invasive fungal infections such as histoplasmosis or parasitic infections. Subject with *Clostridium difficile* infection may be treated and re-tested or re-screened at the discretion of the Investigator.

15. Abnormal findings on the chest x-ray film such as presence of tuberculosis (TB), general infections, heart failure, or malignancy. A chest X-ray or other appropriate diagnostic imaging modality (ie, CT with or without IV contrast or MRI) performed within 12 weeks prior to screening may substitute for the chest X-ray taken at Screening. Documentation of the official negative reading must be located and available in the source documentation prior to Baseline (Day 1) randomization.

16. Any history of either untreated or inadequately treated latent or active TB infection, current treatment for active or latent TB infection or evidence of currently active TB by chest x-ray, residing with or frequent close contact with individual(s) with active TB. Subjects who have a positive Interferon Gamma Release Assay during screening or within 12 weeks prior to randomization, except as noted below. The following are acceptable assays prior to screening: QuantiFERON® - TB Gold test (QFT-G), QuantiFERON® - TB Gold In-Tube test (QFT-GIT) and T-SPOT® - TB test. Covance tests that replace the above specified tests are permitted.

    - Subjects with prior active tuberculosis (except for multi drug resistant TB) that has no current evidence of active disease and has completed an adequate course of therapy for active tuberculosis (a multi-drug regimen recognized by the World Health Organization to which the organism has demonstrated appropriate sensitivity), negative chest radiograph for active disease and negative Interferon Gamma Release Assay (IGRA) are eligible.

    - Subjects that have an indeterminate QFT-G may have QFT-G test repeated and, will be eligible if the repeat (QFT-G) test is negative at time of randomization. Subjects with repeat indeterminate IGRA results may be enrolled after consultation with pulmonary or infectious disease specialist that determines low risk of infection (ie, subject would be acceptable for immunosuppressant (eg, anti-TNF) treatment without additional action).

    - Subjects adequately treated (in the opinion of the appropriately qualified personnel - which may include a pulmonary or infectious disease specialist, or locally acceptable expert as defined by local guidelines) for latent and/or active tuberculosis infection may be enrolled regardless of IGRA results provided the treatment is well documented in the subject's medical records and/or source documentation prior to enrollment in the study.

17. Known history of human immunodeficiency virus (HIV) based on documented history with positive serological test, or positive HIV serologic test at screening, tested at the site's local lab (when feasible).

18. Subjects will be screened for hepatitis B virus infection and will be excluded if positive for hepatitis B surface antigen (HBsAg). Subjects with HBsAg negative testing, but who test positive for hepatitis B core antibody (HBcAb) must have further testing for hepatitis B surface antibody (HBsAb). If HBsAb is negative, the subject will be excluded from the study.

19. Subjects will be screened for hepatitis C virus (HCV Ab). Subjects with positive HCV Ab tests will be reflex tested for HCV ribonucleic acid (HCV RNA). Only subjects with negative HCV Ab or HCV RNA will be allowed to enroll in the study.

20. Clinically significant infections within 6 months of baseline (eg, those requiring hospitalization or parenteral antimicrobial therapy, or opportunistic infections), history of any infection requiring antimicrobial therapy within 2 weeks of baseline, or a history of any infection otherwise judged by the investigator to have the potential for exacerbation by participation in the study.

21. Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (with the exception of subjects with adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ).

22. Presence of transplanted organ; skin grafts are allowed.

23. Have a history (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localized dermatomal herpes zoster.

24. Have current or recent history of clinically significant severe or progressive hearing loss or auditory disease. Subjects with hearing aids will be allowed to enter the study provided their hearing impairment is considered controlled/clinically stable.

25. Significant concurrent medical condition at the time of screening or baseline visit, including but not limited to the following:

    - Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment will substantially increase the risk to the subject if he or she participates in the study;

    - Active renal disease and/or recent kidney stones;

    - Severe hepatic impairment (defined as Child-Pugh C);

    - Acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and any history of cerebrovascular disease within 24 weeks before screening;

    - Heart failure NYHA (New York Heart Association) III, NYHA IV.

26. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

27. Female subjects who are pregnant or wish to become pregnant, breastfeeding female subjects; male subjects with partners currently pregnant; male subjects able to father children and female subjects of childbearing potential who are unwilling or unable to use 2 effective methods (at least 1 highly effective method) of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.

28. Subjects with any condition possibly affecting oral drug absorption (eg, gastrectomy, clinically-significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass). Procedures such as gastric banding that simply divide the stomach into separate chambers are NOT exclusionary.

29. Subjects receiving prohibited concomitant medications, including moderate to potent CYP3A inducers or inhibitors (See Appendix 10) in the time periods described below:

    - For moderate to potent CYP3A inducers, within 28 days or 5 half-lives, whichever is longer, prior to baseline.

    - For moderate to potent CYP3A inhibitors, within 7 days or 5 half-lives, whichever is longer, prior to baseline.

    Note: Simvastatin or simvastatin-containing products from 5 days prior to baseline.

30. Subjects receiving strong P-gp inhibitors (eg, quinidine) within 5 half-lives prior to baseline.

31. Subjects receiving narrow therapeutic index substrates of MDR1 (eg, digoxin), OCT2 or MATE (eg, dofetilide) within 5 half-lives prior to baseline.

32. Prior evidence of liver injury or toxicity due to methotrexate.

33. Abnormality in hematology and/or chemistry profiles during screening:

    - White blood cell (WBC) count $\leq 3.0 \times 10^9$/L (3000 cells/mm^3) or absolute neutrophil count (ANC) <1200 cells/mm^3 or absolute lymphocyte count of $<0.8 \times 10^9$/L (<800 cells/mm^3).

    - Hemoglobin level ≤90 g/L (9.0 g/dL). Platelet count $\leq 100 \times 10^9$/L (100,000 cells/mm^3) or $\geq 1000 \times 10^9$/L (1,000,000 cells/mm^3).

    - eGFR <60 mL/min/1.73m^2 based on the age appropriate calculation.

    - Total bilirubin level ≥1.5 times the ULN; subjects with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin in ≤ ULN.

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥1.5 times the upper limit of normal (ULN).
- Proteinuria ≥3+.
- Creatine kinase (CK) >3 times the ULN and positive urine myoglobin.
- Glycosylated hemoglobin (HbA1C) >10%.
    - Subjects with HbA_{1C} > ULN without a diagnosis of diabetes mellitus should be evaluated prior to randomization for evaluation.

Screening laboratory tests if considered by the investigator to be transient and inconsistent with the subject's clinical condition may be repeated once during the screening period for confirmation.

34. Donation of blood in excess of 500 mL within 8 weeks prior to baseline.
35. History of alcohol or drug abuse with less than 6 months of abstinence prior to baseline.
36. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.
37. History of thrombotic event(s), including deep venous thrombosis (DVT), and known inherited conditions that predispose to hypercoagulability.

4.3. Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject selection criteria. This study will enroll a total of approximately 230-250 subjects (expected to provide approximately 196-210 completers). Eligible subjects will be randomly assigned to a treatment group through the sponsor's interactive response technology (IRT) system in the allocation ratio stratified by:

1. Anti-TNF experience (yes or no).
2. Steroid use at baseline (yes or no).
3. Baseline disease activity/extent (no isolated ileal disease and baseline SES-CD >15, no isolated ileal disease and baseline SES-CD ≤15, or isolated ileal disease).

Upon implementation of PA5, eligible subjects will be randomized to PF-06651600 (ritlecitinib) or matching placebo in a 2:1 ratio. For analyses purposes, the two placebo arms from the induction period will be combined.

There will be no re-randomization at the beginning of the open label extension period.

4.4. Lifestyle Requirements

In order to participate in the study, subjects must be aware of the following lifestyle guideline:

- Agree to avoid strenuous exercise during the study, especially within one week prior to the scheduled study visits and maintain adequate hydration, if possible.

4.4.1. Contraception

In this study, fertile male subjects and female subjects who are of childbearing potential as applicable to the study may receive PF-06651600 (ritlecitinib) or PF-06700841 (brepocitinib), both of which have been associated with demonstrated teratogenicity/fetotoxicity in animals (more details in the IB).

Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of effective contraception (at least 1 highly effective method) throughout the study and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected 2 appropriate methods of contraception for the individual subject and his/her partner(s) from the list of permitted contraception methods (see below) and will confirm that the subject has been instructed in their consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use 2 methods of effective contraception (at least 1 highly effective method) consistently and correctly and document the conversation, and the subject's affirmation, in the subject's chart. In addition, the investigator or designee will instruct the subject to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the subject or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device (IUD).
3. Intrauterine hormone-releasing system (IUS).
4. Bilateral tubal occlusion or tubal ligation.
5. Vasectomized partner:

- Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

   - oral;
   - intravaginal;
   - transdermal.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - oral;
   - injectable.

8. Sexual abstinence:

   - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Effective method:

1. Male condom or female condom.

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose of investigational product. Male subjects must refrain from donating sperm during the study and for 90 days after the last dose of investigational product.

The required contraception methods listed above meet the recommendations of study B7981018.

4.4.2. Dietary Restriction

It is recommended that subjects avoid consumption of grapefruit juice exceeding 8 ounces (~240 ml) total in a day while in the study.

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study portal.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product(s) are PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) tablets.

5.1. Allocation to Treatment

Allocation of subjects to treatment groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the subject number. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

5.2. Breaking the Blind

The study will be sponsor, subject, and investigator blinded.

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. If an investigator believes that immediate unblinding is necessary and time and circumstances allows, he/she is encouraged to discuss unblinding with a member of the study team. However, discussion with a member of the study team in advance of unblinding is not required. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

5.3. Subject Compliance

IP accountability and compliance will be assessed by the site at each clinic visit starting at the visit after the baseline visit up through Week 64. Subject compliance will be verified by the accounting of investigational product at each visit. When investigational product is administered at the research facility, it will be administered under the supervision of study personnel.

Compliance of the IP will be monitored by delegated site personnel by the accounting of unused IP returned by the subject at study visits. Compliance will be documented on the CRF and source document. Non-compliance is defined as taking less than 80% or more than 120% of IP during the double-blind study treatment and/or chronic therapy period(s) and as directed by the dosing instructions, regardless of reason. Subjects are to bring the blister cards and/or bottles with any remaining study drug to each visit for review. The investigator has the discretion to withdraw any subject from the study for reasons of non-compliance with the dosing regimen. Investigators should indicate on appropriate CRF page non-compliance with study treatment and provide an explanation. Inventory control of all IP must be rigorously maintained throughout the duration of the study until all IP has been accounted for and/or returned to the sponsor. Any discrepancies noted between drug dispensing records and drug inventory must be reported to Pfizer.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

For the induction phase, blinded PF-06651600 (ritlecitinib) and matching placebos will be provided as tablets in blister cards for oral administration. For the induction phase of subjects enrolled prior to implementation of PA5, blinded PF-06700841(brepocitinib) and matching placebos will be supplied as tablets in bottles for oral administration. The designation “PF-06651600-15” and “PF-06700841-15” may appear on labeling and indicates a salt. They are equivalent to “PF-06651600” (ritlecitinib) and “PF-06700841” (brepocitinib) with regard to this protocol. The PF-06651600 (ritlecitinib) 50 mg tablets and their matching placebos will be supplied in separate blister cards and labeled according to local regulatory requirements. The PF-06700841 (brepocitinib) 5 mg and 25 mg tablets and their matching

placebos will be supplied in separate bottles and labeled according to local regulatory requirements.

For the open label extension period, PF-06651600 (ritlecitinib) tablets will be supplied in blisters. For the open label extension period, PF-06700841 (brepocitinib) tablets will be supplied in bottles.

5.5. Preparation and Dispensing

The investigational product will be dispensed using an IRT drug management system at each visit from baseline visit through Week 56. A qualified staff member will dispense the investigational product via unique container numbers in the blister cards or bottles provided, in quantities appropriate for the study visit schedule. The subject should be instructed to maintain the product in the blister cards or bottles provided throughout the course of dosing and return the blister cards or bottles to the site at the next study visit. Refer to Appendix 12 for investigational product dispensing during public emergencies if applicable.

5.6. Administration

Subjects will receive IP as outpatients. PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib) tablets and matching placebo for oral administration will be dispensed in blister cards or bottles as described above in Section 5.4.1. Subjects will be dispensed an appropriate number of blister cards or bottles sufficient for administration until the next dispensing visit and given clear dosing instructions.

Sites will be trained on how subjects should take tablets at home through an IP manual and/or other vehicle(s). Sites are responsible for communicating this information.

Subjects should take the IP orally for 12 weeks during the induction period and an additional 52 weeks during the OLE period for a total of 64 weeks. Subjects should swallow the tablets with ambient temperature water to a total volume of approximately 240 mL. Subjects should swallow the IP whole, and will not manipulate or chew the IP prior to swallowing. Subjects will be instructed to take the IP in the morning after breakfast whenever possible even though IP may be taken with or without food; however, for study visit days, subjects are to be instructed to refrain from dosing at home, bring their blister cards or bottles to the site, and are to take the dose in the clinic from their current blister card or bottle.

If a dose is missed and the interval to the next dose is less than 8 hours, the missed dose should not be administered.

During the induction phase, if subjects require discontinuation of investigational product for medically mandated reasons (eg, following instructions from investigator) for more than 7 consecutive days at any time during the study, they will be discontinued from treatment and should undergo the procedures for an Early Term (Induction) visit. During the OLE period, if dosing is missed for more than 7 consecutive days, the subject should be considered for discontinuation following consultation with the sponsor and should undergo the procedures for an Early Term (OLE) visit. Also, the subject will be asked to complete the Follow-up visit approximately 4 weeks after the last dose of study drug.

5.7. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct subjects on the proper storage requirements for take home investigational products.

5.8. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

All blister cards and/or bottles of study drug must be returned to the investigator by the subject at every visit and at the end of the trial.

5.8.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

Returned test article can be destroyed only after the sponsor monitor has verified the accuracy of the dispensing and inventory record. The monitor must verify that site staff follows instructions regarding the return of investigational product to the Supply Chain Organization or vendor for destruction.

5.9. Concomitant Treatment(s)

All concomitant medication(s) and treatment(s) administered/taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant medication at each site visit.

A subject who is receiving metformin as concomitant medication must allow at least two hours after taking either medication and before taking investigational product.

Medication(s) administered/taken following the first dose of IP will be documented as concomitant medication(s).

5.9.1. Oral Corticosteroids

Any oral corticosteroids taken during the screening and treatment periods of the study will be captured on the appropriate CRF.

5.9.2. Permitted Medications

Subjects will be allowed to use the following medications as detailed below:

- Concomitant use of oral 5-ASA or sulfasalazine. Dose must be stable for at least 4 weeks prior to baseline and through end of study (Week 68). If oral 5-ASA treatment has been recently discontinued, it must have been stopped for at least 2 weeks prior to baseline.

- A stable dose of oral corticosteroids (prednisone equivalent up to 25 mg/day; budesonide up to 9 mg/day See Appendix 11) for at least 2 weeks prior to baseline and through end of induction period (Week 12, except for the case of subjects undergoing optional steroid tapering in the OLE period).

- If oral corticosteroids have been recently discontinued, they must have been stopped at least 2 weeks prior to baseline. Rectal steroids are prohibited. Decreases in steroid use due to AEs are allowed.

- Upon a subject achieving remission during the OLE period, steroids may be slowly tapered per local guidelines. Steroid tapering is allowed only in the OLE period. Subject may reduce the daily dose of prednisone or equivalent by 2.5 to 5 mg weekly (based on their symptom's) until the dose of prednisone or equivalent is 10 mg/day, then reduce the daily dose of prednisone or equivalent by 2.5 mg weekly until the dose is 0 mg. If a subject experiences worsening of CD symptoms during the corticosteroid taper that in the opinion of the investigator are attributable to the corticosteroid taper, then the investigator may instruct the subject to revert back to the preceding dose in the taper schedule (ie, "step up"). The signs or symptoms leading to this change (eg, increased stool frequency, increased rectal bleeding) must be recorded on the CRF. Study subjects with signs or symptoms attributed to corticosteroid taper are permitted to step up their corticosteroid dosage one time during study participation and then resume corticosteroid taper to achieve steroid-free status. Subjects requiring a second step up in corticosteroid usage will be required to discontinue the study. See Appendix 11 for guidance on steroid equivalency.

5.9.3. Prohibited Medications

The following medications are prohibited for the specified time periods as described below:

- Oral budesonide (>9 mg/day) or prednisone (>25 mg/day) or equivalent oral systemic corticosteroid within 2 weeks prior to baseline and through end of study (Week 68).

- IV, IM (parenteral), or topical (rectal) treatment of 5-ASA or corticosteroid enemas/suppositories within 2 weeks prior to baseline and through end of study (Week 68).

- Azathioprine, 6-mercaptopurine, or methotrexate within 2 weeks prior to baseline and through Week 68.

- Biologics including anti-TNF inhibitors (eg, infliximab, adalimumab, certolizumab), or biosimilars thereof, within 8 weeks prior to baseline and through end of study (Week 68).

- Anti-integrin inhibitors (eg, vedolizumab) within 8 weeks prior to baseline and through end of study (Week 68).

- Ustekinumab within 8 weeks prior to baseline and through end of study (Week 68).

- Interferon therapy within 8 weeks prior to baseline and through end of study (Week 68).

- Lymphocyte-depleting agents/therapies within 1 year prior to baseline and through end of study (Week 68).
- Leukocyte apheresis including selective lymphocyte, monocyte, or granulocyte apheresis, or plasma exchange within 6 months prior to baseline and through end of study (Week 68).
- Rituximab or other selective B lymphocyte-depleting agents within 1 year prior to baseline and through end of study (Week 68).
- Other marketed immunosuppressants or biologics with immunomodulatory properties within 3 months prior to baseline and through end of study (Week 68).
- Use of immunosupressants used in transplantation (eg, mycophenolate mofetil, cyclosporine, rapamycin, or tacrolimus) within 30 days prior to baseline and through end of study (Week 68).
- Any live (attenuated) vaccines from 30 days prior to baseline and through the end of study (Week 68).
- Anti-motility agents for control of diarrhea (eg, diphenoxylate hydrochloride with atropine sulfate or loperamide) from 5 days prior to baseline through end of study (Week 68).
- Moderate to potent CYP3A inducers or inhibitors as listed in Appendix 10 through end of the study (Week 68).
- Simvastatin or simvastatin-containing products from 5 days prior to baseline and through end of study (Week 68).
- Strong P-gp inhibitors (eg, quinidine) within 5 half-lives prior to baseline and through end of study (Week 68).
- Narrow therapeutic index substrates of MDR1 (eg, digoxin), OCT2 or MATE (eg, dofetilide).

5.9.4. Vaccinations

Vaccination with live virus, attenuated live virus, or any live viral components is prohibited within the 30 days prior to the first dose of study drug and through the end of the study (Week 68). Similarly, current routine household contact with individuals who have been vaccinated with live vaccine components should be avoided during treatment and through the end of the study.

Such vaccines include but are not limited to FluMist® (intranasal influenza vaccine), attenuated rotavirus vaccine, varicella (chickenpox) vaccine, attenuated typhoid fever vaccine, oral polio vaccine, MMR (measles, mumps, rubella) vaccine and vaccinia (smallpox) 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.

5.10. Rescue Medication

During the induction phase, if subjects require rescue medication, they will be discontinued from treatment and should undergo the procedures for an Early Term (Induction) visit.

During the OLE period, if subjects require rescue medication, they will be discontinued from treatment and should undergo the procedures for an Early Term (OLE) visit.

After any discontinuation, subjects will be asked to complete the Follow-up visit approximately 4 weeks after the last dose of study drug.

6. STUDY PROCEDURES

Refer to Appendix 12 for Alternative Measures During Public Emergencies if applicable.

Visits should occur when scheduled, within the time window indicated in the Schedule of Activities. Written informed consent must be obtained prior to performing any protocol-specific procedures, including washout of prohibited medications. To prepare for study participation, subjects will be instructed on the use of Lifestyle Requirements (see 4.4) and Concomitant Treatments (see Section 5.9).

Screening laboratory tests with abnormal results may be repeated **once** to confirm abnormal results; the last value will be used to determine eligibility. If results return to normal within the 6-week screening period, the subject may enter the study. Subjects who do not meet eligibility criteria (ie, screen fail) may be re-screened **once** (with a new screening number).

Where possible the following order of activities should be followed during the clinic visits.

1. Assessments: IBDQ, SF-36, EQ-5D-3L+ VAS, eDiary data collection (stool frequency, abdominal pain, general wellbeing and PGIS).
2. ECGs.
3. Vital signs.
4. Blood and Urine Sample Collection.
5. Investigational Product Dosing.

6.1. Screening

For screening procedures, see Schedule of Activities and ASSESSMENTS section.

Complete medical history should include:

- History of CD, including duration of disease, extent of disease, extra-intestinal manifestations, duration of current flares, number of flares in the preceding year, and CD related hospitalizations;
- History of chicken pox and shingles;
- History if skin rash, skin infection and any abnormalities that may predispose the subject to infection;
- Reasons for previous CD medication intolerance (ie, discontinuation of medication due to an AE as determined by the investigator);
- History of previous vaccinations, specifically influenza, pneumococcal, varicella, and zoster.

Subjects will be instructed on the collection of eDiary data. The number of liquid stools or very soft stools, the intensity of abdominal pain, general well-being and PGIS questionnaire will be collected continuously for 12 weeks throughout the induction phase in the eDiary. During the OLE phase subjects will be requested to complete their eDiary until Visit 16, from Visit 24 to 32, and from Visit 56 to 64.

Colonoscopy should be performed within 10 days of baseline, preferably 5 to 7 days prior to the baseline to allow stool diary data collection.

6.2. Induction Period

For treatment period procedures, see Schedule of Activities and ASSESSMENTS section.

Collect a genomic banked biospecimen (Prep D1) at baseline (Week 0/Day 1). If missed, collect at the next available time point when biospecimens are being collected in conjunction with a subject visit (only for randomized subjects).

6.3. Open Label Extension Period

For open label extension period procedures, see Schedule of Activities and ASSESSMENTS section.

6.3.1. Follow-up Contact

Follow-up contact will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (see the Time Period for Collecting AE/SAE Information section) and to confirm appropriate contraception usage (see the Contraception section). Contact with the subject may be done via a phone call.

For follow-up and end of study procedures, see Schedule of Activities and ASSESSMENTS section.

6.4. Subject Withdrawal

Withdrawal of consent:

Subjects who request to discontinue receipt of study treatment will remain in the study and continue to be followed for protocol specified early term procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Any subjects, who discontinues early from the double-blind induction period prior to the Week 12 visit, should undergo the procedures for an Early Term (Induction) visit on the last day the subject takes the investigational product or as soon as possible thereafter. For subjects who discontinue early from the OLE period (after the Week 12 visit, but prior to the Week 68 visit), the procedures scheduled for an Early Term (OLE) visit will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. After any discontinuation, subjects will be asked to complete the Follow-up visit approximately 4 weeks after the last dose of study drug.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to

complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.5. Guidelines for Monitoring and Discontinuations

The following laboratory abnormalities require monitoring and re-testing ideally within 3-5 days, except as noted below when a shorter re-testing period is required:

- Absolute neutrophil counts <1.2 x 10^9/L (<1200/mm^3).
- Hemoglobin <9.0 g/dL.
- Platelet counts <100 x 10^9/L (<100,000/mm^3).
- Lymphocytes <800/mm^3; <0.8 x 10^9/L.
- CK > 3x ULN (this also triggers urine myoglobin).
- Any single AST and/or ALT elevation ≥3 times the upper limit of normal (repeat laboratory testing should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, PT [prothrombin time] with INR [international normalized ratio], and alkaline phosphatase), regardless of the total bilirubin. (Please note that 3 times the upper limit of normal increases in ALT, AST need confirmation on separate blood draw before undertaking thorough evaluation for liver injury).

- For women of child-bearing potential with any positive urine β-hCG test, the subject will have study drug interrupted and a serum sample submitted to the central laboratory for β-hCG testing.

Additional individual subject safety monitoring in addition to these guidelines is at the discretion of the investigator and dependent on any perceived safety concerns. Unscheduled laboratory testing through the central laboratory may be obtained at any time during the study to assess such concerns, and a subject may be withdrawn at any time at the discretion of the investigator.

Treatment with investigational product will be discontinued and the subject withdrawn from this study for:

- Serious infections meeting criteria that require the infection to be classified as serious adverse event (See Section 7.1.7).

- Two sequential absolute neutrophil counts <1.0 x 10^9/L (<1000/mm^3); repeat testing must be performed as soon as feasible and within 3 days of the initial absolute neutrophil count <1.0 x 10^9/L (<1000/mm^3).

- Two sequential platelet counts <75 x 10^9/L (<75,000/mm^3); repeat testing must be performed as soon as feasible and within 3 days of the initial platelet count <75 x 10^9/L (<75,000/mm^3).

- Two sequential lymphocyte counts <500/mm^3; <0.5x10^9/L; repeat testing must be performed as soon as feasible and within 3 days of the initial lymphocyte count <500/mm^3; <0.5x10^9/L.

- Two sequential hemoglobin values of <8.0 g/dL; <4.96 mmol/L; <80 g/L.

- Symptomatic anemia with hemoglobin <7.0 g/dL; <70 g/L or any anemia requiring a blood transfusion.

- If an individual subject demonstrates **CONCOMITANT serum creatinine-based AND serum cystatin C-based eGFR decline of ≥30% compared to the subject's baseline eGFR**, then the subject should not be dosed further and adequate, immediate supportive measures including evaluation by a nephrologist (preferably within 24 hours) for appropriate management. If the subject cannot be seen by a nephrologist within 24 hours, then the subject should be sent to a local emergency room for assessment of renal function. Results should be repeated as indicated by the nephrologist or weekly at a minimum until the eGFR returns to baseline ±15% or the renal parameters are deemed to be stable by the nephrologist and/or principal investigator (PI).

- AST or ALT elevation >8 times the upper limit of normal.

- Two sequential AST or ALT elevation ≥3 times the upper limit of normal with at least one total bilirubin value ≥2 times the upper limit of normal.

- Two sequential AST or ALT elevation ≥3 times the upper limit of normal accompanied by signs or symptoms consistent with hepatic injury.

- Two sequential AST or ALT elevation ≥5 times the upper limit of normal, regardless of total bilirubin or accompanying signs or symptoms.

- AST or ALT elevation ≥3 times the upper limit of normal with an INR >1.5.

In each of the 5 cases above, there is a need for additional investigations, such as review of ethanol, recreational drug and dietary supplement consumption; testing for acute hepatitis A, B or C infection and biliary tract imaging should be promptly discussed with the Pfizer medical monitor or designee.

- Female subjects found to be pregnant during the study.

- At the discretion of the PI, initiation of any new treatment for CD for disease progression.

- Subjects who are inadequately responding to investigational product in the opinion of the investigator.

- Surgery for CD.

- Clinically meaningful, treatment related decline in hearing from baseline.

- Thrombotic or thromboembolic event occurs (even if not categorized as serious or severe in intensity), unless clearly unrelated to study drug.

- Other treatment related serious or severe AEs, after consultation with the Pfizer medical monitor or designee.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

Refer to Appendix 12 for Alternative Measures During Public Emergencies if applicable.

7.1. Safety

7.1.1. Clinical Laboratory Tests

Safety will be assessed by the spontaneous reporting of AEs, physical examinations, ECGs, and clinical laboratory results in all subjects who received at least 1 dose of study medication. Investigators and Pfizer Clinicians will review individual subject data throughout the conduct of the trial to ensure subjects' well-being.

The following safety laboratory tests will be performed at times defined in the Schedule of Activities.

Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Basophils (Abs) Lymphocytes (Abs) Monocytes (Abs) Reticulocyte count WBEDT Reticulocyte count % PT/INR/PTT	BUN/Urea & Creatinine Cystatin C Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (Bicarbonate) AST, ALT Total Bilirubin Direct bilirubin[a] Alkaline phosphatase Uric acid Albumin Total protein Creatine kinase (CK) CK fractionation[b] Total Cholesterol[c] Triglycerides[c] HDL[c] LDL[c]	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Microscopy[d] Spot urine albumin/creatinine ratio[c]	FSH[f,g] β-hCG[h] HbA_{1C} Hepatitis B, C and HIV[g] QFT-G or other IGRA[g] hsCRP IP-10 TBNK cells Viral Surveillance Stool sample[g] to detect enteric infections and C. difficile toxins A and B Stool sample for microbiome Stool sample for fecal calprotectin Exploratory samples (serum, plasma, blood RNA, DNA) Colonic tissue biopsies Skin biopsies/swabs[i] Urine Myoglobin[j]

a. Only if total bilirubin is elevated.

b. Only if CK is elevated.

c. Fasting.

d. Microscopy analysis is indicated if urinalysis is positive for blood, nitrite, leukocyte esterase and/or protein. Urine culture is performed if urinalysis is positive for nitrite and/or leukocyte esterase or if clinically indicated.

e. At screening only.
f. In females who are amenorrheic for at least 12 consecutive months.
g. Complete at screening.
h. Serum/Urine for women of childbearing potential. Serum pregnancy test must be performed at screening. If serum pregnancy test is borderline positive, the central lab will run a FSH test to confirm menopause.
i. When required in cases of skin rash adverse events.
j. At screening and in case of CK >3x ULN during the study. Additional tests may be performed during the study at the investigator's discretion, as indicated by signs and symptoms of ongoing AEs.

7.1.2. Creatinine and Cystatin C

Serum creatinine is the best known standard test for monitoring renal function. However, serum creatinine based estimates of glomerular filtration rate (eGFR) may be affected by factors other than renal function, including chronic and acute illness. Cystatin C is a test that can be used either as an adjunct to or as a replacement for serum creatinine. The most reliable estimates of GFR use both test results.[2]

Cystatin C is a low molecular weight protein that is used as an alternative to serum creatinine for monitoring of renal function. It seems to correlate more closely with GFR than does serum creatinine concentration and may be a more sensitive detector of early renal dysfunction.[3,4] While use of cystatin C has been limited, its independence of demographic factors (eg, race) has made it an interesting means of determining changes in renal function in clinical settings and it is included in the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Estimated GFR may be calculated via the 2012 CKD-EPI creatinine, cystatin C, or creatinine-cystatin C equations.[5]

Serum creatinine will be measured and creatinine based eGFR will be calculated at times specified in the Schedule of Activities. Serum cystatin C will be measured and cystatin C based eGFR will be calculated at times specified in the Schedule of Activities.

7.1.3. Estimated Glomerular Filtration Rate

Serum creatinine and serum cystatin-C based estimated GFR (eGFR) will be calculated at times specified in the Schedule of activities, in order to facilitate calculation of eGFR at these time points. Corresponding serum creatinine and cystatin-C based eGFR will be determined to assess renal function.

The estimated GFR (eGFR) will be calculated using the 2 sets of equations developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), which utilize serum creatinine (SCr) and serum Cystatin C (S Cystatin C) respectively.[6]

7.1.4. Pregnancy Testing

All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. For female subjects of childbearing potential, 2 negative pregnancy tests are required before receiving investigational product (1 negative pregnancy test at screening and 1 at the baseline visit

immediately before investigational product administration). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and the second negative pregnancy test result will then be required at the baseline visit before the subject may receive the investigational product. In the absence of regular menstrual bleeding, the study candidate should have used 2 forms of contraception for at least 1 month before the second pregnancy test. Pregnancy tests will also be repeated at all visits and at the end of the study to confirm that the subject has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed and when potential pregnancy is otherwise suspected, and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product but will remain in the study in follow-up.

7.1.5. Interferon Gamma Release Assay Tuberculin Test

Subjects may be screened for TB using an IGRA per local guidelines. IGRA will be used locally (where feasible) during screening or within 12 weeks prior to screening to test for active/latent tuberculosis (TB). The following are acceptable assays: QuantiFERON®-TB Gold test (QFT-G), QuantiFERON®-TB Gold In-Tube test (QFT-GIT) and T-SPOT® TB test. Covance tests that replace the above specified tests are permitted. Blood sampling may include 3 mL up to 10 mL of blood. Site personnel should follow the processing and analyses steps based on the assay chosen. The specific IGRA method, or test, used should comply with local country-specific guidelines. The type (name) and results of the IGRA TB test must be known and located in source documentation.

Subjects with a documented positive IGRA TB test performed within 12 weeks prior to Screening are excluded. If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. A positive test on repeat is exclusionary. Subjects with repeat indeterminate IGRA results may be enrolled after consultation with pulmonary or infectious disease specialist that determines low risk of infection (ie, subject would be acceptable for immunosuppressant (eg, anti-TNF) treatment without additional action).

The sample(s) will be analyzed by the site's local laboratory. Refer to local lab for any additional processing information and shipping instructions.

7.1.6. Screening for *Clostridium Difficile*

C. difficile testing is performed at screening and during the study when there is a suspected disease flare or gastroenteritis. *C. difficile* infection in these settings requires treatment as determined by the PI. Subjects with *Clostridium difficile* infection may be treated and re-tested or re-screened at the discretion of the Investigator.

Highly sensitive screening tests, with high negative predictive value, should be employed in evaluating subjects for eligibility for the study. The detection of *C. difficile* by toxigenic stool culture (stool culture followed by detection of toxin) is considered the gold standard for the diagnosis of the colonization or infection with pathogenic *C. difficile*. Comparable

sensitivity may be achieved by direct testing of stool via point of use rapid membrane enzyme immunoassay card for both *C. difficile* toxin A and B and glutamate dehydrogenase (GDH) antigen on a card. Use of the card for point of care screening is encouraged where permitted by local regulation. Molecular techniques such as polymerase chain reaction (PCR) for detection of toxin RNA are also acceptable alternatives.

Refer to the lab manual for further guidance and instruction for *C. difficile* screening.

7.1.7. Infections

Subjects will be monitored for development of any infection (viral, bacterial, and fungal). Infections will be classified as either treated or non-treated infections. All treated infections occurring during the study should be cultured if feasible and the results (eg, any identified organisms or absence of growth) recorded in the CRF.

Treated infections are infections that:

- Require antimicrobial therapy by any route of administration or;
- Require any surgical intervention (eg, incision and drainage).

Treated infections will be further classified as serious or non-serious. Serious infections are treated infections that:

- Require parenteral antimicrobial therapy and present with positive pre-treatment culture;

AND EITHER

- Require hospitalization for treatment;

OR

- Meet other criteria that require the infection to be classified as a SAE.

A subject who experiences a serious infection should be discontinued from the study. A serious infection should be reported as a SAE and should be listed as the reason for discontinuation in the CRF. All serious infections occurring during the study should undergo appropriate laboratory investigations, including culture, and the results (eg, any identified organisms or absence of growth) be recorded in the CRF.

Subjects who experience non-serious infections that require treatment may have their study drug temporarily discontinued during treatment at the investigator's discretion. Consultation with the Pfizer medical monitor is available. Temporary discontinuation of study drug should be recorded in the CRF.

7.1.8. Viral Surveillance

Blood samples for the analysis of viral load for Cytomegalovirus (CMV), Epstein–Barr virus (EBV), Herpes Simplex Virus (HSV1), HSV2 and Varicella Zoster Virus (VZV) will be collected according to the times outlined in the Schedule of Activities. Additional sample collection instructions will be provided in the lab manual.

Note: Due to long turnaround time, the reporting time of these labs could be quite delayed.

In addition to time points specified, a plasma sample for viral surveillance sample may also be taken at the time of an adverse event, as clinically appropriate.

7.1.9. Vital Signs (Blood Pressure, Pulse Rate, and Temperature)

Blood pressure will be measured in the subject's dominant arm and recorded to the nearest mmHg. It is preferred that the same arm be used throughout the study. The same blood pressure cuff, which has been properly calibrated, should be used to measure blood pressure each time. When the timing of these measurements coincides with a blood collection, blood pressure, temperature and pulse rate should be obtained first.

Single sitting blood pressure (BP), pulse rate, and temperature will be measured at times specified in the Schedule of Activities. Additional collection times or changes to collection times will be permitted, as necessary to ensure appropriate collection of safety data.

The use of automated devices for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

It is preferred that body temperature be collected using tympanic, oral, or axillary methods and that the same method be used consistently throughout the study.

Vital signs (including blood pressure, pulse rate and temperature) and ECG should be performed before laboratory blood collection and endoscopic procedure.

7.1.10. Medical History, Physical Examination, Height and Weight

Medical history, including CD history, history of illegal drug, alcohol, tobacco use, skin rash, skin infection, and any abnormalities that may predispose the subject to infection will be collected at the Screening visit. Smoking status and average weekly alcohol consumption (units/week) will also be collected.

Complete Physical Examination:

A standard physical examination will be performed at the visits identified in Schedule of Activities. The following parameters and body systems will minimally be examined and any abnormalities described: General appearance, skin (presence of rash), head, eyes, ears, nose and throat (HEENT), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs, peripheral edema), abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and, lymph nodes.

Targeted Physical Examination:

An abbreviated physical examination will be performed at the visits identified in Schedule of Activities. The following parameters and body systems will minimally be examined and any abnormalities described: Skin, lungs, heart, abdomen and lymph nodes. Additional organ systems may be examined at the investigator decision. Any clinically significant changes from the baseline examination should be recorded as AEs. Body temperature also will be collected at these visits.

Both full and targeted physical examinations must include a full body skin examination. Skin examinations should include a visual inspection of the breasts and external genitalia to assess for rashes, even if a subject does not want to have an examination of the breast and/or external genitalia (these are optional) done as a part of the physical examination.

Complete and Targeted physical examinations are performed at specified timepoints (See Schedule of Activities).

Additional targeted PE may be performed during the study at the investigator's discretion.

Height and weight will be measured without the subject wearing shoes. Height (inches or centimeters) will be measured and recorded at the Screening visit only and weight (lbs or kg) will be measured and recorded at various timepoints (See Schedule of Activities).

Note: Elbow circumference will only be measured for male subjects with height ≤163 cm. This is to allow frame determination (for the weight item in Crohn's Disease Activity Index [CDAI] for only randomized male subjects with height ≤163 cm (only 1 subject at the time of this amendment with a height less than 163). This does not impact the CDAI calculation for subjects with height greater than 163 cm.

7.1.10.1. Dermatology/Skin

As part of the physical examination, all subjects will have a dermatological full body exam at times specified in the Schedule of Activities. Skin lesions will be evaluated as defined in the National Cancer Institute Common Toxicity Criteria for Adverse Events v4.0 (See Appendix 9, for Dermatology/Skin Category) and managed as shown below.

Table 8. Management of Dermatological Events

Dermatologic Event (CTCAE v 4.0)*	Course of Management
Acne/Acneiform Rash/Maculopapular Rash	
Grade 1/2	1. Investigator's discretion for withdrawing IP. 2. Execute reasonable monitoring. 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Grade 3	1. Discontinue IP. 2. Monitor to resolution (defined as a Return to Baseline status). 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Pruritus	
Grade 1 Mild or localized	1. Investigator's discretion for withdrawing IP. 2. Execute reasonable monitoring. 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Grade 2 Intense or widespread	1. Discontinuation of the IP may not be required unless condition is sustained >4 days or at the investigator's discretion. 2. Execute reasonable monitoring. 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Grade 3 Intense or widespread and interfering with activities of daily living	1. Permanently discontinue IP. 2. Monitor to resolution (Return to Baseline). 3. Consider treatment with topical agents such as clindamycin or corticosteroids.

* Refer to Appendix 9 for clarification.

In any event of an unexplained rash, a blood sample for viral surveillance will be collected for the analysis of viral load including but not limited to CMV, EBV, HSV1, HSV2, and VZV. For a suspected infectious rash, a swab (for microbiological assessment) of the affected area will also be taken for culture and sensitivity to assess for any bacterial or fungal pathogens. For any occurrence of a suspected herpetiform rash (eg, herpes zoster and herpes simplex) an additional swab of the affected area will be collected for confirmation. Details for these collections will be provided in the laboratory manual.

Investigators will complete a questionnaire and take appropriate photographs of the rash in order to provide information necessary for a dermatologist's assessment of the event.

All subjects reporting an unexplained skin rash should be referred to a local dermatologist according to local guidelines for formal comprehensive dermatologic evaluation. A 4 mm punch biopsy should be taken and sent to the local laboratory for histological investigation of the rash in order to gain insight into potential etiology of the rash. If the rash is present on the face or other cosmetically exposed area, biopsy can be at the discretion of the dermatologist.

All events of rash should be treated according to international and local guidelines for the treatment of rash, eg, where appropriate, topical corticosteroids and/or agents such as antibiotics or antivirals could be prescribed.

All treatment-related reports of rash will be followed up until resolution or clinically stable or agreement with Pfizer. Upon resolution of a Grade 1 or 2 rash/pruritus, including confirmed herpes zoster, subjects **may** be re-challenged with IP at the discretion of the investigator. Re-challenge is not permitted with Grade 3 rash/pruritus.

All de-identified dermatologic consultation reports, biopsy results, culture results, photographs, and any additional relevant test results will be forwarded to Pfizer/designee for review within 30 days of receipt by the PI.

An independent dermatologist contracted by Pfizer will review all relevant data and summarize the data at the end of the study.

7.1.11. Audiogram

All subjects will have an audiogram at times specified in the Schedule of Activities. Audiograms may be performed within a ±2 week window relative to the study visit. When possible, the subject should have the audiogram performed at the same evaluation center during the study.

If there is a clinically meaningful, treatment related decline in hearing from baseline, the subject will be followed off treatment with appropriate testing at regular intervals, until hearing returns to baseline or is determined to be clinically stable.

The information from the audiogram will be entered into the data collection tool.

Any de-identified audiogram results/reports and any additional relevant test results (if applicable) may be requested to be forwarded to Pfizer (and/or designee) at any time during the study.

Audiogram results may be reviewed by an external audiologist.

7.1.12. Electrocardiogram

Single twelve (12) lead ECGs will be obtained on all subjects. All scheduled ECGs should be performed before laboratory blood collection, endoscopic procedure and after subject has rested quietly for at least 10 minutes in a supine position. When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, BP, and pulse rate.

To ensure safety of the subjects, a qualified individual (eg, sub-investigator) at the investigator site will make comparisons to baseline studies taken at screening. A copy of the ECG should be available as source documents for review. ECGs will be read locally during the dosing period.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range.

QTc prolongations are defined as a QTc ≥480 msec or an absolute change in QTc >60 msec.

7.1.13. Chest Radiograph

Chest x-ray (posterior-anterior and lateral views are recommended however local guidelines should be followed) with no current evidence of untreated latent or active TB infection or evidence of currently active TB, general infections, heart failure or malignancy and read by a qualified radiologist is required at screening or within the 12 weeks prior to screening. A chest X-ray or other appropriate diagnostic chest imaging modality [ie, Computerised Tomography (CT with or without IV contrast) or Magnetic Resonance Imaging (MRI)] performed within 12 weeks prior to screening, may substitute for the Chest X-ray taken at Screening. Documentation of the official reading must be located and available in the source documentation.

7.2. Diagnostic and Efficacy Assessments

7.2.1. Endoscopy

Screening colonoscopy should be performed within 10 days of baseline, preferably 5 to 7 days prior to the baseline. The endoscopic subscore by the Central Reader must be available at the baseline visit. The SES-CD score (see Appendix 2) by the central reader will be used to determine eligibility for entry criteria. The endoscopic and pathology reports and any photographs and /or video recordings taken during the screening colonoscopy must be available in the source documents prior to Baseline (Day 1) randomization. Colonoscopy and SES-CD scoring are also performed during the week prior to the Week 12 and Week 64 visits (or early withdrawal visit where applicable). Bowel prep should be conducted as per local routine. The position of the endoscope will be based on the length of the instrument at various levels of insertion as well as the morphological features of the intestine as seen during screening endoscopy. Colonoscopy should be performed at the Early Termination (ET) visit unless the previous colonoscopy was less than 8 weeks prior to this.

7.2.2. Biopsy Collection from Ileocolonic Mucosa for Histology, RNA, Epigenetic, Tissue microbiome and Tissue Protein

Ileocolonic tissue biopsies will be collected at screening, Week 12, 64, and early withdrawal visits during the endoscopy. Jumbo forceps should be used to obtain biopsies during each colonoscopy procedure. Biopsies should be taken one at a time, and each should be immediately placed into a separate sample collection tube, as specified in the central vendor procedure manual. During each endoscopy procedure, a total of 19 biopsies should be obtained from each subject, if possible, in the following manner:

1. A total of 12 biopsies spanning six segments (rectum, sigmoid, left colon, transverse colon, right colon, and ileum) will be obtained for histology. Two biopsies should be obtained from the most affected areas in each segment. In the case of an unaffected segment, two biopsies should be obtained from a location based on the investigator's discretion.

2. A total of 7 additional biopsies will be obtained for translational medicine assessments. Six biopsies should be taken from inflamed ileocolonic mucosa in the most affected segment (1 biopsy for RNA analysis, 2 biopsies for protein analysis, and 3 biopsies for epigenetic and/or cytometry/microbiome analyses). An additional biopsy should be taken from adjacent uninflamed ileocolonic mucosa for RNA analysis. All inflamed pre-treatment biopsies should be obtained in a targeted manner from the most affected area. During post-treatment endoscopies, samples should be obtained from inflamed mucosa at approximately the same anatomic location as the baseline assessment. If no inflammation is observed, post-treatment biopsies should be obtained at approximately the same anatomic location as the baseline assessment based on the investigator's discretion.

Frankly ulcerated areas should be avoided. For all biopsies collected, record the colonic segment and approximate distance from the anal verge for each sample in the source documents. If 19 biopsies cannot be collected during the endoscopy, then samples from inflamed tissues should be prioritized in the order of histology, RNA analysis, protein analysis, and epigenetic and/or cytometry/microbiome analysis.

Due to the rejection of the Import License for the Fetal Bovine Serum required for the processing of 1 tissue sample for cytometry, this sample will not be collected for subjects in South Africa. Therefore in South Africa, 18 tissue samples will be collected instead of the protocol defined 19 samples.

Histological, gene expression (RNA), protein analysis and epigenetic and/or cytometry/microbiome analysis may be conducted on the biopsy samples that are obtained. Pfizer and the central laboratory vendor will provide sites with instructions for collection, processing, and shipment of biopsy samples. These samples may be used for the evaluation of exploratory biomarkers that may include markers related to CD, UC and/or other inflammatory conditions and/or the mechanism of action of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib). Detailed processing, storage and shipment instructions will be provided in the Lab Manual.

7.2.3. Subject eDiary

An eDiary will be provided to subjects at the screening visit (Visit 1) in order to record the following:

- The number of liquid stools or very soft stools.

- The intensity of abdominal pain.

- General well-being.
- PGIS questionnaire.

Subjects should enter eDiary data continuously for 12 weeks throughout the induction phase. During the OLE phase subjects will be requested to complete their eDiary until Visit 16, from Visit 24 to 32, and from Visit 56 to 64.

Subject Diary data will be assessed by the investigator or designate throughout the study. The information extracted will be used for calculation of stool frequency (SF), abdominal pain (AP) and CDAI score taking into account the continuous 7 days data recorded prior to each study clinic visit. The Subject Diary is a source document for SF, AP and CDAI data collection and is to be collected at the last subject visit and retained in the Site Master File.

7.2.4. Stool Frequency (SF) and Abdominal Pain (AP)

SF and AP calculation will be dependent on the parameters recorded in the subjects' diary (stool frequency and abdominal pain). For any visit that has an endoscopy (screening, Week 12 and Week 64 and Early Term (if required), SF and AP scores should be calculated based on diary data obtained on 7 consecutive days prior to two (2) days of bowel preparation (if applicable), including any dietary modification as part of the bowel preparation. For example, subjects should have their SF and AP scores calculated based on 7-consecutive diary data prior to two (2) days of bowel preparation for colonoscopy. For all remaining visits that do not require an endoscopy, the CDAI calculations including SF/AP scores will need to be calculated based on the 7 days prior to the study visit. For more details please refer to Appendix 3.

7.2.5. Crohn's Disease Activity Index (CDAI)

The Crohn's Disease Activity Index (CDAI) is a validated instrument to measure the response to treatment in Crohn's Disease studies (see Appendix 3). Scores range from 0 to approximately 600. The algorithm for calculating the CDAI score was first published by William Best and colleagues in a 1976 article in the journal Gastroenterology.

CDAI calculation will be dependent on the parameters recorded in the subjects' diary (number of liquid stools, the intensity of abdominal pain, general well-being and the need for antidiarrheal drugs) AND the parameters assessed at clinic visit by investigator (the occurrence of extraintestinal symptoms or signs, the presence of abdominal mass, hematocrit and body weight). Investigators should complete CDAI parameters (need for antidiarrheal drug, abdominal mass and number of complications) at the clinic after the PRO assessments and prior to any clinical assessments at the study visit.

For any visit that has an endoscopy (screening, Week 12 and Week 64 and Early Term (if required)), CDAI scores should be calculated based on diary data obtained on 7 consecutive days without bowel preparation, including any dietary modification as part of the bowel preparation. For example, subjects who have the colonoscopy performed prior to study drug should have their CDAI scores calculated based on 7-consecutive diary data prior to 2 days of bowel preparation. For all remaining visits that do not require an endoscopy, the CDAI

calculations including SF/AP scores will need to be calculated based on the 7 days prior to the study visit.

Please refer to Appendix 3 for review of the CDAI and Appendix 4: Frame Determination as it relates to question 8 of the CDAI. The wrist measurement will be measured at the screening visit to determine frame size and recorded on the appropriate CRF page.

Hematocrit (Hct) value needed for the calculation of the CDAI score:

- An Hct value obtained via the central lab atthe baseline visit and other scheduled study visits during the induction period will be used to calculate the CDAI score. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/Results.cfm?Analyte_Name=Hematocrit&Clia_Complexity=waived&SortColumn=DATE%5FEFFECTIVE%20DESC&PAGENUM=10.

7.2.6. Patient Reported Outcomes (PRO) for Health Outcomes Assessment

Patient reported outcomes (PRO) assessments are self-administered during the study. Refer to Appendix 12 for Alternative Measures During Public Emergencies if applicable.

It is important to note that the PRO measurements are collected and evaluated in a different manner than the observed or volunteered adverse events. Given those differences, no attempt will be made to resolve any apparent discrepancies between observed or volunteered adverse events and PRO data collected from subjects. Adverse event incidence rates will not be calculated from these solicited data but rather from the information recorded on the AE pages on the CRF.

The following PROs will be completed as specified in the Schedule of Activities. Subjects should be encouraged to complete the PROs at the clinic at the beginning of the study visit prior to any clinical assessments. A member of the staff should be available if a subject requires further instruction and to review the PRO questionnaires for completeness prior to leaving the clinic.

- Inflammatory Bowel Disease Questionnaire (IBDQ).
- Short Form-36, version 2, acute (SF-36).
- European Quality of Life Questionnaire – 5 Dimensions-3 Levels (EQ-5D-3L) & Visual Analog Scale (EQ-5D VAS).
- Patient Global Impression of Severity (PGIS).

7.2.6.1. Inflammatory Bowel Disease Questionnaire (IBDQ)

IBDQ is a psychometrically validated PRO instrument for measuring the disease-specific quality of life in subjects with IBD, including CD. The IBDQ is comprised of 32-items, which are grouped into 4 dimensions: bowel function, emotional status, systemic symptoms and social function.[7] The 4 domains are scored as follows:

- Bowel symptoms: 10 to 70.
- Systemic symptoms: 5 to 35.
- Emotional function: 12 to 84.
- Social function: 5 to 35.

The total IBDQ score ranges from 32 to 224. For the total score and each domain, a higher score indicates better quality of life. A score of at least 170 corresponds to clinical remission and an increase of at least 16 points is considered to indicate a clinically meaningful improvement.[7,8] See Appendix 5.

7.2.6.2. Short Form – 36, Version 2, Acute (SF-36)

The SF-36 v2 Acute is a psychometrically valid and reliable health status questionnaire that assesses 8 domains of functional health and well-being: Physical Functioning, Role Limitations due to Physical Health Problems, Bodily Pain, Social Functioning, Mental Health, Role Limitations due to Emotional Problems, Vitality, and General Health Perceptions. A physical health component summary score (PCS) and mental health component summary score (MCS) are calculated from the 8 domain scores. The acute form uses a recall period of one week. Higher scores indicate a better health-related quality of life. See Appendix 6.

7.2.6.3. Euro Quality of Life Questionnaire 5 Dimensions 3 Levels and Visual Analog Scale (EQ-5D-3L & VAS)

The EQ-5D 3L and EQ-5D VAS is a patient completed questionnaire designed to assess impact on health related quality of life in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Additionally, scores from the five domains may be used to calculate a single index value, also known as a utility score. The validity and reliability of the EQ-5D-3L has been established in a number of disease states, including CD.[9] The EQ-5D/VAS records the respondent's self-rated health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). See Appendix 7.

7.2.6.4. Patient Global Impression of Severity (PGIS)

The Patient Global Impression of Severity (PGIS) is a patient completed numeric rating scale question to assess the overall impression of disease severity experienced by the patient. The PGIS score ranges from 0 (None) to 10 (Extremely Severe). The PGIS will be assessed daily beginning approximately 2 weeks prior to screening endoscopy and throughout the induction phase and between Visit 12 to 16, Visit 24 to 32 and Visit 56 to 64 in OLE phase See Appendix 8.

7.3. Pharmacodynamics

The pharmacodynamics (PD) samples must be processed and shipped as indicated in the laboratory manual to maintain sample integrity. Any deviations from the PD processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Depending on sampling and transport constraints, it is possible that not all biomarker samples will be collected in all study regions.

All efforts will be made to obtain the PD samples at the exact nominal time relative to dosing. Please consult the laboratory manual(s) for final instructions on sample collection, storage, and shipping requirements. These manual(s) supersede the instructions listed in the applicable protocol sections. Samples that are handled according to the respective manual guidance are considered "per protocol".

Samples will be analyzed using fit for purpose or validated analytical methods in compliance with Pfizer standard operating procedures.

As part of understanding the pharmacodynamics of the study drug and the disease under study, samples may be used for evaluation of the bioanalytical method. These data will be used for internal (ie, Pfizer) exploratory purposes and will not be included in the clinical report.

7.3.1. High-Sensitivity C-Reactive Protein (hsCRP)

Blood samples for determination of hsCRP will be obtained at the times specified in the Schedule of Activities.

7.3.2. Interferon Gamma-Induced Protein 10 (IP-10)

Blood samples for the analysis of IP-10 will be collected (prior to dosing) into appropriately labeled tubes containing no preservative, anticoagulant or serum separator according to the times outlined in the Schedule of Activities.

7.3.3. FACS Analysis (TBNK Cells)

Whole blood samples will be collected for standard T cell, B cell and NK cell (TBNK) analysis according to the times outlined in the Schedule of Activities.

7.3.4. Exploratory Serum Protein Biomarkers

Blood samples (10 mL) for analysis of exploratory serum biomarkers will be collected into appropriately labeled glass tubes containing no preservatives; anticoagulant or serum separator according to the times specified in the Schedule of Activities and may be analyzed. Serum should be aliquotted before storing.

7.3.5. Fecal Calprotectin

A stool sample for determination of fecal calprotectin will be obtained at the times specified in the Schedule of Activities.

The study site personnel will provide appropriately labeled containers and instructions to the subject on how best to collect a sufficient fecal sample. During screening period, collection of stool MUST be prior to administration of any bowel prep for endoscopy. For example, subject can collect their sample 1 week prior to bowel prep. One week is not a set time period; subject may collect the stool sample sooner than 1 week too. This only applies to stool sample collection during screening period. During treatment period, a sample collected on the day of the visit is preferred, however if this is not possible, a sample from the day before or day after the visit should be collected.

7.3.6. Stool Samples for Microbiome Analysis

A stool sample for microbiome analysis will be obtained at the times specified in the Schedule of Activities. Sequencing of the DNA present in the stool will be performed. DNA generally comes from microorganisms like bacteria, viruses, fungi and parasites that may be present in the stool. During this process, some human DNA may be inadvertently sequenced, but will not be used for the final microbiome analysis. The analysis vendors will analyze the DNA contained in the stool to better understand disease activity and response to therapy.

The study site personnel will provide appropriately labeled containers and instructions to the subject on how best to collect a sufficient stool sample. During screening period, collection of stool MUST be prior to administration of any bowel prep for endoscopy. For example, subject can collect their sample one week prior to bowel prep. One week is not a set time period; subject may collect the stool sample sooner than one week too. During treatment period a sample collected on the day of the visit is preferred, however if this is not possible, a sample from the day before or day after the visit should be collected.

7.4. Pharmacokinetics

7.4.1. Plasma for PK Analysis of Investigational Product

Blood samples for PK analysis will be collected into appropriately labeled tubes at times specified in the Schedule of Activities.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. The exact date and time of the sample collection is noted on the source document and data collection tool (eg, CRF).

Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual. The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures (SOPs).

As part of understanding the PK of the IP, samples may be used for further characterization and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance with local regulations and, if not used within this timeframe, will be destroyed.

7.4.2. Shipment of Plasma Samples for PK Analysis

The shipment address and contact information for the lab will be provided to the investigator site prior to the initiation of the trial.

7.5. Pharmacogenomics

7.5.1. Gene Expression Analysis

Blood samples for the assessment of gene expression (mRNA analysis) will be collected in appropriately labeled PAXgene Blood RNA Tubes. Samples will be collected according to the times outlined in the Schedule of Activities. These samples may be used for the evaluation of exploratory biomarkers that may include markers related to ulcerative colitis, Crohn's disease and/or other inflammatory conditions and/or the mechanism of action of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib). These samples are for biomarker analysis and will not be used for genetic testing. Detailed processing, storage and shipment instructions will be provided in the Lab Manual.

Colon tissue biopsies will also be taken and may be used for histology, gene expression and protein analysis and are described in Section 7.2.2.

7.6. Banked Biospecimens

Banked biospecimens will be collected from subjects for exploratory research relating to the drug response and disease/condition under study. These collections are not typically associated with a planned assessment described in the protocol. They will be handled in a manner that protects each subject's privacy and confidentiality. Banked biospecimens will be assigned the subject's study identification code (ID) at the site. The data generated from these banked biospecimens will also be indexed by this ID. Biospecimens will be kept until destruction in facilities with access limited to authorized personnel, and biospecimen-derived data will be stored on password-protected computer systems. The key between the subject's ID and the subject's direct personally identifying information (eg, name, address) will be held at the study site. Biospecimens will be used only for the purposes described in the protocol and informed consent document; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored for many years (no time limit) to allow for research in the future, including research conducted during the lengthy drug-development process and also postmarketing research. Subjects may withdraw their consent for the use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining biospecimens will be destroyed, but data already generated from the biospecimens will continue to be available to protect the integrity of existing analyses.

Unless prohibited by local regulations or ethics committee decision, a 4-mL blood genomic banked biospecimen **Prep D1 (dipotassium edetic acid [ethylenediaminetetraacetic acid] [K_2EDTA] whole-blood collection optimized for DNA analysis)** will be collected at the time specified in the Schedule of Activities section of the protocol to be retained for potential pharmacogenomic/genomic/biomarker analyses related to drug response and disease/condition under study. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined. The primary purpose is to examine DNA; however, the biospecimen may also be used to study other molecules (eg, RNA, proteins, and metabolites).

Additional banked biospecimens to be retained for such exploratory analyses in this study include the following:

- Prep B1.5 (K_2EDTA plasma collection optimized for biomarker/proteomic/metabonomic analysis): A 4-mL blood biospecimen will be collected at times specified in the Schedule of Activities section of the protocol.

- Prep B2.5 (serum collection optimized for biomarker/proteomic/metabonomic analysis): A 4-mL blood biospecimen will be collected at times specified in the Schedule of Activities section of the protocol.

- Prep R1 (PAXGene whole-blood collection optimized for RNA analysis): A 2.5 mL blood biospecimen will be collected at times specified in the Schedule of Activities section of the protocol.

The banked biospecimens will be collected from all subjects unless prohibited by local regulations or IRB/EC decision.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document that they will not be compensated in this event.

7.6.1. Additional Research

Unless prohibited by local regulations or IRB/EC decision, subjects will be asked to indicate on the consent form whether they will allow banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the Banked Biospecimens section will be used. Subjects may still participate in the study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a

subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal Section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or

- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a

tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Potential Cases of Decreased eGFR

In the PF-06700841 (brepocitinib) FIH study B7931001, serum creatinine elevation was reported across dose levels in both healthy volunteers and psoriasis patients. The proposed mechanism for the observed serum creatinine increases in study B7931001 is inhibition of creatinine transport in the kidney (ie, transporter-mediated rather than direct nephrotoxicity) (See Section 1.5.3.1.1).

Abnormal values in serum creatinine concurrent with absence of increase in blood urea nitrogen (BUN) that meet the below criteria, in the absence of other causes of kidney injury, are considered important medical events.

All subjects will have serum creatinine based and serum cystatin-C based eGFR calculated at times specified in the Schedule of Activities. If an individual subject demonstrates a **CONCOMITANT serum creatinine based AND serum cystatin C based eGFR decline of ≥30% compared to the subject's baseline eGFR,** then the subject should not be further dosed and adequate, immediate, supportive measures including immediate evaluation by a nephrologist (preferably within 24 hours) with appropriate management. If the subject cannot be seen by a nephrologist within 24 hours, then the subject should be sent to a local emergency room for assessment of renal function. Results should be repeated as indicated by the nephrologist or weekly at a minimum until the eGFR returns to baseline ±15% or the renal parameters are deemed to be stable by the nephrologist and/or PI.

eGFR results will be communicated to the treating physician.

Subjects should return to the investigational site and be evaluated as soon as possible, preferably within **24 to 48 hours** from awareness of the abnormal eGFR (CONCOMITANT serum creatinine based AND serum cystatin C based eGFR decline of ≥30% compared to the subject's baseline eGFR) result for a safety follow-up visit. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating serum creatinine and serum cystatin C, laboratory tests should also include: serum BUN, serum CK, serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, calcium), in addition to urine dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the above pre-set laboratory criteria, with no other cause(s) of laboratory abnormalities identified should be considered as important medical event irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal serum creatinine.

All relevant test results will be forwarded to Pfizer immediately by the PI.

This requirement applies to all subjects in all cohorts.

8.4.4. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.4.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.4.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.4.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.5. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.5.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be provided prior to the un-blinding of the trial and maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

Using a 2-sample test of proportions and assuming that the true SES-CD 50 rate is 12% for the placebo group and 29% for PF-06651600 (ritlecitinib) at Week 12, a sample size of approximately 70 completed subjects in PF-06651600 (ritlecitinib) arm and 60 completed subjects in combined placebo arm will have about 80% probability to statistically detect a greater SES-CD 50 response rate in PF-06651600 (ritlecitinib) compared to placebo at the

end of study with a local type-I error 5% 1-sided. A sample size of 50 completed subjects in PF-06700841 (brepocitinib) arm and 60 completed subjects in combined placebo arm will have about 72% probability to statistically detect a greater SES-CD 50 response rate in PF-06700841 (brepocitinib) compared to placebo at the end of study with a local type-I error 5% 1-sided. This takes into account that the first interim analysis didn't stop for early efficacy or futility. Since the probability for the trial stopping for early efficacy at first interim based on CMEI is 3% when there is no treatment effect, the type-I error for the comparison of each active arm to placebo is controlled at 8%. More details on the past interim analyses are described in Section 9.6.

In order to evaluate the primary endpoint of SES-CD 50, we expect that 83 subjects in PF-06651600 (ritlecitinib) arm and 71 subjects in combined placebo arm to be randomized and dosed into the primary study population, assuming a 15% drop out rate. Including subjects already randomized to the PF-06700841 (brepocitinib) arm prior to amendment 5, a total of approximately 230 - 250 subjects would be enrolled for the study.

9.2. Efficacy Analysis During Induction

All subjects who receive at least one dose of randomized study medication and have a baseline and at least one post-baseline measurement (after taking randomized study medication) will be included in the efficacy data analyses. All the comparisons during the induction period will be to placebo. There will be no comparisons between the two active treatments PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib).

9.2.1. Analysis of the Primary Endpoint During Induction

The primary efficacy endpoint is proportion of subjects achieving SES-CD 50 defined as ≥50% reduction in SES-CD from baseline change from baseline in SES-CD at Week 12. The SES-CD 50 data comparing active treatment group and placebo group will be analyzed using the Cochran Mantel Hanzel (CMH) test, adjusting the stratification factors, ie, status of previous treatment of anti TNF therapy. Treatment differences in the SES-CD 50 response and the corresponding 2-sided 90% confidence intervals adjusted for stratification factors will be computed using the methods proposed by Cochran[12] with the minimum risk weights proposed by Mehrotra and Railkar.[11] It is anticipated to have small numbers in each investigation site, so the investigation site effect will not be an adjustment factor.

The observed risk rate and the associated confidence interval of the risk differences will be presented. The unconditional exact method as described by Chan and Zhang (1999)[13] will be used to compute the confidence intervals. More details will be documented in the Statistical Analysis Plan. The primary analysis population will be based on a modified intent-to-treat (mITT) analysis set, which is defined as all randomized subjects who received at least one dose of randomized treatment. Treatment failure approach will be used for missing value imputation from drop out subjects. Additional sensitivity analyses for the primary endpoint will be described in the SAP.

9.2.2. Analysis of Secondary Endpoints During Induction

The binary secondary endpoints are proportion of subjects achieving SES-CD 25 (≥25% reduction from baseline), and CMEI (≥3 points reduction from baseline), endoscopic remission (SES-CD ≤2) and mucosal healing (complete absence of ulcers) at Week 12. These endpoints will be analyzed similar to the primary efficacy endpoint using the CMH test comparing the treatment differences by adjusting the stratification factor, status of previous treatment of anti TNF therapy. Point estimation of difference and 90% CI will be provided using the same methods proposed for the primary endpoints. The continuous secondary endpoint for change from baseline in SES-CD at Week 12 will be analyzed using an analysis of covariance (ANCOVA) model which will include terms for treatment group, the stratification factors (if there are a sufficient number of subjects in each stratum, otherwise, the stratification factors will be dropped from the model), and the baseline SES-CD score.

The analysis population will be on the mITT analysis set. The analyses on continuous secondary endpoints will not account for missing values, ie, it will be based on the Data As Observed (DAO) approach without explicit imputation to handle the missing data. Treatment failure approach will be used for missing value imputation for binary endpoints.

9.3. Analysis of Other Endpoints During Induction

9.3.1. Pharmacokinetic Analysis

The PK concentration population is defined as all enrolled subjects who received at least one dose of PF-06651600 (ritlecitinib) or PF-06700841 (brepocitinib) and in whom at least one concentration value is reported.

PK concentrations will be summarized and presented with summary statistics. A population PK model may be developed for the purpose of estimating PK parameters. Any population PK model developed to characterize the PK data will be reported separately.

9.3.2. PK/PD Unblinding Plan

A PK/PD unblinding plan approved by the clinical lead, clinical pharmacology lead and statistical lead will be in place to describe the procedures to be employed in safeguarding the study blind for members of the study team. These procedures will be in accordance with applicable Pfizer standard operating procedures (SOPs) for releasing randomization codes and breaking the study blind. Under this plan a group of statisticians, PK/PD data provider, PK/PD analyst and PK/PD support would be unblinded in order to initiate the building of statistical models of the PK, dose/response as well as exposure/response analysis models and conduct associated simulations. The aim of this work would be to facilitate a fuller interpretation of the study upon completion of the induction period. This group will not serve on the study team during the period of early unblinding. The unblinding may occur after the last subject has been randomized to the induction period. The details of the procedures will be described in the PK/PD Unblinding Plan for Modeling and Simulation for study B7981007 which will be finalized prior to the start of the PK/PD unblinding.

9.3.3. Analysis of Exploratory Biomarkers

Exploratory biomarkers may be summarized by treatment group and may be graphically displayed. Appropriate analysis may be performed as needed. The analysis population will be based on a mITT analysis set and will not account for missing values.

9.3.4. Unblinding for Biomarkers

In order to expedite the analyses of the biomarkers at the end of the induction period, an unblinded team may review the biomarker data (including exploratory biomarkers) [excluding any biomarker data that is or contributes to a primary endpoint] and exposure data on an ongoing basis. This group will minimally be comprised of a bioanalyst and statistician, but may also include clinicians/precision medicine personnel, clinical pharmacologist and PK/PD analyst/support staff. This group will be unblinded when needed in order to conduct the analyses of the biomarkers in accordance with a biomarker data analysis plan and will be independent of the study team. This unblinding process will be in accordance with Pfizer SOPs related to Releasing Randomization Codes and Breaking the Blind and will not have any impact on the conduct of the study. The biomarker plan, approved by the clinical lead, clinical pharmacology lead and statistical lead, will be in place to describe the procedures to be employed in safeguarding the study blind for members of the study team. The biomarker plan will outline the range of possible analyses and provide details of the decision-making process regarding unblinding.

9.3.5. Analysis of Health Outcomes Endpoints

IBDQ data will consist of 32 individual items, scores for the 4 dimensions (bowel function, emotional status, systemic symptoms and social function) and a total score. All data will be listed and data for the 4 dimensions and total score summarized by time post-dose for each treatment. Week 12 changes from baseline for the 4 dimensions and total score will be plotted and summarized by treatment group to visually assess compound-specific changes. All IBDQ data (baseline and Week 12) will be summarized across time. For binary health outcomes variables, descriptive statistics will be summarized by treatment group and CMH methods proposed above will be used to compare each treatment group to placebo group. For continuous health outcomes variable (eg, IBQD total score and domain scores, EQ-5D/VAS), descriptive statistics will be summarized by treatment group and analysis of variance/ variance/Longitudinal Data Analysis model will be used to compare each treatment group and placebo group. The primary analysis population for the health outcomes will be based on a mITT analysis set. The analyses on continuous endpoints will not account for missing values, ie, it will be based on the Data as Observed (DAO) approach without explicit imputation to handle the missing data. Treatment failure approach will be used for missing value imputation for binary endpoints from drop out subjects.

9.4. Safety Analysis During Induction

All clinical AEs, SAEs, TEAEs, withdrawal due to AEs, ECGs, vital signs and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects.

The safety analysis set will include all subjects who have received at least one dose of IP. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. All safety endpoints will be listed and summarized in accordance with Pfizer Data Standards. Categorical outcomes (eg, AEs, ECGs) will be summarized by subject counts and percentage. Continuous outcome (eg, BP, heart rate, etc) will be summarized using N, mean, median, standard deviation, etc. Change from baseline in laboratory data and vital signs will also be summarized. Subject listings will be produced for these safety endpoints accordingly.

9.5. Analysis During the Open Label Extension Period

9.5.1. Secondary Efficacy Analysis

The secondary efficacy endpoints are:

- Proportion of subjects achieving clinically meaningful endoscopic improvement (CMEI response) at Week 64 among subjects who achieved CMEI response at Week 12.

- Proportion of subjects achieving SES CD 25 at Week 64 among subjects who achieved SES CD 25 at Week 12.

- Proportion of subjects achieving SES CD 50 at Week 64 among subjects who achieved SES CD 50 at Week 12 respectively.

Descriptive statistics will be provided for the secondary efficacy endpoints. These endpoints will be analyzed using the same analysis technique as the primary endpoint. We will also produce graphs for the efficacy endpoint for both the induction and OLE period. Detailed methodologies of these analyses will be described in the SAP.

9.5.2. Exploratory Efficacy Analysis

Descriptive statistics will be provided for the exploratory efficacy analysis. The binary endpoints such as endoscopic response, endoscopic remission, clinical response and remission will be summarized with frequency and percentage by time point. The continuous variables will be summarized with n, mean, median, standard deviation etc. These summaries may be provided by the strata of responding status at entry.

All subjects who have received at least one dose of planned investigational product in the extension part will be included into the exploratory efficacy analysis. Detailed methodologies of these analyses will be described in the SAP.

9.5.3. Pharmacokinetic Analysis

Blood samples will be collected at specified times for analysis of plasma concentrations of PF-06651600 (ritlecitinib) and PF-06700841 (brepocitinib). Plasma concentration data obtained from all subjects will be summarized and presented with summary statistics.

9.5.4. Exploratory Pharmacodynamic Analysis

Exploratory biomarkers will be listed and summarized by visit, and change from baseline for these endpoints will also be summarized at specific time points as reported in the SOA.

Appropriate regression models may be used to look at association between these endpoints and any covariates of clinical interests.

9.5.5. Safety Analysis

Safety and tolerability are the primary endpoint during the open label extension period. A set of safety summary tables will be produced to evaluate potential risks associated with the safety and tolerability of administering the study medication. All clinical AEs, SAEs, on-treatment AEs, as well as discontinuations due to AEs will be summarized with frequency and percentage. Continuous outcomes (eg, vitals, safety lab parameters, etc) will be summarized using n, mean, median, standard deviation etc.

Change from baseline on selected safety endpoints may be additionally summarized. Subject listings may also be produced for these safety endpoints. The safety endpoints will be listed and summarized in accordance with Pfizer Data Standards. Detailed methodologies of these analyses will be described in the SAP.

9.6. Interim Analysis

This protocol may include 2 interim analyses using CMEI for both active treatments. Details regarding the analysis procedures to be used for the interim analysis will be provided in the interim analysis plan (IAP). The first interim analysis will be performed when approximately 60% of subjects have completed or had the chance to complete the Week 12 visit. The objective of this interim analysis is to determine if there is evidence of lack of differentiation ("futility") or significant efficacy for the active treatments compared to placebo. The non-binding futility decision at this interim analysis isbased on conditional power evaluated on a total of approximately 150 subjects who complete or had the chance to complete Week 12.

The study will be stopped for futility for that active treatment arm if conditional probability of claiming efficacy by the end of study is <10% for that active arm. If the non-binding futility condition is met for both active arms, the study may be stopped at this interim point. Efficacy stopping rule will be derived from the Hwang-Shih-DeCani gamma family[16] of spending function, with parameter 0, at each interim. The study may be stopped for efficacy, if efficacy condition is met by at least one active arm.

Second interim analysis may be performed when approximately 80% of the subjects have completed or had the chance to complete the Week 12 visit. The objective of this second interim analysis is to determine if there is evidence of significant efficacy for the active arms compared to placebo. Using the same Hwang-Shih-DeCani gamma family[16] spending function, if one of the active arms enters efficacy region computed from this interim, the trial will stop for efficacy at the second interim look.

The interim analyses results will be used to facilitate internal decision-making. The results will only be distributed to a select list of individuals involved in the internal decision-making process in order to protect the integrity of the study. This list of individuals will be provided in the interim analysis plan/charter. The results of the interim analyses will not enable individuals directly involved in running the study (such as investigators) to identify treatment assignments for individual subjects still in the study.

During these interim analyses, some members of the study team may be unblinded and replaced with blinded colleagues. The subjects, investigators, and individuals from the sponsor (or designee) who interact with the investigators and monitor safety will continue to be blinded to individual study treatments throughout the follow up period of the study.

9.7. Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC).

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The E-DMC will review accumulating renal safety data and propose changes to the protocol as needed to ensure subject safety. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate. Additional information can be obtained in the E-DMC charter.

An internal review committee (IRC) will be formed to assess the interim analyses as described in Section 9.6. Details on the IRC will be included in the interim analysis charter.

9.8. Safety Adjudication Committees

Suspected opportunistic infections, neuroaudiometry and cardiovascular events (eg, thrombotic and embolic events) will be subject to review by separate external blinded adjudication committees based on the known mechanism of action for JAK inhibitors. These events will be forwarded for adjudication either by the study team or by its designee. Event documents may be requested from sites and may include (but not be limited to): hospital discharge summaries, operative reports, clinic notes, diagnostic tests, pathology reports, autopsy reports and death certificate information, as applicable. Obtaining and submitting this documentation will be the responsibility of the study site. Additional events of interest may be adjudicated by an external blinded adjudication committee as needed.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of

Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include ommitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject nameswill be removed and will be replaced by a single specific numerical code based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH Good Clinical Practice (GCP), local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last patient last visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06651600 (ritlecitinib) and/or PF-06700841 (brepocitinib) at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 1 month. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
AA	Alopecia Areata
Ae_{tau}	Cumulative amount of drug recovered unchanged in urine up to 24 hours
ANC	Absolute neutrophil count
ANCOVA	analysis of covariance
AP	Abdominal pain
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AT3	Antithrombin III
ATP	adenosine triphosphate
AUC_{24}	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{0-72}	area under the concentration-time curve from time 0 to 72
BA	bioavailability
BAEP	brainstem auditory evoked potential BAEP
BBS	Biospecimen Banking System
Bcl2	B-cell lymphoma 2
BCG	Bacillus Calmette-Guerin
BCRP	breast cancer resistant protein
BID	twice a day
BMI	body mass index
BMX	bone marrow tyrosine kinase on chromosome X
BP	blood pressure
BSA	body surface area
BSEP	bile salt export pump
BTX	bone marrow tyrosine kinase
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CFB	Change from baseline
CHD	Coronary heart disease
CK	creatine kinase
CK-MB	creatine kinase myocardial band
CL	clearance
CL/F	Apparent clearance
C_{max}	maximum concentration
CMEI	clinically meaningful endoscopic improvement

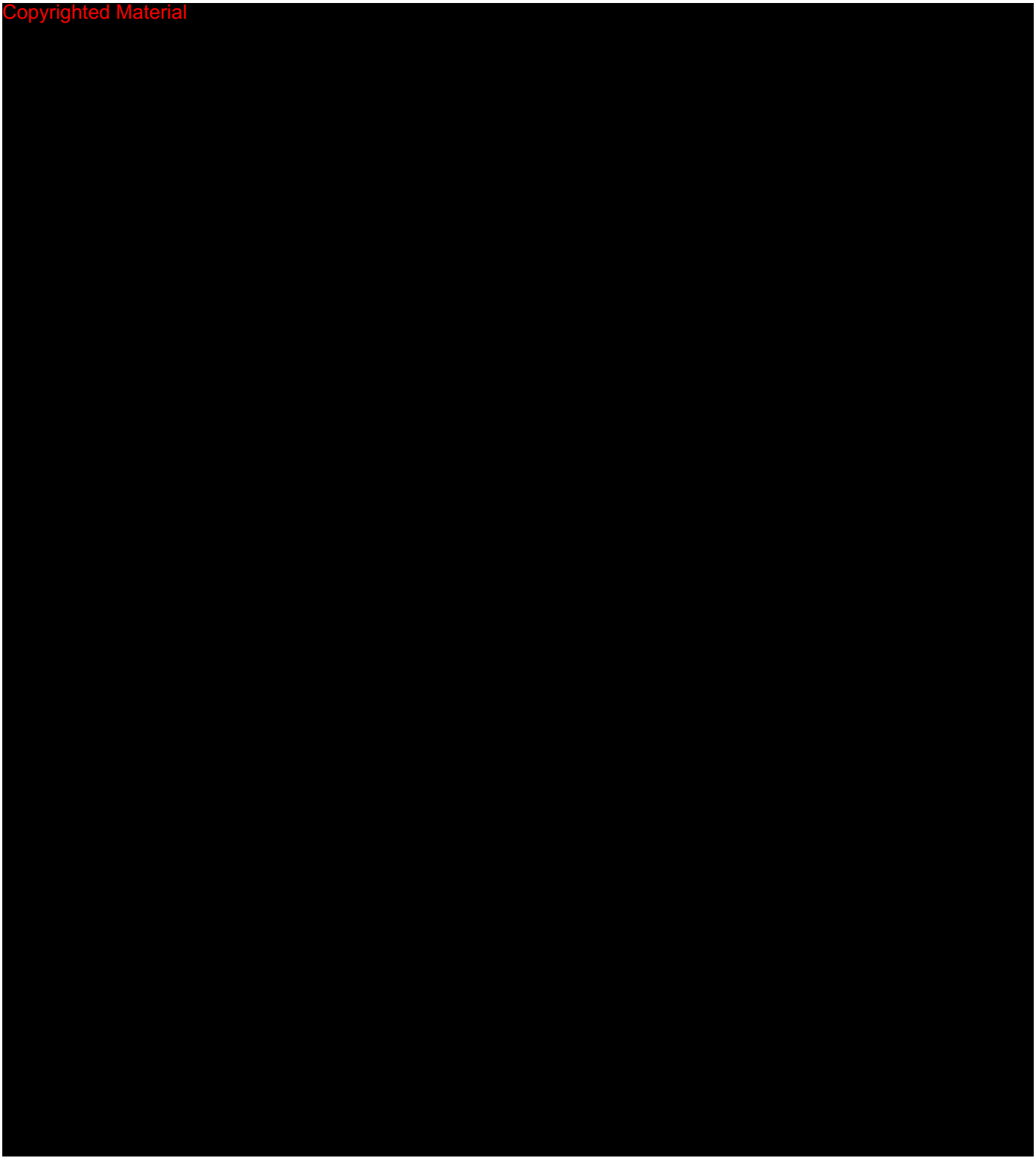
Abbreviation	Term
CMH	Cochran Mantel Hanzel
CMV	cytomegalovirus
CNS	Central nervous system
CO	cross over
COE	Cross over extension
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	coronavirus disease 2019
CRF	case report form
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	Computerized tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
CYP450	cytochrome P450
CYP	cytochrome
DDI	Drug drug interaction
DAO	data as observed
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DVT	Deep vein thrombosis
DU	dispensable unit
ESAI	Eczema Area and Severity Index
eDiary	Electronic diary
EBV	epstein–barr virus
EC	ethics committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EE	ethinyl estradiol
EFD	Embryo fetal development
eGFR	Estimated glomerular filtration rate
ET	Early termination
EU	European Union
EudraCT	European Clinical Trials Database
FIH	First in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDH	glutamate dehydrogenase
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal

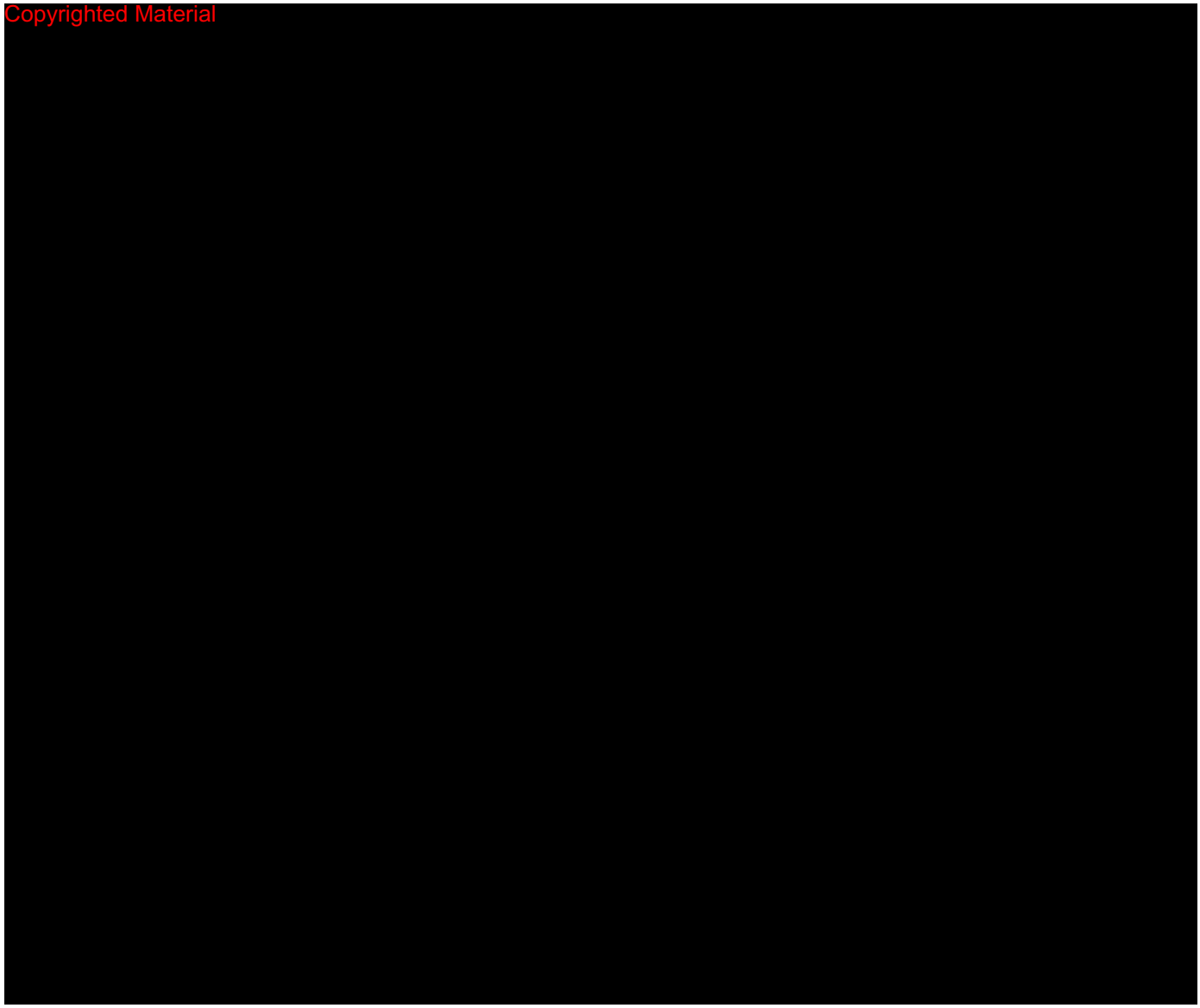
Abbreviation	Term
GLP	Good laboratory practice
GST	glutathione-S-transferase
rGST	recombinant glutathione-S-transferase
Hct	hematocrit
hCG	human chorionic gonadotropin
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HCV RNA PCR	hepatitis C virus ribonucleic acid polymerase chain reaction
HCV Ab	hepatitis C antibody
HDL	high-density lipoprotein
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
HRQL	health-related quality of life
hsCRP	high sensitivity C-reactive protein
HSV	herpes simplex virus
IA	interim analyses
IAP	interim analysis plan
IB	Investigators brochure
IBD	Inflammatory bowel disease
IBDQ	Inflammatory bowel disease questionnaire
IC50	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ID	identification
IFN	interferon
Ig	immunoglobulin
IGRA	Interferon gamma release assay
IL	interleukin
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IP-10	interferon gamma induced protein 10
IR	immediate release
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ITT	Intent to treat
ITK	IL-2 inducible T-cell kinase
IUD	intrauterine device
IUS	Intrauterine hormone-releasing system
IV	intravenous
IWR	interactive web response
JAK	Janus kinase
KDIGO	Kidney Disease: Improving Global Outcomes

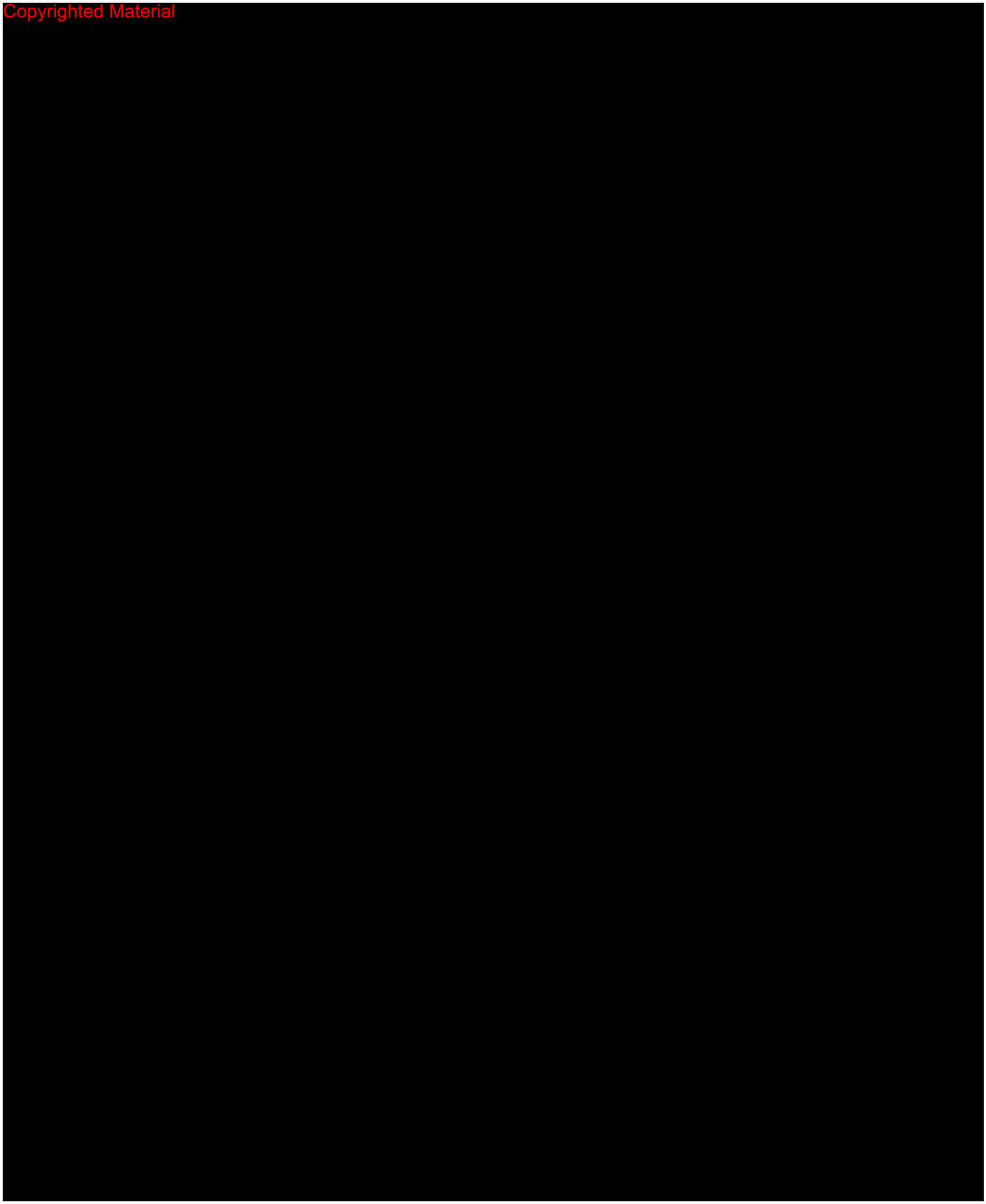
Abbreviation	Term
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LDL	Low density lipoprotein
LFT	liver function test
LLN	Lower Limit of Normal
LLOQ	lower limit of quantitation
LN	levonorgestrel
LOAEL	Lowest Observed Adverse Effect Level
LSLV	last subject last visit
OC	oral contraceptive
OLE	open label extension
M1-1	mu 1-1
mITT	modified intent-to-treat
MAD	Multiple ascending dose
MATE	multidrug and toxin extrusion
MCS	Mental component summary
MDR	Multi drug resistant
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Measles, Mumps, Rubella
MnB	meningitidis serogroup B
MR	modified release
MRA	Magnetic Resonance Angiogram
MRI	magnetic resonance imaging
mRNA	messenger ribonucleotide acid
MTX	methotrexate
N/A	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NCA	National cancer institute
NK	Natural Killer
NOAEL	No observed adverse effect level
NYHA	New York Heart Association
OATP	organic anion transporting polypeptides
OAT	organic anion transporting
OCT	Organic cation transporter
OLE	Open label extension
P1-1	pi 1-1
PA5	Protocol Amendment 5
PASI	psoriasis area and severity index
PCD	primary completion date
PCOA	Patient-Centered Outcome Assessments
PCR	polymerase chain reaction
PCS	Physical component summary
PD	Pharmacodynamics(s)
PE	physical exam

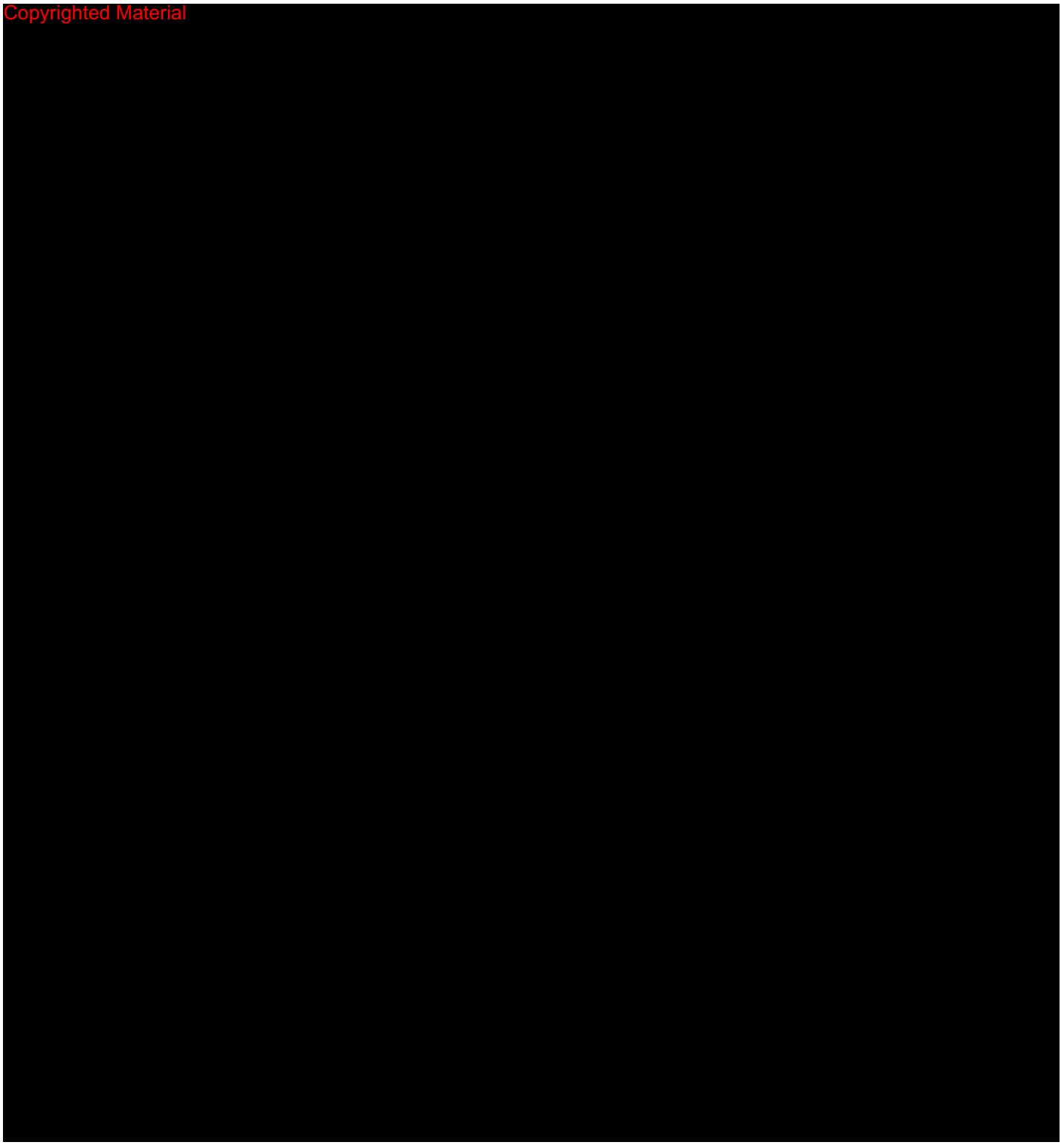
Abbreviation	Term
PFS	prefilled syringe
PGA	Physician's global assessment
P-gp	P-glycoprotein
PGIS	patient global impression of severity
PGx	Pharmacogenomics(s)
PI	principal investigator
PK	pharmacokinetic
PO	oral
POC	proof of concept
PPD	Purified protein derivative
PRO	Patient reported outcome
PT	prothrombin time
rGST	recombinant glutathione-S-transferase
RA	Rheumatoid Arthritis
R_{ac}	Observed accumulation ratio
R_{ss}	Steady state accumulation ratio
RNA	ribonucleic acid
QD	one daily
QFT-G	Quantiferon-gold
QFT-GIT	QuantiFERON® - TB gold in-tube
QTc	corrected QT interval
QTcF	Corrected QT interval by Fredericia
QW	once weekly
SAD	Single ascending dose
SAE	serious adverse event
SALT	Severity of Alopecia Tool
SAP	statistical analysis plan
SBE	Single blind extension
SC	subcutaneous
SCr	serum creatinine
SES-CD	simple endoscopic score for Crohn's disease
SF	stool frequency
SF-36	Short form 36
SLE	Systemic lupus erythematosus
SOC	System organ class
SOP	standard operating procedure
SRSD	single reference safety document
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction
SSC	special safety concern
TBNK	T, B and NK cells
$T_{1/2}$	Terminal half life
TB	tuberculosis

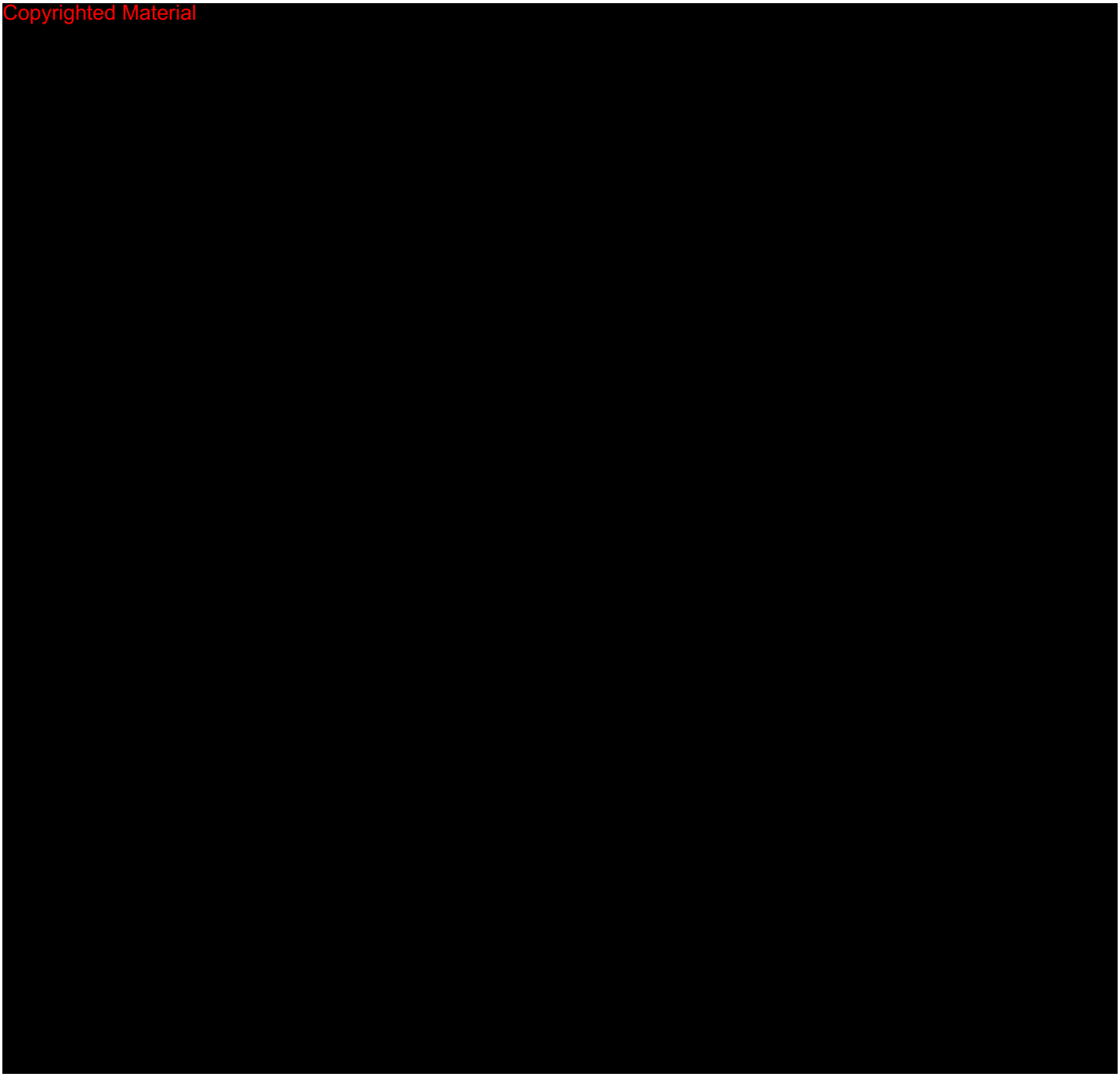
Abbreviation	Term
TBili	total bilirubin
TEAE	Treatment emergent adverse event
TEC	tyrosine kinase expressed in hepatocellular carcinoma (TEC)
TE-SAE	treatment emergent-serious adverse event
Th	T helper
T_{max}	time to reach maximum concentration
TNF	Tumor necrosis factor
TXK	tyrosine kinase expressed in T cells
TPMP	thiopurine methyltransferase
TYK	tyrosine-protein kinase
UC	Ulcerative colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
UDP	uridine 5'-diphospho
UGT	uridine 5'-glucuronosyltransferase
ULN	upper limit of normal
URI	upper respiratory tract infection
US	United States
UV	Ultra violet
V_{ss}	steady state volume of distribution
VAS	visual analog scale
VHP	Voluntary Harmonization Procedure
VZV	varicella zoster virus
Vz/F	apparent oral volume of distribution
WBC	white blood cells
WOCBP	Women of child bearing potential

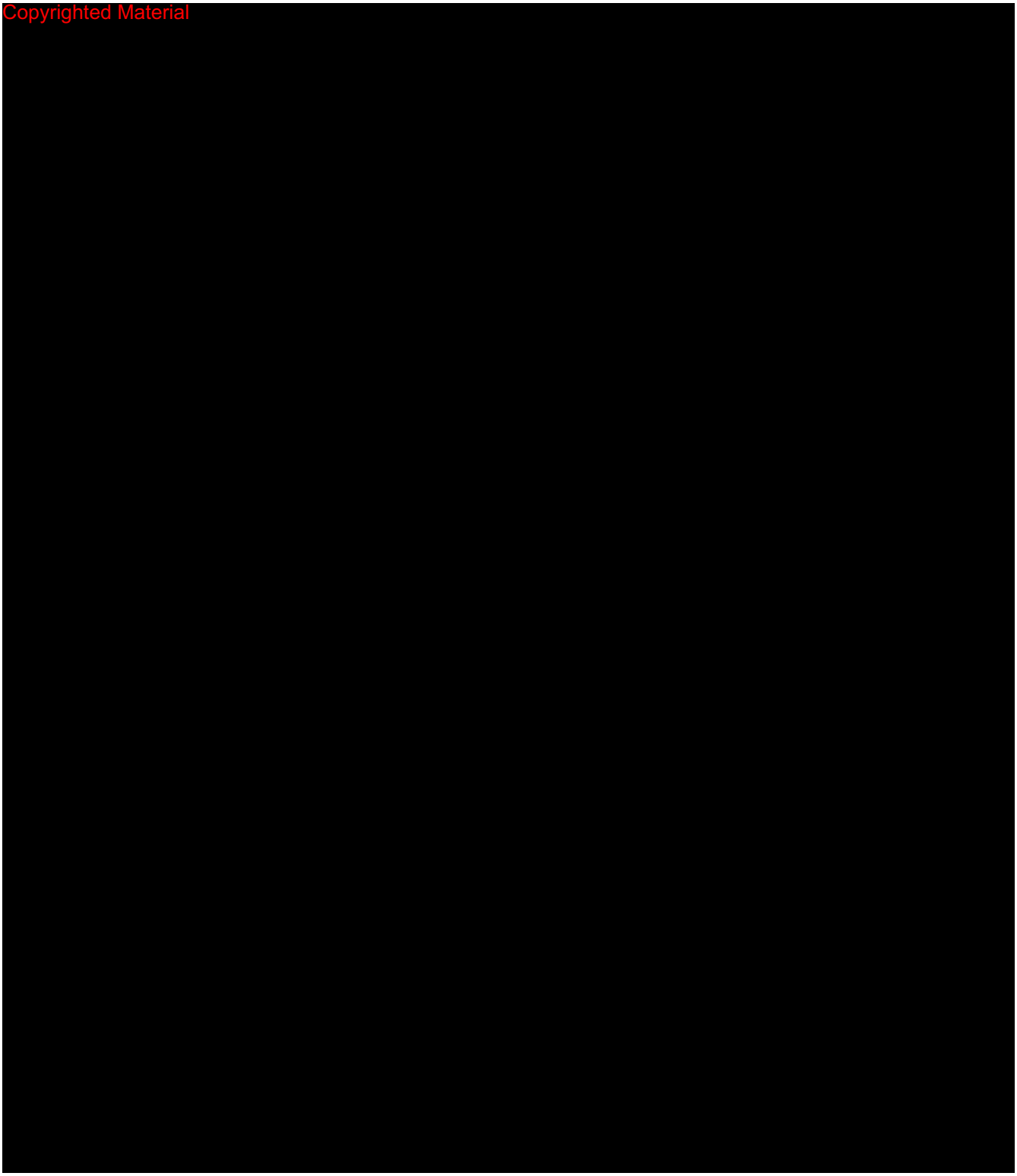


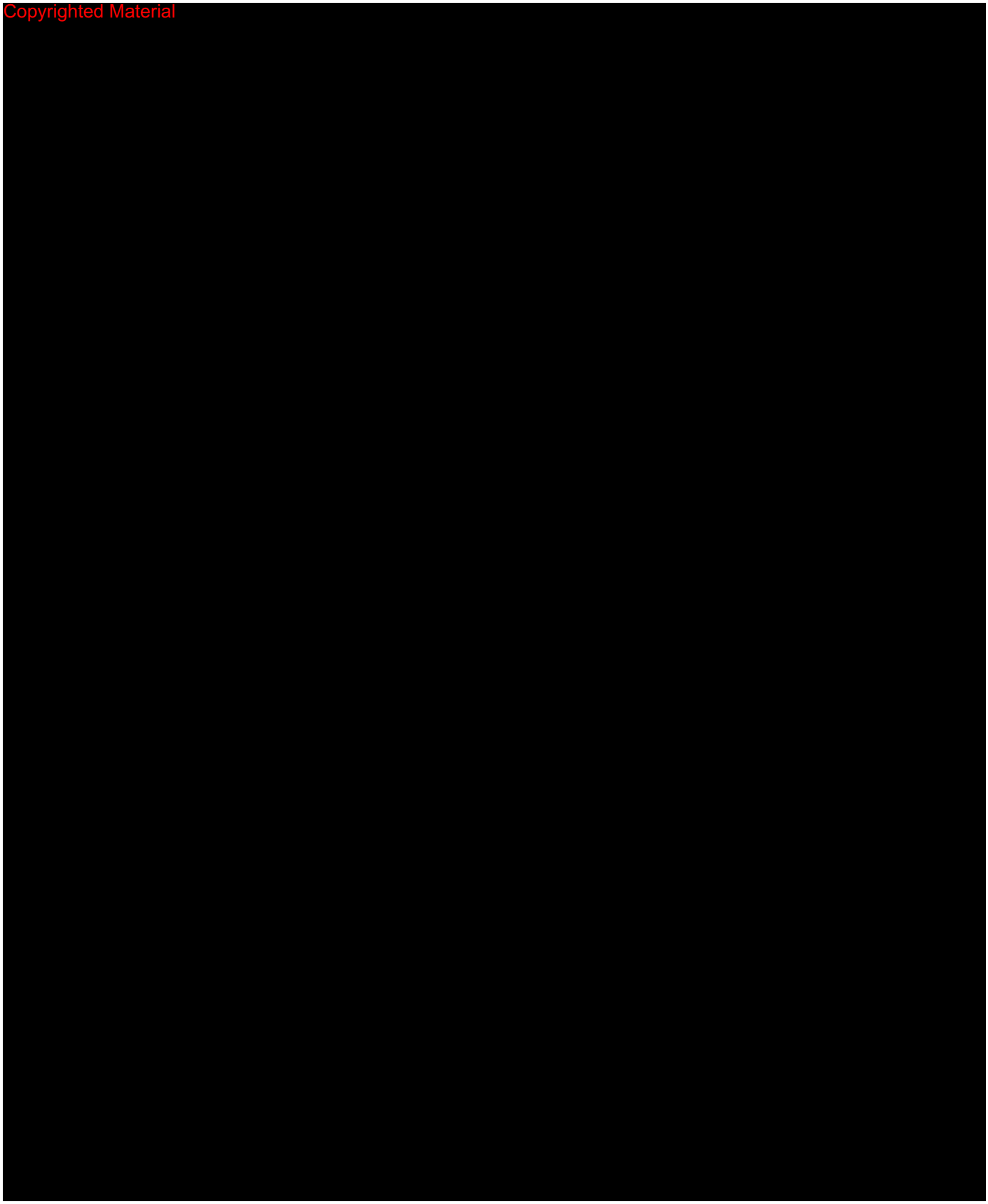


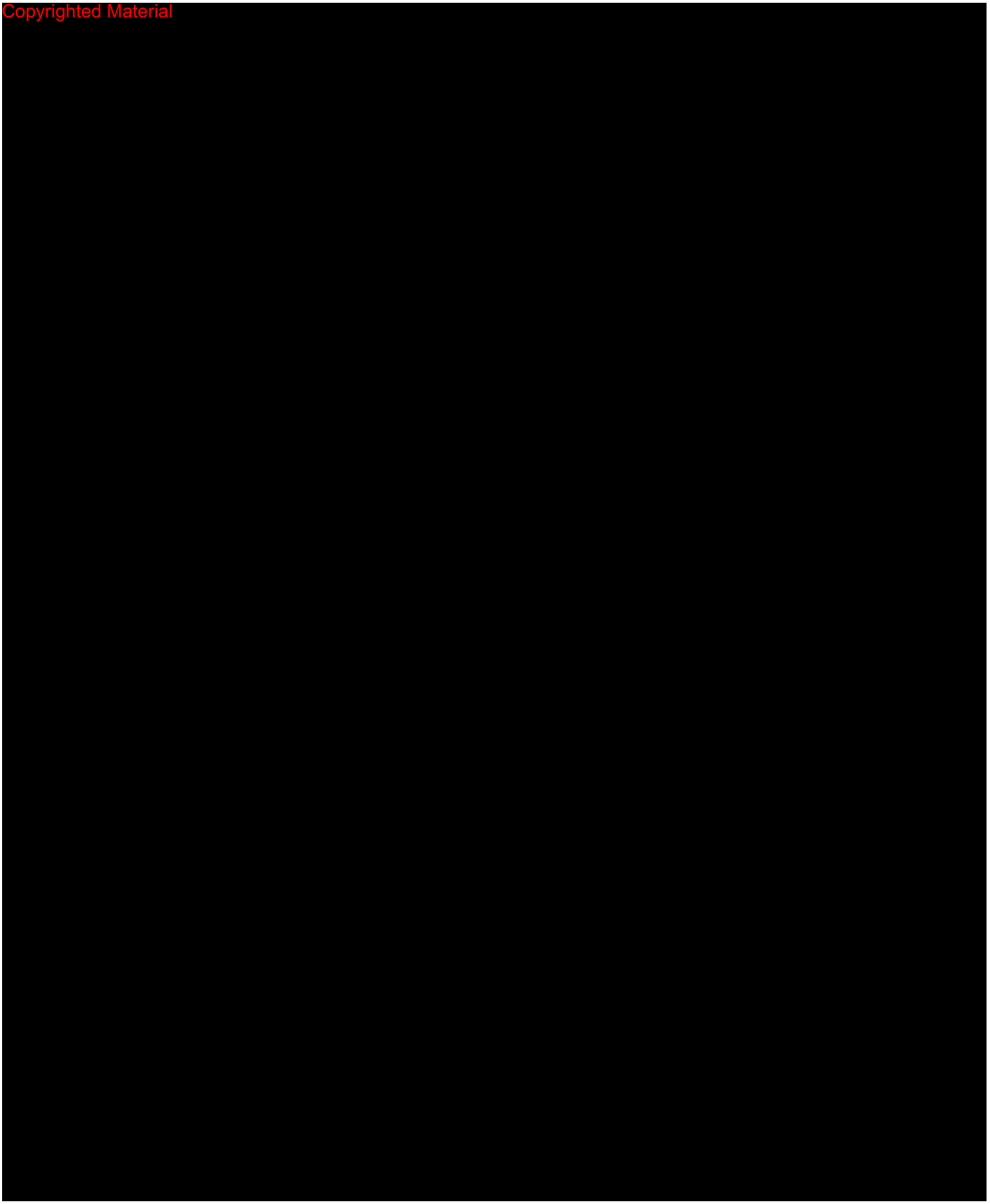


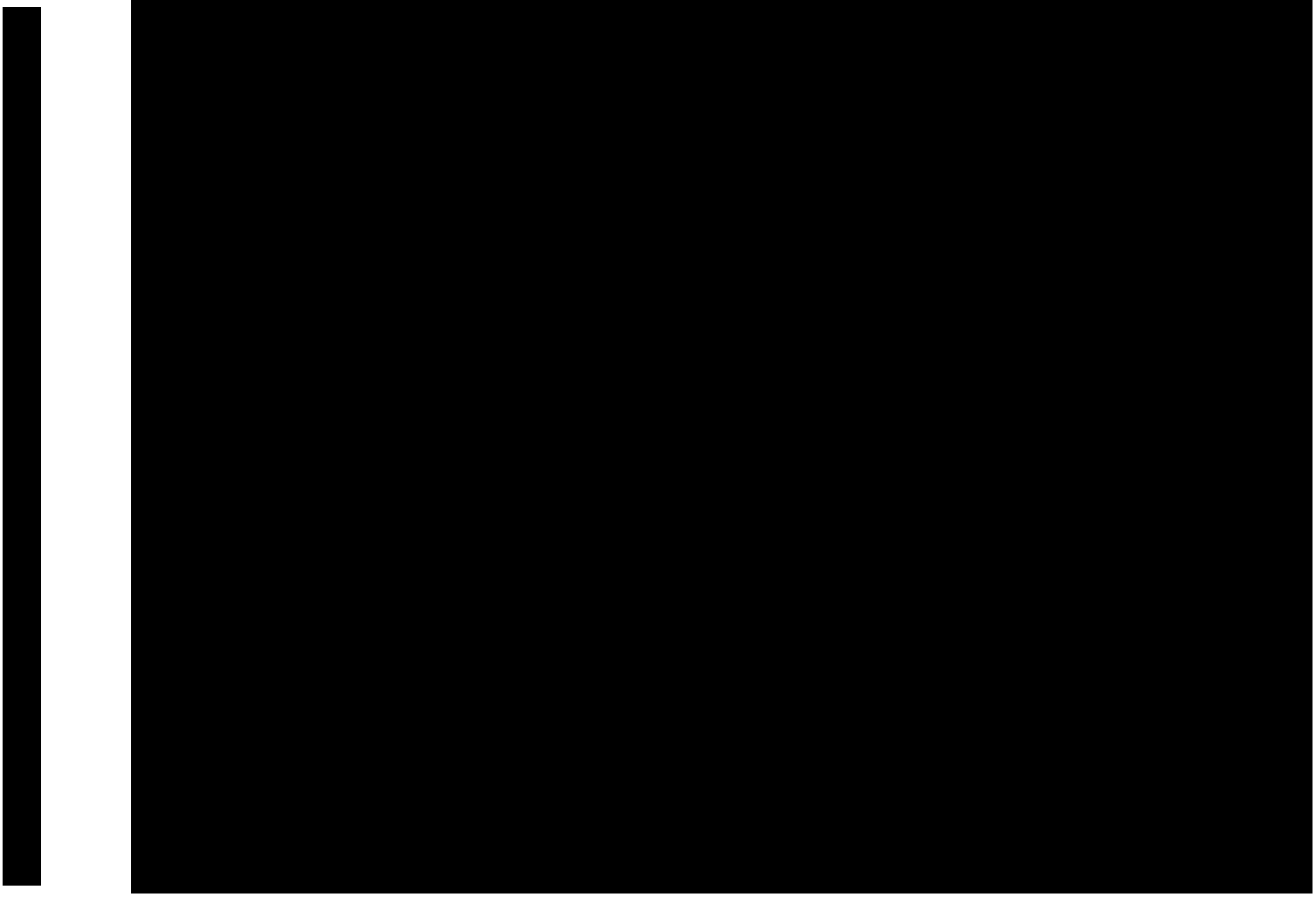


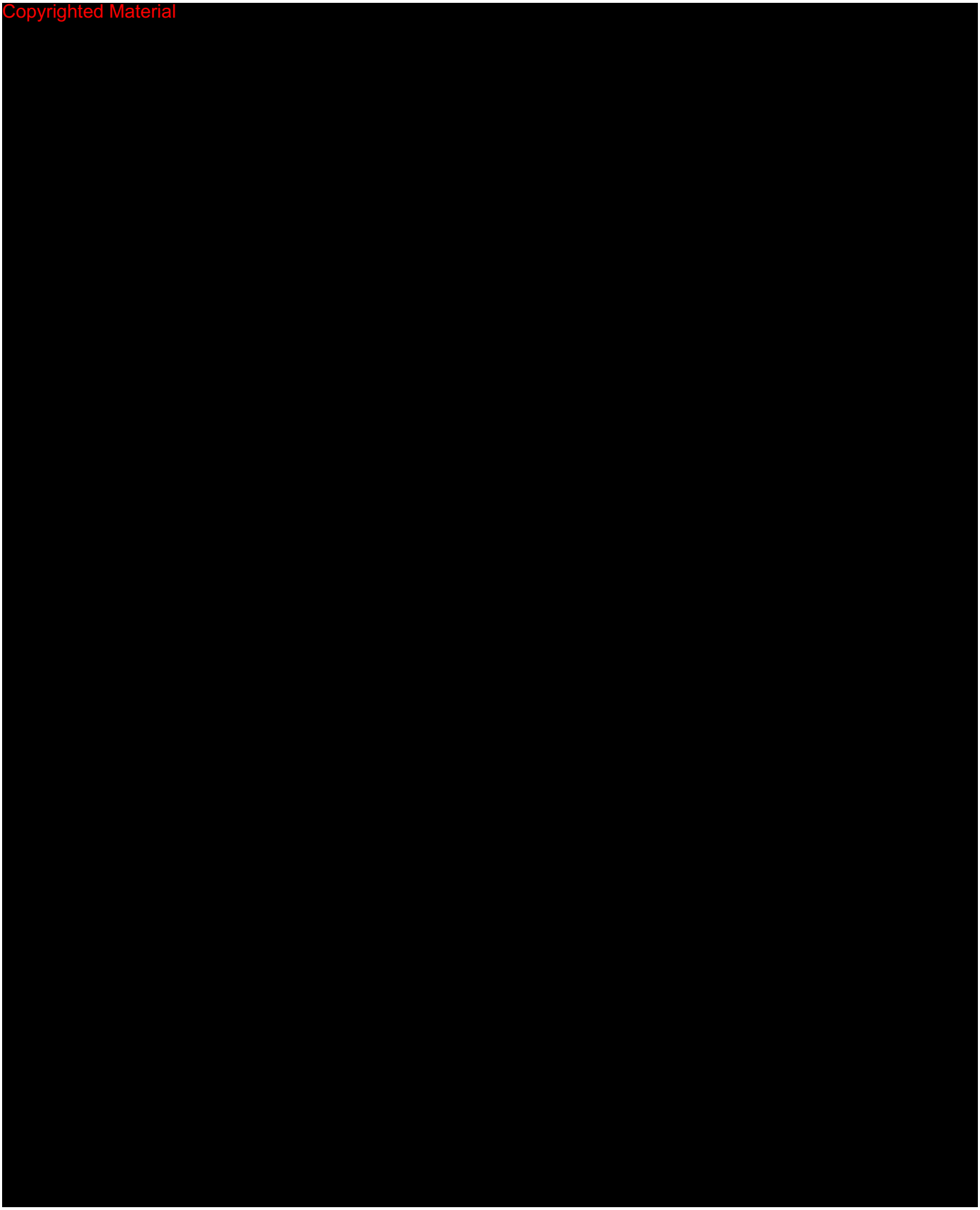


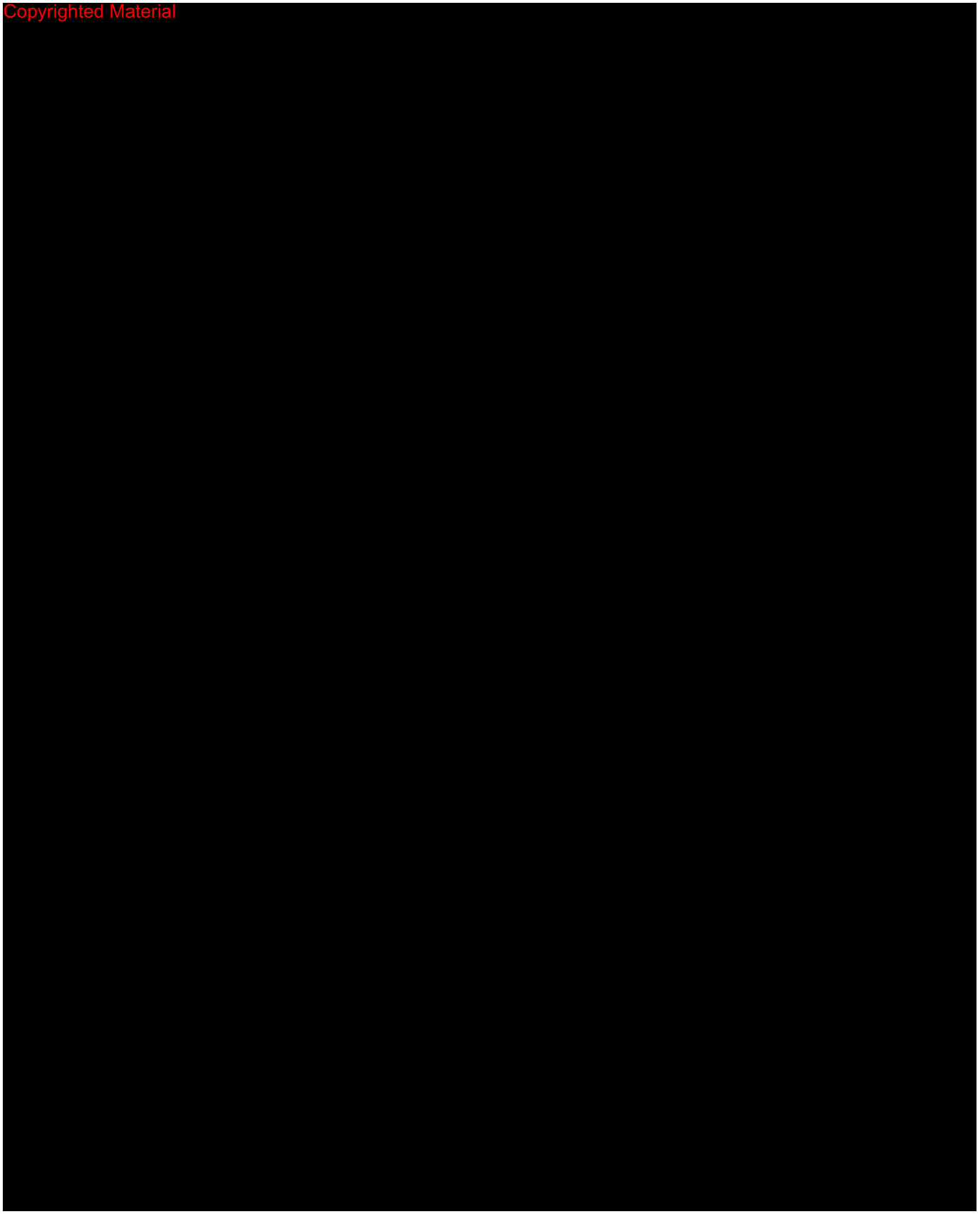


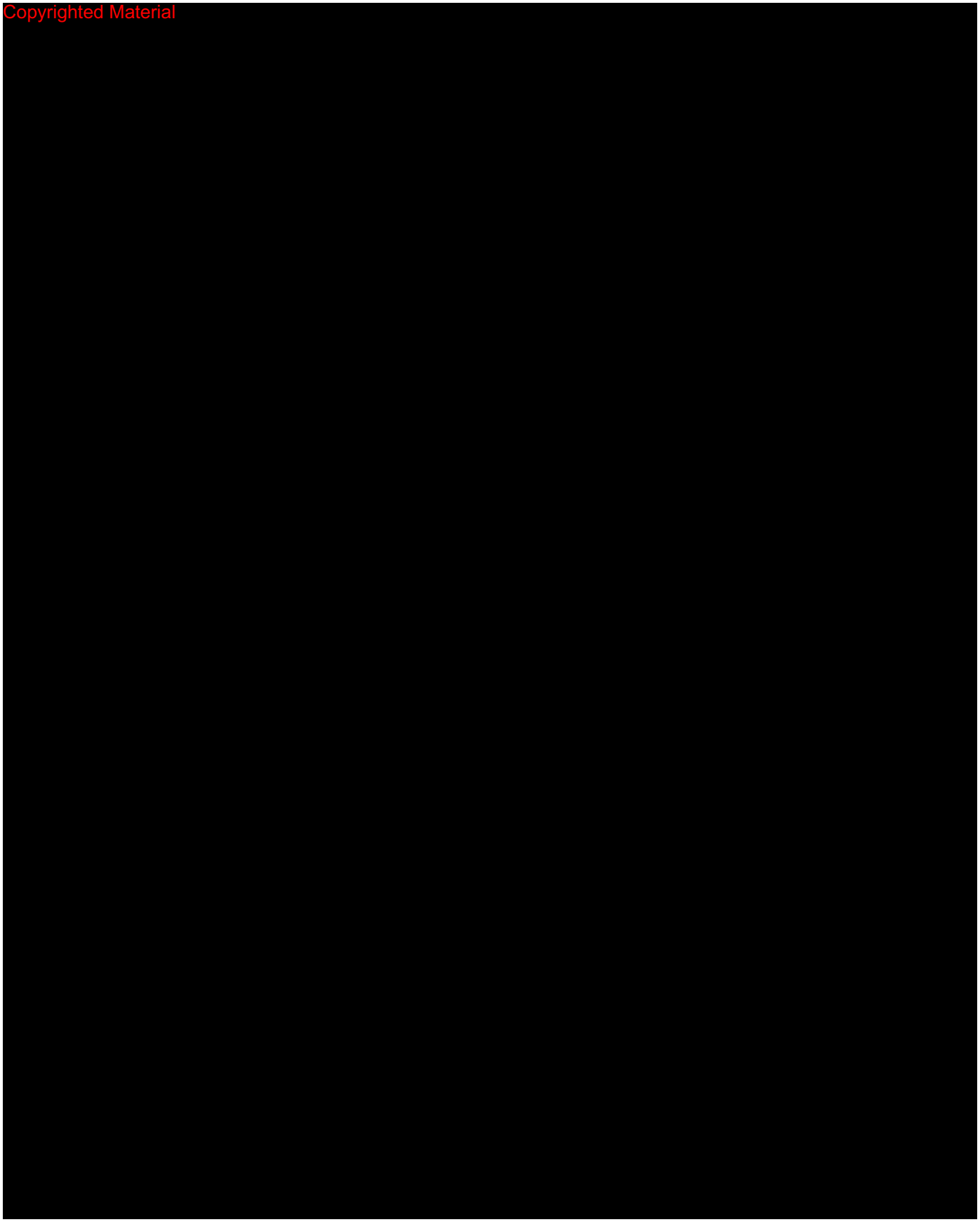


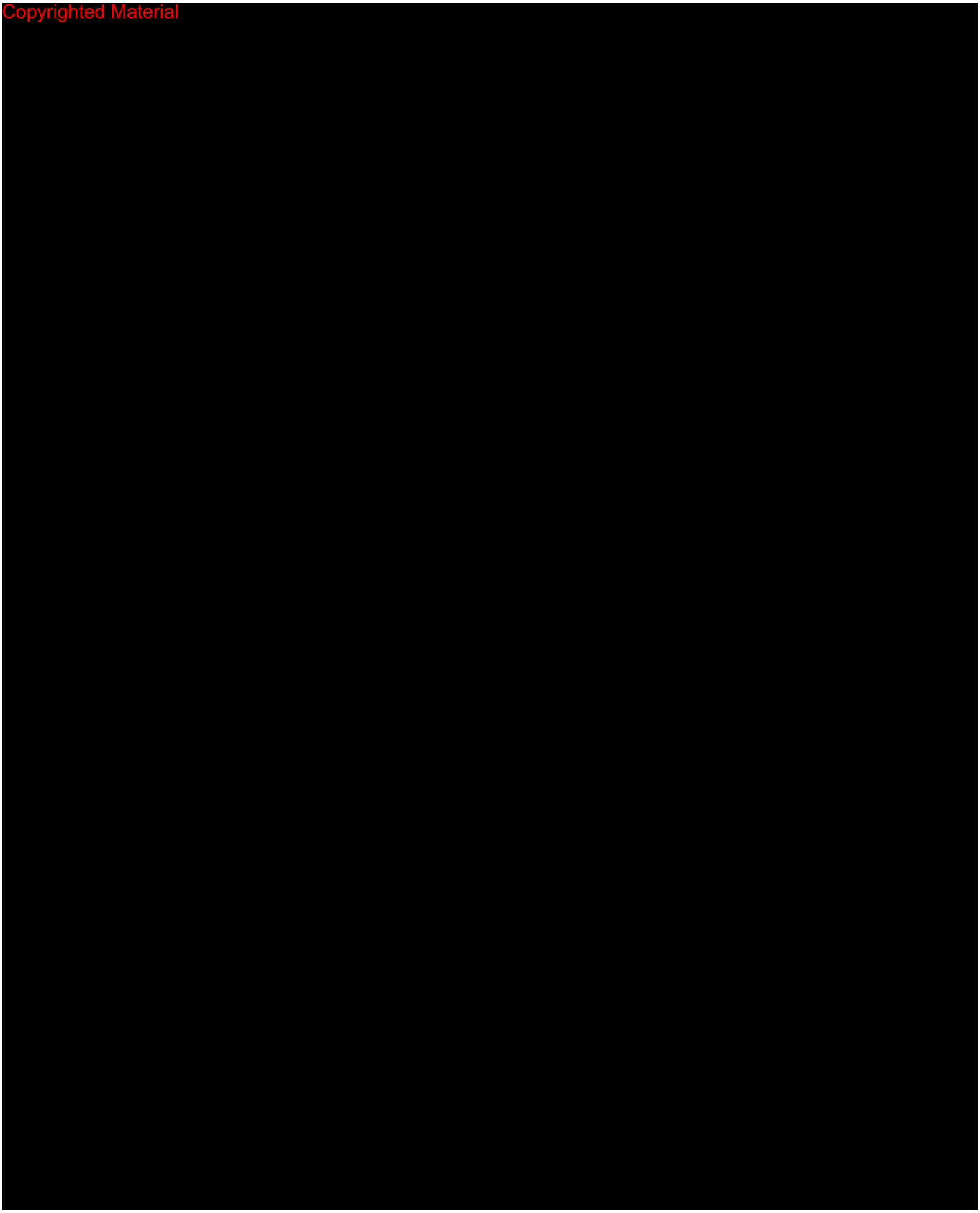


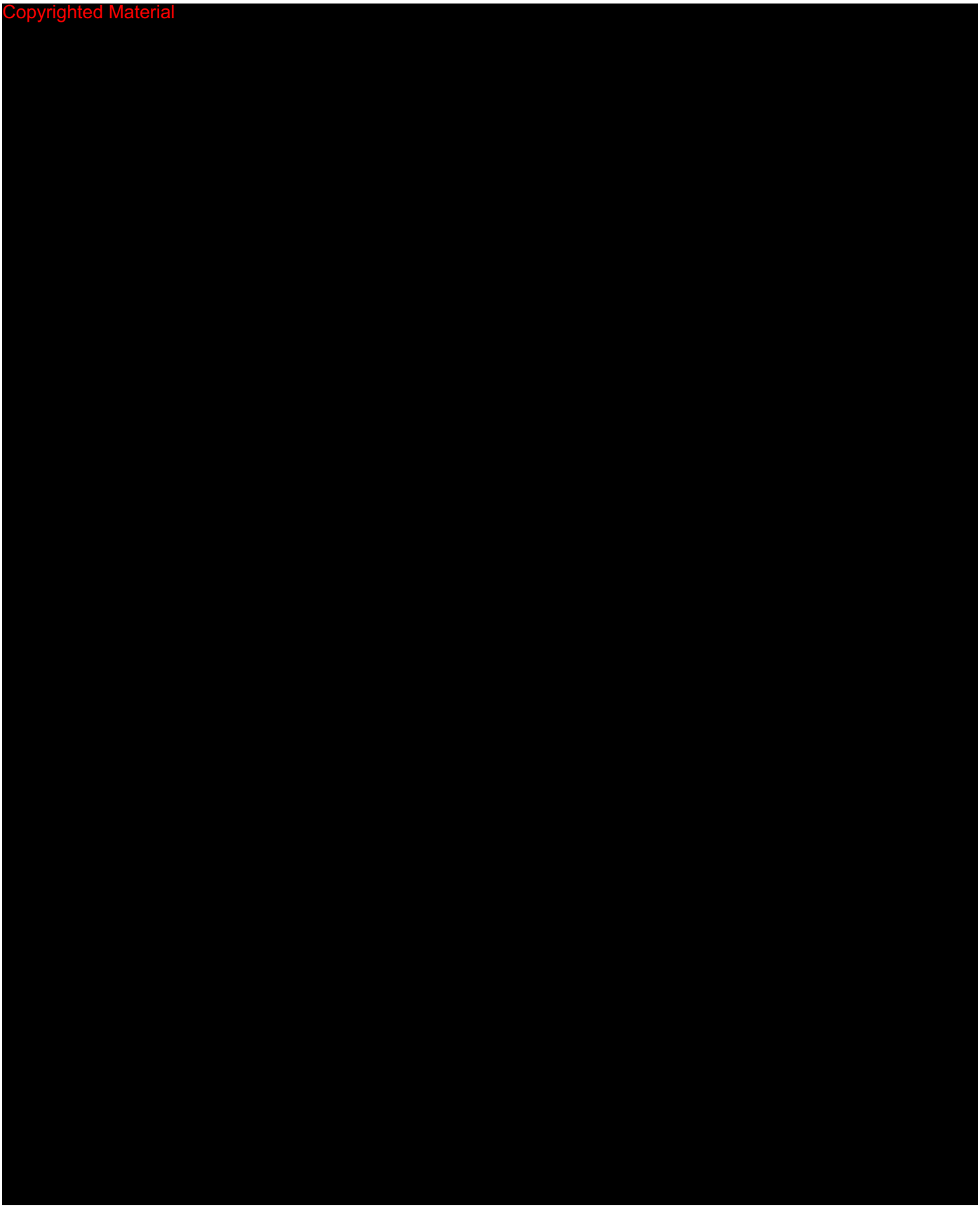


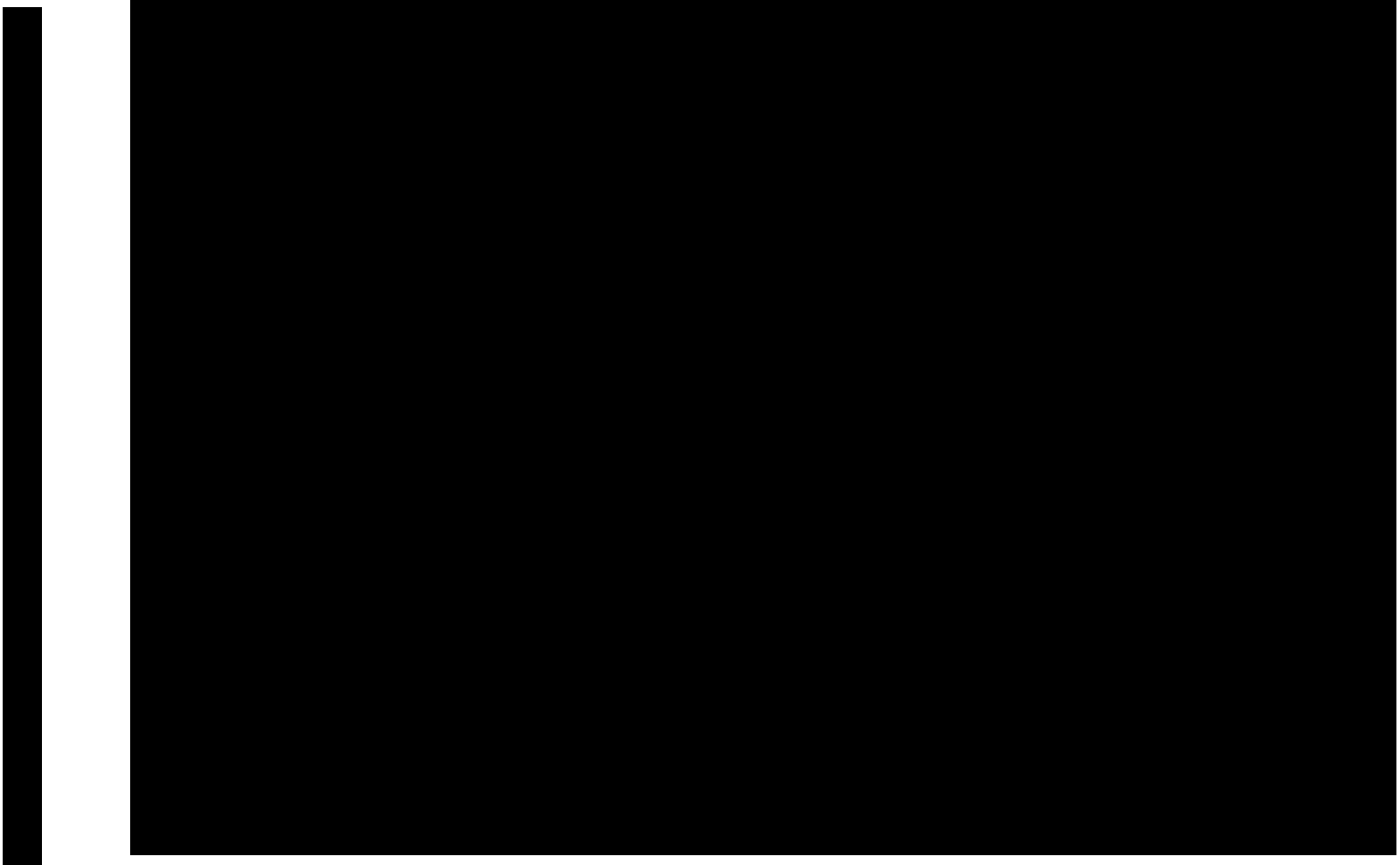


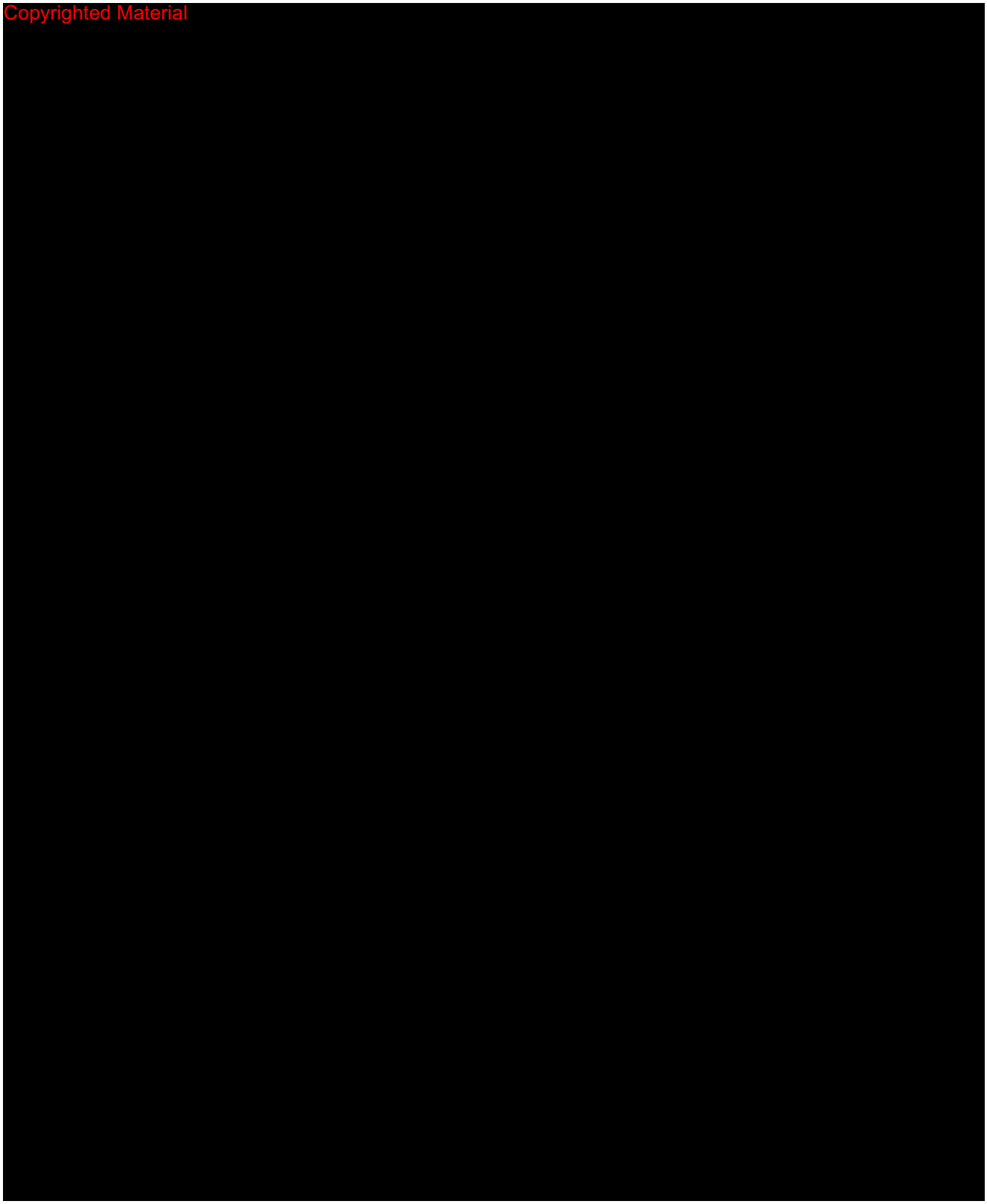


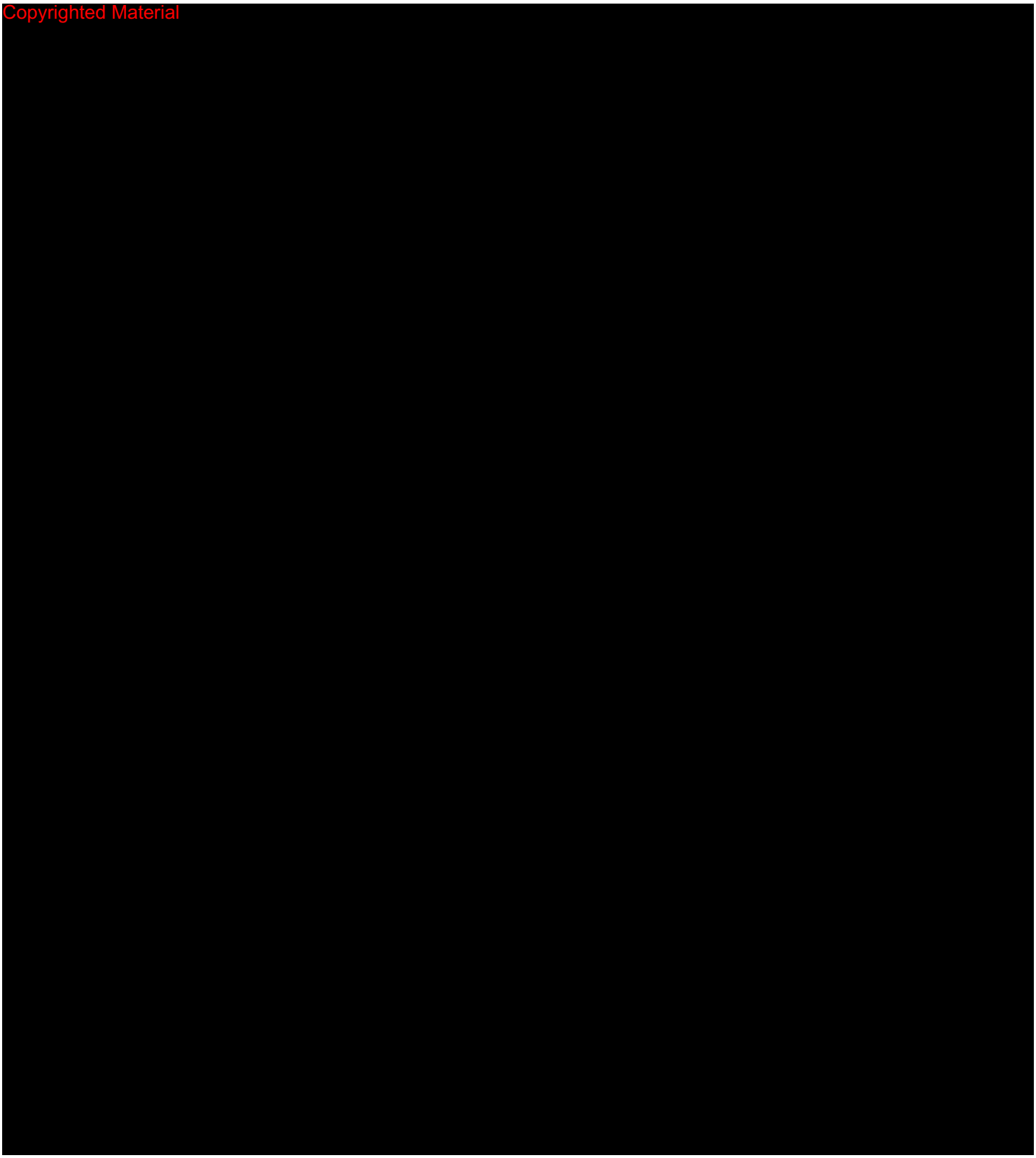


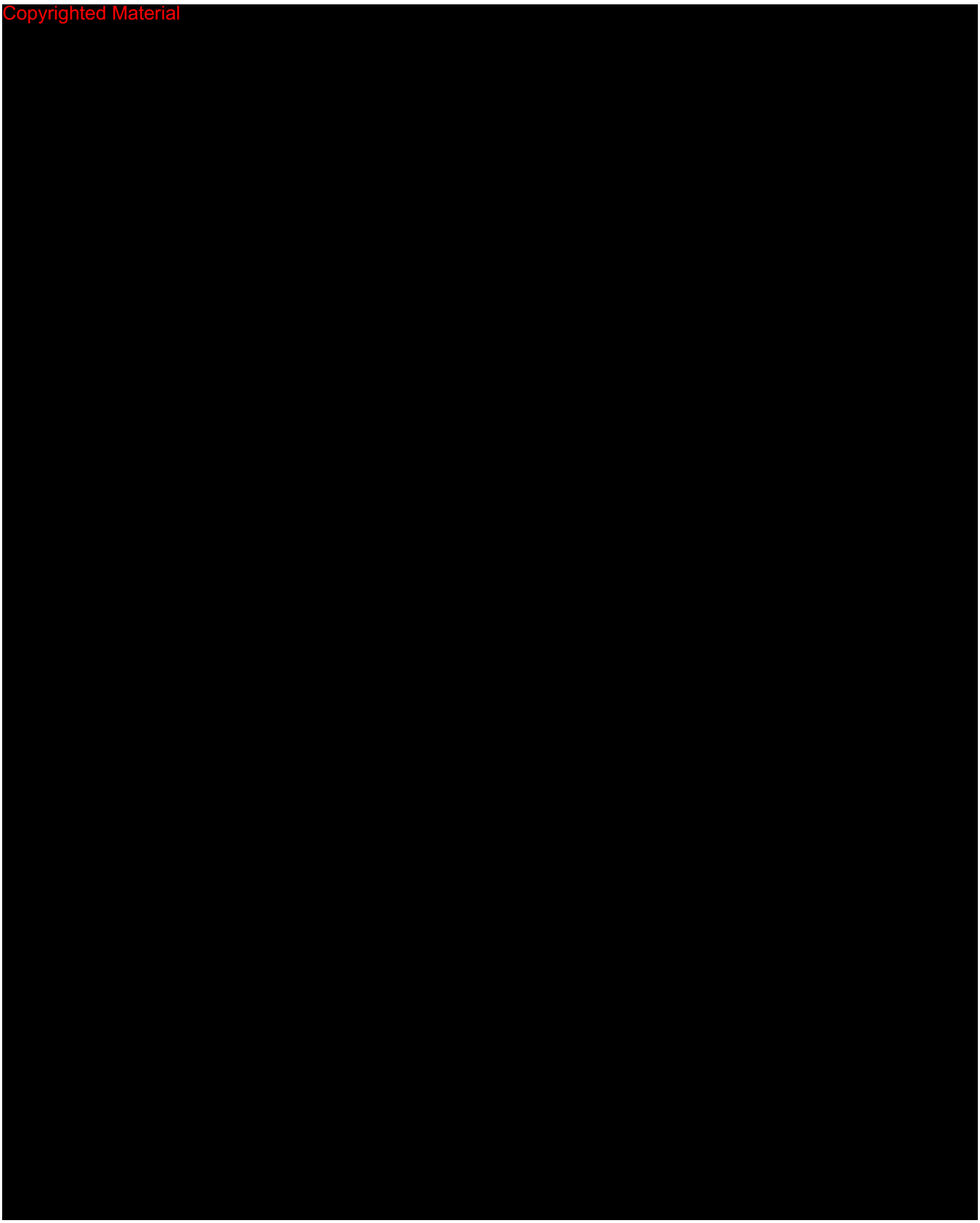


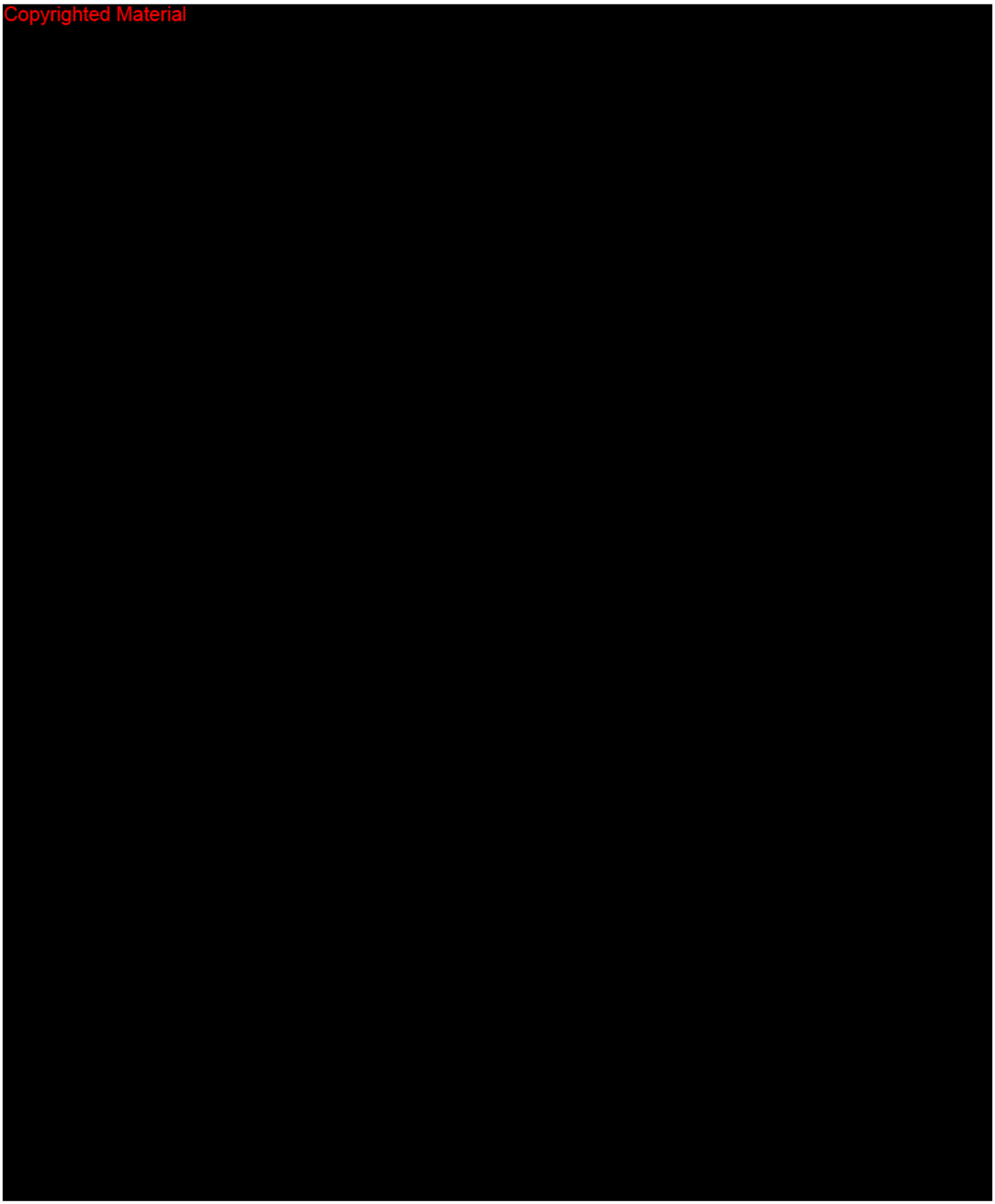


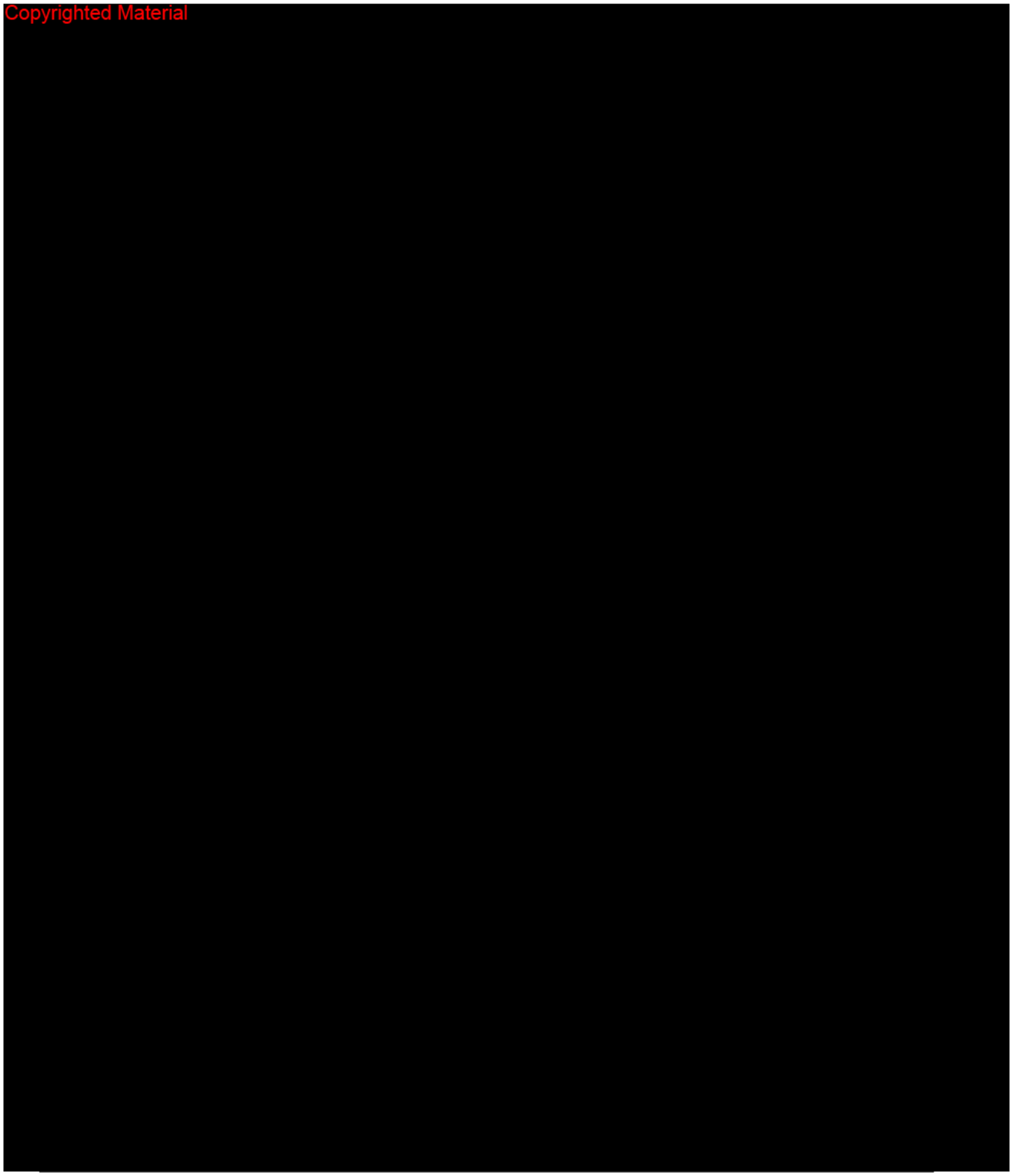


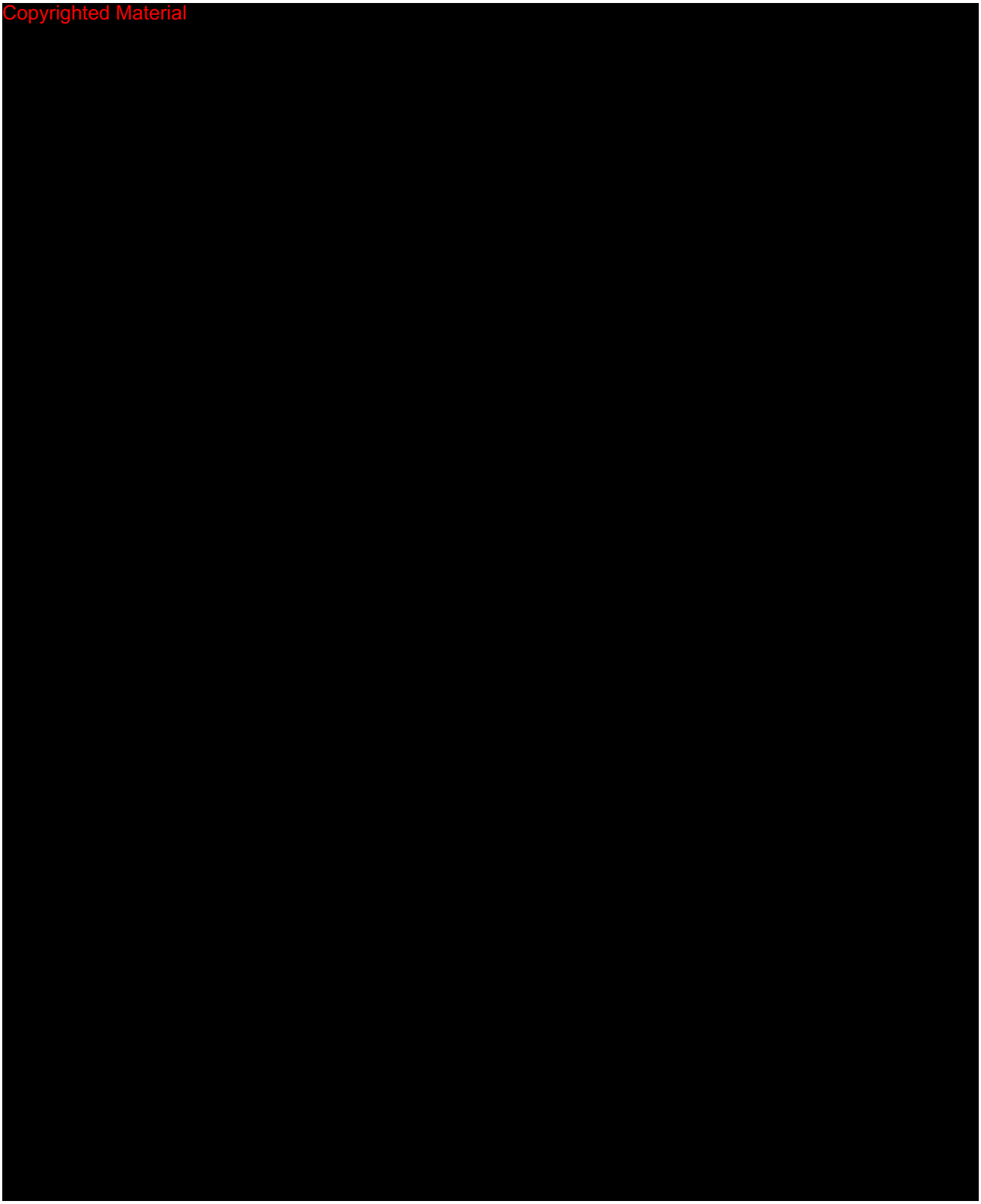


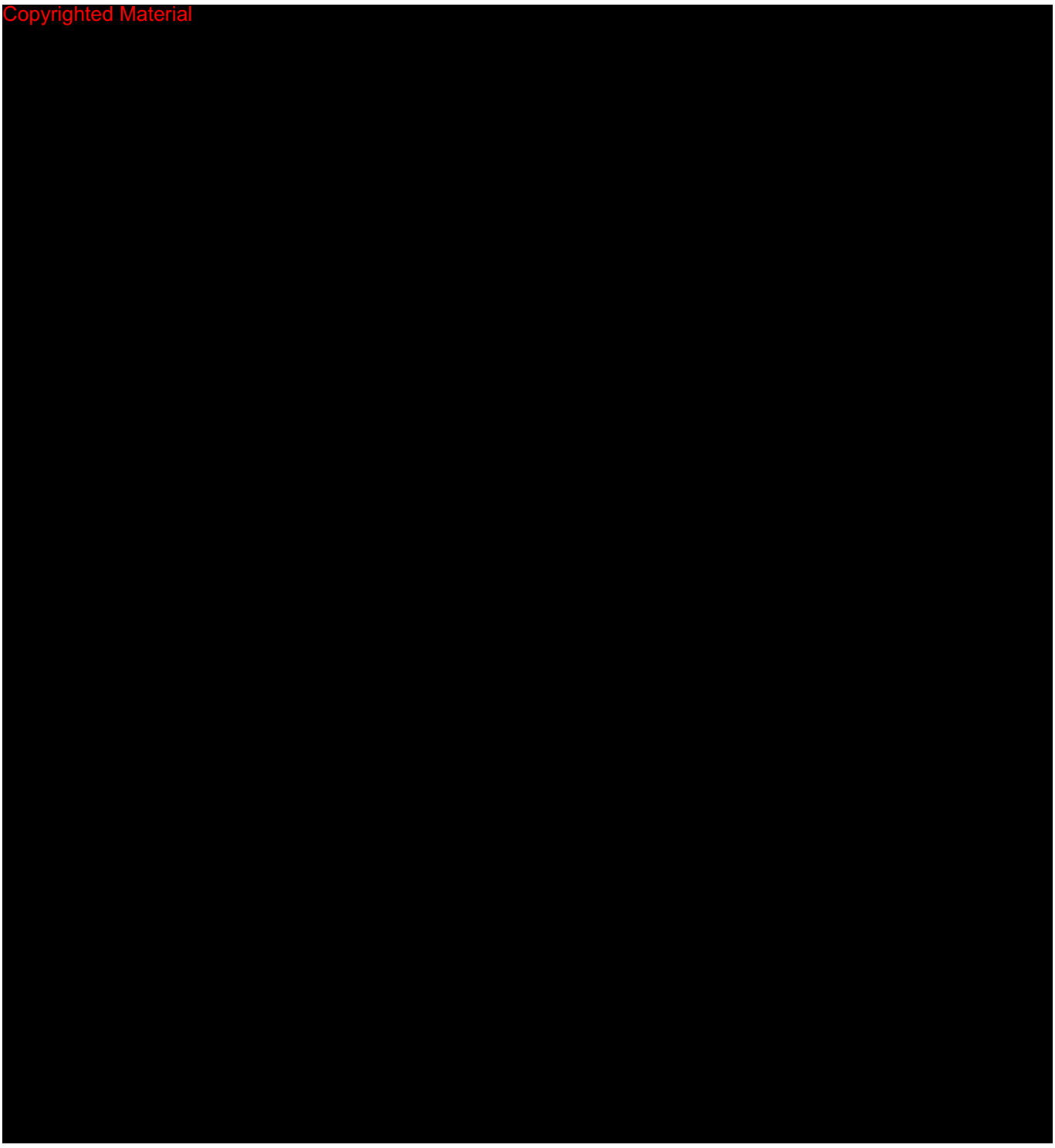


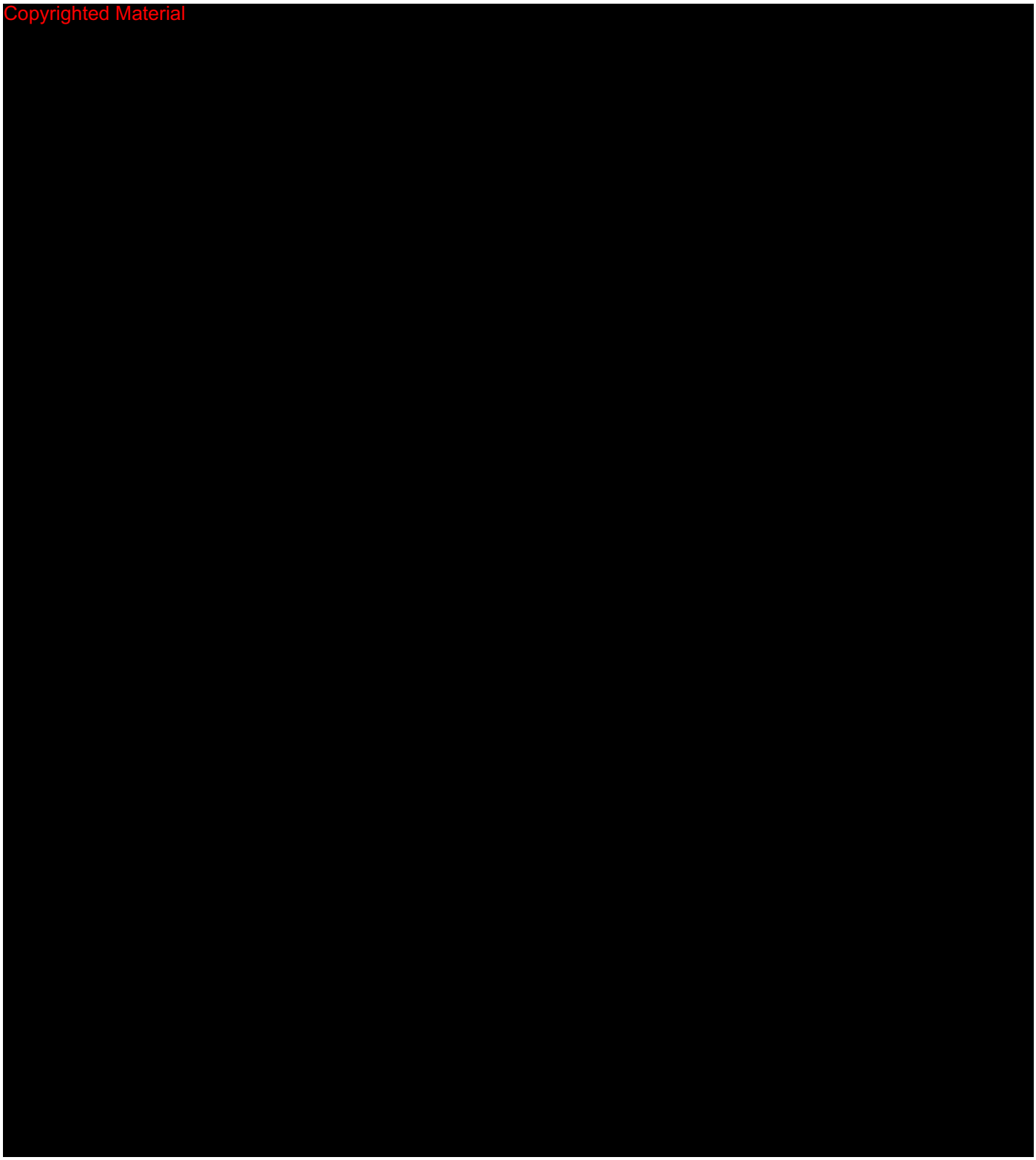












Appendix 8. Patient Global Impression of Severity (PGIS)

Please rate the severity of your Crohn Disease over the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

(None) (Extremely Severe)

Appendix 9. Common Terminology Criteria for Adverse Events v4.0 (CTCAE)-Dermatology

The NCI Common Terminology Criteria for Adverse Events v4.0 is a descriptive terminology that can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term. One page of the Dermatology/Skin Category is presented, which contains listings for Pruritus, Rash/Desquamation, and Rash: Acne/acneiform.

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self-care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	-
Definition: A disorder characterized by an intense itching sensation.					
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	-	-
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker purple color and eventually become a brownish-yellow color.					
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life- threatening consequences	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.					

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADL	-	-
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.					

Rash/desquamation and erythema multiforme progressing to Grade 2, acne/acneiform rash or pruritus progressing to Grade 3 are the severity levels for permanently discontinuing a subject from IP.

Pruritus progressing to Grade 2 sustained (>4 days) is caused to permanently discontinue IP.

Appendix 10. Prohibited Concomitant Medications

This is not an all-inclusive list. Study personnel should stay current and consult with their pharmacy to exclude all concomitant medications that are either moderate to potent CYP3A inhibitors or inducers or substrates, strong P-glycoprotein (P-gp) inhibitors, substrate of MDR1, or substrate of OCT2/MATE.

Moderate to Potent CYP3A Inhibitors*	Moderate to Potent CYP3A Inducers**	Substrates of CYP3A	Strong P-gp inhibitors	Substrates of MDR1	Substrates of OCT2/MATE
Amprenavir	Avasimibe#	Simvastatin or Simvastatin-containing products	Quinidine	Digoxin	Dofetilide
Amiodarone	Bosentan				
Aprepitant	Barbiturates				
Atazanavir	Carbamazepine#				
Boceprevir	Efavirenz				
Casopitant	Etravirine				
Cimetidine	Mitotane#				
Ciprofloxacin	Modafinil				
Clarithromycin#	Nafcillin				
Cobicistat#	Phenobarbital#				
Conivaptan#	Phenytoin#				
Darunavir	Rifabutin#				
Diethyldithiocarbamate	Rifampin #				
Diltiazem	St. John's Wort#				
Dronedarone	Talviraline				
Elvitegravir#					
Erythromycin					
Fluconazole					
Fluvoxamine					
Imatinib					
Indinavir#					
Itraconazole#					
Ketoconazole#					
Lopinavir#					
Mibefradil#					
Mifepristone (RU486)					
Nefazodone#					
Nelfinavir#					
Norfloxacin					
Posaconazole#					
Ritonavir #					
Saquinavir#					
Schisandra sphenanthera					
Telaprevir					
Telithromycin#					
Tipranavir#					
Tofisopam					
Troleandomycin#					
Verapamil					

Moderate to Potent CYP3A Inhibitors*	Moderate to Potent CYP3A Inducers**	Substrates of CYP3A	Strong P-gp inhibitors	Substrates of MDR1	Substrates of OCT2/MATE
Voriconazole#					

* All prohibited drugs that are CYP3A inhibitors require at least a 7 day or 5 half-lives (whichever is longer) prior to the first dose of study drug. Note: Amiodarone requires discontinuation at least 290 days (~5 half-lives, half-life averages ~58 days) prior to the first dose of study drug.

** All prohibited drugs that are CYP3A inducers require at least a 28 day or 5 half-lives (whichever is longer) prior to the first dose of study drug.

\# Noted as potent inhibitors or inducers.

It is recommended that subjects avoid consumption of grapefruit juice exceeding 8 ounces (~240 ml) total in a day while in the study.

In a situation where appropriate medical care of a subject requires the use of a prohibited CYP3A inhibitor or inducer:

Moderate to potent inhibitors and inducers of CYP3A are not permitted in the study EXCEPT in emergency situations requiring no more than one day of administration. ***Note: Amiodarone and mitotane are not permitted for any duration due to their long half-lives.*** Topical (including skin or mucous membranes) application of antimicrobial and antifungal medications is permitted.

Appendix 11. Summary of Corticosteroid Equivalents

Compound	Equivalent Dose (mg)
Prednisone	10
Prednisolone	10
6α-methylprednisolone	8
Triamcinolone	8
Betamethasone	1.2
Dexamethasone	1.5
Hydrocortisone	40
Cortisone	50
Deflazacort	12
Cloprednol	5
Prednylidene	12
Note: these dose relationships apply to oral administration	

Appendix 12. Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

All procedures should be performed per protocol Schedule of Activities to monitor the safety of the participant.

If the sponsor determines that the impact of COVID-19 on protocol visits and procedures and associated timeframe needs to be reported on a CRF, this will be requested.

In situations where participants are quarantined, self-isolating or unable to visit the study site, the participant verbal consent must be documented in the site's source documents prior to performing any protocol procedures or shipping study intervention.

Appendix 12.1. Eligibility

Not Applicable.

Appendix 12.2. TeleHealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits.

Telehealth visits may be used to continue to assess participant safety and collect data points, (if permitted by law or local guidance). Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit.

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing (as available). Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 4.4.1 and Section 7.1.4.

- In situations where participants are unable to attend sites for protocol required pregnancy testing, the participant should, if possible, visit a local laboratory for pregnancy testing (where allowable by law or local guidance). If this is not possible, the study site should make every effort to develop a plan to provide a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL to be performed by the participant at home. The site should document the pregnancy test outcome in a source document and enter the result into the study database and/or CRF as required.

Study participants must be reminded to promptly notify site staff about any change in their health status.

Appendix 12.3. Alternative Facilities for Safety Assessments

Appendix 12.3.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory: See SoA.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

Appendix 12.4. Investigational product

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention (investigational product) must be considered. For participant discontinuation reporting in the CRF: select the most appropriate status for discontinuation; if the discontinuation is associated with the current COVID-19 pandemic, enter "COVID-19" in the "Specify Status" field.

Investigational product may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the investigational product. Pfizer does not permit the shipment of investigational product by mail. The tracking record of shipments and the chain of custody of investigational product must be kept in the participant's source documents/medical records.

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study treatment/intervention must be considered. For participant discontinuation reporting in the CRF: select the most appropriate status for discontinuation; if the discontinuation is associated with the current COVID-19 pandemic, enter "COVID-19" in the "Specify Status" field.

Appendix 12.5. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit: See SoA.

Appendix 12.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. Temporary discontinuation of the study intervention (investigational product) may be medically appropriate until the participant has recovered from COVID-19. See Section 6.5 Guidelines for Monitoring and Discontinuations.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention (investigational product) with the study medical monitor.

For participant discontinuation reporting in the CRF, select the most appropriate status for discontinuation; if the discontinuation is associated with the current COVID-19 pandemic, enter "COVID-19" in the "Specify Status" field.

Appendix 12.7. Patient Reported Outcomes (PROs)

Patient-Centered Outcome Assessments (PCOAs) that were to be administered (via a provisioned site-based device) at the site per protocol may be administered by qualified site personnel via telehealth, if permitted by local regulations, laws, and guidance from regulatory authorities.

- To avoid influencing the study participants' responses, it is recommended that the PCOA questionnaires be administered via telehealth prior to any site staff interactions for other reasons.

- Site staff performing the PCOA administration via telehealth should:

- Conduct this telehealth interaction in a quiet, private area and ask the study participant also to go to a similar setting in which the study participant's safety, privacy and ability to complete the assessment and provide accurate data without interruption or third party input or influence is adequate;

- Read the full text including all instructions, questions, and response choices verbatim and mark the response choice selected by the participant; site staff can read the PCOA from the paper source or provisioned site-based device, but the site staff must read exactly as that specific PCOA appears on the paper source or site provisioned device;

- Speak clearly and at a comfortable pace;

- Let the study participant know that the instructions, question, or response options can be re-read at any time if needed;

- Not interpret any part of the questionnaire for the study participant. If the study participant does not understand, the site staff should repeat the question and response choices verbatim and ask the participant to select the response that they feel best represents his/her experience;

- Encourage the study participant to answer based on his/her first instincts and remind the study participant that there are no right or wrong answers. If needed, use a prompt such as "Which answer most closely matches what you are thinking or feeling?";

- Confirm the study participant's response selection before you record the answer (eg, you would like me to select "moderate pain," is that right?;

- Indicate that the PCOA was administered via telehealth;

- For the telehealth administration of a paper PCOA, indicate this on the participant worksheet (ie, the participant facing source document). Include the name of the site staff administering the PCOA and confirm that the study participant was the one to answer the questions;

- For PCOAs that are collected via telehealth, the PCOA CRF must be completed. Document the administration and completion date in the CRF.

Table A.3

DETERMINE OPTIMAL STANDARD WEIGHT FOR CDAI CALCULATION

Rows Highlighted in Yellow are linear Extrapolated

1999 METROPOLITAN HEIGHT AND WEIGHT TABLES FOR
MEN ON METRIC BASIS According to Frame, Ages 25-59
Weight in kg (In Indoor Clothing)* (*Indoor clothing weighing 2.3 kg for men.)

		WEIGHT (kg)		
GENDER	HEIGHT (cm) Without Shoes	SMALL FRAME	MEDIUM FRAME	LARGE FRAME
Male	153	58.8	61.0	64.4
Male	154	59.1	61.3	64.8
Male	155	59.4	61.6	65.2
Male	156	59.7	61.9	65.6
Male	157	60.0	62.2	66.0
Male	158	60.4	62.6	66.5
Male	159	60.7	62.9	66.9
Male	160	61.1	63.3	67.4
Male	161	61.4	63.7	67.8
Male	162	61.8	64.1	68.4
Male	163	62.2	64.6	68.9
Male	164	62.5	65.0	69.4
Male	165	62.9	65.5	70.0
Male	166	63.2	66.0	70.6
Male	167	63.7	66.6	71.2
Male	168	64.1	67.1	71.8
Male	169	64.6	67.6	72.4
Male	170	65.0	68.1	73.0
Male	171	65.5	68.7	73.7
Male	172	65.9	69.2	74.3
Male	173	66.3	69.7	74.9
Male	174	66.8	70.3	75.5
Male	175	67.3	70.8	76.2
Male	176	67.7	71.3	76.8
Male	177	68.1	71.9	77.4
Male	178	68.6	72.4	78.1
Male	179	69.1	73.0	78.7
Male	180	69.6	73.6	79.3
Male	181	70.2	74.3	80.0
Male	182	70.8	74.9	80.7
Male	183	71.4	75.5	81.4
Male	184	72.0	76.2	82.1
Male	185	72.7	76.9	82.9
Male	186	73.3	77.6	83.7
Male	187	73.9	78.2	84.5
Male	188	74.5	78.8	85.3

GENDER	HEIGHT (cm) Without Shoes	WEIGHT (kg) SMALL FRAME	MEDIUM FRAME	LARGE FRAME
Male	189	75.3	79.6	86.2
Male	190	76.0	80.4	87.1
Male	191	76.7	81.2	88.0
Male	192	77.4	82.1	88.9
Male	193	78.1	82.9	89.8
Male	194	78.8	83.8	90.7

1999 METROPOLITAN HEIGHT AND WEIGHT TABLES FOR

WOMEN ON METRIC BASIS According to Frame, Ages 25-59

Weight in kg (In Indoor Clothing)* (*Indoor clothing weighing 1.4 kg for women.)

GENDER	HEIGHT (cm) Without Shoes	WEIGHT (kg) SMALL FRAME	MEDIUM FRAME	LARGE FRAME
Female	143	47.4	51.2	55.4
Female	144	47.8	51.6	55.9
Female	145	48.1	52.0	56.3
Female	146	48.5	52.4	56.8
Female	147	48.8	52.8	57.2
Female	148	49.0	53.1	57.7
Female	149	49.3	53.6	58.0
Female	150	49.6	54.1	58.6
Female	151	50.0	54.5	59.0
Female	152	50.4	55.0	59.6
Female	153	50.9	55.4	60.2
Female	154	51.3	55.9	60.7
Female	155	51.7	56.4	61.2
Female	156	52.3	57.0	61.9
Female	157	52.8	57.5	62.5
Female	158	53.3	58.1	63.1
Female	159	53.8	58.6	63.7
Female	160	54.4	59.1	64.3
Female	161	54.9	59.6	64.9
Female	162	55.5	60.2	65.5
Female	163	56.0	60.7	66.1
Female	164	56.6	61.3	66.8
Female	165	57.1	61.9	67.5
Female	166	57.6	62.4	68.1
Female	167	58.2	62.9	68.7
Female	168	58.7	63.4	69.3
Female	169	59.2	63.9	69.9
Female	170	59.7	64.5	70.5
Female	171	60.3	65.0	71.2
Female	172	60.8	65.5	71.7
Female	173	61.3	66.0	72.2

		WEIGHT (kg)		
GENDER	HEIGHT (cm) Without Shoes	SMALL FRAME	MEDIUM FRAME	LARGE FRAME
Female	174	61.9	66.6	72.8
Female	175	62.5	67.2	73.3
Female	176	63.0	67.7	73.8
Female	177	63.5	68.3	74.4
Female	178	64.0	68.8	74.9
Female	179	64.6	69.3	75.5
Female	180	65.1	69.8	76.0
Female	181	65.6	70.3	76.5
Female	182	66.1	70.8	77.0
Female	183	66.6	71.3	77.5
Female	184	67.1	71.8	78.0