Clinical Study Protocol

Protocol Title:	A Randomized, Partially Blinded, Placebo- and Comparator-Controlled, Multicenter, Phase 2a, Dose-Ranging, Proof-of-Concept Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of SPR720 as Compared With Placebo or Standard of Care for the Treatment of Patients With *Mycobacterium avium* Complex (MAC) Pulmonary Disease
Protocol Number:	SPR720-201
Clinical Phase:	2a
Protocol Version and Date:	Version 3.0, 17 September 2020
Sponsor:	Spero Therapeutics, Inc. [redacted]

ClinicalTrials.gov Identifier: NCT04553406

This study will be performed in compliance with Good Clinical Practice, the Declaration of Helsinki (with amendments), and local legal and regulatory requirements.

CONFIDENTIAL

SIGNATURE PAGE

Protocol Title: A Randomized, Partially Blinded, Placebo- and Comparator-Controlled, Multicenter, Phase 2a, Dose-Ranging, Proof-of-Concept Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of SPR720 as Compared With Placebo or Standard of Care for the Treatment of Patients With *Mycobacterium avium* Complex (MAC) Pulmonary Disease

The undersigned have reviewed the format and content of this protocol and have approved the clinical study protocol. The undersigned agree that the trial will be carried out in accordance with the clinical study protocol, Good Clinical Practice, with the Declaration of Helsinki (with amendments), and with the laws and regulations of the countries in which the study takes place.

Any modifications of the clinical study protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

Sponsor Approval:

Signature:  Date: 17-Sep-2020

Name (print): DAVID MELNICK, MD

Title: CHIEF MEDICAL OFFICER

INVESTIGATOR AGREEMENT

I have read the clinical study protocol and agree the trial will be carried out in accordance with Good Clinical Practice, with the Declaration of Helsinki (with amendments), and with the laws and regulations of the countries in which the study takes place.

Signature: _____ Date: _____

Name (print): _____

SYNOPSIS

Study Title:	A Randomized, Partially Blinded, Placebo- and Comparator-Controlled, Multicenter, Phase 2a, Dose-Ranging, Proof-of-Concept Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of SPR720 Compared With Placebo or Standard of Care for the Treatment of Patients With *Mycobacterium avium* Complex (MAC) Pulmonary Disease
Protocol Number:	SPR720-201
Name of Study Drug:	SPR720
Phase of Development:	2a
Objectives:	Primary Objective: • To evaluate the pharmacokinetics (PK) of SPR719 generated from the orally (po) administered SPR720 prodrug in a patient population with nontuberculous mycobacteria pulmonary disease (NTM-PD) Secondary Objective: • To evaluate the safety and tolerability of SPR720 in a patient population with NTM-PD [redacted]
Study Design:	This is a Phase 2a, multicenter, randomized, partially blinded, placebo- and comparator-controlled study to evaluate the safety, tolerability, PK, and efficacy of 2 dose levels of SPR720 compared with placebo or SOC for the treatment of patients with NTM-PD due to *Mycobacterium avium* complex (MAC). The SPR720 and placebo arms will be double blinded, and the SOC arm will be open label. Approximately 90 male and female patients 18 years of age and older with a diagnosis of NTM-PD due to MAC will be enrolled and treated for 28 days. Treatment naïve patients must be ready to initiate treatment within the next 3 months. Patients who have received prior treatment may be eligible if they have culture evidence of persistent, recurrent, or relapsed disease; have been off therapy for at least 6 months; and are likely to reinitiate or resume treatment. For the sparse PK sites, enrolled patients will be randomly assigned 5:5:5:4 (Arm 1: Arm 2: Arm 3: Arm 4) into one of the following treatment arms until 72 patients are enrolled (19 to 20 patients each for Treatment Arms 1, 2, and 3 and 15 to 16 patients for Arm 4). For the intense PK sites, enrolled patients will be randomly assigned 1:1:1 (Arm 1: Arm 2: Arm 3) into one of the following treatment arms (6 patients each for Treatment Arms 1, 2, and 3): **Treatment Arm 1: SPR720 Low Dose:** Double-blinded SPR720 investigational product (IP) 500 mg once daily for 28 days. **Treatment Arm 2: SPR720 High Dose:** Double-blinded SPR720 IP 1000 mg once daily for 28 days. **Treatment Arm 3: Placebo:** Double-blinded placebo once daily for 28 days. **Treatment Arm 4: SOC:** At Investigator's discretion. Recommended as follows: 2-drug or 3-drug SOC, including clarithromycin 500 to 1000 mg PLUS ethambutol hydrochloride (HCl) approximately 15 mg/kg or

	azithromycin 250 to 500 mg once daily PLUS ethambutol HCl approximately 15 mg/kg once daily for 28 days. Optional rifampin 600 mg or rifabutin 300 mg once daily for up to 28 days may be added to the SOC regimen. Inform the medical monitor of alternative SOC regimens and discuss concerns or questions. Randomization will be stratified by diagnosis at enrollment as either 1) nodular-bronchiectatic or 2) fibro-cavitary NTM-PD. Clinic study visits will occur on Days 1, 7, 14, 21, and 28 (end-of-treatment [EOT] visit) (± 1 day). Patients in the double-blinded Treatment Arms 1, 2, and 3 will be evaluated at a follow-up- visit on Day 56 (± 2 days). Patients in the open-label SOC Treatment Arm 4 will be discontinued from the study after the EOT visit. Patient-collected pooled expectorated sputum will be collected on Days -1, 6, 13, 20, and 27 (i.e., the day before clinical study visits over an approximate 24-hour (h) period) for all patients and, for patients in Treatment Arms 1, 2, and 3, on Day 55 (i.e., the day before the follow-up visit on Day 56). In all cases, the patient-collected sputum will be collected on the day before the actual clinic visit. Sputum will also be collected at each clinic visit using a standard induction protocol. Patients in Treatment Arms 1, 2, and 3 will participate in the collection of blood samples for PK analysis as follows: • At least 3 selected qualifying sites will enroll a total of at least 18 patients (at least 6 per treatment arm) for intensive PK evaluation. On Days 1 and 28, blood samples for intense PK will be collected at pre-dose and post-dose: 1 h, 2 h, 4 h, 8 h, 12 h, and 24 h. On Days 7, 14, and 21, blood samples will be obtained at: pre-dose, 1 h post-dose, and just before discharge from the clinic. The acceptable windows for the PK collection are specified in the Schedule of Assessments (Table 2). • At all remaining sites, samples will be collected for sparse PK evaluation on Days 1, 7, 14, 21, and 28. Blood samples will be obtained at pre-dose, 1 h after the oral dose, and just before discharge from the clinic. • Patients randomized to the SOC arm will not participate in PK collection. Actual dates and times of blood sampling and dates and times of study drug administration will be recorded.
Planned Sample Size:	Approximately 90 patients at approximately 30 study sites in the United States
Medical Condition or Disease Under Investigation:	NTM-PD due to MAC
Key Patient Selection Criteria:	**Inclusion Criteria** Patients meeting all the following inclusion criteria should be considered for admission to the study: 1. Provided written informed consent 2. Male or female, 18 years of age or older at the time of consent 3. Has a diagnosis of NTM-PD due to MAC 4. Had at least 1 prior positive culture (sputum or bronchoalveolar lavage) for MAC in the previous 6 months 5. Has an induced sputum culture at screening positive for MAC by at least one of the following methods performed by the microbiology laboratory: quantitative culture on solid agar or growth on liquid media (MGIT) 6. Is either treatment naïve and has not received any prior treatment for MAC,

	OR if previously treated for MAC, has culture evidence of persistent, recurrent, or relapsed disease and has been off therapy for at least 6 months 7. In the opinion of the Investigator, is ready to initiate treatment (treatment naïve) or reinitiate treatment (previously treated) within the next 3 months, and for whom a delay, in order to participate in a placebo-controlled clinical trial, is considered reasonable and clinically acceptable 8. Had clinical signs and symptoms within the 6 weeks prior to consent that are consistent with NTM-PD with at least two of the following: a. chronic cough b. fatigue c. frequent throat clearing d. shortness of breath (dyspnea) e. coughing up of blood (hemoptysis) f. excessive mucus (sputum) production g. fever h. night sweats i. loss of appetite j. unintended weight loss k. wheezing l. chest pain 9. Has a measured forced expiratory volume in 1 second (% predicted FEV1) ≥30% on pulmonary function test within 3 months prior to consent 10. Has a chest radiograph (CXR) or computed tomography (CT) scan within 6 months prior to consent with findings consistent with NTM-PD. If no prior CXR or CT scan is available, a CXR or CT scan should be performed at screening to confirm eligibility 11. If female, is of nonchildbearing potential (e.g., postmenopausal as demonstrated by follicle-stimulating hormone or surgical sterilization, i.e., tubal ligation or hysterectomy), or if of childbearing potential, is willing to commit to either sexual abstinence or use of at least 2 medically accepted, effective methods of birth control in combination (e.g., condom, spermicidal gel, oral contraceptive, indwelling intrauterine device, hormonal implant/patch, injections, approved cervical ring) from consent through follow-up. Patients randomized to the SOC arm will be followed until EOT 12. If male, is willing not to donate sperm and, if engaging in sexual intercourse with a female partner who could become pregnant, willing to use a condom in addition to having his female partner use a highly effective method of birth control (such as an intrauterine device, diaphragm, oral contraceptives, injectable progesterone, subdermal implants, or a tubal ligation) from consent through follow-up. Patients randomized to the SOC arm will be followed up until EOT 13. Is willing and able to comply with all study assessments and adhere to the protocol schedule **Exclusion Criteria** Patients meeting any of the following exclusion criteria will not be enrolled in the study: 1. In the opinion of the Investigator, is not a candidate for a 3-month delay in initiation of standard multidrug therapy in order to participate in a placebo-controlled clinical trial or observation (e.g., severe symptoms, extensive disease burden) 2. Has disseminated or extrapulmonary NTM 3. Has end-stage NTM-PD or treatment-refractory NTM-PD and is unlikely to respond to protocol-specified SOC treatment 4. Had isolation on sputum cultures of any species of *Mycobacterium* other than a species included in MAC within the past 6 months

	5. Had prior isolation of MAC with macrolide resistance 6. Has active tuberculosis at time of consent 7. Has received any systemic (oral or intravenous) or inhaled antibiotic with activity against MAC between consent and randomization 8. Has a potentially confounding underlying pulmonary disease, including but not limited to cystic fibrosis, active pulmonary malignancy (primary or metastatic), NTM-hypersensitivity disease pneumoconiosis, or another advanced lung disease with a % predicted FEV1<30% 9. Has a history of a positive test for HIV, known CD4 count <200/mm^3 within the last year before consent, or a diagnosis of AIDS 10. Has an immunodeficiency or an immunocompromised condition, including neutropenia (<1000 neutrophils/mm^3 obtained from the central laboratory at screening), hematologic malignancy, a history of hematopoietic stem cell transplant, a history of solid organ transplant, is receiving immunosuppressive therapy (e.g., cancer chemotherapy, monoclonal antibodies for autoimmune disease, or medications to prevent transplant rejection), and has had long-term use of systemic corticosteroids (e.g., ≥20 mg/day of prednisone or systemic equivalent for at least 2 weeks) 11. Has a history of known or suspected *C. diff* infection 12. Has a history of epilepsy or known seizure disorder (excluding a history of childhood febrile seizures) 13. Has hepatic impairment at screening, as evidenced by alanine aminotransferase or aspartate aminotransferase >2 × upper limit of normal (ULN) or total bilirubin >1.5 × ULN, or clinical signs of cirrhosis or end-stage hepatic disease (e.g., ascites, hepatic encephalopathy) 14. Has renal impairment (creatinine clearance <50 mL/min) or end-stage renal disease requiring hemodialysis or peritoneal dialysis 15. If female, is pregnant or breastfeeding 16. Has a corrected QT (QTc) interval on electrocardiogram (ECG) >470 ms 17. Has consumed drugs or supplements that are strong cytochrome P450 (CYP)3A4 enzyme inducers or strong CYP3A4 inhibitors (see Appendix 1) within 4 weeks of randomization 18. Has consumed drugs or supplements that are substrates of the hepatic transporters OATP1B1 or OATP1B3 (see Appendix 2) within 1 week of randomization 19. Has a documented hypersensitivity reaction or anaphylaxis to SPR720 or any of the specified SOC medications 20. Has received any investigational medication in the year before the time of consent 21. Has any other condition or prior therapy, which, in the opinion of the Investigator, would make the patient unsuitable for this study, including compliance with all study assessments and adherence to the protocol schedule
Test Product, Dose, and Mode of Administration:	SPR720 500 mg dose administered by capsules po once daily for 28 days SPR720 1000 mg dose administered by capsules po once daily for 28 days
Recommended Reference Product, Dose, and Mode of Administration:	• Placebo capsules administered po once daily for 28 days • Standard of Care regimen is at the Investigator's discretion; recommended standard of care is as follows: 2-drug or 3-drug SOC administered po once daily for 28 days as follows o Clarithromycin 500-1000 mg, plus ethambutol HCl 15 mg/kg or o Azithromycin 250-500 mg, plus ethambutol HCl 15 mg/kg

	• Optional rifampin 600 mg or rifabutin 300 mg po once daily may be added to the SOC regimen for up to 28 days.
Duration of Treatment:	For patients in Treatment Arms 1, 2, and 3, study duration is a total of approximately 98 days (including a 42-day screening period, 28-day treatment period, and 28-day follow-up period). For patients in Treatment Arm 4, study duration is a total of approximately 70 days (including a 42-day screening period and 28-day treatment period).
Criteria for Evaluation:	
Primary **Pharmacokinetic Endpoints**	• Maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration-time curve from zero to τ, where τ is the dosing interval ($AUC_{0-\tau}$), and accumulation ratio of SPR719 on Day 1 and Day 28
Secondary **Safety Endpoints**	• Reported adverse events (AEs) • Clinically meaningful change in physical examination findings • Concomitant medication usage • Changes from baseline in laboratory tests • Clinically significant (CS) out-of-normal range laboratory tests • Shifts from baseline in selected laboratory tests using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0 shift categories • Changes from baseline in vital sign measurements (body temperature, pulse, respiratory rate, blood pressure) • 12-lead ECGs
[redacted]	[redacted]

	[redacted]
Statistical Methods:	Presentation of PK and safety data will be produced for the PK Population and Safety Population, respectively. A PK Population model will be developed using data from the completed Phase 1 study of single-ascending/multiple-ascending doses in normal healthy volunteers (Study SPR720-101). This population model will be used to estimate PK parameters for patients in the SPR720-201 study. Dates and times of blood samples as well as dates and times of study drug administration will be recorded. Plasma concentration-time data from intensive PK sampling patients will be subjected to noncompartmental PK analysis. Day 1 and Day 28 PK parameters including, but not limited to, C_{max}, T_{max}, area under the concentration-time curve from zero to last concentration (AUC_{last}), $AUC_{0-\tau}$, accumulation ratio, and plasma concentration at the end of a dosing interval at steady state (taken directly before next administration) (C_{trough}) will be determined for SPR719. Concentration data from sparse sampling will be compiled for summary statistics of C_{trough} across various days. Concentration data from SPR720 recipients will be used for the development of a PK Population model, for PK analysis, and for estimation of individual PK profiles in patients with sparse sampling, which will be reported in a separate report. Patient disposition, demographics and baseline characteristics, IP exposure, and prior and concomitant medications will be summarized. All safety presentations will be descriptive, and all summaries will be displayed by treatment arm. Summary statistics for continuous variables will include the sample size, mean, standard deviation, minimum, median, and maximum. For categorical data, summaries will include the frequency and percentage. The incidence and frequency of AEs and serious AEs will be summarized by treatment arm by severity and relationship. Laboratory results will be summarized by treatment arm for each time point and change from baseline at each postbaseline time point. Frequency and percentage for laboratory tests that are considered CS and out of range will be presented. In addition, shifts from baseline using CTCAE v5.0 by treatment arm for selected laboratory tests (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, alkaline phosphatase, total bilirubin, amylase, lipase, blood urea nitrogen, serum creatinine, creatinine clearance, hemoglobin, hematocrit, neutrophils, lymphocytes, and erythrocytes) will be presented. Vital signs and 12-lead ECG parameters will be summarized and will include change from baseline. Twelve-lead ECGs including QTc intervals will also be summarized as clinically meaningful changes in physical examination findings. [redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical/Therapeutic/Chemical
AUC_{last}	area under the concentration-time curve from zero to last concentration
$AUC_{0-\tau}$	area under the concentration-time curve from zero to τ, where τ is the dosing interval
CFR	Code of Federal Regulations
CFU	colony-forming unit
C_{max}	maximum plasma concentration
CRO	contract research organization
CS	clinically significant
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	plasma concentration at the end of a dosing interval (taken directly before next administration)
CXR	chest radiograph
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
h	hour
HCl	hydrochloride
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	investigational product
IRB	institutional review board

Abbreviation	Definition
IRT	interactive randomization technology
ITT	intent to treat
IV	intravenous
MAC	*Mycobacterium avium* complex
MAC-PD	*Mycobacterium avium* complex pulmonary disease
MedDRA	Medical Dictionary for Regulated Activities
MGIT	Mycobacteria Growth Indicator Tube
micro-ITT	microbiological intent to treat
NTM	nontuberculous mycobacteria
NTM-PD	nontuberculous mycobacteria pulmonary disease
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic(s)
po	orally
PRO	patient-reported outcome
QTc	corrected QT
QTcF	corrected QT interval according to Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
T_{max}	time to reach C_{max}
TTP	time to positivity
ULN	upper limit of normal
US	United States

SAFETY REPORTING CONTACT INFORMATION

Contact details for serious adverse event (SAE) reporting	[redacted]
Medical Monitor	[redacted]

1. INTRODUCTION

1.1. Background

1.1.1. Nontuberculous Mycobacterial Pulmonary Disease

Nontuberculous mycobacterial pulmonary disease (NTM-PD) is a chronic, progressive disease that occurs through inhalation of pathogenic mycobacteria from environmental sources, including aerosols from water and dust from soil (Falkinham 2015). The most commonly reported nontuberculous mycobacterial (NTM) species causing NTM-PD in the United States (US) and worldwide are *Mycobacterium avium* complex (MAC), which includes *Mycobacterium avium*, *Mycobacterium intracellulare*, *Mycobacterium chimaera* and several other species and subspecies, *Mycobacterium kansasii*, and *Mycobacterium abscessus* (Griffith et al 2007; Falkinham 2015; Haworth et al 2017).

Nontuberculous mycobacterial pulmonary disease predominantly occurs in patients with underlying lung disease, including chronic obstructive pulmonary disease and bronchiectasis, patients with cystic fibrosis, older males, and nonsmoking women over the age of 50 years without previously diagnosed lung disease (Lady Windermere syndrome). Development of NTM-PD is based on a variety of pathogen and host-specific factors for which the pathophysiology is poorly understood (Griffith et al 2007). Risk factors for disease include underlying immunodeficiency, treatment with antitumor necrosis factor agents, and exposure to environmental water sources (Griffith et al 2007; Henkle and Winthrop 2015; Adjemian at al 2017; Baldwin et al 2019). The natural history of this disease is varied based on pathogen and host factors, but 5-year mortality rates as high as 35% have been reported for *M. abscessus* pulmonary disease. Risk factors for progressive lung disease include infection with *M. abscessus*, the presence of cavitary lung disease, and low body weight/body mass index (Dhillon and Watanakunakorn 2000; Lam et al 2006; Griffith et al 2007; Gochi et al 2015).

Based on the patient- and pathogen-specific factors contributing to development of disease, there is significant variability in the clinical presentation of patients with NTM-PD, and definitive diagnostic criteria are lacking. As a result, recommendations in current treatment guidelines for pulmonary NTM infections are based predominantly on observational clinical data supported by in vitro susceptibility data and expert opinion. Understanding the epidemiology and treatment of these infections is complicated by the large number of causative species, the varied clinical manifestations of disease (fibronodular, cavitary, bronchiectatic, etc), and geographical variation in the prevalence of infection (Fiske et al 2016; Adjemian et al 2017; Lande et al 2018).

Patients at the US Food and Drug Administration (FDA) NTM Open Public Meeting (CDER 2016) described debilitating symptoms such as a relentless and severe deep cough, hemoptysis, progressive fatigue, stabbing chest pain, loss of appetite, along with fever, night sweats, and weight loss, which often indicate advanced disease (Baldwin et al 2019). In the results of a survey conducted by the NTM Info & Research patient advocacy group and presented at the FDA Workshop, *Development of Antibacterial Drugs for Treatment of Nontuberculous Mycobacterial Disease* (NTMir 2019), the top symptoms that plagued respondents and had the greatest impact on their lives were fatigue, cough, shortness of breath, night sweats, and weight loss. When asked about their preferences in treatment outcomes, the majority of the respondents selected improving quality of life, increasing energy, and reducing fatigue.

Clinical diagnosis of NTM-PD is based on assessment of specific clinical, radiographic and microbiologic criteria as outlined in the 2007 American Thoracic Society and Infectious Disease Society of America treatment guidelines (Griffith et al 2007).

1.1.2. Unmet Need

Therapy for NTM infections generally requires prolonged treatment (months to years) with antibiotic combination regimens that are poorly tolerated and, in many cases, ineffective. The therapeutic regimens vary based on the specific causative pathogen (MAC, *M. abscessus*, *M. kansasii*), the presence or absence of pulmonary cavities at the initiation of therapy, the response to prior attempts at therapy, comorbidities such as renal dysfunction, and the individual patient's ability to tolerate oral, aerosolized, or intravenous (IV) therapy (Griffith et al 2007; Griffith and Aksamit 2016; Haworth et al 2017; Lee et al 2019). There is currently only 1 antimicrobial agent, Arikayce®, that is approved for the treatment of NTM-PD. It is approved for patients with MAC pulmonary disease (MAC-PD) as part of a combination antibacterial drug regimen in adult patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy and who have limited or no alternative treatment options (Insmed 2018). Current standard of care (SOC) therapy for MAC-PD in the US, as outlined in the joint treatment guidelines developed in 2007 by the American Thoracis Society and Infectious Disease Society of America (Griffith et al 2007), recommends prolonged treatment with 3 or 4 antimicrobial agents in combination for up to 18 months, based on pathogen- and patient-specific factors. Suggested agents for MAC-PD include clarithromycin or azithromycin, rifampin or rifabutin and ethambutol, and IV streptomycin or amikacin (Griffith et al 2007; Haworth et al 2017). Among these agents, the macrolide component appears to be particularly important, as emergence of resistance to clarithromycin or azithromycin is a risk factor for disease progression and mortality. This complex multidrug therapy is often complicated by side effects and/or drug interactions that require discontinuation of one or more of the agents and predisposes patients to treatment failure and development of drug-resistant NTM, further complicating therapy (Wallace et al 1994; CDER 2016; Philley et al 2016). Importantly, none of the guideline-based therapeutic options, as individual drugs or combination regimens, have been evaluated for safety and efficacy under controlled conditions in prospectively designed clinical studies in patients with NTM-PD and none are specifically approved for such use.

In addition to complex antimicrobial therapy, patients diagnosed with NTM-PD are required to undertake aggressive daily respiratory hygiene regimens including chest physiotherapy and nebulizer treatments in order to clear copious pulmonary secretions and prevent atelectasis. These adjunctive therapies are time-consuming and can have an adverse impact on patients' quality of life (CDER 2016).

Although up to 86% of patients with pulmonary disease due to MAC may achieve sputum conversion (from positive to negative) on therapy (Wallace et al 2014), the translation of microbiological sputum clearance to immediate or long-term clinical outcomes is unclear since controlled and prospectively designed clinical studies to assess the link are lacking (Griffith et al 2015; ALIS 2018). Once established, NTM-PD can cause progressive destruction of the pulmonary parenchyma, and, despite prolonged therapy, outcomes remain unsatisfactory, with high rates of reinfection and mortality (Jarand et al 2011; Wallace et al 2014). Mortality rates

due to NTM-PD range from 25% to 40% at 5 years (Cadelis et al 2017). The main factors of poor outcomes identified in mortality studies at 5 years corresponded to an advanced age, the existence of respiratory comorbidities, radiological cavity lesions, and specific mycobacterial species, including *Mycobacterium xenopi* (Cadelis et al 2017).

The high rate of intrinsic resistance of NTM species to conventional antibiotics and antimycobacterial agents, as well as the poor tolerability exhibited to agents utilized in current SOC regimens, contributes to relatively high mortality rates for NTM-PD. The development and approval of novel drugs with demonstrated efficacy and improved tolerability for NTM-PD is thus a critical research priority (Baldwin et al 2019).

1.1.3. SPR720

Spero is developing SPR720 as an oral therapy for the treatment of patients with NTM-PD caused by MAC. SPR720 is a chemically stable phosphate prodrug that converts rapidly to SPR719, the active moiety, in vivo.

SPR719 was identified and optimized through structure-guided design and iterative structure-activity relationship studies; it is an aminobenzimidazole, a novel class of antibacterial agents that target the ATPase subunits of gyrase and, when present, topoisomerase. These enzymes are highly conserved and essential in bacteria for DNA replication (Locher et al 2015). In mycobacteria, only gyrase enzymes have been identified. The potent enzyme activity demonstrated by SPR719 translates to growth inhibition of a range of pathogens such as *Mycobacterium tuberculosis* (Locher et al 2015; O'Dowd et al 2015) and nontuberculosis mycobacteria such as MAC, *M. abscessus* complex, and *M. kansasii*, including isolates that are resistant to the current SOC agents amikacin, clarithromycin, and, importantly, the fluoroquinolones (Brown-Elliott et al 2018).

1.1.3.1. SPR720 Nonclinical Development

Nonclinical studies conducted to date on SPR720 and/or its active moiety SPR719 have demonstrated acceptable safety and pharmacokinetic (PK) profiles. No adverse effect levels identified in repeat-dose toxicity studies of SPR720 in rats and in monkeys provide exposure multiples to the anticipated human therapeutic exposure, and, in rats, SPR720 was determined to be nongenotoxic. In safety pharmacology studies in vitro and in monkeys and rats, SPR720 and/or its active moiety SPR719 exhibited no adverse effects on the normal functioning of the cardiovascular, respiratory, or central nervous systems.

1.1.4. SPR720 Clinical Development

Spero has completed a single Phase 1 study in the United Kingdom in healthy volunteers to assess the safety, tolerability, and PK of SPR720 (Study SPR720-101). A comprehensive set of nonclinical studies has also been completed that evaluated the PK/metabolism, safety pharmacology, and toxicity of SPR720 (prodrug) and SPR719 (active moiety).

The advancement of SPR720 into the Phase 1 clinical assessment was based on a favorable profile exhibited in a suite of preclinical in vitro and in vivo safety, toxicology, absorption, distribution, metabolism, and excretion studies, as well as its demonstration of

potency in vitro and in vivo activity versus multiple, clinically important species of NTM, including MAC and *M. abscessus*.

1.2. Risks and Benefits

SPR720 has demonstrated in vitro and in vivo biological activity against a range of NTM species, including MAC, the most common pathogen group in NTM-PD, and *M. abscessus*, a highly resistant organism associated with a high rate of mortality.

The collective preclinical data to date suggests that SPR720 has an acceptable safety profile, encouraging target pathogen efficacy, drug distribution to key sites of infection such as the lung, and a wide therapeutic margin.

SPR720 has been successfully evaluated in a single-ascending-dose/multiple-ascending-dose Phase 1 study in humans (Study SPR720-101). SPR720 was safe and well tolerated in healthy volunteers at doses believed to be in the therapeutic range for up to 14 days of dosing. The safety, tolerability, and PK data from this Phase 1 study further support a favorable risk-benefit profile for SPR720.

SPR720 is a novel agent with the potential to be the first oral antibiotic designed to treat NTM disease, a rare orphan disease.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to evaluate the PK of SPR719 generated from the orally (po) administered SPR720 prodrug in a patient population with NTM-PD.

2.2. Secondary Objective

The secondary objective of this study is to evaluate the safety and tolerability of SPR720 in a patient population with NTM-PD.

[redacted]

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a Phase 2a, multicenter, randomized, partially blinded, placebo- and comparator-controlled study to evaluate the safety, tolerability, PK, and efficacy of 2 dose levels of SPR720 compared with placebo or SOC for the treatment of patients with NTM-PD due to MAC. The SPR720 and placebo arms will be double blinded, and the SOC arm will be open label.

Approximately 90 male and female patients 18 years of age and older with a diagnosis of NTM-PD due to MAC will be enrolled and treated for 28 days. Treatment-naïve patients must be ready to initiate treatment within the next 3 months. Patients who have received prior treatment may be eligible if they have culture evidence of persistent, recurrent, or relapsed disease; have been off therapy for at least 6 months; and are likely to reinitiate or resume treatment.

For the sparse PK sites, enrolled patients will be randomly assigned 5:5:5:4 (Arm 1: Arm 2: Arm 3: Arm 4) into one of the following treatment arms until 72 patients are enrolled (19 to 20 patients each for Treatment Arms 1, 2, and 3 and 15 to 16 patients for Arm 4). For the intense PK sites, enrolled patients will be randomly assigned 1:1:1 (Arm 1: Arm 2: Arm 3) into one of the following treatment arms (6 patients each for Treatment Arms 1, 2, and 3):

- **Treatment Arm 1: SPR720 Low Dose:** Double-blinded SPR720 investigational product (IP) 500 mg once daily for 28 days.
- **Treatment Arm 2: SPR720 High Dose:** Double-blinded SPR720 IP 1000 mg once daily for 28 days.
- **Treatment Arm 3: Placebo:** Double-blinded placebo once daily for 28 days.
- **Treatment Arm 4: SOC:** At Investigator's discretion. Recommended as follows: 2-drug or 3-drug SOC, including clarithromycin 500 to 1000 mg PLUS ethambutol hydrochloride (HCl) approximately 15 mg/kg or azithromycin 250 to 500 mg once daily PLUS ethambutol HCl approximately 15 mg/kg once daily for 28 days. Optional rifampin 600 mg or rifabutin 300 mg once daily for up to 28 days may be added to the SOC regimen.

Inform the medical monitor of alternative SOC regimens and discuss concerns or questions.

Randomization will be stratified by diagnosis at enrollment as either 1) nodular-bronchiectatic or 2) fibro-cavitary NTM-PD.

Clinic study visits will occur on Days 1, 7, 14, 21, and 28 (end-of-treatment [EOT] visit) (± 1 day). Patients in the double-blinded Treatment Arms 1, 2, and 3 will be evaluated in a follow-up visit on Day 56 (± 2 days) (28 days after EOT). Patients in the open-label SOC Treatment Arm 4 will be discontinued from the study after the EOT visit.

Baseline symptoms will include chronic cough, fatigue, frequent throat clearing, dyspnea, hemoptysis, excessive mucus (sputum) production, fever, night sweats, loss of appetite, unintended weight loss, wheezing, and chest pain. A multi-dimensional patient-reported outcome (PRO) (see Appendix 3) instrument assessing severity and changes in these baseline symptoms

will be administered at clinic visits on Days 1, 7, 14, 21, and 28 in all arms and Day 56 in Treatment Arms 1, 2, and 3.

Patient-collected pooled expectorated sputum will be collected on Days –1, 6, 13, 20, and 27 (i.e., the day before clinical study visits over an approximate 24-hour [h] period) for all patients and, for patients in Treatment Arms 1, 2, and 3, on Day 55 (i.e., the day before the follow-up visit on Day 56). In all cases, the patient-collected sputum will be collected on the day before the actual clinic visit. Sputum will also be collected at each clinic visit using a standard induction protocol.

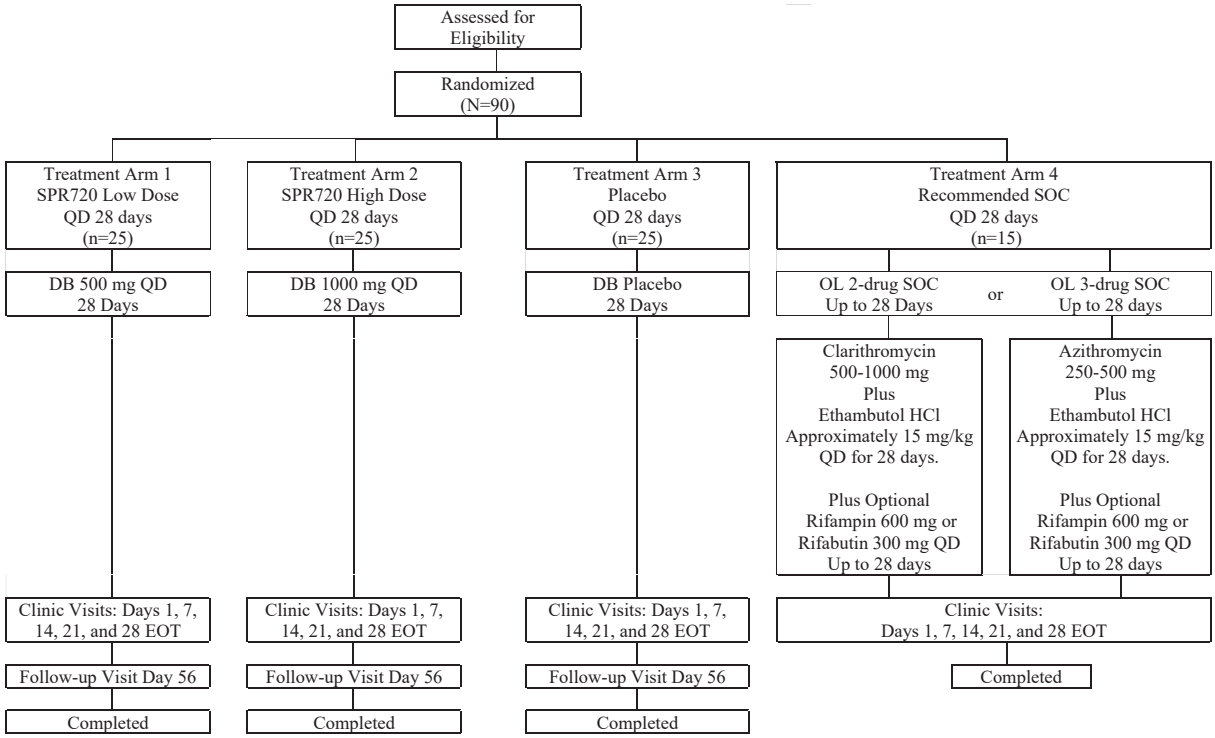
Patients in Treatment Arms 1, 2, and 3 will participate in the collection of blood samples for PK analysis as follows:

- At least 3 selected qualifying sites will enroll a total of at least 18 patients (at least 6 per treatment arm) for intensive PK evaluation. On Days 1 and 28, blood samples for intense PK will be collected at pre-dose and post-dose: 1 h, 2 h, 4 h, 8 h, 12 h, and 24 h. On Days 7, 14, and 21, blood samples will be obtained at: pre-dose, 1 h post-dose, and just before discharge from the clinic. The acceptable windows for PK collection are specified in the Schedule of Assessments (Table 2).
- At all remaining, samples will be collected for sparse PK evaluation, on Days 1, 7, 14, 21, and 28. Blood samples will be obtained at pre-dose, 1 h post-dose, and just before discharge from the clinic.
- Patients randomized to the SOC arm will not participate in PK collection.

Actual dates and times of blood samples as well as dates and times of study drug administration will be recorded. Please refer to the Schedule of Assessments (Table 2) for allowable windows.

A diagram of the study design is presented in Figure 1.

Figure 1: Study Design



Abbreviations: DB=double-blinded; EOT=end of treatment; HCl=hydrochloride; OL=open label; QD=once daily; SOC=standard of care.

3.2. Study Duration

Patients will be screened within 42 days prior to the first dose of study drug. All patients will be treated for 28 days. Patients in Treatment Arms 1, 2, and 3, only, will have a follow-up visit 28 days after the completion of therapy. The maximum duration of participation for each patient will be approximately 98 days (including a 42-day screening period, 28-day treatment period, and 28-day follow-up period) for Treatment Arms 1, 2, and 3, and approximately 70 days (including a 42-day screening period and 28-day treatment period) for Treatment Arm 4 SOC recipients.

3.3. Selection of Study Population

Approximately 90 male and female patients, 18 years of age and older, with a diagnosis of NTM-PD due to MAC will be enrolled in the study.

Specific entry criteria are detailed in Section 3.3.1 and Section 3.3.2.

3.3.1. Inclusion Criteria

Patients meeting all the following inclusion criteria should be considered for admission to the study:

1. Provided written informed consent
2. Male or female, 18 years of age or older at the time of consent
3. Has a diagnosis of NTM-PD due to MAC
4. Had at least 1 prior positive culture (sputum or bronchoalveolar lavage) positive for MAC in the previous 6 months
5. Has an induced sputum culture at screening positive for MAC by at least one of the following methods performed by the microbiology laboratory: quantitative culture on solid agar or growth on liquid media (MGIT)
6. Is either treatment naïve and has not received any prior treatment for MAC, OR if previously treated for MAC, has culture evidence of persistent, recurrent, or relapsed disease and has been off therapy for at least 6 months
7. In the opinion of the Investigator, is ready to initiate treatment (treatment naïve) or reinitiate treatment (previously treated) within the next 3 months, and for whom a delay, in order to participate in a placebo-controlled clinical trial, is considered reasonable and clinically acceptable
8. Had clinical signs and symptoms within the 6 weeks before the date of consent that are consistent with NTM-PD with at least two of the following:
    a. chronic cough
    b. fatigue
    c. frequent throat clearing
    d. shortness of breath (dyspnea)
    e. coughing up of blood (hemoptysis)

f. excessive mucus (sputum) production
g. fever
h. night sweats
i. loss of appetite
j. unintended weight loss
k. wheezing
l. chest pain

9. Has a measured forced expiratory volume in 1 second (% predicted FEV1) ≥30% on pulmonary function test within 3 months prior to consent
10. Has a chest radiograph (CXR) or computed tomography (CT) scan within 6 months prior to consent with findings consistent with NTM-PD. If no CXR or CT scan is available, a CXR or CT scan should be performed at screening to confirm eligibility.
11. If female, is of nonchildbearing potential (e.g. postmenopausal as demonstrated by follicle-stimulating hormone or surgical sterilization, i.e., tubal ligation or hysterectomy), or if of childbearing potential, be willing to commit to either sexual abstinence or use of at least 2 medically accepted, effective methods of birth control in combination (e.g., condom, spermicidal gel, oral contraceptive, indwelling intrauterine device, hormonal implant/patch, injections, approved cervical ring) from consent through follow-up. Patients randomized to the SOC arm will be followed up until EOT
12. If male, is willing not to donate sperm and, if engaging in sexual intercourse with a female partner who could become pregnant, a willingness to use a condom in addition to having his female partner use a highly effective method of birth control (such as an intrauterine device, diaphragm, oral contraceptives, injectable progesterone, subdermal implants, or a tubal ligation) from consent through follow-up. Patients randomized to the SOC arm will be followed up until EOT
13. Is willing and able to comply with all study assessments and adhere to the protocol schedule

3.3.2. Exclusion Criteria

Patients meeting any of the following exclusion criteria will not be enrolled in the study:

1. In the opinion of the Investigator, is not a candidate for a 3-month delay in initiation of standard multidrug therapy in order to participate in a placebo-controlled clinical trial or observation (e.g., severe symptoms, extensive disease burden)
2. Has disseminated or extrapulmonary NTM
3. Has end-stage NTM-PD or treatment-refractory NTM-PD and is unlikely to respond to protocol-specified SOC treatment
4. Had isolation on sputum cultures of any species of *Mycobacterium* other than a species included in MAC within the past 6 months
5. Had prior isolation of MAC with macrolide resistance
6. Has active tuberculosis at the time of consent

7. Has received any systemic (oral or IV) or inhaled antibiotic with activity against MAC between consent and randomization
8. Has a potentially confounding underlying pulmonary disease, including but not limited to cystic fibrosis, active pulmonary malignancy (primary or metastatic), NTM-hypersensitivity disease pneumoconiosis, or another advanced lung disease with a % predicted FEV1<30%
9. Has a history of a positive test for HIV, known CD4 count <200/mm^3 within the last year before time of consent, or a diagnosis of AIDS
10. Has an immunodeficiency or an immunocompromised condition, including neutropenia (<1000 neutrophils/mm^3 obtained from the central laboratory at screening), hematologic malignancy, a history of hematopoietic stem cell transplant, a history of solid organ transplant, is receiving immunosuppressive therapy (e.g., cancer chemotherapy, monoclonal antibodies for autoimmune disease, or medications to prevent transplant rejection), and has had long-term use of systemic corticosteroids (e.g., ≥20 mg/day of prednisone or systemic equivalent for at least 2 weeks)
11. Has a history of known or suspected *C. diff* infection
12. Has a history of epilepsy or known seizure disorder (excluding a history of childhood febrile seizures)
13. Has hepatic impairment at screening, as evidenced by alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × upper limit of normal (ULN) or total bilirubin >1.5 × ULN, or clinical signs of cirrhosis or end-stage hepatic disease (e.g., ascites, hepatic encephalopathy)
14. Has renal impairment (creatinine clearance <50 mL/min) or end-stage renal disease requiring hemodialysis or peritoneal dialysis
15. If female, is pregnant or breastfeeding
16. Has a corrected QT (QTc) interval on electrocardiogram (ECG) >470 ms
17. Has consumed drugs or supplements that are strong cytochrome P450 (CYP)3A4 enzyme inducers or strong CYP3A4 inhibitors (see Appendix 1) within 4 weeks of randomization
18. Has consumed drugs or supplements that are substrates of the hepatic transporters OATP1B1 or OATP1B3 (see Appendix 2) within 1 week of randomization
19. Has a documented hypersensitivity reaction or anaphylaxis to SPR720 or any of the specified SOC medications
20. Has received any investigational medication in the year before the time of consent
21. Has any other condition or prior therapy, which, in the opinion of the Investigator, would make the patient unsuitable for this study, including compliance with all study assessments and adherence to the protocol schedule

Patients who are unable to comply with the requirements of the study or who in the opinion of the Investigator should not participate in the study are not eligible.

3.3.3. Premature Discontinuation of Investigational Product

Premature discontinuation of the IP by the Investigator is an important discussion that should include the Medical Monitor, if feasible, before the IP is discontinued.

Possible reasons for premature discontinuation from IP due to safety reasons include, but are not limited to, the following:

- Occurrence of an AE that, in the opinion of the Investigator, warrants the patient's permanent discontinuation from IP administration
- Hy's law criteria are met, defined by at least 3-fold elevations of ALT or AST above the ULN, elevation of serum total bilirubin to >2 × ULN without elevated serum alkaline phosphatase, and no other disease or condition can be found to explain the liver test abnormalities
- Known pregnancy or breastfeeding during the study drug administration period

Possible reasons for discontinuation from the IP *due to insufficient therapeutic effect* include, but are not limited to, clinical worsening or lack of clinical progress. If the Investigator deems the benefit-to-risk ratio of IP continuance acceptable, study drug administration of at least 48 h is encouraged before discontinuation from IP therapy for insufficient effect.

3.3.4. Withdrawal from Study

A patient will be considered to have completed the study when he or she completes the EOT visit for patients in Treatment Arm 4 and the follow-up visit on Day 56 (± 2 days) for patients in Treatment Arms 1, 2, and 3.

Patients may withdraw from the study or be withdrawn at the request of the Investigator or Sponsor at any time. Examples of reasons for study withdrawal include the following:

- The patient withdraws consent or requests withdrawal from the study for any reason
- The patient is lost to follow-up
- The patient fails to comply with protocol requirements or study-related procedures
- The Investigator determines that it is in the best interest of the patient to withdraw from the study protocol for reasons other than an adverse event (AE)
- The study is terminated or temporarily suspended by the Sponsor or a regulatory authority for any reason including, but not limited to, study drug-related unexpected life-threatening serious AEs (SAEs) detected during safety monitoring (e.g., torsade de pointes or other ventricular arrhythmias), and 2 or more of the same drug-related (possible or probable) treatment-emergent SAE

Patients who wish to withdraw completely from this clinical study during the treatment period should be encouraged to undergo the EOT safety and efficacy assessments at the time of withdrawal as shown in the Schedule of Assessments (Table 2). For a patient who agrees to complete the EOT visit, blood draws for PK will not be conducted. In addition, for women of child-bearing potential a pregnancy test should be conducted at this visit. Once a patient withdraws consent, no further data will be collected.

A patient is considered lost to follow-up if he or she fails to return to the study clinic for scheduled visits and is unable to be contacted by the study site. The site must attempt to contact the patient at least twice by phone or letter, and, if no response is obtained from the patient, a certified letter will be sent requesting that the patient contact the Investigator and asking that they return any unused IP and return to the site for a final evaluation. Documentation of these efforts to contact the patient must be recorded in the patient's study file.

3.3.5. Criteria for Stopping the Study

The Sponsor, in consultation with the Medical Monitor, upon review of available data may stop the study. Possible reasons include, but are not limited to, the following:

- Occurrence of an SAE assessed as probably related to IP and resulting in death
- Occurrence of 2 or more SAEs of the same character that are determined to be clinically significant (CS) and assessed as probably related to IP
- Occurrence of 2 or more AEs of acute pancreatitis, defined as the presence of abdominal pain, elevated pancreatic enzymes (amylase and lipase) ≥5 × ULN and determined to be CS, and an abdominal ultrasound with finding consistent with acute pancreatitis
- Occurrence of 2 or more AEs of acute hepatitis meeting Hy's Law criteria, defined by at least 3-fold elevations of ALT or AST above the ULN, elevation of serum total bilirubin to >2 × ULN without elevated serum alkaline phosphatase, and no other disease or condition can be found to explain the liver test abnormalities

3.3.6. Replacement of Patients

Patients prematurely withdrawn from the study will not be replaced. Patients may be rescreened at the Investigator's discretion.

4. INVESTIGATIONAL PRODUCT

4.1. Identity of the Investigational Product

Investigational product refers to both SPR720 and placebo in this Investigational Product section.

SPR720 will be administered po as 250 mg capsules containing SPR720 as the active substance with no additional excipients. The capsules are white, opaque, size 0, hard gelatin capsules containing a white powder. Placebo doses will also be administered po as white, opaque, size 0, hard gelatin capsules containing an approximately equivalent weight of microcrystalline cellulose (white powder).

SPR720 drug product and placebo are manufactured by Patheon UK Limited (Abingdon, Oxfordshire, UK) under Good Manufacturing Practice conditions and packaged, labeled, and distributed by Almac Clinical Services.

SPR720 and placebo are packaged in blister cards of 28 capsules each and then packaged into wallets that will be given to the patient.

Additional information is provided in the investigator's brochure (IB) and in the Pharmacy Manual.

Standard of care (SOC) will be obtained by the study sites or by prescription. Refer to the Product Package Inserts for detailed information regarding SOC treatments.

4.2. Dosage Schedule

Dosing for each treatment arm is displayed in Table 1. Study drug will be taken po once daily for 28 days (Days 1 through 28). Dosing for Treatment Arms 1, 2, and 3 will take place at the clinic on study visit days. The clinic and patient should try to schedule clinic visits as early as possible in the morning to accommodate pre-dose study activities and dosing, preferably before a meal. Patients in Treatment Arms 1, 2, and 3 should make every effort to take the IP at the same time in the morning approximately an hour before a morning meal on an empty stomach. There are no liquid restrictions. Patients will receive a supply of IP and instructions for documenting at-home dosing. If a patient experiences IP tolerability issues while at home, the site should instruct the patient to call the Investigator. The Investigator may instruct the patient to take their dose with a snack or meal, if clinically indicated, to alleviate tolerability concerns. Dosing for Treatment Arm 4 (SOC) should occur per specific prescribing information instructions.

Table 1: Study Treatments

Treatment Arm 1	Double-blinded SPR720 IP 500 mg (2 capsules of 250 mg SPR720 and 2 capsules of placebo) po once daily
Treatment Arm 2	Double-blinded SPR720 IP 1000 mg (4 capsules of 250 mg SPR720) po once daily
Treatment Arm 3	Double-blinded placebo (4 capsules of placebo) po once daily
Treatment Arm 4	Standard of Care regimen is at the Investigator's discretion; recommended 2-drug or 3-drug SOC, consisting of either: • Clarithromycin 500-1000 mg, plus ethambutol HCl 15 mg/kg po once daily or • Azithromycin 250-500 mg, plus ethambutol HCl 15 mg/kg po once daily Optional rifampin 600 mg or rifabutin 300 mg po once daily may be added to the SOC regimen for up to 28 days. Inform the medical monitor of alternative SOC regimens and discuss concerns or questions.

Abbreviations: HCl=hydrochloride; IP=investigational product; po=orally; SOC=standard of care.
Note: Patients will be treated for 28 days.

4.3. Treatment Assignment

Patients will be randomized (assigned to a treatment) by the site using interactive randomization technology (IRT).

Only the designated unblinded study personnel will have access to the randomization schedule until the study is completed and approval to unblind the treatment arm assignments has been made. Complete details regarding handling, storage, and security of the randomization schedule will be documented.

At the sparse PK sites, patients will be randomized to 1 of 4 treatment arms in a ratio of 5:5:5:4 (SPR720 low dose, SPR720 high dose, placebo, and SOC). The SPR720 and placebo arms will be double blinded, and the SOC arm will be open label. At intense PK sites a total of at least 18 patients will be randomized to Treatment Arms 1, 2, and 3 in a ratio of 1:1:1.

The IRT will stratify randomization by diagnosis at enrollment as either 1) nodular-bronchiectatic or 2) fibro-cavitary NTM-PD.

Patients will be identified by a unique 10-digit patient identifier (e.g., 201-YYY-ZZZZ) in which the first 3 digits indicate the study identifier (e.g., 201), the second 3 digits indicate the site number, and the final 4 digits indicate the number assigned at randomization. For example, the first patient randomized at site 001 will be identified by the number 201-001-0001. Spero Therapeutics, Inc. will assign site numbers. As a double-blind study, the Investigators, the site staff, the Sponsor, and clinical monitors will not be aware of the treatment assigned to the

individual study patients except for Treatment Arm 4 (SOC), which is open label. Specific, documented staff at the sponsor and contract research organization (CRO) will be unblinded to treatment assignments.

4.4. Drug Packaging and Blinding

The IP will be labeled in such a way that the blind is maintained.

The Investigator can receive a patient's assigned treatment through the IRT system if knowledge of the IP is necessary for emergency treatment. If possible, the Medical Monitor should be consulted before breaking the code. In any case, the Investigator must record the date, time, and reason for breaking the code. The Investigator, once unblinded, should not share the treatment assignment with site, Sponsor, or CRO personnel. The Sponsor must be notified as soon as possible if the blind must be broken.

A copy of the randomization code will be maintained securely by the CRO. Designated unblinded personnel will be able to access the randomization code if needed.

Additional information can be found in the Pharmacy Manual.

4.5. Drug Inventory and Accountability

The Investigator must keep an accurate accounting of the number of IP units delivered to the site, dispensed to patients, returned to the Investigator by the patient, and returned to the Sponsor or destroyed locally or other disposition during and at the completion of the study.

The IP is to be used in accordance with the protocol by patients who are under the direct supervision of the Investigator. The IP will be sent home with patients for drug administration between clinic visits. Investigators should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all IP received at the site before final disposition. Procedures for the return or destruction of both the used and unused IP will be described in the Pharmacy Manual.

Investigators are required to report IP quality complaints to the Sponsor as described in the Pharmacy Manual.

Full details of IP receipt and storage will be documented in the Pharmacy Manual.

4.6. Treatment Compliance

All patients will be asked to document in a provided diary the date and time of each IP or SOC dose taken at home, along with other requested information related to IP administration.

Patients will be required to bring the IP wallet the subsequent clinic visit including any remaining capsules that have not been taken. At each visit, the patient's remaining capsules and the diary will be retrieved by the Investigator and compliance assessed.

Investigational product wallets must be returned at each visit, as compliance will be assessed by capsule counts. Investigational product noncompliance for a patient is defined as taking less than 80% or more than 120% of IP during the treatment period (Day 1 through EOT). Discontinuation for noncompliance is at the Investigator's discretion and should be documented accordingly.

4.7. Concomitant Illnesses and Treatments

4.7.1. Concomitant Illnesses

Medical history, including significant illnesses, should be documented in the electronic case report form (eCRF) according to completion guidelines.

Additional illnesses present at the time informed consent is given are to be regarded as concomitant illnesses. Illnesses first occurring or detected after first dose and/or worsening of a concomitant illness during the study are to be documented as AEs in the eCRF.

4.7.2. Concomitant Treatments

Concomitant medications and treatments, defined as treatments taken after the first dose of IP and SOC, should be recorded in the eCRF according to completion guidelines. Medications and treatments taken before the first dose of IP or SOC will not be recorded in the eCRF.

Patients should not have used any systemic (po or IV) or inhaled antibiotic with activity versus MAC between screening and randomization. Drugs or supplements that are strong CYP3A4 enzyme inducers or inhibitors (see Appendix 1) within 4 weeks of randomization and during the study are prohibited. Hepatic transporters, OATP1B1 or OATP1B3, (see Appendix 2) within 1 week of randomization and during the study are prohibited.

Any medication or therapy that is taken by or administered to the patient during the study will be recorded (see completion guidelines for eCRF).

5. ASSESSMENTS

Unless otherwise indicated, all assessments will be performed by the Investigator or designated study personnel.

5.1. Schedule of Assessments

The procedures to be performed throughout the study are outlined in the Schedule of Assessments (Table 2). A detailed description of each assessment may be found in Section 5.2.

Table 2: Schedule of Assessments

	Screening		Treatment													Follow-up	
Assessment ▼ Study Day ▶	**D –42 to –1**	**D –1**	**D1**	**Wk 1**	**D6**	**D7±1[a]**	**Wk 2**	**D13**	**D14±1**	**Wk 3**	**D20**	**D21±1[a]**	**Wk 4**	**D27**	**EOT[b] D28±1**	**D55**	**D56±2[c]**
In clinic visit	x		x			x			x			x			x		x
Informed consent	x																
Medical history	x																
Pulmonary function test	x																
CXR or CT scan[d]	x																
Height and weight[e]	x		x			x			x			x			x		
Physical examination[f]	x		x			x			x			x			x		x
Vital signs[g]	x		x			x			x			x			x		x
12-Lead ECG[h]	x		x						x						x		x
Pregnancy test (females)[i]	x		x														x
Urinalysis[j]	x		x			x			x			x			x		x
Blood for safety[k]	x		x			x			x			x			x		x
Blood samples for intense PK[l]			x			x			x			x			x		
Blood samples for sparse PK[m]			x			x			x			x			x		
Blood sample for biomarker[n]			x			x			x			x			x		
Patient-collected expectorated sputum[o]		x			x			x			x			x		x	
Induced sputum[p]	x		x			x			x			x			x		x
IP administration[q]			x	x	x	x	x	x	x	x	x	x	x	x	x		
[redacted]						▮			▮			▮			▮		
[redacted]			▮			▮			▮			▮			▮		
[redacted]															▮		
Concomitant medication			◄												►		
Adverse events			◄												►		

Abbreviations: CT=computed tomography; CXR=chest radiograph; D=day; ECG=electrocardiogram; EOT=end of treatment; h=hour; IP=investigational product; min=minutes; PK=pharmacokinetics; PRO=patient-reported outcome; SOC=standard of care; Wk=week.

a. As a last resort, with approval from the Sponsor, Days 7 and 21 may be home visits to allow for the collection of induced sputum and blood for PK and safety. Further details will be included in a separate plan.
b. Patients in open-label SOC Treatment Arm 4 will be discontinued from the study after the EOT visit. For a patient who early terminates and agrees to complete the EOT visit, blood draws for PK will not be conducted. Women of child-bearing potential will have a pregnancy test at this visit.
c. The follow-up visit will take place 28 days (±2 days) after the EOT visit for double-blind Treatment Arms 1, 2, and 3.
d. A CXR or CT scan will be done unless one that is less than 6 months old is available. If obtained at screening, eligibility will be confirmed prior to randomization.
e. Height required only at screening. Body weight (kg) will be measured at screening and on Days 1, 7, 14, 21, and 28.
f. Full physical examinations will include the following (at a minimum): skin, head, ears, eyes, nose and throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system. Symptom-directed physical examinations will be conducted at study visits on Days 7, 14, 21, and 28.
g. Vital signs will include systolic and diastolic blood pressure, pulse, temperature, and respiratory rate. Vital sign measurements should be assessed 1 h post-dose (±15 min). For patients randomized to Treatment Arm 4 (SOC), vital sign measurements can be performed at any time.
h. On Days 1, 14, and 28, perform the ECG at 1 h post-dose (±15 min). For patients randomized to Treatment Arm 4 (SOC), ECG can be performed at any time.
i. A serum pregnancy test will be performed on all women of childbearing potential at screening and Day 1, and, for patients in Treatment Arms 1, 2, and 3, at the follow-up visit 28 days after EOT. On Day 1, serum pregnancy should be confirmed pre-dose.
j. Microscopic urinalysis will be performed.
k. Refer to Table 3 for the list of serum chemistry, hematology, coagulation, and calculated creatinine clearance assessments.
l. Intense PK sampling will take place at selected sites only. On Days 1 and 28: pre-dose (no greater than 1 h prior to dose), post-dose at 1 h (±5 min), 2 h (±10 min), 4 h (±10 min), 8 h (±15 min), 12 h (±30 min), and 24 h (±1 h, but –15 min prior to the next daily dose). On Days 7, 14, and 21: pre-dose (±1 h) (no greater than 1 h prior to dose), 1 h post-dose (±30 min), and just before discharge from clinic or at minimum 3 hours post-dose.
m. Sparse PK sampling will take place at remaining sites. On Days 1, 7, 14, 21, and 28: pre-dose (no greater than 1 h prior to dose), 1 h post-dose (±30 min), and just before discharge from the clinic or at minimum 3 hours post-dose.
n. Serum samples for biomarker assessment using the Nanodisk-MS assay will be collected on Days 1, 7, 14, 21 and 28. Biomarker assay will be nanotechnique quantitative detection of NTM specific peptides in serum.
o. Patient-collected pooled expectorated sputum collected on Days –1, 6, 13, 20, and 27 (i.e., on the day before clinical study visits over an approximate 24-h period). The patients will bring the pooled samples to the clinic for processing and shipment to the central laboratory.
p. Respiratory samples using a standard protocol for collecting induced sputum will be used at all sites. Induction will be performed in the clinic with hypertonic saline administered by nebulizer. Induced sputum samples will be collected at screening, and for Treatment Arms 1, 2, and 3 on Day 56 (Follow-up). On Days 1, 7, 14, 21, and 28 sputum samples will be collected pre-dose. Induced sputum samples will be shipped to the central laboratory.
q. Patients randomized to Treatment Arms 1, 2, and 3 will be double blinded, and Treatment Arm 4 (SOC) will be open label. Dosing for patients in Treatment Arms 1, 2, and 3 will take place at the clinic on study visit days. The clinic and patient should try to schedule clinic visits in the morning as early as possible to accommodate pre-dose study activities and dosing, preferably before a meal. Patients randomized to Treatment Arms 1, 2, and 3 should make every effort to take the IP at the same time in the morning approximately 1 h (no less than 30 min) before a morning meal on an empty stomach. There are no liquid restrictions. Patients will receive a supply of IP and instructions for documenting at-home dosing, which will include the date and time of each IP or SOC dose taken, along with other requested information related to IP administration. Dosing for Treatment Arm 4 (SOC) should occur per specific prescribing information instructions.

[redacted]

[redacted]

5.2. Screening (Day -42 to -1)

Before enrollment, patients will undergo screening to determine study eligibility. Screening procedures must be performed within 42 days before the first day of treatment (Day 1).

Patients must sign and date the main full study informed consent form (ICF) before any screening procedures are performed.

5.3. Pharmacokinetic Assessments

Blood samples from patients in Treatment Arms 1, 2, and 3 will be obtained for plasma for PK analysis according to the following schedule. Allowable windows of time for the collection of blood samples are shown in the Schedule of Assessments (Table 2).

At 3 or more selected sites, blood samples will be collected from at least 18 patients (at least 6 per treatment arm) for intensive PK evaluation. Intense blood sampling for PK will occur in the clinic on Days 1 and 28 at the following times relative to the time of the daily oral dose administered in the clinic: pre-dose and 1, 2, 4, 8, 12, and 24 h post-dose. On Days 7, 14, and 21, blood samples will be obtained at the following times relative to the time of the daily oral dose administered in the clinic: pre-dose, 1 h post-dose, and just before discharge from the clinic.

At all remaining sites for sparse PK evaluation, on Days 1, 7, 14, 21, and 28, blood samples will be obtained at the following times relative to the time of the daily oral dose administered in the clinic: pre-dose, 1 h post-dose, and just before discharge from the clinic.

Instructions for sample collection, handling, storage, and shipping can be found in the Laboratory Manual.

5.4. Safety Assessments

Physical Examinations: Full physical examinations will be conducted at screening and Day 1, and for patients in Treatment Arms 1, 2, and 3 at the follow-up visit 28 days after EOT. The full physical examination will include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system. Symptom-directed physical examinations will be conducted at study visits on Days 7, 14, 21, and 28.

Any CS changes from baseline in physical examination findings after dosing will be recorded as AEs. Height without shoes will be recorded at screening.

Vital Signs and Body Weight: Vital signs will be measured at each study visit for systolic and diastolic blood pressure, pulse, temperature (ºC), and respiratory rate.

Body weight (kg) will be measured at screening and Days 1, 7, 14, 21, and 28.

Electrocardiogram: Standard 12-lead ECGs will be measured at screening and Days 1, 14, and 28, and, for patients in Treatment Arms 1, 2, and 3, at the follow-up visit 28 days after EOT.

Laboratory Parameters*:* The following clinical laboratory tests (Table 3) are to be performed as indicated in the Schedule of Assessments (Table 2).

Table 3: Clinical Laboratory Tests

Serum Chemistry	**Hematology (CBC)**	**Urinalysis**
Albumin	Hematocrit	Color and clarity
Alkaline phosphatase	Hemoglobin	pH and specific gravity
ALT	Platelet count	Bilirubin
Amylase	RBC count	Protein
AST	RBC indices:	Glucose
Bicarbonate	--MCH	Ketones
Bilirubin (total and conjugated)	--MCHC	Leukocytes
Blood urea nitrogen	--MCV	Microscopy (if clinically indicated):
Calcium (total)	--% Reticulocytes	--Including bacteria, RBCs, WBCs per HCF
Chloride	RDW	--Sediment
Cholesterol (total)	WBC count	Nitrites
Creatinine	WBC w/differential (% and absolute):	Occult blood
Creatinine kinase	--Basophils	Urobilinogen
GGT	--Eosinophils	
Globulins	--Lymphocytes	
Glucose	--Monocytes	
LDH	--Neutrophils	**Additional Tests**
Lipase		Serum hCG[a]
Magnesium		Calculated creatinine clearance using measured serum creatinine with Cockcroft-Gault formula
Phosphorus		
Potassium		
Protein (total)	**Coagulation**	
Sodium	aPTT	
Triglycerides	PT	
Uric acid	INR	

Abbreviations: ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; CBC=complete blood count; EOT=end of treatment; GGT=gamma glutamyl transferase; hCG=human chorionic gonadotropin; HPF=high-power field; INR=international normalized ratio; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PT=prothrombin time; RBC=red blood cell; RDW=red blood cell distribution width; WBC=white blood cell.

a. Female patients will have a serum pregnancy test at screening and Day 1, and, for patients in Treatment Arms 1, 2, and 3, at the follow-up visit 28 days after EOT.

Laboratory samples will be analyzed by a central laboratory to ensure consistent interpretation of results. Instructions for obtaining and handling laboratory samples are provided in the Laboratory Manual.

In the event of an unexplained clinically noteworthy abnormal laboratory test value, the test should be repeated immediately and followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found.

Concomitant Medications and Adverse Events: Concomitant medications and AEs will be reviewed and recorded at all study visits. All AEs occurring after the first dose of IP and up to the last study event will be recorded.

See Section 6, for additional information.

5.5. Efficacy Assessments

[redacted]

5.6. Appropriateness of Measurements

All assessments to be used in this study are commonly used standard measurements and appropriate for this study in patients with NTM-PD.

6. ASSESSMENT AND MANAGEMENT OF ADVERSE EVENTS

Throughout the course of the study, all AEs will be monitored and recorded in an AE page of the eCRF, including the AE's description, start and end date, seriousness, severity, action taken, and relationship to the IP. If AEs occur, the first concern will be the safety of the study patients. All AEs will be followed until resolved or stable.

6.1. Adverse Event Definitions

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

An **SAE** is any AE occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening (*Note:* The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death, if it were more severe)
- Requires inpatient hospitalization or prolongation of an existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry, are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect
- Is a medically important event or reaction

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that may not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. The Investigator must review the laboratory report, document this review, and record any CS abnormal results in the AE section of the eCRF. The laboratory reports will be reviewed, filed, and handled in accordance with the site's source data list.

Clarification should be made between the terms “serious” and “severe” since the terms are not synonymous. The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as “serious,” which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient’s life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours’ duration may be considered severe nausea but not an SAE. However, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

A **suspected unexpected serious adverse reaction (SUSAR):** An AE or suspected adverse reaction is considered "unexpected" if:

- It is not listed in the IB
- It is not listed at the specificity or severity that has been observed
- The IB is not required or available or not consistent with the risk information described in the general investigational plan or elsewhere in the current application

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

Abnormal laboratory findings (e.g., serum chemistry, hematology, coagulation, and urinalysis) or other abnormal assessments (e.g., ECG parameters, vital signs) that are judged by the Investigator as CS will be recorded as AEs or SAEs if they meet the definitions stated above. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the first dose will be reported as AEs or SAEs. The Investigator will exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is CS.

6.2. Evaluating Adverse Events and Serious Adverse Events

6.2.1. Assessment of Intensity

The Investigator will assess the intensity for each AE and SAE reported during the study. The assessment will be based on the Investigator’s clinical judgment using the latest version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0 as a guideline, wherever possible. The intensity of each AE and SAE recorded should be assigned to one of the following categories:

- **Mild:** An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities
- **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities
- **Severe:** An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe
- **Life-Threatening or Disabling:** An event that poses an immediate risk of death from the reaction as it occurred
- **Death:** The event resulted in death

The following terms and definitions are used in assessing the final outcome of an AE:

- **Recovered/Resolved:** The patient has fully recovered, or by medical or surgical treatment, the condition has returned to the level observed at the first study-related activity after the patient signed the informed consent
- **Recovering/Resolving:** This term is only applicable if the patient has completed the study or has died from another AE, the condition is improving, and the patient is expected to recover from the event
- **Recovered/Resolved with Sequelae:** The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment, or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE
- **Not Recovered/Not Resolved:** The condition of the patient has not improved, and the symptoms are unchanged, or the outcome is not known at the time of reporting
- **Fatal:** This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered/resolved," "recovering/resolving," "recovered/resolved with sequelae," or "not recovered/not resolved." An AE with fatal outcome must be reported as an SAE
- **Unknown:** This term is only applicable if the patient is lost to follow-up

6.2.2. Assessment of Causality

The Investigator (or designee) will make an assessment as to the relationship between the study drug and the occurrence of each AE/SAE. The Investigator (or designee) will use clinical judgment to determine whether the AE/SAE is causally related to the study drug. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug will be considered and investigated. The Investigator (or designee) will also consult the IB in the determination of his/her assessment.

The causal relationship of the study drug to an AE will be rated according to the following 4-point scale:

- **Unrelated:** Clearly and incontrovertibly due only to extraneous causes and does not meet criteria listed under unlikely, possible, or probable
- **Unlikely:** Does not follow a reasonable temporal sequence from administration; may have been produced by the patient's clinical state or by environmental factors or other therapies administered
- **Possible:** Follows a reasonable temporal sequence from administration; may have been produced by the patient's clinical state or by environmental factors or other therapies administered
- **Probable**: Clear temporal association with improvement on cessation of study drug or reduction in dose; reappears upon rechallenge or follows a known pattern of response to the study drug

There may be situations when an SAE has occurred and the Investigator (or designee) has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator (or designee) always assess causality for every event before transmission of the SAE form to the Sponsor. The Investigator (or designee) may change his/her opinion of causality in light of follow-up information, amending the SAE form and the eCRF accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The Investigator (or designee) will provide an assessment of causality as per instructions on the SAE form.

6.3. Time Period, Frequency, and Method of Detecting Adverse Events

As a consistent method of soliciting AEs, the patient shall be asked a nonleading question such as: "How do you feel?"

Any preexisting conditions or signs and/or symptoms present in a patient before the start of the study (e.g., before informed consent) should be recorded as medical/surgical history. In addition, any change in health status, which is reported after informed consent is obtained but before receipt of study drug, will be documented as medical/surgical history.

Any medical occurrence reported or observed after the first dose of study drug will be recorded as an AE. Adverse events will be evaluated by the Investigator (or designee) and recorded.

Any AEs already documented at a previous assessment and designated as ongoing, should be reviewed at subsequent assessments, as necessary. If these have resolved, this should be documented.

6.4. Adverse Event Management

The Investigator (or designee) will provide appropriate medical care for the clinical management of any AEs related to study participation, whether identified during or after the course of study participation. Evaluation and treatment of any AE (or CS laboratory abnormality) is at the discretion of the Investigator based on their clinical judgment. The applied measures should be recorded in the patient's source documents and entered in the eCRF as applicable. Referral or collaborative care will be organized if considered necessary by the Investigator. As noted in

Section 6.7, the Sponsor may request additional supplemental investigations as needed to elucidate the nature and/or causality of an SAE.

Serious AEs will be reported to competent authorities in accordance with national requirements.

6.5. Recording of Adverse Events and Serious Adverse Events

When an AE/SAE occurs, it is the responsibility of the Investigator (or designee) to review all documentation (e.g., hospital progress notes, laboratory results, patient diaries, and diagnostics reports) relative to the event. The Investigator (or designee) will then record all relevant information regarding an AE/SAE in the eCRF. It is not acceptable for the Investigator (or designee) to send photocopies of the patient's medical records to the Sponsor in lieu of completion of the appropriate AE/SAE eCRF pages. However, there may be instances when the Sponsor requests copies of medical records for certain cases. In this instance, all patient identifiers will be blinded on the copies of the medical records before submission to the Sponsor.

The Investigator (or designee) will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

6.6. Serious Adverse Event Reporting

6.6.1. Regulatory Reporting Requirements for Reporting of Serious Adverse Events

The Investigator (or designee) will promptly report all SAEs to the Sponsor (or delegate). Prompt notification of SAEs by the Investigator (or designee) to the appropriate Sponsor (or delegate) contact for SAE receipt **is essential** so that the Sponsor may comply with its regulatory obligations. Serious AEs will be reported to regulatory authorities in accordance with national requirements.

The Sponsor is responsible for notifying the local regulatory authorities of all SAEs that occur at the site. It is the Sponsor's responsibility to report all SUSARs promptly.

The Principal Investigator (or designee) is responsible for notifying the local institutional review board (IRB) or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

6.6.2. Completion and Transmission of the Serious Adverse Event Reports

Once the Investigator (or designee) becomes aware that an SAE has occurred in a study patient, he/she will report the information to the Sponsor (or delegate) and the Sponsor's Medical Monitor within 24 h. The SAE form/eCRF will always be completed as thoroughly as possible with all available details of the event, signed by the Investigator (or designee), and forwarded to the Sponsor (or delegate) and the Sponsor's Medical Monitor within the designated time frames. If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the Sponsor (or delegate) and the Sponsor's Medical Monitor of the event and completing the form/eCRF. The form/eCRF will be updated as soon as possible when additional information becomes available.

The Investigator will always provide an assessment of causality at the time of the initial report.

Completion of the SAE form/eCRF in an electronic data capture (EDC) system is the preferred method to transmit this information to the Sponsor (or delegate) and the Sponsor's Medical Monitor for SAE receipt. In rare circumstances, and in the absence of facsimile, computer and scanner equipment, notification by telephone is acceptable, with a copy of the SAE form sent by overnight mail. Initial notification via the telephone does not replace the need for the Investigator (or designee) to complete and sign the SAE form/eCRF within the outlined time frames.

Any event that in the opinion of the Investigator (or designee) may be of immediate or potential concern for the patient's health or well-being will be reported to the Sponsor's Medical Representative or emergency contact.

Adverse events will be classified as SUSARs if the AE or suspected adverse reaction meets the definition of "unexpected" in Section 6.1. All SUSARs should be reported to the ethics committee and regulatory authority in accordance with applicable regulatory requirements for expedited reporting. It is the Sponsor's responsibility to report SUSARs to the ethics committee and regulatory authority.

6.6.3. Post-study Adverse Events and Serious Adverse Events

A post-study AE/SAE is defined as any event that occurs outside of the nominal AE/SAE study detection period.

Investigators are not obligated to actively seek AE/SAE information in former study patients. However, if the Investigator (or designee) learns of any SAE, including a death, at any time after a patient has completed the study and he/she considers the event reasonably related to the study drug, the Investigator will promptly notify the Sponsor.

6.7. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator (or designee) is required to proactively follow each patient and provide further information to the Sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing will be reviewed at subsequent visits/contacts. All AEs must be followed until the patient has recovered/resolved and all queries have been resolved, or until deemed medically stable by the Investigator (or designee). For cases of chronic conditions or if the patient dies from another event, follow-up until the outcome category is "recovered/resolved" is not required, as these cases can be closed with an outcome of "recovering/resolving" or "not recovered/not resolved."

All patients with SAEs will be followed until they have recovered/resolved, recovered/resolved with sequelae, or the event was fatal, or until all queries have been resolved or the patient is lost to follow-up. Once resolved, the appropriate SAE report will be updated. The Investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the SAE. If a patient dies during participation in the study or during a recognized

follow-up period, the Sponsor will be provided with a copy of any postmortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE form and the eCRF, with all changes signed and dated by the Investigator. The Sponsor should be notified of the updated SAE form/eCRF.

6.8. Clinical Laboratory Evaluations

A change in the value of a clinical laboratory assessment can represent an AE if the change is clinically relevant or if, during treatment with the study drug, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the treatment with study drug, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

The Investigator should decide, based on the above criteria and the clinical condition of a patient, whether a change in a clinical laboratory parameter is CS and therefore represents an AE.

6.9. Pregnancy

Any report of pregnancy for any female study patient or male study patient's partner must be reported within 1 business day to the Sponsor (or designee) and the Sponsor's Medical Monitor. The female study patient must be withdrawn from the treatment.

A serum pregnancy test will be performed on all women of childbearing potential.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification and approximately 30-calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported to the Sponsor (or designee) and the Sponsor's Medical Monitor.

Pregnancy outcomes should be collected for female partners of any males who took the study drug if possible. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Note: An elective abortion is not considered an SAE.

In addition to the above, if the Investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE. The test date of the first positive serum/urine β-human chorionic gonadotropin test or ultrasound result will determine the pregnancy onset date.

6.10. Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the Sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE. *Note:* The 1-business-day requirement for reporting SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse:** Persistent or sporadic intentional intake of study drug when used for a nonmedical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Medication Error**: An error made in prescribing, dispensing, administration, and/or use of a study drug (for studies, medication errors are reportable to the Sponsor)
- **Misuse:** Intentional use of study drug other than as directed or indicated at any dose (*Note:* this includes a situation where the study drug is not used as directed at the dose prescribed by the protocol)
- **Overdose:** Intentional or unintentional intake of a dose of a study drug exceeding a prespecified total daily dose of the product

Cases of patients missing doses of product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is always reportable as a medication error. The administration and/or use of an expired product should be considered as a reportable medication error.

Errors related to administration of study drug are reportable as medication errors.

Intentional overdosing of study drug is unlikely. In the event of overdose in general, treatment should be supportive and symptomatic according the patient's clinical presentation.

6.11. Reference Safety Information

The reference for safety information for this study is the IB, which the Sponsor has provided separately to all Investigators.

The reference for safety information for the comparator in this study are Summary of Product Characteristics/Product Package Inserts.

7. DATA MANAGEMENT

7.1. Data Management Considerations

Electronic case report forms will be employed for this study. Completed eCRFs for this study will be forwarded to the Sponsor or its representative where editing and construction of a quality-assured database will occur. Data will be quality checked and electronically verified after entry into the database. Queries will be issued for any inconsistencies, omissions, and discrepancies and will be resolved by the appropriate parties. The statistical analysis of these data will be performed by the Sponsor or its representative. All AEs will be coded using the Medical Dictionary for Regulated Activities (MedDRA). Concomitant medications will be coded using WHODrug Global. Data management details will be outlined in a separate data management plan.

8. STATISTICAL CONSIDERATIONS

The statistical analysis will be undertaken by Synteract in collaboration with Spero.

A detailed statistical analysis plan (SAP) will be finalized and signed before database lock and before analysis of the study being carried out. Any deviations from the analyses described below will be included in the clinical study report.

Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Other summaries (e.g., quartiles, confidence intervals) may be used as appropriate.

Categorical variables will be summarized by frequency and by percentage of patients in corresponding categories.

All summary tables will be presented by treatment arm. Disposition, demographic, and baseline summaries will also include a total summary column. All data reported for a patient during the study and all derived data will be presented in data listings.

8.1. Endpoints

8.1.1. Primary

- Maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration-time curve from zero to τ, where τ is the dosing interval ($AUC_{0-\tau}$), and accumulation ratio of SPR719 on Day 1 and Day 28

8.1.2. Secondary

- Reported AEs
- Clinically meaningful change in physical examination findings
- Concomitant medication usage
- Changes from baseline in laboratory tests
- Clinically significant out-of-normal range laboratory tests
- Shifts from baseline for selected laboratory tests using National Cancer Institute CTCAE v5.0 shift categories
- Changes from baseline in vital sign measurements (body temperature, heart rate, respiratory rate, blood pressure)
- 12-lead ECGs

[redacted]

[redacted]

8.1.4. Determination of Sample Size

This study will be conducted to evaluate the PK and safety of SPR720 in a patient population with NTM-PD and to evaluate the efficacy of SPR720 compared with placebo in patients with NTM-PD.

There is no formal statistical hypothesis planned, and the sample size is mainly based on an estimated number of patients needed to understand the PK and safety of patients in this study.

8.1.5. Analysis Populations

Safety Analysis Population:

The Safety Population will include all randomized patients who received any amount of IP. Patients will be summarized by the treatment which they received.

[redacted]

[redacted]

Pharmacokinetic Analysis Population:

The PK Population will include all patients treated with at least 1 dose of SPR720 and who have at least 1 analyzable plasma PK sample.

8.1.6. Protocol Deviations

Protocol deviations will be assessed and documented on a case-by-case basis while blinded to treatment arm. Protocol deviations, including the deviation designation (major or minor) and deviation category will be presented in a data listing.

8.1.7. Demographic and Baseline Characteristics

Patient disposition, demographics, and baseline characteristics will be summarized using descriptive statistics for the Safety and micro-ITT Populations. No formal statistical analysis tests will be performed.

8.1.8. Pharmacokinetic Analyses

Dates and times of blood samples as well as dates and times of study drug administration will be recorded. Plasma concentration-time data from intensive PK sampling patients will be subjected to noncompartmental PK analysis. Day 1 and Day 28 PK parameters including, but not limited to, C_{max}, T_{max}, area under the concentration-time curve from zero to last concentration (AUC_{last}), $AUC_{0-\tau}$, accumulation ratio, and plasma concentration at the end of a dosing interval at steady state (taken directly before next administration) (C_{trough}) will be determined when appropriate for SPR719. Concentration data from sparse sampling will be compiled for summary statistics of C_{trough} across various days. Concentration data from SPR720 recipients will be used for the development of a PK Population model, for PK analysis, and for estimation of individual PK profiles in patients with sparse sampling, which will be reported in a separate report.

8.1.9. Safety Analyses

Safety data will be summarized for the Safety Population. All safety presentations will be descriptive, and all summaries will be displayed by treatment arm.

8.1.9.1. Extent of Exposure

The extent of exposure to study drug will be summarized by the number of doses taken, number of missed doses, and compliance with IP administration. Investigational product noncompliance for a patient is defined as taking less than 80% or more than 120% of IP during the treatment period (Day 1 through EOT).

8.1.9.2. Adverse Events

All AEs occurring during the study will be recorded and classified using terminology from MedDRA. A treatment-emergent AE (TEAE) is defined as any AE that has an onset on or after the first dose of IP or any preexisting condition that has worsened on or after the first dose of IP.

The incidence of TEAEs (number and percent of patients reporting the AE at least once during the study), SAEs, AEs related to study treatment, SAEs related to treatment, and AEs leading to study discontinuation will be summarized by treatment. Treatment-emergent AEs will also be summarized by severity and relationship to IP. When summarizing TEAEs by severity or relationship to IP, each patient will only be counted once within a system organ class or preferred term using the event with the greatest severity or causality, respectively, within each category.

A listing of patients who prematurely discontinue from the study due to AEs will be provided as well as a list of patients who reported SAEs.

8.1.9.3. Concomitant Medications

Concomitant medication verbatim terms in the eCRFs will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and Preferred Names using WHODrug Global.

Concomitant medications will be summarized by ATC class and preferred name. These summaries will present the number and percentage of patients using each medication. Patients may have more than 1 medication per ATC class and preferred name. At each level of summarization, a patient will be counted only once if he/she reported 1 or more medications at that level.

8.1.9.4. Laboratory Data

Laboratory results (hematology, serum chemistry, and urinalysis) will be summarized by treatment arm for each time point, change from baseline at each postbaseline time point, shifts from baseline for selected laboratory tests (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, alkaline phosphatase, total bilirubin, amylase, lipase, blood urea nitrogen, serum creatinine, creatinine clearance, hemoglobin, hematocrit, neutrophils, lymphocytes, and erythrocytes)using CTCAE v5.0, and CS out-of-normal range laboratory. In addition, scatterplots of key laboratory values over time will also be produced.

8.1.9.5. Electrocardiographic Data

Baseline and change from baseline in ECG parameters (heart rate, cardiac rhythm, PR interval, RR interval, QRS interval, QT interval, and QTc interval) will be summarized at each postbaseline time point. At each time point, the number of patients with QTc according to Fridericia's formula (QTcF) values of >450 ms, >480 ms, and >500 ms will be presented. At each postbaseline time point, the number of patients with change from baseline values in QTcF of >30 ms and >60 ms will be presented.

8.1.9.6. Vital Signs

Summary statistics for the absolute vital sign value and the changes from baseline will be presented by treatment arm for each visit.

8.1.9.7. Physical Examinations

Clinically meaningful changes in physical examination findings will be identified and summarized by treatment arm.

9. STUDY MANAGEMENT

9.1. Regulations and Guidelines

The study will be performed in accordance with this protocol, US investigational new drug regulations (US Title 21 Code of Federal Regulations [CFR] Part 312), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP), and the regulations on electronic records and electronic signature (Title 21 CFR Part 11).

9.2. Sponsor's Responsibilities

9.2.1. Good Clinical Practice

The Sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations and ICH GCP Guideline E6(R2).

Representatives of the Sponsor and/or the company organizing/managing the research on behalf of the Sponsor to inspect study data, patients' medical records, and eCRFs in accordance with current GCP and the respective government regulations and guidelines conduct visits to sites. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The Sponsor ensures that local regulatory authority requirements are met before the start of the study. The Sponsor (or designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of IP for shipment to the site.

9.2.2. Indemnity/Liability and Insurance

The Sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the CRO/Investigator as necessary.

9.2.3. Public Posting of Study Information

The Sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating Investigators' names and contact information.

9.2.4. Suspension, Discontinuation, and Completion of the Study

The Sponsor reserves the right to suspend or discontinue the study or part of the study at any time for any reason. If the study is suspended or terminated, the Sponsor will ensure that applicable regulatory agencies and IRBs are notified as appropriate. Additionally, the discontinuation of a registered clinical study, which has been posted to a designated public website, will be updated accordingly. Should the study be terminated and/or a site closed, all IP pertaining to the study must be returned to the Sponsor or its representative.

9.3. Investigator Responsibilities

9.3.1. Good Clinical Practice Compliance

The Investigator must undertake to perform the study in accordance with ICH GCP Guideline E6(R2) and applicable regulatory requirements and guidelines.

It is the Investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable patients within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks. *Curricula vitae* for Investigators and Subinvestigators will be provided to the Sponsor (or designee) before starting the study.

If a potential research patient has a primary care physician, the Investigator should, with the patient's consent, inform them of the patient's participation in the study.

9.3.2. Protocol Adherence and Investigator Agreement

The Investigator and any Subinvestigators must adhere to the protocol as detailed in this document. The Investigator is responsible for enrolling only those patients who have met protocol eligibility criteria. Investigators are required to sign an Investigator Agreement to confirm acceptance and willingness to comply with the study protocol.

If the Investigator suspends or terminates the study at their site, the Investigator will promptly inform the Sponsor and the IRB and provide them with a detailed written explanation. The Investigator will also return all IP, containers, and other study materials to the Sponsor. Upon study completion, the Investigator will provide the Sponsor, IRB, and regulatory agency with final reports and summaries as required by national regulations.

Communication with local IRBs, to ensure accurate and timely information is provided at all phases during the study, may be done by the Sponsor, CRO, or Investigator.

9.3.3. Institutional Review Board

Conduct of the study must be approved by an appropriately constituted IRB, which operates in accordance with the principles and requirements described in the US Title 21 CFR Part 56, and the ICH guidelines. Approval is required for the study protocol, protocol amendments, ICFs, patient information sheets, and advertising materials.

9.3.4. Informed Consent

For each trial patient, a written ICF will be obtained before any protocol-specific activities are performed. As part of this procedure, the Investigator or a designated representative must explain orally and in writing the nature, duration, and purpose of the study, and the action of the IP in such a manner that the patient and (if applicable) appointed guardian are aware of the potential risks, inconveniences, or adverse effects that may occur. Patients should be informed that they may withdraw from the study at any time. They will receive all information that is required by federal regulations and ICH guidelines. The Principal Investigator or a designated representative

will provide the Sponsor or its representative with a copy of the approved ICF before the start of the study.

The Sponsor's indemnification of the Investigator and institution during the conduct of this study will be discussed in a separate document.

9.4. Study Documentation

By signing a copy of Form FDA 1572, the Principal Investigator acknowledges that he/she has received a copy of the IB on SPR720 and assures the Sponsor that he/she will comply with the protocol and the provisions stated in Form FDA 1572. No changes in this protocol can be made without the Sponsor's written approval.

9.5. Data Management and Quality Control

9.5.1. Electronic Case Report Forms

Electronic case report forms will be used to collect all patient data during the study. The Investigator is responsible for the accuracy and completeness of all data in the eCRFs.

The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded into the eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. The Investigator or designee as stated in the site delegation log must complete eCRFs.

9.5.2. Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but is not limited to the patient's medical file, patient diaries, original clinical laboratory reports, and histology and pathology reports. All key data must be recorded in the patient's medical records.

The Investigator must permit authorized representatives of the Sponsor, the respective national, local, or foreign regulatory authorities, the IRB, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The Study Monitor (and auditors, IRB or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the patient agrees to the monitor/auditor from the Sponsor or its representatives, national or local regulatory authorities, or the IRB having access to source data (e.g., patient's medical file, appointment books, original laboratory reports, X-rays).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., the FDA or an auditor).

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the Sponsor.

9.5.3. Study Monitoring and Quality Assurance

This study will be monitored for quality assurance at all stages of its development by the clinical research personnel employed by the Sponsor or its representative. Monitoring will include

personal visits and telephone communication to assure that the investigation is conducted according to the protocol, standard operating procedures, GCP guidelines, and applicable regulatory requirements. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. On-site review of eCRFs will include a review of forms for completeness and clarity and consistency with source documents available for each patient. Note that a variety of original documents, data, and records will be considered as source documents in this trial. The eCRF itself is not to be used as a source document under any circumstances.

By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities, for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

All data collected in patient diaries, if applicable, of this study will be entered into a computer database. Verification of entered data will be done by double-data entry procedure. An audit trail will trace every change made in the database. Data management will be performed according to Synteract's standard operating procedures.

The eCRFs for any patient leaving the study should be completed at the time of the final visit or shortly thereafter.

9.5.4. Financial Disclosure

Upon submission of a marketing application to the FDA for any drug, Spero Therapeutics, Inc. must provide the FDA with a list of clinical investigators who conducted a sponsored clinical study and certify or disclose financial arrangements.

The Investigator is required to disclose any financial arrangement during the study and for 1 year following, whereby the value of the compensation for conducting the study could be influenced by the outcome of the study. The following information is collected: any significant payments from the Sponsor or subsidiaries such as a grant to fund ongoing research; compensation in the form of equipment; retainer for ongoing consultation or honoraria; any proprietary interest in IP; and any significant equity interest in the Sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

In consideration of participation in the study, the Sponsor pays the Investigator or nominated payee the sums set out in the payment schedule attached to the Investigator Agreement.

9.6. Use of Study Findings

By signing the study protocol, the Investigator agrees to the use of results of the study for the purposes of national and international registration. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. Reports covering clinical and biometric aspects of the study will be prepared by the Sponsor or its representative.

9.7. Privacy and Confidentiality

All US sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). A site

that is not a Covered Entity as defined by HIPAA must provide documentation of this fact to the CRO/Sponsor.

The confidentiality of records that may be able to identify patients will be protected in accordance with applicable laws, regulations, and guidelines.

After patients have consented to take part in the study, the Sponsor and/or its representatives review their medical records and data collected during the study. Others, including the following, may review these records and data: independent auditors who validate the data on behalf of the Sponsor; third parties with whom the Sponsor may develop, register, or market SPR720; and national or local regulatory authorities and the IRB, which gave approval for the study to proceed. The Sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of patients' identities.

Patients will be assigned a unique identifying number. However, their initials and date of birth may also be collected and used to assist the Sponsor to verify the accuracy of the data, for example, to confirm that laboratory results have been assigned to the correct patient.

The results of studies containing patients' unique identifying number, relevant medical records, and possibly initials and dates of birth will be recorded. They may be transferred to, and used in, other countries that may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would be to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

9.8. Publications

As a multicenter trial, the Sponsor intends to publish clinical data from all centers participating in the investigation. A publication committee selected by the Sponsor will submit draft manuscripts to all participating Investigators for their comments. In conformity with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals published by the International Committee of Medical Journal Editors (Kassirer and Angell 1991), Investigators whose contribution consists solely in the collection of data will not be named individually as authors. Rather, those Investigators will receive a collective authorship as the "SPR720 Study Group" and will be identified in a note.

Individual Investigators and/or their associates subsequently may publish additional findings of this study in scientific journals or present them at scientific meetings, provided that the Sponsor is given many opportunities to review any proposed abstract, manuscript, or slide presentation before its submission. This review is required to ensure that the Sponsor is aware of all written and oral presentations of the data and does not imply any editorial review or restriction of the contents of the presentation or use.

10. REFERENCES

Adjemian J, Frankland TB, Daida YG, Honda JR, Olivier KN, Zelazny A, et al. Epidemiology of nontuberculous mycobacterial lung disease and tuberculosis, Hawaii, USA. Emerg Infect Dis. 2017;23(3):439-47.

Amikacin liposome inhalation suspension (ALIS): Meeting of the antimicrobial drugs advisory committee (AMDAC). FDA Briefing Document. 07 August 2018.

Baldwin SL, Larsen SE, Ordway D, Cassell G, Coler RN. The complexities and challenges of preventing and treating nontuberculous mycobacterial diseases. PLoS Negl Trop Dis. 2019;13(2):e0007083.

Brown-Elliott BA, Rubio A, Wallace RJ Jr. *In vitro* susceptibility testing of a novel benzimidazole, SPR719, against nontuberculous mycobacteria. Antimicrob Agents Chemother. 2018;62(11):e01503-18.

Cadelis G, Ducrot R, Bourdin A, Rastogi N. Predictive factors for a one-year improvement in nontuberculous mycobacterial pulmonary disease: an 11-year retrospective and multicenter study. PLoS Negl Trop Dis. 2017;11(8):e0005841.

Center for Drug Evaluation and Research (CDER), US Food and Drug Administration (FDA). The voice of the patient: A series of reports from the U.S. Food and Drug Administration's (FDA's) patient-focused drug development initiative. Non-tuberculous mycobacterial (NTM) lung infection. Public meeting: October 15, 2015. Report Date: April 2016 [cited 2020 Mar 31]**.** Available from: https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM496941.pdf

Dhillon SS, Watanakunakorn C. Lady Windermere syndrome: middle lobe bronchiectasis and *Mycobacterium avium* complex infection due to voluntary cough suppression. Clin Infect Dis. 2000;30(3):572-5.

Falkinham JO 3rd. Environmental sources of nontuberculous mycobacteria. Clin Chest Med. 2015;36(1):35-41.

Fiske LC, Homeyer DC, Zapor M, Hartzell J, Warkentien T, Weintrob AC, et al. Isolation of rapidly growing nontuberculous mycobacteria in wounds following combat-related injury. Mil Med. 2016;181(6):530-6.

Gochi M, Takayanagi N, Kanauchi T, Ishiguro T, Yanagisawa T, Sugita Y. Retrospective study of the predictors of mortality and radiographic deterioration in 782 patients with nodular/bronchiectatic *Mycobacterium avium* complex lung disease. BMJ Open. 2015;5(8):e008058.

Griffith DE, Adjemian J, Brown-Elliott BA, Philley JV, Prevots DR, Gaston C, et al. Semiquantitative culture analysis during therapy for *Mycobacterium avium* complex lung disease. Am J Respir Crit Care Med. 2015;192(6):754-60.

Griffith DE, Aksamit TR. Understanding nontuberculous mycobacterial lung disease: it's been a long time coming. F1000Res. 2016;5:2797. eCollection 2016.

Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175(4):367-416.

Haworth CS, Banks J, Capstick T, Fisher AJ, Gorsuch T, Laurenson IF, et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax. 2017;72(Suppl 2):ii1-ii64.

Henkle E, Winthrop K. Nontuberculous mycobacteria infections in immunosuppressed hosts. Clin Chest Med. 2015;36(1):91-9.

Insmed Inc. Arikayce® (amikacin liposome inhalation suspension) [USPI]. Bridgewater (NJ). 2018 Sep [cited 2019 Dec 02]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207356s000lbl.pdf

Jarand J, Levin A, Zhang L, Huitt G, Mitchell JD, Daley CL. Clinical and microbiologic outcomes in patients receiving treatment for *Mycobacterium abscessus* pulmonary disease. Clin Infect Dis. 2011;52(5):565-71.

Kassirer JP, Angell M. On authorship and acknowledgments. N Engl J Med. 1991;325(21):1510-2.

Lam PK, Griffith DE, Aksamit TR, Ruoss SJ, Garay SM, Daley CL, et al. Factors related to response to intermittent treatment of *Mycobacterium avium* complex lung disease. Am J Respir Crit Care Med. 2006;173(11):1283-9.

Lande L, George J, Plush T. *Mycobacterium avium* complex pulmonary disease: new epidemiology and management concepts. Curr Opin Infect Dis. 2018;31(12):199-207.

Lee SFK, Laughon BE, McHugh TD, Lipman M. New drugs to treat difficult tuberculous and nontuberculous mycobacterial pulmonary disease. Curr Opin Pulm Med. 2019;25(3):271-80.

Locher CP, Jones SM, Hanzelka BL, Perola E, Shoen CM, Cynamon MH, et al. A novel inhibitor of gyrase B is a potent drug candidate for treatment of tuberculosis and nontuberculosis mycobacterial infections. Antimicrob Agents Chemother. 2015;59(3):1455-65.

Mao L, LaCourse S, Kim S, Mitchell CD, Hu TY. Evaluation of a Blood-based Antigen Test for Tuberculosis in Infants. Poster presented at: 2020 Conference on Retroviruses and Opportunistic Infections; March, 2020; Boston, MA.

NTM Info & Research (NTMir). Presentation at US Food and Drug Administration Public Workshop: development of antibacterial drugs for the treatment of nontuberculous mycobacterial disease. 2019 Apr 8; Silver Spring, MD. Capital Reporting Company [cited 2020 Mar 31]. Available from: https://www.fda.gov/media/127638/download

O'Dowd H, Shannon DE, Chandupatla KR, Dixit V, Engtrakul JJ, Ye Z, et al. Discovery and characterization of a water-soluble prodrug of a dual inhibitor of bacterial DNA gyrase and topoisomerase IV. ACS Med Chem Lett. 2015;6(7):822-6.

Philley JV, DeGroote MA, Honda JR, Chan MM, Kasperbauer S, Walter ND, et al. Treatment of non-tuberculous mycobacterial lung disease. Curr Treat Options Infect Dis. 2016;8(4):275-96.

US Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry. Assessing the effects of food on drugs in INDs and NDAs — clinical pharmacology considerations. Draft guidance. February 2019. Clinical Pharmacology [cited 2020 Mar 31]. Available from: https://www.fda.gov/media/121313/download

Wallace RJ Jr, Brown BA, Griffith DE, Girard WM, Murphy DT, Onyi GO, et al. Initial clarithromycin monotherapy for *Mycobacterium avium*-intracellulare complex lung disease. Am J Respir Crit Care Med. 1994;149(5):1335-41.

Wallace RJ Jr, Brown-Elliott BA, McNulty S, Philley JV, Killingley J, Wilson RW, et al. Macrolide/Azalide therapy for nodular/bronchiectatic *Mycobacterium avium* complex lung disease. Chest. 2014;146(2):276-82.

APPENDIX 1. PROHIBITED INHIBITORS AND INDUCERS OF CYP3A

The following inhibitors and inducers of CYP3A are prohibited within 4 weeks before randomization and during the study:

CYP3A Strong Inhibitors	CYP3A Strong Inducers
Boceprevir	Carbamazepine
Cobicistat	Enzalutamide
Conivaptan	Mitotane
Danoprevir and ritonavir	Phenytoin
Elvitegravir and ritonavir	Rifampin
Grapefruit juice	St. John's wort
Indinavir and ritonavir	
Itraconazole	
Ketoconazole	
Lopinavir and ritonavir	
Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)	
Posaconazole	
Ritonavir	
Saquinavir and ritonavir	
Telaprevir	
Tipranavir and ritonavir	
Troleandomycin	
Voriconazole	
Clarithromycin	
Diltiazem	
Idelalisib	
Nefazodone	
Nelfinavir	

Abbreviation: CYP=cytochrome P450

APPENDIX 2. PROHIBITED SUBSTRATES OF THE HEPATIC TRANSPORTERS OATP1B2 OR OATP2B3

The following substrates of the hepatic transporters OATP1B2 or OATP2B3 are prohibited within 1 week before randomization and during the study:

Asunaprevir

Atorvastatin

Bosentan

Danoprevir

Docetaxel

Fexofenadine

Glyburide

Nateglinide

Paclitaxel

Pitavastatin

Pravastatin

Repaglinide

Rosuvastatin

Simvastatin acid