SPONSOR:	Knopp Biosciences LLC 2100 Wharton Street, Suite 615 Pittsburgh, PA 15203
PROTOCOL NUMBER:	KNS-760704-AS201
PROTOCOL TITLE:	A Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Biomarker Study of the Effects of Dexpramipexole on Eosinophils in Subjects with Eosinophilic Asthma
IND #:	122,746
PRODUCT:	Dexpramipexole (KNS-760704)
DATE:	July 16, 2019
VERSION:	[redacted]

1. SIGNATURE PAGE

Protocol KNS-760704-AS201, Final [redacted] was approved by:

[redacted]

July 16, 2019
Date

2. SPONSOR/CRO INFORMATION

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Knopp Medical Monitor

[redacted]

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3. LIST OF ABBREVIATIONS AND DEFINITIONS

°C	degrees Celsius
ACQ-7	asthma control questionnaire (7-question)
AE	adverse event
AEC	absolute eosinophil count
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AQLQ	asthma quality of life questionnaire
AST	aspartate aminotransferase
ATS/ERS	American Thoracic Society / European Respiratory Society
BID	twice daily
BP	blood pressure
bpm	beats per minute
CBC	complete blood count
CI	confidence interval
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration eGFR formula
Cmax	maximum observed concentration
CRF	case report form
CRSwNP	chronic rhinosinusitis with nasal polyps
CYP	cytochrome
CYP2C8	cytochrome P2C8
CYP2C9	cytochrome P2C9
DDI	drug-drug interaction

dL	deciliter
EAD	eosinophil associated disorders
ECG	electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
FeNO	fraction of exhaled nitric oxide
FEV1	forced expiratory volume in 1 second
GCP	good clinical practice
GINA	Global Initiative for Asthma
hCG	human chorionic gonadotrophin
HES	hypereosinophilic syndrome
HIV	human immunodeficiency virus
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgE	immunoglobulin E
IRB	institutional review board
ITT	intent to treat
kg	kilogram
KNS-760704	dexpramipexole
LDH	lactic acid dehydrogenase
LOCF	last observation carried forward
LS	least square
PK	pharmacokinetic
µM	micromolar
mAbs	monoclonal antibodies
MDI	metered dose inhaler
mg	milligram

ml	milliliter
mmHg	millimeters mercury
MMRM	mixed-effect model, repeat measurement
ms	millisecond
NIAID/NIH	National Institute of Allergy and Infectious Diseases in the National Institutes of Health
PT	preferred term
QT	interval between the start of the QRS complex and the end of the T wave
QTc	interval between the start of the QRS complex and the end of the T wave, corrected for heart rate
RBC	red blood cell count
RR	respiratory rate
SAE	serious adverse event
sd	standard deviation
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
t½	terminal half-life
Tmax	time after administration of drug when Cmax occurred
TPS	total polyp score (bilateral)
WBC	white blood cell
WOCBP	woman of childbearing potential

4. SYNOPSIS

Protocol #:	KNS-760704-AS201
Title:	A Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Biomarker Study of the Effects of Dexpramipexole on Eosinophils in Subjects with Eosinophilic Asthma
Version #:	[redacted]
Treatment:	Dexpramipexole
Indication:	Eosinophilic asthma
Phase:	2
Objectives:	***Primary Objective*** • To evaluate the efficacy of dexpramipexole in reducing blood eosinophil count in subjects with eosinophilic asthma ***Secondary Objectives*** • To evaluate the safety and tolerability of dexpramipexole administered for 12 weeks in subjects with eosinophilic asthma • To evaluate the efficacy of dexpramipexole on pulmonary function, asthma control, and quality of life • To evaluate the relative effect of dexpramipexole 75 mg/day, 150 mg/day, and 300 mg/day on blood eosinophil count ***Exploratory Objectives*** • To evaluate the efficacy of dexpramipexole in reducing tissue eosinophil biomarkers • To evaluate the efficacy of dexpramipexole in reducing blood basophil count • To evaluate the effect of dexpramipexole on blood eosinophil progenitor populations • To evaluate the onset of blood eosinophil lowering • To assess the recovery of blood eosinophil count after dexpramipexole discontinuation • To evaluate the effect of dexpramipexole on asthma biomarkers • To assess the correlation between eosinophil lowering with changes in pulmonary function and asthma control • To evaluate the exposure of dexpramipexole across the dose range used in the study • To examine the relationship between dexpramipexole exposure and eosinophil-lowering response • To investigate potential predictive biomarkers to identify hematologic responders

Endpoints:	***Primary Endpoint*** • Change in blood absolute eosinophil count from Baseline to Week 12 ***Secondary Endpoints*** • Change in pre-bronchodilator FEV1, from Baseline to Week 12 • Change in Asthma Control Questionnaire (ACQ-7) score, from Baseline to Week 12 • Change in post-bronchodilator FEV1, from Baseline to Week 12 • Change in quality of life, as measured by the Asthma Quality of Life Questionnaire (AQLQ), from Baseline to Week 12 • Incidence and severity of AEs, changes in vital signs, clinical laboratory safety tests, physical examination, body weight, and ECGs ***Exploratory Endpoints*** • Change in pharyngeal and nasal eosinophil peroxidase concentration from Baseline to Week 12 • Change in blood basophils, from Baseline to Week 12 • Change in blood eosinophil progenitor populations, from Baseline to Week 12 • Change in fractional exhaled nitric oxide (FeNO), from Baseline to Week 12 • The fraction of hematologic responders, defined as subjects with a ≥90% reduction of blood eosinophil count, from Baseline to Week 12 • Kinetics of eosinophil response, defined at each time point as the fraction of subjects having a hematologic response at that time point or previously, from Baseline to Week 12 • Kinetics of blood eosinophil recovery after discontinuation of dexpramipexole during the Eosinophil Recovery Period, defined as the fraction of subjects with an AEC ≥50% of the Baseline value over time, Week 12 to Week 24 (hematologic responder population) • Changes in biomarkers (e.g., cytokines) in peripheral blood: change from Baseline to Week 12. Serum samples will be collected at the Baseline, Week 12, and Week 24 visits for storage and testing of samples for biomarker evaluations of type 2 inflammation associated mediators, including IL-5, IL-13, IL-33, ST2, CCL2, CCL3, CCL4, CCL11, and CCL17. • Changes in urine eosinophil granule proteins, from Baseline to Week 12 • Dexpramipexole plasma concentration across the study dose range used in the study • Correlation between dexpramipexole exposure, as measured by dexpramipexole trough plasma concentration, and eosinophil-lowering response • Whole genome DNA sequencing to discover potential predictive genetic biomarkers to identify hematologic responders

Study Drug:	Oral administration of dexpramipexole study drug tablets BID for 12 weeks at 75 mg/day, 150 mg/day, 300 mg/day, or placebo
Study Centers:	Up to 25 sites in the United States
# of Subjects:	100 subjects randomized 1:1:1:1; placebo, dexpramipexole 75 mg/day, 150 mg/day, and 300 mg/day (25 per arm)
Study Population:	The protocol will enroll symptomatic eosinophilic asthmatic subjects 18-75 years with moderate or greater disease severity as defined by GINA steps 3-5.[1] Subjects must have an FEV1 of <80% of predicted at Screening and Baseline and have bronchodilator FEV1 reversibility of ≥12% and ≥ 200 ml at Screening.
Rationale for Study:	In a recently completed open-label pilot study in eosinophilic chronic rhinosinusitis with nasal polyps, dexpramipexole 300 mg/day dose lowered blood and nasal polyp eosinophil counts 20-fold.[2] The approved therapeutic monoclonal antibody drugs to interleukin-5 (IL-5) and the IL-5 receptor, benralizumab, mepolizumab, and reslizumab, are understood to exert their clinical efficacy in eosinophilic asthma through their eosinophil-lowering activity.[3-7] This suggests that dexpramipexole may have efficacy in eosinophilic asthma. Blood eosinophil lowering was chosen as the primary endpoint to inform selection of an optimal dose for use in Phase 3 clinical development.
Study Design	This is a randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multi-center study. Subjects will receive open-label placebo during the Run-in Period and double-blind study drug during the Primary Assessment Period of the study.
Duration of Treatment and Follow-up:	***Study Periods*** **Run-in Period:** Screening through initiation of Baseline. • Subjects will undergo Screening assessments to assess whether they satisfy the eligibility criteria. They will participate in the Run-in Period (of at least 12 days duration) to confirm a stable asthma medication regimen and to assess adherence to the dosing schedule, after which eligible subjects will be randomized. **Primary Assessment Period:** Baseline through completion of Week 12. • After the collection of all Baseline assessments, subjects will begin receiving study drug for 12 weeks. Subjects will have a site visit at Week 4, Week 8, and Week 12, and with a CBC will be collected at Week 2 and Week 6 (on site or remotely). The Week 12 visit is the Primary Outcome Visit for the study. Subjects will take the last dose of study drug at the Week 12 visit. **Eosinophil Recovery Period:** Conclusion of Week 12 assessments through Week 24. • Following the Primary Assessment Period, subjects will enter the Eosinophil Recovery Period. During this period, subjects will be seen at the site at either Week 16 or Week 18. Specific sites will be designated to perform either

	Week 16 or Week 18 visits for subjects enrolled at their site. The Week 20 and Week 24 visits may be at the site or may be at a designated remote laboratory facility.
Rationale for Dose Selection:	The dexpramipexole 300 mg/day dose was selected based on the clinical, safety, and eosinophil-lowering data demonstrated in Phase 2 and Phase 3 trials in subjects with amyotrophic lateral sclerosis[8] (ALS), and a Phase 2 trial in subjects with chronic rhinosinusitis with nasal polyps.[2] The 150 mg/day dose was chosen based on the results from the Phase 2 ALS trial, which also showed effective blood eosinophil lowering at that dose in 26 subjects.[8] In that same Phase 2 trial, subjects treated with 50 mg/day showed a biologically modest, but statistically significant, effect on lowering eosinophil count. The 75 mg/day dose was selected for this study based on the likelihood it would provide useful off-plateau dose-response data that would inform future clinical development decisions.
Evaluation of Safety:	Physical examination, vital signs (systolic and diastolic blood pressure, respiratory rate, heart rate, and temperature), body weight, 12-lead ECG, clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), pregnancy testing, adverse event monitoring, and concomitant medication monitoring throughout the study. [redacted] neutrophil counts will be reported using a central laboratory and monitored by the [redacted] Medical Monitor. A neutropenia case report form will be utilized during the study to capture detailed clinical information concurrent with any laboratory events of neutropenia. To assess potential cardiac drug interactions of albuterol and dexpramipexole, Week 8 ECGs will be timed to correspond with approximate Cmax dexpramipexole plasma concentrations.
Evaluation of Efficacy:	Blood eosinophil count, changes in pulmonary function (FEV1), Asthma Control Questionnaire (ACQ-7), Asthma Quality of Life Questionnaire (AQLQ), pharyngeal and nasal eosinophil peroxidase will be collected periodically during the study.
Pharmacokinetic Evaluations:	Blood for plasma drug concentration will be collected at the Week 4 (trough), Week 8 (trough and post-dose at 2 hours), and Week 12 (trough) visits. Dexpramipexole trough plasma concentration will be used to evaluate the relationship between dexpramipexole exposure and eosinophil-lowering response.

Statistics:	The study will use a blocked randomization stratified by study site. The safety sample population will be used for all safety analyses and the modified ITT population will be used for efficacy analyses. The modified ITT population, which consists of all subjects who received at least one dose of study drug and who have at least one post-randomization evaluation for at least one of the efficacy endpoints, will be used for efficacy analyses. The primary endpoint of this study is the change in blood absolute eosinophil count from Baseline to Week 12. Absolute eosinophil counts will be transformed to the log10 scale. To avoid taking the log of zero, zeroes will be replaced with 5 cells/μL in conventional units and 0.005×10^9/L in the International System of Units (SI), which is 50% of the lower limit of quantification. The geometric mean of all eosinophil counts obtained between the Screening and Baseline visits will be used to establish the baseline eosinophil count used in the efficacy analyses. Geometric means and standard deviations will be presented by treatment group for observed values at each visit along with a p-value comparing each dexpramipexole treatment group to placebo based on an analysis of variance (ANOVA). The primary analysis will be a mixed-effect model with repeated-measures (MMRM) with terms for baseline, GINA treatment steps 3 vs. 4/5, treatment, visit, treatment by visit interaction, and baseline by visit interaction as fixed effects, and subjects as a random effect. An unstructured covariance will be used. Dexpramipexole group treatment effects and treatment group effects versus placebo at Week 12 will be tested by contrasts within the MMRM. Estimated LS means of treatment effects and estimated difference in treatment effects at each visit will be back transformed to the original scale to present estimated geometric means for treatment effects and ratio of geometric means of treatment effects along with 95% CI. A contrast will be created to test the treatment effect at Week 12 for the pooled 150 mg/day and 300 mg/day group versus the placebo group. A contrast will be created to test the treatment effect at Week 12 for log-linear dose response. To control the alpha level for testing 3 dose groups versus placebo for the primary endpoint and for testing FEV1, a closed hierarchical testing procedure will be used in the following order: 1. First, the 300 mg/day dose group will be tested versus placebo for change in blood absolute eosinophil count, and if this reaches the <0.05 level then, 2. the 150 mg/day dose group will be tested versus placebo at the 0.05 level for change in blood absolute eosinophil count, and if this reaches the <0.05 level

	then, 3. the 75 mg/day dose group will be tested versus placebo at the 0.05 level for change in blood absolute eosinophil count, and if this reaches the <0.05 level then, 4. the pooled 150 and 300 mg/day dose groups will be tested versus placebo at the 0.05 level for change in FEV1 at Week 12. There may be an interim analysis of efficacy after all subjects have completed the Week 12 visit (Primary Outcome Visit). There will be no p-value adjustment for the interim analysis because subjects will be off study drug after the Week 12 visit and they will have completed the assessment of the primary endpoint. The primary purpose of visits after Week 12 is to observe eosinophil recovery following discontinuation of study drug and to monitor subjects for safety.
Sample Sze Determination:	*Sample Size* The primary endpoint for this study is change in blood absolute eosinophil count from Baseline to Week 12. In an open label study of dexpramipexole in subjects with chronic rhinosinusitis with nasal polyps (KNS-760704-CS201), dexpramipexole reduced eosinophils by 94% (ratio of endpoint to baseline =-2.81 on the log base e scale). The standard deviation for the ratio of endpoint to baseline was 1.82 on the log base e scale. Nineteen subjects per arm will provide approximately 84% power if the true reduction in blood eosinophils is 85% with dexpramipexole and 10% with placebo. The power will be 95% if the true reduction in blood eosinophils is 90% with dexpramipexole and 10% with placebo. The sample size was calculated using methodology for a two-sample t-test. Assuming an approximate 20% dropout rate of subjects who do not have the final observation for blood eosinophils yields a sample size of 25 subjects randomized per arm.

5. SCHEDULE OF EVENTS

	Run-in Period	Baseline	Primary Assessment Period				Primary Outcome Visit	Eosinophil Recovery Period		End of Study Visit
	Screening [1]	Day 1 [2,3]	Week 2 [4]	Week 4 [2]	Week 6 [4]	Week 8 [2]	Week 12 [2,5]	Week 16 or Week 18 [2,6]	Week 20 [4]	Week 24 [4]
Event	*≥ 12 day duration*	*(pre-dose)*	*(±5 days)*	*(±5 days)*	*(±5 days)*	*(±5 days)*	*(±5 days)*	*(±10 days)*	*(±10 days)*	*(±10 days)*
Signed ICD	×									
Medical history	×									
Asthma history	×									
Eligibility Review	×	×[7]								
Smart bottle inventory	×	×		×		×	×			
Structured study dosing adherence counseling	×	×		×		×				
Safety Evaluations										
Physical examination	×	×		×		×	×	×		
Vital signs [8]	×	×		×		×	×	×		
Body weight	×	×		×		×	×	×		
Clinical safety laboratory tests [9,10]	×	×	×[11]	×	×[11]	×	×	×	×	×
Urine β-hCG/ pregnancy test	×	×		×		×	×	×		×
Contraception counseling	×	×		×		×	×	×	×[12]	×[12]
12-lead ECG [13]	×	×		×		×[14]	×			
Adverse events [4]	× →	→	→	→	→	→	→	→	→	→
Prior & Concomitant medication [4]	× →	→	→	→	→	→	→	→	→	→
Neutropenia case report form [15]		×		×		×	×			

	Run-in Period	Baseline	Primary Assessment Period				Primary Outcome Visit	Eosinophil Recovery Period		End of Study Visit
	Screening [1]	Day 1 [2,3]	Week 2 [4]	Week 4 [2]	Week 6 [4]	Week 8 [2]	Week 12 [2,5]	Week 16 or Week 18 [2,6]	Week 20 [4]	Week 24 [4]
Event	*≥ 12 day duration*	*(pre-dose)*	*(±5 days)*	*(±5 days)*	*(±5 days)*	*(±5 days)*	*(±5 days)*	*(±10 days)*	*(±10 days)*	*(±10 days)*
Efficacy Evaluations										
Asthma Control Questionnaire (ACQ-7) [16]	×	×		×		×	×	×		
Asthma Quality of Life Questionnaire (AQLQ) [16]		×					×	×		
Pre-bronchodilator pulmonary function (FEV1) [17]	×[18]	×		×		×	×[19]	×		
Post-bronchodilator pulmonary function (FEV1) [2]	×	×					×			
PK/PD and Exploratory Evaluations										
Fractional exhaled Nitric Oxide (FeNO) [21]		×		×		×	×			
Plasma for dexpramipexole concentration				×[22]		×[23]	×[22]			
Serum IgE		×								
Whole blood collection (eosinophil progenitors and basophils)		×					×			
Whole blood for whole genome DNA sequencing		×								
Serum collection for exploratory biomarkers		×					×			×
Urine eosinophil granule proteins		×					×			
Nasal and pharyngeal eosinophil peroxidase		×					×			
Placebo administration BID	→									
Study drug administration BID		×[24] →								

1. Subject eligibility will be assessed during the Screening visit and confirmed at the Baseline visit. Screening assessments are to be completed between 12-30 days prior to the Baseline visit (first dose of study drug).
2. **Subjects should withhold their AM asthma medication the morning of the Baseline, Week 4, Week 8, Week 12, and Week 16/18 visits.** If the subject has not withheld asthma medications on the morning of the visit, the entire visit must be rescheduled.
3. Baseline assessments must be performed prior to the administration of the first dose of study drug.
4. The blood sample for submission to the central clinical laboratory may either be collected at the study site or at a designated remote laboratory facility at the Week 2, Week 6, Week 20, and/or Week 24 visits. If the blood sample is collected remotely, with associated telephone contact with the subject by appropriately delegated site personnel.
5. Subjects who discontinue study drug prematurely will be asked to return within 4 days of the last dose of study drug to have the Week 12 (Primary Outcome Visit) assessments performed. In such discontinued subjects, a well-being check (telephone interview) will be also completed 30 days after the last dose of study drug and will be documented in the CRF. See Section 8.3.11.
6. Specific sites will be selected to have all subjects enrolled at their site have this visit scheduled to occur on either Week 16 or Week 18.
7. Eligibility review based on completed Screening and Baseline assessments
8. Vital signs will be measured in the seated upright position after the subject has been rested for 5 minutes (systolic and diastolic systemic blood pressure [BP] in mmHg, respiratory rate [RR] per minute, and heart rate [HR] per minute).
9. The clinical laboratory test parameters will be performed by at a designated central laboratory.
10. The CBC (eosinophil count) should be collected between 6 AM and 12 noon, to minimize diurnal variation.
11. CBC only.
12. Contraception counseling required for male subjects only (as needed within 3 months of last dose of study drug).
13. 12-lead ECG triplicate tracings at least 1 minute apart will be recorded with the subject in the supine position after resting for at least 5 minutes.
14. To assess potential cardiac drug interactions of albuterol and dexpramipexole, 2 hours (± 30 minutes) after taking study drug in clinic at Week 8, subjects will have a triplicate ECG collected, as noted above. Afterwards, they will inhale four puffs of albuterol MDI (90-100 µg albuterol base per actuation) under the direction of study staff, wait 15 minutes (± 5 minutes), and have a second, post-bronchodilator ECG collection. See Section 12.1.3.
15. If a subject experiences a laboratory-defined event of neutropenia (absolute neutrophil count $<1.50 \times 10^9$/L), a neutropenia case report form will be completed. The information required for this form will be obtained by the site staff through an interview with the subject contemporaneous with the event.
16. The ACQ-7 and AQLQ should be collected as early as feasible during each visit to minimize the influence of other assessments (e.g., PFTs, ECG, and AE capture).
17. Pre-bronchodilator PFTs at each study visit should be collected between 6 AM and 12 noon local time and should be collected within ±2 hours of the Baseline visit to minimize diurnal variation.
18. Subjects who present for Screening but have already taken their AM asthma medication (see Table 2), should have all other Screening assessments performed and will be required to reschedule the Screening PFT as soon as feasible.
19. **The Week 12 pre-bronchodilator PFT should be performed within ± 1 hour of the time of day that the Baseline PFT was collected.**
20. After completing the pre-bronchodilator PFTs, subjects will inhale the same number of puffs of albuterol metered dose inhaler used to qualify the subject for the study. Spirometry will be repeated 15-30 minutes after inhalation of albuterol. See Section 12.2.2.
21. Fractional exhaled Nitric Oxide (FeNO) should be collected prior to the PFT tests.
22. Week 4 and Week 12 plasma for dexpramipexole concentration collected pre-dose (trough)
23. Week 8 plasma for dexpramipexole concentration pre-dose (trough) and 2 hours (±10 minutes) after dose – See Section 12.4.
24. Dexpramipexole dosing after completing all Baseline assessments.

6. INTRODUCTION AND RATIONALE

6.1. Overview

Asthma is a chronic lung disease characterized by airway inflammation and obstruction (decreased airflow). Asthma prevalence varies across different countries, with some of the highest rates (>8%) in the United States.[9] In the past decades, asthma prevalence has increased in developing countries, particularly in urban populations.[9] Because of its high prevalence, asthma has a major impact on quality of life and is an important source of health care costs, estimated at $56 billion/year in the United States.

In recent years, it has become clear that asthma is actually a syndrome comprised of several different endotypes, each defined by different underlying pathophysiology. Eosinophilic asthma is the best-defined asthma endotype and represents more than 50% of asthma patients.[10] Although eosinophilic asthma was originally defined based on sputum eosinophilia, in recent years elevated blood eosinophils have become an accepted and more convenient means to identify these cases. The last decade has been notable for the clinical development of anti-eosinophil biologic therapies, including the anti-IL-5 monoclonal antibodies (mAbs) mepolizumab and reslizumab and the anti-IL-5 receptor mAb benralizumab. These anti-eosinophil biologics have clearly shown that lowering eosinophils is sufficient to improve asthma clinical outcomes, such as asthma exacerbations.[11] High-magnitude eosinophil lowering was observed in a previous open-label trial of dexpramipexole in chronic rhinosinusitis with nasal polyps (CRSwNP) (KNS-760704-CS201; "CS201").[2] Accordingly, this trial seeks to investigate if similar eosinophil lowering is seen in patients with eosinophilic asthma.

6.2. Dexpramipexole Background

Dexpramipexole is an oral small molecule initially developed by Knopp Biosciences LLC (Knopp) as a treatment for amyotrophic lateral sclerosis (ALS). Dexpramipexole is the (R)-(+) enantiomer of pramipexole, (6S)-4,5,6,7-tetrahydro-N6-propyl-2,6-benzothiazole-diamine dihydrochloride monohydrate. The (S)-(-) enantiomer, pramipexole, is a potent dopamine agonist approved as a treatment for Parkinson's disease and restless legs syndrome in the U.S. and in Europe. Dexpramipexole is approximately 10,000 - 20,000 times less potent a human dopamine agonist than pramipexole.

In 2013, a large Phase 3 trial of dexpramipexole failed to demonstrate efficacy on primary and secondary endpoints in subjects with ALS (233AS302; "EMPOWER"). Unexpectedly, during the preclinical and clinical development program in ALS, a substantial, durable, and targeted reduction in blood eosinophil counts was observed.[8] This finding led Knopp to explore the safety, tolerability, and preliminary evidence of effectiveness in eosinophil-associated disorders

(EAD). In 2016, Knopp completed an open-label Phase 2 study to evaluate dexpramipexole in subjects with eosinophilic CRSwNP (CS201). In a 2017 collaboration with Dr. Amy Klion of the National Institute of Allergy and Infectious Diseases in the National Institutes of Health (NIAID/NIH), Knopp completed a Phase 2 study of dexpramipexole in subjects with hypereosinophilic syndrome (14-I-0063). These studies are now complete, and in both, dexpramipexole demonstrated significant eosinophil-lowering activity in both blood and tissue.[2, 12]

For further details, see the dexpramipexole Investigator's Brochure.

6.3. Previous Experience

6.3.1. Nonclinical Development

Nonclinical studies demonstrate that dexpramipexole is metabolically stable, with high oral bioavailability. Plasma concentration and systemic exposure are generally linear. In animal studies, Tmax generally ranged from 1 to 4 hours; plasma t½ ranged from 3 to 8 hours approximately. No high-affinity interactions were observed for any receptors and other targets examined after screening dexpramipexole in standard in vitro pharmacology panels. For its development in CNS therapeutic indications, dexpramipexole has been shown to cross the blood-brain barrier in rats, mice, and minipigs and to concentrate in the brain relative to plasma. Dexpramipexole was demonstrated to be negative for any mutagenic or genotoxic signal in the full battery of in vitro and in vivo assessments recommended by ICH guidelines.

Dexpramipexole demonstrated very low protein binding in plasma from preclinical species (Sprague Dawley rats and Göttingen minipigs) and humans. It was stable in human liver microsomes and showed no significant inhibition of the major CYP isoforms. Although dexpramipexole may be a weak inducer of CYP2C8 in vitro, at 300 mg/day it is expected to have a low potential for drug-drug interaction (DDI) via modulation of CYP2C8. The concentration of dexpramipexole required for induction of CYP2C8 is ≥ 100 µM, which is significantly greater than its observed therapeutic unbound plasma Cmax concentration of 2 to 4 µM in humans after chronic administration of dexpramipexole 300 mg/day. Because a signal for CYP2C9 induction by dexpramipexole was observed at 10 µM, a clinical DDI study to evaluate dexpramipexole's potential to modulate CYP2C9 activity was conducted; no clinically significant drug-drug interaction was observed.

6.3.2. Clinical Experience with Dexpramipexole

One thousand, two hundred and thirty-six (1,236) subjects have received dexpramipexole in Phase 1 to Phase 3 clinical studies conducted to date. A total of 294 healthy adult subjects and 24 renally impaired subjects received dexpramipexole daily doses ranging from 50 mg/day to 600 mg/day in 10 completed Phase 1 clinical studies.

A total of 888 ALS subjects received dexpramipexole doses of 50 mg/day to 300 mg/day in 4 completed clinical trials. These include the Phase 3 double-blind ALS study (EMPOWER), in which 474 subjects received dexpramipexole 300 mg/day, with a mean exposure time of 11.75 months; 407 were treated for 6 months or longer; 335 of these subjects received dexpramipexole for 12 months or longer.

An open-label Phase 2 study of dexpramipexole 300 mg/day (CS201) was conducted in subjects with CRSwNP with a baseline absolute eosinophil count (AEC) $\geq 0.30 \times 10^9$/L and polyp eosinophilia. The co-primary endpoints were change in AEC and change from baseline in Total Polyp Score (TPS, a measure of bilateral polyp burden) after 6 months of treatment. A total of 20 subjects entered the study and received at least 1 dose of study drug; and 16 subjects were included in the efficacy population. The AEC was 0.525×10^9/L at baseline and decreased to 0.031×10^9/L after 6 months of dexpramipexole treatment, a 94% reduction ($p<0.001$, geometric means). In 12 subjects with nasal polyp biopsies at baseline and after 6 months of dexpramipexole treatment, tissue eosinophils were reduced from a mean of 168 to 5 per high-power field ($p=0.001$), a 97% reduction. There was no significant reduction in TPS or improvement in other clinical endpoints. Dexpramipexole was well-tolerated in this study, with no drug-related SAEs reported. In this study and the optional extension, the median duration of exposure was 179.5 days, with a minimum exposure of 5 days and a maximum exposure of 598 days.

In a collaboration between Knopp and the NIH, an open-label Phase 2 study was conducted to evaluate the safety and preliminary evidence of efficacy of dexpramipexole as a steroid-sparing agent in 10 hypereosinophilic syndrome (HES) subjects (14-I-0063). In this completed trial and its ongoing extension phase, 10 subjects received at least 1 dose of dexpramipexole; as of as of March 2019, the median duration of exposure was 300 days with a minimum exposure of 93 days and a maximum exposure of 4 years and 2 months. Four of these 10 subjects received dexpramipexole for more than 12 months. Dexpramipexole was well-tolerated in this study. No deaths or AEs leading to drug interruption or discontinuation were observed. Two subjects reported transient palpitations and four subjects reported insomnia, all of which resolved without drug discontinuation or modification of dose.

6.4. Rationale for Study Population

In this study (KNS-760704-AS201, "AS201"), dexpramipexole will be added to existing asthma therapy in subjects with Global Initiative for Asthma[1] (GINA) steps 3-5 persistent asthma (requiring at minimum a low dose inhaled corticosteroid in combination with a long-acting β-agonist). The study population is limited to subjects with a physician diagnosis of asthma for ≥12 months and eligibility criteria described in Section 9.

In addition to its role in defining eosinophilic asthma, blood eosinophil count is also a biomarker associated with greater risk of asthma exacerbation.[13] Additionally, AEC is predictive of patients with greater clinical improvement to anti-eosinophil therapies.[7, 14] Accordingly, the eligibility criteria for this trial requires an AEC of $\geq 0.30 \times 10^9$/L. This eligibility criterion was utilized previously in the CS201 trial in CRSwNP subjects and is intended to select an asthmatic population comparable to the package label for approved eosinophil-lowering biologics.

6.5. Rationale for Study Design

Approximately half of asthma patients fail to achieve adequate control of asthma symptoms and exacerbations when treated with approved asthma therapy, typically consisting of inhaled corticosteroids and long acting β-agonists.[15, 16] Although some of the responsible factors are modifiable, such as suboptimal medication adherence and poor inhaler technique, others reflect intrinsic deficiencies in available asthma pharmacotherapy. This deficiency is particularly apparent in patients prone to severe asthma exacerbations. Eosinophil-lowering biologics, such as mepolizumab, reslizumab, and benralizumab, have clearly demonstrated that significant lowering of blood and/or tissue eosinophils results in reduction of asthma exacerbations and improvement in asthma symptoms.

However, all of the biologics require parenteral administration.[3-7] Thus, there is a need and opportunity for an oral eosinophil-lowering drug, such as dexpramipexole, for the management of eosinophilic asthma.

A 4-arm dose ranging placebo-controlled design was chosen to provide a range of drug exposure.[17, 18] Blood eosinophil lowering was chosen as the primary endpoint to facilitate identification of the lowest effective dose for use in future clinical development. The Primary Assessment Period of 12 weeks was chosen to provide adequate time to observe both pharmacodynamic endpoints, such as eosinophil lowering, as well as the clinical endpoints that may improve as a consequence of eosinophil lowering (FEV1, ACQ-7, and AQLQ). The 12-week Eosinophil Recovery Period was chosen based on expected recovery to near baseline count in most subjects.

6.6. Rationale for Dose and Regimen Selection

Clinical pharmacology studies have demonstrated that dexpramipexole administered orally at single doses up to 600 mg and multiple doses up to 300 mg BID (600 mg/day) for 5-7 days is well tolerated with high bioavailability and linear pharmacokinetics (PK). Phase 2 and Phase 3 clinical studies of dexpramipexole in ALS and eosinophil associated disorders (EAD) with durations from three to greater than 12 months have demonstrated that dexpramipexole produces a substantial, durable, and targeted reduction in peripheral blood eosinophil count following

prolonged drug exposure.[8] Dexpramipexole eosinophil lowering takes from several weeks to several months and thus is not an acute effect of the drug.

Evidence for the eosinophil-lowering effects of dexpramipexole was first observed in the two-part, placebo-controlled, double-blind Phase 2 study of dexpramipexole in 102 ALS subjects (KNS-760704-CL201; "CL201"). In Part 1 of CL201 (12 weeks of treatment), mean blood eosinophil count increased by 29.2% in the placebo group and declined by 17.7% ($p=0.038$), 69.9%, ($p<0.0001$), and 43.5% ($p=0.0008$) in the 50 mg/day, 150 mg/day, and 300 mg/day groups, respectively.[8] The decrease in blood eosinophil count was partially reversed by the end of a 4-week washout period that followed Part 1. Following a 4-week placebo washout period, subjects were re-randomized to 50mg/day or 300 mg/day in Part 2. After an additional 6 months of treatment, subjects re-randomized to 300 mg/day had a greater decline in blood eosinophil count than subjects re-randomized to 50 mg/day (78.9% vs. 17.6%, respectively). This was consistent with the dose-dependent effect of dexpramipexole on blood eosinophil count observed in Part 1 of CL201.

Confirmation of the eosinophil-lowering effect of dexpramipexole was observed in the double-blind Phase 3 study (EMPOWER) of dexpramipexole in 942 ALS subjects randomized 1:1 to placebo or dexpramipexole 300 mg daily treatment for up to 18 months. At Month 6, the change from baseline in blood eosinophil count was +18.7% in the placebo group and -69.1% in the dexpramipexole-treated group ($p<0.0001$).[8]

ALS patients are generally non-atopic and have normal eosinophil counts. To explore the relationship between baseline AEC and the magnitude of eosinophil lowering, a post hoc analysis of the Phase 3 ALS study (EMPOWER) was performed in subgroups stratified by baseline AEC. The percentage of subjects with high-magnitude eosinophil lowering, defined as ≥90% reduction from baseline to Months 4-6, was assessed. In the dexpramipexole arm, 18.0% of subjects had high-magnitude eosinophil lowering. In the subgroup with baseline AEC $>0.20 \times 10^9$/L, 40% of subjects had high-magnitude eosinophil lowering. In contrast, few subjects with a baseline AEC $<0.10 \times 10^9$/L had high magnitude lowering. These findings suggest that dexpramipexole may more efficaciously lower blood eosinophil counts in subjects with baseline eosinophilia.

Data from the Phase 2 study of dexpramipexole 300 mg/day in CRSwNP (CS201) confirmed the eosinophil-lowering effects of dexpramipexole in subjects with an eosinophil associated disorder (EAD). The geometric mean baseline AEC of 0.53×10^9/L was reduced 92% by Month 2 ($p<0.001$, $n=16$), and this reduction was durable through the Month 6 primary endpoint, 94% ($p<0.001$).[2] Polyp tissue eosinophil counts decreased significantly from 168 to 5.1 cells/high-powered field (Baseline vs. Month 6; 97% reduction, $p=0.001$, $n=12$). Notably, 80% of the subjects in CS201 had concomitant asthma, almost all of which was mild.

In CS201, AEC reductions in response to dexpramipexole were bimodal, with 10 of 16 subjects (62.5%) having attained an AEC $\leq 0.02 \times 10^9$/L (99% reduction from baseline) at the Month 6 visit. The remaining 6 subjects all had a Month 6 AEC $\geq 0.10 \times 10^9$/L (range: 15% increase to 76% reduction). Dexpramipexole plasma concentration 2 hours post-dose (at or near estimated Cmax) at Month 3 did not account for the heterogeneous eosinophil lowering among subjects.

In the Phase 2 HES study (14-I-0063), 10 subjects with a geometric mean baseline AEC of 0.69×10^9/L, who were taking a stable oral corticosteroid dose at baseline (mean=18.35 mg prednisone), received dexpramipexole 300 mg/day for 3 months. Geometric mean AEC was 0.22×10^9/L at Month 1 (68% decrease), 0.11×10^9/L at Month 2 (84% decrease, p=0.04), and 0.15×10^9/L at Month 3 (78% decrease, p=0.01).[12]

Both the CRSwNP and HES trials (CS201 and 14-I-0063, respectively) showed a faster onset of eosinophil lowering than was observed in the ALS studies (CL201 and EMPOWER). Additionally, in the CRSwNP study, the magnitude of eosinophil lowering was greater than that seen in the ALS studies. These findings suggest that dexpramipexole has greater eosinophil-lowering activity in patients with eosinophilia, which may be consistent with a mechanism of action of dexpramipexole that inhibits eosinophil maturation.

The 300 mg/day high dose for AS201 was chosen because of the extensive clinical, safety, and eosinophil-lowering data observed in the Phase 2 ALS (CL201), Phase 3 ALS (EMPOWER), Phase 2 CRSwNP (CS201), and Phase 2 HES (14-I-006) studies with dexpramipexole.[2, 8] The 150 mg/day mid dose was selected based on the evidence from the Phase 2 ALS trial (CL201), which showed effective blood eosinophil lowering in 26 subjects at that dose.[8] In that same trial, subjects treated with 50 mg/day had biologically modest but statistically significant blood eosinophil lowering. The 75 mg/day low dose was selected as it is expected to provide useful off-plateau dose response data.

The use of dexpramipexole at 75 mg/day, 150 mg/day, and 300 mg/day in the current study (AS201) is expected to yield the greatest amount of data on eosinophil-lowering dose-response relationships to inform future clinical development.

7. STUDY OBJECTIVES AND ENDPOINTS

7.1. Objectives

7.1.1. Primary Objective

- The primary objective of this clinical trial is to evaluate the efficacy of dexpramipexole in reducing blood eosinophil count in subjects with eosinophilic asthma.

7.1.2. Secondary Objectives

The secondary objectives are as follows:

- To evaluate the safety and tolerability of dexpramipexole administered for 12 weeks in subjects with eosinophilic asthma
- To evaluate the efficacy of dexpramipexole on pulmonary function, asthma control, and quality of life
- To evaluate the relative effect of dexpramipexole 75 mg/day, 150 mg/day, and 300 mg/day on blood eosinophil count

7.1.3. Exploratory Objectives

The exploratory objectives are:

- To evaluate the efficacy of dexpramipexole in reducing tissue eosinophil biomarkers
- To evaluate the efficacy of dexpramipexole in reducing blood basophil count
- To evaluate the effect of dexpramipexole on blood eosinophil progenitor populations
- To evaluate the onset of blood eosinophil lowering
- To assess the recovery of blood eosinophil count after dexpramipexole discontinuation
- To evaluate the effect of dexpramipexole on asthma biomarkers
- To assess the correlation between eosinophil lowering with changes in pulmonary function and asthma control
- To evaluate the exposure of dexpramipexole across the dose range used in the study
- To examine the relationship between dexpramipexole exposure and eosinophil-lowering response
- To investigate potential predictive biomarkers to identify hematologic responders

7.2. Endpoints

7.2.1. Primary Endpoint

- The primary endpoint of this study is the relative change in blood absolute eosinophil count from Baseline to Week 12.

7.2.2. Secondary Endpoints

Following are the secondary endpoints of the study:

- Change in pre-bronchodilator FEV1, from Baseline to Week 12
- Change in Asthma Control Questionnaire (ACQ-7) score, from Baseline to Week 12
- Change in post-bronchodilator FEV1, from Baseline to Week 12
- Change in quality of life, as measured by the Asthma Quality of Life Questionnaire (AQLQ), from Baseline to Week 12
- Incidence and severity of AEs, changes in vital signs, clinical laboratory safety tests, physical examination, body weight, and ECGs

7.2.3. Exploratory Endpoints

The following are the exploratory endpoints:

[redacted]

[redacted]

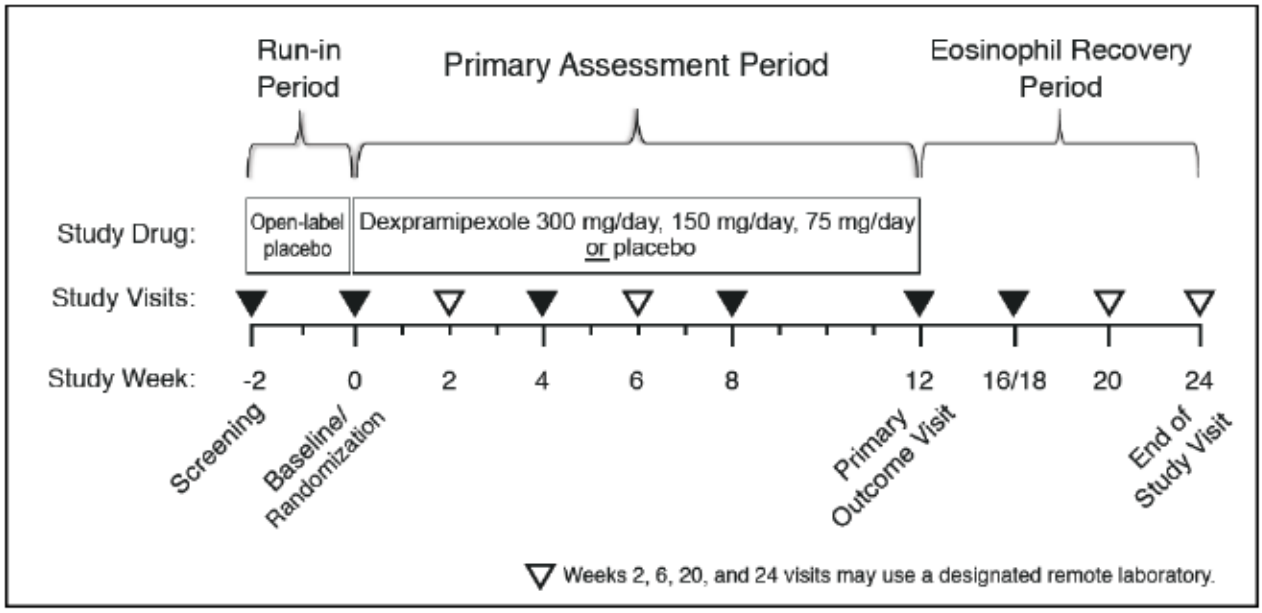
8. STUDY DESIGN

8.1. Study Overview

This is a randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multi-center study to evaluate the clinical effects of oral administration of dexpramipexole for 12 weeks on peripheral blood eosinophil count in subjects with eosinophilic asthma.

One hundred subjects will receive study drug (placebo, dexpramipexole 75 mg/day, 150 mg/day, or 300 mg/day randomly allocated in a 1:1:1:1 ratio) during the Primary Assessment Period of the study (12 weeks of consecutive dosing). The study is expected to be conducted in approximately 25 centers in the United States. After the Screening evaluations are completed, eligible subjects will enter a Run-in Period of at least 12 days. Following the Run-in Period, eligible subjects will enter the Primary Assessment Period and receive twice-daily dosing of study drug for 12 weeks. During the Primary Assessment Period, subjects will have study assessments performed at the site every 4 weeks, with additional safety and laboratory assessments at Week 2 and Week 6. Following Week 12, subjects will discontinue study drug and will begin a 12-week Eosinophil Recovery Period, during which subjects will be monitored for recovery of eosinophil count. See Fig. 1 for details.

Figure 1 Study Schematic



A schedule of study visits and assessments is provided in Section 5.

To maximize study dosing adherence and provide more detailed adherence data, subjects will take study drug from a "smart bottle". The smart bottle device reminds subjects to take

medication via visual cues, audible chimes, and text message reminders. The smart bottle records data regarding the opening of the container. Data are uploaded to a server via a mobile link, to facilitate feedback to Knopp and study staff regarding dosing adherence. The aim of utilizing the smart bottle is to provide timely feedback to the sites and remediate poorly adherent subjects. Subjects must maintain a ≥ 85% study dosing adherence during a minimum of 12 consecutive days in the Run-in Period to be randomized to treatment. During the study, subjects will be regularly counselled regarding the need for study dosing adherence.

As dexpramipexole lowers eosinophil and basophil counts, these laboratory values could indicate active treatment assignment. To protect study data integrity, specific CBC results will be blinded during the conduct of the study. To maintain this blinding, a central lab facility will perform all safety labs for the study. The site staff, [redacted] (CRO), and Knopp personnel will be blinded to absolute eosinophil count, absolute basophil count, total white blood cell (WBC) count and WBC % differential collected during the Primary Assessment Period and Eosinophil Recovery Period (after Baseline through Week 24). All other lab results will be available to the Site Investigator during the study.

8.1.1. Overall Study Duration and Follow-Up

The study includes the following study periods:

Period	Schedule
Screening	Occurs within 30 days of Baseline
Run-in Period	Begins at Screening and concludes with Baseline (at least 12 days duration)
Baseline	Occurs at the conclusion of the Run-in Period *and* immediately prior to administration of the first dose of study drug
Primary Assessment Period	Begins with Baseline and concludes with the Week 12 assessments (Primary Outcome Visit)
Primary Outcome Visit	Site visit at Week 12
Eosinophil Recovery Period	Begins after the Week 12 assessments are complete (Primary Outcome Visit) and ends with the completion of the Week 24 assessments (End of Study Visit)
End of Study Visit	Remote visit at Week 24 (may be performed at site)

Period	Schedule
Primary Outcome Visit for prematurely discontinued subjects	Subjects who discontinue study drug prematurely will complete the Week 12 assessment (Primary Outcome Visit assessment) (See Section 8.3.11). A well-being check (telephone interview) will be also completed 30 days after the last dose of study drug.

8.2. Study Periods

8.2.1. Run-in Period

The Run-in Period will last from the Screening visit through to the start of the Baseline visit. The Run-in Period will be at least 12 days in duration, during which time subjects will be monitored for asthma control, symptoms, study drug dosing adherence, and concomitant medication usage.

After the collection of the initial Screening assessments, potentially eligible subjects will immediately enter the Run-in Period. During the Run-in Period, subjects will take placebo (open-label) administered twice daily (BID) and must demonstrate ≥ 85% study drug dosing adherence over at least 12 consecutive days. Dosing adherence will be monitored using a smart bottle device that tracks the opening/closure of the study drug bottle and by visual verification of unused pill count.

Subjects with Run-in Period dosing adherence of 70%-84.9% may repeat the Run-in Period once to satisfy the dosing adherence requirement. Subjects must demonstrate ≥ 85% study drug dosing adherence over at least 12 consecutive days during the repeat Run-in Period to eligible for the study. The Run-in Period may be extended to 30 days maximum duration to allow for laboratory retests and/or study drug dosing adherence rechecks.

Subjects with study drug dosing adherence <85% will be ineligible.

8.2.2. Primary Assessment Period

The Primary Assessment Period will last from Baseline through the completion of the Week 12 (Primary Outcome Visit) assessments. During the Primary Assessment Period subjects will be administered double-blind study drug twice daily for 12 weeks. Subjects are required to have site visits performed at Week 4, Week 8, and Week 12. Additional study visits for the collection of a CBC will occur at Week 2 and Week 6. The Week 2 and Week 6 visits may be conducted at a designated remote laboratory facility, or as a site visit for convenience.

8.2.3. Eosinophil Recovery Period

The Eosinophil Recovery Period will begin with the completion of the Week 12 (Primary Outcome Visit) assessments and continues through the completion of the Week 24 (End of Study Visit) assessments. The Eosinophil Recovery Period is scheduled to be 12 weeks in duration.

Study visits will occur at Week 16/18, Week 20 and Week 24. The collection of clinical laboratory safety tests at Week 20 and Week 24 may be conducted at a designated remote laboratory facility, or as a site visit for convenience. If a designated remote laboratory facility is utilized for these visits, qualified site personnel will conduct a telephone interview with the subject to collect adverse event and concomitant medication data.

8.3. Study Schedule

See Section 12 for details regarding individual Study Assessments.

8.3.1. Screening

Prior to conducting any study-related assessments, written informed consent must be obtained from the subject. Participation in this study is voluntary. The nature of the study will be fully explained to each subject during the informed consent process and the subject will have the opportunity to ask questions. A copy of the informed consent form (ICF) will be provided to the subject.

Subject eligibility will be assessed during the Screening visit and confirmed at the Baseline visit. Screening assessments are to be completed between 12-30 days prior to the Baseline visit (first dose of study drug).

At the Screening visit, the following assessments are to be completed (the general sequence for performing assessments should follow the order below):

- Confirm Informed Consent
- Asthma Control Questionnaire (ACQ-7)
    - *Should be collected as early as feasible in the visit to minimize the influence of other assessments (e.g., PFTs, ECG, and AE capture)*
- Medical history
- Asthma history
- Physical examination
- Vital signs – See Section 12.1.2
- Body weight
- Clinical safety laboratory tests
- Urine β-hCG/ pregnancy test for females of child bearing potential
- Contraception counseling, all subjects

- 12-lead ECG (*prior to PFTs)* – See Section 12.1.3
- Adverse events
- Prior & concomitant medication
- Pre-bronchodilator pulmonary function (FEV1) – See Section 12.2.2
    - *If the subject has withheld their asthma medications, perform pre-bronchodilator PFTs followed by post-bronchodilator PFTs*
    - *If the subject has not withheld their asthma medications, schedule a return visit to perform pre-bronchodilator and post-bronchodilator PFTs – See Section 8.3.1.1*
- Post-bronchodilator pulmonary function (FEV1) – See Section 12.2.2
- Eligibility review based on Screening assessments
- Smart bottle inventory and structured study dosing adherence counseling – See Study Reference Manual
- Observed administration of study drug (open-label placebo)
- Discharge from site with smart bottle

8.3.1.1. Screening Pulmonary Function Testing

Subjects who present for Screening and have taken their AM asthma medication (see Table 2), should have all Screening assessments performed except the Screening PFT. These subjects will be requested to reschedule the Screening PFT as soon as feasible on a morning when the asthma medication has been withheld.

The pre-bronchodilator FEV1 inclusion criterion must be met at the Screening and Baseline visits. The post-bronchodilator FEV1 inclusion criterion must be met at the Screening visit.

- Subjects who do not meet the pre-bronchodilator FEV1 inclusion criterion of <80% predicted at Screening and Baseline, despite withholding asthma medication per Table 2, may not repeat PFTs in order to qualify for the study.
- At Screening, subjects who do not meet the post-bronchodilator reversibility inclusion criterion, but have ≥10% or ≥160 mL reversibility, may repeat the reversibility PFT assessment once during the Run-in Period.

8.3.2. Baseline

Following the completion of the Run-in Period and confirmation of eligibility, Baseline assessments will be performed prior to dosing on Day 1 of study drug.

Subjects should hold their AM asthma medication the morning of the Baseline visit. If the subject has not withheld their asthma medications according to Table 2, the entire Baseline visit must be rescheduled.

At the Baseline visit, the following assessments are to be completed (the general sequence for performing assessments should follow the order below):

- Confirm Informed Consent
- Asthma Control Questionnaire (ACQ-7)
  - *Should be collected as early as feasible in the visit to minimize the influence of other assessments (e.g., PFTs, ECG, and AE capture)*
- Asthma Quality of Life Questionnaire (AQLQ)
  - *Should be collected as early as feasible in visit to minimize the influence of other assessments (e.g., PFTs, ECG, and AE capture)*
- 12-lead ECG *(prior to dosing dexpramipexole)* – See Section 12.1.3
- Clinical safety laboratory tests
- Serum for IgE
- Whole blood collection (eosinophil progenitors and basophils)
- Whole blood for whole genome DNA sequencing
- Serum collection for exploratory biomarkers
- Urine eosinophil granule proteins
- Urine β-hCG/ pregnancy test for females of child bearing potential
- Contraception counseling, all subjects
- Vital signs – See Section 12.1.2
- Body weight
- Fractional exhaled Nitric Oxide (FeNO) *(prior to PFTs)*
- Pre-bronchodilator pulmonary function (FEV1) – See Section 12.2.2
- Post-bronchodilator pulmonary function (FEV1) – See Section 12.2.2
- Physical examination
- Adverse events
- Neutropenia case report form interview
- Prior & concomitant medication
- Nasal and pharyngeal eosinophil peroxidase
- Eligibility review based on Baseline assessments
- Randomization
- Smart bottle inventory and structured study dosing adherence counseling. See Study Reference Manual
- Observed administration of study drug
- Discharge from site with smart bottle

8.3.2.1. Baseline Pulmonary Function Testing

Subjects who present for the Baseline visit, but have not withheld their asthma medication according to Table 2, should not be randomized and must reschedule the Baseline visit.

8.3.3. Week 2 Visit

At the Week 2 visit, a CBC will be performed.

The clinical laboratory blood sample (CBC) may either be collected at the study site or at a designated remote laboratory facility for convenience.

8.3.4. Week 4 Visit

Subjects should hold their study drug AND AM asthma medication the morning of the Week 4 visit. If the subject has not withheld their asthma medications, the Week 4 visit must be rescheduled.

At the Week 4 visit, the following assessments are to be completed (the general sequence for performing assessments should follow the order below):

- Asthma Control Questionnaire (ACQ-7)
  - *Should be collected as early as feasible in the visit to minimize the influence of other assessments (e.g., PFTs, ECG, and AE capture)*
- 12-lead ECG *(prior to dosing study drug)* – See Section 12.1.3
- Clinical safety laboratory tests
- Plasma for dexpramipexole concentration (*trough*)
- Urine β-hCG/ pregnancy test for females of child bearing potential
- Smart bottle inventory and structured study dosing adherence counseling. See Study Reference Manual
- Physical examination
- Vital signs – See Section 12.1.2
- Body weight
- Contraception counseling, all subjects
- Adverse events
- Neutropenia case report form interview
- Concomitant medication
- Fractional exhaled Nitric Oxide (FeNO) *(prior to PFTs)*
- Pre-bronchodilator pulmonary function (FEV1) – See Section 12.2.2
- Observed administration of study drug
- Distribute coming month's study drug in smart bottle – See Section 11.2
- Discharge from site with smart bottle

8.3.5. Week 6 Visit

At the Week 6 visit, a CBC will be performed.

The clinical laboratory blood sample (CBC) may either be collected at the study site or at a designated remote laboratory facility for convenience.

8.3.6. Week 8 Visit

Subjects should hold their study drug AND AM asthma medication the morning of the Week 8 visit. If the subject has not withheld their asthma medications, the Week 8 visit must be rescheduled.

The expected duration of the Week 8 visit is approximately 3 hours.

At the Week 8 visit, the following assessments are to be completed (the general sequence for performing assessments should follow the order below):

- Asthma Control Questionnaire (ACQ-7)
  - *Should be collected as early as feasible in the visit to minimize the influence of other assessments (e.g., PFTs, ECG, and AE capture)*
- 12-lead ECG *(prior to dosing study drug)* – See Section 12.1.3
- Clinical safety laboratory tests
- Plasma for dexpramipexole concentration (*trough*)
- Urine β-hCG/ pregnancy test for females of child bearing potential
- Smart bottle inventory and structured study dosing adherence counseling. See Study Reference Manual
- Physical examination
- Vital signs – See Section 12.1.2
- Body weight
- Observed administration of study drug
- Plasma for dexpramipexole concentration at 2 hours after dose – See Section 12.4
- Contraception counseling, all subjects
- Adverse events
- Neutropenia case report form interview
- Concomitant medication
- Fractional exhaled Nitric Oxide (FeNO) *(prior to PFTs)*
- Pre-bronchodilator pulmonary function (FEV1) – See Section 12.2.2
- 12-lead ECG *(after PFTs)* at 2 hours post dose (± 30 minutes) – See Section 12.1.3
  - *Initial ECG followed by immediate inhalation of albuterol 4 puffs via metered dose inhaler (90-100 µg albuterol base per actuation)*
  - *Repeat 12-lead ECG 15 minutes (± 5 minutes) after last puff of albuterol*

- Distribute coming month's study drug in smart bottle – See Section 11.2
- Discharge from site with smart bottle

8.3.7. Week 12 - Primary Outcome Visit

Week 12 is designated as the Primary Outcome Visit and will be performed at the site.

Subjects should hold their study drug AND AM asthma medication the morning of the Week 12 visit. If the subject has not withheld their asthma medications according to Table 2, the Week 12 visit must be rescheduled.

The expected duration of the Week 12 visit is 2 hours.

At the Week 12 visit, the following assessments are to be completed (the general sequence for performing assessments should follow the order below:

- Asthma Control Questionnaire (ACQ-7)
  - *Should be collected as early as feasible in the visit to minimize the influence of other assessments (e.g., PFTs, ECG, and AE capture)*
- Asthma Quality of Life Questionnaire (AQLQ)
  - *Should be collected as early as feasible in the visit to minimize the influence of other assessments (e.g., PFTs, ECG, and AE capture)*
- 12-lead ECG *(prior to dosing study drug)* – See Section 12.1.3
- Clinical safety laboratory tests
- Plasma for dexpramipexole concentration *(trough)*
- Whole blood collection (eosinophil progenitors and basophils)
- Serum collection for exploratory biomarkers
- Urine eosinophil granule proteins
- Smart bottle inventory
- Physical examination
- Vital signs – See Section 12.1.2
- Body weight
- Urine β-hCG/ pregnancy test for females of child bearing potential
- Contraception counseling, all subjects
- Adverse events
- Neutropenia case report form interview
- Concomitant medication
- Fractional exhaled Nitric Oxide (FeNO) *(prior to PFTs)*
- Pre-bronchodilator pulmonary function (FEV1) – See Section 12.2.2
  - *The Week 12 Pre-bronchodilator PFT should be collected within ± 1 hour of the time of day that the Baseline PFT was collected.*

- Post-bronchodilator pulmonary function (FEV1) – See Section 12.2.2
- Nasal and pharyngeal eosinophil peroxidase
- Observed administration of final administration of study drug
- Collect remaining study drug and smart bottle
- Discharge from site

8.3.8. Week 16/18 Visit

Specific sites will be selected to have all subjects enrolled at the site to have this visit scheduled to occur on either Week 16 or Week 18. The division of Week 16 and Week 18 visits across sites allows the evaluation of eosinophil recovery over more time points.

Subjects should hold their AM asthma medication the morning of the Week 16/18 visit. If the subject has not withheld their asthma medications, the Week 16/18 visit must be rescheduled.

At the Week 16/18 visit, the following assessments are to be completed (the general sequence for performing assessments should follow the order below):

- Asthma Control Questionnaire (ACQ-7)
  - *Should be collected as early as feasible in visit to minimize the influence of other assessments (e.g., PFTs, ECG, and AE capture)*
- Asthma Quality of Life Questionnaire (AQLQ)
  - *Should be collected as early as feasible in visit to minimize the influence of other assessments (e.g., PFTs, ECG, and AE capture)*
- Physical examination
- Vital signs – See Section 12.1.2
- Body weight
- Clinical safety laboratory tests
- Urine β-hCG/ pregnancy test for females of child bearing potential
- Contraception counseling
- Adverse events
- Concomitant medication
- Pre-bronchodilator pulmonary function (FEV1) – See Section 12.2.2
- Discharge from site

8.3.9. Week 20 Visit

At the Week 20 visit, the following assessments are to be completed:

- Clinical safety laboratory tests
- Contraception counseling, male subjects
- Adverse events

- Concomitant medication

The clinical laboratory blood sample may either be collected at the study site or at a designated remote laboratory facility for convenience. If safety lab tests are collected remotely, adverse event and concomitant medication use will be collected through documented telephone contact with the subject by appropriate site personnel.

8.3.10. Week 24 End of Study Visit

At the Week 24 visit, the following assessments are to be completed:

- Clinical safety laboratory tests
- Urine β-hCG/ pregnancy test for females of child bearing potential
- Contraception counseling, male subjects (as needed within 3 months of last dose of study drug)
- Adverse events
- Concomitant medication
- Serum collection for exploratory biomarkers

The clinical laboratory and serum biomarker blood sample may either be collected at the study site or at a designated remote laboratory facility for convenience. If safety lab tests are collected remotely, adverse event and concomitant medication use will be collected through documented telephone contact with the subject by appropriate site personnel.

8.3.11. Premature Discontinuation Visit

Subjects who discontinue study drug prematurely will be asked to return within 4 days of the last dose of study drug to have the Week 12 (Primary Outcome Visit) assessments performed.

In such discontinued subjects, a well-being check (telephone interview) will be also completed 30 days after the last dose of study drug and will be documented in the CRF.

8.4. Study Stopping Rules

Knopp may terminate this study at any time, after informing Site Investigators. Site Investigators will be notified by Knopp if the study is placed on hold, completed, or closed prematurely.

8.5. End of Study

The End of Study is defined as the last subject's last study-related visit.

9. SELECTION OF SUBJECTS

9.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following criteria:

1. Signed informed consent.
2. Male or female ≥18 and <75 years of age at the time of consent.
3. Willing to practice one highly effective method of contraception or 2 protocol acceptable methods of contraception in tandem, from the time of informed consent through 1 month (females) or 3 months (males) after the last dose of study drug.
4. Physician diagnosis of asthma for ≥12 months (relative to Baseline) based on Global Initiative for Asthma (GINA) 2018 Guidelines.[1]
5. Asthma requiring treatment with, at a minimum, low dose inhaled corticosteroids in combination with a long-acting β2 agonist (GINA steps 3-5[1]), on a stable dose for at least 1 month before Screening. Subjects using other controller options without long-acting β2 agonist are not eligible for the study.
6. Bronchodilator reversibility, as evidenced by ≥12% and ≥200 mL improvement in FEV1 15 to 25 minutes following inhalation of albuterol at Screening.
7. Pre-bronchodilator FEV1 ≥40% and <80% of predicted at Screening and Baseline.
8. AEC ≥0.30 x10^9/L at the Screening visit. May be repeated once if the initial value is between 0.25-0.29x10^9/L; the second AEC must be ≥0.30 x 10^9/L.
9. ACQ-7 ≥1.5 at Screening.
10. Negative pregnancy test at Baseline.
11. Adherence ≥85% with twice-daily placebo taken during the Run-in Period (minimum 12 days of adherence data), as documented by the smart bottle.

9.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following have been documented by Baseline:

1. Asthma considered by the Site Investigator as unstable at Baseline.
2. Treatment for an asthma exacerbation within 8 weeks prior to Baseline visit.
3. Current diagnosis of allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangiitis, eosinophilic gastrointestinal diseases, or hypereosinophilic syndrome, or lung diseases (e.g., chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis) which may confound interpretation of this trial's findings.
4. Infection of the upper or lower respiratory tract, including paranasal sinuses and middle ear within the 4 weeks prior to Baseline.

5. Treatment with systemic corticosteroids in the 8 weeks prior to Screening.
6. Treatment with an investigational drug in the previous 30 days or 5-half-lives prior to Baseline, whichever is longer.
7. Treatment with monoclonal antibody therapy, including benralizumab, dupilumab, mepolizumab, reslizumab, omalizumab, or TNF inhibitors, within 5-half-lives prior to Baseline.
8. Treatment with pramipexole within 4 weeks of Baseline.
9. Treatment with selected drugs known to have a substantial risk of neutropenia (see Appendix A).
10. Planned surgical procedures during the conduct of the study.
11. History of malignancy. Subjects with basal cell carcinoma, localized squamous cell carcinoma of the skin, or in-situ carcinoma of the cervix are not excluded, provided that the subject is in remission and curative therapy was completed ≥12 months prior to Screening. Subjects with other malignancies are not excluded, provided that the subject is in remission and curative therapy was completed ≥5 years prior to Screening.
12. Known history of human immunodeficiency virus (HIV) infection.
13. Active hepatitis B or C infection. Subjects with a history of hepatitis C with undetectable viral load for ≥1 year are not excluded.
14. Renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 at Screening (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula).
15. History of unstable or severe cardiac, hepatic, or renal disease, or other medically significant illness.
16. Medical or other condition likely to interfere with subject's ability to undergo study assessments, adhere to visit schedule, or comply with study requirements.
17. Helminth infection within 6 months prior to Baseline.
18. Use of any smoke or inhaled nicotine delivery device within 1 year prior to Screening or a smoking history ≥10 pack-years.
19. Known or suspected alcohol or other substance abuse.
20. Known or suspected non-adherence with study dosing schedule.
21. Unwillingness or inability to follow the procedures outlined in the protocol, including throat or nasal swab.
22. Absolute neutrophil count <2.0x10^9/L at Screening, or any documented history of absolute neutrophil count <2.0x10^9/L.
23. History of long QT syndrome or arrhythmia.

24. ECG showing prolongation of QTc interval calculated using Fridericia's heart rate correction formula (QTcF) >450 ms at the Screening visit or pre-dose at Baseline. QTcF interval calculated as the mean of triplicate determinations.
25. Clinically important abnormalities in resting ECG at Screening or Baseline, including any of the following:
    a) PR interval >210 ms;
    b) QRS >110 ms;
    c) Heart rate <45 bpm or >100 bpm (average of 3 assessments).
26. Pregnant or breastfeeding women.

10. ENROLLMENT PROCEDURES

10.1. Enrollment

A signed and dated Institutional Review Board-approved informed consent form (ICF) must be obtained from subjects before any study assessments occur.

Participating study sites are required to document all candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion should be documented in the subject's source documents and on the subject screening log.

Subjects signing the informed consent form are considered *enrolled*. Any subject identification number allocated to an enrolled subject will not be reused.

10.2. Randomization

Subjects may be *randomized* after all Baseline assessments have been completed and after the Site Investigator has confirmed eligibility. No subject may be randomized prior to the collection and assessment of all Baseline assessments and confirmation of eligibility (See Section 9).

After the subject has been randomized, the first dose of study drug will be administered at the site under direct observation of the study staff.

10.3. Blinding

Subjects enrolled into the Primary Assessment Period will be randomly allocated in a 1:1:1:1 ratio to receive dexpramipexole 75 mg/day (37.5 mg BID), dexpramipexole 150 mg/day (75 mg BID), dexpramipexole 300 mg/day (150 mg BID), or placebo (BID). Subjects, site staff, vendors, [redacted] (CRO), and Knopp personnel will remain blinded to study assignment.

The study will utilize an automated tele-randomization system incorporating a central randomization scheme. Subjects will be randomly assigned to their treatment group according to a computer-generated pseudorandom code using a method of random permuted blocks stratified by study site.

10.3.1. Blinding of CBC Results

Dexpramipexole lowers eosinophil and basophil counts such that these values could indicate active treatment assignment. All study-related lab results will be processed through a central laboratory facility contracted for the study.

Screening and Baseline CBC results will not be blinded to any study personnel. However, the site staff, CRO, and Knopp personnel will be blinded to absolute eosinophil count, absolute basophil count, total white blood cell (WBC) count, and WBC % differential results from the

central laboratory collected during the Primary Assessment Period and Eosinophil Recovery Period (Baseline through Week 24).

Other CBC results, including absolute neutrophil count, absolute lymphocyte counts, absolute monocyte count, absolute counts of immature or atypical cells, platelet count, and all red blood cell indices will not be blinded during the study.

Site staff must also avoid having subjects (or themselves) inadvertently unblinded by non-study CBC results from tests performed at a lab unaffiliated with the study (i.e., an undesignated local lab) during the time a given subject is participating in this trial. At each site, to maintain blinding of the study staff, a physician not otherwise involved in the study will be designated to review any unblinded outside laboratory results.

11. STUDY DRUG, CONCOMITANT THERAPY AND CONCOMITANT PROCEDURES

11.1. Dexpramipexole and Placebo

Knopp will provide dexpramipexole (KNS-760704), and blinded matching placebo.

Dexpramipexole (and matching placebo) will be supplied at the dose strengths of 37.5 mg, 75 mg, and 150 mg. Subjects will be randomly allocated in a 1:1:1:1 ratio to receive dexpramipexole 75 mg/day, dexpramipexole 150 mg/day, dexpramipexole 300 mg/day, or placebo (as BID dosing).

Dexpramipexole is supplied as [redacted] tablets which contain [redacted].

Placebo is supplied as [redacted] tablets which contain [redacted].

All study drug products will be dispensed to the subject in well-closed containers with child-proof closure ([redacted]).

The label will include conditions for storage and a placeholder for recording the subject identifier and protocol number. Dexpramipexole and placebo should not be used after the retest date unless appropriate retest documentation is provided by Knopp.

11.2. Study Drug Storage

Study drug must be stored in a secure locked location with access limited to site personnel. Study drug should be stored at controlled room temperature ([redacted]° to [redacted]°C, [redacted]° to [redacted]°F) and should be monitored at least weekly. Storage location temperature records must be maintained and available for inspection at each monitoring visit.

11.3. Study Drug Accountability

The study site must maintain accurate records demonstrating dates and amount of study drug received, to whom dispensed (subject-by-subject accounting), amount returned by the subject, and accounts of any study drug accidentally or deliberately destroyed.

Unless otherwise specified, all study drug, both used and unused, must be saved for study drug accountability. At the end of the study, reconciliation must be made between the amount of study

drug supplied, dispensed, and subsequently returned to Knopp or designee. A written explanation must be provided for any discrepancies.

Accountability for study drug is the responsibility of the Site Investigator.

11.4. Study Dosing and Dosing Adherence

Study drug may be dispensed only by a pharmacist or medically qualified staff. Study drug is to be dispensed only to subjects enrolled in this study. Returned study drug may not be dispensed to or administered to another subject.

The first dose of study drug will be administered at the site by authorized site staff at the conclusion of the Baseline assessments. Subjects will be instructed to take the second dose of study drug approximately 12 hours after the first dose. Subjects should be instructed to take a dose at approximately the same time of day each morning and again approximately 12 hours later (evening dose) for the duration of their participation in the study. If a dose of study drug is missed, the subject should be instructed to take the missed dose immediately if less than 24 hours have elapsed since their previous dose. However, no more than 1 missed dose (1 tablet) should be taken at any one time and no more than 2 tablets of study drug should be taken in any 12-hour period.

Adherence with study drug dosing is to be monitored and recorded by site staff. To maximize study dosing adherence, subjects will be given study drug in a "smart bottle". The device reminds subjects to take their study drug via lights, chime, and text message. It records the bottle opening. All data it collects is uploaded to a server via a mobile link, from which is provided feedback to both the subject and study staff on adherence. In addition to providing a timely drug dosing reminder for compliant subjects, the aim is to provide opportunities for timely counselling of poorly adherent subjects. During the Run-in Period and Primary Assessment Period site visits, subjects will have a structured adherence counselling session with the study staff.

11.5. [redacted] Bottle Management

[redacted]

Beginning with Screening, subjects will be dispensed sufficient quantities of study drug product or placebo in the smart bottle to last until the next site visit.

Subjects will be asked to return all unused study drug for accountability at each site visit, ***including the smart bottle for adherence checks and refills***. The Site Investigator is responsible for the accounting of opened and unopened study drug bottles. Final study drug reconciliation will be performed at the Week 12 visit.

11.6. Study Drug Precautions

Dexpramipexole is eliminated from the body by the kidneys. Approximately 80% of dexpramipexole is recovered in the urine as unchanged drug.

The area under the plasma concentration-time curve (AUC) of dexpramipexole increases with increasing severity of renal impairment. There is strong correlation between renal function (eGFR) and dexpramipexole renal clearance. Therefore, caution should be taken when administering dexpramipexole to subjects with kidney (renal) impairment. Subjects with moderate to severe renal impairment should not take dexpramipexole.

[redacted] neutrophil counts during the study will be reported using a central laboratory and monitored by the [redacted] Medical Monitor. However, subjects should be counseled regarding the risk for neutropenia, avoid taking concomitant medication associated with a risk of neutropenia (See Section 11.9.1) and instructed to immediately report to the study site any symptoms of infection, including fever >39°C, sore throat, and mouth sores.

11.7. Discontinuation of Study Drug

A subject must permanently discontinue study drug for any of the following reasons:

- The subject becomes pregnant. Study drug must be discontinued immediately and the subject followed until resolution of the pregnancy. Report the pregnancy, according to the instructions in Section 13.2.7
- The subject withdraws consent.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study drug.
- At the discretion of the Site Investigator for medical reasons.
- At the discretion of the Site Investigator or Knopp for subject non-adherence to the study requirements.

Subjects who discontinue study drug prematurely will be asked to return within 4 days of the last dose of study drug to have the Week 12 (Primary Outcome Visit) assessments performed.

In such discontinued subjects, a well-being check (telephone interview) will be completed 30 days after the last dose of study drug.

11.8. Study Drug Disposal

The Site Investigator must return all unused study drug, as instructed by Knopp.

If any study drug supplies are to be destroyed at the site, the institution/Site Investigator must obtain prior approval by Knopp. After such destruction, the institution/Site Investigator must notify Knopp, in writing, of the method, the date, and the location of destruction.

11.9. Concomitant Therapy and Procedures

11.9.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between the Screening visit and the subject's last study visit. All concomitant medication must be recorded in the subject's source document and on the case report form (CRF).

11.9.2. Concomitant Therapy Restrictions

Inhaled corticosteroids
The dose of any inhaled or intranasal corticosteroids must be stabilized for at least 4 weeks prior to the first dose of study drug and should remain constant throughout the study.

Systemic corticosteroids
Medically indicated use of systemic corticosteroids to treat an asthma exacerbation occurring while on study are allowed on the study.

Investigational drugs
Use of investigational drugs is prohibited for the duration of the study.

Monoclonal antibody therapy
The use of monoclonal antibody therapy, including benralizumab, dupilumab, mepolizumab, reslizumab, omalizumab, or TNF inhibitors is prohibited throughout the duration of the study.

Pramipexole
The use of pramipexole is prohibited throughout the duration of the study.

Selected drugs known to have substantial risk of neutropenia
Drugs known to have a substantial risk of neutropenia, as listed in Appendix A, are prohibited for the duration of the study.[19, 20]

11.9.3. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the Screening visit and the subject's last study visit.

Concomitant therapies or procedures must be recorded on the subject's CRF, according to instructions for CRF completion. AEs related to administration of these therapies or procedures must be documented on the appropriate CRF.

12. STUDY ASSESSMENTS

Refer to Section 5 per Schedule of Events for the timing of assessments.

12.1. Safety Assessments

Clinical safety assessments should be performed by the same staff at each site, whenever possible.

The following clinical assessments will be performed to assess the safety profile of dexpramipexole:

- clinical laboratory tests
- vital sign measurements (seated upright position): systolic and diastolic BP (after subject has rested for 5 minutes, in mmHg), RR per minute, HR per minute, temperature
- 12-lead ECG measurements: triplicate readings will be collected at each specified time-point
- medical history and asthma history evaluation
- physical examinations
- body weight
- concomitant therapy and procedure recording
- adverse event and serious adverse event monitoring and recording

12.1.1. Clinical Laboratory Tests

The clinical laboratory test parameters will be performed by a designated central laboratory. Detailed collection, processing, storage, and shipment instructions will be provided in the *Study Reference Manual*.

The following clinical laboratory tests will be performed according to the schedule of events – *See Section 5*:

- Hematology and differential panel: [redacted]). Certain CBC results will be blinded as detailed in Section 10.3.1.
- Blood chemistry panel: [redacted]

[redacted]

- Urinalysis: [redacted]
- Urine β-hCG/pregnancy, qualitative (for women of childbearing potential).

12.1.2. Vital Signs

Vital signs will be measured in the seated upright position after the subject has been rested for 5 minutes (systolic and diastolic systemic blood pressure [BP] in mmHg, respiratory rate [RR] per minute, and heart rate [HR] per minute).

12.1.3. ECG Assessments

All 12-lead ECGs will be performed in triplicate with tracings at least 1 minute apart. Subjects should be in the supine position after resting for at least 5 minutes for each assessment.

ECGs will be performed prior to the AM dose of study drug at the Baseline, Week 4, Week 8, and Week 12 (Primary Outcome Visit) visits. Circumstances that may induce changes in heart rate or otherwise stimulate the subject should be avoided throughout the resting and ECG recording periods.

At the Week 8 visit, subjects will have 3 separate ECG assessments performed to evaluate potential cardiac drug interactions of albuterol and dexpramipexole.

- First, a 12-lead ECG (three tracings separated by 1 minute) will be performed prior to the AM dose of study drug AND AM asthma medication, followed by an observed administration of study drug.
- Second, an additional 12-lead ECG (three tracings separated by 1 minute) will be collected 2 hours (± 30 minutes) after taking study drug.
- Following the second ECG, subjects will inhale four puffs of albuterol MDI (90-100 µg albuterol base per actuation) under the direction of study staff, wait 15 minutes (± 5 minutes), and have a post-bronchodilator ECG collection performed (three tracings separated by 1 minute).

12.1.4. Physical Examinations

Physical examinations may be conducted by a qualified, delegated physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. The full physical examination will include head, ears, eyes, nose, mouth, throat, skin, heart and lung examinations, lymph nodes, gastrointestinal, and musculoskeletal systems. Abnormal findings will be

characterized as "clinically significant" or "not clinically significant" for the purposes of reporting as adverse events.

12.1.5. Neutropenia Monitoring and Clinical Management

In clinical studies to date, some ALS subjects treated with dexpramipexole at a dose of 300 mg/day developed reductions in absolute neutrophil count (ANC) that were reversible and typically brief (<10 days). [redacted] Subjects must be monitored for the possible development of neutropenia (ANC <1.50x10^9/L) and appropriate action and testing should be performed, as outlined in Table 1. Neutropenia has not been seen at dexpramipexole doses <300 mg/day.

All cases of neutropenia will be followed by repeating the CBC with differential until the neutropenia resolves. The CBC blood sample may either be collected at the study site or at a designated remote laboratory facility for convenience.

Table 1: Neutropenia Dose Interruption and Laboratory Test Repeat Recommendations

Neutrophils	Study Drug	Repeat CBC w/ diff	Neutropenia Case Report Form
Decrease of ≥50% previous value and ≥2.00x10^9/L	No action	Every 2 weeks	Not indicated
≥1.50x10^9/L to <2.00x10^9/L	No action	Every 2 weeks	Not indicated
≥1.00x10^9/L to <1.50x10^9/L	No action	Weekly	Weekly*
<1.00x10^9/L	Withhold	Every 4 days	Weekly*

*Site staff to collect the neutropenia case report form weekly until the ANC is ≥1.50x10^9/L.

The [redacted] Medical Monitor should be consulted regarding all cases of neutropenia. In cases where study drug is withheld, the [redacted] Medical Monitor must be informed.

Restarting study drug after withholding for neutropenia requires authorization from the Knopp Medical Monitor, or designee.

Laboratory-defined events of neutropenia (ANC <1.50x10^9/L) should be reported by the site to the [redacted] Medical Monitor within 24 hours of awareness. If a subject experiences an ANC <1.50x10^9/L the neutropenia case report form will be completed by the site staff. The information required for this form will be obtained by the site staff through an interview with the subject contemporaneous with the event. The site staff should repeat the neutropenia case report form weekly until the ANC is ≥1.50x10^9/L.

To obtain control cases, the neutropenia case report form will be collected from all subjects at the Baseline, Week 4, Week 8, and Week 12 visits.

12.1.6. Contraception Counseling

The Site Investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an allowed method of contraception from the list of permitted methods and will counsel the subject regarding the need for continued contraception adherence.
See Section 13.5.3.

12.2. Efficacy Assessments

The following clinical tests/assessments will be performed to assess the efficacy of dexpramipexole, as found in the subsections below. Refer to Section 5 for the timing of assessments.

12.2.1. Peripheral Blood Absolute Eosinophil Count

Blood eosinophil counts will be obtained at every study visit. Samples need to be collected between 6 AM and 12 noon to minimize diurnal variation. Samples should be collected at approximately the same time of day throughout the study (within ± 1 hour of the Baseline visit collection).

12.2.2. Pulmonary Function Testing (PFT, FEV1)

For in-clinic site visits, (Baseline, Week 4, Week 8, Week 12, and Week 16/18) subjects will be instructed to withhold their AM asthma medication on the morning of the visit. **Every effort should be made to collect the Week 12 Pre-bronchodilator PFT within ± 1 hour of the time of day that the Baseline PFT was collected.**

Subjects who present for Screening, but have not withheld their asthma medication (see Table 2), should have all other Screening assessments performed and will be requested to reschedule the Screening PFT as soon as feasible.

The pre-bronchodilator FEV1 inclusion criterion must be fulfilled during the Run-in Period.

- Subjects who do not meet the initial pre-bronchodilator FEV1 inclusion criterion at Screening and Baseline may <u>not</u> repeat PFT in order to qualify for the study.
- Subjects who do not meet the post-bronchodilator reversibility inclusion criterion at the Screening visit, but have ≥10% or ≥160 mL reversibility, may repeat the reversibility PFTs assessment once during the Run-in Period.

Pre-bronchodilator FEV1 is considered the core clinical outcome measure of airway obstruction in efficacy trials in asthma.[21, 22] FEV1 is the volume of air that can forcibly be expired in one

second. The FEV1 volume in liters may be converted to a percentage of the predicted value based on height, weight, and race.

PFTs will be collected according to the ATS/ERS guidelines on standardization of spirometry[23] according to Section 5, Schedule of Events. PFTs will be obtained on all subjects during the study. Pre-bronchodilator PFTs at each study visit must be collected between 6 AM and 12 noon local time and should be collected within ±2 hours of the Baseline visit to minimize diurnal variation. The Week 12 PFT assessment should be collected within 1 hour of the time of day the Baseline visit PFTs were collected.

For all site visits where pulmonary function testing is performed, subjects must withhold their AM asthma medications. Table 2 provides washout intervals for various asthma medications for pre-bronchodilator PFT testing at the Screening, Baseline, Week 4, Week 8, Week 12, and Week 16/18 visits.

Table 2: Intervals for Holding Asthma Medications Prior to Pulmonary Function Testing

Medication	Examples (proprietary names Capitalized)	Minimum washout prior to performing PFT
Short-acting bronchodilator	albuterol, levalbuterol, Xopenex	6 hours
Long-acting bronchodilator	Advair, arformoterol, Breo, Dulera, formoterol, indacaterol, olodaterol, Symbicort, vilanterol, salmeterol	12 hours
Xanthines	theophylline	12 hours
Short-acting muscarinic antagonist	Atrovent, ipratropium	8 hours
Long-acting muscarinic antagonist	aclidinium, glycopyrrolate, glycopyrronium, tiotropium, umeclidinium	24 hours
Leukotriene antagonist (LTRA)	Accolate, montelukast, Singulair, zafirlukast	12 hours
5-Lipoxygenase Inhibitor	zileuton, Zyflo	6 hours (immediate release) 12 hours (extended release)

At the Screening, Baseline and Week 12 visits, subjects will also perform a post-bronchodilator PFT reversibility test.

At the Screening visit, subjects will additionally perform post-bronchodilator PFTs. After completing the pre-bronchodilator PFTs, subjects will inhale 2-4 puffs of albuterol MDI (90-100 µg albuterol base per actuation). Spirometry may be repeated several times within 15-30 minutes after inhalation of albuterol and additional albuterol puffs may be administered up to a maximum of 4 puffs. Reversibility, which is defined as an increase in absolute FEV1 of ≥12% over the pre-bronchodilator value, with an absolute increase of at least 200 mL, must be demonstrated within 30 minutes of albuterol administration for the subject to be considered

eligible for randomization. If the subject does not meet the reversibility eligibility criterion at the first Screening PFT visit, but has an improvement of ≥10% or ≥160 mL FEV1 reversibility, a second reversibility PFT attempt can be performed at a later visit prior to the Baseline visit.

At the Baseline and Week 12 visits, subjects will repeat the pre- and post-bronchodilator PFT reversibility test. During these visits, the subject will be administered the same number of albuterol puffs utilized during the Screening PFT reversibility testing used to qualify the subject.

Detailed methodology for performing the PFT procedure can be found in the *Study Reference Manual*.

12.2.3. Asthma Control Questionnaire (ACQ-7)

The Asthma Control Questionnaire (ACQ) is a validated tool designed for use as a measurement of asthma symptom control.[24] The ACQ measures both the adequacy of asthma control and change in asthma control, which may occur either spontaneously or as a result of treatment.

The ACQ has 7 questions (the top scoring 5 symptoms, FEV1% pred., and daily rescue bronchodilator use). Subjects are asked to recall how their asthma has been during the previous week and to respond to the symptom and bronchodilator use questions on a 7-point scale (0=no impairment, 6= maximum impairment). Clinic staff score the FEV1% predicted on a 7-point scale. The questions are equally weighted and the ACQ score is the mean of the 7 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled).

A copy of the ACQ-7 questionnaire and instructions for administering the questionnaire may be found in the *Study Reference Manual.*

12.2.4. Asthma Quality of Life Questionnaire (AQLQ)

The AQLQ is a questionnaire developed to measure health status (quality of life) in patients with asthma and will be administered at the site.[25]

There are 32 questions in the AQLQ in 4 domains (symptoms, activity limitation, emotional function and environmental stimuli). The activity domain contains 5 'subject-specific' questions. This allows subjects to select 5 activities in which they are most limited and these activities will be assessed at each follow-up. Subjects are asked to think about how they have been during the previous two weeks and to respond to each of the 32 questions on a 7-point scale (range, '7=not impaired at all' to '1=severely impaired'). The overall AQLQ score is the mean of all 32 responses and the individual domain scores are the means of the items in those domains.

A copy of the AQLQ and instructions for administering the questionnaire may be found in the *Study Reference Manual.*

12.3. Pharmacodynamic Assessments

Methods for the collection, processing, storage, and shipment of serum, whole blood, and nasal/pharyngeal swabs will be described in the *Study Reference Manual*.

Methods for exhaled nitric oxide testing (FeNO) are described in the *Study Reference Manual*.

12.3.1. Blood Absolute Eosinophil Count

Whole blood AEC will be measured as part of the CBC and differential, per Section 5 Schedule of Events.

12.3.2. Basophils

Whole blood will be collected for basophil quantification by flow cytometry, per Section 5 Schedule of Events.

12.3.3. Eosinophil Progenitors

Whole blood will be collected for eosinophil progenitor quantification by flow cytometry, per Section 5 Schedule of Events.

12.3.4. Nasal and Pharyngeal Swabs for Eosinophil Peroxidase

Nasal and pharyngeal swabs will be collected for eosinophil peroxidase, per Section 5 Schedule of Events.

Instructions for collecting nasal and pharyngeal swabs are described in the *Study Reference Manual*.

12.3.5. Urine Eosinophil Granule Proteins

Urine will be collected for eosinophil granule protein immunoassay, per Section 5 Schedule of Events.

12.3.6. Serum IgE

Serum IgE will be collected at Baseline.

12.3.7. Serum Biomarkers and Biobank

Serum will be collected for biomarker research at the Baseline, Week 12, and Week 24 visits, per Section 5 Schedule of Events. These samples will be used to conducted exploratory research including IL-5, IL-13, IL-33, ST2, CCL2, CCL3, CCL4, CCL11, and CCL17.

Specific procedures for collection, storage, and shipping of biomarker samples will be provided in the *Study Reference Manual*.

Biobank samples may also be used for retrospective exploratory analyses associated with the study endpoints (e.g., safety and/or efficacy), the disease being studied in this trial (eosinophilic asthma), the mechanism of action of dexpramipexole, and/or to support future approaches to personalized medicine. Collection of serum for biomarker research is required of all subjects unless prohibited by local law or the by the decision of an IRB.

All biobank samples will be coded with the subject's study identification number to ensure subject confidentiality. No subject identifying information (e.g., name, gender, date of birth) or other information that could be used to directly identify the subject will be on the sample. The key between the study identification number and the subject's protected health information will be held only by the site investigator. The researchers with access to the samples and data generated from the biobank will not have access to the key nor any personally identifying information regarding the subject.

Information obtained on individual subjects will be aggregated and tested at the group level. None of the biomarkers being tested have been validated for diagnostic, prognostic or therapeutic use, and therefore there are no known health or other implications for any individual subject based on his or her exploratory biomarker result.

A subject may, without prejudice, withdraw his or her consent from participation in the collection and storage of samples for exploratory biomarker testing or future testing at any time by notifying the Site Investigator in writing. At the subject's request, no further samples will be collected, no further analysis will be conducted their samples, and any samples remaining in storage will be destroyed. However, data generated from testing before the subject's request to withdraw consent will continue to be stored to protect the integrity of existing analyses.

Biobank samples will be stored at an access-controlled facility that specializes in biomedical sample storage, bio banking, and sample management. Unless restricted by local law or an IRB, samples for exploratory biomarker testing may be stored indefinitely for studies to be determined in the future. Any such future biobank study will be submitted for IRB review and approval prior to study initiation.

Results obtained on individual subjects will not be made available to the subject and subjects will be notified of this stipulation in the informed consent document. No individual subject results will be recorded in the subject's medical record and no follow-up contact with individual subjects is planned.

12.3.8. Whole Genome DNA Sequencing

Whole blood will be collected for whole genome DNA sequencing at the Baseline visit, per Section 5 Schedule of Events. Specific procedures for collection, storage, and shipping of samples will be provided in the *Study Reference Manual*.

DNA samples may be used to determine a possible relationship between specific genes and response to treatment with dexpramipexole, or their possible relationship to adverse reactions to dexpramipexole. The analysis of whole genome sequence data will use a genome-wide association approach to identify single-nucleotide variants and small insertion/deletion variants that differ between dexpramipexole hematologic responders and non-responders. Additional bioinformatic approaches will be used as needed to identify and validate candidate genes.

The DNA extracted from the blood sample as well as all downstream genetic analyses will utilize a second number, a Genetic ID (de-identification code) different from the Subject ID. This "double coding" is performed to further separate a subject's medical and study information from their DNA data. The clinical study data (coded by Subject ID) will be stored in the password-protected data management system, which is a distinct database in a separate environment from the database containing the pharmacogenetic data (coded by Genetic ID). The key linking Subject ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical study data and pharmacogenetic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control.

The extracted DNA remaining unused after DNA sequencing will be destroyed after completion of that specific analysis and issuance of the related analytical data.

Results obtained on individual subject will not be made available to the subject and subjects will be notified of this stipulation in the informed consent document. No individual subject results will be recorded in the subject's medical record and no follow-up contact with individual subject regarding the result is planned.

If required by the IRB, whole genome DNA sequencing may be an optional procedure for that site, with that site's ICF reflecting that status.

After informed consent, a subject may, without prejudice, withdraw his or her consent from participation in the whole genome DNA sequencing by notifying the Site Investigator in writing. At the subject's request, no further analysis will be conducted and any DNA sequencing samples remaining in storage will be destroyed.

12.3.9. Exhaled Nitric Oxide Test (FeNO)

Exhaled nitric oxide analysis will be performed at each site using the NIOX Vero instrument with the result reported in parts per billion. FeNO should be collected prior to the PFT tests.

Further details on the FeNO procedure are provided in the *Study Reference Manual*.

12.4. Pharmacokinetic Assessments

Blood will be collected from each subject to determine the dexpramipexole plasma concentrations.

- Week 4: Pre-dose
- Week 8: Pre-dose and 2 (±10 minutes) hours after dose
- Week 12: Pre-dose

Methods for the collection, processing, storage, and shipment of PK samples will be provided in the *Study Reference Manual*.

13. SAFETY DEFINITIONS, MONITORING, AND REPORTING

Upon signing the ICF, each subject must be provided the names and telephone numbers of study site staff for reporting AEs and medical emergencies. All subject reports of adverse events as defined below, whether solicited or spontaneous, must be documented in the source documents. The interview for adverse events should be conducted often throughout the course of the study. At a minimum, such interviews should occur during each subject visit, including telephone contacts.

Refer to Section 5 per Schedule of Events for the timing of assessments.

13.1. Definitions

13.1.1. Adverse Event

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An *adverse event* (also referred to as an adverse experience) can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Isolated laboratory, vital signs, or ECG abnormalities should be recorded as adverse events only if associated with one of the following:

a) clinical findings (medical history, physical exam signs, symptoms, or disease),
b) corrective treatment, or consultation,
c) study drug interruption or discontinuation, or
d) hospitalization or emergency room admission

To provide a comprehensive review of abnormal laboratory findings, the clinical study report will include tables showing all subjects with clinical laboratory values outside of the reference range.

13.1.2. Suspected Adverse Reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. Adverse reactions are a

subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

13.1.3. Adverse Event [redacted]

Neutropenia is generally defined as an ANC <1.5x10^9/L[20, 26-29]. [redacted] neutrophil counts will be reported using a central laboratory and monitored by the [redacted] Medical Monitor.

If a subject experiences neutropenia, a neutropenia case report form will be completed. The information required for this form will be obtained by the site staff through an interview with the subject contemporaneous with the event.

To obtain control cases, the neutropenia case report form will be collected from all subjects at the Baseline, Week 4, Week 8, and Week 12 visits.

13.1.4. Serious Adverse Event

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the Site Investigator or Knopp, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient/subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

13.2. Monitoring and Recording Adverse Events

13.2.1. All Events (any untoward medical occurrence)

All events must be assessed to determine the following:

- Event meets the criteria for an SAE, as defined in Section 13.1.4
- Relationship of the event to study drug, as defined in Section 13.3.1

- Severity of the event, as defined in Section 13.3.2

13.2.2. Adverse Events

Any AE experienced by the subject between the time the subject provides informed consent and the last study visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study drug.

13.2.3. [redacted]

Laboratory-defined events of neutropenia (ANC is $<1.50x10^9$/L) should be reported by the site to the [redacted] Medical Monitor within 24 hours of awareness. If a subject experiences an ANC $<1.50x10^9$/L the neutropenia case report form will be completed. The information required for this form will be obtained by the site staff through an interview with the subject contemporaneous with the event. The neutropenia case report form should be repeated weekly until the ANC is $\geq 1.50x10^9$/L.

All cases of laboratory-defined neutropenia should be reported to the Medical Monitor and will be followed by repeating clinical safety laboratory work until the neutropenia resolves.
See Appendix A.

13.2.4. Serious Adverse Events

Any SAE experienced by the subject after the subject signs the ICF through the last study visit is to be recorded on the SAE Form, regardless of the severity of the event or its relationship to study drug. SAEs must be reported to Knopp or its designated representative.

Any SAE ongoing when the subject completes the study or discontinues from the study will be followed by the Site Investigator until the event has resolved, stabilized, or returned to baseline status.

13.2.5. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify Knopp within 24 hours of the study site staff becoming aware of the SAE. It is the Site Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs, Pregnancy, and Overdose

Any Serious Event that occurs between the time the subject has signed the Informed Consent Form and the final study visit must be reported to [redacted] within 24 hours of the study site staff becoming aware of the event.

A report ***must be submitted*** to [redacted] regardless of the following:

- whether or not the subject has undergone study-related procedures
- whether or not subject has received study treatment
- the severity of the event
- the relationship of the event to study treatment

To report initial or follow-up information on a Serious Event, fax a completed SAE form to [redacted]:

SAE Fax Number: +1 (734) 468-0866

SAE Mailbox: KnoppDrugSafety@[redacted]

13.2.6. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the appropriate CRF. All causes of death must be reported as SAEs. The Site Investigator should make every effort to obtain and send death certificates and autopsy reports to Knopp or its designated representative.

13.2.7. Pregnancy

Subjects should not become pregnant during the study. If a subject becomes pregnant, study drug must be discontinued *immediately*. Subjects must be counselled to the contraception requirements of the protocol and should contact the site as soon as possible if they (or their partner) suspect a pregnancy.

The Site Investigator must report the pregnancy by faxing the appropriate form to Knopp or its designated representative within 24 hours of the study site staff becoming aware of the pregnancy. The Site Investigator or study site staff must report the outcome of the pregnancy to Knopp or its designated representative.

Please note that congenital abnormalities or birth defects in the offspring of male or female subjects should be reported if conception occurs during the study treatment period and the study follow-up period.

13.3. Safety Classifications

13.3.1. Relationship of Events to Study Drug

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study drug:

Relationship of Event to Study Drug	
Definitely Related	• It has a reasonable temporal relationship to study drug administration. • It follows a known pattern of clinical response to the study drug. • There is strong evidence based on known study drug pharmacology or toxicology to suggest a causal relationship. • There is no alternative etiology. • It reappears if there is re-challenge with the study drug.
Probably Related	• It has a reasonable temporal relationship to study drug administration. • It follows a suspected pattern of clinical response to the study drug (based on similar agents or based on adverse events that could likely be expected to follow from a known adverse drug reaction; e.g., a pulmonary embolus following administration of a drug known to cause deep vein thromboses). • There is reasonable evidence based on known study drug pharmacology or toxicology to suggest a causal relationship. • There is no evidence of a more likely alternative etiology. • It reappears if there is re-challenge with the study drug.
Possibly Related	• It has a reasonable temporal relationship to study drug administration. • It follows a potential pattern of clinical response to the study drug (based on similar agents or based on adverse events that could possibly be expected to follow from a known adverse drug reaction). • There is potential evidence based on known study drug pharmacology or toxicology to suggest a causal relationship. • There is little evidence of a more likely alternative etiology. • There is no re-challenge with the study drug.

Relationship of Event to Study Drug	
Unlikely Related	• It does not have a reasonable temporal relationship to study drug administration. • It does not follow a suspected pattern of clinical response to the study drug. • There is not reasonable evidence based on known study drug pharmacology or toxicology to suggest a causal relationship. • There is good evidence of a more likely alternative etiology. • It does not reappear if there is re-challenge with the study drug.
Unrelated	• It does not have a temporal relationship to study drug administration. • It does not follow a suspected pattern of clinical response to the study drug. • There is no evidence based on known study drug pharmacology or toxicology to suggest a causal relationship. • There is evidence of a definite alternative etiology. • It does not reappear if there is re-challenge with the study drug.

Note: Causality assessment is based on available information at the time of the assessment of the AE. The investigator may revise the causality assessment as additional information becomes available.

13.3.2. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; treatment not ordinarily needed for relief of symptom(s) but may be given.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause discontinuation of treatment with study drug; treatment for symptom(s) may be given and/or subject may be hospitalized.

13.3.3. Expectedness of Events

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the currently approved investigator brochure or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure 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.

13.4. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized; the study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Site Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.

13.5. Procedures for Handling Special Situations

13.5.1. Overdose

An overdose is any dose of study drug given to a subject or taken by a subject that exceeds the dose described in the protocol (more than 2 doses in a 12 hour period). Overdoses are not considered AEs; however, all overdoses should be recorded on an SAE Form and faxed to [redacted] Drug Safety within 24 hours. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded in the CRF; dosing information is recorded on a CRF.

There is no known antidote for an overdose of dexpramipexole.

13.5.2. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Site Investigator or designee should contact the [redacted] Medical Monitor.

13.5.3. Contraception Requirements

For the purpose of this protocol, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchiectomy.

All fertile male subjects and women of childbearing potential who are, in the opinion of the Site Investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use at least one highly effective method of contraception, or 2 protocol acceptable methods of contraception used in tandem consistently and correctly for the duration of the active treatment period and for 1 month (females) or 3 months (males) after the last dose of study drug (See Table 3 and Table 4). The Site Investigator or his or her designee, in consultation with the subject, will confirm that the subject continues to use a highly effective / protocol acceptable birth control method during this time period of the study.

Highly effective birth control methods that result in a failure rate of less than 1% per year when used consistently and correctly include those methods in Table 3.

Table 3: Highly Effective Birth Control

• combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1]
  ○ oral
  ○ intravaginal
  ○ transdermal

• progestogen-only hormonal contraception associated with inhibition of ovulation [1] o oral o injectable o implantable [2]
• intrauterine device (IUD) [2]
• intrauterine hormone-releasing system (IUS) [2]
• bilateral tubal occlusion [2]
• vasectomized partner [2,3]
• sexual abstinence [4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

[2] Contraception methods considered to have low user dependency.

[3] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[4] In the context of this protocol sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Protocol acceptable birth control methods that result in a failure rate of more than 1% per year include those methods in Table 4. If a highly effective method of birth control is not used by the subject or partner, a combination of two forms of protocol acceptable birth control must be used in tandem, consistently and correctly for the subject to qualify for the study.

Table 4: Protocol Acceptable Birth Control (when used in tandem)

• progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
• male or female condom with or without spermicide [1]
• cap, diaphragm or sponge with spermicide [1]

[1] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.

13.5.4. Regulatory Reporting

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are unexpected and judged by Knopp to be related to the study drug administered.

Knopp will submit SUSARs to Site Investigators and Regulatory Agencies according to local requirements.

13.6. Site Investigator Responsibilities

The Site Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study drug.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and follow-up on the outcome of the pregnancy.
- Complete an SAE form for each serious event and fax it to [redacted] Drug Safety within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to [redacted] Drug Safety within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Report SAEs to local ethics committees, as required by local law.

13.7. Knopp Responsibilities

Knopp's responsibilities include the following:

- Knopp will adhere to its responsibilities as study sponsor, as specified in relevant FDA and ICH guidance documents.
- Before study site activation and subject enrollment, Knopp or its designee is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Knopp or its designee is to notify all appropriate regulatory authorities, central ethics committees, and Site Investigators of SAEs, as required by local law, within required time frames.

14. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1. Description of Objectives

See Section 7: Study Objectives and Endpoints.

14.2. Description of Endpoints

See Section 7: Study Objectives and Endpoints.

14.3. Analysis Populations

The safety population will consist of all subjects who were randomized and received at least one dose of study drug. The efficacy population will be a modified ITT sample and consist of all subjects in the safety population who have at least one post-randomization evaluation for at least one of the efficacy endpoints. The per-protocol population will consist of all subjects in the efficacy population who complete the Week 8 CBC and do not have a major protocol deviation. Major protocol deviations will be defined in the SAP prior to study un-blinding.

14.4. Demography and Baseline Characteristics

Demography, medical history and baseline disease characteristic data (duration of symptoms, severity of symptom scores, concomitant medication at baseline, etc.) will be summarized at study baseline for the safety population.

Gender, race, and ethnicity will be summarized using counts and percentages. Age, height (cm), weight (kg), and body mass index (kg/m^2; calculated) will be summarized with descriptive statistics (number of subjects [n], mean, standard deviation [sd], median, minimum, and maximum). Age will also be summarized according to the categories of less than 50 years, 50 to 65 years, and more than 65 years, using counts and percentages.

14.5. General Methods of Analyses

The study will use a blocked randomization stratified by study site. The safety population will be used for all safety analyses and the modified ITT population will be used for efficacy analyses. Descriptive statistics, including means, medians, and standard error will be presented for efficacy measures for observed values and changes from baseline by scheduled evaluation time and treatment group. If the endpoint is one that requires a log transformation, then descriptive statistics will be geometric means and ratios. If the endpoint is one that requires a rank transformation, then descriptive statistics will be median and intra-quartile values.

To control the alpha level for testing three dose groups versus placebo for the primary endpoint and for testing FEV1, a closed hierarchical testing procedure will be used in the following order:

1) First, the 300mg/day dose group will be tested versus placebo for change in blood absolute eosinophil count at Week 12, and if this reaches the <0.05 level then,
2) the 150 mg/day dose group will be tested versus placebo at the 0.05 level for change in blood absolute eosinophil count at Week 12, and if this reaches the <0.05 level then,
3) the 75 mg/day dose group will be tested versus placebo at the 0.05 level for change in blood absolute eosinophil count at Week 12, and if this reaches the <0.05 level then,
4) the pooled 150 and 300 mg/day dose groups will be tested versus placebo at the 0.05 level for change in pre-bronchodilator FEV1 at Week 12.

Statistical testing for the other secondary study endpoints will be performed at the 0.05 level without adjustment.

The primary endpoint and the secondary endpoints will also be analyzed using the per-protocol population.

14.5.1. Interim Analysis of the Primary Assessment Period

There may be an interim analysis of efficacy after all subjects have completed the Primary Assessment Period (Week 12 visit). This interim analysis of efficacy may include the following data through Week 12: primary and secondary efficacy endpoints and clinical laboratory data. Subjects will be off study drug after the Week 12 visit and the primary purpose of visits after Week 12 is to collect eosinophil recovery data and follow-up safety data. Prior to an interim analysis of efficacy through Week 12, all the data (efficacy and safety) up to and through Week 12 will be 'soft' locked. There will be no adjustment of p-values for the interim analysis because all subjects will have completed the Primary Assessment Period and the results of the final analysis of efficacy through the Primary Assessment Period should be identical to the results of the interim analysis of efficacy through the Primary Assessment Period. Any changes to the efficacy results between the interim analysis of efficacy through Week 12 and the final analysis of efficacy through Week 12 will be noted, although none is expected. The team carrying out the interim analysis of efficacy through Week 12 will be a different team from the team responsible for cleaning and locking the data after Week 12. The team responsible for cleaning and locking the data after Week 12 will not have access to any of the unblinded data from the interim analysis.

At the same time as the interim analysis of efficacy through Week 12, an interim analysis of key safety data through Week 12 may be carried out: Incidence AEs and AEs leading to discontinuation of study drug; potentially clinically significant changes in vital signs, neutrophils; LFTs, and ECGs. The team carrying out the interim analysis of safety through

Week 12 will be a different team from the team responsible for cleaning and locking the data after Week 12. The team responsible for cleaning and locking the data after Week 12 will not have access to any of the unblinded data from the interim analysis. Safety data from this interim analysis may be unlocked, for instance, if an AE that was ongoing at Week 12 has resolved. After all subjects complete the End of Study Visit, the study data will be locked, and the final analysis will be completed.

14.6. Efficacy Analyses

14.6.1. Primary Endpoint Analyses

The primary endpoint of this study is the change in blood absolute eosinophil count from Baseline to Week 12. Absolute eosinophil count will be transformed to the log10 scale. To avoid taking the log of zero, zero values (not null values) will be replaced with 5/µL in conventional units or 0.005×10^9/L in the International System of Units (SI), which is 50% of the lower limit of quantification. The geometric mean of all eosinophil counts obtained between the Screening and Baseline visits will be used to establish the baseline eosinophil count used in the efficacy analyses. Geometric means and standard deviations will be presented by treatment group for observed values at each visit along with a p-value comparing each dexpramipexole treatment group to placebo based on an analysis of variance (ANOVA).

The primary analysis will be a mixed-effect model, repeated-measures (MMRM) with terms for baseline, GINA treatment steps 3 vs. 4/5, treatment, visit, treatment by visit interaction, and baseline by visit interaction as fixed effects, and subject as a random effect. An unstructured covariance will be used. Dexpramipexole dose group treatment effects and treatment group effects versus placebo at Week 12 will be tested by contrasts within the MMRM. Estimated LS means of treatment effects and estimated difference in treatment effects at each visit will be back transformed to the original scale to present estimated geometric means for treatment effects and ratio of geometric means of treatment effects versus placebo along with 95% CI.

A contrast will be created to test the treatment effect at Week 12 for the pooled 150 mg/day and 300 mg/day group versus the placebo group. A contrast will be created to test the treatment effect at Week 12 for log-linear dose response.

Two sensitivity analyses will be performed.

1) An analysis of covariance (ANCOVA) model adjusting for baseline and GINA treatment steps 3 vs. 4/5. Missing data will be replaced using multiple imputation. The Markov chain Monte Carlo method will be used and prediction variables will be baseline eosinophil count, eosinophil count at visits prior to the missing data, and GINA treatment steps 3 vs. 4/5. SAS PROC MI will be used to generate multiple complete datasets. To ensure robustness of results, 10 complete datasets will be

created. Each of the 10 complete data sets will be separately analyzed as in the ANCOVA described above, and the results synthesized by SAS procedure MIAnalyze.

2) Dexpramipexole dose group treatment effects versus placebo at Week 12 will be tested on the original (non-log10 transformed) scale (ratio of Week 12 value to baseline value) using a Wilcoxon/Mann-Whitney rank sum test with last observation carried forward to replace missing Week 12 observations.

14.6.2. Secondary Endpoint and Exploratory Endpoint Analyses

For continuous endpoints measured more than once on treatment (pre-bronchodilator FEV1, ACQ-7), the analysis will use the method used for the analysis of the primary endpoint, MMRM. The model will contain terms for baseline, GINA treatment steps 3 vs. 4/5, treatment, visit, treatment by visit interaction, and baseline by visit interaction as fixed effects, and subject as a random effect to compare treatment group effects.

For continuous endpoints measured only at Baseline and Week 12 (post-bronchodilator FEV1, AQLQ) the analysis will use ANCOVA, adjusting for the Baseline value and GINA treatment step 3 vs. 4/5. If a subject has a missing score at Week 12 and an evaluation was performed at the time of drop out, last observation carried forward (LOCF) will be used to impute the missing value at Week 12.

14.7. Pharmacokinetics

Dexpramipexole concentrations in plasma will be summarized using means, SD, standard error of the mean, coefficient of variation, minimum, median, and maximum by treatment per visit. Dexpramipexole trough concentrations in plasma will be used to evaluate the relationship between dexpramipexole exposure and eosinophil-lowering response. Additional details of the analysis plan and the results will be provided in a separate document.

14.8. Safety Analyses

14.8.1. Methods of Analyses - Safety

The safety summary will include adverse events (AEs), serious adverse events (SAEs), clinical laboratory safety data, vital signs, physical examination, and ECG data. Descriptive statistics will be presented for clinical safety laboratory data, vital signs, and ECG measures for observed values and changes from baseline by scheduled evaluation time and treatment group. Potentially clinically significant changes for select clinical safety laboratory data, vital signs, and ECG measures will be defined in the statistical analysis plan and the incidence of each will be presented by treatment group.

14.8.1.1. Adverse Events

All treatment-emergent AEs will be summarized by system organ class (SOC) and preferred term (PT). Treatment-emergent AEs will be defined as those with an onset date on or after the first day of study drug and within 30 days of the last dose of study drug. AE with onset date more than 30 days after the last dose of study drug will be listed and clinically reviewed. All treatment-emergent AEs, regardless of intensity (i.e., severity) and relationship to study treatment will be summarized. AEs will also be presented by maximum intensity and the highest relationship to study treatment. AEs leading to premature discontinuation and treatment-emergent SAEs will be classified by PT and SOC and tabulated. Any reported deaths will be listed.

AEs will only be counted once per SOC and once per PT. For the summary of AEs by severity, if a subject has multiple events occurring in the same body system or same preferred term, then the event with the highest severity will be counted. The relationship to study treatment will be classified as related or not related.

Listings will be presented by subject for all AEs as well as for SAEs, AEs associated with death, and AEs leading to discontinuation of study drug.

14.8.1.2. Clinical Laboratory Evaluations

For hematology and blood chemistry, descriptive statistics for raw values as well as change from baseline for each test will be presented for each visit and treatment group. For hematology and blood chemistry, the number and percentage of subjects with potentially clinically significant laboratory results will be tabulated.

[redacted]. To better characterize any episodes of neutropenia that may occur, a neutropenia case report form will be utilized to capture detailed clinical information concurrent with any laboratory-defined events of neutropenia.

For the analysis of neutropenia, there will be tabulation of ANC<0.50×10^9/L, ANC<1.00×10^9/L, and ANC<1.50×10^9/L with a temporally occurring AE potentially related to neutropenia. The incidence of infection temporally related to neutropenia for dexpramipexole and placebo subjects will be compared with the incidence for dexpramipexole and placebo subjects without neutropenia.

14.8.1.3. Vital Signs

Vital sign measurements as well as change from Baseline will be summarized using descriptive statistics by visit and by treatment group.

Vital signs collected after the first dose of treatment will be examined to determine the incidence of clinically relevant abnormalities. These abnormalities are defined in Table 5.

Table 5: Criteria to Determine Potentially Clinically Significant Vital Sign Abnormalities

Vital Sign Parameter	Criteria for Abnormalities
systolic blood pressure	>180 mmHg or an increase from pre-dosing of more than 40 mmHg, or <90 mmHg or a decrease from pre-dosing of more than 30 mmHg
diastolic blood pressure	>105 mmHg or an increase from pre-dosing of more than 30 mmHg, or <50 mmHg or a decrease from pre-dosing of more than 20 mmHg
pulse	>120 beats per minute or an increase from pre-dosing of more than 30 beats per minute, or <50 beats per minute or a decrease from pre-dosing of more than 20 beats per minute
temperature	>39°C and an increase from pre-dosing of at least 1°C
body weight	>7% from Baseline value, or ≤7% from Baseline value

The number of subjects evaluated and the number and percentage of subjects with the defined abnormality at any time post-baseline will be presented by treatment group.

14.8.1.4. Electrocardiograms

ECG measures as well as change from Baseline will be summarized using descriptive statistics by visit and by treatment group.

ECG findings that are determined to be potentially clinically significant will be summarized.

The QT/QTc analysis approach will follow the ICH E14 Guideline: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.[30] The incidence of AEs potentially related to QTc increase will be presented for individual AEs and the incidence will be presented for the pool of any AEs potentially related to QTc increase. AEs potentially related to QTc increase will include: torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, seizures, and others identified during a review of all AEs observed in the study.

For the evaluation of heart rate change, absolute heart rate, and changes from Baseline by scheduled evaluation time will be tabulated by treatment group. The incidence of subjects with >120 beats per minute or an increase from pre-dosing of more than 30 beats per minute will be tabulated by treatment group. The incidence of AEs potentially related to heart rate increase will be presented for individual AEs and the incidence will be presented for the pool of any AEs potentially related to heart rate increase. A tabulation of AEs that could be linked to a heart rate effect of the drug will be presented with appropriate grouping of terms, e.g.:

a) Preferred terms: related to myocardial ischemia (angina, AMI, unstable angina, etc.)
b) Preferred terms related to congestive heart failure
c) Preferred terms related to tachycardia (atrial fibrillation, tachycardia, ventricular tachycardia, etc.)
d) Cardiac SAEs and relevant SAEs in the general System Organ Class (e.g., sudden death).

14.8.1.5. Physical Examination

The physical examination findings will be presented in data listings.

14.9. Sample Size Considerations

The primary endpoint for this study is reduction in blood eosinophils from Baseline to Week 12. In an open label study of dexpramipexole in subjects with chronic rhinosinusitis with nasal polyps, dexpramipexole reduced eosinophils by 94% (ratio of endpoint to baseline = -2.81 on the log base e scale). The standard deviation for the ratio of endpoint to baseline was 1.82 on the log base e scale.

Nineteen subjects per arm will provide approximately 84% power if the true reduction in blood eosinophils is 85% with dexpramipexole and 10% with placebo. The power will be 95% if the true reduction in blood eosinophils is 90% with dexpramipexole and 10% with placebo. The sample size was calculated using methodology for a two-sample t-test. Assuming an approximate 20% dropout rate of subjects who do not have the final observation for blood eosinophils yields a sample size of 25 subjects per arm to be randomized.

15. ETHICAL REQUIREMENTS

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

15.1. Institutional Review Board

The Site Investigator must obtain approval of the protocol, ICF, and other required study documents prior to starting the study.

If the Site Investigator makes any changes to the ICF, Knopp must approve the changes before the ICF is submitted to the IRB. A copy of the approved ICF must be provided to Knopp. After approval, the ICF must not be altered without the agreement of the relevant IRB and Knopp.

It is the responsibility of the Site Investigator to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations.

Knopp must receive a letter documenting IRB approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the IRB at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the IRB and Knopp.

15.2. Subject Information and Consent

Prior to performing any study-related activities under this protocol, written informed consent with the approved ICF must be obtained from the subject or the subject's legally authorized representative, as applicable, in accordance with local practice and regulations. Written informed consent must be obtained from all subjects participating in a clinical study conducted by Knopp.

The background of the proposed study, the assessments, the benefits, and the risks of the study and the voluntary nature of study participation must be explained to the subject. The subject must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the subject, must be provided to the subject. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol.

Each consent form should contain an authorization allowing the Site Investigator and Knopp to use and disclose subject/patient health information in compliance with local law.

The signed consent form will be retained with the study records.

15.3. Subject Data Protection

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law. The subjects will not be identified by name in the CRF or in any study reports, and these reports will be used for research purposes only.

15.4. Conflict of Interest

The Site Investigator and staff must disclose all potential conflicts of interest (e.g., financial interest in Knopp, or in a Knopp competitor). The Site Investigator must also disclose all potential conflicts of interest to the subject before the subject is invited to participate in the study.

15.5. Registration of Study and Disclosure of Study Results

Knopp will register the study and post study results regardless of outcome on a publicly accessible website (www.ClinicalTrials.gov) in accordance with the applicable laws and regulations.

16. ADMINISTRATIVE PROCEDURES

16.1. Study Site Initiation

Before subjects are screened, Knopp or its designee will review study responsibilities with the Site Investigators and other study site staff. The Site Investigator must not enroll/screen any subjects prior to completion of a study initiation visit. The initiation visit will include a detailed review of the protocol and study assessments. Formal approval to begin enrolling subjects will be provided by Knopp, or their designee.

16.2. Quality Assurance

During and/or after completion of the study, quality assurance officers named by Knopp or the regulatory authorities may wish to perform on-site audits. The Site Investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

16.3. Monitoring of the Study

The Site Investigators must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

Knopp, or its designee, will visit the Site Investigator at regular intervals during the course of the study and after the study has completed, as appropriate. During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

17. GENERAL INFORMATION

Knopp will be responsible for all administrative aspects of this study.

17.1. External Contract Research Organizations

Knopp will be responsible for vendor oversight of the selected Contract Research Organization ([redacted] will be the designated contact for the quality execution of procedural aspects of the study.

17.2. Electronic or Remote Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture (EDC) tool.

17.3. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by Knopp to analyze all hematology, blood chemistry, and urine samples collected for this study. Further details on the collection, processing, storage, and shipment requirements of study samples can be found in the *Study Reference Manual.*

17.4. Central Pharmacovigilance Organization

A Central Pharmacovigilance Organization will be selected by Knopp as the pharmacovigilance vendor for dexpramipexole. The identified partner will be responsible for activities related to serious adverse event reports from the Site Investigators, including receiving reports, evaluating reports for follow-up, evaluating events for regulatory reporting, and disseminating safety information on Knopp's behalf.

17.5. Central Facility for Bioanalytical services

Central research/laboratory facilities will be selected by Knopp to provide bioanalytical services to perform plasma drug concentration and biomarker analyses.

17.6. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and Regulatory Authorities if required by regional and local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the IRB before implementation of such modifications to the conduct of the study. If required by local law, such amendments must also be approved by the appropriate regulatory agency prior to implementation.

However, Knopp may at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the amendment, in accordance with local regulations.

In the event of a protocol modification, the subject consent form may require similar modifications (See Section 15.1 and Section 15.2).

17.7. IRB Notification of Study Completion or Termination

Where required, the Health Authorities and IRBs must be notified of completion or termination of this study. As required by local laws, a copy of the study report synopsis will be provided to the IRB in accordance within the local timeline requirements.

17.8. Retention of Study Data

The Site Investigator must maintain all Essential Documents (as listed in the ICH Guideline for GCP) until notified by Knopp and in accordance with all regional and local laws regarding retention of records.

18. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A randomized, double-blind, placebo-controlled dose-ranging biomarker study of the effects of dexpramipexole on eosinophils in subjects with eosinophilic asthma" [redacted], and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____ _____

Site Investigator's Signature Date

_____

Site Investigator's Name (Print)

_____

Institution (Print)

19. APPENDIX A: SELECTED DRUGS KNOWN TO HAVE SUBSTANTIAL RISK OF NEUTROPENIA[19, 20]

[redacted]

[redacted],

http://www.uptodate.com/contents/drug-induced-neutropenia-and-agranulocytosis

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