NCT #: NCT06164704

Title Page

Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled, Multi-center Study to Assess the Efficacy and Safety of Verekitug (UPB-101) in Participants with Chronic Rhinosinusitis with Nasal Polyps on a Background of Nasal Corticosteroids (VIBRANT)
Brief Title:	A Study to Investigate the Efficacy and Safety of Verekitug (UPB-101) in Participants with Chronic Rhinosinusitis with Nasal Polyps on a Background of Nasal Corticosteroids (VIBRANT)
Acronym	Not Applicable
Compound:	Verekitug (UPB-101)
Indication:	Chronic Rhinosinusitis with Nasal Polyps
Study Sponsor:	Upstream Bio, Inc. 460 Totten Pond Road, Suite 420 Waltham, MA 02451, US
Protocol Number:	UPB-CP-03
Study Phase:	2
Regulatory Agency Identifying Number:	IND-162964
EU CT Number:	2023-508231-31-00
Protocol Version:	V2.1/Region-Specific Amendment
Approval Date:	13 September 2024
Previous Version:	V1.3/Country-Specific Amendment (Germany-2), 28 February 2024

Sponsor Signatory:

For information about the Sponsor Signatory refer to Appendix 13 Section 10.13.1.

Medical Monitor Name and Contact Information:

This information will be provided separately.

Confidentiality Statement:

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Protocol Amendment Summary of Changes

Document History

Document	Date	Substantial	Region
Version 2.1/Region-specific Amendment	13 September 2024	Yes	Europe
Version 2.0/Global Amendment	09 July 2024	Yes	Global
Version 1.3 / Country-Specific Amendment (Germany-3)	28 February 2024	Yes	Germany
Version 1.2 / Country-Specific Amendment (Germany-2)	16 January 2024	No	Germany
Version 1.1 / Country-Specific Amendment (Germany-1)	30 November 2023	Yes	Germany
Version 1.0 / Original Protocol	17 July 2023		Global

Protocol Amendment 2.0 (13 September 2024)

This amendment is considered to be substantial based on the criteria set forth in Regulation (EU) No 536/2014, Article 2 paragraph 2 No 13 of the European Parliament and of the Council of 16 April 2014.

Overall Rationale for the Protocol Amendment

This protocol Version 2.1 Amendment 2.0, dated 13 September 2024, includes changes made in previous amendments that apply globally (except as noted in the text), as well as to incorporate changes requested by regulatory authorities in Czechia. These changes include:

- Revisions to inclusion criteria (age range, nasal congestion score, dosing compliance) and exclusion criteria (screening labs, eGFR calculations, cardiac disease/ECG abnormalities)
- Removal of references to legally authorized representative
- Clarification of criteria for adverse events and adverse events of special interest
- Addition of volumetric CT scan exploratory endpoint analysis; exception of sites in Czechia to perform CT scans

All references to the protocol version and date were updated. Additional minor editorial and formatting changes were made,

Description of Changes in the Amendment

Substantive changes to the protocol are described below. The table below does not include clerical changes (such as change to headers and footers, changes in dates, and updates of abbreviations) and administrative changes (such as addition of regulatory identifiers) to the protocol. Italics shows text taken directly from the protocol; new text is marked in bold; deleted text is struck through.

No.	Sections Affected	Prior Text	New Text	Rationale
1	Sections 7.1.1; 8.4; 10.1.3	(References to the participant's LAR or legally authorized representative.)	(None; references to LAR removed from protocol.)	Inclusion Criterion 1 specifies that the participant signs the informed consent form and makes no allowance for incapacitated participants.
2	Synopsis; Table 1-1; Sections 3; 5.4.2; 8; 8.2.1; 9.3.3; 10.8;	*CT scans not performed in Germany*	*CT scans not performed in Germany* ***and Czechia***	Added exception to requirement for CT scans in Czechia per regulatory authority request.
3	Synopsis; Section 3	*Time to nasal polyposis surgery and/or time to systemic corticosteroids for nasal polyposis up to Week 24*		Clarification of secondary endpoint.
4		(Objective) • *To assess the effect of verekitug (UPB-101) on the need for treatment with systemic corticosteroids or NP surgery compared to placebo* (Endpoints) • *Change from Baseline over Week 24 in the proportion of participants requiring systemic corticosteroids or NP surgery* • *Estimate of percentage of participants with ≥ 1 event by Week 24 obtained using Kaplan-Meier method*	• ~~*To assess the effect of verekitug (UPB-101) on the need for treatment with systemic corticosteroids or NP surgery compared to placebo*~~ • ~~*Change from Baseline over Week 24 in the proportion of participants requiring systemic corticosteroids or NP surgery*~~ • ~~*Estimate of percentage of participants with ≥ 1 event by Week 24 obtained using Kaplan-Meier method*~~	This objective and endpoint are redundant with another objective and endpoint.

5		(None)	• ***To assess the effect of verekitug (UPB 101) on CT scan opacification of the sinuses compared to placebo (CT scans not performed in Germany and Czechia)*** • ***Change from baseline to Week 24 in three Dimensional CT volumetric measurement of the paranasal sinuses***	Added volumetric CT scan as an exploratory endpoint to allow additional analyses based on data that will already be collected (i.e, a new analysis but not a new assessment), with country-specific exceptions.
6	Table 1-1; Appendix 2	*Urinalysis (dipstick)*	*Urinalysis* ~~*(dipstick)*~~	Clarification of procedure.
7	Table 1-1	*Serum PK sample collected at Week 0, 4, 12, 18, 24, 28*	*Serum PK sample collected at Week 0,* ***2,*** *4, 12, 18, 24, 28*	Addition of PK sample at Week 2 to aid in additional PK analyses.
8		(Footnote a) *Expected order of activities is detailed in Section 8.*	*Expected order of activities is detailed in Section 8.* ***It is noted that the CT or nasal endoscopy procedure may occur on a different date than the study visit date due to restrictions in scheduling these procedures for the participant.***	To allow flexibility for timing of procedures that may occur on different dates.
9		(Footnote k) *Serum and urine pregnancy test (for POCBP): A negative result of serum pregnancy test at Visit 1 and urine pregnancy test must be obtained prior to randomization at Visit 3. Participants considered menopausal must have a FSH ⩾25 IU/mL at Visit 1, if clinically indicated to confirm menopause. At the EOS Visit, a home pregnancy testing kit will be issued to participants who are POCBP to be used at approximately Day 120 post-last dose. Results should be reported to the Investigator.*	*Serum and urine pregnancy test (for POCBP): A negative result of serum pregnancy test at Visit 1 and urine pregnancy test must be obtained prior to randomization at Visit 2. Participants* ***<50 years old who are amenorrheic for >12 months who are*** *considered menopausal must have a FSH* ***⩾ 40*** ~~*⩾25*~~ *IU/mL at Visit 1*~~*, if clinically indicated to confirm menopause*~~*. At the EOS Visit, a home pregnancy testing kit will be issued to participants who are POCBP to be used at approximately Day 120 post-last dose. Results should be reported to the Investigator.*	Changes to footnote added to clarify FSH testing for participants who are amenorrheic.
10	Section 2.3	*More detailed information about the known and expected benefits and risks and*	*More detailed information about the known and expected benefits and risks and reasonably expected AEs of verekitug (UPB-*	Incorporate within the global version of the protocol a change previously incorporated as part

		reasonably expected AEs of verekitug (UPB-101) may be found in the IB.	*101) may be found in the IB.* ***Relevant clinical findings from the ongoing or completed trials will be taken into account for the present clinical trial and participants will be informed accordingly.***	of a country-specific amendment.
11	Section 2.3.1, Table 2-1	*Participants will be monitored for unusual signs and symptoms of ISRs such as pain, localized swelling, tenderness, or erythema.*	*Participants will be monitored for unusual signs and symptoms of ISRs such as pain, localized swelling, tenderness, or erythema.* ***Severe ISRs are considered AESIs and must be reported to the Sponsor promptly, per protocol.***	The risk assessment in the Investigator's Brochure was updated.
12	Section 4.1	*This study is a Phase 2, randomized, double-blind, placebo-controlled, multinational, multi-center study to assess the efficacy and safety of verekitug (UPB-101) administered SC in participants with CRSwNP on background therapy with stable dosage of INCSs. This study consists of a 3 to 5-week Screening Period, a* CCI *Treatment Period, and a 12-week Follow-up Period.*	*This study is a Phase 2, randomized, double-blind, placebo-controlled, multinational, multi-center study to assess the efficacy and safety of verekitug (UPB-101) administered SC in participants with CRSwNP on background therapy with stable dosage of INCSs. This study consists of a 3 to 5-week Screening Period, a* CCI *Treatment Period, and a ~~12~~* ***4****-week Follow-up Period* ***(Figure 1–1)****.*	Corrected error in length of Follow-up Period.
13	Section 4.3	*A* CCI *mg* CCI *SC dose of verekitug (UPB-101) was selected for this study based on the population PK modeling, pharmacology, and safety data with verekitug (UPB-101) across nonclinical and clinical studies (Study 7266-PH-9002, 7266-TX-0006, Study 7266-CL-0001).* *Based on the population PK modeling predictions, the* CCI *mg* CCI *SC dose provides trough concentration higher than the expected maximally therapeutic concentration threshold derived from pharmacology data in asthmatic subjects (Study UPB-CP-01). In addition, the*	*A* CCI *mg* CCI *SC dose of verekitug (UPB-101) was selected for this study based on the population PK modeling, pharmacology, and safety data with verekitug (UPB-101) across nonclinical and clinical studies (Study 7266-PH-9002, 7266-TX-0006, Study 7266-CL-0001****, and UPB-CP-01****).* *Based on the population PK modeling predictions, the* CCI *mg* CCI *SC dose provides trough concentration higher than the expected maximally therapeutic concentration threshold derived from pharmacology data in asthmatic subjects (Study UPB-CP-01).* ***The proposed dose and***	Revised to include updated PK modeling to include results from Study UPB-CP-01.

		selected dose provides adequate safety margins of > 100-fold (for both C_{max} and area under the concentration [AUC]) when compared to exposures achieved at the highest dose and no-observed-adverse-effect level (NOAEL) of CCI *mg/kg evaluated in the chronic toxicology study in cynomolgus monkeys (7266-TX-0006). In addition, the predicted exposure at* CCI *mg* CCI *SC dose is lower than the observed exposure in the completed SAD clinical study wherein verekitug (UPB-101) was considered safe and well-tolerated up to IV dose of* CCI *mg in healthy male and female adults. (Study 7266-CL-0001).*	***dosing regimen in the study is appropriate from a safety perspective and the predicted steady state exposure*** ~~*In addition, the selected dose*~~ *provides adequate safety margins of >* ***79***~~*100*~~*-fold (for both C_{max} and area under the* ***plasma*** *concentration****-time curve*** *[AUC]) when compared to exposures achieved at the highest dose and no-observed-adverse-effect level (NOAEL) of* CCI *mg/kg evaluated in the chronic toxicology study in cynomolgus monkeys (7266-TX-0006). In addition, the predicted exposure at* CCI *mg* CCI *SC dose is lower than the observed exposure in the completed SAD clinical study wherein verekitug (UPB-101) was considered safe and well-tolerated up to IV dose of* CCI *mg in healthy male and female adults. (Study 7266-CL-0001).*	
14	Section 5.1	*2. Participant is aged 18 to 75 years of age (inclusive) at the time of signing the ICF.*	*2. Participant is aged 18 to* ***85*** ~~*75*~~ *years of age (inclusive) at the time of signing the ICF.*	Increased upper limit of age to allow additional eligible patient population who have limited standard of care surgical options.
15		*3. Participant has physician diagnosed CRSwNP for at least 6 months prior to Visit 1 that fulfils all of the following:* • *Severity consistent with need for surgery as defined by an endoscopic bilateral nasal polyp score (NPS) of at least 5 out of 8 and a minimum score of 2 in each nasal cavity at Visit 1 based on central reading, as well as reconfirmed at Visit 2 based on local reading.*	*3. Participant has physician diagnosed CRSwNP for at least 6 months prior to Visit 1 that fulfills all of the following:* • *Severity consistent with need for surgery as defined by an endoscopic bilateral nasal polyp score (NPS) of at least 5 out of 8 and a minimum score of 2 in each nasal cavity at Visit 1 based on central reading, as well as reconfirmed at Visit 2 based on local reading.*	Clarified nasal congestion score calculation for inclusion criterion.

		• *Nasal congestion score (NCS) ⩾ 2 at Visit 2.*	• ***Average n~~N~~****asal congestion score (NCS) ≥ 2 **~~at~~over 14 days before** Visit 2* ***(calculation noted in Section 8.2.2.1)****.*	
16		*7. ≥70% diary compliance for MFNS (or equivalent) in the 14 days prior to Visit 2. Note: Compliance is verified based on MFNS (or equivalent) use recorded on the participant's diary, with an expected dosing regimen of 2 actuations (50 µg/actuation) in each nostril, or equivalent, twice a day (for a total daily dose of 400 µg). If participant cannot tolerate, as determined at Visit 1, the expected dosing regimen is 2 actuations (50 µg/actuation) in each nostril, once daily, for a total daily dose of 200 µg. Compliance will be calculated based on the number of doses taken (morning and evening) relative to the expected dosing regimen.*	*7. ≥70% **dosing** ~~diary~~ compliance for MFNS (or equivalent) in the 14 days prior to Visit 2. Note: Compliance is verified based on MFNS (or equivalent) use recorded on the participant's diary, with an expected dosing regimen of 2 actuations (50 µg/actuation) in each nostril, or equivalent, twice a day (for a total daily dose of 400 µg). If participant cannot tolerate, as determined at Visit 1, the expected dosing regimen is 2 actuations (50 µg/actuation) in each nostril, once daily, for a total daily dose of 200 µg. Compliance will be calculated based on the number of doses taken (morning and/**or** evening) relative to the expected dosing regimen.*	Clarified as "dosing" compliance in this criterion, not "diary" compliance.
17		*8. Participants capable of producing sperm:* • *Agree to refrain from donating sperm during the intervention period and for a period of 120 days after the last dose of study intervention or after the Final Visit, whichever occurs last.* *AND* • *Agree to follow the contraceptive guidance in Appendix 4 of this protocol during the intervention period and for a period of 120 days after the last dose of study intervention or after the Final Visit, whichever occurs last.*	*8. Participants capable of producing sperm:* • *Agree to refrain from donating sperm during the intervention period and for a period of 120 days after the last dose of study intervention or **at~~after~~** the Final Visit, whichever occurs last.* *AND* • *Agree to follow the contraceptive guidance in Appendix 4 of this protocol during the intervention period and for a period of 120 days after the last dose of study intervention or **at~~after~~** the Final Visit, whichever occurs last.* *AND*	Clarified time frame for donating sperm or egg and following contraceptive guidance.

		AND • *Agree to use a condom when engaging in any activity that allows for passage of ejaculate to another person during the intervention period and for a period of 120 days after the last dose of study intervention or after the Final Visit, whichever occurs last.* *Participants of childbearing potential:* • *Agree to refrain from donating eggs for a period of 120 days after the last dose of study intervention or after the Final Visit, whichever occurs last.* • *Participants are eligible to participate if they are not pregnant (see Appendix 4), not breastfeeding, and at least one of the following conditions applies:* o Not a participant of childbearing potential (POCBP) as defined in Appendix 4; OR A POCBP who agrees to follow the contraceptive guidance in Appendix 4 during the intervention period and for 120 days after the last dose of study intervention or after the Final Visit, whichever occurs *last.*	• *Agree to use a condom when engaging in any activity that allows for passage of ejaculate to another person during the intervention period and for a period of 120 days after the last dose of study intervention or* ***at~~after~~*** *the Final Visit, whichever occurs last.* *Participants of childbearing potential:* • *Agree to refrain from donating eggs for a period of 120 days after the last dose of study intervention or* ***at~~after~~*** *the Final Visit, whichever occurs last.* • *Participants are eligible to participate if they are not pregnant (see Appendix 4), not breastfeeding, and at least one of the following conditions applies:* o Not a participant of childbearing potential (POCBP) as defined in Appendix 4; OR A POCBP who agrees to follow the contraceptive guidance in Appendix 4 during the intervention period and for 120 days after the last dose of study intervention or **at~~after~~** the Final Visit, whichever occurs last.	
18	Section 5.2	*16. Abnormal medical history, physical finding or safety finding that in the opinion of the Investigator may obscure the study data or interfere with the participant's safety.*	*16. Abnormal medical history, physical finding or safety finding that in the opinion of the Investigator may obscure the study data or interfere with the participant's safety.* ***Participants with any clinically significant cardiac***	Clarified by adding exclusion for clinically significant cardiac disease and/or ECG abnormality.

			disease and/or ECG abnormality, in the opinion of the Investigator, obtained during the Screening Period should be excluded from the study.	
19		*17. Any clinical laboratory test result outside of the reference ranges considered by the Investigator as clinically significant and that may obscure the study data or interfere with the participant's safety. Note: out of range screening values may be repeated one time per Investigator's discretion.*	*17. Any clinical laboratory test result outside of the reference ranges considered by the Investigator as clinically significant and that may obscure the study data or interfere with the participant's safety. Note: out of range screening values may be repeated ~~one time~~ per Section 5.4.1**)**.*	Modified the text to allow investigators flexibility in repeat laboratories by removing "one time" from the Note.
20		*23. Estimated glomerular filtration rate of < 60 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation with correction factor for Black/African American participants. Note: Non-clinically significant out of range value may be repeated one time per Investigator's discretion.*	*23. Estimated glomerular filtration rate of < 60 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation ~~with correction factor for Black/African American participants~~ **(2021)**. Note: Non-clinically significant out of range value may be repeated ~~one time~~ per Investigator's discretion (see Section 5.4.1).*	Removed the text "with correction factor for Black/African American participants" to align with new recommendations on GFR measurements. Modified the text to allow Investigator's discretion and flexibility in repeat laboratories by removing "one time" from the note.
21		24. History of malignancy of any type, other than in-situ cervical cancer or surgically excised non-melanomatous skin cancers, within 5 years before Visit 1.	*24. History of malignancy of any type, other than **curatively treated** in-situ cervical cancer or surgically excised non-melanomatous skin cancers, within 5 years before Visit 1.*	Modified criterion according to regulatory authority request.
22		*27.* Positive hepatitis B surface antigen (HBsAg), or hepatitis C antibodies.	*27. Positive hepatitis B surface antigen (HBsAg), **hepatitis B core antibody (HBcAb)**, or hepatitis C antibodies **(HCV Ab)**.*	Modified criterion according to regulatory authority request.
23		*28.* Known active tuberculosis at Visit 1. A tuberculosis test may be performed if required based on local guidelines.	28. *Known active tuberculosis (TB) at Visit 1. A tuberculosis test may be performed*	Modified criterion according to regulatory authority request.

			if required based on local guidelines. ***For participants in Czechia:*** • ***All participants will have TB screening at Visit 1*** • ***Participants treated within 12 months of Visit 1for active TB will be excluded from study.*** • ***For participants with a history of active TB treated > 12 months prior to Visit 1 or a history of treated latent TB, written prior approval by a TB specialist or an infectious disease specialist is required prior to initiation of study drug. Such participants may be eligible for the study under the following conditions:*** o ***If history of active or latent TB: documented initiation or completion of a full course of anti-TB therapy.*** o ***If TB screening test at Visit 1 is positive or indeterminate: documented initiation or completion of adequate anti-TB treatment.***	
24	Section 5.4.1	*Participants who fail one or more criteria for reasons which in the opinion of the Investigator are likely to be remedied, may perform a one-time repeat of the test(s) associated with those criteria (either at a subsequent Screening Visit or at an unscheduled visit), provided re-testing can be performed within the screening window.*	*Participants who fail one or more criteria for reasons which in the opinion of the Investigator are likely to be remedied, may ~~perform a one time~~ repeat ~~of~~ the test(s) associated with those criteria (either at a subsequent Screening Visit or at an unscheduled visit)* ***a maximum of two times****, provided re-testing can be performed within the screening window.*	Modified the text to allow investigators flexibility in repeat laboratories by removing "one time" from the text.
25	Section 5.4.2	*Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened. Rescreening will be permitted only once and only if the*	*Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened. Rescreening will be permitted only once and only if the situation*	Modified in order to allow participants to be rescreened if investigator determines the nasal polyp burden may have

		situation leading to the screen failure is considered likely to change based on the discretion of the Investigator and/or Medical Monitor. Participants who do not meet NPS criteria will not be rescreened. *Participants who are rescreened will receive a new participant number. A participant who is rescreened is not required to sign another ICF at rescreening, unless a new version of the ICF becomes available. During rescreening, all screening procedures will be repeated with the following exceptions: nasal endoscopy and CT scan if performed within 3 weeks and 4 weeks, respectively, prior to rescreening.*	*leading to the screen failure is considered likely to change based on the discretion of the Investigator and/or Medical Monitor.* ~~*Participants who do not meet NPS criteria will not be rescreened.*~~ *Participants who are rescreened will receive a new participant number. A participant who is rescreened is not required to sign another ICF at rescreening, unless a new version of the ICF becomes available. During rescreening, all screening procedures will be repeated with the following exceptions: nasal endoscopy and CT scan* ***(CT scans not performed in Germany and Czechia)*** *if performed within 3 weeks and* ~~*4 weeks*~~ ***4 months****, respectively, prior to rescreening.*	increased over time. Given NPS failure rescreenings are permitted, the baseline CT scan would not be repeated before 4 months from prior scan to minimize radiation exposure. Added exception to requirement for CT scans in Czechia.
26	Section 6.9	*All CRSwNP medications taken in the 6 months prior to Visit 1 must be recorded in the electronic case report form (eCRF) along with reason for treatment.*	*All CRSwNP medications taken in the 6 months prior to Visit 1 must be recorded in the electronic case report form (eCRF) along with reason for treatment.* ***Biologics used for urticaria, atopic dermatitis, asthma or CRSwNP during the participant's lifetime must also be documented with reason for treatment.***	Additional clarification that any biologics used for urticaria, atopic dermatitis, asthma or CRSwNP during the participant's lifetime must also be documented with reason for treatment.
27	Section 6.9.1	• *Intranasal corticosteroid drops or corticosteroid-administering devices/stents, except study MFNS (or equivalent)*	*Intranasal corticosteroid drops or* ***intranasal*** *corticosteroid-administering devices/stents* ***(e.g., Xhance)****, except study* ***intranasal spray*** *MFNS (or equivalent)*	Clarification on intranasal devices that are prohibited.
28	Section 7.1	*It may be necessary for a participant to permanently discontinue study intervention. See the SoA (Table 1–1) for data to be collected at the time of*	*It may be necessary for a participant to permanently discontinue study intervention. See the SoA (Table 1–1) for data to be collected at the time of discontinuation of*	Schematic added to describe the options visually. Text moved from paragraph below to paragraph above.

		discontinuation of study intervention (EOT visit) and follow-up (EOS visit) and for any further evaluations that need to be completed. *A participant who decides to discontinue study intervention should always be asked about the reason(s) and the presence of any AEs. The reason for discontinuing study intervention and the date of last administration should always be recorded in the eCRF.*	*study intervention (EOT visit) and follow-up (EOS visit) and for any further evaluations that need to be completed.* ***See Figure 7–1 for a schematic of the visit and data collection options for participants who permanently discontinue study intervention.*** *A participant who decides to discontinue study intervention should always be asked about the reason(s) and the presence of any AEs. The reason for discontinuing study intervention and the date of last administration should always be recorded in the eCRF.* ***The participant should then be encouraged to return for all regular study visits and perform all scheduled assessments per SoA until completion of the study.***	
29		*If study intervention is permanently discontinued, the participant should return to the study center for all regularly scheduled study visits per the SOA (Table 1–1) complete the EOT assessments approximately 12 weeks after the last dose of study intervention and complete the EOS assessments approximately 16 weeks after the last dose of study intervention. The participant should then be encouraged to return for all regular study visits and perform all scheduled assessments until completion of the study. In participants who decline to return for all regular study visits, the following options should be offered:* • *The participant will be offered follow-up on a monthly basis via telephone calls while continuing diary assessments (no further procedures will be performed) until completion of*	~~*If study intervention is permanently discontinued, the participant should return to the study center for all regularly scheduled study visits per the SOA (Table 1–1) complete the EOT assessments approximately 12 weeks after the last dose of study intervention and complete the EOS assessments approximately 16 weeks after the last dose of study intervention. The participant should then be encouraged to return for all regular study visits and perform all scheduled assessments until completion of the study. In participants who decline to return for all regular study visits, the following options should be offered:*~~ ***When study intervention is permanently discontinued:*** • ***If the participants agree to continue in the study, the participants will return to the study center for all regularly scheduled***	Clarification of the assessments to be performed for those participants who discontinue study intervention permanently prior to the EOT/EOS visits. Schematic added to describe the options visually.

		the Treatment Period. The key information to be collected during the telephone calls are AEs/SAEs, changes in concomitant medication, MFNS use, and nasal polyposis symptoms. The participant should return for the last visit of the Treatment Period and for a follow-up visit approximately 16 weeks after the last dose of study intervention. If the participant cannot or does not wish to comply with any of the options above, (or any component of them such as only telephone-based visits without completion of the diary assessment), they will complete a follow-up visit approximately 12 weeks after the last dose of study intervention. After this visit, the Investigator will only contact the participant at the last visit of the Treatment Period. No other study assessments will be performed prior to this contact. The key information to be collected during the telephone call are AEs/SAEs, and changes in concomitant medication. *Participants who do not wish to have any follow-up contact will be discontinued from the study. All discontinued participants must return the diary device, as applicable at the EOT visit.*	***study visits per the SoA (Table 1–1) and in addition complete the EOT assessments approximately 12 weeks after the last dose of study intervention and complete the EOS assessments approximately 16 weeks after the last dose of study intervention.*** • ***If the participants decline to return for all regular study visits but agree to return for the end of study procedures, EOT assessments approximately 12 weeks after the last dose of study intervention and complete the EOS assessments approximately 16 weeks after the last dose of study intervention.*** • ***If participants decline to return for any regular study visits, the*** ~~*The*~~ *participant will be offered follow-up on a monthly basis via telephone calls while continuing diary assessments (no further procedures will be performed) until completion of the Treatment Period. The key information to be collected during the telephone calls are AEs/SAEs, changes in concomitant medication, MFNS use, and nasal polyposis symptoms. The participant should return for the last visit of the Treatment Period and for a follow-up visit approximately 16 weeks after the last dose of study intervention. If the participant cannot or does not wish to comply with any of the options above, (or any component of them such as only telephone-based visits without completion of the diary assessment),*	

			they will complete a follow-up visit approximately 12 weeks after the last dose of study intervention. After this visit, the Investigator will only contact the participant at the last visit of the Treatment Period. No other study assessments will be performed prior to this contact. The key information to be collected during the telephone call are AEs/SAEs, and changes in concomitant medication. *Participants who do not wish to have any follow-up contact will be discontinued from the study. All discontinued participants must return the diary device, as applicable at the EOT visit.* (Figure added): ***Figure 7–1 Study Visits and Assessments for Participants Who Permanently Discontinue Study Intervention***	
30	Section 7.1.1	*1.* Diagnosis of a malignancy during study participation, other than squamous cell or basal cell carcinomas or in situ cervical carcinoma.	• *Diagnosis of a malignancy during study participation, other than squamous cell or basal cell carcinomas or in situ cervical carcinoma.* ***The Investigator's written benefit-risk assessment of continuation of study treatment in those participants who develop squamous cell carcinoma, basal cell carcinoma, or in situ cervical carcinoma must be documented and approved by Sponsor Medical Monitor before continuation of study drug.*** • ***Diagnosed with latent TB, or has positive or indeterminate TB test.*** • ***Confirmed HIV, HBV, or HCV infection during study participation.***	Clarified procedures for participants diagnosed with malignancies and added confirmed TB and hepatitis infection as a criterion for permanent treatment discontinuation.

31	Section 8	*In case, wherein, 1 or more of the following activities appear during a single visit, the order of activities should be:* *1. Participant-Reported Outcomes* *2. Procedures* *o Urine pregnancy test and urine sampling* *o Height and weight* *o Vital signs* *o Physical examination* *o ECG* *o Spirometry (in participants with comorbid asthma)* *o CT scan* *o Nasal endoscopy* *3. Safety and other laboratory assessments (e.g., blood sampling)* *o blood sampling requiring anticoagulants should be drawn before drawing samples which do not require anticoagulants* 4. *Study intervention administration*	*In the case that one or more of the following activities appear during a single visit, the* ***suggested*** *order of activities* ~~*should be*~~ ***is as follows****:* *1. Participant-Reported Outcomes* *2. Procedures* *o Urine pregnancy test and urine sampling* *o Height and weight* *o Vital signs* *o Physical examination* *o ECG* *o Spirometry (in participants with comorbid asthma)* *o CT scan (CT scans not performed in Germany* ***and Czechia****)* *o Nasal endoscopy* *3. Safety and other laboratory assessments (e.g., blood sampling)* ***Refer to the Laboratory Manual for order of laboratory assessments.*** ~~o blood sampling requiring anticoagulants should be drawn before drawing samples which do not require anticoagulants~~ *4. Study intervention administration*	Clarification of "Order of Procedures" section that procedures may occur on different days and PROs should be collected prior to NE if occurring on same day. Added exception to requirement for CT scans in Czechia.
31		*All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The Investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of intervention allocation/randomization, site personnel*	*All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The Investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of intervention allocation/randomization, site personnel will*	Clarification that the participant identification card does not contain contact information for the emergency unblinded call center.

		will add the intervention/randomization number to the participant identification card. *The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about the study intervention in emergency situations where the Investigator is not available.*	*add the intervention/randomization number to the participant identification card.* ~~*The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about the study intervention in emergency situations where the Investigator is not available.*~~	
32	Section 8.2.1.2	(None)	***Three-Dimensional Volumetric Measurement of the Sinuses*** ***The % change in opacification from Baseline to the Week 24 CT scan will be calculated based on the following method on each side per each of the 5 anatomic sinuses (Deeb 2011):*** ***The following measurements will also be captured as part of the CT scans:*** • ***The volume of the air (mL)*** • ***The volume of mucosa (mL)*** • ***Percent occupied by disease*** • ***Thickness of lateral wall***	Addition of volumetric CT scan as an exploratory endpoint to allow additional analyses based on data that will already be collected (i.e, a new analysis but not a new assessment).
33	Section 8.2.2	*To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered early in the clinic visit, before the participant receives any information on his or her disease status and prior to the performance of non-PRO assessments (e.g., endoscopy), unless otherwise specified. Additionally, PROs should be collected prior to the administration of study intervention. PROs assessed during the clinic visits will be captured on a tablet device provided by a central vendor. The study center staff*	*To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered early in the clinic visit, before the participant receives any information on his or her disease status and prior to the performance of non-PRO assessments (e.g., endoscopy), unless otherwise specified. Additionally, PROs should be collected prior to the administration of study intervention. PROs assessed during the clinic visits will be captured on a* ***handheld*** ~~*tablet*~~ *device provided by a central vendor. The study center staff will be trained on how to use the*	Clarified the devices used.

		will be trained on how to use the tablet during the clinic visits and will be responsible for instructing participants on how to complete the questionnaires. Should there be any issues with the tablet, web back-up may be used as an alternative.	***web diary*~~*tablet*~~ *during the clinic visits and will be responsible for instructing participants on how to complete the questionnaires. Should there be any issues with the* ***handheld device*~~*tablet*~~*, web back-up may be used as an alternative.***	
34	Section 8.4.4	*Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.*	*Investigator safety reports must be prepared for suspected unexpected serious adverse reactions* ***(SUSARs)*** *according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.* ***See Appendix 3 Section 10.3.4 for reporting SUSARS to regulatory authorities.***	Incorporate within the global version of the protocol a change previously incorporated as part of a country-specific amendment.
35	Section 8.4.6	• *Allergic reactions.* • *Severe infections which are defined as:* o *Life-threatening or,* o *Requiring hospitalization or,* o *Requiring treatment with antiviral medications, IV antibiotics or medications for helminth parasitic infection or,* o *Requiring permanent discontinuation of study intervention.* • *Injection site reactions.*	• ~~*Allergic*~~***Anaphylaxis*** *reactions* • *Severe infections which are defined as:* o *Life-threatening or,* o *Requiring hospitalization or,* o *Requiring treatment with* ~~***antiviral medications***~~*IV* ***anti-infectives***~~*anti-biotics or medications for helminth parasitic infection*~~ *or,* o *Requiring permanent discontinuation of study intervention.* • ***Helminth parasitic infection requiring treatment.*** • *Injection site reaction* ***(ISR) that is CTCAE Grade 3 or higher.***	Clarification for AESIs to include anaphylaxis reactions instead of allergic reactions as allergic reaction is not as specific. Clarification for AESIs as multiple criteria were used to define severe infections that may not be appropriate.
36	Section 8.5.1	No PK sample collected at Visit 3	Visit 3 (± 3 days) PK sample added	Addition of PK sample at Week 2 to aid in additional PK analyses.
37	Section 8.6.1	*Nasal secretions will be obtained by inserting nasal swabs bilaterally into the nasal cavity for 5 minutes. Precise instructions for isolating nasal secretions from the swabs and preserving aliquots*	*Nasal secretions will be obtained* ***per laboratory collection manual instructions.*** ~~*by inserting nasal swabs bilaterally into the nasal cavity for 5 minutes. Precise instructions for isolating nasal secretions*~~	Collection of nasal secretions revised to refer to laboratory collection manual instructions.

		will be provided separately. Nasal secretions at Visit 2 will be used for validation of assay methodology for this unique biomatrix. The nasal secretions collected at Visits 4, 6, 7, and 8/EOT will be preserved for analysis of additional biomarkers related to nasal polyposis and responses to verekitug (UPB-101) treatment.	~~*from the swabs and preserving aliquots will be provided separately. Nasal secretions at Visit 2 will be used for validation of assay methodology for this unique biomatrix.*~~ *The nasal secretions collected at Visits* ***2****, 4, 6, 7, and 8/EOT will be preserved for analysis of additional biomarkers related to nasal polyposis and responses to verekitug (UPB-101) treatment.*	
38	Section 9	*The analysis and reporting will be done on all data from all participants at the time the study ends.*	~~*The analysis and reporting will be done on all data from all participants at the time the study ends.*~~ ***Two database locks (DBLs) are planned for this study. A first DBL will be conducted after the last participant has reached WK 24. The second and final DBL will be conducted after all participants complete their safety follow-up visits (EOS). Upon the first DBL, Sponsor and the CRO analysis team will be unblinded to the treatment assignment to perform all analyses related to the primary and secondary study objectives according to the SAP using the first DBL data. Other personnel will remain blinded to the treatment, including investigators, study site staff, participants, and the CRO staff who are not involved in the analysis.***	The potential for preparing 2 databases for analyses has been added.
39	Section 9.3.3	• *Change from baseline at Week 24 in the 28-day mean NCS. The analysis will be similar to the primary endpoint.*	• *Change from baseline at Week 24 in the* ~~*28-day*~~***bi-weekly*** *mean NCS. The analysis will be similar to the primary endpoint.*	Correction and clarification in statistical section for endpoints derived from NCS and NPSD (changed “28-day” to “bi-weekly”).
40		• *Time to surgery and/or systemic corticosteroids for nasal polyposis, time to nasal polyposis surgery, and time to systemic corticosteroids for*	• ~~*Time to surgery and/or systemic corticosteroids for nasal polyposis, time to nasal polyposis surgery, and time to systemic corticosteroids for nasal*~~	Correction and clarification in statistical section for endpoints derived from need for treatment

		nasal polyposis up to Week 24. Analysis will be performed using Log Rank Test and Kaplan-Meier Plots will be presented.	~~*polyposis up to Week 24. Analysis will be performed using Log-Rank Test and Kaplan-Meier Plots will be presented.*~~	with corticosteroids or NP surgery.
41	Section 9.3.4	• *Change from baseline over Weeks 24 and 28 in NCS evaluated by the NPSD. The analysis will be performed using ANCOVA with factors similar to primary endpoint analysis.* • *Change from baseline over Weeks 24 and 28 in NPSD TSS. The analysis will be performed using ANCOVA with factors similar to primary endpoint analysis.*	• *Change from baseline over Weeks 24 and 28 in* ***bi-weekly*** *NCS evaluated by the NPSD. The analysis will be performed using ANCOVA with factors similar to primary endpoint analysis.* • *Change from baseline over Weeks 24 and 28 in* ***bi-weekly*** *NPSD TSS. The analysis will be performed using ANCOVA with factors similar to primary endpoint analysis*	Correction and clarification in statistical section for other endpoints derived from NCS, NPSD, and NPSD TSS (added "bi-weekly").
42		(None)	• ***Change from baseline to Week 24 in three-Dimensional CT volumetric measurement of the paranasal sinuses.***	Addition of volumetric CT scan as an exploratory endpoint to allow additional analyses based on data that will already be collected (i.e, a new analysis but not a new assessment).
43	Section 10.1.4	*Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.* *The participant must be informed that their personal study related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant who will be required to give*	***To ensure confidentiality of records and personal data of participants, p****~~P~~**articipants will be assigned a unique identifier. Any participant records or datasets that are transferred to the Sponsor* ***or to representatives of the Sponsor*** *will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.* ***Such personal data will therefore be "pseudonymized" and only accessed by authorized persons who are subject to written confidentiality obligations.***	Data Protection process and procedures updated and clarified.

		consent for their data to be used as described in the informed consent. *The participant must be informed that their medical records may be examined by Clinical Quality Assurance (QA) auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.*	*The participant must be informed that their personal study related data will be* ***processed and disclosed*** ~~*used*~~ *by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the* ***applicable*** *informed consent* ***form(s)****.* ***As applicable, the participant will receive all information as required by the EU General Data Protection Regulation (EU) 2016/679 of the European Parliament and of The Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (EU GDPR), including the identity of the controller, the clinical research purposes, the fair processing of the data, and all his/her data subjects rights. All details are listed in the informed consent form.*** *The participant must be informed that their medical records may be examined by Clinical Quality Assurance (QA) auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.* ***To protect data subject privacy per EU GDPR, collected study data will be pseudonymized (as described above) and maintained in a secure system.***	

			Sponsor will implement organizational and technical arrangements to avoid unauthorized access, disclosure, dissemination, alteration, or loss of information and personal data processed. Such arrangements will entail that the Sponsor, Study Center(s), and any other authorized parties, implement a series of technical and organizational measures, as appropriate, including but not limited to the encryption of the personal data at rest and in transit, implementation of appropriate security policies and procedures, regular training procedures, pseudonymization of participants' personal data, implementation of appropriate physical and electronic access controls, employees' access restriction controls and control logging for any electronic systems containing personal data, adequate network protection, implementation of back-up and recovery plans to ensure data availability, and the ability to ensure the ongoing confidentiality, integrity, availability, and resilience of the processing systems used for the personal data. ***In case of a data security breach, Sponsor, sites, and other authorized parties, as may be applicable, will implement appropriate measures in order to mitigate the possible adverse effects of the data security breach, including promptly investigating the data security breach to identify the vulnerability that led to the data security breach and undertaking the appropriate remediation efforts to remedy the vulnerability identified and limit the impact of the data security breach. Sponsor will be informed without undue delay of any data security breaches***	

			suffered by the sites or other authorized parties. Sponsor, with the full cooperation of the sites and other authorized parties, will assess the likely risk to participants as a result of the data security breach. Sponsor will assess its obligations, if any, to report such breach to the supervisory authorities (or other law enforcement agencies) and the affected individuals, as applicable, in accordance with applicable local regulations. Sponsor, sites, and any other authorized parties will fully document all relevant facts relating to the data security breach, including its effects and any remedial action taken, and keep a related record of each data security breach. ***The Investigator agrees that all information received from the Sponsor or designee including, but not limited to, the IB, the protocol, eCRFs, the protocol specified treatment, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The Investigator further agrees to take all reasonable precautions to prevent the disclosure of confidential patient information to any unauthorized party or otherwise into the public domain. The Investigator will notify Upstream Bio within 24 hours of a security event that impacts or has the potential to impact confidentiality, integrity, or availability study data.***	

44	Section 10.2, Appendix 2	*FSH and estradiol (participants considered menopausal, if clinically indicated to confirm menopause)*	***FSH if <50 years old and amenorrheic for >12 months.*** ~~*FSH and estradiol (participants considered menopausal, if clinically indicated to confirm menopause)*~~	Revised to clarify FSH testing in amenorrheic participants based on regulatory feedback.
45	Section 10.3.1	(None)	***Mild ISRs will not be reported as AEs. If after discharge from the site, the participant reports an ISR which in the Investigator's judgment was moderate or severe, the Investigator or qualified designee will complete the AE eCRF page and additional eCRF questions about the ISR. Refer to CTCAE v5 for instructions on grading of mild ISR.***	Clarification of criteria for injection site reactions (ISRs) to be reported as AEs.
46	Section 10.3.4	*The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor/CRO will evaluate the seriousness and the causal relationship of the event to study intervention. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the Reference Safety Information (IB or Summary of Product Characteristics). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.*	*The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor/CRO will evaluate the seriousness and the causal relationship of the event to study intervention. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the Reference Safety Information (IB or Summary of Product Characteristics).* ***As defined in the safety management plan, all suspected unexpected serious adverse reactions (SUSARs) will be electronically reported through EudraVigilance safety reports by the designated Sponsor/CRO team in accordance with EMA/873138/2011 Rev 2.*** *Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.*	Clarification of reporting of SUSARs.
47	Section 10.4.1	○ *A high follicle-stimulating hormone (FSH) level in the postmenopausal reference range (> 40 U/mL) may be*	○ *A high follicle-stimulating hormone (FSH) level in the postmenopausal reference range (≥~~>~~ 40 U/mL) may be used to*	Revised to clarify when FSH testing is required and when

		used to confirm a postmenopausal state in participants not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with one FSH measurement is required.	*confirm a postmenopausal state in participants not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea,* ***a single FSH measurement is insufficient*** ~~*confirmation with one FSH measurement is required*~~*.*	single FSH testing is insufficient.

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Abbreviations and Definitions

Abbreviation	Description
ACQ-6	Asthma Control Questionnaire-6
ADA	Antidrug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the concentration curve
$CD4^+$	Cluster of differentiation 4^+
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum observed concentration
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CRP	C-reactive protein
CRS	Chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis without nasal polyps
CRSwNP	Chronic rhinosinusitis with nasal polyps
CT	Computed tomography
C_{trough}	Pre-dose (trough) drug concentration
DMC	Data Monitoring Committee
DPI	Dry Powder Inhaler
DSS	Difficulty with sense of smell
ECG	Electrocardiogram
eCRF	Electronic case report form(s)
EDC	Electronic data capture
EOT	End of treatment
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice

Abbreviation	Description
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCV Ab	Hepatitis C antibody
HDL	High-density lipoprotein
HFA	Hydrofluoroalkane propellant
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonisation
ICS	Inhaled corticosteroid
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IgM	Immunoglobulin M
IL	Interleukin
INCS	Intranasal corticosteroid
IND	Investigational New Drug
IRB	Institutional Review Board
ISR	Injection site reaction
ITT	Intention to Treat Analysis Set
IV	Intravenous
LMK	Lund Mackay
LSM	Least square means
mAb	Monoclonal antibody
MFNS	Mometasone furoate nasal spray
MMRM	Mixed model repeated measures
NAb	Neutralizing antibody
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Nasal congestion score

Abbreviation	Description
NOAEL	No-observed-adverse-effect level
NP(s)	Nasal polyp(s)
NPS	Nasal polyp score
NPSD	Nasal polyposis symptom diary
NSAID	Non-steroidal anti-inflammatory drug
NSAID-ERD	Non-steroidal anti-inflammatory drug-exacerbated respiratory disease
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKAS	Pharmacokinetic Analysis Set
pMDI	Pressurized metered dose inhaler
PNV	Predicted normal Value
POCBP	Participants of childbearing potential
PRO	Patient reported outcome
QA	Quality assurance
CCI [redacted]	
QTL	Quality tolerance limit
RNA	Ribonucleic acid
SAD	Single ascending dose
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous/subcutaneously
SoA	Schedule of activities
$t_{1/2}$	Terminal elimination half-life
CCI [redacted]	
TEAE	Treatment-emergent adverse event
Th2	T helper cell type-2
TSLP	Thymic stromal lymphopoietin
TSLPR	Thymic stromal lymphopoietin receptor
TSS	Total symptom score
ULN	Upper limit of normal

1 Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 2, Randomized, Double-blind, Placebo-controlled, Multi-center Study to Assess the Efficacy and Safety of Verekitug (UPB-101) in Participants with Chronic Rhinosinusitis with Nasal Polyps on a Background of Nasal Corticosteroids (VIBRANT)

Brief Title: A Study to Investigate the Efficacy and Safety of Verekitug (UPB-101) in Participants with Chronic Rhinosinusitis with Nasal Polyps on a Background of Nasal Corticosteroids (VIBRANT)

Sponsor Protocol No.: UPB-CP-03

Study Phase: 2

Sponsor: Upstream Bio

Regulatory Agency Identifier Number: IND-162964; EU CT#: 2023-508231-31-00

Rationale:

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a predominantly adult disease with a prevalence estimated to be 2.5% to 2.7% and it increases with age. Chronic rhinosinusitis (CRS) and nasal polyps (NPs) can be demonstrated on sinus computed tomography (CT) scan and/or nasal endoscopy. The 4 cardinal symptoms of CRSwNP include anterior or posterior rhinorrhea, nasal congestion, hyposmia or anosmia, and facial pain or pressure. Patients with CRSwNP usually have more severe sino-nasal symptoms and even following sinus surgery, patients can continue to have more severe disease and on average are more likely to require revision sinus surgeries. Additionally, ear pain, sneezing, severe difficulty breathing through the nose, severe nasal congestion and severe loss of smell are significantly more likely to be reported in CRSwNP patients with eosinophilic versus non-eosinophilic NP.

Rhinosinusitis is a disease characterized by inflammation of one or more of the paranasal sinuses. Chronic rhinosinusitis is divided into 2 clinical subtypes: (1) CRSwNP; (2) chronic rhinosinusitis without nasal polyps (CRSsNP). Nasal polyps are inflammatory outgrowths of the paranasal sinus mucosa along the middle and superior meatus that occur primarily in adults. In CRSwNP, NPs are benign and typically develop bilaterally in the sino-nasal cavity.

Treatment of NP includes medical and surgical therapy aimed at either complete elimination of polyps or sufficient reduction in polyp size to alleviate nasal obstruction and associated symptoms. Both topical corticosteroids and nasal saline irrigations are recommended as initial medical therapies in CRSwNP. Intranasal and oral corticosteroids can reduce NP size, lessen sino-nasal symptoms, and improve quality of life. However, the adverse effects of long-term systemic corticosteroid use outweigh their advantages and should only be considered for short-term administration.

Biologic therapies provide new therapeutic options for patients with severe uncontrolled CRSwNP. However, their frequent administration, side effects and costs may limit their usage. Therefore, there is a continued need to develop additional therapies to further improve the significantly impaired quality of life of these patients.

Verekitug (UPB-101) is a novel recombinant fully human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) targeting human thymic stromal lymphopoietin (TSLP) signaling by blocking the TSLP receptor (TSLPR).

Non-clinical studies have demonstrated that verekitug (UPB-101) binds to monkey TSLPRs and inhibits TSLPR-mediated signal transduction (Studies 7266-PH-0001, 7266-PH-9002, 7266-PH-9003, 7266-PH-9005, 7266-PH-9007). Furthermore, verekitug (UPB-101) has been observed to inhibit TSLP-stimulated myeloid dendritic cell-mediated differentiation of naïve cluster of differentiation 4+ ($CD4^+$) T-cells into mature T cells *in vitro* (Study 7266-PH-9004). In sensitized monkeys, verekitug (UPB-101) suppressed ascaris extract-induced skin reactions, suggesting verekitug (UPB-101) inhibits T helper cell type-2 (Th2) type allergic responses (Study 7266-PH-9006). Verekitug (UPB-101) is currently under development for the treatment of moderate to severe asthma.

Given the role of TSLP in the pathogenesis of a variety of allergic diseases triggering type 2 inflammatory responses, and the increased expression or activity of TSLP in NP tissue in CRSwNP, there is a biological and pathophysiological plausibility to develop verekitug (UPB-101) for the treatment of CRSwNP.

The purpose of this study is to evaluate the efficacy and safety of verekitug (UPB-101) in participants with CRSwNP who are on a background of nasal corticosteroids. Additionally, pharmacodynamics (PD), pharmacokinetics (PK), health-related quality of life, immunogenicity, and improvement in lung function in participants with comorbid asthma will also be assessed.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the effect of verekitug (UPB-101) on endoscopic NPS compared to placebo	• Change from Baseline at Week 24 in NPS
Secondary	
• To assess the effect of verekitug (UPB-101) on NCS compared to placebo	• Change from Baseline at Week 24 in the NCS evaluated by the NPSD
• To assess the effect of verekitug (UPB-101) on CT scan opacification of the sinuses compared to placebo (CT scans not performed in Germany)	• Change from Baseline at Week 24 in opacification of sinuses measured by LMK Score evaluated by quantitative CT assessment (CT scans not performed in Germany and Czechia)
• To assess the effect of verekitug (UPB-101) on loss of smell compared to placebo	• Change from Baseline at Week 24 in DSS evaluated by the NPSD
• To assess the effect of verekitug (UPB-101) on the need for treatment with systemic corticosteroids or NP surgery compared to placebo	• Proportion of participants requiring systemic corticosteroids or NP surgery • Time to first nasal polyposis surgery and/or use of systemic corticosteroids for nasal polyposis up to Week 24
• To assess the effect of verekitug (UPB-101) on total symptoms of CRSwNP compared to placebo	• Change from Baseline at Week 24 in NPSD TSS
Safety	
• To assess safety and tolerability of verekitug (UPB-101) compared to placebo	• AEs, SAEs, physical examinations, clinical laboratory assessments, vital signs, and ECGs from Baseline over study duration, including the Follow-Up Period
Other	
• To assess the effect of verekitug (UPB-101) on endoscopic NPS compared to placebo	• Change from Baseline over Week 24 in NPS
• To assess the effect of verekitug (UPB-101) on NCS compared to placebo	• Change from Baseline over Weeks 24 and 28 in NCS evaluated by the NPSD
• To assess the effect of verekitug (UPB-101) on loss of smell compared to placebo	• Change from Baseline over Weeks 24 and 28 in DSS evaluated by the NPSD
• To assess the effect of verekitug (UPB-101) on total symptoms of CRSwNP compared to placebo	• Change from Baseline over Weeks 24 and 28 in NPSD TSS

Objectives	Endpoints
•	•
• To assess the effect of verekitug (UPB-101) on the resolution of NP compared to placebo	• Proportion of participants at Week 24 who achieve a maximum NPS of 1 in each nostril
• To assess immunogenicity of verekitug (UPB-101)	• Incidence of ADAs during the study (including the Follow-up Period) • In participants with ADAs, incidence of NAbs during the study (including the Follow-up Period)
• To assess the PK of verekitug (UPB-101)	• Summary of serum concentrations of verekitug (UPB-101) from baseline, Treatment, and Follow-Up Periods
• To assess the PD effect of verekitug (UPB-101) on blood and nasal secretion biomarkers	• Absolute and percent change from baseline over Week 24 in blood and nasal secretion biomarkers
• To assess the effect of verekitug (UPB-101) on adequacy of asthma control in participants with comorbid asthma	• Change from Baseline over Week 24 in ACQ-6 in participants with comorbid asthma
• To assess the effect of verekitug (UPB-101) on lung function in participants with comorbid asthma	• Change from Baseline over Week 24 in FEV_1 in participants with comorbid asthma
• To assess the effect of verekitug (UPB 101) on CT scan opacification of the sinuses compared to placebo (CT scans not performed in Germany and Czechia)	• Change from baseline to Week 24 in three Dimensional CT volumetric measurement of the paranasal sinuses

Abbreviations: ACQ-6=Asthma Control Questionnaire-6, ADA=antidrug antibody, AE=adverse event, CRSwNP=chronic rhinosinusitis with nasal polyps, CT=computed tomography, DSS=difficulty with sense of smell, ECG=electrocardiogram, FEV_1=forced expiratory volume in 1 second, LMK=Lund Mackay, NAb=neutralizing antibody, NCS=nasal congestion score, NP=nasal polyps, NPS=nasal polyp score, NPSD=nasal polyposis symptom diary, PD=pharmacodynamics, PK=pharmacokinetics, SAE=serious adverse event, TSS=total symptom score.

Primary, Secondary, and Other Estimand Attributes:

The comparison will include all participants who are randomized.

Treatment policy and composite variable strategies will be used to deal with intercurrent events (ICEs) including study treatment discontinuation, start of another biologic treatment for CRSwNP, surgery for NPs as rescue treatment, and other non-surgical rescue treatments.

Overall Design Summary:

This study is a Phase 2, randomized, double-blind, placebo-controlled, multinational, multi-center study to assess the efficacy and safety of verekitug (UPB-101) administered subcutaneously (SC) in participants with CRSwNP on background therapy with stable dosage of intranasal corticosteroids (INCS). This study consists of a 3 to 5-week Screening Period, a CCI Treatment Period, and a 4-week Follow-up Period (Figure 1–1).

Screening Period:

Participants will be evaluated for eligibility during the Screening Period before randomization and dosing. A total of approximately CCI participants will be enrolled in the study.

The Screening Period is also used to standardize at least 21 days of background INCS to mometasone furoate (or equivalent INCS) 2 actuations (50 µg/actuation) in each nostril twice daily for a total daily dose of 400 µg, which is the recommended dosage for mometasone furoate for the treatment of NP (Nasonex® [mometasone furoate monohydrate]). If participants cannot tolerate this dose, they are allowed to stay on a lower dose of 200 µg daily.

Treatment Period:

The Treatment Period is CCI where participants will be randomized in 1:1 ratio to receive verekitug (UPB-101) CCI mg or matching placebo. The randomization will be stratified by the presence of comorbid asthma and/or non-steroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD), and prior NP surgery.

The study intervention will be administered SC CCI. After each administration of the study intervention, participants will be monitored at the site for a minimum of 90 minutes to assure their safety. A description of rescue medication is provided in Section 6.9.3.

Follow-up Period:

Following completion of the CCI Treatment Period, participants will be followed for 4 weeks (16 weeks following the last dose of study intervention) to evaluate their disease activity, PK, biomarkers, safety, and immunogenicity.

Brief Summary:

The purpose of this study is to evaluate the efficacy and safety of verekitug (UPB-101) in participants with CRSwNP on a background of nasal corticosteroids. Approximately [redacted] participants are planned for enrollment and will be randomized in 1:1 ratio to receive verekitug (UPB-101) or matching placebo. Background INCS will be standardized. The randomization will be stratified by the presence of comorbid asthma and/or NSAID-ERD, and prior NP surgery.

Study details include:

Study duration: Approximately 31 to 33 weeks including Screening Period.

Treatment duration: [redacted].

Visit frequency: Visit 1 (Screening), Visit 2 (Baseline), 3, 4, 5, 6, 7, 8 (end of treatment [EOT] or early termination), and 9 (Follow-up Period). Following the final visit of the Treatment Period, participants will be followed once at the Follow-up Visit (Visit 9/End of Study [EOS]).

Number of Participants:

Approximately [redacted] participants will be enrolled into the study and randomized into a 1:1 ratio to receive either verekitug (UPB-101) or matching placebo.

Note: "Enrolled" means participants' agreement to participate in a clinical study following completion of the informed consent process, Screening Period, and study intervention assignment. Participants who are screened for the purpose of determining eligibility for the study, but who are not assigned a study intervention, are not considered enrolled and will be deemed screen failure.

Study Groups and Duration:

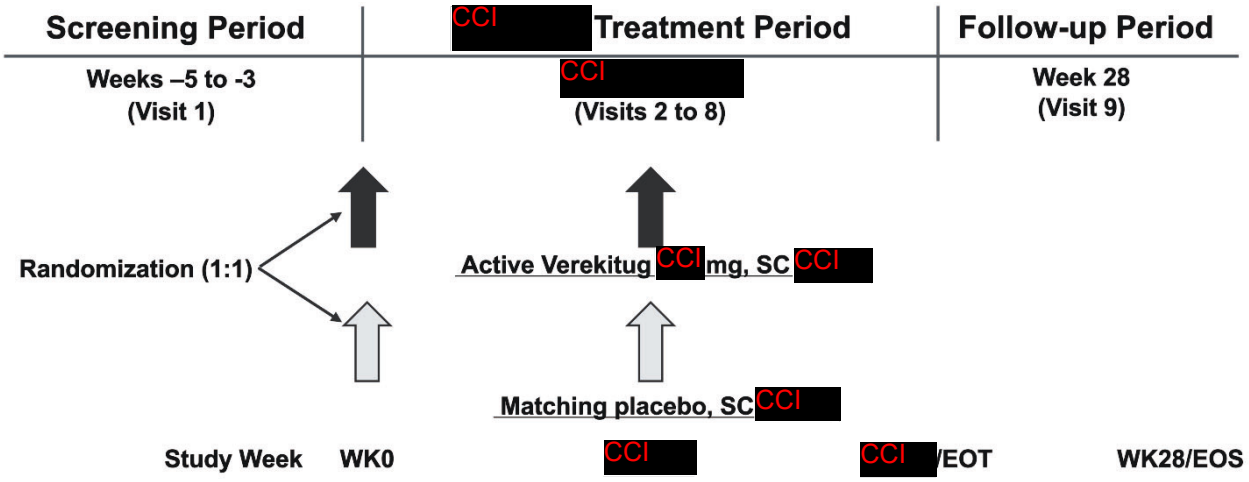
This study will consist of 2 treatment arms, verekitug (UPB-101) and placebo arms. Each participant will receive SC dose of verekitug (UPB-101) or placebo [redacted] (i.e., 2 doses). Study intervention may be administered in the SC tissue of any extremity or on either side of the abdominal wall.

Data Monitoring Committee:

A data monitoring committee (DMC) will be appointed for this study. The DMC is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding study modifications or the stopping of a study for harm. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring this study. Additional details will be provided in a DMC Charter.

1.2 Schema

Figure 1–1 Study Design



Note: The Screening Period includes at least 21 days of standardization of background INCS to MFNS or equivalent. The Follow-Up Period WK 28/EOS Visit will occur approximately 4 weeks after completion of the EOT and approximately 16 weeks after the last dose of study intervention.
EOS=End of Study, EOT=End of Treatment, MFNS=mometasone furoate nasal spray, CCI, SC=subcutaneous, and WK=week.

1.3 Schedule of Activities

Table 1–1 Schedule of Activities (SoA)

Procedure [a, b]	**Screening Period**	**Treatment Period**							**Follow-up Period**	**Reference Section**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/EOT**[c]	**9/EOS**	
Study Week	**-5 to -3**	**Day 1 (WK 0)**	**WK 2**	**WK 4**	**WK 8**	**WK 12**	**WK 18**	**WK 24**	**WK 28**	
Visit Window (±days)		**NA**	**± 2**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	
Informed Consent	X									Section 10.1.3
Inclusion/Exclusion Criteria	X	X								Section 5.1 and Section 5.2
Participant Demography	X									Section 9.3.1.2
Medical/Surgical History	X	X								Section 8.1
Medication History	X	X								Section 6.9
CRSwNP History	X	X								Section 6.9 and Section 8.1
Asthma History[d]	X	X								Section 6.9 and Section 8.1
Height	X									Section 8.3.1
Weight	X							X	X	Section 8.3.1
Complete Physical Examination	X					X		X		Section 8.3.2
Targeted Physical Examination		X	X	X	X		X		X	Section 8.3.2
Record concomitant medication		<==========							==========>	Section 6.9.1
Dispense and/or Download Diary	X									Section 8.2.2
Assess Background INCS Usage	X									Section 4.1 and Section 6.9
Assess MFNS (or equivalent) Usage		X	X	X	X	X	X	X	X	Section 6.9.2

Procedure [a, b]	**Screening Period**	**Treatment Period**							**Follow-up Period**	**Reference Section**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/EOT**[c]	**9/EOS**	
Study Week	**-5 to -3**	**Day 1 (WK 0)**	**WK 2**	**WK 4**	**WK 8**	**WK 12**	**WK 18**	**WK 24**	**WK 28**	
Visit Window (±days)		**NA**	**± 2**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	
Treatment:										
Randomization/ Study Intervention Assignment		X								Section 6.3
Administration of Study Intervention		X				X				Section 6.1.1
Injection Site Reactions Assessment		<==========							==========>	Section 2.3.1
Efficacy:										
Nasal Endoscopy for NPS[e]	X	X				X		X		Section 8.2.1.1 and Section 10.6
Sinus CT Scan (CT scans not performed in Germany and Czechia)[f]	X							X		Section 8.2.1.2 and Section 10.8
Daily Diary/PRO (NPSD)	<==========Background MFNS or equivalent, Nasal Polyposis Symptoms==========								>	Section 8.2.2 and Section 10.7
Training and/or Compliance with Daily Diary/PRO (NPSD)	X	X	X	X	X	X	X	X	X	Section 8.2.2 and Section 10.7
Spirometry (in participants with comorbid asthma only)	X[g]					X		X		Section 8.2.3
ACQ-6 (in participants with comorbid asthma only)		X				X		X	X	Section 8.2.2.4
Safety:										
AE/SAE Review	X	X	X	X	X	X	X	X	X	Section 8.4
Vital Signs[h]	X	X[h]	X	X	X	X[h]	X	X	X	Section 8.3.3
12-lead ECG (local reading)[i]	X	X[i]				X		X	X	Section 8.3.4

Procedure [a, b]	**Screening Period**	**Treatment Period**							**Follow-up Period**	**Reference Section**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/EOT**[c]	**9/EOS**	
Study Week	**-5 to -3**	**Day 1 (WK 0)**	**WK 2**	**WK 4**	**WK 8**	**WK 12**	**WK 18**	**WK 24**	**WK 28**	
Visit Window (±days)		**NA**	**± 2**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	
Laboratory Testing:										
Hematology[j]	X	X	X	X	X	X	X	X	X	Table 10–3
Chemistry	X	X		X		X	X	X	X	Table 10–3
Coagulation	X								X	Table 10–3
Viral Serology	X									Table 10–3
Urinalysis	X	X		X		X		X	X	Table 10–3
Serum Pregnancy Test (for POCBP only)/FSH as applicable[k]	X							X	X	Section 8.3.6
Urine Pregnancy Test (POCBP only)[k]		X	X	X	X	X	X			Table 10–3
Serum PK		X	X	X		X	X	X	X	Section 8.5.1
Serum ADA and NAb		X				X		X	X	Section 8.9 and Section 8.5.1
Serum for IgA, IgE[l], IgG, and IgM		X		X		X	X	X		Table 10–3
Serum for PD biomarkers CCI CCI		X		X		X	X	X		Section 8.8 and Section 8.6.1.1
Nasal Secretion Sampling for Biomarkers CCI , CCI		X		X		X	X	X		Section 8.6.1.2

ACQ-6=Asthma Control Questionnaire-6, ADA=antidrug antibody, AE=adverse event, CRSwNP=chronic rhinosinusitis with nasal polyps, CT=computed tomography, ECG=electrocardiogram, EOS=end of study, EOT=end of treatment, FSH=follicle-stimulating hormone, IgA=immunoglobulin A, CCI INCS= intranasal corticosteroid, CCI MFNS=mometasone furoate nasal spray, NAb=neutralizing antibody, NPS=nasal polyp score, NPSD=nasal polyposis symptom diary, PD= p ic, PK=pharmacokinetics, POCBP=participants of childbearing potential, PRO=patient reported outcome, SAE=serious adverse event, CCI

a. Expected order of activities is detailed in Section 8. It is noted that the CT or nasal endoscopy procedure may occur on a different date than the study visit date due to restrictions in scheduling these procedures for the participant.
b. In an unfavorable situation, wherein study centers are closed, or in case of restrictions or for any other local/regional factors, or for any reason wherein participant's travel to the study center is not feasible due to conveyance issue, home visit(s), phone call visit(s), and/or remote assessments and/or site monitoring may be considered. To maintain/preserve data integrity (versus risking losing the data points), the assessments will be labeled as having been obtained remotely (home or non-site location) and will be subject to a separate statistical analysis (Section 8).
c. Participants who discontinue treatment early will, if at all possible, remain in the study to be evaluated for clinical observation and safety monitoring.
d. For participants with comorbid asthma.
e. Nasal endoscopy will be performed after all other efficacy assessments have been completed for the respective visit. At Visit 2, the Investigator will review the Visit 1 results from the central reader to confirm entry criteria have been met, as well as reconfirm eligibility based on Visit 2 endoscopy local reading. On dosing visits, endoscopy will be performed pre-dose.
f. Computed tomography scan will be performed during the Screening Period (at Visit 1 or after, provided results are available prior to Visit 2). In case of early termination, the Investigator will determine whether to perform an EOT CT scan, based on the age, clinical condition, and overall risk to the participant and timing of the EOT visit. (CT scans not performed in Germany and Czechia.)
g. To accommodate withholding of background therapies prior to spirometry, screening spirometry may be performed on a separate day during the Screening Period.
h. On dosing visits, vital signs will be measured at pre-dose, post-dose, and within 30 minutes prior to discharge.
i. At Visit 2 there will be 2 ECGs performed: pre-dose and within 30 minutes prior to discharge.
j. Hematology panel includes blinded/masked eosinophils, monocytes and basophils starting at Visit 2 (unblinded/unmasked prior to Visit 2).
k. Serum and urine pregnancy test (for POCBP): A negative result of serum pregnancy test at Visit 1 and urine pregnancy test must be obtained prior to randomization at Visit 2. Participants <50 years old who are amenorrheic for >12 months who are considered menopausal must have a FSH ≥ 40 IU/mL at Visit 1. At the EOS Visit, a home pregnancy testing kit will be issued to participants who are POCBP to be used at approximately Day 120 post-last dose. Results should be reported to the Investigator.
l. IgE will be blinded/masked for all applicable visits.

2 Introduction

Verekitug (UPB-101), previously referred to as ASP7266, is a novel recombinant fully human IgG1 mAb targeting the human TSLP signaling by blocking the TSLPR.

The term “study intervention” throughout the protocol, refers to verekitug (UPB-101) and placebo.

2.1 Study Rationale

Rhinosinusitis is a disease characterized by inflammation of one or more of the paranasal sinuses. Chronic rhinosinusitis is divided into 2 clinical subtypes: (1) CRSwNP; (2) CRSsNP. Nasal polyps are inflammatory outgrowths of the paranasal sinus mucosa along the middle and superior meatus that occur primarily in adults. In CRSwNP, NPs are benign and typically develop bilaterally in the sino-nasal cavity.

Treatment of NP includes medical and surgical therapy aimed at either complete elimination of polyps or sufficient reduction in polyp size to alleviate nasal obstruction and associated symptoms. Both topical corticosteroids and nasal saline irrigations are recommended as initial medical therapies in CRSwNP. Intranasal and oral corticosteroids can reduce NP size, lessen sino-nasal symptoms, and improve quality of life. However, the adverse effects of long-term systemic corticosteroid use outweigh their advantages and should only be considered for short-term administration. Surgery to remove nasal polyps is typically reserved for refractory cases. Up to 50% of patients with CRSwNP have a history of sino-nasal surgery (Philpott et al. 2015). The rate of nasal polyp recurrence after surgery is between 40-60% (DeConde et al. 2017; Rosenfeld et al, 2015).

Biologic therapies provide new therapeutic options for severe uncontrolled CRSwNP patients. However, their frequent administration, side effects and costs may limit their usage. Therefore, there is a continued need to develop additional therapies to further improve the significantly impaired quality of life of these patients.

Verekitug (UPB-101) is a novel recombinant fully human IgG1 mAb targeting the human TSLP signaling by blocking the TSLPR.

Non-clinical studies have demonstrated that verekitug (UPB-101) binds to monkey TSLPRs and inhibits TSLPR-mediated signal transduction (Studies 7266-PH-0001, 7266-PH-9002, 7266-PH-9003, 7266-PH-9005, 7266-PH-9007). Furthermore, verekitug (UPB-101) has been observed to inhibit TSLP-stimulated myeloid dendritic cell-mediated differentiation of naive $CD4^+$ T-cells into mature T-cells *in vitro* (Study 7266-PH-9004). In sensitized monkeys, verekitug (UPB-101) suppressed ascaris extract-induced skin reactions, suggesting verekitug (UPB-101) inhibits Th2 type allergic responses (Study 7266-PH-9006). Verekitug (UPB-101) is currently under development for the treatment of moderate to severe asthma.

Given the role of the TSLP in the pathogenesis of a variety of allergic diseases triggering type-2 inflammatory responses, and the increased expression or activity of TSLP in NP tissue in CRSwNP, there is a biological and pathophysiological plausibility to develop verekitug (UPB-101) for the treatment of CRSwNP.

The purpose of this study is to evaluate the efficacy and safety of verekitug (UPB-101) in participants with CRSwNP on a background of nasal corticosteroids. Additionally, PD, PK, health-related quality of life, immunogenicity, and improvement in lung function in participants with comorbid asthma will be assessed.

2.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of verekitug (UPB-101) is provided in the Investigator's Brochure (IB).

2.2.1 Background on Chronic Rhinosinusitis with Nasal Polyps

Chronic rhinosinusitis with NPs is a predominantly adult disease with a prevalence estimated to be 2.5% to 2.7% and it increases with age (Fokkens et al, 2020; Stevens et al, 2016). Chronic rhinosinusitis and NPs can be demonstrated on sinus CT scan and/or nasal endoscopy (Rosenfeld et al, 2015). The 4 cardinal symptoms of CRSwNP include anterior or posterior rhinorrhea, nasal congestion, hyposmia or anosmia, and facial pain or pressure (Fokkens et al, 2020). Patients with CRSwNP usually have more severe sino-nasal symptoms and, even following sinus surgery, patients can continue to have more severe disease and on average are more likely to require revision sinus surgeries (Deal et al, 2004; Dietz de Loos et al, 2013; Fokkens et al, 2020; Poetker et al, 2007; Toros et al, 2007). Additionally, ear pain, sneezing, severe difficulty breathing through the nose, severe nasal congestion and severe loss of smell are significantly more likely to be reported in CRSwNP patients with eosinophilic versus non-eosinophilic NP (Thompson et al, 2016).

Nasal polyps cause severe morbidity due to sleep disturbances, headaches, and loss of smell. Several studies showed impaired quality of life in patients with NP (decreased general health, emotional function, ability to perform daily activities, sleep quality, and productivity) comparable to congestive heart failure, asthma, and chronic obstructive pulmonary disease (Glicklich et al, 1995).

Chronic rhinosinusitis with NPs is described by a type 2 inflammatory signature with enhanced tissue eosinophilia. Levels of eosinophilic granule proteins and eosinophil chemotactic proteins are shown to be elevated (Bachert et al, 2001; Derycke et al, 2014; Olze et al, 2006; Van Bruaene et al, 2008; Van Zele et al, 2006; Yao et al, 2009). TSLP is now widely recognized as a key regulator of type 2 inflammation. It is an epithelial derived interleukin (IL)-7-like cytokine that stimulates dendritic cells to induce naive $CD4^+$ T-cell differentiation into Th2 cells (Ito et al, 2005; Liu et al, 2006; Liu et al, 2007, Comeau et al, 2010). TSLP synergizes with the inflammatory cytokine IL-1 to potently activate mast cells to produce Th2 cytokines including IL-5 and IL-13 (Nagarkar et al, 2012). Considerable evidence now implicates TSLP in the pathogenesis of several type 2 related inflammatory disease including CRSwNP (Kimura et al, 2011; Liu et al, 2011). Also, TSLP activity is shown to be elevated in the NP (Nagarkar et al, 2013).

2.2.2 Summary of Findings from Non-clinical Studies with Potential Clinical Relevance

Non-clinical studies have demonstrated that verekitug (UPB-101) binds to monkey TSLPRs and inhibits TSLPR-mediated signal transduction. Verekitug (UPB-101) has been observed to inhibit TSLP-stimulated myeloid dendritic cell-mediated differentiation of naive $CD4^+$ T-cells into mature T-cells *in vitro.* In sensitized monkeys, verekitug (UPB-101) suppressed ascaris extract-induced skin reactions, suggesting that verekitug (UPB-101) inhibits Th2 type allergic responses.

2.2.3 Summary of Findings from Previous Clinical Study

One clinical study (7266-CL-0001) with verekitug (UPB-101) has been completed in healthy subjects.

This study was a randomized, subject- and Investigator-blinded, placebo-controlled, single ascending dose (SAD) study to evaluate the safety, tolerability, PK, and PD of verekitug (UPB-101) (formerly referred to as ASP7266) in healthy adult male and female subjects. Six sequential cohorts of healthy subjects received placebo or verekitug (UPB-101) (0.03-10 mg/kg body weight) by intravenous (IV) administration. One cohort of healthy subjects received

placebo or verekitug (UPB-101) (1 mg/kg) by SC administration. All cohorts included 8 subjects (6 active and 2 placebo) each.

Bioavailability after SC administration of 1 mg/kg verekitug (UPB-101) was 70%. The mean maximum observed concentration (C_{max}) was CCI µg/mL and this was observed at 3 to 12 days post-dose (median 6.3 days). The apparent terminal elimination half-life ($t_{1/2}$) was CCI days.

Twenty-one out of 42 subjects who received verekitug (UPB-101) (16 via IV dosing and 5 via SC dosing) and 3 out of 14 subjects who received placebo (IV) experienced treatment-emergent adverse events (TEAEs). There was no dose-related increase in the incidence and severity of TEAEs. The most frequently reported TEAEs overall were headache (3 subjects in the Total verekitug [UPB-101] IV group, 1 subject in the verekitug [UPB-101] SC group, and 3 subjects in the Placebo IV group) and dysmenorrhea (3 subjects in the total verekitug [UPB-101] IV group and 2 subjects in the verekitug [UPB-101 SC group]). One subject (1 mg/kg verekitug [UPB-101] IV) had a serious adverse event (SAE) of nephrolithiasis; the event was severe and considered not related to study intervention by the Investigator. No deaths or TEAEs that led to discontinuation of treatment were reported. Less than half of the reported TEAEs were considered by the Investigator to be drug-related; only headache was reported in more than 1 subject (2 subjects in the Placebo IV group).

There were no AEs of possible hepatic or renal origin and there were no acute or chronic hypersensitivity reactions reported. Five subjects had the following non-serious TEAEs in the System Organ Class of infections and infestations:

No clinically relevant trends were observed in any of the clinical laboratory analyses and no subjects had laboratory values that met the potentially clinically significant criteria for hepatotoxicity or required further liver function investigation. None of the subjects who received verekitug (UPB-101) SC (1 mg/kg) developed injection site AEs.

Overall, 1, 2, 3, 3, and 1 subjects in the 0.03, 0.1, 0.3, 1, and 3 mg/kg verekitug (UPB-101) IV treatment groups, respectively, and 3 subjects in the 1 mg/kg verekitug (UPB-101) SC treatment group had positive results for anti-verekitug (UPB-101) antibody formation; however, the titers were low and there was no consistent pattern that would indicate a dose -related effect, or an effect related to the administration route.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of verekitug (UPB-101) may be found in the IB. Relevant clinical findings from the ongoing or completed trials will be taken into account for the present clinical trial and participants will be informed accordingly.

2.3.1 Risk Assessment

Based on available non-clinical data, as well as known adverse effects of currently available biologic disease-modifying asthma agents, several potential risks have been identified for which mitigation actions have been developed to minimize the relevant risks in clinical studies of verekitug (UPB-101). In addition, AE monitoring and other routine clinical and laboratory monitoring (including laboratory safety such as hematology and biochemistry, vital signs, physical examination, and electrocardiograms [ECGs]) will be conducted. Based on the potential risk of clinical significance identified in the toxicology studies, the risk minimization actions that will be included in clinical studies are presented in Table 2–1. Verekitug (UPB-101) is a novel recombinant fully human IgG1 mAb targeting the human TSLP signaling by blocking the TSLPR in NP tissue intended for the treatment of CRSwNP. Verekitug (UPB-101) is currently under development for the treatment of asthma.

The protocol has been designed to minimize the risk to research participants. Participants will be monitored to detect AEs during the study and followed appropriately to ensure resolution or stabilization of AEs. Based on verekitug (UPB-101) inhibition mechanism of action, the adverse events of special interest (AESIs) will be monitored as described in Section 8.4.6.

Given the safety and tolerability profile of verekitug (UPB-101) in preclinical studies and the ongoing Phase 1 studies (multiple ascending dose study UPB-CP-01 and ethno-bridging study UPB-CP-02), the overall risk to the participants in this study is deemed to be low.

Table 2–1 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): Verekitug (UPB-101)		
ISR	Risks common to the biologics based on mode of action include ISR. In the first -in -human Phase 1a single-dose study in healthy volunteers conducted with verekitug (UPB-101), none of the subjects who received verekitug (UPB-101) SC (1 mg/kg) developed ISR AEs.	Participants will be monitored for unusual signs and symptoms of ISRs such as pain, localized swelling, tenderness, or erythema. Severe ISRs are considered AESIs and must be reported to the Sponsor promptly, per protocol.
Embryo-fetal toxicity	There are no studies of the effects on embryo-fetal development.	Participants of childbearing potential, participants who produce sperm and who have partners of childbearing potential are required to use highly effective contraception methods as specified in Appendix 4 (Section 10.4). Participants of childbearing potential will have pregnancy testing as specified in the SoA (Section 1.3). Participants who become pregnant will discontinue verekitug (UPB-101) dosing and contact their physician immediately.

Abbreviations: AE=adverse event, ISR=injection site reaction, SC=subcutaneous, SoA=schedule of activities.

2.3.2 Benefit Assessment

Verekitug (UPB-101) is a novel recombinant fully human IgG1 mAb targeting the human TSLP signaling by blocking the TSLPR in NP tissue intended for the treatment of CRSwNP. Verekitug (UPB-101) is currently under development for the treatment of asthma. As summarized in Section 2.1, there is ample rationale to study verekitug (UPB-101) as a potential future therapy for CRSwNP.

The results of this study will help to further define the effects of verekitug (UPB-101) as potential treatment for patients with CRSwNP in the future and will guide researchers to plan and design future studies in CRSwNP. Therefore, the Sponsor considers that it is medically and ethically acceptable to perform the proposed study.

2.3.3 Overall Benefit/Risk Conclusion

Given the safety and tolerability profile of verekitug (UPB-101) in preclinical studies and the ongoing Phase 1 studies, the overall risk to the participants in this study is deemed to be low. Taking into account the measures taken to further minimize risk to participants in this study, the

potential risks identified in association with verekitug (UPB-101) are justified by the anticipated benefits that may be afforded to participants with CRSwNP.

3 Objectives, Endpoints, and Estimands

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effect of verekitug (UPB-101) on endoscopic NPS compared to placebo	• Change from Baseline at Week 24 in NPS
Secondary	
• To assess the effect of verekitug (UPB-101) on NCS compared to placebo	• Change from Baseline at Week 24 in the NCS evaluated by the NPSD
• To assess the effect of verekitug (UPB-101) on CT scan opacification of the sinuses compared to placebo (CT scans not performed in Germany and Czechia)	• Change from Baseline at Week 24 in opacification of sinuses measured by LMK Score evaluated by quantitative CT assessment (CT scans not performed in Germany and Czechia)
• To assess the effect of verekitug (UPB-101) on loss of smell compared to placebo	• Change from Baseline at Week 24 in mean DSS evaluated by the NPSD
• To assess the effect of verekitug (UPB-101) on the need for treatment with systemic corticosteroids or NP surgery compared to placebo	• Proportion of participants requiring systemic corticosteroids or NP surgery • Time to first nasal polyposis surgery and/or use of systemic corticosteroids for nasal polyposis up to Week 24
• To assess the effect of verekitug (UPB-101) on total symptoms of CRSwNP compared to placebo	• Change from Baseline at Week 24 in NPDS TSS
Safety	
• To assess safety and tolerability of verekitug (UPB-101) compared to placebo	• AEs, SAEs, physical examinations, clinical laboratory assessments, vital signs, and ECGs from Baseline over study duration, including the Follow-Up Period
Other	
• To assess the effect of verekitug (UPB-101) on endoscopic NPS compared to placebo	• Change from Baseline over Week 24 in NPS
• To assess the effect of verekitug (UPB-101) on NCS compared to placebo	• Change from Baseline over Weeks 24 and 28 in NCS evaluated by the NPSD
• To assess the effect of verekitug (UPB-101) on loss of smell compared to placebo	• Change from Baseline over Weeks 24 and 28 in DSS evaluated by the NPSD

Objectives	Endpoints
• To assess the effect of verekitug (UPB-101) on total symptoms of CRSwNP compared to placebo	• Change from Baseline over Weeks 24 and 28 in NPSD TSS
•	•
• To assess the effect of verekitug (UPB-101) on the resolution of NP compared to placebo	• Proportion of participants at Week 24 who achieve a maximum NPS of 1 in each nostril
• To assess immunogenicity of verekitug (UPB-101)	• Incidence of ADAs during the study (including the post-treatment Follow-Up Period) • In participants with ADAs, incidence of NAb during the study (including the Follow-Up Period)
• To assess the PK of verekitug (UPB--101)	• Summary of serum concentrations of verekitug (UPB-101) from Baseline, Treatment, and Follow-Up Periods
• To assess the PD effect of verekitug (UPB-101) on blood and nasal secretion biomarkers	• Absolute and percent change from Baseline over Week 24 in blood and nasal secretion biomarkers
• To assess the PD effect of verekitug (UPB-101) on adequacy of asthma control in participants with comorbid asthma	• Change from Baseline over Week 24 in participant ACQ-6 in participants with comorbid asthma
• To assess the effect of verekitug (UPB-101) on lung function in participants with comorbid asthma	• Change from Baseline over Week 24 in FEV_1 in participants with comorbid asthma
• To assess the effect of verekitug (UPB 101) on CT scan opacification of the sinuses compared to placebo (CT scans not performed in Germany and Czechia)	• Change from baseline to Week 24 in three Dimensional CT volumetric measurement of the paranasal sinuses

Abbreviations: ACQ-6=Asthma Control Questionnaire-6, ADA=antidrug antibody, AE=adverse event, CRSwNP=chronic rhinosinusitis with nasal polyps, CT=computed tomography, DSS=difficulty with sense of smell, ECG=electrocardiogram, FEV_1=forced expiratory volume in 1 second, LMK=Lund Mackay, NAb=neutralizing antibody, NCS=nasal congestion score, NP=nasal polyps, NPS=nasal polyp score, NPSD=nasal polyposis symptom diary, PD=pharmacodynamic, PK=pharmacokinetic, SAE=serious adverse event, TSS=total symptom score.

Estimands

For the primary efficacy endpoint, the estimand is described in Section 9.3.2.2, including treatment policy and composite variable strategies to deal with ICE like study treatment

discontinuation, start of another biologic treatment for CRSwNP, surgery for NPs as rescue treatment, and other non-surgical rescue treatments.

4 Study Design

4.1 Overall Design

This study is a Phase 2, randomized, double-blind, placebo-controlled, multinational, multi-center study to assess the efficacy and safety of verekitug (UPB-101) administered SC in participants with CRSwNP on background therapy with stable dosage of INCSs. This study consists of a 3 to 5-week Screening Period, a CCI Treatment Period, and a 4-week Follow-up Period (Figure 1–1).

Screening Period:

Participants will be evaluated for eligibility during the Screening Period before randomization and dosing. Approximately CCI participants will be enrolled in the study.

The Screening Period is also used to standardize at least 21 days of background INCS to mometasone furoate (or equivalent INCS) 2 actuations (50 µg/actuation) in each nostril twice daily for a total daily dose of 400 µg, which is the recommended dosage for mometasone furoate for the treatment of NP (Nasonex® [mometasone furoate monohydrate]). If participants cannot tolerate this dose, they are allowed to stay on a lower dose of 200 µg daily.

Treatment Period:

The Treatment Period is CCI where participants will be randomized in 1:1 ratio to receive verekitug (UPB-101) CCI mg or matching placebo. The randomization will be stratified by the presence of comorbid asthma and/or NSAID-ERD, and prior NP surgery.

The study intervention will be administered SC CCI. After each administration of the study intervention, participants will be monitored at the site for a minimum of 90 minutes to assure their safety. A description of rescue medication is provided in Section 6.9.3.

Follow-up Period:

Following completion of the [redacted] Treatment Period or in case of early termination, participants will be followed for 4 weeks to evaluate their disease activity, PK, biomarkers, safety, and immunogenicity.

4.2 Scientific Rationale for Study Design

The study is to evaluate the efficacy and safety of verekitug (UPB-101) in participants with CRSwNP on a background of nasal corticosteroids. The current study design is appropriate to meet the objectives of this clinical study.

Generally, a double-blind, placebo-controlled study is appropriate and standard for a proof-of-concept study. This design will minimize bias and provide reference data (i.e., data from placebo-treated participants) which will aid in the interpretation of results. Standard of care rescue medication(s) or treatment allowed for CRSwNP exacerbations are described in Section 6.9.3.

The safety assessments for the study are accepted measures for ensuring safety of participants during a clinical study. The justification for dose selection is discussed in Section 4.3.

4.3 Justification for Dose

A [redacted] mg [redacted] SC dose of verekitug (UPB-101) was selected for this study based on the population PK modeling, pharmacology, and safety data with verekitug (UPB-101) across nonclinical and clinical studies (Study 7266-PH-9002, 7266-TX-0006, Study 7266-CL-0001, and UPB-CP-01).

Based on the population PK modeling predictions, the [redacted] mg [redacted] SC dose provides trough concentration higher than the expected maximally therapeutic concentration threshold derived from pharmacology data in asthmatic subjects (Study UPB-CP-01). The proposed dose and dosing regimen in the study is appropriate from a safety perspective and the predicted steady state exposure provides adequate safety margins of > 79-fold (for both C_{max} and area under the plasma concentration time curve [AUC]) when compared to exposures achieved at the highest dose and no-observed-adverse-effect level (NOAEL) of [redacted] mg/kg evaluated in the chronic toxicology study in cynomolgus monkeys (7266-TX-0006). In addition, the predicted exposure at [redacted] mg [redacted] SC dose is lower than the observed exposure in the completed SAD clinical study wherein verekitug (UPB-101) was considered safe and well-tolerated up to IV dose of [redacted] mg in healthy male and female adults. (Study 7266-CL-0001).

4.4 End-of-Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study globally or last scheduled procedure shown in the SoA (Table 1–1) for the last participant in the study.

A participant is considered to have completed the study if the participant has completed all periods of the study including the Week 28/EOS Visit, as shown in the SoA (Table 1–1).

5 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

The study population will consist of participants with CRSwNP. Participants must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

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

Informed Consent

1. Participant has signed, dated and received a copy of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent form (ICF) as described in Appendix 1 (Section 10.1.3), which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Age

2. Participant is aged 18 to 85 years of age (inclusive) at the time of signing the ICF.

Type of Participant and Disease Characteristics

3. Participant has physician diagnosed CRSwNP for at least 6 months prior to Visit 1 that fulfils all of the following:
    - Severity consistent with need for surgery as defined by an endoscopic bilateral nasal polyp score (NPS) of at least 5 out of 8 and a minimum score of 2 in each nasal cavity at Visit 1 based on central reading, as well as reconfirmed at Visit 2 based on local reading.
    - Average nasal congestion score (NCS) ≥ 2 over 14 days before Visit 2 (calculation noted in Section 8.2.2.1).

- Ongoing symptoms of CRSwNP for at least 8 weeks prior to Visit 1 such as rhinorrhea and/or reduction in smell.

4. Participant has at least one of the following:
   - In the 24 months prior to Visit 1, had a documented exacerbation of nasal polyposis requiring treatment with systemic corticosteroid, and/or;
   - A medical contraindication/intolerance to systemic corticosteroid, and/or;
   - Had prior surgery for NP (cannot be within 6 months prior to Visit 1 – see Section 5.2).
5. Stable standard of care treatment for CRSwNP for at least 30 days prior to Visit 1.
6. At Visit 2, at least 21 days of background mometasone furoate nasal spray (MFNS) (or equivalent) background therapy.
7. ≥70% dosing compliance for MFNS (or equivalent) in the 14 days prior to Visit 2. *Note: Compliance is verified based on MFNS (or equivalent) use recorded on the participant's diary, with an expected dosing regimen of 2 actuations (50 µg/actuation) in each nostril, or equivalent, twice a day (for a total daily dose of 400 µg). If participant cannot tolerate, as determined at Visit 1, the expected dosing regimen is 2 actuations (50 µg/actuation) in each nostril, once daily, for a total daily dose of 200 µg. Compliance will be calculated based on the number of doses taken (morning and evening) relative to the expected dosing regimen.*

Contraceptive/Barrier Requirements

8. Contraceptive use by the participant must be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

NOTE: The reliability of sexual abstinence for participant enrollment eligibility needs to be evaluated in relation to **the duration of the clinical study and the preferred and usual lifestyle of the participant**. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception.

Participants capable of producing sperm:

- Agree to refrain from donating sperm during the intervention period and for a period of 120 days after the last dose of study intervention or at the Final Visit, whichever occurs last.

  AND

- Agree to follow the contraceptive guidance in Appendix 4 of this protocol during the intervention period and for a period of 120 days after the last dose of study intervention or at the Final Visit, whichever occurs last.

AND

- Agree to use a condom when engaging in any activity that allows for passage of ejaculate to another person during the intervention period and for a period of 120 days after the last dose of study intervention or at the Final Visit, whichever occurs last.

Participants of childbearing potential:

- Agree to refrain from donating eggs for a period of 120 days after the last dose of study intervention or at the Final Visit, whichever occurs last.
- Participants are eligible to participate if they are not pregnant (see Appendix 4), not breastfeeding, and at least one of the following conditions applies:
  - Not a participant of childbearing potential (POCBP) as defined in Appendix 4;

    OR

  - A POCBP who agrees to follow the contraceptive guidance in Appendix 4 during the intervention period and for 120 days after the last dose of study intervention or at the Final Visit, whichever occurs last.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has undergone any intranasal and/or sinus surgery (including polypectomy) within 6 months prior to Visit 1.
2. Expected need, in the opinion of the investigator, for NP surgery within 12 weeks of Visit 2.
3. Comorbid asthma having forced expiratory volume in 1 second (FEV_1) 50% or less of predicted normal at Visit 1.
4. Conditions making participants non-evaluable at Visit 1 for the primary endpoint such as sino-nasal or sinus surgery changing the lateral wall structure of the nose, antrochoanal polyps, nasal septal deviation occluding at least one nostril, acute sinusitis, upper respiratory infection, ongoing rhinitis medicamentosa, fungal rhinosinusitis, nasal cavity benign or malignant tumors.

Prior/Concomitant Therapy

5. Concurrent participation in a clinical study or has been treated with an investigational drug within 28 days or 5 half-lives, whichever is longer, prior to Visit 1.
6. Previous exposure to verekitug (UPB-101) or known allergy/sensitivity to any of its excipients.
7. Biologic therapy or systemic immunosuppressant to treat inflammatory disease or autoimmune disease within 6 months or 5 half-lives before Visit 1, whichever is longer, with the exception of oral corticosteroids. Treatment with cyclophosphamide and rituximab within 12 months of Visit 1.
8. Any experimental mAb within 5 half-lives or within 6 months before Visit 1 if the half-life- was unknown.
9. Leukotriene antagonists/modifiers at Visit 1 unless used as a continuous treatment at same dose for at least 30 days prior to Visit 1.
10. Allergen immunotherapy within 12 weeks (unless maintenance dose) prior to Visit 1 or plans to begin therapy or change dosing during the study. *Note: Stable maintenance doses of allergen immunotherapy within 12 weeks prior to Visit 1 are allowed.*
11. Administration of the T2 cytokine inhibitor suplatast tosilate within 15 days prior to Visit 1.
12. Oral, IV, or intramuscular steroid within 8 weeks prior to Visit 1. Intrathecal or intra-articular steroids are permitted.
13. Treatment with a live (attenuated) vaccine within 12 weeks before Visit 2.
14. Any vaccination within the Screening Period.
15. For participants with comorbid asthma, inhaled corticosteroid (ICS) total daily dose > 1000 µg fluticasone propionate (or equivalent dose of another ICS [Section 10.5]) or participants not on a stable dose of ICSs for ≥ 30 days prior to Visit 1.

Concomitant Conditions and Disease

16. Abnormal medical history, physical finding or safety finding that in the opinion of the Investigator may obscure the study data or interfere with the participant's safety. Participants with any clinically significant cardiac disease and/or ECG abnormality, in the opinion of the Investigator, obtained during the Screening Period should be excluded from the study.
17. Any clinical laboratory test result outside of the reference ranges considered by the Investigator as clinically significant and that may obscure the study data or interfere with the

participant's safety. *Note: out of range screening values may be repeated per Investigator's discretion (see* Section *5.4.1*).

18. Allergic granulomatous angiitis (Churg-Strauss syndrome), granulomatosis with polyangiitis (Wegener's granulomatosis), Young's syndrome, Kartagener's syndrome or other dyskinetic ciliary syndromes, concomitant cystic fibrosis.
19. Participant with comorbid asthma that also has a history or evidence of a clinically significant pulmonary condition (other than asthma), including significant restrictive findings on pulmonary function testing, chronic bronchitis, emphysema, bronchiectasis, pulmonary fibrosis, or any other related condition that may obscure the study data (e.g., gastro-esophageal reflux and vocal cord paralysis/dysfunction).
20. Evidence of active or suspected bacterial, viral, fungal, or parasitic infections within 2 weeks prior to Visit 2 (e.g., sinusitis, common cold, viral syndrome, flu-like symptoms).
21. History compatible with, or diagnosis of, a parasitic infection and has not been treated or has not responded to the standard of care therapy.
22. Type I or II diabetes under poor glucose control, as assessed by the Investigator.
23. Estimated glomerular filtration rate of < 60 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation (2021). *Note: Non-clinically significant out of range value may be repeated per Investigator's discretion (see* Section *5.4.1*).
24. History of malignancy of any type, other than curatively treated in-situ cervical cancer or surgically excised non-melanomatous skin cancers, within 5 years before Visit 1.
25. Participant underwent surgery requiring general anesthesia within 8 weeks of Visit 1, or surgery without full recovery within 4 weeks of Visit 1, or donated blood or blood products, experienced loss of blood ≥500 mL or received blood products within 8 weeks of Visit 1.
26. Immunodeficiency disorder or positive for human immunodeficiency virus (HIV) antibodies.
27. Positive hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibodies (HCV Ab).
28. Known active tuberculosis (TB) at Visit 1. A tuberculosis test may be performed if required based on local guidelines. For participants in Czechia:
    - All participants will have TB screening at Visit 1.
    - Participants treated within 12 months of Visit 1for active TB will be excluded from study.

- For participants with a history of active TB treated > 12 months prior to Visit 1 or a history of treated latent TB, written prior approval by a TB specialist or an infectious disease specialist is required prior to initiation of study drug. Such participants may be eligible for the study under the following conditions:
    - If history of active or latent TB: documented initiation or completion of a full course of anti-TB therapy.
    - If TB screening test at Visit 1 is positive or indeterminate: documented initiation or completion of adequate anti-TB treatment.

29. History of chronic alcohol or substance use disorder within 12 months prior to Visit 1.
30. Current tobacco smokers, nicotine vapers (including electronic cigarettes), snuff users or participants who have smoked and/or vaped and/or used snuff within the last 6 months prior to Visit 1.
31. Positive coronavirus disease 2019 (COVID-19) test within 28 days before Visit 1. *Note: Participants with a positive COVID-19 test within 28 days before Visit 1 can be reassessed after a negative COVID-19 test is obtained.*
32. Pregnant or breastfeeding or planning to become pregnant or breastfeed during the study or unwilling to use adequate birth control, if of reproductive potential and sexually active.

Administrative

33. Participant is an employee, consultant, and/or immediate family member (i.e., first degree relative, spouse, adoptee, or legal dependent) of the site or the Sponsor.
34. Participant is unreliable; incapable of adhering to the protocol and visit schedule according to the judgment of the Investigator; or has any disorder that may compromise their ability to give informed consent.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants are not required to fast before visits.

5.3.2 Nicotine

Usage of nicotine containing products (including but not limited to smoking, snorting, or vaping tobacco, use of snuff, cigars, cigarettes, pipes and/or patches) will not be permitted for the duration of the study.

5.3.3 Exercise Restriction

Participants with comorbid asthma should avoid vigorous exercise for at least 1 hour before visits with spirometry.

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure (e.g., eligibility requirements failed), and documentation of any medical occurrences that qualify as SAEs.

5.4.1 Re-testing

Participants who fail one or more criteria for reasons which in the opinion of the Investigator are likely to be remedied, may repeat the test(s) associated with those criteria (either at a subsequent Screening Visit or at an unscheduled visit), a maximum of 2 times, provided re-testing can be performed within the screening window. In such situations the reasons for the repeat tests must be documented in the source notes and results which meet the criteria must be obtained prior to randomization.

5.4.2 Re-Screening

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened. Rescreening will be permitted only once and only if the situation leading to the screen failure is considered likely to change based on the discretion of the Investigator and/or Medical Monitor.

Participants who are rescreened will receive a new participant number. A participant who is rescreened is not required to sign another ICF at rescreening, **unless a new version of the ICF becomes available**. During rescreening, all screening procedures will be repeated with the following exceptions: nasal endoscopy and CT scan (CT scans not performed in Germany and Czechia) if performed within 3 weeks and 4 months, respectively, prior to rescreening.

5.4.3 Screening and Enrollment Log and Participant Identification Numbers

The participant’s enrollment will be recorded in the Screening and Enrollment Log.

Upon enrollment, each participant will receive a unique participant identification number. Participant numbers must not be re-used for different participants.

6 Study Intervention(s) and Concomitant Therapy

Study interventions are all pre-specified, investigational and non-investigational medicinal products, medical devices and other interventions (e.g., surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 Study Interventions Administered

Table 6–1 Study Interventions Administered

Intervention Label	Verekitug (UPB-101)	Placebo
Intervention Name	Verekitug (UPB-101)	Placebo
Intervention Description	Verekitug (UPB-101) or matching placebo is subcutaneously administered [redacted]	
Type	Biologic	
Dosage Formulation	[redacted] mM Histidine, [redacted] mM Glycine, 0.03% (w/v) Polysorbate 80, pH [redacted]	20 mM Histidine, [redacted]% Sucrose, 16% Dextran [redacted], pH [redacted]
Unit Dose Strength(s)	[redacted] mg verekitug (UPB-101)	Not applicable
Dosage Level(s)	[redacted] mg, [redacted]	Matching placebo
Route of Administration	SC	
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor, subsidiary, or designee.	
Packaging and Labeling	Study Interventions will be provided in a vial. Each vial will be packaged and labeled as required per country requirements.	

Abbreviations: AxMP=auxiliary medicinal product, IMP=investigational medicinal product, NIMP=non investigational medicinal product, [redacted] SC=subcutaneous.

Table 6–2 Study Arms

Arm Title	Verekitug (UPB-101)	Placebo
Arm Type	Experimental	Matching placebo
Arm Description	Delivered as [redacted] mL of the formulated solution per SC injection (containing [redacted] mg verekitug [UPB-101])	Delivered as [redacted] mL of placebo per SC injection

SC=subcutaneous.

6.1.1 Administration of Study Intervention

Study intervention will be administered SC in any extremity or on either side of the abdominal wall. After each administration of the study intervention, participants will be monitored at the site for a minimum of 90 minutes to assure their safety.

If any of the following occur, the Investigator should reschedule the visit and the study intervention should not be administered until the rescheduled visit:

- Participant received allergen immunotherapy injection or aspirin desensitization on the same day as the scheduled study intervention administration.
- Participant has an intercurrent illness that, in the opinion of the Investigator, may compromise the safety of the participant in the study (e.g., viral illnesses).
- Participant is febrile (≥38°C; ≥100.4°F) within 72 hours prior to the study intervention administration.

6.2 Preparation, Handling, Storage, and Accountability

The Investigator or designee must download and file the temp-tale data from each shipment to document appropriate conditions (e.g., temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

All supplies of study intervention must be stored in accordance with the manufacturer's instructions; study intervention should be stored at 2°C [36ºF] to 8°C [46 ºF]. Study intervention for injection should acclimatize to room temperature for approximately 30 to 60 minutes prior to administration. The study intervention will be stored in a securely locked area, accessible to authorized persons only, until needed for dosing.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, or administer study interventions.

The Investigator, or delegated responsible site staff, is responsible for study intervention accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the study reference manual or other specified location.

6.3 Assignment to Study Intervention

All participants will be centrally randomized using a validated randomization system. Each participant will be assigned a unique participant number that encodes the participant's assignment to one of the 2 arms of the study (1:1 randomization ratio), according to the randomization schedule generated by the randomization system using a validated computer program. The randomization will be stratified by comorbid asthma and/or NSAID-ERD status (yes or no) and prior NP surgery (yes or no).

Details of the procedure are described in the applicable randomization system Manual provided to all sites.

6.4 Blinding

This is a double-blind study in which participants/care providers/Investigators/outcomes assessors, etc. are blinded to study intervention. The randomization system will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator determines that unblinding is warranted, the Investigator is advised to contact the Sponsor to discuss the situation prior to unblinding a participant's study intervention assignment unless this could delay emergency treatment for the participant. If a participant's study intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded in the source data.

Specific assessments and variables will be blinded to the sites in order to preserve the blind. Since PK data and PD assessments from individual participants may be unblinded, such data will not be available to blinded parties. Therefore, until the entire study has been concluded and the database locked, results of eosinophil numbers, monocytes, basophils, IgE, PK, and PD biomarkers as listed in SoA Table 1–1 will be masked/blinded starting at Visit 2 and will be accessible only to unblinded parties. A Blinding Maintenance Plan will describe the details for handling those data.

Sponsor safety staff and/or any unblinded designee/delegates/unblinded contract research organization (CRO) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

6.5 Study Intervention Compliance

Participants will receive study intervention directly from the Investigator or designee under medical supervision. The date, time and location of each dose administered in the clinic will be recorded in the source documents.

6.6 Dose Modification

Not applicable.

6.7 Continued Access to Study Intervention After the End of the Study

Study intervention for CRSwNP will not continue beyond this study. Following discontinuation or completion of study treatment, some participants may need additional therapy. The Investigator should ensure participants re-establish care with a physician at completion of their participation in the study.

6.8 Treatment of Overdose

Twice the intended dose of verekitug (UPB-101) within 6-week span of time will be considered an overdose for this study. **All overdoses (whether suspected or confirmed) will be recorded and reported to the Sponsor or designee within 24 hours of awareness.**

There is no specific treatment other than supportive care in case of an overdose.

In the event of an overdose, the Investigator/treating physician should:

- Evaluate the participant to determine, in consultation with the medical monitor if possible, whether study intervention should be interrupted or whether subsequent doses should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
- Document the quantity of the excess dose.

6.9 Prior and Concomitant Therapy

All CRSwNP medications taken in the 6 months prior to Visit 1 must be recorded in the electronic case report form (eCRF) along with reason for treatment. Biologics used for urticaria, atopic dermatitis, asthma or CRSwNP during the participant's lifetime must also be documented with reason for treatment.

A history of background medication and prior surgery, when applicable, as mentioned in Inclusion Criterion should be documented in source and recorded in the eCRF.

A history of INCS as mentioned in Inclusion Criterion should be documented in source and recorded in the eCRF. No changes are allowed to background MFNS (or equivalent) throughout the duration of the study.

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1 Prohibited Concomitant Medications and Treatments

The following concomitant treatments are prohibited during the study, unless provided as rescue therapy (Section 6.9.3):

- Intranasal medication that would interfere with the symptoms of diseases (e.g., antihistamines, nasal atropine, ipratropium bromide, nasal cromolyn) except nasal saline
- Intranasal corticosteroid drops or intranasal corticosteroid-administering devices/stents (e.g., Xhance), except study intranasal spray MFNS (or equivalent)
- Intranasal or systemic decongestant, except for study required nasal endoscopy
- Long term use of oral antibiotics (> 2 weeks) or parenteral antibiotics
- Any marketed biologic therapy or any systemic immunosuppressant treatment including but not limited to imatinib, methotrexate, cyclosporine A, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, cyclophosphamide, ambrisentan, bosentan
- Anti-IgE therapy (e.g., omalizumab)

- Any marketed non-biologic drug that modulates type-2 cytokines (e.g., suplatast tosilate)
- Leukotriene antagonists/modifiers, unless participants were on a continuous treatment for ≥ 30 days prior to Visit 1
- Aspirin or non-steroidal anti-inflammatory drug (NSAID) in participants with hypersensitivity to aspirin or NSAID (unless previously desensitized)
- Changes in allergen immunotherapy and/or aspirin desensitization therapy or initiation of new allergen immunotherapy and/or aspirin desensitization within 12 weeks prior to Visit 1 and throughout the study
- Any vaccination within the Screening Period
- Live (attenuated) vaccine throughout the study
- Any Investigational therapy other than the study drug verekitug (UPB-101)
- Medications which are not currently licensed for the treatment of CRSwNP
- Sino-nasal surgical procedures, including polypectomies
- Immunoglobulins or other blood products.

6.9.2 Permitted Concomitant Medication

- Mometasone furoate nasal spray (or equivalent) during screening and throughout the study. See Section 10.11.

  Note: The usage of background MFNS (or equivalent) will be assessed at planned timepoints as presented in SoA (Table 1–1).
- Nasal saline
- For study required endoscopy: topical decongestants and topical anesthetics
- Short term use of antibiotics (≤ 2 weeks)

- For participants with asthma:
  - Short-acting beta agonist, Long-acting beta agonist
  - Short-acting anti-muscarinic, long-acting anti-muscarinic
  - Methylxanthines (e.g., theophylline, aminophylline)
  - Inhaled corticosteroids with a stable, total daily dose ≤ 1000 µg fluticasone propionate (or the equivalent dose of another ICS) (Section 10.5) only for participants that were on a stable dose ≥ 30 days prior to Visit 1
- Leukotriene antagonists/modifiers are permitted during the study for participants that were on a continuous treatment for ≥ 30 days prior to Visit 1
- Systemic antihistamines
- Maintenance allergen immunotherapy for participants with allergen immunotherapy in place for ≥ 3 months prior to Visit 1, if they stay on a stable dose during the study intervention and dose adjustment is not required

Participants should withhold their background therapies on days when spirometry is performed as mentioned in Section 8.2.3.1.

6.9.3 Rescue Treatment

During the Treatment and Follow-up Periods, the Investigator can prescribe rescue treatment with any of the following:

- Saline nasal lavage
- Systemic antibiotics (up to 2 weeks)
- Oral corticosteroids
- Surgery for NPs

Based on previous experience, 12 weeks of the study intervention is recommended prior to surgery to allow a treatment effect. Participants receiving any rescue treatment other than surgery will continue the study intervention unless the Investigator decides otherwise. For participants undergoing surgery for NP, the study intervention will be permanently discontinued. Before

starting oral corticosteroids, participants should undergo endoscopy and Patient Reported Outcome (PRO) assessments.

The study site will supply rescue medication.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded. There will be no restrictions on how many times rescue medication can be used.

7 Discontinuation of Study Intervention and Participant Discontinuation

Discontinuation of specific sites or of the study as a whole are, handled as part of the appendix on Governance, Appendix 1, Section 10.1.9.

Participants are free to discontinue study intervention or withdraw from the study at any time without prejudice. Discontinuing study intervention is not the same as study withdrawal.

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. See the SoA (Table 1–1) for data to be collected at the time of discontinuation of study intervention (EOT visit) and follow-up (EOS visit) and for any further evaluations that need to be completed. See Figure 7–1 for a schematic of the visit and data collection options for participants who permanently discontinue study intervention.

A participant who decides to discontinue study intervention should always be asked about the reason(s) and the presence of any AEs. The reason for discontinuing study intervention and the date of last administration should always be recorded in the eCRF. The participant should then be encouraged to return for all regular study visits and perform all scheduled assessments per SoA until completion of the study.

Permanent study intervention discontinuation is any study treatment discontinuation associated with the definitive decision from the Investigator or the participant not to re-expose the participant to the study intervention at any time.

Any abnormal, clinically significant laboratory value or ECG parameter will be re-checked for confirmation before making a decision of permanent discontinuation of the study intervention for the concerned participant.

When study intervention is permanently discontinued:

- If the participant agrees to continue in the study, the participant will return to the study center for all regularly scheduled study visits per the SOA (Table 1–1) and, in addition, complete the EOT assessments approximately 12 weeks after the last dose of study intervention and complete the EOS assessments approximately 16 weeks after the last dose of study intervention.

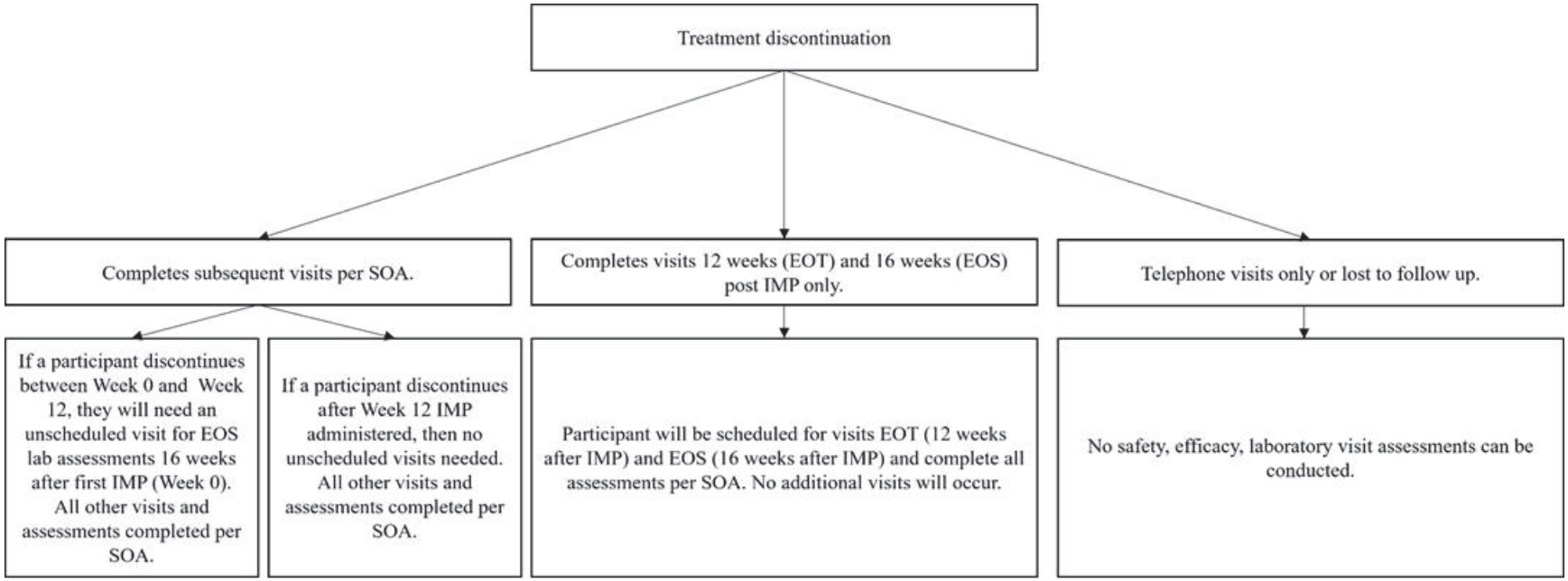
- If the participant declines to return for all regular study visits but agrees to return for the end of study procedures, the participant will complete EOT assessments approximately 12 weeks

after the last dose of study intervention and complete the EOS assessments approximately 16 weeks after the last dose of study intervention.

- If the participant declines to return for any regular study visits, the participant will be offered follow-up on a monthly basis via telephone calls while continuing diary assessments (no further procedures will be performed) until completion of the Treatment Period. The key information to be collected during the telephone calls are AEs/SAEs, changes in concomitant medication, MFNS use, and nasal polyposis symptoms. The participant should return for the last visit of the Treatment Period and for a follow-up visit approximately 16 weeks after the last dose of study intervention. If the participant cannot or does not wish to comply with any of the options above, (or any component of them such as only telephone-based visits without completion of the diary assessment), they will complete a follow-up visit approximately 12 weeks after the last dose of study intervention. After this visit, the Investigator will only contact the participant at the last visit of the Treatment Period. No other study assessments will be performed prior to this contact. The key information to be collected during the telephone call are AEs/SAEs, and changes in concomitant medication.

Participants who do not wish to have any follow-up contact will be discontinued from the study. All discontinued participants must return the diary device, as applicable at the EOT visit.

Figure 7–1 Study Visits and Assessments for Participants Who Permanently Discontinue Study Intervention



EOT=End of Treatment, EOS=End of Study, IMP=investigational medicinal product; SOA=Schedule of Activities.

7.1.1 List of Criteria for Permanent Treatment Discontinuation

All efforts should be made to document the reasons for treatment discontinuation in the eCRF. Participants must be withdrawn from the study (i.e., from any further study intervention or study procedure) for the following reasons:

- At their own request.
- If, in the Investigator's opinion, continuation in the study would be detrimental to the participant's well-being
- If there is need for sino-nasal surgery (may continue study drug up to the time of surgery)
- In case of an anaphylactic reaction to the study intervention requiring administration of epinephrine.
- In case of a helminth parasitic infestation requiring hospitalization
- In case of recurrent infectious episodes requiring systemic antibiotics
- At the specific request of the Sponsor or Regulatory Agency
- In the event of a protocol deviation, at the discretion of the Sponsor
- Diagnosis of a malignancy during study participation, other than squamous cell or basal cell carcinomas or in situ cervical carcinoma. The Investigator's written benefit-risk assessment of continuation of study treatment in those participants who develop squamous cell carcinoma, basal cell carcinoma, or in situ cervical carcinoma must be documented and approved by Sponsor Medical Monitor before continuation of study drug.
- Hy's Law criteria (≥ 3 × upper limit of normal [ULN] for alanine aminotransferase [ALT] or aspartate aminotransferase [AST] with total bilirubin ≥ 2 × ULN and no other explanation for these elevations)
- Significant AEs posing a risk for the participant as judged by the Investigator and/or the Sponsor
- Confirmed pregnancy during study participation
- Diagnosed with latent TB or has positive or indeterminate TB test.
- Confirmed HIV, HBV, or HCV infection during study participation.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may discontinue the study at any time at the participant's own request or for any reason (or without providing any reason). At the time of discontinuing from the study, if possible, an early termination visit (EOT) should be conducted, as shown in the SoA (Table 1–1).

A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. The participant will be permanently discontinued from the study intervention. If the participant does not withdraw consent when study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for clinical observation and safety monitoring. If the participant withdraws consent when study intervention is discontinued, the participant will be permanently discontinued from the study at that time.

If the participant withdraws their consent, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. The participant may request destruction of any samples taken and not tested and the Investigator must document this in the site study records.

7.3 Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible (and within the visit window, where one is defined), counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- In cases in which the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. Three (3) contact attempts, followed by a certified letter of contact to the participant must be documented in the participant's record for all participants who are believed to be lost to follow-up.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up.

8 Study Assessments and Procedures

General Guidance

- Study procedures and their timing are summarized in the SoA (Table 1–1).
- Adherence to the study design requirements, including those specified in the SoA, is required for study conduct. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. **Protocol waivers or exemptions are not allowed.**
- The Investigator or delegate will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- The total amount of blood taken from each participant will vary depending on the course of their disease, duration on treatment and laboratory requirements. At any time during the study, if any laboratory abnormalities are found for a participant, additional blood may be drawn to perform safety monitoring tests. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- The approximate amount of blood collected from each participant over the duration of the study is 225 mL.

Order of Activities

In the case that one or more of the following activities appear during a single visit, the suggested order of activities is as follows:

1. Participant-Reported Outcomes
2. Procedures
    - Urine pregnancy test and urine sampling
    - Height and weight
    - Vital signs
    - Physical examination
    - ECG

- Spirometry (in participants with comorbid asthma)
- CT scan (CT scans not performed in Germany and Czechia)
- Nasal endoscopy

3. Safety and other laboratory assessments (e.g., blood sampling). Refer to the Laboratory Manual for order of laboratory assessments.
4. Study intervention administration

The visit windows given in SoA (Table 1–1) are anchored to the date of first dose administered and all visits following Visit 2 should be scheduled based on the Visit 2 date (and not off of each other).

Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The Investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of intervention allocation/randomization, site personnel will add the intervention/randomization number to the participant identification card.

Calibration of Equipment

The Investigator or qualified designee is responsible for ensuring that any device or instrument used for a clinical evaluation/test during the study is suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.1 Administrative and Baseline Procedures

Medical History

A medical history will be obtained by the Investigator or qualified designee. The medical history will include all active conditions as well as any condition diagnosed within the prior 5 years. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

Chronic Rhinosinusitis with Nasal Polyps/Asthma History

Details regarding each participant's CRSwNP and asthma history will be recorded separately and not listed as medical history.

8.2 Efficacy Assessments

8.2.1 Physician-Reported Outcomes

8.2.1.1 Nasal Polyp Score by Nasal Endoscopy

Bilateral endoscopic NPS is a physician-reported scoring system to estimate the extent or severity of NPs. The NPS assessment is based on video recorded during nasal endoscopy. Nasal polyp score will be assessed by scoring each nostril on a scale of 0 to 4.

Nasal endoscopy will be performed after all other efficacy assessments have been completed for respective visit as described in SoA (Table 1–1). Video sequences will be provided to the central reader via secured transfer. Study centers will remove personal identifying information from the imaging data header prior to sending to the central reader.

For eligibility, central reading of Visit 1 NPS will be used. At Visit 2, the Investigator will review the Visit 1 results from central reading to confirm entry criteria have been met, as well as reconfirm eligibility based on Visit 2 local read. Central reading will be used for comparing Baseline to EOT.

Two central readers will review each endoscopy and provide their scoring. A third central reader may be required to adjudicate the scoring, as applicable per prespecified adjudication process in case of disagreements. The process will be described in a central reader manual.

The NPS will be assessed with the NPS scale provided in Appendix 6, Section 10.6.

8.2.1.2 Computed Tomography Assessments

Lund Mackay Score by Quantitative Computed Tomography Assessment

Lund Mackay (LMK) score or Sinus Opacification Score is a physician-reported quality staging system for evaluation of severity of NP based on assessments of the sinuses by computer tomography. The LMK score staging system assigns values of 0, 1, or 2 to each of 5 sinuses. In addition, the Osteomeatal Complex is also scored.

Computed tomography scan will be performed during the Screening Period (at Visit 1 or after, provided results are available prior to Visit 2), as shown in SoA (Table 1–1) (CT scans not

performed in Germany and Czechia). Central reading will be used for comparing Baseline to EOT. The process will be described in a central reader manual.

The details of method of assessment are given in Appendix 8, Section 10.8.

Three-Dimensional Volumetric Measurement of the Sinuses

The % change in opacification from Baseline to the Week 24 CT scan will be calculated based on the following method on each side per each of the 5 anatomic sinuses (Deeb 2011):

The following measurements will also be captured as part of the CT scans:

- The volume of the air (mL)
- The volume of mucosa (mL)
- Percent occupied by disease
- Thickness of lateral wall

8.2.2 Participant Reported Outcomes

Participant-reported outcome data will be collected to document the treatment effect of verekitug (UPB-101). The questionnaires, translated into the local language as appropriate, will be completed in their entirety at specified timepoints during the study, as outlined in the SoA (Table 1–1).

To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered early in the clinic visit, before the participant receives any information on his or her disease status and prior to the performance of non-PRO assessments (e.g., endoscopy), unless otherwise specified. Additionally, PROs should be collected prior to the administration of study intervention. PROs assessed during the clinic visits will be captured on a handheld device provided by a central vendor. The study center staff will be trained on how to use the web diary during the clinic visits and will be responsible for instructing participants on how to complete the questionnaires. Should there be any issues with the handheld device, web back-up may be used as an alternative.

Electronic Diary is used for daily recording of MFNS (or equivalent) use, nocturnal awakenings, and rhinosinusitis symptom scores. The electronic diary is dispensed at Visit 1 and information is downloaded on an ongoing basis.

Participants should be informed that the recordings made electronically cannot be retrospectively or prospectively entered and must be completed within a defined time window. Participants will also be provided with information about when and where to request help if problems occur. Participants will be instructed to complete the questions in their electronic diary in the morning, within approximately 1 hour of awakening. The device will be programmed to lock data entry in the afternoon. For participants on twice daily MFNS (or equivalent), the evening dose will also be recorded in the evening. The electronic device and/or instructions for completing the questionnaires electronically will be provided by site staff. The data will be transmitted to a centralized database maintained by a central vendor. The data will be available for access by appropriate study personnel.

Should there be any issues with the device, a web back-up diary may be used as an alternative.

Participants must bring the PRO device to each study visit, and compliance with all PRO assessments will be checked by center staff.

8.2.2.1 Nasal Polyposis Symptom Diary - Nasal Congestion Score

The NCS will be derived from Question 2 of the Nasal Polyposis Symptom Diary (NPSD), based on participant-reported evaluation of nasal congestion severity. Nasal congestion will be reported by participants daily, recalling nasal congestion severity over the previous 24 hours as none, mild, moderate, or severe (scores of 0, 1, 2, or 3, respectively). The NCS will be calculated as the 14-day average of the daily scores. A higher score means worse outcome. The average of the last 14 days before Visit 2 is required to determine the Baseline value. The NCS will be assessed through an electronically filled questionnaire with nasal symptom questions by the participants at timepoints described in SoA (Table 1–1). The NPSD questionnaire is provided in Appendix 7, Section 10.7.

8.2.2.2 Nasal Polyposis Symptom Diary - Total Symptom Score

Participants complete an NPSD each morning. Questions are asked to report common symptoms of nasal polyposis and symptom impacts. Participants report severity of each symptom and symptom impact at its worst using a 4-point rating scale (0=no symptoms; 1=mild symptoms; 2=moderate symptoms; 3=severe symptoms). The Total Symptom Score (TSS) is calculated by taking the sum of the 8 equally weighted symptom items over a period of 2 weeks.

The TSS will be completed electronically at specified timepoints, as outlined in the SoA (Table 1–1). The questionnaire for assessment is given in Appendix 7, Section 10.7.

8.2.2.3 Nasal Polyposis Symptom Diary - Loss of Smell

Loss of smell will be derived from Question 8 of the NPSD, based on participant-reported assessment of symptom severity of difficulty with sense of smell (DSS), recalled over the past 24 hours (usually in the morning) (Table 1–1). For the assessment, participants will be asked to assess their DSS for the previous day on a scale of 0 to 3 and record it in the electronic Diary. The DSS will be calculated as the 14-day average of the daily scores (Section 10.6). Higher daily DSS score indicates greater severity.

DSS will be assessed at timepoints shown in SoA (Table 1–1). The details of scoring are given in Appendix 7, Section 10.7.

8.2.2.4 Asthma Control Questionnaire

Effect of adequacy of asthma control in participants with comorbid asthma will be assessed by the participant completed Asthma Control Questionnaire-6 (ACQ-6). The participant ACQ-6 has 6 questions: the top scoring 5 symptoms and daily rescue bronchodilator use. Participants will be asked to recall how their asthma has been during the previous week and to respond to the symptom and bronchodilator use questions on a -6-point scale (0=no impairment; 6=maximum impairment). ACQ-6 is completed during clinic visits at specified timepoints, as outlined in the SoA (Table 1–1). The details on assessment methodology are given in Appendix 9, Section 10.9.

8.2.3 Spirometry

Spirometry assessment will be done in participants with comorbid asthma at timepoints scheduled in SoA (Table 1–1).

Spirometry assessment will be done in participants at timepoints scheduled in SoA (Table 1–1).

8.2.3.1 General Requirements

Lung function (FEV_1) will be measured by spirometry using the equipment provided by a central vendor. Spirometry will be performed by the Investigator or designee according to the American Thoracic Society (ATS)/ European Respiratory Society (ERS) spirometry guidelines (Miller et al. 2005) and the central vendor spirometry manual.

After completion of subject spirometry testing, the study staff will electronically transmit the spirometric measurements for centralized quality assurance review. Feedback on the quality of the spirometry data will be provided to the site and to the Sponsor or designee for central data management.

The vendor providing central spirometry is responsible for assuring that the spirometer meets ATS/ERS recommendations and that the study center personnel who will be performing the testing are properly certified. Spirometry calibration will be detailed in a separate spirometry procedures manual

Spirometry testing should be done according to the SoA (Table 1–1) at specified visits. If possible, it is preferable that spirometry be initiated within ±2 hours of the time that the screening spirometry was initiated.

IMPORTANT: The following instructions should be provided to the participants for study visits involving spirometry:

- Participants should avoid vigorous exercise for at least 1 hour prior to visit with spirometry assessment
- Participants should withhold their usual background therapies on day(s) when spirometry is performed, as per instructions below:
    - Short-acting beta-agonists and short-acting muscarinic-antagonists: at least 6 hours prior to scheduled spirometry
    - Twice daily long-acting BD inhalers or long-acting muscarinic antagonists containing therapies: at least 12 hours prior to scheduled spirometry
    - Once daily long-acting BD inhalers or long-acting muscarinic antagonists containing therapies: at least 24 hours prior to scheduled spirometry
    - Leukotriene receptor antagonists: at least 24 hours prior to scheduled spirometry
    - Twice daily theophylline: at least 12 hours prior to scheduled spirometry
    - Once daily theophylline: at least 24 hours prior to scheduled spirometry

To accommodate these requirements, screening spirometry may be performed on a separate day during the Screening Period.

8.2.3.2 Spirometry Technique

Detailed procedure for performing spirometry will be described in a separate central vendor spirometry manual. This manual will also include information regarding assessment of the quality of spirometry and associated process.

The participant should use mouthpieces of the same dimension and shape for all spirometry sessions.

The FEV1 maneuver should start with tidal breathing followed by maximal inspiration. After inhalation to full lung capacity, a fast and forceful expiration that should last for at least 6 seconds. It is important to encourage the participant to continue the expiration to be fast and forceful throughout the maneuver. The maneuver is completed with full and rapid inspiration. Ensure that none of the following has occurred: coughing during the first second, glottis closure, leak, or obstruction of the mouthpiece (by the tongue).

Multiple forced expiratory efforts (at least 3, but no more than 8) should be performed for each spirometry session. Spirometry grading will conform to ATS/ERS acceptability and reproducibility criteria. The highest FEV1 will be based on the best efforts that meet acceptability criteria.

8.2.3.3 Spirometry References

The Global Lung Function Initiative (GLI) equations will be used to determine the Predicted Normal Values (PNVs) and are pre-programmed into the spirometer (Quanjer et al 2012).

FEV_1, expressed as percent of the PNV, will be calculated as follows:

FEV_1% of PNV = (FEV_1 measured/FEV_1PNV) x 100

8.2.3.4 Record Keeping

A copy of the spirometry printout signed and dated by the Investigator or qualified designee should be kept at the study site for source data verification. The printout must be marked with the study code, assigned study ID, date, time of measurement, and visit number.

8.3 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1–1).

8.3.1 Height and Weight

Height and weight will be measured at Visit 1. Weight will also be measured at Visits 8/EOT and Visit 9/EOS.

8.3.2 Physical Examinations

Physical examination will be performed at timepoints as described in the SoA (Table 1–1).

- A complete physical examination will include an assessment of general appearance, skin, eyes, ear/nose/throat, lung, heart, abdomen, reflexes, lymph nodes, spine, and extremities. Clinically significant findings should be assessed and recorded as determined by the Investigator.

- A targeted physical examination will include, at a minimum, assessments of the general appearance, skin, ear/nose/throat, lungs, and heart. Investigators should also pay special attention to signs related to previous, clinically significant findings.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.3 Vital Signs

Temperature (may be assessed through oral, tympanic, or temporary artery route, although the same route must be used throughout the study), pulse rate, respiratory rate, and blood pressure will be recorded (before blood collection for laboratory tests). Vital signs will be obtained at timepoints shown in SoA (Table 1–1).

Assessments should be obtained while the participant is resting for 5 minutes in either the supine, semi-supine or seated position.

Heart rates are best obtained electronically, if available. If heart rate data are obtained electronically, the results may not be obtained from an ECG scheduled at the same time. If these data are obtained manually, a minimum observation period of 30 seconds is required.

Respiratory rate will be determined following a minimum observation of 30 seconds.

8.3.4 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (Table 1–1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, RR, and QT corrected for heart rate (QTc) intervals.

A standard 12-lead ECG will be recorded after the participant has been supine for at least 5 minutes. The Investigator or designated physician will review all ECGs and interpret the findings. A paper printout of every ECG will be stored at the site.

All ECGs will include at a minimum the participant's study number as well as the time and date of each recording. ECG assessments will be performed prior to any scheduled blood tests. ECG assessments will also be performed prior to study intervention administration, except on the first

dosing visit, where ECGs will be conducted pre-dose and post-dose, within 30 minutes prior to discharge.

All ECGs must be evaluated by a qualified physician for the presence of abnormalities and signed and dated by the Investigator or qualified designee.

8.3.5 Clinical Laboratory Tests and Examinations

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Table 1–1) for the timing and frequency.

The Investigator, or qualified designee, must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.

Abnormal laboratory findings associated with the pre-existing conditions are not considered clinically significant unless judged by the Investigator to be more severe than expected or a worsening of the participant's condition.

All laboratory tests with values considered clinically abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.

- If clinically significant, any values which do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, where possible, and the Sponsor notified.
- All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Table 1–1).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE. When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms.

8.3.6 Pregnancy Testing

Serum pregnancy test (for POCBP) at Visit 1 and urine pregnancy tests at other visits will be performed. A negative result of a serum pregnancy test at Visit 1 and a negative urine pregnancy test must be obtained prior to randomization at Visit 2.

At the EOS Visit, a home pregnancy testing kit will be issued to participants who are POCBP to be used at approximately Day 120 post-last dose. Results should be reported to the Investigator.

8.3.7 Unscheduled Visits

If during the study, a participant experiences any study related difficulties and/or problems, the investigator decides whether an unscheduled visit to the site is necessary. During an unscheduled visit, standard safety measures will apply and at a minimum, the following information will be recorded on the "Unscheduled Visit" eCRF:

- Date and time of visit,
- Main complaint prompting the visit. If the reason is an AE, the applicable safety procedures should be followed as described in Section 8.4,
- Review of AEs (if the complaint is not safety related),
- Review of concomitant medication.

If the investigator withdraws the participant from study intervention or from the study, the applicable procedures should be followed as described in Section 7. Unscheduled visits are not considered protocol violations.

8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3.

The Investigator, or qualified designee(s) is responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention (see Section 7). This includes events reported by the participant.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.4.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs and SAEs will be collected from the time of the signing of ICF until the follow-up visit at the timepoints specified in the SoA (Table 1–1).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of awareness, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obliged to actively seek information on AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.4.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AESIs (as defined in Section 8.4.6), will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for Serious Adverse Event

Prompt notification (within 24 hours of becoming aware, see Appendix 3) by the Investigator, or delegee, to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

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

An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary. See Appendix 3 for reporting SUSARS to regulatory authorities.

An event that leads to hospitalization under the following circumstances should not be reported as an AE or SAE:

- Hospitalization for respite care,
- Planned hospitalization required by the protocol if required by site (e.g., for nasal endoscopy),
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease,
    - The participant has not experienced an AE.

An event that leads to hospitalization under the following circumstances is not considered to be an SAE, but should be reported as an AE instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours.

8.4.5 Pregnancy

Details of pregnancies in POCBP and partners of participants capable of producing sperm will be collected after the start of study intervention and until 120 days after the final dose of study intervention or the Final Visit whichever is later.

If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of pregnancy (for pregnant partners, the necessary signed informed consent must be obtained from the partner prior to submitting any information).

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., maternal serious complications, therapeutic abortion, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs and will be reported as such.

The participant/pregnant partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant partner and the neonate and the information will be forwarded to the Sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former study participants/pregnant partners, he or she may learn of an SAE through spontaneous reporting.

Any POCBP who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.4.6 Adverse Events of Special Interest

Certain AEs have been identified as AESIs due to the class of drug being studied. These AEs will be captured through spontaneous reporting in the eCRF and the reporting of these AESIs will be described in the Statistical Analysis Plan (SAP). An AESI may be serious or non-serious. For this study, AESIs based on the class of drugs include:

- Anaphylaxis reactions.
- Immune complex disease.
- Severe infections which are defined as:
  - Life-threatening or,
  - Requiring hospitalization or,
  - Requiring treatment with anti-infectives or,
  - Requiring permanent discontinuation of study intervention.
- Helminth parasitic infection requiring treatment.
- Injection site reactions (ISR) that is CTCAE Grade 3 or higher.

8.4.7 Medication Error

If a medication error occurs in the course of the study, then the Investigator or other site personnel will inform the appropriate Sponsor representatives as described in the instruction manual or other document.

8.5 Pharmacokinetics

8.5.1 Pharmacokinetic Blood Sample Collection

Serum samples for PK analysis of verekitug (UPB-101) will be collected at the timepoints described in Table 8-1.

Table 8-1 PK Sampling Points and Time Windows

Study Visit	Study Week	Dose [redacted] × 2	PK sample	ADA/NAb
Visit 2	Week 0	Dose #1, baseline	X (pre-dose) sample must be taken prior to dose	X (pre-dose) sample must be taken prior to dose
Visit 3	Week 2	N/A	X (± 3 days)	None
Visit 4	Week 4	N/A	X (± 3 days)	None
Visit 5	Week 8	N/A	None	None
Visit 6	Week 12	Dose #2	X (pre-dose, C_{trough}, sample must be taken prior to dose)	X (pre-dose, sample must be taken prior to dose)
Visit 7	Week 18	N/A	X (± 3 days)	None
Visit 8	Week 24	N/A	X (± 3 days)	X (± 3 days)
Visit 9	Week 28	N/A	X (± 3 days)	X (± 3 days)

Abbreviations: ADA=antidrug antibody, C_{trough}=pre-dose (trough) drug concentration, N/A=not applicable, NAb=neutralizing antibody, PK=pharmacokinetic, [redacted]

Serum samples will be collected for measurement of verekitug (UPB-101) concentrations as specified in the SoA (Table 1–1). A maximum of 5 samples may be collected at additional timepoints during the study if warranted and agreed upon between the Investigator and the Sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak serum concentrations) to ensure appropriate monitoring. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. The PK samples that are not labeled as pre-dose have a sampling window of plus or minus 3 days to accommodate participant appointment flexibility.

Samples will be used to evaluate the PK of verekitug (UPB-101). Placebo samples may or may not be analyzed. Samples collected for analyses of verekitug (UPB-101) serum concentration may also be used to evaluate safety or efficacy aspects that address concerns arising during or after the study.

Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained. At visits during which samples for the determination of serum concentration of verekitug (UPB-101) will be taken, 1 blood draw of sufficient volume can be used.

Blood sample collection, processing and shipping details will be outlined in a separate laboratory manual. Blood will be processed, and serum analyzed using a validated assay.

Intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of timepoints for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

For details on the future use for PK samples, refer to Section 8.11.

8.6 Pharmacodynamics

8.6.1 Pharmacodynamic Assessments

The assessments described in this section will be conducted to assess CRSwNP-related PD biomarkers. Samples will be collected as indicated in the SoA (Table 1–1); the actual date and time of each sample collection will be recorded in the eCRF. Blood sample and biopsy collection, handling, and storage will be described in the specimen collection and processing instructions. Blood samples for biomarker analysis will be taken and frozen. The decision to assay the frozen samples may be based on results from earlier sample analyses. On dosing days, all PD assessments must be completed prior to initiation of the study intervention administration. Initially, select samples from those collected will be analyzed and the resulting data assessed. Following this, should analysis of the remaining samples be deemed informative, they too may be analyzed.

8.6.1.1 Blood Eosinophils

A detailed description of CRSwNP and its relation to eosinophils is provided in Section 2.2.

Absolute numbers of blood eosinophils will be measured using blood collected as part of the automated complete blood count clinical laboratory test which includes a differential count of white blood cells. Results will be reported at the highest precision (level of significant figures) offered by the clinical laboratory. Assessment of blood eosinophils will be conducted at the visits reflected in the SoA (Table 1–1). The sites will be blinded to eosinophil count.

The blood eosinophils may be used in subsequent PK/PD analyses to examine relationships between serum concentrations of verekitug (UPB-101) and blood eosinophils.

It is suggested that the timing of the collection for eosinophils occurs consistently across study visits.

8.6.1.2 Nasal Secretions

Nasal secretions will be obtained per laboratory collection manual instructions. Nasal secretions at Visit 2 will be used for validation of assay methodology for this unique biomatrix. The nasal secretions collected at Visits 2, 4, 6, 7, and 8/EOT will be preserved for analysis of additional biomarkers related to nasal polyposis and responses to verekitug (UPB-101) treatment.

For details on the future use for PD samples, refer to Section 8.11.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Blood samples and nasal secretions will be collected to assess the PD effect of UPB-101 on biomarkers related to the [redacted] Samples will be collected according to the schedule described in the SoA (Table 1–1) and as detailed in the laboratory manual provided separately to sites.

Selected biomarkers may be used in subsequent PK/PD analyses to examine relationships between serum concentrations of verekitug (UPB-101) and biomarkers.

For details on the future use for biomarker samples, refer to Section 8.11.

8.9 Serum Immunoglobulins

The levels of serum immunoglobulin A (IgA), IgE, IgG, and IgM will be assessed according to the SoA (Table 1–1).

8.10 Immunogenicity Assessments

Serum samples for the assessment of verekitug (UPB-101) antidrug antibodies (ADAs) and neutralizing antibodies (NAbs) will be collected from all participants according to the SoA (Table 1–1). Immunogenicity testing will follow a 3-tiered approach of screening, confirmation, and titration. Placebo samples may or may not be analyzed. For samples that are ADA positive, NAb data may or may not be generated depending on the availability of a validated assay, and the NAb data may be reported separately from the Clinical Study Report (CSR).

For details on the future use for immunogenicity samples, refer to Section 8.11.

8.11 Storage and Future Use of Biological Samples

The Sponsor will be responsible for safeguarding all biological sample collection and storage with adequate measures to protect confidentiality, per all applicable local regulations.

The Sponsor will store biological samples related to serum samples and nasal secretion samples collected as part of the PK/PD/biomarker/immunogenicity assessments. With participants' consent, samples may be used for further research by the Sponsor, per all applicable local regulations.

8.12 Health Economics

Health economics parameters are not evaluated in this study.

8.13 Guidance on Significant Study Continuity Issues

In an unfavorable situation, wherein the study center is closed, or in case of restrictions or geopolitical instability, for any other local/regional factors, or for any reason wherein participant's travel to the study center is not feasible due to conveyance issue, alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements. These alternate strategies may include home visit(s), phone call visit(s), and/or remote visits and/or site monitoring.

All study assessments must be performed by trained clinical study staff in clinic, or where possible, via tele-visits and/or home healthcare visits.

- Vital signs and physical exams may be modified if adapted to telemedicine or home visits.
- Participants will be regularly assessed by the physician at site, tele-visits, or home visits (if applicable).

- The study site will supply participants with take-home rescue medication.
- All study medication dosing will be supervised in the clinic or by home health administration.

To maintain/preserve data integrity (vs risking losing the data points), the assessments will be labeled as having been obtained remotely (home or non-site location) and will be subject to a separate statistical analysis. Home visits and telemedicine may reduce the risk of missed visits due to study site closures and reduce the need for participants to visit the study site and therefore minimize the overall burden on participants.

9 Statistical Considerations

Two database locks (DBLs) are planned for this study. A first DBL will be conducted after the last participant has reached Week 24. The second and final DBL will be conducted after all participants complete their safety follow-up visits (EOS). Upon the first DBL, Sponsor and the CRO analysis team will be unblinded to the treatment assignment to perform all analyses related to the primary and secondary study objectives according to the SAP using the first DBL data. Other personnel will remain blinded to the treatment, including investigators, study site staff, participants, and the CRO staff who are not involved in the analysis.

The SAP will be finalized prior to unblinding, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

In this study, the NPS mean change from baseline to Week 24 will be compared between verekitug (UPB-101) and placebo. The null hypothesis is that there is no difference between those means whereas the one-sided alternative hypothesis is a (favorable) negative difference between them:

- H_0: $\mu_1 - \mu_2 = 0$ versus H_1: $\mu_1 - \mu_2 < 0$
- μ_1: Mean for UPB-101 and μ_2: Mean for Placebo

9.1.1 Multiplicity Adjustment

Not applicable.

9.2 Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Table 9–1 Participant Analysis Sets

Population/Analysis set	Description
Screened	All participants who sign the ICF.
Intention to Treat Analysis Set (ITT)	All participants who are randomized. All participants in ITT will be evaluated according to the treatment assigned at randomization.
Safety Analysis Set (SAF)	All participants who are randomized and received any study intervention. Participants are evaluated according to the actual treatment they received.
PK Analysis Set (PKAS)	All participants in the safety set who received verekitug (UPB-101) and have at least one evaluable PK sample.
PD Analysis Set	All participants in the safety set who received study treatment and have at least one evaluable PD sample.
Comorbid Asthma Set	All participants in the ITT set who have comorbid asthma.

9.3 Statistical Analyses

The Intention to Treat Analysis Set (ITT) is the primary analysis set to be used for efficacy analyses.

9.3.1 General Considerations

Efficacy assessed during the Follow Up period (EOT – EOS) will be summarized separately from the Treatment period (Day 1 – EOT).

Continuous variables will be summarized by verekitug (UPB-101) and placebo and by dosing frequency with descriptive statistics (e.g., number of observations, mean, standard deviation, median, quartiles, maximum, and minimum). Categorical variables will be tabulated by frequency and percent of participants per verekitug (UPB-101) and placebo.

Mixed model repeated measures (MMRM) analysis will be conducted on changes from baseline in selected continuous measurements/endpoints defined in the SAP. In this model, study treatment, visit and treatment-by-visit interaction will be fixed effects, participant will be random effect and baseline value of the respective measurement will be a covariate in addition to stratification factors used in the randomization. Other explanatory baseline variables may be included in the model.

Study treatment groups will be compared within this model framework.

Analysis of covariance (ANCOVA) will also be conducted on changes from baseline in selected continuous measurements/endpoints. In this model, study treatment, baseline value of other measurement will be a covariate in addition to the stratification factors used in randomization. Other explanatory baseline variables may be included in the model.

More details will be provided in the SAP.

9.3.1.1 Participant Disposition

The number and the percentages of participants enrolled and included in each of the analysis sets will be tabulated. The reason for participant exclusions from analysis sets will also be listed. In addition, the number of discontinued participants with their reason for discontinuation (from study and study treatment) will be tabulated.

9.3.1.2 Demographic and Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment arm. This analysis will be conducted on the ITT.

9.3.1.3 Treatment Compliance

Treatment compliance will be presented on the ITT.

9.3.1.4 Protocol Deviation

Protocol deviations will be reviewed and classed as major or minor during blinded data review. Major protocol deviations are defined as deviations liable to bias the evaluation of the primary efficacy endpoint and safety endpoints. The following deviations will be considered as major (non-exhaustive list):

- Non-compliance with the inclusion or exclusion criteria
- Non-compliance with the study treatment
- Intake of prohibited medication

Protocol deviations (missing assessments/visits) related to COVID-19 will be listed separately.

9.3.2 Primary Analysis

9.3.2.1 Definition of Endpoints

The primary endpoint is change from baseline in NPS at Week 24.

9.3.2.2 Estimand

An ICE is defined as an event occurring after randomization/treatment initiation that affects either the interpretation or the existence of the primary efficacy endpoint associated with the clinical question of interest.

The following ICEs are expected to happen during the study:

- ICE 1: Treatment discontinuation
- ICE 2: Use of rescue surgical treatment for CRSwNP
- ICE 3: Use of rescue systemic corticosteroids for CRSwNP or for comorbid conditions
- ICE 4: Escalation of maintenance/background treatment by adding another drug (e.g., an unblinded biologic therapy) for CRSwNP

Attribute	Specification
Treatment conditions	Condition of interest: randomized to UPB-101 Alternative condition: randomized to Placebo
Participant population	As defined by study protocol eligibility criteria
Variable	Change from baseline in NPS at Week 24
Population level summary	Mean Difference between the treatment groups in the change from baseline at Week 24
Main estimator	Least square means (LSM) difference between UPB-101 and Placebo at Week 24 as assessed by MMRM

For ICE 1 and ICE 3, treatment policy strategy will be applied: observed NPS after study treatment discontinuation will be used for the analysis.

For ICE 2 and ICE 4, composite variable strategy will be applied: NPS after the start of another treatment for CRSwNP will be replaced by worst possible value 8.

9.3.2.3 Main Analytical Approach

The primary endpoint will be analyzed using MMRM with the following factors.

1. Treatment (2 levels; verekitug [UPB-101] or placebo)
2. Baseline NPS (Week 0)
3. Visit (Weeks 12 and 24) and visit-by-treatment interaction
4. Asthma and/or NSAID-ERD status (Two levels; either presence of comorbid asthma and/or NSAID-ERD or absence)

5. Prior NP surgery (2 levels [Yes/No])

Missing NPS (not affected by ICE with composite variable strategies) will be imputed by a multiple imputation approach assuming mechanism of missingness as missing at random.

The number and percentage of participants, LSM for each treatment arm, difference between verekitug (UPB-101) and placebo LSMs, the corresponding 95% confidence interval (CI) and the p-value will be presented.

9.3.2.4 Sensitivity Analyses

Sensitivity analysis will be performed for the primary endpoint to assess the robustness of the main analysis results. Details will be provided in the SAP.

9.3.3 Secondary Endpoint Analysis

The following secondary endpoints will be analyzed using the ITT Analysis Set. Two-sided significance level of $\alpha = 0.05$ will be applied without adjustment for multiplicity.

- Change from baseline at Week 24 in thebi-weekly mean NCS. The analysis will be similar to the primary endpoint.
- Change from baseline at Week 24 in opacification of sinuses measured by LMK Score evaluated by quantitative CT assessment (CT scans not performed in Germany and Czechia). The analysis will be similar to the primary endpoint.
- Change from baseline at Week 24 in DSS evaluated by the NPSD (assessed as a 24-hour recall at all visits). The analysis will be similar to the primary endpoint.
- Proportion of participants requiring systemic corticosteroids or NP surgery. The Frequency distribution will be presented, and analysis will be performed using the Cochran Mantel Haenszel test.
- Change from baseline at Week 24 in bi-weekly mean NPSD TSS, NCS, DSS. The analysis will be similar to the primary endpoint.

Additional details will be specified in the SAP.

9.3.4 Other Analyses

The following other endpoints will be analyzed. The analysis will be done on ITT population.

- Change from baseline over Weeks 24 and 28 in bi-weekly NCS evaluated by the NPSD. The analysis will be performed using ANCOVA with factors similar to primary endpoint analysis.

- Change from baseline over Weeks 24 and 28 in bi-weekly DSS evaluated by the NPSD. The analysis will be performed using ANCOVA with factors similar to primary endpoint analysis.
- Change from baseline over Weeks 24 and 28 in bi-weekly NPSD TSS. The analysis will be performed using ANCOVA with factors similar to primary endpoint analysis.
- The proportion of participants requiring systemic corticosteroids or NP surgery. Frequency distribution will be presented, and Cochran Mantel Haenszel Test will be performed.
- Estimate of percentage of participants treated with systemic corticosteroids or NP surgery by Week 24 obtained using Kaplan-Meier method.
- Proportion of participants at Week 24 who achieve a maximum NPS of 1 in each nostril. Frequency distribution will be presented, and Cochran Mantel Haenszel Test will be performed.
- Incidence of ADAs during the study (including the post-treatment follow-up period). Frequency distribution will be presented.
- In participants with ADAs, incidence of NAbs during the study (including the post-treatment follow-up period). Frequency distribution will be presented.
- Summary of serum concentrations of verekitug (UPB-101) from baseline, Treatment and Follow-Up Periods. Population PK and/or PK/PD analyses may be conducted and may be presented in a separate report.
- Change from baseline over Weeks 24 in blood and nasal secretion biomarkers. The analysis will be performed using ANCOVA with factors similar to primary endpoint analysis.
- Numbers in participants with comorbid asthma. Frequency distribution will be presented.
- Change from baseline over Week 24 in participant ACQ-6 in participants with comorbid asthma. The analysis will be performed using ANCOVA with factors similar to primary endpoint analysis.
- Change from baseline over Week 24 in FEV_1 in participants with comorbid asthma. The analysis will be performed using ANCOVA with factors similar to primary endpoint analysis.
- Change from baseline to Week 24 in three-dimensional CT volumetric measurement of the paranasal sinuses.

9.3.5 Safety Analyses

Safety data will be descriptive summarized for the SAF.

Adverse events will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class, preferred term, and

treatment group for the number and percent of participants reporting TEAEs (those that start or worsen after first dose of study interventions), the number of events, and the number of participants with any TEAE. Summaries for TEAEs related to study intervention, leading to study intervention discontinuations and SAEs will be provided as well. All AEs will be listed including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome.

Absolute values and change from baseline laboratory evaluations, vital signs assessments, and ECG parameters will be summarized by visit and by treatment group. The frequency of participants with safety laboratory results outside of normal reference ranges will be tabulated by treatment and visit.

9.4 Interim Analyses

The change from baseline in NPS at Week 24 will be monitored based on blinded data to reach a decision on the final sample size prior to completion of the enrolment. The mean and standard deviation of the changes will be estimated. If the estimated mean and/or deviation vary substantially from the assumptions stated in this protocol, sample size may be increased but will not exceed 1.5 times the original size. Sample size reduction will not be considered. Any decision to increase the sample size will be made early enough to inform sites before enrollment closes. The Sponsor will determine the final sample size, ensuring adequate statistical power for the primary outcome. Technical details will be provided in the SAP.

9.5 Sample Size Determination

For the sample size/power calculation, the following assumptions are made:

CCI [redacted]

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines.
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following, as applicable:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.

- Overall conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH GCP guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations 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.

10.1.3 Informed Consent Process

The Investigator or qualified designee will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. The potential participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before any screening procedure was performed and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant.

A participant who is rescreened is not required to sign another ICF at rescreening, unless a new version of the ICF becomes available.

The ICF will contain a separate section (or in some cases a separate ICF for optional samples) that addresses the use of remaining mandatory samples for optional exploratory research, as applicable. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their specimens which are traceable to them at any time and for any reason during the storage period. A separate signature will be required to document a participant’s agreement

to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all participants subsequently enrolled in the study as well as those currently enrolled in the study.

10.1.4 Data Protection

To ensure confidentiality of records and personal data of participants, participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the Sponsor or to representatives of the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. Such personal data will therefore be "pseudonymized" and only accessed by authorized persons who are subject to written confidentiality obligations.

The participant must be informed that their personal study related data will be processed and disclosed by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the applicable informed consent form(s).

As applicable, the participant will receive all information as required by the EU General Data Protection Regulation (EU) 2016/679 of the European Parliament and of The Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (EU GDPR), including the identity of the controller, the clinical research purposes, the fair processing of the data, and all his/her data subjects rights. All details are listed in the informed consent form.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance (QA) auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

To protect data subject privacy per EU GDPR, collected study data will be pseudonymized (as described above) and maintained in a secure system.

Sponsor will implement organizational and technical arrangements to avoid unauthorized access, disclosure, dissemination, alteration, or loss of information and personal data processed. Such arrangements will entail that the Sponsor, Study Center(s), and any other authorized parties,

implement a series of technical and organizational measures, as appropriate, including but not limited to the encryption of the personal data at rest and in transit, implementation of appropriate security policies and procedures, regular training procedures, pseudonymization of participants' personal data, implementation of appropriate physical and electronic access controls, employees' access restriction controls and control logging for any electronic systems containing personal data, adequate network protection, implementation of back-up and recovery plans to ensure data availability, and the ability to ensure the ongoing confidentiality, integrity, availability, and resilience of the processing systems used for the personal data.

In case of a data security breach, Sponsor, sites, and other authorized parties, as may be applicable, will implement appropriate measures in order to mitigate the possible adverse effects of the data security breach, including promptly investigating the data security breach to identify the vulnerability that led to the data security breach and undertaking the appropriate remediation efforts to remedy the vulnerability identified and limit the impact of the data security breach. Sponsor will be informed without undue delay of any data security breaches suffered by the sites or other authorized parties. Sponsor, with the full cooperation of the sites and other authorized parties, will assess the likely risk to participants as a result of the data security breach. Sponsor will assess its obligations, if any, to report such breach to the supervisory authorities (or other law enforcement agencies) and the affected individuals, as applicable, in accordance with applicable local regulations. Sponsor, sites, and any other authorized parties will fully document all relevant facts relating to the data security breach, including its effects and any remedial action taken, and keep a related record of each data security breach.

The Investigator agrees that all information received from the Sponsor or designee including, but not limited to, the IB, the protocol, eCRFs, the protocol specified treatment, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The Investigator further agrees to take all reasonable precautions to prevent the disclosure of confidential patient information to any unauthorized party or otherwise into the public domain. The Investigator will notify Upstream Bio within 24 hours of a security event that impacts or has the potential to impact confidentiality, integrity, or availability study data.

10.1.5 Committees Structure

10.1.5.1 Data Monitoring Committee

Participant safety will be continuously monitored by the DMC, which includes safety signal detection at any time during the study. The DMC is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the stopping of a study for harm. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study. Additional details will be provided in a DMC Charter.

All safety data collected will be summarized and reviewed by the DMC for agreement of next steps.

Case unblinding may be performed for above reviews if necessary.

10.1.6 Dissemination of Clinical Study Data

A summary of the results of the clinical study together with a summary that is understandable to a layperson will be provided after the global end of the study in all countries concerned to ensure full availability of all clinical data under this protocol, within 12 months.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the eCRF completion instructions.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and Regulatory Agency inspections and provide direct access to source documents.

Monitoring details describing strategies, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions accountable to the study Sponsor which are delegated to other individuals (e.g., CROs).

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

All data generated by the site personnel will be captured electronically at each study center using validated eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the electronic data capture (EDC) application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.

The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

10.1.7.1 Quality Tolerance Limits

Quality tolerance limits (QTLs) will be predefined in a separate plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.

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

The Investigator must maintain accurate documentation (source data) that supports the information entered into the eCRF.

The Sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the first participant consented to participate in clinical study (first act of recruitment/screening).

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
- If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

The results of this study may be published or presented at scientific meetings, subject to the terms of this section and the Clinical Trial Agreement. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

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

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

10.1.11 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all applicable ethical and legal requirements for the study have been met before the first participant is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). In the US: Following approval, the protocol amendment(s) will be submitted to the Investigational New Drug (IND) under which the study is being conducted.

Administrative changes (not affecting the participants benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

10.1.12 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance coverage in accordance with all legal requirements.

10.1.13 Monitoring and Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare the eCRF entries and individual participant's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that participant confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs, IECs, or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor, and CRO if involved in monitoring/data management, of the necessary support at all times.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10–3 will be performed by the central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make a study intervention decision, the results must be recorded.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Investigators or qualified designees must document their review of each laboratory safety report.

Table 10–3 Protocol-required Clinical Laboratory Tests

Laboratory Tests	Parameters	
Hematology	Platelet count Total red blood cell count Hemoglobin Hematocrit	WBC count with differential: Neutrophils Lymphocytes Monocytes (masked/blinded starting at Visit 2) Eosinophils (masked/blinded starting at Visit 2) Basophils (masked/blinded starting at Visit 2)
Coagulation (only at Visit 1 and EOS)	Prothrombin time Activated partial thromboplastin time INR	
Clinical chemistry	Creatinine BUN Glucose Uric acid Total cholesterol, HDL and Triglycerides, LDL (calculated or direct) Total protein Albumin Total bilirubin (if abnormal, differentiation in conjugated and non-conjugated bilirubin)	AST (SGOT) ALT (SGPT) Alkaline phosphatase Electrolytes (calcium, sodium, potassium, chloride, phosphate) Bicarbonate CPK CRP
Immunoglobulins	IgA, IgE (masked/blinded starting at Visit 2), IgG, IgM	
Routine urinalysis	Specific gravity pH, blood, glucose, WBC, protein, ketones, bilirubin, nitrite Microscopic examination (if blood or protein is abnormal).	
Pregnancy testing	Highly sensitive serum hCG pregnancy test (as needed for POCBP) at Visit 1 and urine pregnancy tests at other visits as shown in the detailed in the SoA (Table 1–1). FSH if <50 years old and amenorrheic for >12 months. At the EOS Visit, a home pregnancy testing kit will be issued to participants who are POCBP to be used at approximately Day 120 post-last dose. Results should be reported to the Investigator.	
Viral serology (only at Visit 1)	HIV 1 and 2 antibodies, HbsAg, HbcAb, HCV Ab. A confirmatory HIV 1 / 2 differentiation will be performed if HIV 1 / 2 Ab is positive. A confirmatory Hepatitis C viral load RNA will be performed if HCV Ab is positive.	

Abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CPK=creatine phosphokinase, CRP=C-reactive protein, EOS=end of study, FSH=follicle-stimulating hormone, HBcAb=hepatitis B core antibody, HBsAg=hepatitis B surface antigen, HCV Ab=hepatitis C antibody, hCG=human chorionic gonadotropin, HDL= high-density lipoprotein, HIV=human immunodeficiency virus, Ig=immunoglobulin, INR=international normalized ratio, LDL=low-density lipoprotein, POCBP=participants of childbearing potential, SGOT=serum glutamic-oxaloacetic transaminase, SGPT=serum glutamic-pyruvic transaminase, SoA=schedule of activities, WBC=white blood cell.

Note: Eosinophils and IgE data collected after screening will be blinded/masked and will not be available to the site (starting at Visit 2). To remove the possibility of eosinophil data being calculated from the remaining haematology parameters, data relating to monocytes and basophils collected (starting at Visit 2) will also not be provided to site personnel.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

An AE is any untoward medical occurrence in a participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition

Any abnormal laboratory test results or other safety assessments, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator and requiring further evaluation or intervention. Repeating a lab test to confirm the abnormality is not considered further evaluation.

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.

Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the disease under study or pre-existing condition, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- 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.
- Mild ISRs will not be reported as AEs. If after discharge from the site, the participant reports an ISR which in the Investigator's judgment was moderate or severe, the Investigator or qualified designee will complete the AE eCRF page and additional eCRF questions about the ISR. Refer to CTCAE v5 for instructions on grading of mild ISR.

10.3.2 Definition of Serious Adverse Event

An SAE is an AE that:

a. **Results in death**

b. **Is life-threatening**

The term life-threatening in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs

hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

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

d. **Results in persistent or significant disability/incapacity**

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

f. **Important medical event**

Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-up of AE and SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Sponsor required form.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

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

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). For AEs/SAEs NOT included in NCI-CTCAE, the Investigator will make an assessment of intensity using the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe.

An event is defined as ‘serious’ when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

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.

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 as underlying disease(s), 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 IB and/or Product Information, for marketed products, in their assessment.

For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report in the electronic data collection tool. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the electronic data collection tool.**

The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The following "binary" decision choice will be used by the Investigator to describe the initial causality assessment:

- Related: Reasonable possibility of a relatedness
- Not related: No reasonable possibility of relatedness.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed form.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAE

SAE Reporting via Electronic Data Collection Tool

The Investigator must report any SAEs to the Sponsor's designated safety services within 24 hours of becoming aware of the event.

Email or facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information.

The site will complete the SAE paper data collection tool and transmit within 24 hours.

In rare circumstances and in the absence of email/facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes. A written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

When calling to report an SAE, state that you are reporting an SAE and give the Investigator's name, your name, the telephone number where you can be reached, and the protocol number and title.

The event must also be recorded on the standard AE eCRF/eSource. Preliminary reports of SAEs must be followed up by detailed descriptions later on and may include clear and pseudonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents only when requested and applicable. SAE reports must be made whether or not the investigator considers the event to be related to the investigational drug.

The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor/CRO will evaluate the seriousness and the causal relationship of the event to study intervention. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the Reference Safety Information (IB or Summary of Product Characteristics). As defined in the safety management plan, all suspected unexpected serious adverse reactions (SUSARs) will be electronically reported through EudraVigilance safety reports by the designated Sponsor/CRO team in accordance with EMA/873138/2011 Rev 2. Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

Contacts for SAE reporting can be found below. SAEs suspected to be related to the study treatment (SARs) occurring after the end of study have to be reported by email to Syneos Health

Safety and Pharmacovigilance email address within 24 hours after the event becomes known to the investigator, using the SAE Report Form.

SERIOUS ADVERSE EVENT REPORTING CONTACT DETAILS

Email address: safetyreporting@syneoshealth.com
Fax Number: +1 877-464-7787

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Participants in the following categories are considered POCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal reference range (≥ 40 U/mL) may be used to confirm a postmenopausal state in participants not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea,a single FSH measurement is insufficient.
    - Participants on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

10.4.2 Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the POCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a participant capable of producing sperm can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable o implantable[d]
• Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
a) Contraceptive use by participants should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d) Contraception methods that in the context of this guidance are considered to have low user dependency. Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix 5: Low, Medium and High Daily Metered Doses of Inhaled Corticosteroids for Participants with Asthma

Inhaled corticosteroid	Total daily ICS dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100-200	>200–400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200-400	>400–800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100-250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100-250	>250–500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information		
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400

Abbreviations: DPI=dry powder inhaler, HFA=hydrofluoroalkane propellant, ICS: inhaled corticosteroid, pMDI=pressurized metered dose inhaler, ICS by pMDI should preferably be used with a spacer.

Source: Global Initiative for Asthma (GINA, 2023). Global Strategy for Asthma Management and Prevention, 2023 (www.ginasthma.org).

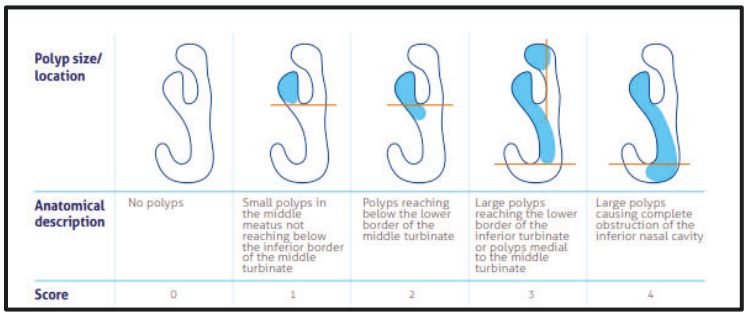
10.6 Appendix 6: Nasal Polyp Score

Bilateral endoscopic NPS is a physician-reported scoring system to estimate the extent or severity of NPs based on assessments by nasal endoscopy (Messerklinger et al, 1970; Johansen et al, 1993; Slavin, 1991; Lildholt et al, 1988; Drake-Lee, 1991; Johansson et al, 2022). Each nostril is scored on a categorical scale of 0 to 4.

The degree of NPs is classified in relation to fixed anatomical landmarks:

0=no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4=large polyps causing complete obstruction of the inferior nasal cavity).

The total score is the sum of the right and left scores (0-8).



10.7 Appendix 7: Nasal Polyposis Symptom Diary (NPSD)

Nasal Polyposis Symptom Diary is an 11-item nasal polyposis symptoms diary. The participant is asked to record their experience with nasal polyposis over the past 24 hours (preferably in the morning) when responding to each question (nasal blockage, nasal congestion, runny nose, postnasal drip, headache, facial pain, facial pressure, sense of smell; and symptom impacts on sleep and daily activities). Participants report the severity of each symptom and symptom impact at its worst using a 4-point verbal scale (0=none to 3=severe). Endpoints will be measured by change from baseline in bi-weekly mean nasal polyposis symptoms diary scores:

- Nasal Congestion Score (NCS): it is calculated from participant report of nasal congestion severity (Question 2), using a 4-point verbal scale (0=none to 3=severe).
- Loss of Smell: it is calculated from participant report of difficulty of sense of smell (Question 8), using a 4-point verbal scale (0=none to 3=severe).
- A TSS is calculated by taking the sum of the 8 equally weighted symptom items from Questions 1-8.

The nasal polyposis symptoms diary is provided below (O'Quinn et al, 2022):

Please answer the following questions based on your experience with nasal polyposis/nasal polyps over the past 24 hours.
1. Rate your worst nasal blockage over the past 24 hours
2. Rate your worst nasal congestion over the past 24 hours
3. Rate your worst runny nose over the past 24 hours
4. Rate your worst postnasal drip (mucus drainage down the throat) over the past 24 hours
5. Rate your worst headache over the past 24 hours
6. Rate your worst facial pain over the past 24 hours
7. Rate your worst facial pressure over the past 24 hours
8. Rate your worst difficulty with sense of smell over the past 24 hours
9. Rate your difficulty with sleeping due to nasal symptoms last night
10. Rate your difficulty with daily activities due to nasal symptoms over the past 24 hours
11. Did you take your nasal medication as scheduled yesterday?

10.8 Appendix 8: Lund Mackay Score for Severity of Nasal Polyps by Computer Tomography

LMK Score (Sinus Opacification Score) is a physician-reported quality staging system for evaluation of severity of NPs based on assessments of the sinuses by computer tomography (Lund and Mackay, 1993; Rosenfield et al, 2007; Likness et al, 2014) (CT scans not performed in Germany and Czechia). The LMK staging system assigns a value of 0, 1, or 2 to each of the following 5 sinuses: maxillary, anterior ethmoid, posterior ethmoid, frontal, and sphenoid.

The score assignment is:

- 0=sinus is totally patent
- 1=sinus is partially opacified
- 2=sinus completely opacified

The Osteomeatal Complex is scored either 0 if not occluded or 2 if occluded. The maximum score for each side is thus 12, with a total score determined out of 24.

Lund-Mackay Staging System		
Scores Each Sinus 0–2, OMC 0 or 2		
0 = Normal, 1 = Partial Opacification, 2 = Total Opacification		
	Right	Left
Maxillary		
Anterior ethmoid		
Posterior ethmoid		
Sphenoid		
Frontal		
Osteomeatal complex		
Total (maximum = 24)		

10.9 Appendix 9: Asthma Control Questionnaire

Effect of adequacy of asthma control in participants with comorbid asthma will be assessed by participant-filled ACQ-6 questionnaire. The questions are equally weighted and the ACQ score is the mean of the questions and, consequently, ranges from 0 (totally controlled) to 6 (severely uncontrolled). Participants with a score below 1.0 will have adequately controlled asthma and above 1.0, their asthma will not be well controlled. However, there is a very grey area between 0.75 and 1.25 where participants are on the borderline of adequate control. On the 6-point scale of the ACQ, a change or difference in score of 0.5 is the smallest that can be considered clinically important. The questionnaire has been validated for use against ACQ-7 (Juniper et al, 2005).

The ACQ-6 questionnaire is given below (Juniper, 1999):

ASTHMA CONTROL QUESTIONNAIRE©

Please answer questions 1–6.

Circle the number of the response that best describes how you have been during the past week

1. On average, during the past week, how often were you **woken by your asthma** during the night?	0	Never
	1	Hardly ever
	2	A few minutes
	3	Several times
	4	Many times
	5	A great many times
	6	Unable to sleep because of asthma
2. On average, during the past week, how **bad were your asthma symptoms when you woke** up in the morning?	0	No symptoms
	1	Very mild symptoms
	2	Mild symptoms
	3	Moderate symptoms
	4	Quite severe symptoms
	5	Severe symptoms
	6	Very severe symptoms
3. In general, during the past week, how **limited were you in your activities** because of your asthma?	0	Not limited at all
	1	Very slightly limited
	2	Slightly limited
	3	Moderately limited
	4	Very limited
	5	Extremely limited
	6	Totally limited
4. In general, during the past week, how much **shortness of breath** did you experience because of you asthma?	0	None
	1	A very little
	2	A little
	3	A moderate amount
	4	Quite a lot
	5	A great deal
	6	A very great deal
5. In general, during the past week, how much of the time did you **wheeze**?	0	Not at all
	1	Hardly any of the time
	2	A little of the time
	3	A moderate amount of the time
	4	A lot of the time
	5	Most of the time
	6	All the time
6. On average, during the past week, how many **puffs of short-acting bronchodilator** (eg. Ventolin) have you used each day?	0	None
	1	1–2 puffs most days
	2	3–4 puffs most days
	3	5–8 puffs most days
	4	9–12 puffs most days
	5	13–16 puffs most days
	6	More than 16 puffs most days
To be completed by a member of the clinic staff		
7. FEV_1 pre-bronchodilator:	0	>95% predicted
	1	95–90%
FEV_1 predicted	2	89–80%
	3	79–70%
FEV_1 % predicted	4	69–60%
(Record actual values on the dotted lines and score the FEV_1 % predicted in the next column)	5	59–50%
	6	<50% predicted

10.10 Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

Protocol Amendment 2.1 (13 September 2024)

This amendment is considered to be substantial based on the criteria set forth in Regulation (EU) No 536/2014, Article 2 paragraph 2 No 13 of the European Parliament and of the Council of 16 April 2014.

Overall Rationale for the Protocol Amendment

This V2.1 region-specific amendment, dated 13 September 2024, has been developed to include changes that were made in the V2.0 global amendment and to address changes requested by Czechia.

Protocol Amendment 1.3 (28 February 2024)

This amendment was considered to be substantial based on the criteria set forth in Regulation (EU) No 536/2014, Article 2 paragraph 2 No 13 of the European Parliament and of the Council of 16 April 2014.

Overall Rationale for the Protocol Amendment

This V1.3 Country-Specific Protocol Amendment (Germany-3), dated 28 February 2024, was developed to include changes requested by the Regulatory Authority. These changes include:

- Revised Eudra CT to EU CT
- Removed references to legally authorized representative (LAR)
- Added statement that relevant clinical findings from the ongoing Phase 1 trials will be taken into account for the present trial
- Clarified and specified any clinically significant cardiac disease and/or ECG abnormality, in the opinion of the Investigator, obtained during the Screening Period, as an exclusion criterion
- Corrected citation to regulatory guidance

Protocol Amendment 1.2 (16 January 2024)

This amendment was considered to be nonsubstantial based on the criteria set forth in Regulation (EU) No. 536/2014, Article 2 paragraph 2 No. 13 of the European Parliament and of the Council of 16 April 2014.

Overall Rationale for the Protocol Amendment

This V1.2 Country-Specific Protocol Amendment (Germany-2), dated 16 January 2024, was developed to include the EU CT No. on the Title Page.

Protocol Amendment 1.1 (30 November 2023)

This amendment was considered to be substantial based on the criteria set forth in Regulation (EU) No. 536/2014, Article 2 paragraph 2 No. 13 of the European Parliament and of the Council of 16 April 2014.

Overall Rationale for the Protocol Amendment

This V1.1 Country-Specific Protocol Amendment (Germany-1), dated 30 November 2023, was developed to specify that CT scans described in the global protocol will not be performed in Germany. In addition, the eGFR correction factor for Black/African American participants was removed.

10.11 Appendix 11: Equipotent Daily Doses of MFNS

Intranasal steroid	Dose equivalent for MFNS 200 mcg/day
Beclomethasone aerosol (40 mcg or 80mcg/actuation)	320 mcg/day
Beclomethasone suspension (42 mcg/spray)	168 mcg/day
Budesonide suspension (32mcg/spray) [a]	64 mcg/day
Ciclesonide aerosol (37 mcg/actuation)	74 mcg/day
Ciclesonide suspension (50 mcg/spray)	200 mcg/day
Flunisolide suspension (25 ug/spray) [b]	200 mcg/day
Fluticasone furoate suspension (27.5 mcg/spray)	110 mcg/day
Fluticasone propionate suspension (50 mcg/spray) [c]	200 mcg/day
Triamcinolone suspension (55 mcg/spray)	220 mcg/day

Abbreviations: MFNS=mometasone furoate nasal spray.

[a] Bende et al. A randomized comparison of the effects of budesonide and mometasone furoate aqueous nasal sprays on nasal peak flow rate and symptoms in perennial allergic rhinitis. Ann Allergy Asthma Immunol 2002;88:617–623.

[b] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7c72c954-3758-40c3-9977-d03b25d71e0a

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10.12 Appendix 12: COVID Guidance

Respiratory disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may impact certain regions during the conduct of this study. Appropriate medical measures will be taken as per site standard to confirm eligibility of participants and safely conduct the study.

Management of COVID-19 for enrolled participants will include:

- Signs and symptoms related to COVID-19 will be closely monitored as per standard safety monitoring.
- Confirmation of COVID-19 infection by available approved laboratory standard testing should be conducted at the Investigator's discretion.
- Participants may be referred to the local health care system for further follow up and treatment if they have suspected reports or have come in contact with a person who has tested positive for SARS-CoV-2.

Measures to mitigate potential operational challenges caused by COVID-19 for enrolled participants will include:

- In participants unable to attend on-site visits, the Investigator may have to determine whether samples can be collected, and safety data can be recorded on-site. If on-site is not possible, risk mitigation measures may include remote study visits, home healthcare visits, tele-medicine, handling of protocol deviations, and remote site monitoring. Note that these risk mitigation measures also apply to other significant situations impacting ability to perform on-site visits.

  Home healthcare and tele-medicine may reduce the risk of missed visits due to study site closures and reduce the need for participants to visit the study site and therefore minimize the overall burden on participants. All study assessments must be performed by trained clinical study staff in clinic, or where possible, via tele-visits and/or home healthcare visits (see Section 8.13).

Prevention of pathogen transmission:

- Site practice and relevant and applicable regulations and/or guidelines will be followed to prevent pathogen transmission.
- Study will start enrolling only when deemed safe by the Sponsor and CRO in collaboration. In addition, the study will not start until the local containment measures or other safety restrictions linked to the COVID19 pandemic allow.
- Current national laws and local recommendations for prevention of the pandemic will be strictly adhered to.
- For prevention of SARS-CoV-2 infection the recommended interval between vaccination and study intervention is 7 days to allow for the potential occurrence of injection site reactions (ISRs). The study intervention will be administered at an alternative site compared to the vaccine. Participants will follow site policy in order to mitigate the additional risks caused by COVID-19.

Participants will follow site policy in order to mitigate the additional risks caused by COVID-19.

10.13 Appendix 13: Protocol Elements for Redaction

Not applicable

10.13.1 Information about Sponsor Signatory and Medical Monitor

Protocol Title: A Phase 2, Randomized, Double-blind, Placebo-controlled, Multi-center Study to Assess the Efficacy and Safety of Verekitug (UPB-101) in Participants with Chronic Rhinosinusitis with Nasal Polyps on a Background of Nasal Corticosteroids (VIBRANT)

Compound: Verekitug (UPB-101)

Indication: Chronic Rhinosinusitis with Nasal Polyps

Protocol Number: UPB-CP-03

Protocol Version: V2.1/Region-Specific Amendment

Approval Date: 13 September 2024

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Sponsor Signatory:

Signed by PPD

PPD

PPD

I approve this document
17 September 2024 | 11:30:24 EDT

D

PPD

PPD

17 September 2024 | 14:55:28 EDT

Date

Upstream Bio, Inc.

10.13.2 List of Study Staff

List of study staff will be provided as a separate document.

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