Clinical Study Protocol

INCB 54707-202

A Phase 2, Open-Label, Single-Arm Study of the Safety of INCB054707 in Participants With Hidradenitis Suppurativa

Product:	**INCB054707**
IND Number:	**137,156**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**07 DEC 2017**
Amendment (Version) 1	**19 JUL 2018**

INVESTIGATOR'S AGREEMENT

I have read the INCB 54707-202 Protocol Amendment 1 (Version 1 dated 19 JUL 2018) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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[redacted]

LIST OF TABLES

LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this clinical study Protocol.

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AN	abscess and inflammatory nodule
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BALT	bronchial-associated lymphoid tissue
CFR	Code of Federal Regulations
Cl/F	apparent oral dose clearance
CRF	case report form
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CYP	cytochrome P450
DLQI	Dermatology Quality of Life Index
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
EOT	end of treatment
EOS	end of study
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HiSCR	Hidradenitis Suppurativa Clinical Response
[redacted]	[redacted]
HIV	human immunodeficiency virus
HS	hidradenitis suppurativa
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation

Abbreviation	Definition
ID	identification
IEC	independent ethics committee
[redacted]	[redacted]
IL	interleukin
IPL	intense pulsed light
IRB	institutional review board
ITT	intent to treat
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Affairs
Nd:YAG	Neodymium-doped yttrium aluminium garnet; Nd:$Y_3Al_5O_{12}$
NRS	numeric rating scale
PGIC	Patient Global Impression of Change
P-gp	P-glycoprotein
[redacted]	[redacted]
PK	pharmacokinetic
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	ribonucleic acid
SAE	serious adverse event
SOP	standard operating procedure
STAT	signal transducer and activator of transcription
TB	tuberculosis
TEAE	treatment-emergent adverse event
Th	T helper cell
TNF-α	tumor necrosis factor alpha
TYK	tyrosine kinase
ULN	upper limit of normal
V_d/F	apparent volume of distribution after non-intravenous administration
WBC	white blood cell

1. PROTOCOL SUMMARY

Protocol Title: A Phase 2, Open-Label, Single-Arm Study of the Safety of INCB054707 in Participants With Hidradenitis Suppurativa

Protocol Number: INCB 54707-202

Objectives and Endpoints

Table 1 presents the primary and key secondary objectives and endpoints.

Table 1: Primary and Key Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of INCB054707.	• Frequency, duration, and severity of AEs, clinical laboratory test results, vital signs results, ECGs, and physical examination findings.
Key Secondary	
To evaluate the systemic exposure to INCB054707.	• Population PK parameters of INCB054707.
To evaluate the efficacy of INCB054707.	• Proportion of participants with a HiSCR at each visit. • Proportion of participants achieving an AN count of 0 to 2 at each visit. • Mean change from baseline in the HS Pain NRS scores, worst and average pain, at each visit. • Mean change from baseline to Week 8 in the modified Sartorius scale score. • Mean change from baseline in the number of draining fistulas count at each visit. • Proportion of participants at each category of Hurley Stage at baseline and Week 8. • Proportion of participants with change from baseline in Hurley Stage at Week 8. • Proportions of participants in each HS-PGIC category during the treatment period.

Overall Design:

Table 2 presents the key study design elements. Further study details are presented after the table.

Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	HS
Population	Men and women aged 18 to 75 years with moderate to severe HS for at least 6 months
Number of Participants	Approximately 10 participants are expected to be enrolled.
Study Design	Multicenter, open-label, and single-arm
Estimated Duration of Study Participation	Up to 28 days for screening, an 8-week open-label, single-arm treatment period, and a 4-week safety follow-up period. The estimated total duration of study participation is approximately 16 weeks for each participant.
Data Safety Monitoring Board	No

Treatment Groups and Duration:

The study design is shown in Figure 1. The schedule of assessments is detailed in Table 3.

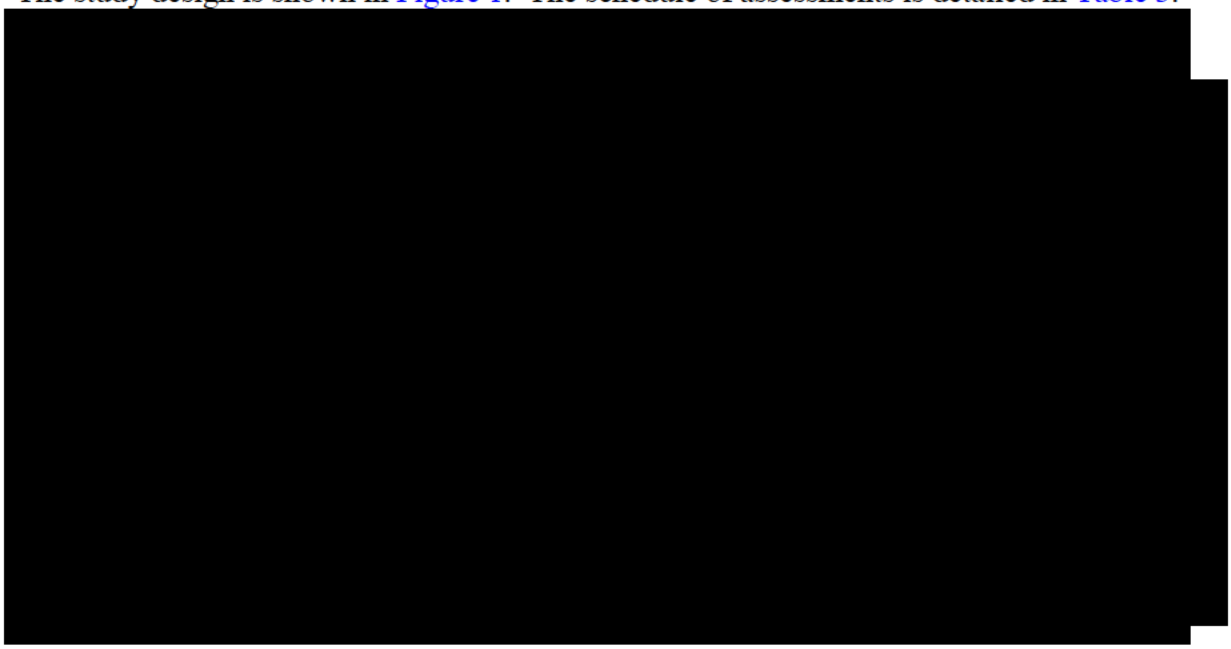


Table 3: Schedule of Assessments

Evaluation	Section	Screening	Treatment						Follow-Up
		Day -28 to -1	Day 1[a]	Wk 1 ± 1 day	Wk 2 ± 3 days	Wk 4[a] ± 3 days	Wk 6 ± 3 days	Wk 8[a] ± 3 days (EOT)	Wk 12 + 7 days (EOS)
Administrative/screening procedures									
Informed consent	8.1.1	X							
Demography/medical history	8.1.4	X							
Inclusion/exclusion criteria	5	X	X						
Prior/concomitant medications	6.6	X	X	X	X	X	X	X	X
Serology	8.3.5.2	X							
Urinalysis	8.3.5.2	X							
TB screening	8.3.5.2	X							
FSH[b]	8.3.5.2	X							
Pregnancy test[c]	8.3.5.3	X	X	X	X	X	X	X	X
Dispense study drug	6.1		X			X			
Distribute reminder cards	8.1.3	X	X	X	X	X	X	X	
Distribute diary	8.1.3	X	X	X	X	X	X	X	
Collect study drug and assess compliance	6.4			X	X	X	X	X	
Safety procedures/assessments									
Comprehensive physical examination	8.3.2	X						X	
Targeted physical examination	8.3.2		X	X	X	X	X		X
Vital signs	8.3.3	X	X	X	X	X	X	X	X
Hematology and chemistry assessments	8.3.5.1, 8.6	X	X	X	X	X	X	X	X
Lipid panel	8.3.5.1		X					X	
CRP	8.3.5.1		X					X	
12-lead ECG (screening)[d]	8.3.4	X							
12-lead ECG (predose and postdose)[d]	8.3.4		X						
12-lead ECG (postdose only)[d]	8.3.4				X		X		
12-lead ECG (predose only)[d]	8.3.4							X	
Assess AEs	8.3.1, 9	X	X	X	X	X	X	X	X
Efficacy assessments									
Hurley Stage	8.2.1	X	X					X	X
AN count (HiSCR)	8.2.2	X	X	X	X	X	X	X	X
Modified Sartorius score	8.2.3		X					X	X
Record rescue lesional treatment	8.2.4			X	X	X	X	X	X
HS Pain NRS[e]	8.2.5	X	X	X	X	X	X	X	X
Analgesic use	8.2.6	X	X	X	X	X	X	X	X
HS-PGIC	8.2.7			X	X	X	X	X	X
DLQI	8.2.8	X	X	X	X	X	X	X	X
Optional photography (target area)	8.2.9		X			X		X	

Table 3: Schedule of Assessments (Continued)

2. INTRODUCTION

INCB054707 is a JAK1 inhibitor. Janus kinase signaling regulates many different proinflammatory signaling pathways and is now well-recognized as a key driver for numerous inflammatory skin diseases. [redacted]

2.1. Background

2.1.1. Hidradenitis Suppurativa

Hidradenitis suppurativa is a chronic disease characterized by recurrent, painful, deep-seated, rounded nodules and abscesses of apocrine gland-bearing skin. Abscesses typically rupture and release purulent drainage. Abscesses and nodules may heal with scarring and the formation of fistulas or sinus tracts (Revuz 2009). Thus, many patients with HS develop permanent sequelae of past inflammation that are only remediable through surgical excision of the involved skin areas. Onset is usually after puberty, although it is most common during the third decade of life and may persist in old age. The prevalence rate is about 1% (range: 0.2%-4%; Jemec et al 1996, Revuz et al 2008). Axillary and inguinal involvement is more common in females; perianal and buttocks localizations are prevalent in males. Genetic susceptibility, smoking, and obesity are important risk factors for the development of HS. An association between HS and metabolic syndrome has recently been established (Miller et al 2014).

Hidradenitis suppurativa significantly affects healthcare costs and health-related quality of life. A recent study indicates that HS imposes a greater negative impact on quality of life than does psoriasis (Hamzavi et al 2017). Rare complications of HS include fistula formation into the urethra, bladder, rectum, or peritoneum; lymphedema of the limbs or scrotal elephantiasis; and squamous cell carcinomas of the skin originating from HS lesions.

The pathogenesis of HS has not yet been fully elucidated. It has been suggested that follicular plugging followed by the release of follicular material into the dermis are primary events that activate the immune system. Defects in host defense mechanisms as well as innate and adaptive immunity may also contribute. Unravelling which cytokines are involved has been the main objective of several studies. Recently, it has been shown that the IL-23/Th17 and IL-12/Th1 pathways are expressed in HS skin (Schlapbach et al 2011). Although TNF-α presents in inflammatory HS skin, several studies indicate that it may not be one of the key contributors in the pathogenesis of this disease (Kelly et al 2015, van der Zee et al 2012, Moran et al 2017), suggesting opportunities for other potential therapeutic targets.

2.1.2. Current Treatment and Unmet Need in Hidradenitis Suppurativa

Treatment of HS depends on the extent and activity of disease. Current European guidelines for the treatment of HS generally recommend topical clindamycin or oral tetracycline as first-line therapy for mild disease (Gulliver et al 2016, Zouboulis et al 2015). For moderate to severe disease, oral clindamycin and rifampin combination therapy are used as first-line treatment, and adalimumab (TNF-α inhibitor) is used as a second-line treatment. Of note, the latter is the only

US FDA-approved systemic therapy for HS. In more severe cases with extensive scarring, surgical intervention is used to remove the nondynamic components of HS (eg, scarring, fistulas, and sinus tracts) that are not expected to respond to drug therapy. These comprise a number of surgical procedures (eg, incision and drainage, de-roofing, and excision) laser (Nd:YAG) and radiation therapy (Jemec 2012). Other systemic/pharmacologic therapies include drugs such as acitretin, isotretinoin, dapsone, antiandrogens (in female patients), intralesional injections of triamcinolone, and a number of TNF-α inhibitors (Rambhatla et al 2012).

Given that the current pharmacologic treatments are moderately effective at best, are not approved for HS (except for adalimumab), and are often associated with significant side effects, there is a need for new effective agents for the treatment of HS. Although several biologic agents are undergoing clinical investigation at this time (IL-17 inhibitors: bimekizumab and secukinumab), an oral treatment with a JAK1-inhibitor such as INCB054707 has the potential to address an unmet medical need for patients with HS.

2.1.3. JAK-STAT Signaling in Inflammatory Skin Disease

The JAK family of kinases includes JAK1, JAK2, JAK3, and TYK2. The JAK-STAT pathway is used by cytokines including ILs, interferons, and other molecules to transmit signals from the cell membrane to the nucleus. Upon engagement of extracellular ligands, intracellular JAK proteins, which associate with type I/II cytokine receptors, become activated and phosphorylate STAT proteins, which dimerize and then translocate into the nucleus to directly regulate gene expression. Among all JAK family members, JAK1 signaling relates primarily to cytokines involved in inflammation (Rawlings et al 2004).

Numerous inflammatory dermatoses are driven by soluble inflammatory mediators, which rely on JAK-STAT signaling. [redacted]

To date in dermatology, psoriasis has been the most heavily studied indication for JAK inhibitors including tofacitinib, baricitinib, and ruxolitinib. The sponsor has completed 4 clinical studies with JAK1 and JAK2 inhibitors for the treatment of psoriasis. Both topical ruxolitinib (Punwani et al 2015) and oral INCB039110 (Bissonnette et al 2013) have been associated with clinical improvement and benefit in patients with chronic plaque psoriasis. [redacted]

2.1.4. INCB054707

INCB054707 potently inhibits JAK1 with approximately 45- to > 1000-fold selectivity over other JAK family members (ie, JAK2, JAK3, and TYK2). It is highly selective in that it does not significantly inhibit a broad panel of other kinases. INCB054707 is being developed for oral administration, a route of administration that is widely used and helps promote patient compliance with medication dose administration. Preclinical *in vitro* results indicate that INCB054707 inhibits T-cell proliferation and production of proinflammatory cytokines (eg, IL-17). *In vivo*, INCB054707 is efficacious in animal models of rheumatoid arthritis and psoriasis.

2.2. Study Rationale

Given that TNF-α may not be the major driver for HS pathogenesis, and that there is a relatively high number of patients who do not sufficiently respond to therapy with the only approved HS medication impacting that pathway (adalimumab, a TNF-α inhibitor), there remains a significant unmet need for new treatments for HS.

2.2.1. Scientific Rationale for Study Design

Recent literature suggests that the main cytokines involved in HS pathogenesis are IL-1β, IL-17, IL-23, IL-10, and, to a lesser extent, TNF-α (Kelly and Prens 2016). The expression and/or activity of these cytokines is mediated at the intracellular level through JAK-STAT signaling, and primarily JAK1 inhibition (see Section 2.1.3).

In the current study, the clinical safety and efficacy of 15 mg QD INCB054707 will be evaluated in adult participants with moderate to severe HS. The primary endpoint is to evaluate the safety and tolerability of INCB054707.

For participants experiencing bothersome symptoms related to either rapid abscess formation or secondary infection at the diseased sites, appropriate rescue treatments will be offered to immediately evacuate pus (incision and drainage), alleviate the level of inflammation (intralesional triamcinolone), or control infection (see Sections 6.6.2 and 8.2.4)

It is expected that the outcome of this study will be instrumental in informing the dose-ranging Phase 2b study.

2.2.2. Justification of Dose

[redacted]

This study will evaluate up to 8 weeks of oral self-administration of INCB054707 15 mg QD. The selected dose is within a dose range previously shown to be safe and well-tolerated in 10 days of administration in healthy participants as well as within the estimated safety margins using the exposures at the no-observed-adverse-effect-levels from the 6-month toxicity study in the rat and the 9-month toxicity study in the dog. Approximately 10 participants with moderate to severe HS will be enrolled.

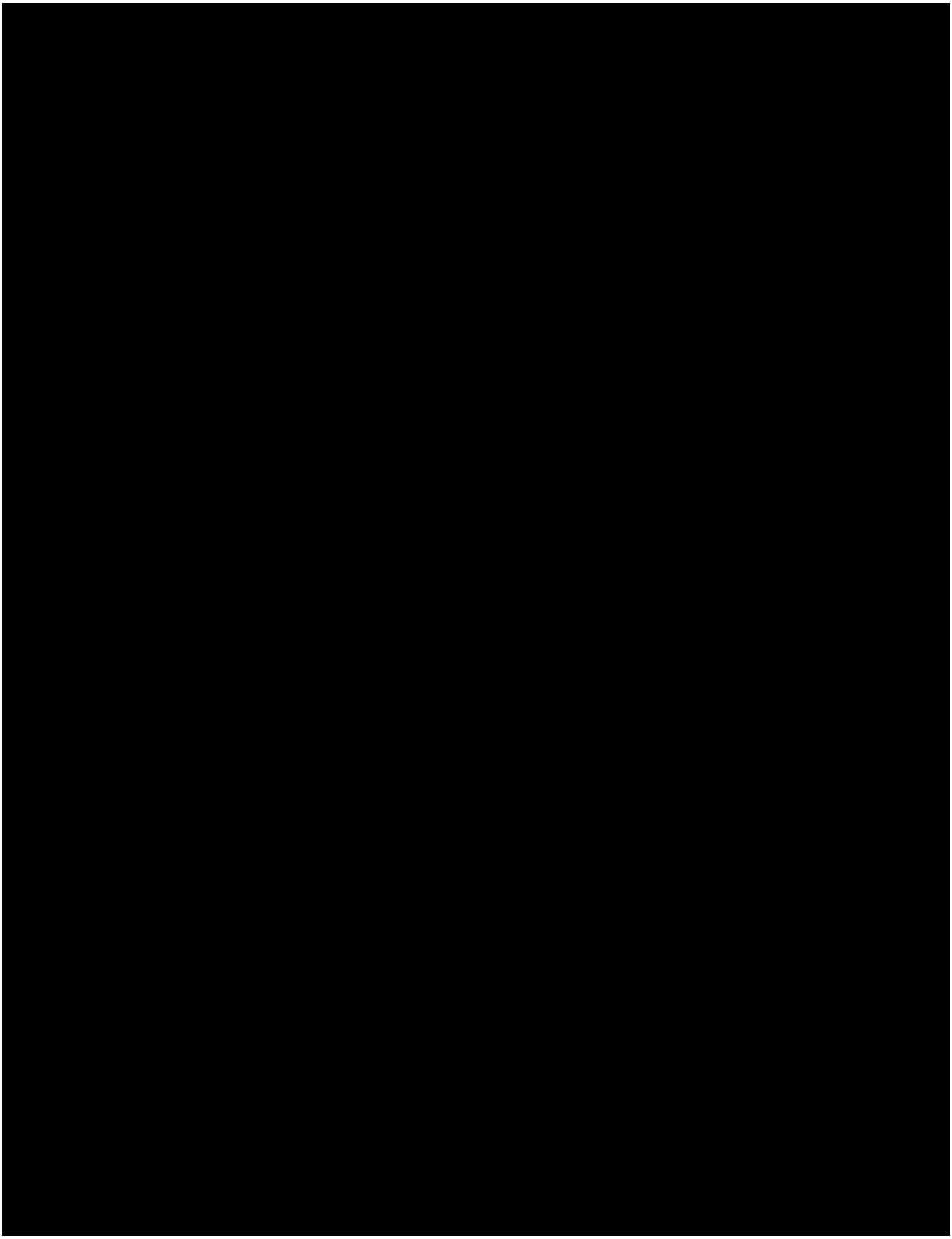
[redacted]

- [redacted]

2.3.2. Clinical Studies

In 2 healthy volunteer studies with single doses of INCB054707 up to 405 mg, multiple doses of INCB054707 up to 120 mg, or placebo for up to 10 days, mild to moderate headaches were reported in up to 31% of participants in the multiple-dose study. The events resolved spontaneously following discontinuation of INCB054707.

[redacted]



2.3.3. Benefit Assessment

Participants may experience clinically meaningful improvements in their HS lesions during the study and may additionally benefit from the comprehensive safety assessments conducted as part of the study (eg, clinical laboratory tests, physical examinations, ECGs).

They will also contribute to the process of developing a novel anti-inflammatory agent for HS, a disease with high unmet need that is severely debilitating to participants' well-being and daily functioning.

2.3.4. Benefit-Risk Conclusion

Taking into account the safety measures taken to minimize risk to participants in this study, the potential risks identified in association with INCB054707 are justifiable and appropriately balanced by the anticipated efficacy benefits expected to be afforded to this specific group of participants and, more broadly, to the general population of patients with HS. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of INCB054707 may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

Table 5 presents the objectives and endpoints.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of INCB054707.	• Frequency, duration, and severity of AEs, clinical laboratory test results, vital signs results, ECGs, and physical examination findings
Secondary	
To evaluate the systemic exposure to INCB054707.	• Population PK parameters of INCB054707.
To evaluate the efficacy of INCB054707.	• Proportion of participants with a HiSCR at each visit. • Proportion of participants achieving an AN count of 0 to 2 at each visit. • Mean change from baseline in the HS Pain NRS scores, worst and average pain, at each visit. • Mean change from baseline to Week 8 in the modified Sartorius scale score. • Mean change from baseline in the number of draining fistulas count at each visit. • Proportion of participants at each category of Hurley Stage at baseline and Week 8. • Proportion of participants with change from baseline in Hurley Stage at Week 8 • Proportions of participants in each HS-PGIC category during the treatment period.
To assess the need for rescue lesional treatment.	• Proportion of participants requiring rescue lesional treatment. • Number of interventions with rescue lesional treatment.
To assess patient-reported quality of life burden.	• Proportion of participants at each scoring category of DLQI at each visit.

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, multicenter, open-label, single-arm study to assess the safety of 15 mg QD INCB054707 over 8 weeks in men and women aged 18 to 75 years with moderate to severe HS with a targeted enrollment of up to 10 participants.

Safety assessments include monitoring of AEs, clinical laboratory tests, vital signs, ECGs, and physical examinations.

Efficacy assessments include HiSCR as assessed by the AN count, HS Pain NRS, modified Sartorius scale, draining fistula count, and need for rescue lesional treatment. Quality of life will be assessed using the DLQI (participant-reported). [redacted] Optional medical photographs of a target lesion will be taken at selected anatomic sites to illustrate the outcome of the study.

4.2. Overall Study Duration

The study will consist of a screening period of up to 28 days, an 8-week open-label, single-arm treatment period, and a 4-week safety follow-up period. The estimated total duration of study participation is approximately 16 weeks for each participant.

4.3. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively or if required by regulatory decision. If the study is terminated prematurely, the sponsor or designee will notify the investigators, the IRBs/IECs, and regulatory bodies of the decision and reason for termination of the study.

5. STUDY POPULATION

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or participant safety. Therefore, adherence to the criteria as specified in the Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Men and women aged 18 to 75 years at the time of consent.
2. Diagnosis of HS (confirmed by a dermatologist) with a disease duration of at least 6 months before screening.
3. Stable course of HS for at least 90 days before screening, as determined by the investigator.
4. HS lesions present in at least 2 distinct anatomic areas, 1 of which must be Hurley Stage II (ie, recurrent abscessed with tract formation and cicatrization; single or multiple, widely separated lesions) or Hurley Stage III (ie, diffuse, or near diffuse involvement or multiple interconnected tracts and abscesses across the entire area) at screening and baseline.
5. Total AN count of at least 3 at screening and baseline.
6. Willingness to avoid pregnancy or fathering children based on the criteria below:
    a. Male participants must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through 90 days after the last dose of study drug. Male participants must also refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participant and his understanding confirmed.
    b. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first dose on Day 1 and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    c. Women of nonchildbearing potential (ie, surgically sterile [hysterectomy, bilateral oophorectomy, or bilateral salpingectomy] OR postmenopausal, defined as ≥ 12 months of amenorrhea before screening without an alternative medical cause, confirmed by FSH levels at screening) are eligible.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Women who are currently pregnant or lactating.
2. Presence of > 20 draining fistulas at screening and baseline.
3. Participants with concurrent conditions or history of other diseases, as follows:
   a. Any clinically significant medical condition other than HS, as determined by the investigator, that is not adequately controlled with appropriate treatment.
   b. Any other active skin disease or condition (eg, bacterial, fungal, or viral infection) that may interfere with the course, severity, or assessments of HS.
   c. Active systemic viral infection or any active viral infection that, based on the investigator's clinical assessment, make the participant an unsuitable candidate for the study.
   d. Current herpes zoster infection, a history of recurrent herpes zoster, a history of disseminated herpes simplex, or a history of herpes zoster.
   e. History of malignancy, including lymphoma and leukemia within 5 years before baseline, other than a successfully treated nonmetastatic cutaneous squamous cell carcinoma, basal cell carcinoma, or localized carcinoma *in situ* of the cervix.
   f. Albinism.
4. Prolonged QT interval corrected for heart rate using Fridericia's formula (QTcF), defined as ≥ 450 msec.

   Note: Prolonged QTcF values of ≥ 450 msec at screening are to be confirmed by performing 2 additional ECGs and averaging the results to determine if the averaged value meets the exclusion criterion.
5. Positive test result for TB from the QuantiFERON-TB Gold test, or equivalent, at screening (or, if 2 indeterminate tests or not available, then as evaluated by a purified protein derivative test with a result of < 5 mm of induration within 3 months of screening) or a history of active TB.

   Note: If the participant has possible evidence of a latent TB infection, the participant must have documented completion of an adequate course of therapy for latent TB and provide recent (within 3 months) posteroanterior and lateral views chest x-ray without changes suggestive of active or latent TB, prior to baseline.
6. Positive serology test results for HIV, HBsAg, HBV core antibody, or HCV (HCV-antibody with positive HCV-RNA) at screening.
7. Decreased blood cell counts at screening, defined as follows:
   a. Leukocytes < 3.0×10^9/L (< 2.5×10^9/L for participants who are African-American).
   b. ANC < 1.5×10^9/L.
   c. Lymphocytes < 0.8×10^9/L.
   d. Hemoglobin < 10 g/dL.
   e. Platelets < 150×10^9/L.

8. Severely impaired liver function (Child-Pugh Class C) or ALT or AST levels ≥ 1.5 × ULN.
9. Impaired renal function with serum creatinine > 1.5 mg/dL.
10. Use of the following medications:
    a. Previous use of JAK inhibitors, systemic or topical (eg, ruxolitinib, tofacitinib, baricitinib, filgotinib, lestaurtinib, and pacritinib).
    b. Previous use of adalimumab or any other TNF-α treatment, investigational, or any experimental treatments within 12 weeks or 5 half-lives (whichever is longer) before baseline.
    c. Systemic immunosuppressive or immunomodulating drugs (eg, oral or injectable corticosteroids, methotrexate, cyclosporine, and azathioprine) within 4 weeks or 5 half-lives (whichever is longer) before baseline.
    d. Other systemic therapies for HS (eg, retinoids and antiandrogens) with potential therapeutic impact for HS within 4 weeks or 5 half-lives (whichever is longer) before baseline.
    e. Surgical, laser, or IPL intervention in area with HS lesion within 4 weeks before baseline.
    f. Systemic anti-infectives (eg, antibiotics, antivirals, antifungals) within 4 weeks or topical anti-infectives on HS lesions (eg, antibiotics, antivirals, antifungals) within 2 weeks before baseline.
    g. Received live vaccine within 6 weeks before baseline or planning to receive live vaccine during the course of the study or within 6 weeks after EOT.
    h. Topical antiseptic washes, creams, soaps, ointments, gels, and liquids containing antibacterial agents to treat HS, except those listed in Sections 6.6.2.3 and 6.6.2.4, within 2 weeks before baseline.
    i. Potent systemic CYP3A4 inhibitors and inducers (see Appendix B) or fluconazole within 2 weeks or 5 half-lives (whichever is longer) before baseline.
    Note: Topical agents with limited systemic availability are permitted.
11. Known or suspected allergy to INCB054707 or any component of the study drug.
12. Known history of clinically significant drug or alcohol abuse in the last year prior to baseline.

[redacted]

14. Inability or unlikeliness of the participant to comply with the dose schedule and study evaluations, in the opinion of the investigator.

15. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
16. Inability of the participant (or parent, guardian, or legally authorized representative) to comprehend or unwilling to sign the ICF.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered into the study.

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be in error. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent and be assigned a new participant number.

5.5. Replacement of Participants

No participants will be replaced at any time during this study.

6. STUDY TREATMENT

6.1. Study Treatment Administered

Information regarding study drug and administration is provided in Table 6. Participants will record study drug administration in a daily diary. Participants will take the study drug once daily, preferably in the morning.

Table 6: Study Treatment Information

Study treatment name:	INCB054707
Dosage formulation:	Tablet
Unit dose strength/dosage level:	INCB054707 15 mg QD
Route of administration:	Oral
Administration instructions:	INCB054707 will be taken orally with water without regard to food.
Packaging and labeling:	INCB054707 will be provided as 15 mg tablets and labeled as required per country requirement.
Storage:	Ambient (15°C-30°C/59°F-86°F)

6.2. Preparation, Handling, and Accountability

The investigator (or designee) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Participant use of the study drug including tablet counts from each supply dispensed.
- Return of study drug to the investigator or designee by participants.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that participants were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and participants.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional SOPs. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

Further guidance and information for the final disposition of unused study treatments are provided in the Study Reference Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable. This is an open-label study.

6.4. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with INCB054707 will be calculated by the sponsor based on the drug accountability documented by site personnel and monitored by the sponsor/designee using tablet counts. Participants will be instructed to bring all study drug with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

6.5. Dose Modifications

In some circumstances, it may be necessary to temporarily interrupt treatment with INCB054707 as a result of AEs or laboratory abnormalities that have an unclear relationship to the study drug (see Table 7). Except in cases of emergency, it is recommended that any laboratory findings be confirmed and that the investigator consult with the sponsor medical monitor (or other representative of the sponsor) before temporarily interrupting study drug.

Table 7: Guidelines for Interrupting, Restarting, and Discontinuing Study Drug

ADVERSE EVENT	ACTION TAKEN
Chemistry	
AST and/or ALT > 3.0 × ULN	**Step 1:** Interrupt study drug administration up to 2 weeks (14 days) until the toxicity has resolved to ≤ 3.0 × ULN. **Step 2:** Restart study drug, and monitor as clinically indicated.
AST and/or ALT > 5.0 × ULN	Discontinue study drug administration, and monitor as described in Section 9.3.
Hematology	
Platelet counts 50 to ≤ 100 × 109/L or ≥ 50% decrease from baseline	**Step 1:** Interrupt study drug administration up to 2 weeks (14 days) until the toxicity has resolved to > 100 × 10^9/L. **Step 2:** Restart study drug, and monitor as described in Section 9.3.
ANC ≤ 1.0 × 109/L	**Step 1:** Interrupt study drug administration up to 2 weeks (14 days) until the toxicity has resolved to > 1 × 10^9/L or the baseline value. **Step 2:** Restart study drug, and monitor as clinically indicated.
Hemoglobin 8 to ≤ 10 g/dL	**Step 1:** Interrupt study drug administration up to 2 weeks (14 days) until the toxicity has resolved to > 10 g/dL. **Step 2:** Restart study drug, and monitor as clinically indicated.
• Platelet count < 50 × 10^9/L • ANC < 0.5 × 10^9/L • ANC ≤ 1.0 × 10^9/L with an oral temperature of at least 38.5°C OR with ≥ Grade 3 infection • Hemoglobin < 8 g/dL	Discontinue study drug administration, and monitor as described in Section 9.3.

Table 7: Guidelines for Interrupting, Restarting, and Discontinuing Study Drug (Continued)

ADVERSE EVENT	ACTION TAKEN
Other toxicities	
Any Grade 1 or Grade 2 toxicity	Continue study drug and treat the toxicity; monitor as clinically indicated.
Any Grade 3 toxicity except those that are clearly and incontrovertibly due to underlying disease or extraneous causes	**Step 1:** Interrupt study drug up to 2 weeks (14 days), until toxicity resolves to ≤ Grade 1. **Step 2:** Restart study drug and monitor as clinically indicated.
Any other Grade 4 toxicity	Discontinue study drug administration and follow-up as described in Section 8.7.

Note: The investigator will make an assessment of intensity for each AE and SAE reported during the study and assess severity as described in Section 9.3.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication received up to 28 days before the first dose of study treatment and 28 days after the last dose of study treatment will be recorded in the eCRF.

Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Prior Medications and Therapies

Prior and current medications and procedures will be reviewed to determine eligibility. All medications taken within 28 days before the first dose of study treatment will be recorded in the eCRF. A detailed history of prior medications use related to HS in the year before screening will be also be collected, as well as response to each treatment and reason for discontinuation.

6.6.2. Permitted Medications and Procedures

6.6.2.1. Antibiotic Therapy

After Week 4, if a participant experiences signs or symptoms indicative of an infection at an HS site (eg, fever and local/regional lymphadenopathy), the following antibiotic therapy may be initiated without interruption of study drug administration:

- Amoxicillin 500 mg/clavulanic acid 125 mg, 2 tablets, 3 times daily for 3 days

In participants for whom amoxicillin is contraindicated, the investigators should consult with the sponsor or designee to discuss alternative treatment options.

6.6.2.2. Analgesic Therapy

If a participant experiences significant pain after baseline, one of the following analgesic regimens may be initiated at any time:

- Ibuprofen (at a dose of up to 800 mg orally every 6 hours) not to exceed 3200 mg/24 hours.
- Acetaminophen not to exceed 4 g/24 hours.

If pain is not sufficiently controlled with one of the above regiments, a revised analgesic regiment can be considered in consultation with the sponsor or designee.

Dose adjustments in these analgesics on an as needed basis up to the maximum permitted dose and frequency are allowed during the study.

Analgesic usage (yes/no) will be recorded daily (see Appendix F).

6.6.2.3. Antiseptic Therapy

It is recommended that participants can use a daily antiseptic wash on their HS lesions. Permitted antiseptic washes are limited to one of the following: chlorhexidine gluconate, triclosan, benzoyl peroxide, or diluted bleach in bathwater.

6.6.2.4. Wound Care

Concomitant use of wound care dressings on HS wounds is allowed. Options are limited to alginates, hydrocolloids, and hydrogels.

6.6.3. Prohibited Medications and Procedures

The following medications are prohibited for all participants in the study:

- JAK inhibitors, systemic or topical (eg, ruxolitinib, tofacitinib, baricitinib, filgotinib, lestaurtinib, and pacritinib).
- Adalimumab or any other TNF-α treatment or any experimental treatments.
- Systemic immunosuppressive or immunomodulating drugs (eg, oral or injectable corticosteroids, methotrexate, cyclosporine, and azathioprine).
- Systemic and/or biologic therapies with potential therapeutic impact for HS.
- Surgical, laser, or IPL intervention in area with HS lesion, except as specified in Section 8.2.4 for rescue lesional treatment.
- Systemic anti-infectives (eg, antibiotics, antivirals, and antifungals), except as described in Section 6.6.2.1 for antibiotic therapy, or topical anti-infectives on HS lesions.
- Conventional therapies with potential therapeutic impact for HS.
- Topical antiseptic washes, creams, soaps, ointments, gels, and liquids containing antibacterial agents to treat HS, except those listed in Sections 6.6.2.3 and 6.6.2.4.

- Potent systemic CYP3A4 inhibitors or inducers or fluconazole.

  Note: Topical agents with limited systemic availability are permitted.

- Concomitant uses of P-gp inhibitors and inducers (see Appendix C) need to be consulted with the medical monitor.
- Live vaccines (during the study and within 6 weeks after EOT).

6.6.4. Rescue Lesional Treatments

Rescue lesional treatments are described in Section 8.2.4, as the need for rescue lesional treatment is considered an efficacy assessment.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

Participants **must** be withdrawn from study treatment for the following reasons:

- Consent is withdrawn.

  Note: Consent withdrawn means that the participant can no longer be followed. Participants who choose to discontinue study treatment will be encouraged to remain in the study for safety monitoring.

- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A participant **may** be discontinued from study treatment as follows:

- If, during the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be discontinued from the study treatment.
- If a participant is noncompliant with study procedures or study drug administration in the investigator's opinion, the sponsor should be consulted for discussion regarding the participant's continued participation.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in Table 3 and Section 8.7. The last date of the last dose of study drug and the reason for discontinuation of study treatment will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the participant's medical record and the primary reason for withdrawal must be included in the eCRF.
- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the eCRF.
- Participants must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, participants will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments.

7.2. Participant Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See Table 3 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant will be counseled regarding the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address

or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the country in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Participants must provide consent to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

8.1.2. Screening Procedures

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number.

Screening is the interval between obtaining informed consent and the day of the first administration of study drug (Day 1). Screening assessments for determination of eligibility may be performed over a period lasting up to 28 days.

Procedures conducted as part of the participant's routine clinical management (eg, clinical laboratory tests) and collected before informed consent is obtained may be used for screening or baseline purposes, provided the procedure meets the protocol-defined criteria and has been performed within 28 days before Day 1. All information associated with eligibility requirements, including demography and medical history, must be entered into the appropriate eCRF pages.

Results from the screening assessments will be reviewed to confirm eligibility before administration of study drug. Tests results that do not meet eligibility requirements may be repeated once during screening if the investigator believes there is a reasonable possibility that the participant would be eligible if retested. For screening assessments that are repeated, the most recent available result before administration of study drug will be used to determine eligibility. See Section 5.4 regarding screen failures.

8.1.3. Distribution of Reminder Cards and Diaries

Participants will be provided with a reminder card at the visits indicated at Table 3. The reminder card will indicate the date/time of the next visit and will also remind the participant that they should not take study drug on Day 1, Week 4, and Week 8 visits, as they will take it after blood draws for safety evaluation have been completed. The reminder cards will have an area on which the date and time of the last dose taken (from the previous evening) for Week 4 and Week 8 visits and the time of their last meal before the visit for Day 1, Week 2, Week 4, Week 6, and Week 8 will be recorded.

Diaries will be provided to participants at the visits indicated at Table 3 to record HS pain NRS (see Section 8.2.5) and analgesic use (see Section 8.2.6).

8.1.4. Demography and Medical History

8.1.4.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include date of birth, race, ethnicity, medical and surgical history, and current illnesses. Medical history will include relevant medical or surgical treatment within the last year that are considered to be clinically significant by the investigator.

8.1.4.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. A detailed history of prior medications use related to HS in the year before screening will be also be collected, as well as response to each treatment and reason for discontinuation.

8.2. Efficacy Assessments

An example of the lesion count worksheet is provided in Appendix D and will be used for assessment of Hurley Stage, HiSCR, modified Sartorius scale, and [redacted] (see Section 8.5.3). It includes assessment of 12 anatomic regions: left/right axilla, left/right sub/inframammary area, intermammary area, left/right buttock, left/right inguino-crural fold, perianal area, perineal area, and other areas. Additionally, the need for rescue lesional treatment, including number of interventions, will be documented in this worksheet.

8.2.1. Hurley Stages of Hidradenitis Suppurativa

Hurley Stages of HS are defined in Table 8. The investigator will determine the Hurley Stage in each affected anatomical region at the designated study visits listed in Table 3. If more than 1 stage is present in a region, the worst stage in each region should be documented. The participant is assigned Hurley Stage corresponding to the Hurley Stage of his or her worst involved anatomic region.

Table 8: Hurley Stages of Hidradenitis Suppurativa

Stage	Description
I	abscess formation (single or multiple) without sinus tracts and cicatrization
II	recurrent abscesses with tract formation and cicatrization; single or multiple, widely separated lesions
III	diffuse or near-diffuse involvement or multiple interconnected tracts and abscesses across the entire area

8.2.2. Hidradenitis Suppurativa Clinical Response (Abscess and Inflammatory Nodule Count)

An HiSCR is defined as at least 50% reduction in AN count with no increase in abscess count and no increase in draining fistula (see definition below) count relative to baseline at each visit (see Appendix D; Kimball et al 2016).

A fistula is a pathologic passageway connecting to the skin surface from dermis or subcutaneous tissue. Draining fistulas are fistulas that drain serous or purulent fluid, either spontaneously or by gentle palpation.

8.2.3. Modified Sartorius Scale

The modified Sartorius scale is a measure of the severity of HS (see Appendix D and Appendix E; Sartorius et al 2003).

Points are given as follows for each body area: 2 points for each nodule (both inflammatory and non-inflammatory); 4 points for each abscess; 4 points for each fistula (both draining and non-draining); 1 point for each scar; 2 to 6 points for the longest distance between 2 lesions or 0 points if no lesions; and 6 points if lesions are not separated by normal skin or 0 points if lesions are separated by normal skin. The "other area" only with the highest modified Sartorius scale at baseline will be calculated, and the same area should be evaluated throughout the study. The total modified Sartorius scale score is the sum of the 12 anatomic region scores.

8.2.4. Need for Rescue Lesional Treatment

The need for lesional rescue treatment will be recorded as a measure of efficacy.

In the event of an acutely painful lesion that requires immediate intervention, investigators will have the option to perform protocol-allowed interventions. Two types of interventions are permitted: injection with intralesional triamcinolone acetonide suspension (up to 30 mg in total at the same visit) and/or incision and drainage. If incision and drainage is performed, participants should continue using the same over-the-counter antiseptic as previously. New systemic and topical therapies following incision and drainage, including antibiotics, are prohibited. Concomitant use of wound care dressings is allowed as described in Section 6.6.2.4. Participants should continue using any oral and topical therapies during the study, consistent with the allowances and restrictions described in Section 6.6.2.

From Day 1 through Week 8, an intervention can occur on a maximum of 2 different lesions at the same visit or on the same lesion at 2 different study visits. The same lesion cannot be treated 2 times during the same visit. If participants require more than 2 interventions before Week 8, then study drug will be discontinued for those participants.

Study procedures must be performed before any interventions. Any lesion undergoing an intervention will be documented in the lesion count worksheet (see Appendix D). The site will be required to count any lesion that undergoes an intervention as permanently present from the date of the intervention, and must account for it in the source and on the appropriate eCRF.

8.2.5. Hidradenitis Suppurativa Pain Numeric Rating Scale

The HS Pain NRS (see Appendix F) will be completed in a daily diary by participants from screening through EOS. An 11-point scale will be used to assess the worst skin pain and the average skin pain due to HS. Ratings for the 2 items range from 0 (no skin pain) to 10 (skin pain as bad as you can imagine). Assessments will be recorded before bedtime or midnight (whichever comes first) and will be based on a recall period of the last 24 hours.

8.2.6. Analgesic Use

From screening through EOS, participants will complete a daily diary of their analgesic use (yes/no; see Appendix F). All analgesics and dose adjustments will be captured in the source and on the appropriate eCRF.

8.2.7. Hidradenitis Suppurativa Patient Global Impression of Change

Participants will complete the HS-PGIC questionnaire at the designated study visits listed in Table 3. The HS-PGIC consists of 1 self-administered item that assesses change in the severity of skin in the HS area. Participants are asked to indicate their impression of change compared with their last visit. The participant will answer the following: Since your last visit, your HS is: (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, or (7) very much worse.

The participant should complete the questionnaire before site personnel perform any efficacy assessments.

8.2.8. Dermatology Life Quality Index

Participants will complete a DLQI questionnaire (see Appendix G) from screening through EOS. The DLQI will be used to assess the symptoms and the impact of skin problems on quality of life (Hongbo et al 2005). The DLQI can be used to evaluate 6 areas: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Participants will be asked to respond to the 10 items of the DLQI based on a recall period of "the last week." Decreased scores indicate improved health-related quality of life. The participant should complete the questionnaire before site personnel perform any efficacy assessments.

8.2.9. Photography of Target Lesions

For participants who consent to photography, a target area will be identified at screening and photographed for purposes of documentation. The lesion should be located in an area with inflammatory nodules and/or abscesses that are a good representation of the disease severity.

8.3. Safety Assessments

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 28 days after the last dose of study treatment. Adverse events that begin or worsen after informed consent should be recorded on the Adverse Event Form in the eCRF regardless of the assumption of a causal relationship with the study drug. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following-up on AEs that are serious,

considered related to the study treatment, or that caused the participant to discontinue the study treatment. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?" is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits, or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.2. Physical Examinations

Physical examinations will be conducted at the time points listed in Table 3.

A comprehensive physical examination will include height and body weight, and assessment of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes. A brief neurological examination will also be performed.

A targeted physical examination should be conducted as indicated by symptoms reported by the participant, AEs, or other findings. Abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

Physical examinations must be performed by a medically qualified individual such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits.

8.3.3. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Any abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

8.3.4. Electrocardiograms

All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after at least 5 minutes of rest.

Electrocardiograms should be performed as indicated in Table 3. Additional 12-lead ECGs may be performed at other visits as deemed clinically necessary. Electrocardiograms will be interpreted by the investigator at the site, and the results will be used for immediate management of the participant's care. The decision to include or exclude a participant or withdraw a participant from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as

appropriate. Any abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

Table 9: Electrocardiogram Schedule

Study Visit	Timing of ECG Relative to Administration of Study Drug		
	Not Applicable	**Predose (trough) ECG[a]**	**Postdose ECG[b]**
Screening	Single → Triple		
Day 1		Triple[c]	Single → Triple
Week 2			Single → Triple
Week 6			Single → Triple
Week 8 (EOT)		Single → Triple	

[a] Predose ECG should be performed 5 to 10 minutes before the predose PK assessment.
[b] Postdose ECGs will be performed when participants arrive at the study sites [redacted] If abnormality ECG results are observed, an additional 2 ECGs will be measured within the next 5 minutes. Postdose ECG will be measured [redacted].
[c] Day 1 predose 12-lead ECGs will be performed in triplicate, and values will be averaged to calculate the baseline values.
Note: Single → Triple: Single ECG will be performed first. If abnormal ECG results are observed, an additional 2 ECGs will be measured within the next 5 minutes.

8.3.5. Laboratory Assessments

8.3.5.1. Safety Assessments

Required laboratory tests are listed in Table 10. Safety laboratory tests include hematology, chemistry, CRP, and lipid panel (see Table 3). Participants may have a light snack before this visit, but should allow for an overnight fast (at least 8 hours) before sample collection for the lipid panel.

If there is any abnormality in hematology assessment (particular for platelet counts) at Week 2, an unscheduled visit at Week 3 (see Section 8.6) to repeat hematology assessments will be required.

Clinical laboratory tests will be performed at a central laboratory (see the Laboratory Manual for sample handling and shipping instructions).

8.3.5.2. Screening Assessments

Screening laboratory tests include urinalysis, serology, TB screening, pregnancy test, and an FSH test for confirmation of nonchildbearing status in women who are postmenopausal, defined as amenorrhea at least 12 months before screening. See the Laboratory Manual for screening assessment instructions.

8.3.5.3. Pregnancy Test

A serum pregnancy test will be required for all women of childbearing potential during screening. Urine pregnancy tests will be conducted as outlined in Table 3, as medically indicated, or per country-specific requirement. Urine pregnancy tests will be performed locally. If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test, which may be performed locally.

If the serum pregnancy test is negative after a urine test was positive, the investigator will assess the potential benefit/risk to the participant and determine whether it is in the participant's best interest to resume study drug and continue participation in the study.

If a pregnancy is confirmed by a serum pregnancy test, see Section 9.6 for reporting requirements.

[redacted]

[redacted]

8.6. Unscheduled Visits

Unscheduled visits may occur at any time at the investigator's discretion, and appropriate clinical and laboratory tests may be performed, as clinically indicated.

If there is any abnormality in hematology assessment (particular for platelet counts) at Week 2, an unscheduled visit at Week 3 to repeat hematology assessments will be required. Refer to Section 6.5 for the instruction of dose interruption and restart. The investigator must inform and consult sponsor with any hematological abnormality.

8.7. End of Treatment and/or Early Termination

If a participant permanently discontinues study drug or has completed the protocol-specified duration of treatment, an EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The participant should be encouraged to return for the follow-up visit.

8.8. Follow-Up

8.8.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled safety follow-up visit, which should occur 28 to 35 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until the end of follow-up period, the date of the follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period.

For purposes of analysis, participants who complete through Week 8 will be considered to have completed the study.

9. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

9.1. Definition of Adverse Event

Adverse Event Definition

- An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.
- An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the Adverse Event Definition

- Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Abnormal laboratory test results constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal lab result (eg, low hemoglobin, platelet count decreased).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the Adverse Event Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or considered to be treatment-related by the investigator.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE if it occurred after signing the ICF. If present before entering the study, the condition should be captured as medical history.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.2. Definition of Serious Adverse Event

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurred. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations (Important Medical Event):

An event that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

9.3. Recording an Adverse Event and/or Serious Adverse Event

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Event Form in the eCRF. Conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator (or delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the AE eCRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

To the extent possible, each AE/SAE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study drug: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Event Form, and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v4.03 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity.

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate activities of daily living.
- **Grade 3:** Severe or medical significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Fatal.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- The investigator will also consult the RSI in the IB and/or Product Information, for marketed products, in his/her assessment.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data** to sponsor or designee.
  - The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE/SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- Any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.
- Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves.

9.4. Reporting of Serious Adverse Events

All SAEs, regardless of suspected causality (eg, relationship to study drug or study procedure[s]), occurring after the participant has signed the ICF through the last study visit (or 28 days after the last dose of study treatment, whichever occurs later) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Serious Adverse Event Reporting
• Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF. • The investigator must also complete the Incyte Serious Adverse Event Report Form, in English. Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form. • Facsimile or email transmission of the Serious Adverse Event Report Form is the preferred method to transmit this information to the PhV/designee. The contact information of the sponsor's study-specific representatives is listed in the investigator manual provided to each site. The original copy of the Serious Adverse Event Report Form and the confirmation sheet must be kept at the study site. • Follow-up information is recorded on an amended or new Serious Adverse Event Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous Serious Adverse Event Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs. • In rare circumstances and in the absence of facsimile or computer equipment, notification by telephone is acceptable with a copy of the Incyte Serious Adverse Event Report Form sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames. • Contacts for SAE reporting can be found in the study manual.

9.5. Emergency Unblinding of Treatment Assignment

Not applicable.

9.6. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a participant's partner during paternal exposure to study drug, the following procedures should be followed in order to ensure safety:

- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcomes are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

If abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are reported in a study participant's partner, the events should be reported to the sponsor on the Clinical Trial Pregnancy Form.

9.7. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the participant during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

9.8. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be recorded as described in Section 9.3.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

9.9. Treatment of Overdose

For this study, any dose of INCB054707 greater than 15 mg within a 24-hour time period will be considered an overdose. Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until INCB054707 can no longer be detected systemically (at least 3 days).
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

10. STATISTICS

10.1. Sample Size Determination

The sample size was based on the precedent of other safety and PK studies and was not based on statistical power calculations.

10.2.1. Level of Significance

This is a safety study. No formal efficacy hypotheses will be tested.

10.3. Statistical Analyses

10.3.1. Safety Analyses

Safety endpoints are listed in Section 3. Safety analyses will be conducted using the safety evaluable population and are summarized in Table 13.

Table 13: Safety Analyses

Endpoint	Statistical Analysis Methods
Secondary	**Adverse Events** A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be coded using MedDRA and tabulated by preferred term and system organ class. Severity of AEs will be based on the CTCAE v4.03 using Grades 1 through 4. The subset of AEs considered by the investigator to have a relationship to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, then the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. **Clinical Laboratory Tests** Actual values and changes from baseline in clinical laboratory test results will be summarized using descriptive statistics. Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values will be tabulated. Laboratory data will be classified into Grades 1 through 4 using CTCAE v4.03. The following summaries will be produced for the laboratory data: Number and percentage of participants with worst postbaseline CTCAE grade (regardless of baseline value). Each participant will be counted only for the worst grade observed postbaseline. Shift tables from baseline to the worst postbaseline value using CTCAE grade. For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value using the low/normal/high classifications based on laboratory reference ranges.

10.3.2. Efficacy Analyses

Efficacy analyses will be conducted using the FAS. The baseline value for a variable will be defined as the last nonmissing value for this variable before or on Day 1, unless otherwise specified.

Categorical variables, including proportions of participants achieving HiSCR, with an AN count of 0 to 2, requiring rescue lesional treatment, and with a change in Hurley Stage, will be summarized using descriptive statistics including sample size, frequency, and percentages. Mean, change from baseline, and percentage change from baseline in HS pain NRS, modified Sartorius scale, and DLQI scores will be summarized using descriptive statistics, including sample size, mean, median, standard deviation, standard error of the mean, minimum, and maximum.

[redacted]

10.4. Interim Analysis

No formal interim analysis is planned in this study.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.

- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

11.2. Data Management

Data management will be performed in a validated EDC system. The investigator will be provided with access to an EDC system so that an eCRF can be completed for each participant.

The site will be provided eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

The sponsor (or designee) will be responsible for:

- The data management of this study including quality checking of the data.
- Ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

The investigator will be responsible for:

- Ensuring participant data relating to the study is recorded in the eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data) or as otherwise specified in the Protocol. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

  - Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.

  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.

  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.

  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data privacy laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Participant names will not be supplied to the sponsor or its designee. Only the participant number and the participant's initials (participant's initials will only be recorded if allowable by local regulations) will be recorded in the eCRF, where permitted; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with local data protection laws.

11.4. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to 21 CFR Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure Form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research participants, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

11.5. Publication Policy

By signing the study protocol, the investigator and his or her institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined in line with International Committee of Medical Journal Editors authorship requirements.

11.6. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For male participants in the study:

Male participants should use a condom during treatment and through 90 days after the end of systemic exposure. If the male participant has a partner that is of childbearing potential, the partner should also use contraception through 90 days after the end of relevant systemic exposure. In addition, male participants must refrain from donating sperm during the study through 90 days after the end of relevant systemic exposure. Males who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.

For female participants and for female partners of male participants in the study:

The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable[1]
- Intrauterine device (IUD)[1]
- Intrauterine hormone-releasing system (IUS)[1]
- Bilateral tubal occlusion[1]
- Vasectomised partner[1,2]
- Sexual abstinence[3]

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide[4]
- cap, diaphragm or sponge with spermicide[4]
- tubal ligation

[1] Contraception methods that in the context of this guidance are considered to have low user dependency.
[2] Vasectomised partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the woman and that the vasectomised partner has received medical assessment of the surgical success.
[3] In the context of this guidance, 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 treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.
[4] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.
Source: CTFG 2014.

APPENDIX B. CYTOCHROME P450 3A4 INHIBITORS AND INDUCERS

Highlighted rows indicate recent additions to the lists at the time the database search was performed. The sponsor should be contacted with any questions regarding concomitant medications that might be considered potent CYP3A4 inhibitors and inducers but are not on this list.

University of Washington School of Pharmaceutics: Drug Interaction Database Program. 2002. http://www.druginteractioninfo.org. Accessed May 2015.

Information also can be found at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

In Vivo CYP3A Inhibitors

Inhibitor	Therapeutic Class	Inhibitor dosing (oral)	Object[1] (oral, unless otherwise specified)	AUC_{ratio}	PMID or NDA #	Published
Potent CYP3A Inhibitors (yielding substrate AUCr > 5)						
indinavir /RIT	Protease Inhibitors	800/100 mg BID (1 day)	alfentanil	36.5	19225389	2009 Mar
tipranavir/RIT	Protease Inhibitors	500/200 mg BID (2 days)	midazolam	26.91	20147896	2010 Jun
ritonavir	Protease Inhibitors	3 doses of 100 mg over 24 h	midazolam	26.41	20002087	2009 Dec
cobicistat (GS-9350)	None	200 mg QD (14 days)	midazolam	19.03	20043009	2010 Mar
indinavir	Protease Inhibitors	800 mg TID (7 days)	vardenafil	16.25	NDA # 021400	2003 Aug
ketoconazole	Antifungals	400 mg QD (4 days)	midazolam	15.9	8181191	1994 May
troleandomycin	Antibiotics	500 mg single dose	midazolam	14.8	15536460	2004 Dec
telaprevir	Antivirals	750 mg TID (16 days)	midazolam	13.5	22162542	2012 Oct
danoprevir / RIT	Antivirals	200/100 mg QD (14 days)	midazolam	13.42	23872824	2013 Nov
elvitegravir / RIT	Treatments of AIDS	150/100 mg QD (10 days)	midazolam	12.8	NDA # 203100	2012
saquinavir / RIT	Protease Inhibitors	1000/100 mg BID (14 days)	midazolam	12.48	19792991	2009 Oct
lopinavir / RIT	Protease Inhibitors	400/100 mg BID (2 days)	alfentanil	11.47	24067429	2013 Dec
itraconazole	Antifungals	200 mg QD (4 days)	midazolam	10.8	8181191	1994 May
voriconazole	Antifungals	200 mg BID (9 days)	midazolam	9.63	21937987	2011 Nov
mibefradil	Calcium Channel Blockers	100 mg single dose	midazolam	8.86	14517191	2003 Oct
LCL161	Cancer Treatments	600 mg single dose	midazolam	8.8	23585187	2013 Jun
clarithromycin	Antibiotics	500 mg BID (7 days)	midazolam	8.39	16432272	2006 Feb
posaconazole	Antifungals	400 mg BID (7 days)	midazolam	6.23	19302901	2009 Feb
telithromycin	Antibiotics	800 mg QD (6 days)	midazolam	6.2	NDA# 021144	2004
grapefruit juice DS[2]	Food Products	240 mL TID (2 days) and 90 min, 60 min, 30 min prior to midazolam	midazolam	5.95	12953340	2003 Aug
conivaptan	Diuretics	40 mg BID (5 days)	midazolam	5.76	NDA # 021697	2005
nefazodone	Antidepressants	100-200 mg BID (12 days)	midazolam	5.44	14551182	2003 Nov
nelfinavir	Protease Inhibitors	1250 mg BID (14 days)	midazolam	5.29	21406602	2011 Jun
saquinavir	Protease Inhibitors	1200 mg TID (5 days)	midazolam	5.18	10430107	1999 Jul
idelalisib	Kinase Inhibitors	150 mg BID (8 days)	midazolam	5.15	NDA # 206545	2014
boceprevir	Antivirals	800 mg TID (6 days)	midazolam	5.05	NDA # 202258	2011
Moderate CYP3A Inhibitors (AUCr ≥ 2 and < 5)						
erythromycin	Antibiotics	1000 mg single dose	midazolam	4.99	25139487	2014 Dec
fluconazole	Antifungals	400 mg single dose	midazolam	4.93	16172184	2005 Oct
atazanavir / RIT	Protease Inhibitors	300/100 mg BID	maraviroc	4.9	18333863	2008 Apr
darunavir	Protease Inhibitors	1200 mg BID (14 days)	saquinavir	4.9	NDA # 021976	2006
diltiazem	Calcium Channel Blockers	60 mg TID (2 days)	midazolam	4.06	21209240	2011 Nov
darunavir / RIT	Protease Inhibitors	400/100 mg BID (8 days)	sildenafil	4.0	NDA # 021976	2006
dronedarone	Antiarrhythmics	400 mg BID (14 days)	simvastatin	3.66	NDA # 022425	2009
crizotinib	Kinase Inhibitors	250 mg BID (28 days)	midazolam	3.65	NDA # 202570	2011
atazanavir	Protease Inhibitors	400 mg QD (7 days)	maraviroc	3.57	18333863	2008 Apr
aprepitant	Antiemetics	80-125 mg QD (5 days)	midazolam	3.29	12891225	2003 Aug
casopitant	Antiemetics	120 mg QD (14 days)	midazolam	3.13	20840445	2010 Oct
amprenavir	Protease Inhibitors	1200 mg BID (10 days)	rifabutin	2.93	11158747	2001 Feb
imatinib	Antineoplastic Agents	400 mg QD (7 days)	simvastatin	2.92	14612892	2003 Nov
verapamil	Calcium Channel Blockers	80 mg TID (2 days)	midazolam	2.92	8198928	1994 Mar
ledipasvir	Antivirals	30 mg QD (10 days)	simeprevir	2.69	NDA # 205123	2013
netupitant	Antiemetics	300 mg single dose	midazolam	2.44	23729226	2013 Oct
grapefruit juice	Food Products	240 mL QD (4 days)	midazolam	2.39	10546919	1999 Oct
tofisopam	Benzodiazepines	100 mg TID (9 days)	midazolam	2.36	17989974	2008 Jan
cyclosporine	Immunosuppressants	Not provided (1-5 years)	midazolam	2.21	21753749	2011 Sep
ACT-178882	Renin Inhibitors	300 mg QD (14 days)	midazolam	2.19	22849770	2013 Dec
ciprofloxacin	Antibiotics	500 mg single dose	sildenafil	2.12	16372380	2005 Dec
schisandra sphenanthera	Herbal Medications	3 capsules (= 11.25 mg deoxyschizandrin) BID (7 days)	midazolam	2.05	19552749	2009 May

cimetidine	H-2 Receptor Antagonists	200-400 mg QID (1.5 days)	midazolam	2.02	6152615	1984 Sep
FK1706	Central Nervous System Agents	60 mg QD (14 days)	midazolam	2.01	19889885	2010 Feb
lomitapide	Other Antilipemics	60 mg QD (7 days)	simvastatin	2.0	NDA # 203858	2012
		Weak CYP3A Inhibitors (AUCr ≥ 1.25 and < 2)				
tabimorelin	Hormone Replacement	2.86-3.21 mg QD (7 days)	midazolam	1.93	12610745	2003 Feb
ranolazine	Cardiovascular Drugs	1000 mg BID (7 days)	simvastatin	1.89	NDA # 021526	2006
amlodipine	Calcium Channel Blockers	10 mg QD (9 days)	simvastatin	1.8	23965645	2014 Apr
lomitapide	Other Antilipemics	60 mg QD (7 days)	simvastatin	1.77	24734312	2014 Mar
fosaprepitant (IV)	Antiemetics	150 mg single 30-min infusion	midazolam	1.76	21209230	2011 Dec
Seville orange juice	Food Products	240 mL single dose	felodipine	1.76	11180034	2001 Jan
amiodarone	Antiarrhythmics	400 mg QD (4 days)	simvastatin acid	1.76	17301736	2007 May
chlorzoxazone	Muscle Relaxants	250 mg single dose (part of a 6-drug cocktail)	midazolam	1.68	11736864	2001 Nov
M100240	Antihypertensive Agents	50 mg single dose	midazolam	1.66	15051745	2004 Apr
fluvoxamine	Antidepressants	50-00 mg BID (12 days)	midazolam	1.66	14551182	2003 Nov
ranitidine	H-2 Receptor Antagonists	150 mg BID (1.5 days)	midazolam	1.66	6135440	1983 Jun
goldenseal	Herbal Medications	1,323 mg (= 24.1 mg isoquinoline alkaloids) TID (14 days)	midazolam	1.63	17495878	2008 Jan
clotrimazole	Antifungals	10 mg TID (5 days)	midazolam	1.61	20233179	2010 Feb
tacrolimus	Immunosuppressants	Not provided (1-5 years)	midazolam	1.61	21753749	2011 Sep
cilostazol	Antiplatelets	100 mg BID (7 days)	lovastatin	1.56	10702889	1999
ticagrelor	Antiplatelets	180 mg bid (7 days)	simvastatin	1.56	NDA # 022433	2011
peppermint oil	Food Products	600 mg (= 300 uL peppermint oil) single dose	felodipine	1.55	12235445	2002 Sep
ivacaftor	Cystic fibrosis treatments	150 mg BID (6 days)	midazolam	1.54	NDA # 203188	2012
GSK2248761	Transcriptase Inhibitors	100 mg QD (12 days)	midazolam	1.54	22288567	2012 Aug
roxithromycin	Antibiotics	300 mg QD (6 days)	midazolam	1.47	7995324	1994
suvorexant	Hypnotics - Sedatives	80 mg QD (14 days)	midazolam	1.47	NDA # 204569	2014
propiverine	Anticholinergics	15 mg BID (7 days)	midazolam	1.46	16183781	2005 Dec
isoniazid	Antibiotics	90 mg BID (4 days)	triazolam	1.46	6140941	1983 Dec
berberine	Herbal Medications	300 mg TID (14 days)	midazolam	1.45	21870106	2012 Feb
oral contraceptives	Oral contraceptives	OC with low doses of estrogen (< 35 ug ethinylestradiol) (> 3 months)	triazolam	1.44	6149030	1984 Nov
delavirdine	NNRTIs	400 mg TID (9 days)	indinavir	1.44	9665503	1998 Jul
daclatasvir	Antivirals	60 mg QD (7 days)	simeprevir	1.44	NDA # 205123	2013
faldaprevir	Antivirals	240 mg BID (8 days)	ethinyl estradiol	1.44	25385099	2015 Jan
simeprevir	Protease Inhibitors	150 mg QD (11 days)	midazolam	1.43	NDA # 205123	2013
atorvastatin	HMG CoA Reductase Inhibitors (Statins)	10-40 mg/day (chronic treatment)	midazolam IV	1.41	12911366	2003 Sep
tolvaptan	Vasopressin Antagonists	60 mg single dose	lovastatin	1.41	NDA # 022275	2009
almorexant	Hypnotics - Sedatives	200 mg QD (9 days)	midazolam	1.37	22990330	2013 Mar
GSK1292263	Other Antilipemics	300 mg BID (9 days)	simvastatin	1.36	23256625	2013 Jun
linagliptin	Dipeptidyl Peptidase 4 Inhibitors	10 mg QD (6 days)	simvastatin	1.34	20497745	2010 Jun
resveratrol	Food Products	1 g QD (4 weeks)	buspirone	1.33	20716633	2010 Sep
lacidipine	Calcium Channel Blockers	4 mg QD (8 days)	simvastatin	1.33	11259986	2001 Feb
cranberry juice	Food Products	240 mL double strength juice, 1 glass q 15 min x 3	midazolam	1.33	19114462	2009 Mar
pazopanib	Kinase Inhibitors	800 mg QD (17 days)	midazolam	1.32	20881954	2010 Nov
everolimus	Immunosuppressants	10 mg QD (5 days)	midazolam	1.31	23426978	2013 Apr
blueberry juice	Food Products	two doses of 300 mL, separated by 16 hours	buspirone	1.31	22943633	2013 Apr
nilotinib	Kinase Inhibitors	600 mg single dose	midazolam	1.3	NDA # 022068	2007
AMD070	Fusion Inhibitors	200 mg BID (8 days)	midazolam	1.29	18362694	2008 Apr
alprazolam	Benzodiazepines	1 mg TID (7 days)	buspirone	1.29	8300893	1993 Nov
bicalutamide	Antiandrogens	150 mg QD (>3 months)	midazolam	1.27	15509184	2004
sitaxentan	Endothelin Receptor Antagonists	100 mg QD (7 days)	sildenafil	1.27	20078609	2010 Jan
azithromycin	Antibiotics	500 mg QD (3 days)	midazolam	1.27	8720318	1996 Feb
ginkgo	Herbal Medications	120 mg TID (28 days)	midazolam	1.25	17050793	2006 Nov
teriflunomide	Other Immunomodulators	14-70 mg QD (14 days)	midazolam	1.25	NDA # 202992	2012

[1] To allow better comparability, DDI studies with the probe substrate midazolam were selected first.
When no study with midazolam was available, the AUCratio of another probe or sensitive substrate is presented.

[2] 240 mL GFJ double-strength administered TID for 3 days

In Vivo CYP3A Inducers

Inducers	Therapeutic class	Object (oral, unless otherwise specified)	% ↓ AUC	% ↑ oral CL	Precipitant Dose (oral)	PMID or NDA #	Published
Potent Inducers (AUC decreased by ≥ 80% or CL increased by more than 5 fold (400%))							
rifampin	Antibiotics	budesonide	99.7	36904.5	600 mg QD (7 days)	15726657	2005 Mar
mitotane	Other Antineoplastics	midazolam	94.5	Not Provided	maximum of 3.5 g TID (chronic therapy)	21220434	2011 Apr
avasimibe	Other Antilipemics	midazolam	93.5	Not Provided	750 mg/day (7 days)	12766253	2003 Sep
phenytoin	Anticonvulsants	nisoldipine	89.5	Not Provided	200-450 mg/day (chronic treatment)	8917062	1996 Nov
carbamazepine	Anticonvulsants	quetiapine	86.6	643.1	200 mg TID (26 days)	16390352	2006 Jan
enzalutamide	Antiandrogens	midazolam	85.9	Not Provided	160 mg QD (85±3 days)	NDA # 203415	2012
St John's Wort	Herbal Medications	midazolam	80.0	Not Provided	300 mg TID (14 days)	16341856	2006 Jan
rifabutin	Antibiotics	delavirdine	Not Provided	458.0	300 mg QD (14 days)	9224961	1997 Jun
phenobarbital	Anticonvulsants	verapamil	76.6	400.9	100 mg QD (21 days)	3392664	1988 Jul
Moderate Inducers (AUC decreased by 50-80% or CL increased by 2-5 fold (100-400%))							
ritonavir and St. Johns wort	None	midazolam	77.2	Not Provided	ritonavir: 300 mg BID and SJW: 300 mg TID (14 days)	19924124	2010 Feb
semagacestat	Alzheimer's Treatments	midazolam	76.4	324.6	140 mg QD (10 days)	22789530	2012 Oct
efavirenz	NNRTIs	alfentanil	76	369.4	600 mg QD (20 days)	22398970	2012 Apr
tipranavir and ritonavir	Protease Inhibitors	saquinavir	75.6	Not Provided	tipranavir: 500 mg and ritonavir: 200 mg BID (14 days)	18176328	2008 Apr
bosentan	Endothelin Receptor Antagonists	sildenafil	69.0	239.8	62.5-125 mg BID (8 weeks)	15963102	2005 Jul
genistein	Food Products	midazolam	13.7	136.9	1000 mg QD (14 days)	21943317	2012 Feb
thioridazine	Antipsychotics	quetiapine	68.7	104.5	100-300 mg QD (15 days)	22569350	2012 Jun
nafcillin	Antibiotics	nifedipine	62.6	145.1	500 mg 4 times daily (5 days)	12814453	2003 Jun
talviraline	NNRTIs	indinavir	61.7	181.2	500 mg TID (14 days)	10516944	1999 Oct
lopinavir	Protease Inhibitors	amprenavir	59.7	Not Provided	400 mg BID (4 weeks)	15060509	2004 Apr
modafinil	Psychostimulants	triazolam	57.6	35.7	200-400 mg QD (28 days)	11823757	2002 Jan
etravirine	NNRTIs	sildenafil	56.7	Not Provided	800 mg BID (13.5 days)	NDA# 022187	2008
lersivirine	NNRTIs	midazolam	51.4	105.5	1000 mg BID (14 days)	22527351	2012 Nov
Weak Inducers (AUC decreased by 20-50% or CL increased by less than 2 fold (100%))							
eslicarbazepine	Anticonvulsants	simvastatin	49.4	98.4	800 mg QD (14 days)	23726291	2013 Sep
telaprevir	Antivirals	darunavir	48.4	Not Provided	1125 mg BID (4 days)	NDA# 201917	2011
garlic	Food Products	saquinavir	44.7	Not Provided	caplet of GarliPure BID (20 days)	11740713	2002 Jan
bexarotene	Other Antineoplastics	atorvastatin	45.3	Not Provided	400 mg/m2 QD (at least two 4-week cycles)	22057855	2012 Feb
amprenavir	Protease Inhibitors	lopinavir	43.0	Not Provided	700 mg BID (2-4 weeks)	15668539	2005 Jan
raltegravir	HIV-Integrase Strand Transfer Inhibitors	darunavir	42.0	Not Provided	400 mg BID	21958880	2012 Feb
vemurafenib	Kinase Inhibitors	midazolam	39.4	Not Provided	960 mg BID (15 days)	NDA # 202429	2011
troglitazone	Thiazolidinediones	simvastatin	37.7	Not Provided	400 mg QD (24 days)	11361054	2001 May
sorafenib	Kinase Inhibitors	sirolimus	36.9	Not Provided	200 mg BID (11 days)	21045832	2010 Nov
rufinamide	Anticonvulsants	triazolam	36.7	53.4	400 mg BID (11.5 days)	NDA # 021911	2008
pleconaril	Antivirals	midazolam	34.6	52.8	400 mg TID (6 days)	16467135	2006 May
ginseng	Herbal Medications	midazolam	34.2	50.7	500 mg BID (28 days)	21646440	2012 Jun
boceprevir	Antivirals	darunavir	34.2	41.0	800 mg every 8 hrs (6 days)	23155151	2013 Mar
sulfinpyrazone	Antigout and Uricosuric Agents	cyclosporine	33.9 (change in C_{ave})		200 mg/day	11124491	2000 Dec
gingko	Herbal Medications	midazolam	33.7	52.6	120 mg BID (28 days)	18205997	2008 Feb
vinblastine	Vinca Alkaloids	midazolam IV	33.2	48.8	not provided (4 cycles)	20959500	2010 Nov
nevirapine	NNRTIs	indinavir	32.5	Not Provided	200 mg QD (14 days), then BID (19 days)	10191212	1999 May
armodafinil (R-modafinil)	Psychostimulants	midazolam	32.2	54.7	100-250 mg/day (31 days)	18076219	2008
ticagrelor	Anticoagulants and Antiplatelets	midazolam	31.7	46.5	400 mg QD (6 days)	23870610	2013 Jul
LCL161	Cancer Treatments	midazolam	29.8	34.0	600 mg single dose	23585187	2013 Jun
vicriviroc and ritonavir	Treatments of AIDS	ethinyl estradiol	29.4	Not Provided	30 mg vicriviroc and 100 mg ritonavir QD (10 days)	22015327	2011 Oct

ritonavir	Protease Inhibitors	ethinyl estradiol	**29.2**	Not Provided	100 mg QD (10 days)	22015327	2011 Oct
prednisone	Corticosteroids	tacrolimus	**29.0**	Not Provided	1.5 mg/kg/day	15787787	2005 Apr
oxcarbazepine	Anticonvulsants	felodipine	**28.1**	Not Provided	450 mg BID (7 days)	8451779	1993 Feb
danshen	Herbal Medications	midazolam	**27.9**	**32.8**	4 g TID (14 days)	20565457	2010 Jun
clobazam	Benzodiazepines	midazolam	**27.7**	Not Provided	40 mg QD (15 days)	22422635	2012 Apr
echinacea	Herbal Medications	midazolam	**27.3**	**37.5**	500 mg TID (28 days)	20393696	2010 Aug
ticlopidine	Anticoagulants and Antiplatelets	alfentanil	**27.0**	**50.0**	250 mg BID (4 days)	23361846	2013 Mar
brivaracetam	Anticonvulsants	ethinyl estradiol	**26.8**	**37.3**	200 mg BID (21 days)	24386664	2013 Dec
Stribild*	Treatments of AIDS	ethinyl estradiol	**26.2**	**31.3**	150 mg ELV + 150 mg COB + 200 mg EMT+ 300 mg TEN	NDA # 203100	2012
pioglitazone	Thiazolidinediones	midazolam	**26.0**	Not Provided	45 mg QD 7 days	Actos® Product Label	
dexamethasone	Corticosteroids	aprepitant	**25.0**	Not Provided	8 mg/day (5 days)	NDA # 021549	2003
terbinafine	Antifungals	midazolam	**24.5**	Not Provided	250 mg QD (4 days)	8527290	1995 Sep
quercetin	Food Products	midazolam	**23.6**	Not Provided	500 mg QD (13 days)	21680781	2012 Jun
glycyrrhizin	Herbal Medications	midazolam	**23.0**	Not Provided	150 mg BID (15 days)	20393696	2010 Aug
aprepitant	Neurokinin-1 Receptor Antagonists	midazolam IV	**22.1**	**28.5**	125/80 mg QD (3 days)	14973304	2004 Mar
PA-824	Antibiotics	midazolam	**22.1**	**20.7**	400 mg QD (14 days)	23689718	2013 Aug
oritavancin	Antibiotics	midazolam	**18.7**	**23.9**	1200 mg IV single infusion	NDA # 206334	2014
AZD 7325	Anxiolytics	midazolam	**18.7**	**22.6**	10 mg QD (12 days)	22122233	2012 Jul
methylprednisolone	Corticosteroids	cyclosporine	**15.8**	**35.0**	16 mg/day (12 days) then 8 mg/day (6 months)	12164891	2002 Sep
topiramate	Anticonvulsants	ethinyl estradiol	**12.0**	**20.2**	50 mg/day (21 days)	12681003	2003 Apr

1- Ritonavir has dual effects of simultaneous CYP3A inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP3A activity.

2- All the substrates presented in the table are sensitive CYP3A substrates (see definition in FDA guidance) except verapamil, cyclosporine, ethinyl estradiol, and delavirdine.

* **Stribild** is a combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF

APPENDIX C. *IN VIVO* P-GLYCOPROTEIN INHIBITORS AND INDUCERS

Highlighted rows indicate recent additions to the lists at the time the database search was performed. The sponsor should be contacted with any questions regarding concomitant medications that might be considered potent P-gp inhibitors and inducers but are not on this list.

University of Washington School of Pharmaceutics: Drug Interaction Database Program. 2002. http://www.druginteractioninfo.org. Accessed May 2015.

Information also can be found at:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

In Vivo P-gp Inhibitors

Inhibitor*	Therapeutic Class	Inhibitor Dose (oral)	Substrate[a]	Max AUC ratio	Accession or NDA #	Published
alogliptin	Dipeptidyl Peptidase-4 Inhibitors	100 mg QD (7 days)	fexofenadine	1.26	NDA # 022271	2013
amiodarone	Antiarrhythmics	400 mg/day (5 days)	digoxin (IV)	-26.5% (CL)	3964797	1985 Jan
		800 mg/day (7 days)	digoxin	1.68	2487521	1989 Mar
AZD5672	CCR5 Receptor Antagonists	150 mg QD (13 days)	digoxin	1.33	21075975	2011 Feb
azithromycin	Antibiotics	250 mg QD (5 days)	fexofenadine	1.72	11318079	2001 Mar
canagliflozin	Sodium-dependent Glucose Cotransporter 2 Inhibitors	300 mg QD (7 days)	digoxin	1.20	NDA # 204042	2013
captopril	ACE Inhibitors	12.5 mg TID (7 days)	digoxin	1.39	11471775	2001 Jul
carvedilol	α/β Adrenergic Antagonists	6.25 mg BID (7 days)	digoxin	1.57	16767433	2006 Jul
clarithromycin	Antibiotics	500 mg BID (7 days)	digoxin	1.68	18214850	2008 Jul
conivaptan	Diuretics	40 mg BID (10 days)	digoxin	1.43	NDA # 021697	2005
cremophor RH40	Transporter Modulators	600 mg TID (9 days)	digoxin	1.21	12732840	2003 May
curcumin	Food Products	1000 mg QD (14 days)	talinolol	1.54	22725663	2012 Dec
diltiazem	Calcium Channel Blockers	60 mg TID (10 days)	digoxin	1.44	12070557	2002 Jun
dronedarone	Antiarrhythmics	400 mg BID (10 days)	digoxin	2.33	NDA # 022425	2009
eliglustat	Glucosylceramide Synthase Inhibitors	100 mg (PMs) and 150 mg (others) (7 days)	digoxin	1.49	NDA # 205494	2014
erythromycin	Antibiotics	500 mg TID (7days)	fexofenadine	2.09	NDA # 021963	1996
		2 g single dose	talinolol	1.52	10783825	2000 Apr
felodipine	Calcium Channel Blockers	2.5 mg single dose	digoxin	1.49	3443063	1987
fluvoxamine	Selective Serotonin Reuptake Inhibitors	50 mg QD (7 days)	fexofenadine	1.78	22367658	2012 Apr
ginkgo	Herbal Medications	120 mg TID (14 days)	talinolol	1.25	19280523	2009 Mar
indinavir	Protease Inhibitors	80 mg TID (21 days)	fexofenadine	3.31	22273859	2012 Feb
indinavir/ritonavir	Protease Inhibitors	800 mg/100 mg BID (1 day)	fexofenadine	4.84	19225389	2009 Mar
itraconazole	Antifungals	200 mg QD (5 days)	digoxin	1.68	9421099	1997 Dec
		100 mg BID (5 days)	fexofenadine	3.01[b]	16084853	2006 May
ivacaftor	Other	150 mg (9 days)	digoxin	1.32	25103957	2015 Jan
ketoconazole	Antifungals	400 mg QD (7 days)	fexofenadine	2.74	Allegra® Product Label	1996
lapatinib	Kinase Inhibitors	Not Provided	digoxin (IV)	2.80	Tykerb® Product Label	2007
lopinavir/ritonavir	Protease Inhibitors	400 mg/100 mg BID (14 days)	digoxin	1.81	18183034	2008 Jul
		400 mg/100 mg single dose	fexofenadine	4.14	16809801	2006 July
mibefradil	Calcium Channel Blockers	150 mg QD (7 days)	digoxin	1.31	7669484	1995 May
milk thistle	Herbal Medications	140 mg TID (14 days)	talinolol	1.30	19555315	2009 Sep
mirabegron	Beta3-Adrenoreceptor Agonist	100 mg QD (14 days)	digoxin	1.16	NDA # 202611	2012
nelfinavir	Protease Inhibitors	1250 mg BID (14 days)	digoxin	1.35	22190694	2012 Mar
nifedipine	Calcium Channel Blockers	10 mg TID (7 days)	digoxin	1.23	3943268	1986 Jan
nitrendipine	Calcium Channel Blockers	20 mg QD (7 days)	digoxin	1.16	3816917	1986
paroxetine	Selective Serotonin Reuptake Inhibitors	20 mg QD (7 days)	fexofenadine	1.38	22367658	2012 Apr
propafenone	Antiarrhythmics	300 mg TID (3 days)	digoxin (IV)	1.29	2708548	1989 Jan
		600 mg QD (7 days)	digoxin	-31% (CL)	2911842	1989
		250-500 mg/kg QD (7 days)	digoxin	-67% (CL)	2299507	1990 Feb
quercetin	Food Product	500 mg TID (7days)	fexofenadine	1.56	19221726	2009 Jun
quinidine	Antiarrhythmics	200 mg QID (6 days)	digoxin (IV)	-64% (CL)	7309901	1981 Oct
		600 mg BID (8 days)	digoxin	2.66	3997300	1985 Mar
		25 mg single dose	fexofenadine	2.14	24722393	2014 Sep
ranolazine	Cardiovascular Drugs	750 mg BID (6 days)	digoxin	1.88	NDA # 021526	2006
rifampin	Antibiotics	600 mg QD (28 days)	digoxin	1.46	21191377	2011 Feb
		600 mg QD single dose	fexofenadine	(S) 3.57 (R) 3.21[c]	23115085	2013 Jan
ritonavir	Protease Inhibitors	300 mg BID (11 days)	digoxin (IV)	1.86	15229466	2004 Jul
		400 mg BID (14 days)	digoxin	1.47	22190694	2012 Mar
		200 mg TID (1 day), 300 mg BID (7 days), 400 mg BID (13 days)	fexofenadine	2.75	19238656	2008 Oct

saquinavir/ritonavir	Protease Inhibitors	1000 mg/100 mg BID (16 days)	digoxin	**1.68**	20197013	2010 Mar
schisandra chinensis extract	Herbal Medications	300 mg BID (14 days)	talinolol	**1.52**	19280523	2009 Mar
simeprevir	Protease Inhibitors	150 mg QD (7 days)	digoxin	**1.39**	NDA # 205123	2013
st johns wort extract	Herbal Medications	900 mg single dose	fexofenadine	**1.31**	12087344	2002 Jun
suvorexant	Hypnotics - Sedatives	40 mg (11 days)	digoxin	**1.26**	NDA # 204569	2014
talinolol	α/β Adrenergic Antagonists	100 mg single dose	digoxin	**1.23**	10945310	2000 Jul
telaprevir	Antivirals	750 mg TID (16 days)	digoxin	**1.82**	NDA # 201917	2011
telmisartan	Angiotensin II Inhibitors	120 mg QD (7 days)	digoxin	**1.22**	11185636	2000 Dec
ticagrelor	Anticoagulants and Antiplatelets	400 mg QD (16 days)	digoxin	**1.28**	NDA # 022433	2011
tipranavir/ritonavir	Protease Inhibitors	500/200 mg BID (2 days)	digoxin (IV)	**1.46**	20147896	2010 Jun
		500/200 mg BID (2 days)	digoxin	**1.65**	20147896	2010 Jun
tolvaptan	Vasopressin Antagonist	60 mg QD (5 days)	digoxin	**1.18**	20679500	2011 May
valspodar (PSC 833)	Transporter Modulators	200 mg BID (5 days)	digoxin	**3.05**	10546923	1999 Oct
vandetanib	Kinase Inhibitors	300 mg single dose	digoxin	**1.22**	25117183	2014 Sep
verapamil	Calcium Channel Blockers	80 mg BID (4 days) then TID (10 days)	digoxin	**1.51**	2967742	1988 Jun
		80 mg TID (6 days)	fexofenadine	**2.51**[d]	15637528	2005 Jan
voclosporin	Immunosuppressants	0.4 mg/kg every 12 h (11 days)	digoxin	**1.25**	24330024	2014 Jun
vorapaxar	Anticoagulants and Antiplatelets	2.5 and 40 mg (7 days)	digoxin	**+52.5% (C_{max})**	NDA # 204886	2014

Highlighted entries are new as of March 2015

*Inhibitors are presented alphabetically due to differences in the sensitivity of substrates.

[a] - Oral, unless otherwise indicated. Substrates queried are digoxin, fexofenadine, and talinolol. Note - fexofenadine and talinolol are also transported by other transporters, such as OATPs.

[b] - AUC ratios for separate enantiomers: (S) - 3.28, (R) - 2.65 (Accession #18294330)

[c] - AUC ratios for repeated dosing of rifampin (6 days): (S) - 2.40, (R) - 1.90 (Accession #23115085)

[d] - AUC ratios for separate enantiomers: (S) - 2.87, (R) - 2.17 (Accession #19552748)

In Vivo P-gp Inducers

Inducer*	Therapeutic Class	Inducer Dose (oral)	Substrate[a]	% ↓ AUC	% ↑ oral CL	PMID #	Published
avasimibe	Antilipemics	750 mg/day (10 days)	digoxin	36.4	51.2	12766253	2003 Sep
carbamazepine	Anticonvulsants	100 mg TID (7 days)	fexofenadine	(S) 61.1 (R) 52.1	(S) 159.7 (R) 104.8	21950458	2012 Mar
efavirenz	NNRTIs	600 mg QD (20 days)	fexofenadine	22.6	43.1	22398970	2012 Apr
genistein	Food Products	1000 mg QD (14 days)	talinolol	11.9 ($p<0.05$)	13.5 ($p<0.05$)	21943317	2012 Feb
phenytoin	Anticonvulsants	0.2 g BID (8 days)	digoxin	22.8	26.6	1490820	1992 Nov
quercetin	Food Products	500 mg (14 days)	talinolol	19.7	Not Provided	23422925	2013 Apr
rifampin	Antibiotics	300 mg BID (7 days)	digoxin	30.4	Not Provided	18214850	2008 Jul
		600 mg QD (7 days)	fexofenadine	65.4	154.8	24722393	2014 Sep
		600 mg QD (9 days)	talinolol	35.3	53.5	11061574	2000 Oct
st Johns Wort extract	Herbal Medications	4 g encapsulated powder QD (14 days)	digoxin	28	Not Provided	15179409	2004 Jun
		300 mg TID (12.5 days)	fexofenadine	Not Provided	86.7	12545142	2003 Jan
		300 mg TID (12 days)	talinolol	31.0	93.2	17392718	2007 May

*Inhibitors are presented alphabetically due to differences in the sensitivity of substrates.

[a] - Oral, unless otherwise indicated. Substrates queried are digoxin, fexofenadine, and talinolol. Note - fexofenadine and talinolol are also transported by other transporters, such as OATPs.