CLINICAL STUDY PROTOCOL

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single-Centre Study of Single, Twice Daily (BID) Doses, and Repeated BID Dosing of Ascending Doses, to Evaluate the Safety, Tolerability, and Systemic Exposure of Intranasal Apo-Si-K170A-C76 in Healthy Adult Subjects

Short Title	Safety, Tolerability, and Systemic Exposure of Apo-Si-K170A-C76 in Healthy Volunteers
Protocol Number:	Sir-001
Investigational Product:	Apo-Si-K170A-C76
Phase:	1
Sponsor:	Interna Therapeutics Ltd. (formerSirVir Ltd. /ApoSense Ltd.) 5 Odem St., P.O. Box 7119, Petach Tikva 4917002, Israel Tel: 972-73-2397600
Protocol Date:	6 Nov, 2024
Protocol Version:	Version 4.0

Compliance Statement
This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

PROTOCOL APPROVAL – SIGNATURE PAGE

Protocol Title:	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single-Centre Study of Single, Twice Daily (BID) Doses and Repeated BID Dosing of Ascending Doses, to Evaluate the Safety, Tolerability, and Systemic Exposure of Intranasal Apo-Si-K170A-C76 in Healthy Adult Subjects
Protocol Number:	Sir-001
Investigational Products:	Apo-Si-K170A-C76

Interna Therapeutics Ltd. (former SirVir Ltd. / Aposense Ltd.) commits to conduct the study as described herein in accordance with the current Declaration of Helsinki and the guidelines on Good Clinical Practices (cGCPs) and in compliance with the obligations and requirements of the local regulations and the Sponsor's Standard Operating Procedures (SOPs). The above -titled study protocol was subjected to critical review and the information presented is consistent with the current knowledge of the risks and benefits of the investigational product. The following individuals approve the Sir-001 protocol, Version 1.0, dated December 12th, 2023. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.

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INVESTIGATOR PROTOCOL ACKNOWLEDGMENT

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Protocol Number: Sir-001

Investigational Products: Apo-Si-K170A-C76

By signing below, I, the Investigator, approve the protocol and agree to conduct the clinical study according to all stipulations of the protocol as specified in both the clinical and administrative sections, electronic case report form (eCRF) and any protocol-related documents (subject to any amendments agreed to in writing between the Sponsor and Principal Investigator).

I agree to comply with the International Council for Harmonization (ICH) Good Clinical Practices (GCP), World Medical Association Declaration of Helsinki (and relevant updates) and applicable local regulations.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Interna Therapeutics Ltd.

I understand that the study may be terminated, or enrollment suspended at any time by Sponsor, or by me, at my center, if it becomes necessary in my opinion to protect the best interests of the study participants.

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Investigator's Signature

8 Nov 2024

Date

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Investigator's Printed Name

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LIST OF TERMS AND ABBREVIATIONS

AE(s)	Adverse Event(s)
BMI	Body Mass Index
CFR	Code of Federal Regulations
cGCP	current Good Clinical Practice
DSMC	Data Safety Monitoring Committee
dsiRNA	double stranded short interfering RNA
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
ET	Early Termination
F/U	Follow-up
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization Identification
IN	Intranasal
IP	Investigational Product
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
MNMs	Molecular Nano Motors
MOH	Ministry of Health
NA	Not Applicable
NOAEL	No-Observed-Adverse-Effect Level
PI	Principal Investigator
PIS	Patient Information Sheet
PK	Pharmacokinetics
PP	Per Protocol (population)
PT	Preferred Term
RISC	RNA-induced silencing complex
RU	Research Unit
SAE	Serious Adverse Event
siRNA	Small interfering RNA

SOC	System Organ Class
SOP	Standard Operating Procedure
SSC	Safety Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAEs	Treatment-Emergent Adverse Events
TNSS	Total Nasal Symptom Score

PROTOCOL SYNOPSIS

Title	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single-Centre Study of Single, Twice Daily (BID) Doses and Repeated BID Dosing of Ascending Doses, to Evaluate the Safety, Tolerability, and Systemic Exposure of Intranasal Apo-Si-K170A-C76 in Healthy Adult Subjects.
Study number	Sir-001
Study Phase	First in Human (phase 1)
Investigational Site	Hadassah Clinical Research Center, Israel
Indication	Healthy volunteers
Study Design and Periods	This is a prospective, randomized, double-blind, placebo-controlled study designed to assess the safety, tolerability, and systemic exposure of single, BID dosed and repeated BID dosing of ascending doses of intranasal Apo-Si-K170A-C76 in healthy adult subjects. Upon signing the informed consent, the subjects will undergo a screening period for eligibility evaluation. Subjects will be admitted to the Research Unit (RU) on Day 1 and eligibility will be confirmed again. Eligible subjects, as determined by the Principal Investigator (PI), will be randomized as close as possible prior to 1st drug administration on Day 1 to receive either intranasal Apo-Si-K170A-C76 or matching placebo. Dosing will depend on the cohort the subjects are assigned to. Intranasal (IN) administration is performed to both nostrils of all participants. The nasal spray device contains the Study Drug at 20 mg/mL and delivers 0.1 mL volume per actuation. The subjects will receive 1-3 actuations per nostril alternately according to dosing group. After each actuation, an inspiration will be performed, and around a 5-second delay will be introduced between each new actuation. Thus, during each administration cohort, dosages registered as dose/nostril are received twice per subject, one dose to each nostril. The study will be composed of 7 dosing cohorts. Cohort 1 will involve an initial administration of a single (low) dose of Apo-Si-K170A-C76 (2mg/100µl/nostril, to both nostrils). Cohort 2 will involve administration of a single dose of Apo-Si-K170A-C76 at a double dose of the first dose (4mg/200µl/nostril, to both nostrils). Cohort 3 will involve administration of a single dose of Apo-Si-K170A-C76 at the target dose (x3 of first dose, 6mg/300µl/nostril, to both nostrils). Cohort 4 will involve BID administration of the same dose as cohort 2, separated by 6 hours, and cohort 5 will involve BID administration of the same dose as cohort 3, separated by 6 hours, with a new bottle. Administration in cohorts 1-5 will take place on Day 1. Cohort 6 will involve administration of repeated BID

	doses of Apo-Si-K170A (at the same dose level or lower than that administered in Cohort 4) taken from Day 1 to Day 5. Cohort 7 will involve administration of repeated BID doses of Apo-Si-K170A-C76 (at the target dose level or lower than that administered in Cohort 5) taken also from Day 1 to Day 5. The study drug (or placebo) will be administered to both nostrils via intranasal spray, while the subject is seated. To note: In cases where more than 1 actuation in each nostril is required (Cohorts 2-7), the actuations will be performed in an **alternately** manner. It is necessary to prime the pump bottle by spraying it into the air four times prior to using each new bottle. In case of failure by the fourth prime actuation, up to 2 more actuations are allowed. If by the 6^{th} priming actuation, no or minimal liquid is delivered the bottle will be discarded and replaced with another bottle. Subjects will remain in bed for at least 2 hours post administration. An examination of the nasal cavity will be performed by a study physician at screening, 24 hours ($\pm$1hr) after each dose and at the last follow up visit for all subjects in all cohorts. The initial dose for this study is based on the non-clinical No-Observed-Adverse-Effect Level (NOAEL). All study staff (with the exception of specified unblinded pharmacy staff), study subjects, and the Sponsor will remain blinded to study drug/placebo allocation. Each subject will participate in one cohort. Subjects will be screened and randomized to active Apo-Si-K170A-C76 or matching placebo in a 3:1 ratio:

Part 1	Dose Concentration	Number of Subjects	
		Apo-Si-K170A-C76	Placebo
Cohort 1	2mg/nostril, 4mg/both nostrils	6	2
Cohort 2	4mg/nostril, 8mg/both nostrils	6	2
Cohort 3	6mg/nostril, 12mg/both nostrils	6	2
Cohort 4	4mg/nostril, 8 mg/both nostrils BID (16mg/day/both nostrils)	6	2
Cohort 5	6mg/nostril, 12 mg/both nostrils BID (24mg/day/both nostrils)	6	2
Cohort 6	4mg/nostril, 8 mg/both nostrils BID (16mg/day/both nostrils) for 5 days	6	2
Cohort 7	6mg/nostril, 12 mg/both nostrils BID (24mg/day/both nostrils) for 5 days	6	2
Total Subjects		**42**	**14**

Randomization will be performed on Day 1 in a staggered manner: initially, two sentinel subjects (one active and one placebo) will be randomized and dosed with blinded treatment prior to the remaining subjects. One sentinel subject will be dosed with active drug (Apo-Si-K170A-C76) and the other with matching placebo. The remaining 6 subjects in the dose cohort will be randomized and dosed if no safety concerns (without clinically significant AEs) are identified in the sentinel subjects; The decision to proceed and dose additional subjects following the first 2 sentinel subjects, according to the randomization schedule, will be at the discretion of the investigator and following his review of all their medical data. Following completion of cohorts 1, 2 and 3, subjects will be dosed in cohort 4. The second dose in this cohort will be administered 6 hours after the first one. Cohort 5 will follow in the same manner. Subjects in cohorts 6 and 7 will be dosed with 4mg/nostril BID or 6mg/nostril BID (of the initial dose), respectively, for 5 days. If safety concerns are observed at any time after the repeated administration, a lower dose will be selected.

The decision to escalate to the next dose level, to investigate lower, intermediary, or higher doses, will be done by the Safety Steering Committee (SSC) which will review blinded emerging data of subjects in a given cohort including safety and tolerability. A minimum of 7 days post-dose safety data will be reviewed by the SSC to determine the next dose level. **All dose escalation decisions, except for the transitions between cohort 3 to cohort 4 and cohort 5 to cohort 6, will be taken by the SSC.** If the SSC considers that an unblinded review of data is required to make a decision, then the independent Data Safety Monitoring Committee (DSMC) will be asked to undertake this review and make their

	recommendations. The transition between cohort 3 to cohort 4 and between cohort 5 to cohort 6 will be reviewed and confirmed by the DSMC. The transition from cohort 5 to cohort 6 will involve, in addition to safety data, the review of all systemic exposure results obtained from 5. To note that based on the results of the systemic exposure of Cohort 5, the levels of systemic exposure for all or part of Cohorts 1-4 samples will be analyzed as well. The subjects will be admitted to the clinic on Day 1. For cohorts 1-5, overnight confinement between Day 1 to Day 2 is mandatory and will be discharged on Day 2 after all assessments have been completed for this day. For cohorts 6-7, confinement to the clinic between Day 1 and through Day 6 is required i.e., subjects will be discharged from the clinic on Day 6, after all required assessments and procedures have been completed for that day. All subjects will arrive at the clinic for a follow up visit 7±2 days after last day of administration, i.e., in cohorts 1-5, subjects will arrive on Day 8±2 and subjects in cohorts 6-7 will arrive on Day 12±2. Subjects in all cohorts will receive the treatment after standardized meals. Water will be freely available at all other times. Grapefruit juice and Caffeine containing beverages should be avoided until after the 24-hour (±1 hour) post dose blood sampling.
Investigational Products	**Active:** Intranasal Apo-Si-K170A-C76: Solution of 20 mg/ml in 5% glucose, 0.5% benzyl alcohol in RNase free water **Placebo:** 5% glucose, 0.5% benzyl alcohol in RNase free water
Study Objectives	**<u>Primary Objectives</u>** To evaluate the safety and tolerability of single, BID doses and repeated BID, ascending doses of Apo-Si-K170A-C76 administered intranasally (IN) in healthy adult subjects. **<u>Secondary Objective</u>** To evaluate the systemic exposure of Apo-Si-K170A-C76 following intranasal administration in healthy adult subjects.
Study Population and Number of planned Subjects	56 healthy subjects are planned to be enrolled (42 active and 14 placebo subjects) Family members can participate in the study.
Methodology	Screening will take place only once for each participant. **<u>Cohorts 1-5</u>**

	Screening Up to 21 days prior to dosing: 1. Visit 1 /Screening **Treatment Period:** 2. Visit 2 / Day 1, admission to the RU and treatment administration (single dose (cohorts 1-3) or BID (cohorts 4-6)) 3. Visit 3 / Day 2, 24h post dose assessments Discharge from the RU will occur on Day 2 **Follow Up (EOS)** 4. Visit 4 / Day 8 (± 2 days), FU / EOS 7±2 days after administration. **<u>Cohorts 6-7</u>** **Screening Up to 21 days prior to dosing:** 1. Visit 1 /Screening **Treatment Period:** 2. Visit 2 / Day 1, admission to the RU and treatment administration (BID) 3. Visit 3 / Day 2, treatment administration (BID) 4. Visit 4 / Day 3, treatment administration (BID) 5. Visit 5 / Day 4, treatment administration (BID) 6. Visit 6 / Day 5, treatment administration (BID) 7. Visit 7 / Day 6, 24h post Day 5-1st dose assessments Discharge from the RU will occur on Day 6. **Follow Up (EOS)** 8. Visit 8 / Day 12 (± 2 days), 7±2 days after last administration, FU / EOS For detailed clinical and safety procedures performed at each visit, please refer to the Schedule of Assessments (Table 1, Table 2 and Table 3 for cohorts 1-3, 4-5 and 6-7, respectively. From ICF signature up until the first treatment - only Serious Adverse Events (SAEs) and non-serious protocol-related (procedure-related) adverse events will be reported in the subject's source and eCRF.

	Following initiation of study treatment and until EOS (during the study period) - all related and non-related adverse events will be recorded in the subject's eCRF. Based upon GCP rules, the relevant AE's will be reported by the Principal Investigator to the Local Ethics Committee.
Clinical Study Duration	The total duration for each participating subject is up to 35 days: Up to 21 days of screening and 14 days (7±2 days after last dose) including treatment and the follow up visit period (depending on the cohort the subject is assigned to)
Subject Inclusion Criteria	1. Male and female participants must be ≥ 18 years old. 2. Understands the study procedures described in the Informed Consent Form (ICF), be willing and able to comply with the protocol, and provides written consent. 3. Not pregnant or lactating and willing to comply with the contraceptive requirements from enrolment to 3 months post last dose. Contraceptive requirements include the following: a. Use a condom with a spermicide to prevent pregnancy in a female partner or to prevent exposure of any partner (male and female) to the study intervention treatment. b. Male sterilization with the appropriate post vasectomy documentation of the absence of sperm in the ejaculate (please note that the use of condom with spermicide will still be required to prevent partner exposure). This applies only to males participating in the study. c. In addition, for female partners and female participants of child-bearing potential, must use another form of contraception such as one of the highly effective methods (pills, Intra Uterine Device (IUD)). d. True abstinence - sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study 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. e. In addition to the contraceptive requirements above, male subjects must agree not to donate sperm for 3 months post last dose. 4. In good health with no history of clinically significant medical conditions (as described in Exclusion criteria) that would interfere with subject safety, as defined by relevant medical history, physical examination and routine laboratory tests, ECG and determined by the Investigator at an admission evaluation. 5. Subjects will have a documented relevant medical history either prior to entering the study and/or following relevant medical history review with the study physician at screening.

Subject Exclusion Criteria	The presence of any of the following will exclude the potential study participant from entering the study: **Clinical History** 1. History or evidence of any clinically significant or currently active cardiovascular, (including thromboembolic events), respiratory, dermatological, gastrointestinal, endocrine, hematological, hepatic, immunological, rheumatological, metabolic, urological, renal, neurological, or psychiatric illness. Specifically: a. Subjects with any history of physician diagnosed and/or objective test-confirmed asthma, chronic obstructive pulmonary disease, pulmonary hypertension, reactive airway disease, or chronic lung condition of any etiology or who have experienced: o Significant/severe wheeze in the past o Respiratory symptoms including wheeze which has ever resulted in hospitalization. o Known bronchial hyper-reactivity to viruses. b. History of thromboembolic, cardiovascular, or cerebrovascular disease c. History or evidence of diabetes mellitus d. Any concurrent serious illness including history of malignancy that could interfere with the aims of the study or a subject completing the study. Basal cell carcinoma within 5 years of treatment or with evidence of recurrence is also an exclusion. e. Migraine with associated neurological symptoms such as hemiplegia or vision loss. Cluster headache/migraine or prophylactic treatment for migraine f. History or evidence of autoimmune disease or known immunodeficiency of any cause. g. Other major disease that, in the opinion of the Investigator, could interfere with a subject completing the study and necessary investigations. h. Immunosuppression of any type 2. Any significant abnormality altering the anatomy or function of the nose or nasopharynx in a substantial way (including loss of or alterations in smell or taste), a clinically significant history of epistaxis (large

	nosebleeds) within the last 3 months, nasal or sinus surgery within 6 months of screening. 3. Clinically active rhinitis (including hay fever) or history of moderate to severe rhinitis, or history of seasonal allergic rhinitis likely to be active at the time of inclusion into the study and/or requiring regular nasal corticosteroids on at least a weekly basis, within 30 days prior to screening. 4. History of anaphylaxis and/or a history of severe allergic reaction or significant intolerance to any food or drug, as assessed by the PI. 5. History or presence of alcohol addiction, or excessive use of alcohol. The subject has a history of consuming more than 7 units of alcoholic beverages per week for male subjects and more than 5 units for females or has a history of alcoholism or drug/chemical/substance abuse within the past 2 years prior to screening (Note: one unit = 330 mL of beer, 110 mL of wine, or 28 mL of spirits), or use of drugs of abuse. 6. Psychiatric illness, including subjects with a history of depression and/or anxiety with associated severe psychiatric comorbidities, for example psychosis. Specifically, (a) Subjects with history of anxiety-related symptoms of any severity within the last 2 years if the Generalized Anxiety Disorder-7 score is ≥4; (b)Subjects with a history of depression of any severity within the last 2 years if the Patient Health Questionnaire-9 score is ≥4 7. Subjects who have smoked ≥5 pack years at any time [5 pack years is equivalent to one pack of 20 cigarettes a day for 5 years]). • Subjects who have smoked <5 pack years - at any time in the 3 months prior to screening, have used tobacco in any form (e.g., smoking or chewing) or other nicotine-containing products in any form (e.g., gum, patch) or electronic cigarettes. **Measurements and investigations** 8. A Body Mass Index (BMI) ≤18 Kg/m^2 and ≥28 Kg/m^2. The upper limit of BMI may be increased up to 30 Kg/m^2 at the PI's discretion, in the case of physically fit muscular individual. 9. Venous access deemed inadequate for the phlebotomy and cannulation demands of the study. 10. At the discretion of the PI, any clinically significant abnormal finding on screening biochemistry, hematology, serology , microbiology blood tests or urinalysis or a. Positive HIV, active/chronic hepatitis B or C test.

	b. Positive β -HCG or positive alcohol test 11. Confirmed positive test for drugs of abuse and/or urinary cotinine at screening and on admission (Day 1). 12. Twelve-lead ECG recording with clinically relevant abnormalities as judged by the study physician/PI. **Recent respiratory infection** 13. Presence of cold-like symptoms and/or fever (defined as subject presenting with a temperature reading of >37.9ºC) at screening or on admission (Day 1). **Receipt of medications and interventions** 14. Receipt of blood or blood products, or loss (including blood donations) of 550 mL or more of blood during the 3 months prior to screening. 15. Medications a. Use of any medication or product (prescription or over-the-counter) for symptoms of hay fever, nasal congestion or respiratory tract infections, or dermatitis/eczema including the use of regular nasal or medium-high potency dermal corticosteroids, antibiotics and First Defence™ (or generic equivalents) within 7 days prior to screening. The sporadic use of paracetamol or other medications will be acceptable only as agreed by the Principal Investigator. b. Receipt of any investigational drug within 3 months prior to screening. c. Receipt of three or more investigational drugs within the previous 12 months prior to screening. d. Receipt of systemic (intravenous and/or oral) glucocorticoids or systemic antiviral drugs within 6 months prior to screening. e. Over the counter medications (e.g., paracetamol or ibuprofen) where the dose taken over the preceding 7 days prior to screening had exceeded the maximum permissible 24-hour dose (e.g., >4g per day of paracetamol over the preceding week). f. Chronically used medications, including any medication known to be a moderate/potent inducer or inhibitor of cytochrome P450 enzymes, within 21 days prior to screening. g. Subjects who have received any systemic chemotherapy agent, immunoglobulins, or other cytotoxic or immunosuppressive drugs at any time.

	Other 16. Subjects who are currently employed by or are first-degree relative of someone employed by the Sponsor or participating clinical trial site, or any Contract Research Organization involved in this study. 17. Any other reason that the Investigator considered made the subject unsuitable to participate.
Safety and Tolerability Endpoints	• Frequency and severity of Adverse Events (AEs), including Serious Adverse Events (SAEs) and Treatment-emergent AEs (TEAEs) occurring at any time during the study. • Change from Baseline to End of Study (EOS) in: o Laboratory tests including urinalysis and blood tests o Vital signs o Physical examination o TNSS

Systemic Exposure Measurements	Systemic exposure will be determined by measuring concentrations of serum Apo-Si-K170A obtained from subjects who receive Apo-Si-K170A in each dose cohort, at specific time points. Based on the results of the systemic exposure of Cohort 5, the levels of systemic exposure for all or part of Cohorts 1-4 samples will be analyzed as well. Pharmacokinetic (PK) analysis will be considered if required, according to the concentrations measured. In case required, the following PK variables will be determined using serum samples: • Cmax - Maximum concentration achieved. • Tmax - Time to reach maximum concentration (hours). • AUClast – The area under the concentration vs. time curve, calculated as sum of AUCs using linear trapezoidal summation from time 0 to the last measurable data point. • AUCpartial – The area under the concentration vs. time curve, calculated as sum of AUCs using linear trapezoidal summation from time 0 to the maximal measurement (Tmax). • λz (Lambdaz)- Individual estimate of the terminal elimination rate constant, was calculated using log-linear regression of the terminal portions of the plasma concentration-versus-time curves. • AUCinf - The area under the serum concentration-time curve extrapolated to infinity, calculated as: AUCinf was calculated as AUClast + Clast/λz, where Clast is the last measurable concentration. • T1/2 - Apparent terminal elimination half-life time (hours), defined as 0.693/λz.
Statistical Methods	**Sample size rationale and justification** This is a Phase 1 safety study designed to evaluate the safety, tolerability, and systemic exposure of Apo-Si-K170A-C76. The sample size is not based on power calculations. It is chosen based on clinical experience and typical SAD and multiple administration designs and considered to be adequate to fulfil the objectives of the study. **General:** Tabulation of descriptive statistics, calculation of inferential statistics (if relevant), and graphical representations (if relevant) will be performed using SAS® version 9.4 or higher for Windows. All demography, baseline characteristics and safety analyses will be performed on the Safety Analysis Set. All measured variables will be listed individually. All measured variables and derived variables will be tabulated by dose cohort and overall (for all treatment arms, not including placebo) for the following descriptive statistics:

	• Continuous variables will be summarized by the number of observations (n), mean, standard deviation, median, minimum, and maximum and 95% CI for means of variables if appropriate, by dose group (cohort) and treatment arm. • Categorical variables will be summarized by frequency counts and percentages [n (%)] for each category. Unless otherwise stated, percentages will be calculated out of the number of subjects in the relevant Analysis Set (Safety Analysis Set), by dose group (cohort) and treatment arm. No data imputation will be performed. **Safety Endpoints:** Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, most updated version) terminology and presented in tables by System Organ Class (SOC) and Preferred Term (PT). AE data will be listed individually and summarized by SOC and by PT within a system organ class. Frequency of TEAEs (Treatment-Emergent Adverse Events) and drug-related adverse events will be summarized in tables by SOC, PT and by seriousness. Concomitant medications entered into the database will be coded using the public World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Change from Baseline to EOS in safety laboratory, vital signs and physical examination will be summarized in appropriate tables.

Table 1 Schedule of Assessments: Cohorts 1, 2 and 3 (single dose)

	Screening[1] -21 to Day 1	Treatment administration Day 1[2]	Day 2	EOS: Day 8 (± 2 day) F/U
Visit No.	**1**	**2**	**3**	**4**
Informed consent[3]	X			
Complete medical history	X			
Height[4], weight, and BMI calculation	X			
Vital signs[5]	X	X	X	X
TNSS[6]	X	X	X	X
Complete physical examination[7]	X			
Focused physical examination[8]		X	X	X
12-lead safety ECGs[9]	X	X	X	X
Blood and urine for safety analyses[10]	X			X
SARS-CoV-2 screening test[11]	X	X		
Blood sampling for systemic exposure[12]		X	X	
Blood for hep B, hep C, HIV serology	X			

[1] Screening must occur within 21 days prior to the start of dosing. Screening will take place only once for each participant.

[2] Overnight confinement to the clinic between Day 1 and Day 2 is mandatory (through 24 hours post dose); i.e., subjects will be discharged on Day 2 after all required assessments and procedures have been completed for that day. The PI or designee will confirm that the subject is fit for discharge on Day 2.

[3] Informed Consent must be obtained prior to initiating any study procedure. Subject eligibility should be confirmed also on Day 1 prior to dosing.

[4] Height to be measured only at screening.

[5] Vital signs will be obtained at Screening, within 2 hours prior to and 1, 2, 4, and 8 hours (all ± 20 minutes) post dose on Day 1, at 24 hours (± 1 hour) post dose on Day 2 and at F/U. Vital signs should be captured after 5 minutes of rest while the subject is in a supine or seated position.

[6] Subjects will complete the TNSS scale to rate their nasal symptoms. TNSS will be tested at screening, within 2 hours prior to dosing, and 1 hour (± 20 minutes) after dosing. Also, TNSS will be recorded on Day 2, 24 hours (± 1 hour) after the dose administered on Day 1, and at the EOS visit.

[7] A complete physical examination (i.e., general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest [heart, lungs], abdomen, skin, neurological, extremities, back, neck, musculoskeletal, lymph nodes) will be performed at Screening.

[8] A focused physical examination consisting of the chest (heart, lungs), abdomen, skin, neurological, and musculoskeletal examinations will be performed within 2 hours prior to dosing of Treatment, upon discharge on Day 2, and at the F/U visit.

[9] Safety ECGs will be obtained at Screening Visit. A single 12-lead safety ECG will also be obtained on Day 1, pre-dose (within 2 hours prior to dosing) and at 1 hour ± 20 minutes and 24 hours (± 1 hour) post dose. Safety ECGs will be obtained at F/U. The ECGs should be captured after 5 minutes of rest in a semi-supine / supine position.

[10] Blood samples will be collected for chemistry, hematology, and coagulation at Screening and at F/U. Urine samples will be collected for urinalysis (and urine microscopy if urinalysis is + or above for red blood cells, white blood cells, protein, or nitrite) at Screening and at F/U.

[11] Performed locally using a kit.

[12] On Day 1, obtain blood for systemic exposure prior to dosing (within 2 hour before), at 30 and 60 minutes (all ± 5 minutes) and 2, 3, and 4 hours (all ± 10 minutes), 6 and 8 hours (all ± 20 minutes) post dose. A 24-hour (± 1 hour) post dose sample will be collected on Day 2.

	Screening[1] -21 to Day 1	Treatment administration Day 1[2]	Day 2	EOS: Day 8 (± 2 day) F/U
Visit No.	**1**	**2**	**3**	**4**
Alcohol test and urine test for drugs of abuse, cotinine and pregnancy[13]	X	X		
Eligibility confirmation	X[3]	X[3]		
Randomization[14]		X		
IN administration of treatment		X		
Assess for AEs[15]	X	X	X	X
Prior and concomitant medications[16]	X	X	X	X
Examination of nasal cavity	X		X	X

Abbreviations: AEs = Adverse events; BMI = Body mass index; ECG = Electrocardiogram; EOS = End of Study; F/U = Follow-up; HIV = Human immunodeficiency virus; I.N. = Intranasal (administration); TNSS = Total nasal symptom score.

[13] At screening, alcohol and pregnancy will be tested in blood and drugs and cotinine in urine (all central lab). On Day 1 prior to dosing, alcohol, drugs, cotinine, and β-HCG will be tested locally in urine.

[14] Randomization to placebo or active will occur as close as possible prior to the first administration of Treatment.

[15] Adverse events will be collected from the time of informed consent through the F/U visit.

[16] Prior and concomitant medication history includes all medications (including over-the-counter medications, vitamins, and supplements) taken from 30 days prior to informed consent signing through the F/U visit.

Table 2 Schedule of Assessments: Cohorts 4 and 5 (BID dose)

	Screening[1] -21 to Day 1	Day 1 Treatment administration[2]	Day 2	EOS: Day 8 (± 2 day) F/U
Visit No.	**1**	**2**	**3**	**4**
Informed consent[3]	X			
Complete medical history	X			
Height[4], weight, and BMI calculation	X			
Vital signs[5]	X	X	X	X
TNSS[6]	X	XX	X	X
Complete physical examination[7]	X			
Focused physical examination[8]		X	X	X
12-lead safety ECGs[9]	X	X	X	X
Blood and urine for safety analyses[10]	X			X
SARS-CoV-2 screening test[11]	X	X		
Blood sampling for systemic exposure[12]		X	X	
Blood for hep B, hep C, HIV serology	X			

[1] Screening must occur within 21 days prior to the start of dosing. Screening will take place only once for each participant.

[2] Overnight confinement to the clinic between Day 1 and Day 2 is mandatory (through 24 hours post dose); i.e., subjects will be discharged from the clinic on Day 2 after all required assessments and procedures have been completed for that day. The PI or designee will confirm that the subject is fit for discharge on Day 2.

[3] Informed Consent must be obtained prior to initiating any study procedure. On Day -1, subject eligibility should be confirmed.

[4] Height to be measured only at screening.

[5] Vital signs will be obtained at Screening, within 2 hours prior to and 1, 2, 4, 6 (but pre-2nd dose) and 8 hours (all ± 20 minutes) post 1st dose on Day 1, at 24 hours (± 1 hour) post 1st dose on Day 2 and at F/U. Vital signs should be captured after 5 minutes of rest while the subject is in a supine / seated position.

[6] Subjects will complete the TNSS scale to rate their nasal symptoms. TNSS will be tested at screening, within 2 hours prior to the 1st dose on Day 1, and 1 hour (± 20 minutes) after each dose. Also, TNSS will be recorded on Day 2, 24 hours (± 1 hour) after the 1st dose administered on Day 1, and at the EOS visit.

[7] A complete physical examination (i.e., general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest [heart, lungs], abdomen, skin, neurological, extremities, back, neck, musculoskeletal, lymph nodes) will be performed at Screening.

[8] A focused physical examination consisting of the chest (heart, lungs), abdomen, skin, neurological, and musculoskeletal examinations will be performed within 2 hours prior to the 1st dose of Treatment, on Day 2 and F/U visit.

[9] Safety ECGs will be obtained at Screening Visit. A single 12-lead safety ECG will also be obtained on Day 1, pre-dose (within 2 hours prior to 1st dosing) and at 1, 6 hours (but pre-2nd dose), 7 hours (i.e. 1 hour post 2nd dose) (all ± 20 minutes) and 24 hours (± 1 hour) post 1st dose. Safety ECGs will be obtained at F/U. The ECGs should be captured after 5 minutes of rest in a semi-supine/ supine position.

[10] Blood samples will be collected for chemistry, hematology, and coagulation at Screening and at F/U. Urine samples will be collected for urinalysis (and urine microscopy if urinalysis is + or above for red blood cells, white blood cells, protein, or nitrite), at Screening and at F/U

[11] Performed locally using a kit.

[12] On Day 1, obtain blood for systemic exposure prior to 1st dosing (within 2 hour before), and then at 30 and 60 minutes (all ± 5 minutes), and 2, 3, and 4 hours (all ±10 minutes), 6, 6.5, 7, 8, 9, and 10 hours (all ±20 minutes) after 1st dosing. A 24-hour (± 1 hour) post 1st dosing sample will be collected on Day 2.

	Screening[1] -21 to Day 1	**Day 1 Treatment administration[2]**	**Day 2**	**EOS: Day 8 (± 2 day) F/U**
Alcohol test and urine test for drugs of abuse, cotinine and pregnancy [13]	X	X		
Eligibility Confirmation	X[3]	X[3]		
Randomization[14]		X		
IN administration of treatment		XX (BID)		
Assess for AEs[15]	X	X	X	X
Prior and concomitant medications[16]	X	X	X	X
Examination of nasal cavity	X		X	X

Abbreviations: AEs = Adverse events; BMI = Body mass index; ECG = Electrocardiogram; EOS = End of Study; F/U = Follow-up; HIV = Human immunodeficiency virus; I.N. = Intranasal (administration); TNSS = Total nasal symptom score.

[13] At screening, alcohol and pregnancy will be tested in blood and drugs and cotinine in urine (all central lab). On Day 1 prior to dosing, alcohol, drugs, cotinine, and β-HCG will be tested locally in urine.

[14] Randomization to placebo or active will occur as close as possible prior to the first administration of Treatment.

[15] Adverse events will be collected from the time of informed consent through the F/U visit.

[16] Prior and concomitant medication history includes all medications (including over-the-counter medications, vitamins, and supplements) taken from 30 days prior to informed consent signing through the F/U visit.

Table 3 Schedule of Assessments: Cohorts 6 and 7 (repeated dose BID)

Day / Visit	Screening[1] -21 to Day 1	Day 1 Treatment administration[2]	Day 2 to Day 4 Continued Dosing of Treatment	Day 5 Final Treatment administration	Day 6	EOS: Day 12 (±2 day) F/U
Visit No.	**1**	**2**	**3, 4, 5**	**6**	**7**	**8**
Informed consent[3]	X					
Complete medical history	X					
Height[4], weight, and BMI calculation	X					
Vital signs[5]	X	X	X	X	X	X
TNSS[6]	X	XX	XX	XX	X	X
Complete physical examination[7]	X					
Focused physical examination[8]		X		X	X	X
12-lead safety ECG[9]	X	X	X	X	X	X
Blood and urine for safety analyses[10]	X		X			X
SARS-CoV-2 screening test[11]	X	X				
Blood sampling for systemic exposure[12]		X	X	X	X	

[1] Screening must occur within 21 days prior to the start of dosing. Screening will take place only once for each participant.

[2] Confinement to the clinic between Day 1 and through 24 hours post 1st dose of last treatment day, is mandatory; i.e., subjects will be confined from Day 1 through the morning of Day 6 in the research unit and will be released after all required assessments and procedures have been completed on Day 6. The PI or designee will confirm that the subject is fit for discharge.

[3] Informed Consent must be obtained prior to initiating any study procedure. On Day 1 subject eligibility should be also confirmed.

[4] Height to be measured only at screening.

[5] Vital signs will be obtained at Screening, within 2 hours prior to and 1, 2, 4, 6 and 8 hours (all± 20 minutes) after the 1st dose of study drug on Days 1 to 5, at 24 hours (± 1 hour) post the 1st dose of study drug on the previous day on Day 6, and at F/U. Vital signs should be captured after 5 minutes of rest while the subject is in a supine/ seated position.

[6] Subjects will complete the TNSS scale to rate their nasal symptoms. TNSS will be tested at screening, within 2 hours prior to the 1st dose of each treatment day, and 1 hour (± 20 minutes) after each dose. Also, TNSS will be recorded on Day 6, 24 hours (± 1 hour) after the 1st dose administered on Day 5, and at the EOS visit.

[7] A complete physical examination (i.e., general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest [heart, lungs], abdomen, skin, neurological, extremities, back, neck, musculoskeletal, lymph nodes) will be performed at Screening.

[8] A focused physical examination consisting of the chest (heart, lungs), abdomen, skin, neurological, and musculoskeletal examinations will be performed within 2 hours prior to the 1st dose of Treatment on Day 1, on Days 5 and 6, and at the F/U visit.

[9] Safety ECGs will be obtained at Screening Visit. A single 12-lead safety ECG will also be obtained on Day 1, pre-dose (within 2 hours prior to 1st dosing) and at 1, 6 hour (but pre-2nd dose), 7 hours (i.e. 1 hour post 2nd dose) (all ± 20 minutes). On Days 2-5, ECG will be recorded pre-dose (within 2 hours prior to 1st dosing) and 1 hour post 2nd dosing of the same day. On Day 6, ECG will be recorded 24 hours (± 1 hour) post 1st dose of Day 5. Safety ECGs will be obtained at F/U. The ECGs should be captured after 5 minutes of rest in a semi-supine / supine position.

[10] Blood samples will be collected for chemistry, hematology, and coagulation at Screening, on Day 3 (prior to 1st dosing), and at F/U. Urine samples will be collected for urinalysis (and urine microscopy if urinalysis is + or above for red blood cells, white blood cells, protein, or nitrite) at Screening, on Day 3 (prior to 1st dosing) and at F/U.

[11] Performed locally using a kit.

[12] On Day 1, obtain blood for systemic exposure prior to 1st dosing (within 2 hour before), and then at 30 and 60 minutes (all ± 5 minutes), and 2, 3, and 4 hours (all ±10 minutes), 6, 6.5, 7, 8, 9, and 10 hours (all ±20 minutes) after 1st dosing. A 24-hour (± 1 hour) post 1st dosing sample will be collected on Day 2 (this will be the pre-dose sample of Day 2). On Days 2-5, the same time points as on Day 1 will be collected. A 24-hour (±1 hour) post Day 5-1st dosing sample will be collected on Day 6.

Day / Visit	Screening[1] -21 to Day 1	Day 1 Treatment administration[2]	Day 2 to Day 4 Continued Dosing of Treatment	Day 5 Final Treatment administration	Day 6	EOS: Day 12 (±2 day) F/U
Blood for hep B, hep C, HIV serology	X					
Alcohol test and urine test for drugs of abuse, cotinine and pregnancy[13]	X	X				
Eligibility Confirmation	X[3]	X[3]				
Randomization[14]		X				
IN administration of treatment[15]		XX (BID)	XX (BID)	XX (BID)		
Assess for AEs[16]	X	X	X	X	X	X
Prior and concomitant medications[17]	X	X	X	X	X	X
Examination of nasal cavity	X		X	X	X	X

Abbreviations: AEs = Adverse events; BMI = Body mass index; ECG = Electrocardiogram; EOS = End of Study; F/U = Follow-up; HIV = Human immunodeficiency virus; I.N. = Intranasal (administration); TNSS = Total nasal symptom score.

[13] At screening, alcohol and pregnancy will be tested in blood and drugs and cotinine in urine (all central lab). On Day 1 prior to dosing, alcohol, drugs, cotinine, and β-HCG will be tested locally in urine.
[14] Randomization to placebo or active will occur as close as possible prior to the first administration of Treatment.
[15] The 1st Treatment dosing will occur on Day 1. Subjects will receive IN study drug twice a day (q6h) on Days 1 through 5.
[16] Adverse events will be collected from the time of informed consent through the F/U visit.
[17] Prior and concomitant medication history includes all medications (including over-the-counter medications, vitamins, and supplements) taken from 30 days prior to informed consent signing through the F/U visit.

1. INTRODUCTION AND BACKGROUND

1.1 Interna Therapeutics Ltd. Technology

SARS-CoV-2 remains a Public Health Emergency of International Concern [as determined by the World Health Organization (WHO)] over three and a half years after the first cases of atypical pneumonia were identified in Wuhan, China. An unprecedented global effort to contain the virus has so far failed to consistently prevent its spread. The virus's remarkably high replication rate and highly mutagenic nature have greatly limited the efficacy of nation-scale lockdowns, rapid development, and massive deployment of novel vaccine technologies, as well as the rapid development of novel treatments. As of this writing, and despite 4.62 billion individuals having been fully vaccinated, 2023 has seen over 868,000 new COVID-19 cases and over 3,700 deaths were reported in July 2023 (26 June to 23 July 2023). As of 23 July 2023, over 768 million confirmed cases and over 6.9 million deaths have been reported globally (WHO report 27Jul2023). In addition to vaccines, whose efficacy against the Wuhan strain and corresponding decrease in efficacy against Omicron has been well established, numerous novel antiviral treatments have been developed in record time. Due to the monumental efforts to develop SARS-CoV-2 vaccines and antiviral therapies in response to the COVID-19 pandemic, SARS-CoV-2 is to the view of pas emerging pandemics, such as MERS, SARS and SARS-CoV-2, a possible emergence of novel strains and new pandemic potential. Numerous novel antiviral treatments were developed over the course of the SARS-CoV-2 pandemic. However, the most significant of these, LAGEVRIO (molnupiravir) and PAXLOVID (nirmatrelvir and ritonavir), also suffer from significant limitations, including low efficacy and the potential for significant adverse events. Furthermore, molnupiravir is an isopropylester prodrug of a nucleoside analogue and thus has the potential to cause mutations in both the SARS-CoV-2 virus and the patients using the drug. Nirmatrelvir, based on unpublished studies by Pfizer, has exhibited greater efficacy than molnupiravir. However, nirmatrelvir must be co-administered with ritonavir, which is used to extend the serum half-life of PAXLOVID. Ritonavir, as a potent inhibitor of a human protease, will also interfere with the metabolism of many other drugs, including anticoagulants and immunosuppressive medications used in organ transplant patients and patients being treated for autoimmune diseases. In these patients, who are also vulnerable to SARS-CoV-2 infections, the dosage of these other drugs will need to be modified. In addition, the combined use of nirmatrelvir and ritonavir requires a total dose of 30 pills given over a 5-day period.
The limitations of these therapeutics, the limited long-term efficacy of vaccines in preventing the spread of new variants, and the corresponding magnitude of the ongoing pandemic, all highlight the critical need for the continued development of novel antiviral treatments. New treatment options orthogonal to existing vaccination and treatment approaches, with prophylactic as well as therapeutic capabilities, and which are efficacious against all currently known variants, would doubtless prove as critical tools in the ongoing efforts to mitigate the pandemic.

-Interna Therapeutics Ltd. has developed a unique delivery modality (Molecular Nano Motors (MNMs)) that harnesses the dipole potential present within all cell membranes. The potential is large (10^8-10^9 V/m), and can be leveraged for the delivery of genetic cargo. The Interna Therapeutics Ltd. delivery modality exploits this universal property of phospholipid bilayer membranes for medical applications for the first time.

Two MNMs are attached to a Small interfering RNA (siRNA) through a linkage that is cleaved only upon entry into cells, thereby releasing the siRNA and trapping it in the cytoplasm. Once released, the siRNA can exert its biological effect, while the remnant MNM is metabolized and excreted.

Once inside the cytoplasm, the siRNA guide strand associates with the RISC (RNA-induced silencing complex) machinery to direct targeted mRNA degradation. The siRNA-RISC complex can remain active for many days and even weeks, meaning that this therapeutic approach is targeted, potent and durable.

The sequence of the siRNA can be tailored to target universally conserved viral genes and can be rapidly modified to keep pace with mutagenesis. This same approach can be used to rapidly generate drug candidates for all 23 human respiratory viruses.

1.2 Investigational Therapy (Apo-Si-K170A-C76)

Apo-Si-K170A-C76 is a double-stranded short interfering RNA (dsiRNA), which is specifically designed to target mRNA of the RNA-dependent RNA polymerase (RdRp) gene of SARS-CoV-2. The RdRp protein is crucial for the replication and transcription of SARS-CoV-2, and the *RdRp* gene is the most conserved region in the SARS-CoV-2 viral genome. RdRp plays a crucial role in the viral life cycle and is essential for viral survival; hence, targeting the corresponding mRNA sequence to hinder its translation or induce its enzymatic degradation may be an effective therapeutic strategy.

Therapeutic oligonucleotides have attracted great interest due to their potency and potential for changing the therapeutic landscape of many pathological conditions, including those of viral origin. Targeting conserved SARS-CoV-2 RNA sequences essential for viral replication offers a rational approach to inhibit viral infection, thereby halting disease progression. Bioinformatics analysis of approximately 6,000,000 viral genome sequences showed full coverage of all current variants; therefore, Apo-Si-K170A-C76 is expected to be efficacious for treatment of disease caused by all known mutations and probably emerging variants in the future. The efficacy of several variants has recently been experimentally confirmed.

The method by which siRNA causes the silencing of genes is as follows:

1. The dsiRNA enters the cell and is cleaved by the Dicer enzyme within the cytosol, producing siRNA.
2. The duplex separates, to form the sense and the antisense single-stranded siRNA.
3. The antisense strand of the siRNA interacts with cellular proteins to form an RNA-induced silencing complex (RISC).
4. RISC scans all mRNA in the cytoplasm for complementary sequences.
5. Once mRNA bearing complementary sequence(s) is identified, cleavage of the mRNA is induced, and the gene translation is silenced.

Despite the great promise of siRNA-based therapy and the significant resources that have been committed in efforts to bring such therapies into the clinic, only six siRNA-based drugs have been

approved to date. The primary hurdle on the road to the widespread use of siRNA therapy is the difficulty in efficiently delivering siRNA into the cytoplasm. The obstacle preventing siRNA duplexes from gaining entry into cells is an energetic barrier inherent to all interactions between large, charged molecules, such as nucleic-acids, and the phospholipid bilayer of cell membranes. This energetic barrier is the result of the low dielectric constant of the hydrocarbon interior of all phospholipid bilayers, which prevents the penetration of polar molecules, especially those bearing fixed charges.

Various approaches for delivery have been developed, including transfection, viral-mediated delivery, chemical modifications of the nucleic acid backbone, conjugation to N-Acetylgalactosamine (GalNAc), as well as formulations encapsulating the RNA cargo into lipid nanoparticles (LNP) or DNA nanostructures. However, all these approaches suffer from significant limitations. The most widely applied approach is transfection, which is limited to use *in-vitro*. Viral-mediated delivery is often inefficient, requiring large doses of virus, which result in toxicity. LNPs have been employed to great effect in delivery of mRNA cargo, but they are unstable and thus require ultra-low temperature storage conditions. Additionally, LNP siRNA particles (such as patisiran) require that the patient be premedicated with steroids and antihistamines to prevent unwanted immune response. To date, only GalNAc has a proven clinical track-record, meaning that the applications of siRNA therapy have been mainly limited to the targeting of disease drivers present in the liver. Consequently, realization of the true therapeutic potential of siRNA-mediated gene silencing has awaited the establishment of a siRNA-delivery mechanism capable of safe and efficient delivery into any cell type.

The development of Apo-Si-K170A-C76, a modified oligonucleotide, addresses the challenge of delivery of siRNA therapeutics *via* a novel mechanism of action. The active drug is a construct of a double strand dsiRNA sequence attached to two Molecular Nano-Motors (MNM), one on each 5'-end of the RNA. The two MNMs interact with the strong electric field inherent in all phospholipid bilayer membranes and effect trans-membrane delivery of the "cargo" dsiRNA. In the cytoplasm, the MNMs are detached, leaving the siRNA free to exert its biological function of gene silencing. The MNM delivery platform is universal and can be applied to any oligonucleotide sequence.

Following intracellular delivery, the "cargo" dsiRNA targets the mRNA responsible for the production of RdRp of the SARS-CoV-2 virus, inhibiting viral replication. RdRp is the main enzyme involved in the replication and transcription of viral RNA genomes, including that of SARS-CoV-2, and is highly conserved across viral genomes. The sequence was carefully designed to be specific to viral RdRp, taking attention of exclusion of potentially common bases in the core sequence (Alvarez, 2009). To ensure the specificity of the target sequences, it was verified by Blast homology and tested against *Homo sapiens* and *Mus musculus* mRNA reference sequence. The designated sequences had maximal 16 bases match in the final siRNA with *Homo sapiens* genome. The selected sequence was structurally modified and elongated according to M.A. Behlke publications and IDT design manual to created dicer substrate (25/27 dsiRNA).

1.3 Non-Clinical Studies

The Apo-Si-K170A-C76 Construct has been characterized in terms of establishing the drug substance and drug product specifications, including the acceptance criteria. The efficacy has been

evaluated *in vitro*, using a rapid bioassay for antiviral drug screening in Vero-E6 cells and inhibition of SARS-CoV-2 induced cytopathic effects (CPE), showing a 3 order of magnitude reduction of CPE at 24 hours post-infection. In addition, the efficacy of Apo-Si-K170A-C76 showed a long-lasting inhibition of up to a 3-log reduction in SARS-CoV-2 viral load in the nostrils of non-human primates, African green monkeys.

A series of range-finding and pivotal toxicology studies has been conducted in Sprague-Dawley (SD) rats using intranasal (IN) dosing. The Apo-Si-K170A-C76 Construct was administered in all studies.

The following toxicology studies were conducted:

- A 7-day dose-range toxicology study has been conducted in rats using once-daily IN instillation of Apo-Si-K170A-C76 and a follow-up 7-day toxicology study using twice a day (BID) intranasal instillation was conducted in rats.
- A 14-day GLP BID IN instillation toxicology study in the rat has been recently completed. In all studies, all animals survived and there were no Study Drug-related effects on any parameter, including histopathology.
- We have evaluated the toxicity of the construct in African green monkey, following repeated IN and IT administration. There was no evidence of toxicity following the IN, intratracheal (IT) or inhalation administration of Apo-Si-K170A-C76.
- The target of Apo-Si-K170A-C76 Construct is viral-specific and not found in the mammalian genome. Because of this, and following the procedure adopted for biotechnology-derived products with foreign targets (ICH S6 R1), a single-species is considered to be acceptable.
- The local target tissue, *i.e.*, the nasal cavity's exposure to Apo-Si-K170A-C76 Construct in rats involved the maximum achievable dose based on administering the maximum feasible concentration at the maximum feasible dose volume; therefore, the derived toxicity data, which has confirmed the safety of the compound, represents a worst-case scenario. Also, no local irritation in the nasal cavity and respiratory tract were observed in these studies.
- Pharmacokinetic studies, conducted in mice following a single IN administration, have revealed that limited circulatory exposure is obtained.
- A GLP-compliant respiratory safety pharmacology study was conducted in male SD rats following a BID IN administration. There were no effects on any of the respiratory parameters at any dose. All measurements were comparable to the pre-dose values and/or to the concurrent control.
- AMES study indicated that the Study Drug has no mutagenic activity in the tested bacterial strains (*Salmonella typhimurium* TA98, *Salmonella typhimurium* TA1535, *Salmonella typhimurium* TA1537, and *Escherichia coli* WP2 uvrA).
- hERG and *in vitro* micronucleus tests will also be conducted shortly.

1.4 Rationale for the Use of Apo-Si-K170A-C76 and Study Design

Based on non-clinical studies with Apo-Si-K170A-C76, IN administration of Apo-Si-K170A-C76 is predicted to result in minimal systemic exposure. In the absence of infection with SARS-CoV-2, the pharmacology of Apo-Si-K170A-C76 will also not be engaged. The study is therefore designed to provide a preliminary assessment of safety and systemic exposure of IN administration of Apo-Si-K170A-C76. This will be achieved by an exploration of three dose levels, the first expected to be associated with minimal pharmacology and the highest dose ('target dose') is expected to be pharmacologically active. These dosages will be first administered once. In the second phase of the study (Cohorts 4, 5), subjects will receive a twice-daily (BID) administration of the 2nd and 3rd dosage levels. Finally, for the third phase (Cohorts 6, 7), subjects will receive a twice-daily dosage (2nd and 3rd dosage levels) for 5 consecutive days. This will represent 5 days of treatment with repeated BID dosing at the target dose level and at one-level lower dosage. Given the route of administration and anticipated limited systemic exposure, conduct of this part in a single cohort of volunteers is considered appropriate. The transition between dosing cohorts will be performed following adequate review of safety data before the next dosing cohort. The transition from cohort 5 to cohort 6 will also involve reviewing of systemic exposure results obtained from the previous cohorts 1-5. Cohort size is not based on a formal powered comparison but 6 subjects on active treatment are considered adequate for a preliminary assessment of safety and systemic exposure. Two additional subjects will be randomized to placebo to maintain the blindness of this part of the study.

1.5 Risk Assessment

This is the first Human study with Apo-Si-K170A-C76. Although similar and higher doses of Apo-Si-K170A-C76 have been tested in several animal studies and results support the dose levels to be tested in humans, this will be the first clinical exposure of the drug and thus there may be risks which are unknown at this time.

The potential risks which may be associated with Apo-Si-K170A-C76 are based on theoretical considerations, and findings from non-clinical studies. The 14 days BID toxicology study in rats, safety pharmacology studies in rats, and the African green monkey efficacy studies did not reveal potential signs for safety concern. At the present time, no significant risk has been identified.

However, a safety framework is applied in the proposed study:

The study will be conducted in healthy volunteers. The proposed inclusion/ exclusion criteria have been selected to minimize the risk to participants from any potential risks associated with the investigational product.

Also, a double-blind design is proposed to facilitate objective assessment. Sentinel dosing will be employed in all parts.

Safety review will be performed between each dosing cohort.

The review will be conducted by the Safety Steering Committee (SSC). This will consist of the PI, the Sponsor's Medical Monitor (MM), and chaired by a senior clinician independent of the study team. The SSC will review blinded data (systemic exposure data will not identify specific subjects). If the SSC considers that an unblinded review of data is required to make a decision, then the independent Data Safety Monitoring Committee (DSMC) will be asked to undertake this review and make their recommendation. The chair of the SSC may also refer to the DSMC if unblinding is required.

2. STUDY OBJECTIVES AND ENDPOINTS

The objectives of this study are to assess the safety, tolerability, and systemic exposure of Apo-Si-K170A-C76 in healthy adult subjects.

2.1 Study Objectives

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of single, BID doses, and repeated BID ascending doses of Apo-Si-K170A-C76 administered intranasally (IN) in healthy adult subjects.	• Incidence, nature, and severity of AEs, and SAEs • Use of concomitant medication • Changes from baseline in vital signs, clinical laboratory values, ECG and physical examination • Changes from baseline in TNSS score
Secondary	
• To evaluate the systemic exposure of Apo-Si-K170A-C76 following intranasal administration in healthy adult subjects.	• Characterize the systemic exposure based on concentration in serum. • PK analysis will be considered in case required.

2.2 Safety Endpoints

- Frequency and severity of Adverse Events (AEs), including Serious Adverse Events (SAEs) and Treatment-emergent AEs (TEAEs) occurring at any time during the study.
  - Change from Baseline to End of Study (EOS) in:
    - Laboratory tests including urinalysis and blood tests
    - Vital signs
    - Physical examination
    - TNSS

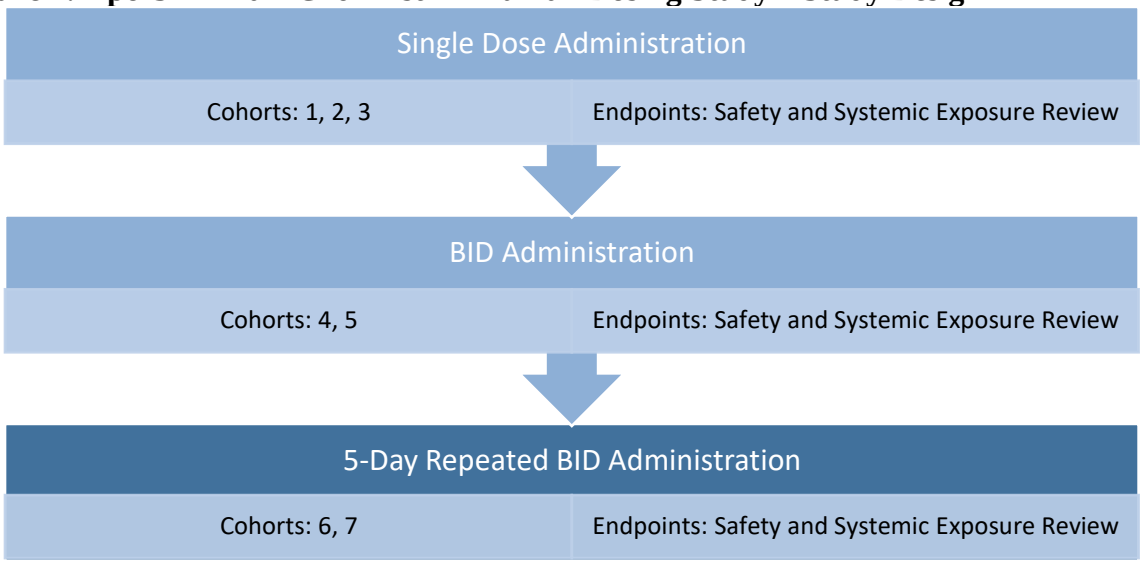
3. OVERALL STUDY DESIGN

This is a first-in-human, phase 1, single-center, randomized, double-blind, placebo-controlled study aimed to evaluate the safety, tolerability, and systemic exposure of Apo-Si-K170A-C76 in healthy adult subjects following intranasal administration of single ascending doses (SAD), twice daily (BID) ascending dosing, and repeated BID ascending doses.

Subjects will participate in 7 dosing cohorts, see also **Figure 1**:

- Cohort 1 will involve an initial administration of a single (low) dose of Apo-Si-K170A-C76 (on Day 1) to both nostrils, 2mg/nostril.
- Cohort 2 will involve a single alternately dose administration of Apo-Si-K170A-C76 at a double dose of the first dose (on Day 1) to both nostrils, 4mg/nostril.
- Cohort 3 will involve a single alternately dose administration of Apo-Si-K170A-C76 at the target dose (x3 of the first dose, on Day 1) to both nostrils, 6mg/nostril.
- Cohort 4 will involve BID administration (on Day 1) of Apo-Si-K170A-C76 at the same dose as cohort 2, separated by6 hours (+15 min) : 4mg/nostril BID to both nostrils.
- Cohort 5 will involve BID administration (on Day 1) of Apo-Si-K170A-C76 at the same dose as cohort 3, separated by 6 hours (+15 min)-: 6mg/nostril BID to both nostrils.
- Cohort 6 will involve administration of repeated doses of Apo-Si-K170A-C76 twice daily (BID on Days 1-5), at the same dose level or lower than that administered in Cohort 4: 4mg/nostril BID to both nostrils, for 5 days.
- Cohort 7 will involve administration of repeated doses of Apo-Si-K170A-C76 twice daily (BID on Days 1-5), at the target dose level or lower than that administered in Cohort 5: 6mg/nostril BID to both nostrils, for 5 days.

Figure 1: Apo-Si-K170A-C76 First-In-Human Dosing Study – Study Design



IN administration is performed to both nostrils of all participants. The nasal spray device contains the Study Drug at 20 mg/mL and delivers 0.1 mL volume per actuation. After each actuation, an inspiration will be performed, and around a 5-second delay will be introduced between each new actuation. The subjects will receive 1-3 actuations per nostril in an alternately manner according to dosing group. Thus, during each administration cohort, dosages registered as dose/nostril are received twice per subject one dose to each nostril. An examination of the nasal cavity will be performed by a study physician at screening, 24 hours (±1hr) after each dose and at the last follow up visit for all subjects in all cohorts.

Subjects will be randomized to receive either placebo or active treatment on each dosing cohort and sentinel dosing will be employed. Staggered dosing will be employed in all cohorts, i.e., 2 sentinels will always be dosed before the remaining 6 subjects.

The initial dose for this study is based on the non-clinical No-Observed-Adverse-Effect Level (NOAEL). The starting dose (Cohort 1) and the proposed subsequent doses are shown in Table 4.

Table 4 Study Dosing Plan

Part 1	**Dose Concentration**	**Number of Subjects**	
		Apo-Si-K170A-C76	**Placebo**
Cohort 1	2mg/nostril, 4mg/both nostrils	6	2
Cohort 2	4mg/nostril, 8mg/both nostrils	6	2
Cohort 3	6mg/nostril, 12mg/both nostrils	6	2
Cohort 4	4mg/nostril, 8 mg/both nostrils BID (16mg/day/both nostrils)	6	2
Cohort 5	6mg/nostril, 12 mg/both nostrils BID (24mg/day/both nostrils)	6	2
Cohort 6	4mg/nostril, 8 mg/both nostrils BID (16mg/day/both nostrils) for 5 days	6	2
Cohort 7	6mg/nostril, 12 mg/both nostrils BID (24mg/day/both nostrils) for 5 days	6	2
Total Subjects		**42**	**14**

All study staff (with the exception of specified unblinded pharmacy staff), each subject, and the Sponsor will remain blinded to study drug allocation. Subjects will be screened and randomized to treatment of active Apo-Si-K170A-C76 or matching placebo, in a 3:1 ratio.

Randomization will be performed as close as possible prior to the 1st administration of study drug (preferably on Day 1) in a staggered manner: initially, two sentinel subjects (one active and one placebo) will be randomized and dosed with blinded treatment prior to the remaining subjects. One sentinel subject will be dosed with active drug (Apo-Si-K170A-C76) and the other with matching placebo. The remaining 6 subjects in the dose cohort will be randomized and dosed if no safety concerns (without clinically significant AEs) are identified in the sentinel subjects; The decision to proceed and dose additional subjects following the first 2 sentinel subjects, according to the randomization schedule, will be at the discretion of the investigator and following his review of all their medical data.

The decision to escalate to the next dose level, to investigate lower, intermediary, or higher doses, will be done by the Safety Steering Committee (SSC) which will review blinded emerging data of subjects of a given cohort including safety and tolerability. A minimum of 7 days post-dose safety data will be reviewed by the SSC to determine the next dose level. **All dose escalation decisions, except for the transitions between cohort 3 to cohort 4 and cohort 5 to cohort 6, will be taken by the SSC.** If the SSC considers that an unblinded review of data is required to make a decision, then the independent DSMC will be asked to undertake this review and make their recommendations. As mentioned above, the transition between cohort 3 to cohort 4 and between cohort 5 to cohort 6 will be reviewed and confirmed by the DSMC. In addition, the transition from cohort 5 to cohort 6 will also involve (in addition to safety data) reviewing of the systemic exposure results obtained from the previous cohorts 1-5.

In all cohorts, subjects will be admitted to the Research Unit (RU) on Day 1 at a time designated by the RU. Randomization in each dose cohort will occur as close as possible prior to the 1st administration of study treatment, preferable on Day 1. Treatment administration will occur on Day 1.

In cohorts 1-5:

Overnight confinement to the clinic between Day 1 and Day 2 is mandatory (i.e., subjects will be discharged from the clinic on Day 2 after all required assessments and procedures have been completed for that day). The PI or designee will confirm that the subject is fit for discharge. Subjects will return to the RU for the follow-up (F/U)/EOS visit on Day 8 (± 2 days).

In Cohorts 6 and 7:

Treatment administration (BID) will occur on Day 1 and continue twice daily up to Day 5. Confinement to the clinic between Day 1 and through the 24 hours post 1st dose of last treatment day, is mandatory; (i.e., subjects will be confined from Day 1 through morning of Day 6 in the research unit) and will be released after all required assessments and procedures have been completed on Day 6. The PI or designee will confirm that the subject is fit for discharge.

Subjects will return to the RU for the follow-up (F/U) / EOS visit on Day 12 (± 2 days).

Subjects in all cohorts will receive treatment after standardized meals. Water will be freely available at all other times. Grapefruit juice and caffeine containing beverages should be avoided until after the 24-hour (± 1 hour) post last dose blood sample.

Study Periods and Visits

The study will consist of three periods: Screening, Treatment and Follow up, with the following visits:

Cohorts 1-5

Screening Up to 21 days prior to dosing:

1. Visit 1 / Screening

Screening will take place only once for each participant.

Treatment Period:

2. Visit 2 / Day 1, admission to the RU and treatment administration single dose (cohorts 1-3) or BID (cohorts 4-5))
3. Visit 3 / Day 2, 24h post dose assessments

Discharge from the RU will occur on Day 2

Follow Up

4. Visit 4 / Day 8 (± 2 days), FU / EOS

Cohorts 6-7

Screening Up to 21 days prior to dosing:

1. Visit 1 / Screening

Treatment Period:

2. Visit 2 / Day 1, admission to the RU and treatment administration (BID)
3. Visit 3 / Day 2, treatment administration (BID)
4. Visit 4 / Day 3, treatment administration (BID)
5. Visit 5 / Day 4, treatment administration (BID)
6. Visit 6 / Day 5, treatment administration (BID)
7. Visit 7 / Day 6, 24h post Day 5 assessments

Discharge from the RU will occur on Day 6.

Follow Up (EOS)

8. Visit 8 / Day 12 (± 2 days), FU / EOS

Investigational Plan

For the complete schedule of assessments to be performed in each visit, please see Table 1, Table 2 and Table 3 for cohorts 1-3, 4-5 and 6-7, respectively.

End of Study

A subject is considered to have completed the study if he has completed all periods of the study including the last visit (F/U), EOS, for the cohort he was assigned to.
The end of the study is defined as the date of the last EOS visit of the last subject in the study.

Drinks, Meals and Other Restrictions

Subjects in all cohorts will receive treatment after standardized meals (breakfast and lunch (lunch in case of BID administration). Water will be freely available at all other times.

Subjects will be required to abstain from alcohol for 48 hours before the start of dosing until after the 24h post last dose blood sampling.

In addition, subjects will be required to abstain from grapefruit juice and caffeine products until after the 24h (±1 hours) post last dose blood sampling.

Physical activity while staying in the RU is prohibited.

Early Discontinuation Visit

If a subject discontinues prematurely from the study for the reasons specified in Section 4.3, the same procedures planned for EOS visit will be conducted. Additional procedures and evaluations will be completed as deemed necessary by the PI. Reasons for withdrawals and discontinuation of any subject from the protocol will be recorded in the eCRF. The DSMC will be systematically involved in every important decision concerning conduct of the study, including discontinuation.

Unscheduled Visit

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the PI. The date and reason for the unscheduled visit will be recorded. AE monitoring and concomitant medication recording will be performed by the PI during the visit. Other procedures and evaluations will be completed as deemed necessary by the PI and may include (but will not be limited to) laboratory tests, vital signs and a physical examination. The date, reason, and procedures conducted during the unscheduled visit will be recorded in the subject's file and the eCRF.

Data Safety Monitoring Committee (DSMC)

The DSMC as described in the DSMC charter, found in the Safety and Medical Monitoring Study Plan, will review unblinded emerging data of subjects in a given cohort including safety and tolerability at the transition between cohort 3 to cohort 4 and between cohort 5 to cohort 6, i.e, the transition between single to BID dosing and from BID to repeated BID dosing. A minimum of 7 days post-dose safety data will be reviewed by the DSMC to determine the next dose level. The DSMC will also review the systemic exposure results of cohorts 1-5 (in addition to safety data) prior to confirming the transition between cohort 5 to cohort 6.

Also, if the SSC considers that an unblinded review of data is required to make a decision, then the independent DSMC will be asked to undertake this review and make their recommendations.

Unblinding will take place if needed, as according to the Blinding and Unblinding section of the Safety and Medical Monitoring Study Plan.

Members of the committee will be established before initiation of study screening. Details for the committee will be outlined in a separate charter in the Safety and Medical Monitoring Study Plan, the governing document that will supersede this section of the protocol.

Safety data to be reviewed by the committee will include details on any clinically significant events experienced on study-related safety parameters, with a table listing an aggregate of AEs reported during the study.

At each decision stage (i.e., dose escalation or at other times), the committee will review safety data, including those from previous cohorts, and together make one of the following recommendations:

- To continue the study as planned.
- To continue the study with modifications.
- To temporarily suspend or terminate the study. If, at any time, the study is terminated, a written statement fully documenting the reasons for study termination will be provided to the IRB/IEC.

4. STUDY POPULATION

This study will be conducted in healthy adult subjects.

4.1 Inclusion Criteria

Subjects may participate in the study if they meet all the following criteria:

1. Male and female participants; must be ≥ 18 years old.
2. Understands the study procedures described in the Informed Consent Form (ICF), be willing and able to comply with the protocol, and provides written consent.
3. Not pregnant or lactating and willing to comply with the contraceptive requirements from enrolment to 3 months post last dose. Contraceptive requirements include the following:
    a. Use a condom with a spermicide to prevent pregnancy in a female partner or to prevent exposure of any partner (male and female) to the study intervention treatment.
    b. Male sterilization with the appropriate post vasectomy documentation of the absence of sperm in the ejaculate (please note that the use of condom with spermicide will still be required to prevent partner exposure). This applies only to males participating in the study.
    c. In addition, female partners and female participants of child-bearing potential, must use another form of contraception such as one of the highly effective methods (pills, Intra Uterine Device (IUD))
    d. True abstinence - sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study 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.
    e. In addition to the contraceptive requirements above, male subjects must agree not to donate sperm for 3 months post last dose.
4. In good health with no history of clinically significant medical conditions (as described in Exclusion criteria) that would interfere with subject safety, as defined by relevant medical history, physical examination and routine laboratory tests, ECG, and determined by the Investigator at an admission evaluation.
5. Subjects will have a documented relevant medical history either prior to entering the study and/or following relevant medical history review with the study physician at screening.

4.2 Exclusion Criteria

Any potential subject who meets any of the criteria below will be excluded from participating in this study:

Clinical History

1. History or evidence of any clinically significant or currently active cardiovascular, (including thromboembolic events), respiratory, dermatological, gastrointestinal, endocrine, hematological, hepatic, immunological, rheumatological, metabolic, urological, renal, neurological, or psychiatric illness. Specifically:
    a. Subjects with any history of physician diagnosed and/or objective test-confirmed asthma, chronic obstructive pulmonary disease, pulmonary hypertension, reactive airway disease, or chronic lung condition of any etiology or who have experienced:
        - Significant/severe wheeze in the past
        - Respiratory symptoms including wheeze which has ever resulted in hospitalization
        - Known bronchial hyper-reactivity to viruses
    b. History of thromboembolic, cardiovascular, or cerebrovascular disease
    c. History or evidence of diabetes mellitus
    d. Any concurrent serious illness including history of malignancy that could interfere with the aims of the study or a subject completing the study. Basal cell carcinoma within 5 years of treatment or with evidence of recurrence is also an exclusion.
    e. Migraine with associated neurological symptoms such as hemiplegia or vision loss. Cluster headache/migraine or prophylactic treatment for migraine.
    f. History or evidence of autoimmune disease or known immunodeficiency of any cause.
    g. Other major disease that, in the opinion of the Investigator, could interfere with a subject completing the study and necessary investigations.
    h. Immunosuppression of any type.
2. Any significant abnormality altering the anatomy or function of the nose or nasopharynx in a substantial way (including loss of or alterations in smell or taste), a clinically significant history of epistaxis (large nosebleeds) within the last 3 months, nasal or sinus surgery within 6 months of screening.
3. Clinically active rhinitis (including hay fever) or history of moderate to severe rhinitis, or history of seasonal allergic rhinitis likely to be active at the time of inclusion into the study and/or requiring regular nasal corticosteroids on at least a weekly basis, within 30 days prior to screening.
4. History of anaphylaxis and/or a history of severe allergic reaction or significant intolerance to any food or drug, as assessed by the PI.
5. History or presence of alcohol addiction, or excessive use of alcohol. The subject has a history of consuming more than 7 units of alcoholic beverages per week for male subjects and more than 5 units for females or has a history of alcoholism or

drug/chemical/substance abuse within the past 2 years prior to screening (Note: one unit = 330 mL of beer, 110 mL of wine or 28 mL of spirits)), or use of drugs of abuse.

6. Psychiatric illness including subjects with a history of depression and/or anxiety with associated severe psychiatric comorbidities, for example psychosis. Specifically, (a) Subjects with history of anxiety-related symptoms of any severity within the last 2 years if the Generalized Anxiety Disorder-7 score is ≥4; (b)Subjects with a history of depression of any severity within the last 2 years if the Patient Health Questionnaire-9 score is ≥4
7. Subjects who have smoked ≥5 pack years at any time [5 pack years is equivalent to one pack of 20 cigarettes a day for 5 years]).
    - Subjects who have smoked <5 pack years - at any time in the 3 months prior to screening, have used tobacco in any form (e.g., smoking or chewing) or other nicotine-containing products in any form (e.g., gum, patch) or electronic cigarettes.

Measurements and investigations

8. A Body Mass Index (BMI) ≤18 Kg/m^2 and ≥28 Kg/m^2. The upper limit of BMI may be increased up to 30 Kg/m^2 at the PI's discretion, in the case of physically fit muscular individual.
9. Venous access is deemed inadequate for the phlebotomy and cannulation demands of the study.
10. At the discretion of the PI any clinically significant abnormal finding on screening biochemistry, hematology, serology microbiology blood tests or urinalysis or

a. Positive HIV, active/chronic hepatitis B or C test.

b. Positive β -HCG or positive alcohol test

11. Confirmed positive test for drugs of abuse and/or urinary cotinine at screening and on admission (Day 1).
12. Twelve-lead ECG recording with clinically relevant abnormalities as judged by the study physician/PI.

Recent respiratory infection

13. Presence of cold-like symptoms and/or fever (defined as subject presenting with a temperature reading of >37.9ºC) at screening or on admission (Day 1).

Receipt of medications and interventions

14. Receipt of blood or blood products, or loss (including blood donations) of 550 mL or more of blood during the 3 months prior to screening.
15. Medications

    a. Use of any medication or product (prescription or over-the-counter), for symptoms of hay fever, nasal congestion or respiratory tract infections or dermatitis/eczema including the use of regular nasal or medium-high potency dermal corticosteroids, antibiotics and First Defence™ (or generic equivalents) within 7 days prior to

screening. The sporadic use of paracetamol or other medications will be acceptable only as agreed by the Principal Investigator.

b. Receipt of any investigational drug within 3 months prior to screening.

c. Receipt of three or more investigational drugs within the previous 12 months prior to screening.

d. Receipt of systemic (intravenous and/or oral) glucocorticoids or systemic antiviral drugs within 6 months prior to screening.

e. Over the counter medications (e.g., paracetamol or ibuprofen) where the dose taken over the preceding 7 days prior to screening had exceeded the maximum permissible 24-hour dose (e.g., >4g per day of paracetamol over the preceding week).

f. Chronically used medications, including any medication known to be a moderate/potent inducer or inhibitor of cytochrome P450 enzymes, within 21 days prior to screening.

g. Subjects who have received any systemic chemotherapy agent, immunoglobulins, or other cytotoxic or immunosuppressive drugs at any time.

Other

16. Subjects who are currently employed by or are first-degree relative of someone employed by the Sponsor or participating clinical trial site, or any Contract Research Organization involved in this study.
17. Any other reason that the PI considered made the subject unsuitable to participate.

4.3 Subject Withdrawal Criteria

Subjects will be withdrawn from the study for the following reasons:

- A subject may withdraw from the study at any time at his own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- Reasons for withdrawing subjects from the study might include, but are not limited to, AEs, withdrawal of consent, administrative decision by the investigator or the Sponsor, protocol deviation, or subject noncompliance.
- At the time of withdrawing from the study, if possible, an EOS visit (FU visit) should be conducted. See Table 1, Table 2 and Table 3 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
- Subjects who withdraw from the study will be permanently discontinued from the study intervention.
- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

4.4 Discontinuation of Study Intervention

In some cases, it may be necessary for a subject to permanently discontinue study treatment. Please also refer to stopping rules described in Section 11.6.

A subject may discontinue study intervention for reasons including but not limited to:

- Adverse event
- Death
- Non-compliance with study intervention
- Physician decision
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by subject

The reason for subject discontinuation from study intervention will be recorded in the eCRF. If a subject discontinues study intervention because of an AE, the investigator must arrange for the subject to have appropriate follow-up care until the AE is resolved or has stabilized. Unresolved AEs will be followed until the last scheduled follow-up visit or until the investigator, and study MM (and/or designee) determine that further follow-up is no longer indicated.

4.5 Lost to Follow Up

A subject will be considered lost to follow-up if he fails to return for the scheduled FU visit and is unable to be contacted by the study site.

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he will be considered to have withdrawn from the study.

4.6 Subject Identification

A unique screening number will be assigned when an individual subject signs an informed consent from. The subject will also be identified with this number and/or randomization number if found eligible to participate in the study and randomized to receive either placebo or active.

4.7 Subject Replacement

Subjects who discontinue from the study after randomization without receiving any treatment will be replaced. Subjects discontinuing the study before the full course of treatment will be replaced by a subject who will be assigned the same treatment/dose as the subject being replaced.
Dose administration will be considered incomplete if subject has not received all the scheduled dosing.
If treatment was not completed due to an AE, subject replacement should be discussed with the relevant Study Committee.
Subjects that were replaced after receiving an incomplete course of treatment will still complete the rest of the study protocol procedures.

5. STUDY PROCEDURES

Subject Informed Consent

Information about the study, including the objectives, procedures, and potential risks versus benefits, will be given to the subject in writing and verbally.

The study personnel will review the Institutional Review Board (IRB) approved ICF with each subject and give the subject an opportunity to have all questions answered before proceeding. The IRB/IEC-approved Informed consent will be signed prior to any study related procedure. A copy of the signed ICF will be given to every subject and the original will be maintained within the subjects' records.

Demographics/Medical History/Prior and Concomitant Medications

A demographic profile (birth date, race, and ethnicity) and complete relevant medical history will be recorded at screening and prior to study procedures. The relevant medical history will include a complete review of all current diseases and past medical conditions. Their respective medical treatments will be recorded as prior and/or concomitant medications. This information will be collected at screening to ensure suitability of the subject per the inclusion and exclusion criteria.

All medications (including prescription and over-the-counter medications, supplements, and vitamins) taken within 30 days prior to signing the ICF and throughout the last F/U visit will be recorded as prior and/or concomitant medications (using their generic name, if known) with the corresponding indication.

Safety Procedures

General note: Where study procedures coincide at the same time point, order of collection is suggested to be: ECGs, vital signs, and blood draws and nasal cavity examination where possible, provided that systemic exposure samples are collected within permitted windows. When ECG and vital signs occur at the same time, the rest time may be shared between the assessments. If the procedures are completed within the window outlined in the tables included in the protocol, variances to the suggested order of procedures are not considered protocol deviations.

Physical Examination

- A Complete physical examination will be performed at screening to ensure suitability per the inclusion and exclusion criteria. Complete physical examination will include general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest (heart, lungs), abdomen, skin, neurological, extremities, back, neck, musculoskeletal, and lymph nodes.

- In cohorts 1-5, brief physical examinations will be performed within 2 hours prior to the first dose of study treatment, on Day 2 and at the F/U visit. In cohort 6-7, the brief examination will be performed within 2 hours prior to the first dose of study drug on Day 1, on Days 5 and 6, and at the F/U visit. The brief, focused physical examination will include chest (heart, lungs), abdomen, skin, neurological, and musculoskeletal examinations.
- Any clinically relevant changes occurring from screening until the last study visit will be recorded on the Adverse Event Sections of the eCRF.

Vital Signs

Vital signs will be measured at each visit (screening, treatment days, 24h post last dose and EOS visits) and will include: blood pressure and heart rate at all time points. Oral temperature and respiratory rate will be measured only prior to dosing and before discharge from the research unit on treatments days

- Cohorts 1-5: on dosing days, vital signs will be obtained within 2 hours prior to and 1, 2, 4 and 8 hours (all ±20 minutes) post first dose on Day 1 and on Day 2 at 24 hours (±1 hour) post 1st dose. In cohorts 4-5, vital signs will also be measured 6 hours post 1st dose (but pre-2nd dose)
- Cohorts 6-7: on dosing days, vital signs will be obtained within 2 hours prior to and 1, 2, 4, 6 (but pre-2nd dose), and 8 hours (all± 20 minutes) after the first dose of treatment on Days 1 to 5, and on Day 6 at 24 hours (± 1 hour) post the Day 5-1st dose of treatment.
- Vital signs should be captured after 5 minutes of rest while the subject is in a supine or seated position.

Vital signs should be checked prior to blood draws when blood draws and vital signs occur at the same time, provided that blood samples for systemic exposure are collected within permitted windows.

If deemed appropriate by the investigator, clinically significant findings in the vital signs will exclude a subject from study participation. Any abnormal finding related to vital signs that the investigator considers to be clinically significant must be recorded as an AE.

In addition, height will be collected only at screening and weight will be collected at screening and upon admission to the RU.

12-Lead ECG

ECG recording will be performed at screening, on treatment days, on Day 2 / Day 6 (depending on the cohort) and at the EOS visit. The ECGs should be captured after 5 minutes of rest in a semi-supine/supine position.

- Cohorts 1-3: A single 12-lead safety ECG will be obtained on Day 1, pre-dose (within 2 hours prior to dosing) and at 1 hour ± 20 minutes and 24 hours (± 1 hour) post dose.

- Cohorts 4-5: A single 12-lead safety ECG will be obtained on Day 1, pre-dose (within 2 hours prior to 1st dosing) and at 1, 6 hours (but pre-2nd dose), 7 hours (1 hour post 2nd dose) (all ± 20 minutes) and 24 hours (± 1 hour) post 1st dose.
- Cohorts 6-7: A single 12-lead safety ECG will be obtained on Day 1, pre-dose (within 2 hours of dosing) and at 1, 6 hours (but pre-2nd dose), 7 hours (1 hour post 2nd dose) (all ± 20 minutes) after the 1st dose of treatment on Day 1. On days 2-5, ECG will be recorded pre-dose (within 2 hours prior to 1st dosing) and 1 hour post 2nd dosing of the same day. On Day 6, ECG will be recorded 24 hours (± 1 hour) post 1st dose of Day 5.

The Investigator will record in eCRF if ECG is normal, abnormal (not clinically significant) or abnormal (clinically significant, with description of findings). In all cases in which an ECG has a potentially clinically significant finding, it will be repeated in triplicate within about 30 minutes and reviewed by the investigator or designee prior to subsequent dosing or study disposition decisions that do not constitute a subject emergency.

Clinically significant findings in the ECG obtained at screening should exclude a subject from study participation (as deemed appropriate by the investigator). Any clinically significant change following enrollment into the study will be reported as an AE.

Safety Clinical Laboratory

Laboratory testing will be performed in AML laboratories.
For the timing and frequency of each laboratory panel, see the schedule of assessments for all cohorts (see Table 1, Table 2 and Table 3 for cohorts 1-3, 4-5 and 6-7, respectively.) In brief, urinalysis and blood samples will be collected at screening and at the F/U visit. For subjects participating in cohorts 6 and 7 - also pre-1st dosing on Day 3.

The following safety parameters will be tested:

SERUM BIOCHEMISTRY	**HAEMATOLOGY**
ALP	Red Blood Cell (RBC) Count
Total bilirubin, Indirect/direct bilirubin	Hemoglobin (HGB)
Calcium	Hematocrit (HCT)
Sodium	Mean Cell Hemoglobin (MCH)
Chloride	Mean Cell Hemoglobin Concentration (MCHC)
Blood urea nitrogen (BUN)	Mean Corpuscular Volume (MCV)
Magnesium	White Blood Cell (WBC) Count and Differential (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils – absolute and %)
Potassium	
Phosphorus	
Glucose	Platelet Count
Total cholesterol	C-reactive protein (CRP)
SGPT/ALT	
SGOT/AST	**URINALYSIS**

GGT Albumin Urea Creatinine (estimated glomerular filtration rate [eGFR] calculated based on standard equation) Creatine kinase Bicarbonate Total protein Uric acid Lactic dehydrogenase (LDH), Triglycerides **COAGULATION TESTS** PT aPTT INR **PREGNANACY TEST** blood testing at screening (central) urine testing on Day 1 (local)	Dipstick, including microscopic and macroscopic analysis: appearance, bilirubin, occult blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen Microscopic examination of the sediment if blood, protein, nitrites or leukocytes esterase are positive on the dipstick **SEROLOGY (at inclusion only)** HBsAg, HCV antibody HIV antibody or antigen SARS-CoV-19 PCR test* **SUBSTANCE ABUSE SCREENING (at inclusion only)** Urine drugs, cotinine** and blood alcohol Drugs including: AMP, Amphetamine BAR, Barbiturates BZD, Benzodiazepines COC, Cocaine MDMA, Methylenedioxy methamphetamine MET, Methamphetamine MOR/OPI, Morphine/Opiate MTD, Methadone TCA, Tricyclic Antidepressants THC, Marijuana
* Will be locally performed using a kit. ** At screening, alcohol and pregnancy will be tested in blood, and drugs and cotinine in urine, all by a central laboratory. On Day 1 prior to dosing, alcohol, drugs cotinine and pregnancy will be tested locally in urine.	

The investigator must review the laboratory report, document this review, and record any clinically significant adverse changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. All laboratory tests with values considered clinically significant during participation in the study or on or before the last follow-up visit (EOS) should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study MM.

TNSS

Total Nasal Symptom Score (TNSS) (Downie 2004) will be completed at each visit. On dosing days, it will be completed prior to and post dosing (applies for all cohorts). The TNSS is a 4-item questionnaire used to rate the symptoms of rhinitis. The total score is the sum of scores for each of nasal congestion, runny nose, nasal itching and sneezing at each time point, based on the degree of quality of life interference rated subjectively on a 4-point Likert scale: (0 = no interference / no symptoms, 1 = mild interference / mild symptoms that are easily tolerated, 2 = moderate interference / symptoms which are bothersome but tolerable, 3 = severe interference / hard to tolerate and interfere with daily activity). TNSS will be tested at screening, within 2 hours prior to the 1st dose of the day, and 1 hour (± 20 minutes) after each dose. Also, TNSS will be recorded 24 hours (± 1 hour) after the 1st dose administered on the previous day (on Day 2 or Day 6 for cohorts 1-5 or cohorts 6-7, respectively) and at the EOS visit.

Adverse Events

AEs will be collected starting from signing the ICF until the end of the study.

Any AEs that occur throughout the study will be recorded. Any new AE that occurs between scheduled visits should be brought to the attention of the Investigator and recorded in the subject's medical file and on the appropriate eCRF page.

Any AEs or clinically significant out of range lab/test results related to study drug administration should be followed until resolution. Unrelated AEs should only be followed until the end of the study.

Concomitant Medications

Relevant information about all concomitant medications (including prescribed, over-the-counter, or dietary supplements) taken prior to (i.e., within 30 days of Screening) and during the study must be recorded in the source documents and eCRF.

Systemic Exposure

Systemic exposure will be determined by analyzing blood serum samples for concentration of Apo-Si-K170A-C76 obtained from subjects who receive Apo-Si-K170A-C76 in each dose Cohort. The actual 24-clock time and date of each sample collection will be recorded. A more detailed description of serum sample preparation will be provided in the laboratory manual. Blood samples for systemic exposure will be analyzed with validated methods.

Blood (serum) for systemic exposure analysis will be collected at the following time-points:

Cohorts 1, 2 and 3:

Blood

- On Day 1, obtain blood for systemic exposure prior to dosing (within 2 hour before), at 30 and 60 minutes (all ± 5 minutes) and 2, 3 and 4 hours (all ± 10 minutes), 6 and 8 hours (all ± 20 minutes) post dose. A 24-hour (± 1 hour) post dose sample will be collected on Day 2.

Cohorts 4 and 5:

Blood

- On Day 1, obtain blood for systemic exposure prior to dosing (within 2 hour before and then at 30 and 60 minutes (all ± 5 minutes), and 2, 3, and 4 hours (all ± 10 minutes), 6 (pre-2nd dose), 6.5, 7, 8, 9, and 10 hours (all ± 20 minutes), after 1st dosing. A 24-hour (± 1 hour) post 1st dosing sample will be collected on Day 2.

Cohorts 6 and 7:

Blood

- On Day 1, obtain blood for systemic exposure prior to dosing (within 2hour before and then at 30 and 60 minutes (all ± 5 minutes), and 2, 3 and 4 hours (all ± 10 minutes), 6 (but pre-2nd dose), 6.5, 7, 8, 9, and 10 hours (all ± 20 minutes), after 1st dosing. A 24-hour (± 1 hour) post 1st dosing sample will be collected on Day 2 (this will be the pre-dose sample of Day 2). On Days 2-5, the same time points as Day 1 will be collected. A 24-hour (± 1 hour) post Day 5-1st dosing sample will be collected on Day 6.

6. INVESTIGATIONAL PRODUCT

6.1 The Investigational Products administered

Table 5 Study Products administered:

ARM Name	**Active**	**Control**
Drug Name	Apo-Si-K170A-C76	Placebo
Dose Formulation	5% glucose, 0.5% benzyl alcohol in RNase free water	5% glucose, 0.5% benzyl alcohol in RNase free water
Unit Dosage Strength(s)	2 mg/100 µL/nostril	100 µL/nostril
Nasal Spray Device	The Nemera SP270+ multi-dose pump system was selected as a nasal spray device. This is a commercially available product (https://www.nemera.net/products/ear-nose-throat/multidose-pumps/sp270-sp370/). Pump: White plastic nasal pump with 100 µL metered delivery Bottle: Amber glass, containing 1.2 mL	
Daily dose Level(s) (both nostrils)	Cohort 1: 4 mg Cohort 2: 8 mg Cohort 3: 12 mg Cohort 4: 16mg, BID dosing Cohort 5: 24mg, BID dosing Cohort 6: 16mg, BID for 5 days Cohort 7: 24mg, BID for 5 days	Not applicable (NA), however, dosing schedule is the same
Route of Administration	Intranasal	Intranasal
Administration instruction	Pharmacy staff will be unblinded to subject treatment assignment (as assigned by the designated randomization system for the study). All other study site staff, including the investigator and subjects, will be blinded to study intervention assignment. Study intervention doses will only be administered by study staff in the clinic setting. No at-home dose administration will be allowed. The study drug (or placebo) will be administered to both nostrils via a ready-to-use nasal spray device, while the subject is seated. After each actuation, an inspiration will be performed, and around a 5-second delay will be introduced between each new actuation. To note: In cases where more than 1 actuation in each nostril is required (Cohorts 2-7), the actuations will be performed in an alternately manner. It is necessary to prime the pump bottle by spraying it into the air four times prior to each new bottle. In case of failure by the fourth prime actuation, up to 2 more actuations are allowed. If by the	

	6th priming actuation no or minimal liquid is delivered the bottle will be discarded and replaced with another bottle. A separate bottle will be used for each dosing, i.e., 2 bottles will be used for each subject in cohorts 4-5 and 10 bottles will be used for each subject in cohorts 6-7. Subjects will remain in bed for at least 2 hours post administration. In cohorts 1-5, subjects will be discharged from the clinic on Day 1 or on Day 2. In cohorts 6-7, subjects will be confined to the research clinic throughout all treatment days and will be discharged on Day 6, after all required assessments and procedures for that day have been completed including assessment of safety laboratory values. In all cases, the PI or designee should confirm that the subject is fit for discharge.
Sourcing	Study intervention will be provided to the site centrally by the Sponsor or designated representative.
Manufacturing	Intertek Inc., UK.
Packaging and Labeling	Ready-to-use nasal application devices will be packed, 60 per box, with appropriate label. Each bottle will be labeled with the following text: Protocol: Sir-001 One bottle of Apo-Si-K170A-C76 20mg/ml or placebo; 1.2 ml Intranasal spray Batch number: XXXXXX Expiry date: December 2024 Subject No.: _____ Kit no. XXX Sponsor: / Interna Therapeutics Ltd. (former Sirvir Ltd. /ApoSense Ltd.) 5 Odem St., P.O. Box 7119, Petach Tikva 4917002, Israel Tel: 972-73-2397600
Storage Condition	Ready-to-use nasal spray bottles and devices will be stored at 2-8°C. About half an hour before use, they will be put at room temperature for temperature equilibration.

6.2 Dispense and Return of the Investigational Product

The study pharmacist will acknowledge receipt of all shipments of Apo-Si-K170A-C76 to the site. The investigator or pharmacist should keep all the records relating to how much of the Investigational Product (IP) was used by each subject. The study monitors must periodically check the supplied Apo-Si-K170A-C76 to ensure expiration date and sufficient amount of the IP.

Apo-Si-K170A-C76 must be kept in a secured area with access limited to designated study personnel. Only personnel under the supervision of either the Investigator or the local pharmacist are authorized to handle Apo-Si-K170A-C76.

The Investigator (or designee) must return all used and unused IP or discard it, according to site regulations, and the Sponsor's and/or delegate's instructions. A copy of the clinical supplies return or destruction documentation will be forwarded to the Sponsor (or designee). Drug/placebo accountability records, clinical drug/placebo supply receipts, and returns must be maintained by the Investigator (or designee).

6.3 Accountability of the Investigational Product

Apo-Si-K170A-C76 accountability records must be maintained by the clinical investigation site at all times. All used and unused Apo-Si-K170A-C76 will be assessed for accountability by the study monitor.

The subject number, date, kit number as well as the correct randomization allocation and quantity of Apo-Si-K170A-C76 used for each subject will be checked for correctness and recorded on the appropriate accountability forms. At the end of the study, a copy of all the clinical supply and the corresponding accountability forms will be accounted for reconciliation and destruction. The original records will be kept at the clinical investigation site.

6.4 Measures to Minimize Bias: Randomization and Blinding

Subjects who complete the screening visit and meet all the inclusion and none of the exclusion criteria will be randomized to receive either placebo or active on Day 1 prior to the first administration of treatment (8 subjects per cohort; within each cohort, randomization ratio - 6 Apo-Si-K170A-C76: 2 placebo). One of the first two subjects (sentinel subjects) enrolled in each cohort will be randomized to receive Apo-Si-K170A-C76 and the second will receive placebo.

Randomization assignments will be provided by electronic data capture (EDC) to the study site pharmacist(s) who will access the EDC. Following randomization, study intervention will be dispensed in a double-blind manner. The Sponsor and all clinical unit personnel except the Pharmacist, designated pharmacy staff and unblinded study personnel (if employed), will be blinded to the treatment group for each subject. Subjects will also be blinded to the treatment they receive.

In the event of a medical emergency, the investigator will be able to receive the treatment assignment, if required to provide optimal care of the subject. The Sponsor or designee should be contacted prior to breaking the blind unless the subject is in immediate risk. Any occurrence of unblinding should be reported to the Sponsor and documented. In the case of unblinding, disclosure of the cohort/dose should be limited to only those site personnel required to know treatment assignment for the care of the subject.

6.5 Disallowed Medication

Medications specifically prohibited in the exclusion criteria (see Exclusion criterion #15) are not allowed during the ongoing study up to EOS.

The study PI (and/or designee) should be contacted if there are any questions regarding concomitant medications.

7. SAFETY AND PHARMACOVIGILANCE

7.1 Adverse Event

Definition
An Adverse Event (AE) is defined as any untoward medical occurrence in a subject administered a medicinal product whether or not considered related to the investigational medicinal product. An AE can therefore be any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this IP.

Events meeting the AE definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

In this study, any event occurring after the subject has signed the study informed consent and until the end of the Follow-up visit (up to the EOS) will be collected (or until AE is resolved or no further follow-up is required). From consent to dosing, only collect AEs related to study procedures).

The reporting of abnormal laboratory values should be avoided unless considered clinically significant by the investigator.

AEs occurring during the study, whether or not attributable to the study treatment, observed by the Investigator or reported by the subject spontaneously, or in response to a direct question, will be recorded in the subject's source documents and eCRF as long as they occurred after signing the ICF and until last F/U visit.

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as AE(s).

Suspected adverse reaction is "any adverse event for which there is a reasonable possibility that the drug caused the adverse event." AEs that are related or possibly related would be suspected adverse reactions; AEs that are not related or unlikely related would not be suspected adverse reactions.

The Investigator will document, according to his/her opinion, the AE term of each event, start and end date, whether the event is serious, severity grade, action taken in response to the event, outcome and relationship to the IP.

AE severity will be recorded and graded by the investigator in accordance with the NCI CTCAE v5.0. For AEs that are not adequately addressed in the NCI CTCAE, the investigator should classify the intensity of the AE using the following guidelines:

Description
Grade 1: Mild: Aware of sign or symptom, but easily tolerated; no intervention needed.
Grade 2: Moderate: Discomfort enough to cause interference with usual activity, minimal non-invasive intervention indicated (e.g., short course of antibiotics)
Grade 3: Severe: Medically significant but not immediately life-threatening; incapacitation with inability to work or do usual activity
Grade 4: Life-threatening: Refers to an event in which the subject was at risk of death at the time of the event, as judged by the investigator; urgent/emergent intervention indicated. This category should not be used for an event that hypothetically might have caused death if it were more severe.
Grade 5: Fatal outcome

Relationship to the IP (Assessment of causality) will be classified as follows:

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

- **Related** – There is a plausible temporal relationship between the onset of the AE and administration of study intervention, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to study intervention; and/or the AE abates or resolves upon discontinuation of study intervention or dose reduction and, if applicable, reappears upon re-challenge.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he has reviewed the AE/SAE and has provided an assessment of causality.

Adverse Events outcome will be classified as follows:

- Recovered: The subject has fully recovered from the AE with no residual effects observable
- Recovered with Sequelae: The subject has recovered from the AE with residual effects observable
- Recovering: The subject status improved but has not been fully recovered
- Not Recovered (ongoing): The subject status has not recovered from the AE
- Fatal: Termination of life as a result of the AE
- Unknown: Not known, not observed, not recorded, lost for follow-up or refused

All entries must be clearly documented in the source documents and the source documentation should be signed and dated by a physician Investigator. AEs documented in the eCRF without a stop date should be reviewed at subsequent visits. Documentation on AEs should be updated as necessary. In case of worsening of an AE (i.e. AE grade increase) the event should be captured with the maximal severity observed providing that the AE is ongoing while the AE grade increased.

7.2 Serious Adverse Event

An SAE is defined as an AE that results in any of the following:

- Death
- Life-threatening (at the time of the event)
- Requires inpatient hospitalization or prolongs existing inpatient hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- An important medical event that requires medical intervention to prevent any of the above outcomes

Important medical events are those that may not be immediately life-threatening, but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.
Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of AE, or that they occurred as a consequence of the event. It does not refer to pre-planned elective hospital admission for treatment of a pre-existing condition that has not significantly worsened, or to diagnostic procedure.
The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
Any SAE occurring after the subject has signed the ICF and up to the EOS should be reported (Or until SAE is resolved or no further follow-up is required).

7.3 Unexpected Adverse Event

An unexpected adverse drug experience (event) is any adverse event, the specificity or severity of which is not consistent with information in the current Investigator’s brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product.

7.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a serious adverse reaction assessed as unexpected by the Sponsor and that is judged by either the reporting investigator or the Sponsor to have a reasonable causal relationship to a medical product. AEs that are not related or unlikely related would not be suspected adverse reactions.

Since this is a first-in-human clinical trial with Apo-Si-K170A-C76 and the efficacy and safety of the IP has not been yet established - in this clinical study all serious adverse reactions will be considered unexpected for the purpose of safety reporting.

7.5 Serious Adverse Events/SUSAR Reporting

Each SAE must be reported by the Investigator to the pharmacovigilance group within 24 hours of its occurrence, even if it is not considered to be treatment-related.
Follow-up information about a previously-reported SAE must also be reported within 24 hours of the Investigator receiving it.

The primary mechanism for reporting an SAE to the Sponsor will be a paper SAE report form and the corresponding event will be recorded in EDC.

All SAE forms should be sent to the Chief Medical Officer (CMO) and/or appropriate contacts mentioned in the Safety and Medical Monitoring Study Plan:
CMO: Prof. Gary K. Schoolnik
Email: gks007@stanford.edu

Any fatal or life-threatening event should be reported immediately to the pharmacovigilance representative. These preliminary reports will be followed within 24 hours by detailed descriptions that include a completed SAE form, copies of hospital case reports, autopsy reports and other documents, when requested and applicable.
The Investigator must complete the SAE Report Form, assess the relationship to study treatment and submit it via fax or email within 24 hours to the pharmacovigilance group listed above.
Follow-up information is to be submitted on a new SAE form. The new form should clearly state that it is a follow-up to the previously-reported SAE and give the date of the original report. The follow-up SAE report should describe whether the event has resolved or continues, if and how it was treated and whether the subject continued or discontinued study participation.

The following information should be provided in the SAE form to accurately and completely record the event:

1. Investigator name and site address
2. Subject study identification number
3. Subject demographics (gender, year of birth or age, weight, height)
4. Clinical Event:
    - Description
    - Date and time of onset, stop date, or duration
    - Severity
    - Treatment (including hospitalization)
    - Relationship to the IP (causality)
    - Action(s) taken regarding the IP
    - Information on recovery and any sequelae
    - If the SAE resulted in death, cause of death (whether or not the death was related to the IP) and Autopsy findings (if available)
    - Medical History case report form (copy)
    - Concomitant Medication case report form (copy)
    - Any relevant reports (laboratory, discharge, etc.)

Accompanying documentation, such as copies of hospital case reports, autopsy reports and other documents when applicable, should be summarized on the SAE form and a copy of the source document may be sent if required. The subject's personal details will be removed and replaced with study identifiers i.e. study number and initials, if applicable.

The Sponsor and/or delegate will notify the appropriate regulatory agencies and participating Investigator Expedited Safety Reports that occur during the trial within the time frames required by each regulatory agency.

In addition, all AEs / SAEs / SUSARs will be reported to the local ethics committee (EC / IRB) and regulatory authorities as required by local regulations and International Conference on Harmonization (ICH)-GCP guidelines.

Documentation of the submissions to IRBs / IECs and health authorities (as applicable) must be retained in the appropriate trial file(s). As instructed by the Sponsor, Safety Reports/Expedited Safety Reports should be retained in the appropriate Investigator site trial files, or with the IB.

7.6 SAE & AEs Requiring Discontinuation of Investigational Product

Any SAE, which occurs after a subject has signed the ICF, whether or not related to study product, must be reported to the Sponsor or its designee immediately (within 24 hours) via telephone, email or facsimile. If initially reported via telephone, this must be followed-up by email or a facsimile of the written SAE report within 24 hours of the call to the sponsor or its designee.

Non-serious events that require discontinuation of IP (including laboratory abnormalities) should be reported to the Sponsor or its designee immediately and within 24 hours.

Subjects who discontinue study participation due to experiencing IP related AE(s) should be followed-up clinically until the adverse event has resolved, becomes clinically insignificant, is stabilizes, or the subject is lost to follow-up.

A subject who experiences an SAE related to IP will be discontinued from the study. Regardless of the duration of the study participation, subject who exhibit an SAE, will be followed up by the Investigator until the SAE has resolved, becomes clinically insignificant, is stabilizes, the subject is lost to follow-up or is considered to be chronic (stabilized for at least 30 days) based on the Investigator’s medical judgment. For safety reporting instructions see SAE and Pregnancy Form Report Instructions.

7.7 Pregnancy

Female subjects who become pregnant or **male subjects with partners who become pregnant**

- The investigator will attempt to collect pregnancy information on any female or male subject's female partner who becomes pregnant while participating in this study. With regard to male subjects with partners who become pregnancy - this applies only to male subjects who receive study intervention.
- The investigator will record pregnancy information on the appropriate Pregnancy Form and submit it to the Sponsor within 24 hours of being notified of the pregnancy (for female partners - after obtaining the necessary signed informed consent from the pregnant female partner directly).
- The female will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be reported to the Sponsor or its designee within 24 hours of being notified of the outcome.

7.8 Adverse Events Follow up

Subjects who have had an AE during the treatment period must be followed up clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained. In exceptional cases, it may be defined as "ongoing without further follow-up" by the Investigator and Sponsor's decision.

SAEs that are identified on the End of Treatment visit (or the Early Termination visit) or End of Study visit, must be recorded on the AE eCRF page and reported to the Sponsor or its designee according to the procedures outlined above. Subjects with unresolved previously reported SAE(s), or any new SAE(s) identified on the End of Study visit, should be followed-up until the event has resolved, becomes clinically insignificant, is stabilized, or the Subject is lost to follow-up, based on the Investigator's medical judgment. Resolution means the subject has returned to the baseline state of health, or all parameters have stabilized, and the PI does not expect any further improvement or worsening of the SAE. The PI should continue to report any significant follow-up information to the Sponsor or its designee up to the point that the event has resolved. Any SAE or AE reported by the subject to the Investigator or study personnel that occurs within 30 days after the last subject's last IP dose and is determined by the PI to be reasonably associated with the use of the IP, should be reported to the Sponsor. In case of an SAE, the SAE should be reported within 24 hours of when the Investigator or the site personnel first learns of the occurrence of the event.

7.9 Emergency Unblinding

In the event of a medical emergency, when knowledge of treatment assignment is needed for immediate medical management of the subject's health, investigators can obtain unblinded treatment assignment through the EDC system at any time, according to the Blinding and Unblinding section of the Safety and Medical Monitoring Study Plan. Thorough documentation of the rationale for unblinding is required. Consultation of the study MM is recommended for all unblinding requests.

8. STATISTICAL METHODOLOGY

Sample size considerations

This is a Phase 1 safety study designed to evaluate the safety, tolerability, and systemic exposure of Apo-Si-K170A-C76. The sample size is not based on power calculations. It is chosen based on clinical experience and typical SAD and repeated dose designs and considered to be adequate to fulfill the objectives of the study.

General

Tabulation of descriptive statistics, calculation of inferential statistics (if relevant), and graphical representations (if relevant) will be performed using SAS® version 9.4 or higher for Windows.
All demography, baseline characteristics and safety analyses will be performed on the Safety Analysis Set.
All measured variables will be listed individually.
All measured variables and derived variables will be tabulated by dose cohort and overall (for all treatment arms, not including placebo) for the following descriptive statistics:

- Continuous variables will be summarized by the number of observations (n), mean, standard deviation, median, minimum, and maximum and 95% CI for means of variables if appropriate, by dose group (cohort) and treatment arm.
- Categorical variables will be summarized by frequency counts and percentages [n (%)] for each category. Unless otherwise stated, percentages will be calculated out of the number of subjects in the relevant Analysis Set (Safety Analysis Set), by dose group (Cohort) and treatment arm.

No data imputation will be performed.

Safety Analysis

Adverse Events

An overall summary of the number and percentage of subjects in each of the categories listed below will be presented by dose group and treatment arm and for the pooled dose groups.

- All Treatment Emergent AE (TEAE)
- Serious TEAEs
- Study intervention related TEAEs
- TEAEs with NCI CTCAE ≥ Grade 3
- Study intervention related serious TEAEs
- Study intervention related TEAEs with NCI CTCAE ≥ Grade 3
- TEAEs leading to discontinuation
- TEAEs leasing to death

For each of the above categories data will be further summarized by MedDRA system organ class and preferred term.

All AEs will be listed in subject listing.
If there is insufficient data to create a meaningful summary (e.g. for SAEs, AEs leading to death), data will be listed only.

Vital Signs

All data recorded in the eCRF will be listed. Vital signs data and relative changes from baseline will be summarized descriptively by time point and by dose cohort and overall.

Clinical Laboratory Values

All laboratory data recorded provided from the central lab will be listed. Out-of-reference range values will be flagged as high (H) or low (L) in the listings. Laboratory assessments will be categorized as high/normal/low and whether clinically significant or not by visit and by dose cohort and overall. Relative changes from baseline will be calculated and summarized.

Electrocardiogram (ECG)

Abnormalities identified from ECG data recorded in the eCRF will be listed. ECG will be categorised as normal/abnormal and whether clinically significant or not by visit and by dose cohort and overall.

Physical Examination

Abnormalities identified from physical examination will be listed. Physical Examination will be categorized as normal/abnormal and whether clinically significant or not by body system, by visit and by dose cohort and overall.

Concomitant medications

Prior medications recorded at screening will be listed separately from concomitant medications given post-treatment.A summary of the number of subjects receiving concomitant medications given at any time post treatment will be produced by WHO generic name (ATC level 5).

Other Safety Endpoints

TNSS score

The scores for nasal congestion, rhinorrhea, nasal itching, and sneezing are summed to obtain the Total Nasal Symptom Score for a subject at a specific time point.
All data recorded in the eCRF will be listed. TNSS scores data and relative changes from baseline will be summarized descriptively by time point and by dose cohort and overall.

Systemic Exposure Analysis

The systemic exposure will be based on the serum concentrations of Apo-Si-K170A-C76 measured in serum at specific time points. A PK analysis will be considered if required. In case required, the following PK parameters will be calculated :

- Cmax - Maximum concentration achieved.
- Tmax - Time to reach maximum concentration (hours).
- AUClast – The area under the concentration vs. time curve, calculated as sum of AUCs using linear trapezoidal summation from time 0 to the last measurable data point.
- AUCpartial – The area under the concentration vs. time curve, calculated as sum of AUCs using linear trapezoidal summation from time 0 to the maximal measurement (Tmax).
- λz (Lambdaz)- Individual estimate of the terminal elimination rate constant, was calculated using log-linear regression of the terminal portions of the plasma concentration-versus-time curves.
- AUCinf - The area under the plasma concentration-time curve extrapolated to infinity, calculated as:

  AUCinf was calculated as AUClast + Clast/λz, where Clast is the last measurable concentration.
- T1/2 - Apparent terminal elimination half-life time (hours), defined as 0.693/λz.

Individual serum concentrations (or PK parameters if required) will be listed by dose group and summarized in tables presenting sample size (N), mean, Standard deviation, Standard Error, Median, minimum and maximum values, Coefficient of variation (CV%) and 95% CI (Confidence Interval) for means of variables by treatment.
Graphical displays will be generated presenting mean concentration by treatment as well as individual graphs per subject.
Samples with plasma concentrations below the LLOQ at early time-points will be set to as zero.

9. ETHICS

9.1 Institutional Review Board or Ethics Committee (IRB/EC)

Prior to initiation of the study, the Investigator will submit the study protocol, sample ICF and any other documents that may be requested to the Institutional Review Board (IRB) or Ethics Committee (EC) for review and approval. The Investigator will request that the IRB/EC provide written approval of the study and will keep on file records of approval of all documents pertaining to this study. The Investigator will not begin the study until the protocol and ICF have been approved by the IRB/EC. The Investigator must agree to make any required progress reports to the IRB, as well as reports of SAEs, life-threatening conditions, or death.

9.2 Ethical Conduct of the Study

All clinical work conducted under this protocol is subject to GCP guidelines. This includes an inspection by Sponsor or its designee, health authority or IRB/IEC representatives at any time. The Investigator must agree to the inspection of study-related records by health authority representatives and/or Sponsor or its designee.

The study will be conducted in accordance with Sponsor's and delegate standards operating procedures and the following guidelines:

- ICH-GCP
- Declaration of Helsinki
- Local Israeli laws, regulations and guidelines for conducting clinical trials

9.3 Protocol Revisions and/or Deviations

Changes to the protocol may be made only by the Sponsor (with or without consultation with the Investigator). All protocol modifications must be submitted to the IRB/IEC in accordance with local requirements and, if required, to Regulatory Agencies, either as an amendment or a notification. Approval for amendments must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the changes involve only logistical or administrative aspects of the trial. No approval will be required for notifications.

9.4 Subject Information and Consent

Prior to screening for the study each subject will be informed in detail about the study drug to be administered and the nature of the clinical investigation with its risks and discomforts to be expected. The basic elements of informed consent as specified by the FDA (21 CFR 50.25) and ICH-GCP will be followed. Written consent will be obtained from each subject to be involved in the clinical trial by using the IRB/IEC-approved ICF/ Patient Information Sheet (PIS) prior to the conduct of any study-related activity. Each subject will be given a copy of the signed ICF/PIS. The subjects will also be instructed that they are free to withdraw their consent and discontinue their participation in the study at any time without prejudice. Each subject's chart will include the original signed ICF/PIS for study participation. The ICF/PIS will be kept in the Investigator's central study file for the required period of time. Regulatory authorities may check the existence of the signed ICF/PIS in this central study folder if not having done so during the study. If the ICF/PIS is modified during the study, in a way that can affect the subject judgment to participate, all subjects still ongoing will be re-consented and the original re-consent forms will be included in the subject's chart.

9.5 Subject Insurance

The Sponsor has an insurance policy for the total duration of the study and for at least 30 days after the end of the study covering the subjects and Investigators in respect of the risks involved in conducting this study according to this protocol. The insurance policy will be filed in the Investigator's file or can be made available to the Investigator and to the IRB/IEC upon request.

9.6 Personal Data Protection

The Sponsor complies with the principle of subject's right to protection against invasion of privacy. Throughout this trial, all data will be identified only by the subject's identification number. The data will be blinded in all data analyses. The subject must be informed and written consent is required that authorized personnel of the Sponsor and/or designee (Study Monitor, Auditor, CRO, Sponsor's Strategic Partner, etc.) and relevant health regulatory agency may have direct access to personal medical data to assure a high-quality standard of the study, and/or to obtain regulatory approvals. The data will be de-identified where appropriate and consistent with study needs. If results of this study are published, only numbers or symbols will be used to identify the subjects.

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Audits and Inspections

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor Quality Assurance or its designees or to regulatory authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents. These audits or inspections may take place at any time, during or after the study and are based on the national regulations, as well as ICH guidelines.

10.2 Study Monitoring

Monitoring of the study is the responsibility of the Sponsor and may be delegated to a CRO or a contract monitor. The study monitor will advise the Investigator regarding the practical conduct of the study and maintaining compliance with the protocol, GCP and all applicable regulatory requirements. Throughout the course of the study, the study monitor will oversee the conduct and the progress of the study by frequent contacts with the Investigator. This will include telephone calls and on-site visits. During the on-site visits, the CRF will be reviewed for completeness with corresponding source documents. As part of the data audit, source documents must be made available for review by the study monitor. The study monitor will also perform drug accountability checks and may periodically request review of the Investigator's study file to ensure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period. The Investigator or appointed delegate will receive the study monitor during these on-site visits; cooperate in providing the documents for inspection and respond to inquiries.

10.3 Source Documents

The Investigator will permit study-related monitoring, audits by or on behalf of the Sponsor, IRB/IEC review and regulatory inspections providing direct access to source data documents whether they are in paper or electronic form. Source documents are original records in which raw data is first recorded. These may be office/clinic/hospital records, charts, diaries, x-rays and laboratory results, printouts, pharmacy records, care records, completed scales for each study participant. Source documents should be kept in a secure and limited access area. All source documents must be accurate, clear, unambiguous, permanent and capable of being audited. The subject study file should contain all relevant historic and contemporary records in a permanent form of recording (ink, typing, printing, optical disc etc.). They should not be obscured by correcting fluid or have temporary attachments (such as removable self-stick notes). Source documents that are computer generated and stored electronically must be printed, signed and dated by the Investigator.

Source data for subjects registered to the study should indicate date informed consent was signed, participation in clinical protocol number and title, treatment number, evidence that inclusion/exclusion criteria have been met.

10.4 Electronic Case Report Form (eCRF)

eCRFs will be used to capture data for all subjects and must be completed for all subjects who have signed an ICF. The eCRFs will be monitored against source documents.

The eCRF must be reviewed and electronically signed and dated by the Investigator. Access to the eCRF will be password protected and limited to authorized personnel only. Data should be entered into the eCRFs by the treating personnel or the study coordinator. The eCRF must be completed as soon as possible after any subject assessment or communication, but not longer than 5 business days afterwards. If data is to be changed due to erroneous input or any other reason, an electronic audit trail will track these changes.

10.5 Quality Laboratory Standards

Laboratory tests or evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the SOPs of the lab.

10.6 Data Management

An eCRF will be used for the current study to capture the data according to the protocol and sponsor requirements and a data management plan will be prepared by -Interna Therapeutics Ltd. and/or its designated representative.

Data will be transcribed directly from the clinic source documents into the eCRF system.

AEs will be coded using the MedDRA (latest version available). Prior and concomitant medications will be coded according to the public WHO Drug Dictionary.

The Investigator is responsible for the final review, approval and sign-off of all the eCRFs for the study.

Database lock will be conducted after all data reviews have been completed, all queries have been resolved and appropriate approvals have been obtained.

Data management processes will be described in detail in the Data Management Plan.

11. STUDY ADMINISTRATION

11.1 Participating Centers

This is a single-center study in Israel. The participating center is Hadassah Clinical Research Center (HCRC), Israel.

11.2 Required Documents Prior to Study Initiation

Prior to the start of this study, all pre-investigational requirements must be met by the Investigator and study site. These may include:

1) Appropriate local health authority documentation, properly signed and dated by the required Investigators (i.e., the submission package)

2) Signed copy (original) of the approved protocol

3) Completed and signed statement of the Investigator

4) A signed Clinical Trial Agreement

5) Curriculum vitae for the Investigator and sub-Investigators

6) IRB/EC name and address and membership lists

7) Letter of approval from the IRB/EC / MOH / Director of Hospital (DOH) for study documentation (protocol, ICF, IB and all subject facing documents)

Upon satisfactory receipt of all required regulatory documents, I Interna Therapeutics Ltd. will arrange that the IP be delivered to the study site. Supply of all other study materials will be the responsibility of Interna Therapeutics Ltd. and/or its designee. Subject recruitment should not begin until after the required regulatory documents are confirmed as received. All personnel expected to be involved in the conduct of the study will undergo orientation to include review of study protocol, instructions for eCRF completion, AE reporting and overall responsibilities including those for the IP accountability and study file maintenance.

An Investigator's study file will be in place and should be used for all trial-related documents. The Investigator will be responsible for keeping the Investigator's file updated and ensuring that all required documents are filed. The file will be inspected periodically during monitoring visits.

11.3 Clinical Trial Supplies

The Sponsor and/or designated representative will be responsible for supplying clinical trial supplies. The Investigator will be responsible for inventory and accountability of all clinical trial supplies at his/her site, exercising accepted medical and pharmaceutical practices. An accurate and timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory record must be made available for inspection upon request. Upon completion or termination of the study the Investigator will keep a copy of the inventory record, destruction record (if relevant) and a record of the clinical supplies returned. Study drugs are to be used only as directed by this protocol.

Clinical trial supplies include, however, are not limited to study drugs.

11.4 Investigator's Site File

The investigator's site file will be provided by the Sponsor and/or delegate up to the initiation visit. All documents required for the conduct of the study as specified in the ICH-GCP guidelines will be maintained by the Investigator in an orderly manner in the investigator's site file and made available for monitoring and/or auditing by the Sponsor and/or delegate and regulatory agencies.

11.5 Study Completion

The end of the study is defined as the date of the last EOS visit of the last subject in the study.

Data and materials that are required for the study to be considered complete and/or terminated are:

• Laboratory findings, clinical data and all special test results from screening through to the end of the follow-up period

• eCRF properly completed by appropriate study personnel and signed by the Investigator

• Completed Drug Accountability Records

• Statement of outcome for each serious adverse event reported to the sponsor and/or delegate and IRB/IEC

• Copies of protocol amendments and IRB/IEC as well as relevant health authority approval/notification (if applicable)

All collected data whether it is in paper or electronic form must be reviewed, signed and dated by the investigator or appropriate designee before study completion.

11.6 Study Termination and Stopping Rules

The RU reserves the right to terminate the study or to terminate an individual subjects' participation in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

The SMG and DSMC will monitor safety throughout the study. The SMG and DSMC will meet periodically to review available safety data to make decisions regarding continuation, modification, suspension, or termination of the study.

Dose escalation or administration of study intervention in a dose cohort may be stopped and additional subjects will not receive study intervention until a consultation has taken place among the SMG and DSMC members, investigator, and the Study Medical Monitor (or designee), if one of the following circumstances occurs in subjects treated with study intervention, unless it is determined by the SMG/DSMC in consultation with the study investigator/medical monitor that the occurrence is not related to the administration of the study intervention:

- Two or more subjects in a cohort experience a common terminology criteria for adverse events (CTCAE) Grade 3 or higher clinical or laboratory abnormality that is considered to be related to study intervention by the investigator.
- An AE or group of AEs that singularly or in aggregate suggests to the investigator or Sponsor that the study intervention is poorly tolerated and further treatment per protocol may not be safe.
- If one or more subject(s) in a cohort experience any treatment-related, treatment-emergent SAEs, dose escalation will be stopped to re-evaluate the dose in question.

If any of these criteria occur, the SMG/DSMC will review all available data; if an event is determined to be related to a specific dose level, doses in subsequent cohorts may be either modified, the current dose level can be expanded, or dose escalation may be terminated. Prior to any required dose level adjustment, the clinical and laboratory safety parameters from the previous dosing cohort(s) will be reviewed and discussed by the SMG/DSMC to allow a recommendation on advancing to the next dose level. The suggested next doses may be the protocol-defined escalation dose, an equivalent dose, an intermediate dose, or an adjusted-downward dose based on evaluation of safety and tolerability data from previous cohorts.

The Sponsor, investigator and the institutional review board (IRB) / independent ethics committee (IEC) reserve the right to terminate or suspend the study at any time; however, this should be discussed between the relevant parties beforehand and the reason for such decision recorded. Should this occur, all data available will also be recorded in eCRFs. The investigator should notify the IRB/IEC in writing of the study's completion or early termination.

11.7 Final Report

A final study report will be generated at the completion of data analysis. This report will be a clinical and statistical integrated report, according to ICH E3 guidelines.

11.8 Retention of Study Records

The Investigator will retain copies of the approved protocol, completed CRF, ICFs, relevant source documents, and all other supporting documentation related to the project for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by Interna Therapeutics Ltd. or designee, whichever is longer, in a secure and safe facility with limited access.

If the Investigator is unable to retain the study documents for the required amount of time, Sponsor or designee must be informed of the individual who will be assuming this responsibility.

Further retention, if required, will be negotiated at the end of this retention period. In that case, Interna Therapeutics Ltd. will notify, in writing, the Investigator when the clinical study data may be discarded. The Investigator will take measures to prevent accidental or premature destruction of these documents.

These files must be made available for inspection upon reasonable request by authorized representatives of Sponsor and/or the relevant regulatory agencies.

At the end of the minimum period, the Investigator should obtain written authorization from the Sponsor prior to the destruction of any records.

11.9 Confidentiality and Publication

Subject medical information obtained by the study is confidential and disclosure to third parties other than those noted below in this section is prohibited. Throughout the study, all data will be identified only by the subject identification number.

Subject to, and dependent upon, the subject's written request, subject medical information from the study may be given to his personal physician or other appropriate medical personnel responsible for his welfare. In accordance with local regulations, when appropriate, the personal physician of the study participant will be notified by the Investigator of subject participation in the study.

All information supplied by the Sponsor and/or delegate. in association with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator’s Brochure, the protocol, CRFs and other scientific data. Any data collected during the study is also considered confidential.

This confidential information shall remain sole property of the Sponsor, shall not be disclosed to others without the prior written consent of the Sponsor and shall not be used except in the performance of this study.

11.10 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Neither the Sponsor nor the site is financially responsible for further testing or treatment of a subject for any medical condition that may be detected during the screening process.

12. REFERENCES

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13. APPENDICES

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