STATISTICAL ANALYSIS PLAN

A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Intranasal Midazolam (USL261) in the Outpatient Treatment of Subjects with Seizure Clusters
ARTEMIS-1: Acute Rescue Therapy in Epilepsy with Midazolam Intranasal Spray-1

Protocol Number P261-401

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CONFIDENTIAL

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Final 2.9

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LIST OF ABBREVIATIONS

Abbreviation	Definition
µL	Microliter
ACLS	Advanced Cardiac Life Support
AE	Adverse event
AED	Antiepileptic Drugs
ATC	Anatomic Therapeutic Chemical
B-SIT	Brief Smell Identification Test
C-SSRS	Columbia-Suicide Severity Rating Scale
CFR	Code of Federal Regulations
CI	Confidence interval
CRO	Contract Research Organization
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EMS	Emergency Medical Services
ER	Emergency Room
ET	End of Treatment
GCP	Good Clinical Practice
IAMC	Interim Analysis Monitoring Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IN	Intranasal
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITI	Intranasal Therapeutics, Inc.
ITIQ	Intranasal Therapy Impact Questionnaire
ITT	Intent-to-treat
LAR	Legally acceptable representative
MCS	Mental Health Component Score (SF-12v2)
MDZ	Midazolam
Mg	Milligram
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
OAA/S	Observer's Assessment of Alertness/Sedation
IV	Intravenous
PCS	Physical Health Component Score (SF-12v2)
PK	Pharmacokinetic
PMP	Patient Management Plan
PT	Preferred Term in MedDRA
RSAF	Randomized Safety Population
SAS	Statistical Analysis Software
SD	Standard deviation
USL	Upsher-Smith Laboratories, Inc.
USL261	Midazolam Nasal Spray, study drug (formally ITI-111)
SOC	System Organ Class in MedDRA
TEAE	Treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
WHO	World Health Organization

1. INTRODUCTION

Acute repetitive seizures and seizure clusters occur in a subset of epilepsy patients. Seizure clusters have distinguishable characteristics that are easily recognized by patients, caregivers, and physicians and include a consistent onset (auras, prodrome) that may be indicative of convulsive or non-convulsive symptoms. Although patients typically recover between seizures, these seizure can last anywhere from minutes to hours.[1] When a cluster of seizures occurs outside a hospital, the patient must often be transported to an acute care facility so medical personnel can administer intravenous (IV) therapy to stop the seizure(s).[2]

The primary goals of seizure cluster treatment are seizure cessation and prevention of seizure recurrence.[1] Acute benzodiazepine treatment is effective for seizure control and often results in rapid seizure cluster termination; however, most treatment options rely on intervention by emergency medical personnel and, therefore, delay treatment while the patient is transported to a medical facility.[3] The development of an easily administered outpatient treatment of seizure clusters may reduce emergency medical intervention and decrease seizure cluster duration.

This statistical analysis plan covers the detailed procedures for performing statistical analyses and producing tables, listings, and figures of the Phase 3 study Protocol P261-401 (Fifth Issue, Amendment 4, 20 May 2015).

2. STUDY DESIGN

2.1. General Study Design and Plan

This is a Phase 3 multicenter study, with 2 distinct phases and 4 study center visits as depicted in Figure 1. The first phase is the Test-Dose Phase where subjects will receive 2 doses of open-label 5.0 mg USL261 10 minutes apart at the study center. The Test-Dose Phase is designed to assess the safety, tolerability and pharmacokinetics of USL261 in a monitored setting and provide the caregivers with training on the study procedures. The Test-Dose Phase will be followed by an outpatient, double-blind, placebo-controlled, parallel-group phase, referred to as the Comparative Phase. In the Comparative Phase, all subjects will be randomized 2:1 to receive 5.0 mg USL261 or placebo. The subject's caregiver will administer the double-blind study drug at the time of a seizure cluster that meets the study criteria, according to the subject's individualized Patient Management Plan (PMP). The double-blind dose of study medication may be followed by an open-label single dose of 5.0 mg USL261 if any of the following occurs:

- The treated seizure cluster has not terminated within 10 minutes after the initial drug administration or
- Another seizure occurs between 10 minutes and 6 hours after administration of the study drug, and the subject does not have <8 breaths per minute, does not require emergency rescue treatment and assisted breathing intubation, and does not have excessive uncharacteristic sedation

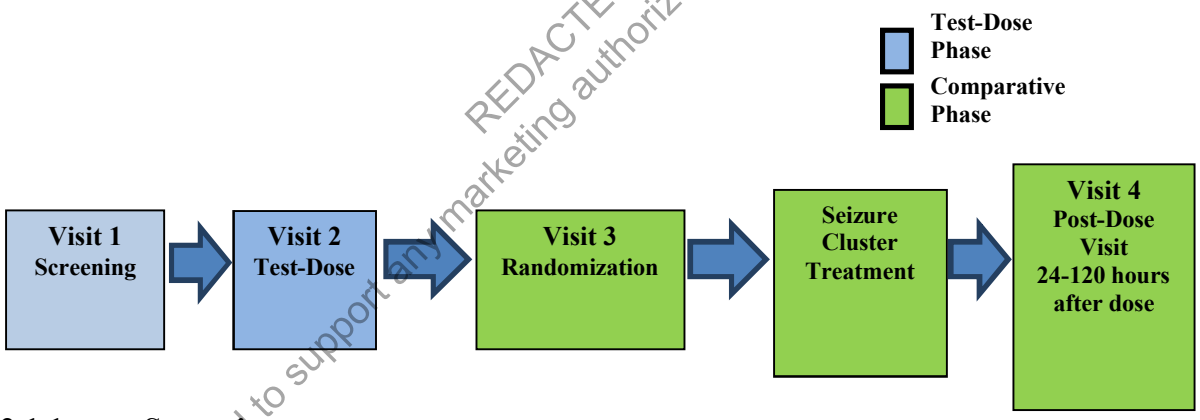
Anytime between 24 to 120 hours after study drug administration, subjects and caregivers will return to the study center for a post-dose study visit (Visit 4).

A maximum of approximately 350 subjects, aged 12 years and older, with a documented history of seizure clusters and on a stable AED regimen (no change in type[s] of drug) will be enrolled in the Test-Dose Phase in order to achieve a maximum of 240 subjects completing the Comparative Phase. Before any subject continues to the Comparative Phase, safety data from at least 25 subjects in the Test-Dose Phase will be reviewed by an independent Data and Safety Monitoring Board (DSMB). Enrollment will temporarily halt once approximately 25 subjects complete the Test-Dose Phase, to allow the DSMB to review the safety data. If the safety data from this initial cohort supports continuation of the trial according to the DSMB, enrollment into the Test-Dose Phase will resume and the initial 25 subjects will proceed to the Comparative Phase. All subsequent subjects will progress directly from Test-Dose Phase to the Comparative Phase.

A classic group sequential design, with 3 interim analyses and a maximum sample size of 240 subjects who have completed the Comparative Phase is utilized in order to reach sufficient overall power (approximately 90%) for this study with possible study stopping at interims for efficacy or futility. In this group sequential design, interim analyses will occur after 132, 165, and 204 subjects have completed the Comparative Phase.

Figure 1 shows the overall study scheme with regard to screening, Test-Dose Phase, and Comparative Phase.

Figure 1: Study Design



2.1.1. Screening

After subjects and caregivers have provided informed consent (and assent, where appropriate), subjects will undergo screening procedures at Visit 1 (see Table 1). At Visit 1, training will be provided to the caregivers for self-study, which will be completed at or before Visit 2. The screening period (time between Visit 1 and 2) will be a maximum of 28 days. The screening period may be extended in certain cases; however, the extension of the screening period must be approved by the Sponsor or CRO designee. If a screening period extension is granted for a given subject, that subject will have to undergo repeat screening laboratory and ECG assessments within 28 days before Visit 2.

2.1.2. Test-Dose Phase

The Test-Dose Phase, which occurs at Visit 2, will take place at the study center under the supervision of the study investigator within 28 days of Visit 1. The investigator, or other qualified study personnel, will review, assess, and (if needed) re-instruct subjects and caregivers on the information provided in the self-study training. Caregivers must demonstrate hands-on competence in performing timed assessments and recording information in the Subject Workbook, as well as airway management techniques.

Subjects who meet eligibility criteria at Visit 2 will receive a test dose of 5.0 mg USL261 administered by a member of the study center personnel followed by a second dose of 5.0 mg USL261 10 minutes later administered by the caregiver under the supervision of a member of the study center personnel. Caregivers and study center personnel will monitor the subject during the observation period for at least 4 hours after the test doses are administered and the assessments outlined in Table 1 will be performed. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, caregivers and study center personnel will monitor the subject during the observation period for at least 1 hour after test dose administration. A subject who experiences signs or symptoms at Visit 2 that are concerning in the investigator's judgment or are exclusionary per exclusion criterion number 22 must be monitored until resolved or longer as deemed appropriate by the investigator.

At least one study center personnel who is trained and qualified to perform airway assessment and management, including endotracheal intubation (or local country /site equivalent) and Advanced Cardiac Life Support (ACLS) (or local country/site equivalent), will be available at the site for the entire observation period following the administration of the first test dose.

2.1.3. Comparative Phase

Subjects and caregivers will return to the study center for Visit 3 within 24 hours to 28 days of Visit 2 (unless DSMB review of first 25 subjects is not yet completed). At Visit 3, the investigator, or other qualified study personnel, will review, assess, and (if needed) re-instruct caregivers on the information provided in the self-study training. Before subjects are randomized, caregivers must have demonstrated hands-on competence in administering the study drug, performing timed respiration rate measurements and recording them in the practice Subject Worksheet, as well as airway management techniques.

If the subject continues to meet eligibility criteria at Visit 3, he/she will be randomized to receive either USL261 5.0 mg or placebo. Caregivers will receive a study materials kit, which includes the Subject Workbook, the subject's Patient Management Plan (PMP), and the study drug kit. The PMP will specify the criteria for seizure cluster recognition, the procedure for contacting the central study nurse hotline after study drug administration, the requirements for administering a second dose of study drug (active USL261), and a rescue protocol individualized for the subject.

During the Comparative Phase, caregivers will administer the double-blind study medication at the time of a seizure cluster that meets study criteria (according to the subject's individualized PMP) and call the central study nurse hotline as soon as possible following study drug administration. If the treated seizure has not terminated within 10 minutes after the initial drug administration or another seizure occurs between 10 minutes and 6 hours after administration of the study drug, and the subject does not have < 8 breaths per minute, does not require emergency

rescue treatment with assisted breathing or intubation, and does not have excessive uncharacteristic sedation (as defined by the investigator in the PMP), the second dose of study drug (ie, 5.0 mg dose of USL261) may be administered. If the second dose of study drug is administered, the caregiver will again call the central study nurse hotline as soon as possible after its administration. The caregiver will monitor the subject after study drug administration to record safety and efficacy measurements.

If the subject encounters persistent seizure cluster activity or seizure recurrence (as defined in the subject's PMP), has < 8 breaths per minute, or is excessively and uncharacteristically sedated, caregivers will follow the rescue protocol in the subject's PMP. The subject's rescue protocol will outline rescue instructions individualized for the subject, including when and how to contact EMS (or local equivalent).

Subjects and caregivers will return to the study center 24 to 120 hours after study drug administration for Visit 4. Subjects who are prematurely discontinued from study participation or terminate their participation should return to the study center for Visit 4 (Early Termination). The subject or caregiver will report to the investigator (or his/her designee) as soon as possible any significant medical event (including events that are life-threatening or that result in death, hospitalization or prolonged hospitalization, persistent or significant disability, or incapacity of the subject) that occurs to the subject from the time written informed consent is obtained until completion of the final study visit (Visit 4 [Post-Dose Assessment or ET]) or 7 days after last administration of study drug , whichever is later. The subject or caregiver may also call the central study nurse hotline at any time during the study for help or advice regarding study procedures.

This study will be conducted in accordance with International Conference on Harmonization (ICH) E6, Guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements including the US Code of Federal Regulations dealing with clinical studies (21 Code of Federal Regulations [CFR] including § 50 and 56 concerning informed consent and Institutional Review Board [IRB] regulations, respectively).

2.2. Randomization and Method of Treatment Assignment

A stratified, blocked randomization schema will be generated by an unblinded statistician and used to assign subjects to treatment. Treatment assignments will be assigned and kept strictly confidential by the Interactive Response Technology (IRT) System. Randomization will be stratified by age (< 18 vs. ≥ 18). Within each stratum, subjects will be randomized in a 2:1 ratio of USL261 5.0 mg nasal spray (active) or matching placebo nasal spray using an appropriate randomly permuted block.

Subjects who meet eligibility requirements at Visit 3 will be randomized to treatment. At the time of randomization, subjects will be assigned unique subject identification numbers. Numbers will be assigned in consecutive increasing order without replacement or reuse of any assigned number. The study will be double-blinded to the treatment group assignment accessible only to authorized persons per sponsor's (or designee's) Standard Operating Procedures (SOPs) until the time of unblinding.

2.3. Study Procedures

The schedule of study procedures and evaluations is summarized in Table 1.

Table 1: Schedule of the Study Procedures

Phase	Screening	Test-Dose Phase	Comparative Phase		
Visit Number	**1**	**2[a]**	**3[b]**	**Treatment[c]**	**4 or ET[d]**
Study Assessments					
Informed consent[e]	X				
Register subject with IRT	X				
Inclusion/Exclusion evaluation	X	X	X		
Caregiver training[f]	X	X	X		
Demographics	X				
Medical/surgical history[g]	X				
Concomitant medication review	X	X	X		X
ER and EMS Visit Review[h]	X				X
Physical exam[i]	X	X	X		X
Neurological exam[j]	X	X	X		X
B-SIT		X	X		X
Clinical laboratory testing[k]	X				X
FSH level (females only)	X				
Pregnancy testing[l] (all females)	X	X	X		X
Drug screen[m]	X				
Patient Management Plan (PMP)[n]	X	X	X		
Central review of seizure cluster description[o]	X				
Treatment administration		X[p]		X	
Call central study nurse hotline [q]				X	
Pharmacokinetic blood sampling[r]		X			
Observer's Assessment of Alertness/Sedation (OAA/S)[s]		X			
12-lead ECG	X	X[t]			
Body weight	X	X	X		X
Height	X				X
Vital signs[u]	X	X	X		X
Caregiver-recorded respiration rate[v]		X		X	
Pulse oximetry[u]		X			
Report test dose information on IRT		X			
Columbia- Suicide Severity Rating Scale [w]	X	X	X		X
Outcome Assessments		X			X
Randomization using IRT			X		
Dispense study materials kit [x]			X		
Record seizure activity in Subject Workbook			X		
Evaluate subject's return to baseline functionality [y]				X	
Adverse event collection	X	X	X	X	X
Collect study drug containers, used and unused					X

Review/collect Subject Workbook					X
Telephone follow-up			X[z]		

[a] Visit 2 assessments occurring at the same time should be completed in the following order: ECG, OAA/S, vitals, pulse oximetry, PK blood draw, and second dose; Visit 2 will occur within 28 days of Visit 1. If necessary, assessments may be performed up to 1 minute before or 1 minute after the scheduled time.
[b] For patients enrolled in the study after the initial DSMB review, Visit 3 will occur a minimum of 24 hours and a maximum of 28 days after Visit 2.
[c] These assessments will be performed by the caregiver.
[d] Visit 4 will occur between 24 and 120 hours after double-blind study drug administration. Any subject who has not treated a seizure cluster meeting the study criteria within 6 months of Visit 3 (Randomization) will return to the study center for Visit 4 (Early Termination).
[e] Informed consent provided by subject (or subject's LAR) and caregiver before any other study-specific procedures; assent may also be required for some subjects
[f] Caregiver training includes, but is not limited to, providing self-study training to the caregiver and review of that training by the study center personnel. It also includes CPR and airway management training for caregivers.
[g] Includes seizure history and current/past medication use; complete at Visit.
[h] At Visit 1, collect number of calls to EMS and ER visits for a seizure cluster or other seizure emergency in the year prior to screening. At Visit 4, collect number of calls to EMS and ER visits for a seizure cluster or other seizure emergency since last visit or follow-up phone call. Number of calls to EMS and ER visits for a seizure cluster or other seizure emergency since last visit or follow-up phone call will also be collected on each monthly telephone follow-up call between Visit 3 and Visit 4 or ET.
[i] Physical examination includes assessments of the skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, abdomen, lymph nodes, and extremities, and a nasal cavity examination using a nasal speculum.
[j] A complete neurological examination will be performed at Visits 1 and 4/ET. A partial neurological examination will be performed at Visits 2 and 3.
[k] Includes hematology, serum chemistry, and urinalysis; phenobarbital levels will be assessed at Visit 1 for subjects taking phenobarbital and in subjects for which the investigator deems it necessary.
[l] Serum pregnancy test at Visit 1, urine pregnancy tests at Visits 2, 3, and 4/ET.
[m] Includes barbiturates, benzodiazepines, cocaine, marijuana, methamphetamine, opiates, and phencyclidine (all in urine) and alcohol (blood).
[n] PMP preparation begins at Visit 1. PMP should be completed before a subject receives the first test dose of USL261 at Visit 2. PMP provided to and reviewed with subject and caregiver at Visit 3.
[o] Approval of each subject's seizure cluster pattern by central reviewer is required for study inclusion
[p] At Visit 2, subjects will receive a test dose of 5.0 mg USL261 administered by a member of the study center personnel followed by a second dose of 5.0 mg USL261 10 minutes later administered by the caregiver under the supervision of study center personnel.
[q] Caregivers to call the central study nurse hotline as soon as possible after administering study drug.
[r] Blood samples for PK assessment will be collected before and at 5, 10, 20, 30 minutes and 1, 2, and 4 hours after the first test dose. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, blood samples will be collected before and at 5, 10, 20, 30 minutes and 1hour after administration of the first 5.0 mg test dose of USL261 at Visit 2.
[s] At Visit 2, the OAA/S will be administered before and at 5, 10, 20, 30 minutes and 1, 2, and 4 hours after the first test dose by a trained member of the study center personnel. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, the OAA/S will be administered before and at 5, 10, 20, 30 minutes and 1 hour after the first test dose by a trained member of the study center personnel.
[t] ECG will be performed twice at Visit 2: once before and once 15 minutes after the first test dose
[u] Vital signs include blood pressure (BP), heart rate (HR), respiration rate (RR), and temperature. At Visit 2, BP, HR, RR, and pulse oximetry are recorded before and at 5, 10, 15, 20, 30, 45 minutes and 1, 1.5, 2, 3 and 4 hours after the first test dose. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, BP, HR, RR, and pulse oximetry will be recorded before and at 5, 10, 15, 20, 30, 45 minutes and 1 hour after the first test dose. Temperature will be measured only at the pre-dose time point.
[v] Caregiver counts the number of breaths taken by the subject during a 30-second interval. At Visit 2, caregivers will measure respiration rate before and at 5, 10, 15, 20, 30, 45 minutes and 1, 1.5, 2, 3 and 4 hours after the first test dose. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, caregivers will measure respiration rate before and at 5, 10, 15, 20, 30, 45 minutes and 1 hour after the first test dose. On the day of treatment, caregivers will measure respiration rate at approximately 15 and 30 minutes and 1, 2, and 4 hours after study drug administration.
[w] Baseline/Screening version of the C-SSRS is administered at Visit 1. The Since Last Visit version is administered at Visits 2, 3 and 4/ET.
[x] The study materials kit will include at a minimum: Individualized PMP, summary of the PMP, Subject Workbook (used for collecting and recording seizure activity information, study drug administration, respiration rate, and other observations made by the caregiver), study drug kit, and dosing instructions.

[y] Caregiver will evaluate the subject's return to baseline functionality by recording the time when the subject was able to return to what he/she was doing.
[z] After Visit 3, telephone follow-up calls with the subject, subject's LAR, or subject's caregiver are to occur monthly until Visit 4 or ET. Abbreviations: BP = blood pressure; ECG = electrocardiogram; ET = early termination; FSH = follicle stimulating hormone; HR = heart rate; IRT = Interactive Response Technology System; LAR = legally acceptable representative; OAA/S = Observer's Assessment of Alertness/Sedation; PMP = patient management plan; QOL = quality of life; RR = respiration rate

3. STUDY OBJECTIVES

3.1. Primary Efficacy Objective

The primary efficacy objective is to evaluate the efficacy of USL261 compared with placebo for the outpatient treatment of seizure clusters based on Treatment Success, which is defined as achieving both of the following:

- Termination of seizure(s) within 10 minutes after study drug administration, and
- No recurrence of seizure(s) beginning 10 minutes after study drug administration to 6 hours after study drug administration.

3.2. Secondary Efficacy Objectives

The secondary efficacy objectives of this study are to evaluate the efficacy of USL261 compared with placebo for the outpatient treatment of seizure clusters using the following:

- Time to next seizure with a start time >10 minutes after the study drug administration
- Proportion of subjects with recurrence of seizure(s) beginning 10 minutes after study drug administration to 4 hours after study drug administration

3.3. Exploratory Efficacy Objectives

The exploratory efficacy objectives of this study are detailed for the comparison of USL261 and placebo for the outpatient treatment of seizure clusters.

- Proportion of subjects with recurrence of seizure(s) beginning 10 minutes after study drug administration to 24 hours after study drug administration.
- Time to return to full baseline functionality (as determined by the caregiver)
- Analyses for subjects receiving 2 doses of study drug
- Subject and caregiver outcome assessments
  - SF-12v2 for both subject and caregiver
  - Treatment Satisfaction Questionnaire for Medication (TSQM)
  - Intranasal Therapy Impact Questionnaire (ITIQ)

3.4. Safety Objectives

The safety objectives are to evaluate the safety and tolerability of USL261 for the treatment of seizure clusters using the following assessments:

- Adverse events (AEs)
- Caregiver-recorded respiration rate at 15 minutes, 30 minutes, 1 hour, 2 hours and 4 hours after study drug administration in the Comparative phase
- Requirement for unscheduled emergency room (ER) or emergency medical service (EMS) visit within 24 hours after study drug administration

- Brief Smell Identification Test (B-SIT; United States only)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Observer's Assessment of Alertness/Sedation Scale
- Physical, nasal, and neurological examinations
- Clinical laboratory tests
- Vital signs (systolic and diastolic blood pressure, heart rate, respiration rate and temperature) as recorded by the study center personnel

3.5. Pharmacokinetic Objectives

The Pharmacokinetic (PK) objective is to evaluate the PK profile of USL261 after administration of USL261 using the following PK parameters.

- $AUC_{0\text{-last}}$ – the area under the plasma concentration-time curve from time 0 to the last measurable concentration. Estimation by the linear-up/log-down trapezoidal method is preferred.
- $AUC_{0\text{-x}}$ – the area under the plasma concentration-time curve from time 0 to time x, where x =1, 2 and 4 hours
- C_{max} – the maximum plasma concentration
- t_{max} – the time to maximum plasma concentration
- t_{lag} – the time before the first measurable plasma concentration

4. ANALYSIS POPULATIONS

4.1. Screened Population

The Screened Population includes all subjects who signed an Informed Consent Form (ICF) or assent form.

4.2. Safety Population

The Safety Population includes all subjects who received at least 1 dose of study drug even if they were not randomized. Therefore, this population includes all treated subjects, including those who terminate following the test dose (Visit 2), but before randomization (Visit 3), as well as subjects who are randomized.

4.3. Randomized Population

The Randomized Population includes all subjects who are randomized to receive double-blind treatment. The Randomized Population is also the Intent-to-treat (ITT) Population.

4.4. Randomized Safety Population

The Randomized Safety Population (RSAF) is the group of subjects who are randomized and receive at least one dose of double-blind study drug. If a subject received the wrong treatment in the double-blind period or until discontinuation, the safety data for that subject will be summarized under the actual treatment group received. The demographic, baseline characteristics and safety data will be summarized under the following treatment groups:

- USL261 5 mg: USL261 group who received only the first dose of double-blind study drug
- USL261 5 + 5 mg: USL261 group who received the first dose of double-blind study drug and the second dose of open-label USL261
- Placebo: Placebo group who received only the first dose of double-blind study drug
- Placebo + USL261 5 mg: Placebo group who received the first dose of double-blind study drug and the second dose of open-label USL261

4.5. Modified Intent-to-Treat Population (mITT)

The mITT Population includes all subjects in the Randomized Population who received at least 1 dose of study drug during the Comparative Phase, who had post-treatment efficacy assessment (ie, with any seizure diary data). This mITT definition was chosen because Randomized subjects may be discontinued from the study prior to treatment in the Comparative Phase. Following the intent-to-treat principle, all efficacy analyses will be conducted using the mITT Population, analyzed according to the randomized treatment assignment. The potential biases arising from excluding randomized subjects who did not receive study medication are negligible since exclusion is not influenced by knowledge of whether being assigned to USL261 or placebo.

4.6. Per Protocol Population

The Per Protocol Population includes all subjects in the mITT Population who did not discontinue study participation or have any excludable protocol deviations (see Section 7.2).

All protocol deviations will be reviewed in a blinded manor prior to DB lock and it will be determined prior to DB lock if a patient should be excluded from the Per Protocol population. The Per Protocol population will be used for supportive analysis to assess robustness of the primary analysis.

4.7. Pharmacokinetic Population

The PK Population includes all subjects who received a test dose of USL261 in the Test-Dose Phase, have at least one quantifiable post-dose concentration and have no excludable protocol deviations (see Section 7.2). All protocol deviations will be reviewed in a blinded manor prior to DB lock and it will be determined prior to DB lock if a patient should be excluded from the PK population.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Level of Significance

Statistical comparisons will be performed using two-sided tests at the α=0.05 significance level except as discussed in the interim analysis section.

To control Type I error for the primary and secondary efficacy endpoints, a statistical gate-keeping procedure will be applied to control for multiplicity. The primary and secondary efficacy endpoints will be tested individually using the following hierarchical procedure:

First step: The proportion of subjects that are classified as Treatment Success during the Comparative Phase (two sided p-value) will be determined.

To proceed to the next step in the hierarchy, the previous step must be statistically significant (ie, two sided p-value is significant favoring USL261).

Second step: Time to next seizure following first dose of study drug (p-value from the log-rank test) will be determined.

Third step: The proportion of subjects with recurrence of seizure(s) beginning at 10 minutes after to 4 hours following the first dose of study drug.

All null hypotheses will be defined as no treatment difference.

5.2. Handling of Missing Data

Any specific imputation procedures for missing or incomplete data will be discussed in the section describing analytic methods for the efficacy/safety variable in question. Unless otherwise stated, observed data will be presented in tables and listings without imputation of missing values.

AEs with non-complete start dates and complete stop dates after the first double-blind study drug administration will be considered TEAEs during the Test Dose Phase if:

- Time is missing and the date is equal to or after the date of test-dose administration and is equal to or before the date of the first double-blind study drug administration;
- Day and month are missing and the year is equal to or after the year of test-dose administration but is equal to or before the year of the first double-blind study drug administration;
- Day is missing and the year is equal to or after the year of test-dose administration but is equal to or before the year of the first double-blind study drug administration;
- Day is missing, the year is equal to the year of test-dose administration, and the month is equal to or after the month of test-dose administration but is equal to or before the month of the first double-blind study drug administration;
- Year is missing;
- Complete date is missing.

AEs with partial start dates and complete stop dates after administration of the first double-blind study drug will be considered TEAEs during the Comparative Phase if:

- Time is missing and the date is after the date of the first double-blind study drug administration;
- Day and month are missing and the year is after the year of the first double-blind study drug administration;
- Day is missing and the year is after the year of the first double-blind study drug administration;
- Day is missing, the year is equal to the year of the first double-blind study drug administration, and the month is after the month of the first double-blind study drug administration.

Missing AE relationships will be presented as 'related' in tables but missing in listings. Missing AE intensity will be considered as 'severe' in tables but will be reported as missing in listings.

Medications with non-complete dates will be considered concomitant if partial dates show that medications were taken between the day of first dose of study drug at Visit 2 and the end of study. Medications will be considered prior if partial dates show that medications were taken within 30 days prior to the first dose of study drug at Visit 2. Medications can be categorized as both prior and concomitant.

5.3. Interim Analyses

Three interim analyses will be conducted to evaluate the treatment success rate for possible early stopping for success or futility. The interim analyses will occur after 132, 165, and 204 subjects complete the Comparative Phase (ie, subjects have received at least 1 dose of study drug during the Comparative Phase). All interim analyses will be performed on the mITT population, ie, subjects that are randomized and experience a cluster seizure event during the comparative phase. Subjects lost to follow-up or with missing primary outcome information will be considered treatment failures.

Treatment success is defined in Section 7.6.1.1.

5.3.1. Early Success

Early success will be declared as shown in Table 2. A group sequential design is used to allow for multiple interim analyses for efficacy, yet control the type I error rate at 2.5%. The Lan-DeMets spending function approximation of the Pocock boundary, is used for the efficacy boundary. The critical values for this efficacy boundary were obtained using R package gsDesign (version 2.8-8).

At each interim analysis, a one-sided Fisher's Exact test on the two proportions will be performed and compared to the Lan-DeMets Pocock approximation boundary critical values. For the three planned interim analyses and the final analysis, the critical values are presented in Table 2.

Table 2: Required p-values for declaring success according to Lan-DeMets Pocock Approximation Spending Function

Interim Analysis	P-value
132	0.0166
165	0.0094
204	0.0089
240	0.0085

5.3.2. Early Futility

Also at each of the pre-specified interim analyses (N=132, 165, 204), the predictive probability of success at the maximum sample size is computed (futility is not applicable to the final analysis at 240 subjects). The predictive probability calculation begins by assuming non-informative uniform prior distributions, Beta(1,1), on the treatment success rates for the placebo/control arm (p_C) and the probability of treatment success in the treatment arm (p_T), and computing the posterior distribution with the currently available data. The predictive distribution of the final data assuming the maximal sample size of N=240 is then computed. The number of future treatment successes for each arm has a Beta-Binomial distribution which is then added to the fixed number of current treatment successes in each arm. We may then compute the predictive probability that a trial success is reached at N=240 subjects. If this predictive probability is less than 10%, the trial is stopped for futility. Note that the success boundaries are computed assuming no futility stopping, and thus controls type I error regardless of the method used for futility stopping.

5.3.3. Early Termination not related to Success or Futility

If the trial has not crossed a boundary for early success or early futility and yet is stopped early before reaching the pre-specified maximum sample size of 240 subjects, the final analysis will be conducted with the enrolled patients in the mITT population. The p-value required for study success will remain as the p-value required at the final analysis according to the pre-specified Lan-DeMets Pocock boundary as if the trial had performed all planned interim analyses and continued to the maximum sample size. Therefore the p-value required for success will be p=0.0085 as described in Table 2 (Section 5.3.1).

5.3.4. Logistical details for interim analyses

The interim analyses will be conducted by an unblinded statistician and reviewed by an unblinded interim analysis monitoring committee (IAMC), both independent of the sponsor. The IAMC will consist of two individuals with adaptive design expertise to ensure the pre-specified adaptations are performed as planned, and to react to any unanticipated issues. The IAMC will be independent of the DSMB. IAMC membership, responsibilities, timelines, and communication channels will be clearly specified in a charter. In particular, the IAMC communication channels with the sponsor will be limited to maintain the blind of the sponsor study team in order to minimize the chance of operational bias. To this end, the IAMC will inform senior management first of the decision to continue the trial or stop according to the

statistical analysis plan. The senior management will in turn inform the team to continue or not to continue the study only with no further information on the interim analysis.

5.4. Examination of Subgroups

Further analysis of the primary and secondary endpoints may be examined for consistency across the subgroups listed below. Any subgroup analyses will be exploratory in nature.

- Age (< 18 years, ≥ 18 - < 65 years, ≥ 65 years)
- Sex (male/female)
- Race (white/non-white)
- Enzyme-inducing AEDs used within 14 days before the study drug administration (see Appendix 2) vs. others
- Weight categories (</≥ Median weight of the safety population)
- Region (North America and similar [this includes USA, Canada, Australia and New Zealand], Eastern Europe [Hungary, Poland, Ukraine], and Western Europe [Spain, Germany, Italy, and Israel])
- BMI standardized categories (underweight/normal [<25], overweight [≥25-<30], and obese 1-3 categories combined [≥30])

5.5. Data Collected from Unscheduled Visits

The data collected from the unscheduled visits are excluded from the by visit summary analysis.

However, when defining baseline for each assessment, the data collected from the unscheduled visits are still included.

6. DESIGN OPERATING CHARACTERISTICS

6.1. Simulation Scenarios

The estimated placebo treatment success rate is 0.40. The study is powered under the hypothesis that the USL261 treatment will lead to a clinically meaningful odds ratio of 2.9. With these assumptions, the sample size of 240 subjects who have completed the Comparative Phase (160 USL261/80 placebo) is sufficient to obtain approximately 90% power.

We examined a range of odds ratios/treatment success rates for placebo treatment success rates of 40% and performed 10,000 simulations to determine the power and average sample size (type I error is controlled analytically through the group sequential design). Simulations were performed using R version 3.1.0. For a given set of data we computed the success and futility criteria analytically. To simulate an individual trial, placebo and treatment data were simulated from the appropriate Binomial distributions (using the required sample sizes and placebo and treatment rates) and compared to the success and futility bounds. Trials that continued at an interim had additional data simulated, and so on until the trial reached completion. After

simulating 10,000 trials, the overall power, expected sample size, and other operating characteristics were computed by taking the observed mean values throughout the simulations.

6.2. Operating Characteristics

Assuming treatment success rates of 0.40 for the placebo arm, and Odds Ratio of 2.9, the power of this design is approximately 90% while maintaining at most 2.5% type I error. The expected (average) sample size will be approximately 150.

7. STATISTICAL ANALYSIS

Categorical variables will be summarized using counts and percentages. Continuous variables, including the change from baseline, will be summarized using descriptive statistics [n, mean, standard deviation (SD), minimum, median, maximum]. For modeling results, least squares means and standard errors will be presented.

Unless otherwise stated, all summaries will be presented by treatment group (USL261 or Placebo).

The Test Dose Phase is defined as the period of time from the date of first dose of study drug administration at Visit 2 up to, but not including, the date of randomization. The Comparative Phase is defined as the period of time from the date of randomization to the date of the last assessment in the study.

Table 3: Study Phases Start and End

Epoch Name	Start Date	End Date
Before Screening (BS)	Birth date	Date of Screening – 1 day
Screening (SC)	Date of screening	Date of Visit 2 – 1 day
Test-Dose (TD)	Visit 2	Visit 3 (not including the date of randomization)
Double-blind (DB)	Visit 3 day	Visit 4
Post Treatment but in Study (PD)	Study drug discontinuation visit +1 day	Visit 4
Post Study Follow-up (PS)	If enter Double-blind: Visit 4 +1 day If failed during TD: Visit 3 + 1 day	Open ended

Baseline values are the last available values before Test-Dose administration. For rescreened subject who underwent two Test-Dose administration, the last available values before the later Test-Dose administration will be defined as Baseline values.

Data listings will include all subjects with at least one applicable value. Listings will be sorted by treatment group, site, subject number, and date (if applicable).

All datasets and output will be produced using SAS® Version 9.1.3 or higher (SAS Institute, Inc., Cary, North Carolina, USA).

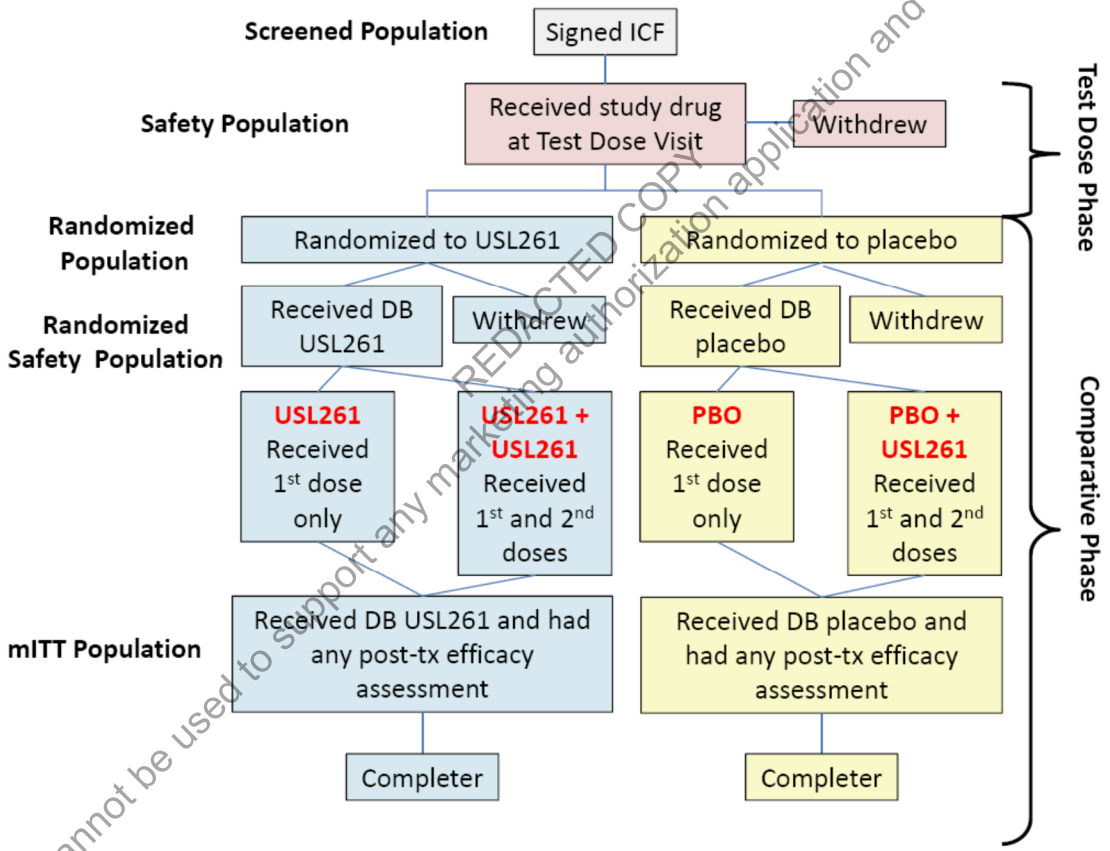
7.1. Subject Disposition

All individual subject disposition data will be listed by clinic/investigator site for screen failures separately, and for subjects in the Safety Population separately.

The primary reason for screen failure will be listed for all screen failed subjects.

Subject disposition will be presented by the primary reason for early withdrawal for the Safety Population during the Test Dose Phase. The number and percent of subjects who completed the study and the number and percent of subjects who discontinued the study along with the distribution of the reasons for study discontinuation will be presented in total and by phases for all study populations wherever applicable (see Figure 2).

Figure 2: Disposition Flow Chart



7.2. Protocol Deviations

All instances of protocol non-compliance will be tracked during the study and CSR Reportable protocol deviations will be finalized by a blinded Sponsor review prior to database lock. CSR Reportable deviations are deviations that materially affect the evaluation of efficacy or safety. CSR Reportable deviations will be reviewed in a blinded manner to determine if the data should

be excluded from an analysis population. A subject with a CSR Reportable protocol deviation will not necessarily be excluded from the analysis populations. The excludable protocol deviations will be classified by the sponsor for each population. Protocol deviation categories will be presented in a data listing and summarized using counts and percentages by treatment group. Major protocol deviations may include, but are not limited to:

- Failure to obtain informed consent
- Failure to report a Serious Adverse Event (SAE)
- Enrolling patients outside of inclusion/exclusion criteria
- Drug dispensing/dosing errors

7.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be presented for the Safety Population and repeated for the Randomized Safety and mITT Populations. Subject demographics include age, gender, weight, height, BMI, race, clinical site region, and ethnicity. Weight recorded in pounds will be converted to kilograms, and height recorded in inches will be converted to centimeters. Weight will also be categorized and summarized based on median for safety population (<median weight and ≥ median weight).

Age (years) will be calculated as the integer number of years between date of birth and informed consent date. If the informed consent data is missing then the assent date will be used instead.

In addition subject age (years) will be categorized as follows:

- < 18 years
- ≥ 18 - < 65 years
- ≥ 65 years

Subject baseline characteristics will include: IQ (if available), epilepsy type, developmentally delayed status, EEG history, CT scan and/or MRI history, previous and current seizure types, seizure etiology including primary cause of epilepsy, and seizure cluster episode history. For seizure cluster episodes, if duration are collected in free-text which covers a period of time, average of the upper bound and the lower bound will be used for the analysis.

Subject demographics will additionally be presented for the mITT Population by the Treatment Success status of their first double-blind dose of study drug (see Section 7.6.1 for the definition of treatment success). These data presentations will include columns for "Treatment Success of first dose" and "Not Treatment Success of first dose" for each treatment group.

Comparability of treatment groups will be evaluated using descriptive statistics.

7.4. Medical and Surgical History

Medical and surgical history will be coded using the MedDRA coding dictionary version 14.1. Coded medical history terms will be summarized by MedDRA system organ class (SOC) and preferred term (PT) for the Safety, Randomized Safety and mITT Populations. SOC will be sorted alphabetically and then preferred term will be sorted in order of frequency of the total

column within each SOC. At each level of summarization, a subject will be counted only once for each medical and surgical history he/she has within that level. Subject listings of coded medical history terms will be provided.

For subjects who were rescreened after study drug exposure and have two subject identifiers, all medical and surgical history data will be combined into one subject identifier.

7.5. Prior and Concomitant Medications

Prior medications are defined as medications taken within 30 days prior to the first dose of study drug at Visit 2. Concomitant medication is defined as any medication taken between the day of first dose of study drug at Visit 2 and the end of study.

The World Health Organization Drug Dictionary (WHO Drug) of version December 2011 will be used to classify prior and concomitant by therapeutic class and preferred name based on ATC code level 4. Medication start and end dates will be compared with the start date of study drug and classified as per Table 4.

In case of partial or missing dates, comparisons will be made based on the level of detail available. For example, if start date of study drug administration is 04Jan2013, and a medication has a start date of Jan2013 but missing date the medication will be classified as concomitant.

Table 4: Classification of Prior and Concomitant Medications

Start date \ End date	Before start of study drug administration at Visit 2	On or after start of study drug administration at Visit 2	Missing
Before start of study drug administration at Visit 2	Prior	Prior/Concomitant	Prior/Concomitant
On or after start of study drug administration at Visit 2	–	Concomitant	Concomitant
Missing	Prior	Prior/Concomitant	Prior/Concomitant

Prior medications will be summarized for the Safety, Randomized, and Randomized Safety Populations. Concomitant medications will be presented for the Safety Population during the Test Dose Phase and for the Randomized and Randomized Safety Populations during the Comparative Phase. Levels of summarization will include global, WHO Anatomic Therapeutic Chemical (ATC) Classification System level 3 drug class, ATC level 4 drug class, and WHO preferred term.

At each level of summarization, a subject will be counted only once for each concomitant medication he/she has within that level. The percentage of subjects having had at least one medication at each level will be calculated.

Prior/Concomitant medications excluding AEDs, prior/concomitant AEDs, prior/concomitant AEDs used for epilepsy, and prior/concomitant AEDs used for indications other than epilepsy will be summarized separately and similar to concomitant medications. AEDs will be further classified as enzyme-inducing and non-inducing AEDs.

Listings will be provided for prior/concomitant medications and prior/concomitant AEDs for all subjects. AEDs collected from AED page on CRF will be presumed to have 'Epilepsy' as indication. AEDs collected from concomitant medication page will be listed by indication captured on CRF.

For subjects who were rescreened after study drug exposure and have two subject identifiers, all medication data will be combined into one subject identifier.

7.6. Analyses of Efficacy Endpoints

Information recorded by the caregiver in the Subject Workbook will be used for analysis of the primary, secondary, and exploratory efficacy endpoints. Any seizures occurring within 24 hours after administration of study drug will be recorded. Subjects without any recurrent seizures recorded with a start time >10 minutes after administration of study drug will be considered seizure-free in all analyses.

The following covariates will be used in the analyses of efficacy endpoints, where specified:

- Age (< 18 years, 18 - <65 years, ≥65 years)
- Sex (male/female)
- Weight (kg)
- BMI standardized categories (underweight/normal [<25], overweight [≥25-<30], and obese 1-3 categories combined [≥30])
- Geographic region of clinical site (North America and similar [this includes USA, Canada, Australia and New Zealand], Eastern Europe [Hungary, Poland, Ukraine], and Western Europe [Spain, Germany, Italy, and Israel])
- Enzyme-inducing AEDs used within 14 days before the study drug administration (see Appendix 2) vs others

Additional covariates may also be explored.

7.6.1. Primary Efficacy Endpoint

All statistical analyses of the primary efficacy endpoint will be conducted for the mITT Population and analyzed as described in Section 5.3. The primary efficacy endpoint analyses will also be conducted on the Per Protocol Population as supportive analyses. The following null (H_o) and alternative (H_a) hypotheses will be evaluated:

- H_o: The proportion of subjects who meet the criteria for Treatment Success is not different between the USL261 and the placebo groups in the Comparative Phase;
- H_a: The proportion of subjects who meet the criteria for Treatment Success is different between the USL261 and the placebo groups in the Comparative Phase.

Treatment Success is a composite measure of efficacy that will be assessed based upon the first seizure cluster treated with study drug during the Comparative Phase. Treatment Success is defined as achieving the following:

- Termination of seizure(s) within 10 minutes after the double-blind study drug administration, and
- No recurrence of seizure(s) beginning 10 minutes after study drug administration to 6 hours after the double-blind study drug administration

7.6.1.1. Derivation of Treatment Success Endpoint

Treatment Success will be determined based on data reported in the CRFs and derived programmatically. An imputation will be conducted first for the seizure start time and end time.

If the end time of a seizure is missing, impute the end time to the next subsequent seizure's start time if the two aforementioned seizures occrurred within the same date; otherwise, the missing end time will be imputed as 23:59.

If the start time of a seizure is missing, impute the start time to the previous seizure's end time if the two aforementioned seizures occurred within the same date; otherwise, the missing start time will be imputed as 00:00.

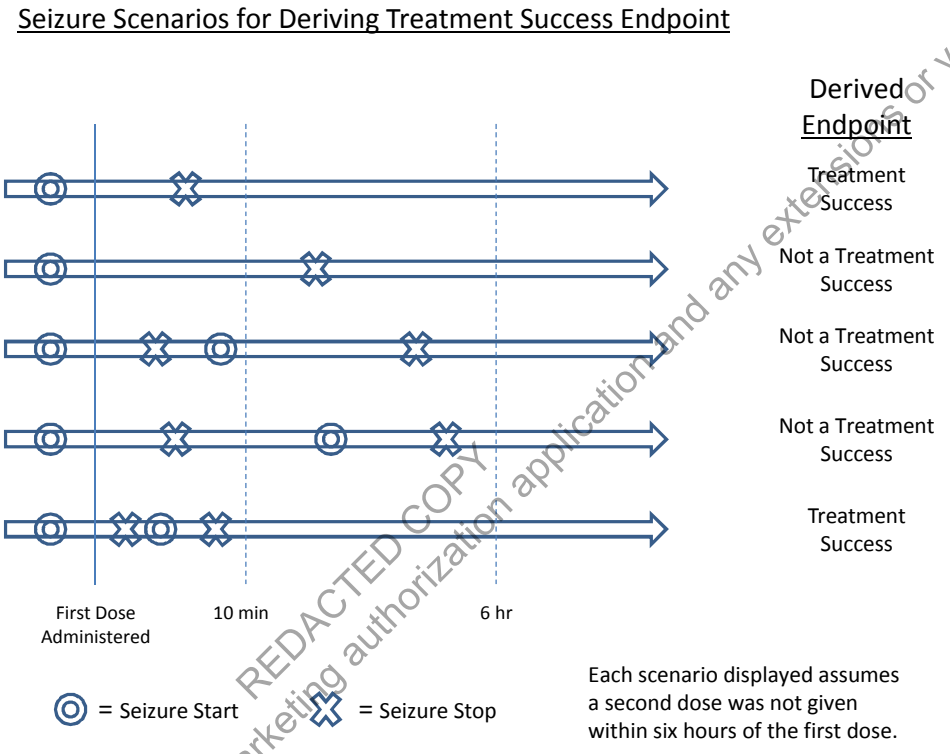
There are three components to be assessed in the programmatic derivation:

1. Termination of seizure(s) within 10 minutes: The initial seizure stopped within (≤) 10 minutes from the time of dosing and any subsequent seizures also stopped within 10 minutes of dosing. Data used in this derivation includes the time of first dose as recorded on the "Study Drug Administration (First Dose)" CRF, and seizure data recorded on the "Report All Seizures for 24 Hours" and the "Seizure Diary" CRFs.
2. No recurrence of seizure(s) beginning 10 minutes after study drug administration to 6 hours after study drug administration. The times of reported seizures will be used to assess if there are any seizures with start time from >10 minutes up to (≤) 6 hours after the first dose of study drug. Data used in this derivation includes seizure data recorded on the "Report All Seizures for 24 Hours" CRF.
3. No second dose given within 6 hours of the first dose of study drug administration as receiving the second dose within (≤) 6 hours confounds the efficacy evaluation of the first dose. Data used in this derivation include the time of second dose as recorded on the "Study Drug Administration (Second Dose)" CRF.

Subjects who meet all three of these components will be defined as a "Treatment Success." If a subject does not meet all three of these components, (which may or may not be due to missing data), they will be defined as "Not a Treatment Success."

Possible scenarios for seizure data start and stop times within the 6 hour period following the first dose of study drug are displayed below in Figure 3, along with the treatment success endpoint derivation (assuming no second dose was given):

Figure 3: Possible Scenarios for Seizure Data Start and Stop Times Within the 6 Hour Period Following the First Dose of Study Drug Are Displayed Below, Along with the Treatment Success Endpoint Derivation (Assuming No Second Dose was given)



7.6.1.2. Analysis of the Primary Endpoint

Treatment Success will be analyzed by Fisher's Exact test. The 95% confidence intervals (CIs), using normal approximation around the proportions, will be presented. In addition, each component (seizure termination and recurrence) of treatment success will be summarized by treatment group. Chi-squared test will be performed as a sensitivity analysis. Results from both tests (Fisher and Chi-squared) will be presented together. In addition, the Cochran-Mantel-Haenszel (CMH) test, stratified by age (< 18 years, ≥18 - <65 years, ≥ 65 years) will be used to analyze Treatment Success.

Subjects who do not have sufficient available data to confirm whether they can be classified either as "Treatment Success" or as "Not a Treatment Success" as described in Section 7.6.1.1 are considered to have missing data. For the primary analysis of Treatment Success, subjects with missing data impacting the Treatment Success endpoint described above will be considered as "Not a Treatment Success."

Similarly, for each component of the Treatment Success endpoint (seizure termination and recurrence), when available data do not allow to determine the classification, subjects with

missing data will be considered as having an unfavorable outcome for the corresponding component. Sensitivity analysis will be conducted for the Treatment Success endpoint in order to assess robustness of study conclusions to missing data using a tipping point approach.[4] This approach will provide the results for the analysis of the primary endpoint under an exhaustive set of possible outcomes among subjects with missing data in the USL261 and Placebo treatment groups. Clinical interpretation of the plausibility of different combination of outcomes will be provided in the Clinical Study Report. The tipping point analysis will be conducted as follows.

Let n_{1m} and n_{2m} be the number of subjects with missing data in the USL261 and Placebo treatment groups respectively.

Step 1: Let $k_1=0$.

Step 2: Let $k_2=0$.

Step 3: Repeat the analysis of the primary endpoint as described above by considering k_1 subjects from the USL261 treatment group as "Not a Treatment Success" and $(n_{1m} - k_1)$ subjects as "Treatment Success," while considering k_2 subjects from the Placebo treatment group as "Not a Treatment Success" and $(n_{2m} - k_2)$ subjects as "Treatment Success."

Step 4: Let $k_2= k_2+1$. Repeat Steps 3 - 4 while $k_2 \leq n_{2m}$.

Step 5: Let $k_1= k_1+1$. Repeat Steps 2 - 5 while $k_1 \leq n_{1m}$.

The results of the analysis for each possible combination of outcomes for subjects with missing data (k_1 and k_2) will be presented in a table. Additionally, a graph will be produced presenting the number of subjects with missing data considered as "Not a Treatment Success" on the X and Y axes for the USL261 and Placebo treatment groups respectively, and dots marking the combinations of X- and Y-axis values for which the null hypothesis was not rejected in favor of the USL261 treatment.

An additional exploratory logistic regression on Treatment Success will include the covariates specified in Section 7.6. A backward selection of covariates will be used to obtain the final model. All covariates with a $p>0.10$ will be dropped from the model. The covariates remaining in the final model that are identified as having significant association with the outcome ($p<0.05$) may be explored in a subgroup analysis. The odds ratio between USL261 and Placebo and its associated 95% confidence intervals will be reported. This analysis will be conducted considering all subjects with missing data as "Not a Treatment Success", similar to the primary analysis.

7.6.2. Secondary Efficacy Endpoints

All secondary efficacy analyses will be based on the mITT population. Multiplicity adjustments are described in Section 5.1).

7.6.2.1. Proportion of Subjects with Recurrence of Seizure(s) Beginning 10 Minutes after Administration of Double-Blind Study Drug to 4 Hours after Double-Blind Study Drug Administration

The proportion of subjects with recurrence of seizure(s) recorded in the diary with start time >10 minutes and ≤4 hours after the administration of double-blind study drug will be analyzed using Fisher's Exact test. The 95% CIs will be presented for the proportion. In addition, Chi-squared

test will be performed as a sensitivity analysis. Subjects who have been administered the second dose of study drug (ie, 5.0 mg dose of USL261) within 4 hours of double-blind study drug administration will be derived as if they had a recurrence of seizure. Subjects who do not have a seizure recorded, or whose first seizure occurs >4 hours after study drug administration, will be counted as not having a seizure.

7.6.2.2. Time to Next Seizure with a Start Time >10 Minutes after Double-Blind Study Drug Administration

Kaplan-Meier estimates will be used to summarize the time-to-next seizure after double-blind study drug administration. Subjects who do not have another seizure before the end of the 24-hour observation period, and have not been administered the second dose of study drug (ie, 5.0 mg dose of USL261) will be censored at the end of the observation period. Subjects administered the second dose of study drug (ie, 5.0 mg dose of USL261) who did not have a seizure before the administration of the second dose will be censored at the time of the second dose (5.0 mg USL261) administration. The time-to-next seizure percentiles (defined based on the data) with associated 95% CIs will be displayed. The probabilities of experiencing the next seizure after double-blind study drug administration at each hour with associated standard error and 95% confidence intervals will be presented. The log-rank test will be used to compare the time to next seizure after double-blind study drug administration between treatment groups. In addition, the hazard ratio for treatment (USL261: placebo) and its 95% CI will be calculated from a Cox proportional hazards model. Kaplan-Meier curves by treatment group will also be presented.

Additional analysis will be conducted based on a different censoring method that subjects administered the second dose of study drug (ie, 5.0 mg dose of USL261) who did not have a seizure before the administration of the second dose will be considered as events (failure).

The Cox proportional hazards regression model will be used to evaluate the difference between treatment groups adjusting for the covariates specified in Section 7.6. Interactions between treatment and each covariate will be evaluated at the 0.10 significance level; if not significant, they will be removed from the final model.

7.6.3. Exploratory Efficacy Analyses

Exploratory efficacy analyses will be conducted using the mITT population. All tests performed will test a two-sided hypothesis of no difference between groups at a significance level of 0.05 for all exploratory outcome measures.

7.6.3.1. Proportion of Subjects with Recurrence of Seizure(s) Beginning 10 Minutes after Study Drug Administration to 24 Hours after Study Drug Administration

The proportion of subjects with recurrence of seizure(s) with a start time >10 minutes and ≤24 hours after study drug administration will be analyzed using Fisher's Exact Test. The 95% CIs will be presented for the proportion. In addition, Chi-squared test will be performed as a sensitivity analysis. Subjects who do not have a seizure recorded with a start time >10 minutes and ≤24 hours after the administration of double-blind study drug will be counted as not having a seizure. Subjects who have been administered the second dose of study drug (ie, 5.0 mg dose of USL261) within 24 hours will be assumed to have had a seizure.

7.6.3.2. Return to Full Baseline Functionality within 24 Hours after Study Drug Administration (as determined by the caregiver)

The proportion of subjects who have documented return to full baseline functionality will be analyzed using Fisher's Exact Test. The 95% CIs will be presented for the proportion. In addition, Chi-squared test will be performed as a sensitivity analysis. Subjects who did not have a time of return to full baseline functionality recorded within 24 hours of study drug administration or who have been administered the second dose of study drug (ie, 5.0 mg dose of USL261) prior to returning to full functionality will be counted as not having returned to full baseline functionality.

Kaplan-Meier estimates will be used to summarize the time to return to full baseline functionality. Subjects who do not have a time of return to full baseline functionality recorded within 24 hours of study drug administration and have not been administered the second dose of study drug (ie, 5.0 mg dose of USL261) will be censored at the end of the observation period. Subjects who were administered the second dose of study drug (ie, 5.0 mg dose of USL261) prior to returning to full functionality will be censored at the time that the second dose (USL261) was administered. The probabilities of return to full baseline functionality after double-blind study drug administration at each hour with associated standard error and 95% confidence intervals will be presented. The log-rank test will be used to compare the time to return to full baseline functionality between treatment groups. In addition, the hazard ratio for treatment (USL261: placebo) and its 95% CI will be calculated from a Cox proportional hazards model. Kaplan-Meier curves by treatment group will also be presented.

The Cox proportional hazards regression model will be used to evaluate the difference between treatment groups adjusting for the covariates specified in Section 7.6. Interactions between treatment and each covariate will be evaluated at the 0.10 significance level; if not significant, they will be removed from the final model.

7.6.3.3. Analyses for Subjects Receiving 2 Doses of Study Drug

Data from subjects randomized to USL261 and placebo who received the first dose of double-blind study drug and the second dose of open-label study drug (ie, 5.0 mg dose of USL261) will be used for the analyses of subjects receiving 2 doses of study drug.

7.6.3.3.1. Treatment Success of the Second Dose of Study Drug (5.0 mg of USL261)

Treatment Success of the second dose for subjects receiving the second dose of study drug (ie, 5.0 mg of USL261) will be presented for each treatment group. For the active group, this represents two doses of 5.0 mg of USL261. The placebo group has received one dose of 5.0 mg of USL261 (preceded by a dose of placebo). Since the administration of the second dose is not a randomized treatment, the analysis includes only subjects whose seizure was not stopped by the first dose and were given the second dose of study drug (ie, 5.0 mg of USL261).

For this analysis, Treatment Success of the second dose is defined as achieving the following:

- Termination of seizure(s) within 10 minutes after the second dose of study drug (5.0 mg of USL261)

- No recurrence of seizure(s) beginning 10 minutes after administration of the second dose of study drug (ie, 5.0 mg of USL261) to 6 hours after the second dose of study drug (5.0 mg of USL261)

Subjects whose Subject Workbook indicates seizure termination within 10 minutes of the second dose and who have no seizures recorded with start time > 10 minutes and ≤ 6 hours after the second dose of study drug will be considered a Treatment Success of the second dose. Subjects who do not meet either of these criteria will not be considered a Treatment Success of the second dose. Similar derivation rules as used for the primary endpoint will be used for defining Treatment Success of the second dose, with the exception of not including the rule pertaining to the second dose.

Number and percentage will be presented for Treatment Success of the second dose and each component (seizure termination and recurrence) for subjects who received two doses of study drug. The 95% CIs for the proportions will also be presented.

7.6.3.3.2. Additional Second Dose Data Presentations / Analyses

A summary of subjects receiving the second dose of study drug by randomized treatment arm will be presented. In addition to the total number of subjects receiving the second dose, counts of subjects receiving the second dose in specific time categories post first dose (0 to <10 minutes, >=10 to ≤20 minutes, >20 minutes to ≤1 hr, >1 hr to 6 hrs, and >6 hrs) will also be presented.

Kaplan-Meier estimates will be used to summarize the time-to-second dose. Subjects who do not receive the second dose of study drug (ie, 5.0 mg dose of USL261) within 6 hours of the initial study drug administration will be censored at the end of this 6 hour period. The time-to-second dose percentiles (defined based on the data) with associated 95% CIs will be displayed. Kaplan-Meier curves by treatment group will also be presented.

As an additional exploratory analysis, a logistic regression with response treatment success of the second dose will be examined including time from first dose to second dose as a continuous covariate with treatment as an effect.

Kaplan-Meier estimates will also be used to summarize the time-to-next seizure following the second dose. Subjects who do not have another seizure before the end of the 24-hour observation period following the second dose of study drug (ie, 5.0 mg dose of USL261) will be censored at the end of this observation period. The time-to-next seizure following the second dose percentiles (defined based on the data) with associated 95% CIs will be displayed. The probabilities of experiencing the next seizure following the second dose at each hour with associated standard error and 95% confidence intervals will be presented. Kaplan-Meier curves by treatment group will also be presented.

7.6.3.4. Treatment Success of all Dose of Study Drug

Treatment Success of all doses will be assessed based upon the Treatment Success of the first dose and Treatment Success of the second dose taken within 6 hours after first dose during the Comparative Phase. If the second dose taken later than 6 hours after first dose, then treatment success of all doses will only be based on the result of treatment success for the first dose.

The same analysis as described in Section 7.6.3.3.1 (Treatment Success of the Second Dose of Study Drug) will be performed for treatment success of all doses.

7.6.3.5. Subject and Caregiver Outcome Assessments

7.6.3.5.1. SF-12v2

The SF-12v2 is a 12-item questionnaire which will be administered to both the subject and caregiver at Visits 2 and 4. All analyses will be presented separately for the subject and caregiver. Eight domains make up the SF-12v2: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. In addition, the physical functioning, role-physical, bodily pain, and general health domains will be combined to obtain the Physical Health Component Score (PCS); the vitality, social functioning, role-emotional, and mental health domains will be combined to obtain the Mental Health Component Score (MCS). The scores for each domain, the PCS and the MCS range from 0 to 100, where zero indicates the lowest level of health by the scales and 100 indicates the highest level of health.[5]

Summary scores for PCS and MCS for each patient will be computed using published algorithms.[4] Each summary measure is scored and standardized using a t-score transformation, such that a higher score represents better health status, with a mean score of 50 and a standard deviation of 10 in the general population.[6] Missing data on the SF-12v2 will be handled as follows: domain scores will not be calculated for domains in which data are missing. Subsequently, component scores in which domain scores are missing will not be calculated.

Summarization and analysis of SF-12v2 data will be performed for the mITT and the Randomized Safety population. The domain and component scores will be presented for Visit 2 (baseline) and Visit 4/ET, including change from baseline. For each domain and component score a paired t-test will be used to assess the within-group mean change from baseline. An analysis of covariance (ANCOVA), with treatment and baseline as covariates, will be used for between-group comparison of change from baseline for the domain and component scores.

7.6.3.5.2. Treatment Satisfaction Questionnaire for Medication (TSQM)

The TSQM is a 14- item questionnaire that will be administered to the subject. The four TSQM scale scores calculated from the questionnaire are: effectiveness, side-effects, convenience, and global satisfaction. The TSQM scale scores are computed by adding the items loading on each factor. The lowest possible score is subtracted from the composite score and divided by the greatest possible score minus the lowest possible score. This will provide a transformed score between 0 and 1 that is then multiplied by 100. If more than one item is missing from each scale, the scale will not be calculated. Calculation of each scale score is provided below.[7]

Effectiveness

([Q1 + Q2 + Q3) – 3]/18) * 100

If one item is missing then, ([Qx + Qy – 2]/12) * 100 where x and y = 1, 2, or 3, with x≠y.

Side-Effects

If Q4 is 'No' then score = 100

Else, ([Q5 + Q6 + Q7 + Q8 – 4]/16) * 100

If one item is missing then, ([Qx + Qy + Qz – 3]/12) * 100 where x, y, and z = 5, 6, 7, or 8, with x≠y≠z.

Convenience

([Q9 + Q10 + Q11) – 3]/18) * 100

If one item is missing then, ([Qx + Qy – 2]/12) * 100 where x and y = 9, 10, or 11.

Global Satisfaction

([Q12 + Q13 + Q14) – 3]/14) * 100

If one item is missing then, ([Qx + Qy – 2]/8) * 100 where x and y = 12, 13, or 14.

Summarization and analysis of TSQM data will be performed for the mITT population. The 4 scale scores will be presented for Visit 2 (baseline) and Visit 4/ET, including change from baseline. For each score a paired t-test will be used to assess the within-group mean change from baseline. An analysis of covariance (ANCOVA), with treatment and baseline as covariates will be used for between-group comparison of change from baseline.

7.6.3.5.3. Intranasal Therapy Impact Questionnaire (ITIQ)

The ITIQ is a two item questionnaire that is completed by both the subject and caregiver at Visit 4/ET. The level of anxiety change since subject received intranasal therapy is a scale with a range from -7 to 7, and confidence about travelling having a spray the subject can take with them is a scale from 1 to 5. The change in level of anxiety since subject received intranasal therapy will be compared between treatment groups using the t-test. The chi-square will be used to compare treatment groups for confidence about travelling having a spray the subject can take with them.

7.7. Safety Analyses

All safety analyses will be presented by phase of the study based on the Safety Population and Randomized Safety Population, unless otherwise specified.

7.7.1. Adverse Events (AEs)

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 16.1. Coding includes SOC and preferred term (PT). All verbatim descriptions and coded terms will be listed for all AEs.

For subjects who screen fail prior to the start of the Test Dose Phase for the reason of an adverse event, the event will be recorded on the Screening Failure Log.

7.7.1.1. Pre-treatment AEs

Pre-treatment AEs will be defined as any AE that started before the study drug administration at Visit 2. Pre-treatment AEs will be flagged out in a listing named as ‘Adverse Events’.

7.7.1.2. Treatment-emergent AEs (TEAEs)

TEAEs will be categorized as TEAEs during the Test Dose Phase and TEAEs during the Comparative Phase based on the date and time of onset.

The following AEs will be defined as TEAEs during the Test Dose Phase:

- AEs with onset on or after study drug administration at Visit 2 and up to first dose of study drug in Comparative Phase;
- AEs that started prior to study drug administration at Visit 2, but worsened in severity following study drug administration at Visit 2 up to first dose of study drug in Comparative Phase.

The following AEs will be defined as TEAEs during the Comparative Phase:

- AEs with onset on or after the first dose of study drug in Comparative Phase;
- AEs that started prior to study drug administration at Visit 2, but worsened in severity following the first dose of study drug in Comparative Phase.

All AEs will be listed by subject and by MedDRA SOC and PT.

The number of events and the frequency and percentage of subjects with TEAEs/SAEs will be summarized for the Safety Population during the Test Dose Phase and for the Randomized Safety Population during the Comparative Phase. An overall summary of all AEs for Screened Population will also be presented. Summary tables of TEAEs and SAEs will be presented by SOC and PT. At each summary level, a subject will be counted only once for each AE he/she experiences within that level, regardless of how many occurrences of that AE that subject experienced. The percentage of subjects having had at least one TEAE/SAE at each level will be calculated. All the TEAE analysis will also be repeated for the subset of all TEAEs that started within two days of study drug administration.

Tabular summaries will include all TEAEs, TEAEs by age group (< 18 years, ≥18 - <65 years, ≥65 years), TEAEs by severity (mild, moderate, severe), TEAEs by relationship to study drug, TEAEs of interests, serious TEAEs (SAEs) including SAEs leading to permanent discontinuation or death, SAEs by severity, and SAEs by relationship to study drug. If there are any deaths while on study, they will be presented in a listing that includes the AE leading to death, demographic data, details of study treatment, and relationship of the AE leading to death to the study drug. In addition, all TEAEs, SAEs, and AEs leading to discontinuation will be flagged out in the listing of Adverse Events.

In instances where a subject may have multiple TEAEs with differing levels of severity or relatedness, the most severe or most related event, respectively, will be reported for the severity and relatedness tables. For the purpose of analysis, TEAEs with a reported relatedness of "Related", "Possibly Related", "Unlikely Related", or missing the relationship will be classified as related to study drug. TEAEs assessed as "Not Related" will be classified as not related to study drug. TEAEs with missing severity will be presented as severe in the tables but will be listed as missing.

The following AEs of special interest (AESIs) will be summarized by AESI category:

- Taste and smell disorders
- Acute central respiratory depression
- Route of administration

- Depression and suicidality/self-injury
- Abuse-related AEs

Abuse-related TEAEs will be further broken out by the following categories:

- Drug Abuse, Dependence, Withdrawal and Substance-Related Disorders, Including Diversion
- Euphoria-related Term
- CNS Depressant Effects
- Stimulation and Anxiety Symptoms
- Perceptual Disturbances/Psychotomimetic Effects
- Mood Disorders and Disturbances
- Mental and Cognitive Impairment

Additional summaries will be made for abuse-related treatment-emergent SAEs and abuse-related TEAEs resulted in discontinuation from study drug or the study.

SMQs and/or a USL-defined algorithm will be used to search AESIs. Search strategies are described in Table 5.

Table 5: Search Strategy for AESI

AESI category	Search Strategy
Taste and smell disorders	Modified Taste and Smell Disorders SMQ - broad
Acute central respiratory depression	Modified Acute Central Respiratory Depression SMQ - broad
Depression and suicidality/self-injury	Modified Depression and Suicidality/Self-Injury SMQ – broad
Route of administration	USL-defined [Oral Soft Tissue Conditions HLT (Gastrointestinal Disorders SOC); Respiratory Disorders NEC (Respiratory, Thoracic and Mediastinal Disorders SOC); Upper Respiratory Tract Disorders (Exclude Infections) (Respiratory, Thoracic and Mediastinal Disorders SOC)] – excluding overlapping terms with Acute Central Respiratory Depression SMQ and terms unrelated to USL261's nasal route of administration, e.g., terms for conditions in the respiratory tract below the larynx or terms with defined causes
Abuse-related AEs	USL-defined algorithm

Abbreviations: HLT=High Level Term; SMQ=Standardized MedDRA Queries; NEC=Not Elsewhere Classified.

Standard MedDRA Queries (SMQs) defined by the Council for International Organizations of Medical Sciences (CIOMS) Working Group are groupings of terms from one or more MedDRA SOCs that relate to a defined medical condition or area of interest. Modifications of SMQs will be documented. For hierarchical SMQs, the portion of the hierarchy to be used will be that part or those parts determined to be most relevant. A list of AE terms in each category is presented in Appendix 3. Summary tables will be presented by SOC and PT.

In addition, potentially clinically important AESI will be presented for each category of AESI. AE which meets at least one of the following criteria is defined as a potentially clinically important AE:

- AE is a SAE
- AE led to discontinuation
- AE is severe in intensity and related to study drug
- AE required intervention and is related to study drug.

If action taken and other action taken of a AE are not "none", "not applicable", "unknown" or "dose not changed", then it will be considered requiring intervention.

7.7.2. Observer's Assessment of Alertness/Sedation (OAA/S)

The OAA/S scale is a validated qualitative categorical measure of sedation.[8] The OAA/S Scale is composed of four assessment categories: responsiveness, speech, facial expression, eyes. Responsiveness has possible scores of 1, 2, 3, 4, or 5; speech has scores of 2, 3, 4, or 5; and facial expression and eyes have scores of 3, 4, or 5. The OAA/S Scale is scored in two ways as described below. Descriptive statistics and graphical presentations will be used to present results by time point at Visit 2 for the Safety Population.

7.7.2.1. Composite Score

The composite score has a range between 1 (deep sleep) and 5 (alert); the lowest level checked by the study center personnel in any one of the four assessments will be analyzed. The composite score will be set to missing if all 4 of the assessment categories are missing.

Number of subjects with an OAA/S composite score of 1 at Visit 2 will be presented by time point and overall total.

7.7.2.2. Sum Score

The sum score is the sum of the 4 assessments. If one of the assessment categories is missing, the sum score will be set to missing.

Summaries for the composite score and sum score will be based on the calculation specified above. However, an imputation approach on each domain score will be employed for the derivation of pharmacodynamic parameters described in the next section. Specifically, for each individual domain score, if a subject who has completely missing data at all timepoints for a single domain, the median domain score of all available data from all other subjects at each timepoint will be used as the domain score for this subject. For subjects with complete missing scores for two or more domains at all timepoints, each domain score will be treated as missing at all timepoints and OAA/S sum and composite scores will not be calculated.

7.7.2.3. Pharmacodynamic (PD) Parameters

The following PD parameters will be calculated by subject using non-compartmental methods for the OAA/S composite score and sum score following midazolam dosing:

Table 6: Pharmacodynamic Parameters

Parameter	Definition
$AUEC_{0-t}$	Area under the effect (AUEC) versus time curve, from time 0 to the time of last measurable value. Calculated using the linear trapezoidal method.
$AUEC_{0-x}$	Area under the effect (AUEC) versus time curve, calculated using the linear trapezoidal method from time 0 to the x time, where x =1, 2 and 4 hours.
E_{max}	Maximum observed PD effect. Note – For OAA/S sum and composite scores, this will represent the lowest observed score (as lower scores indicate greater sedation)
T_{effect}	Time to Peak "E_{max}" Effect

Among these parameters, the calculated OAA/S sum score and composite score will be used for calculating the unadjusted E_{max}. The E_{max} will also be adjusted by using change from baseline values of OAA/S composite score and sum score. For parameters $AUEC_{0-t}$, $AUEC_{0-x}$ (x=1, 2, 4), the calculation will be based on the change from baseline values of OAA/S composite score and sum score.

Actual time will be used for AUEC calculation. If actual time for pre-dose values is before the Test dose, 0 will be used for time point calculation. If equal to or greater than 50% domain data for a subject is missing, then all their AUEC values (including $AUEC_{0-last}$, $AUEC_{0-1hr}$, $AUEC_{0-2hr}$ and $AUEC_{0-4hr}$) will be treated as missing. If less than 50% domain data for a subject is missing, then last observation carried forward approach will be used to impute all missing time points after the last non-missing time point.

Individual PD parameter values will be listed and descriptive statistics will be used to present PD parameters at Visit 2 for the Safety Population.

7.7.3. Requirement for Unscheduled ER or EMS Visit

The number and percent of subjects requiring an unscheduled ER or EMS visit within 24 hours after study drug administration in the Comparative Phase will be compared between treatment groups for the Randomized Safety Population using Fisher's Exact Test. In addition, Chi-squared test will be performed as a sensitivity analysis.

7.7.4. Brief Smell Identification Test (B-SIT; United States only)

For olfactory examination, the B-SIT final scores and changes from baseline will be presented and plotted by visits. Baseline value is defined as the Visit 2 (pre-dose) value. An analysis of covariance (ANCOVA), with treatment and baseline as covariates, will be used for between-group comparison of change from baseline for the B-SIT final scores.

7.7.5. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is collected referencing two time points for suicidal ideation (lifetime, past 6 months) and two time points for suicidal behavior (lifetime, past 5 years) at Visit 1 (screening). For all analyses the 'lifetime' time point will be used for Visit 1 assessments. In addition, a 'Since Last Visit' version will be administered at Visits 2, 3 and 4/ET.

7.7.5.1. Suicidal Ideation

The number and percent of subjects with each of the following suicidal ideation scores will be summarized for each visit by treatment group (See Table 7). The highest score for suicide ideation will be used for each subject by visit.

Table 7: Suicidal Ideation Scores

Suicidal ideation	Score
Wish to be dead	1
Non-specific active suicidal thoughts	2
Active suicidal ideation with any methods (not planned) without intent to act	3
Active suicidal ideation with some intent to act, without specific plan	4
Active suicidal ideation with specific plan and intent	5

Any suicidal ideation regardless of type will also be presented.

Each suicidal ideation severity rating will range from 0 (no ideation present) to 5 (active ideation with plan of intent). Descriptive statistics will be presented for suicidal ideation severity rating at each visit by treatment group.

Descriptive statistics will also be presented for suicidal ideation intensity at each visit by treatment group. The five intensity items (frequency, duration, controllability, deterrents, and reason for ideation) will be combined to create a total sum score ranging between 0 and 25. If the subject did not have any suicidal ideation, the total score will be 0. If the subject had suicidal ideation and if one intensity item is missing, the total score will not be calculated.

7.7.5.2. Suicidal Behavior

The number and percent of the following suicidal behaviors will be summarized for each visit by treatment group.

- Actual attempt
- Engaged in non-suicidal self-injurious behavior
- Aborted attempt
- Interrupted attempts
- Preparatory acts or behavior
- Suicidal behavior
- Any suicidal behavior regardless of type
- Completed suicide

Descriptive statistics will be presented for the following suicidal behaviors for each visit by treatment group.

- Number of attempts
- Aborted attempts

- Interrupted attempts

The number and percent of subjects with any suicidal ideation or behavior will be presented for each visit by treatment group.

7.7.6. Physical, Nasal, and Complete Neurological Examinations

The number and percent of patients having normal and abnormal findings (clinically significant vs. not clinically significant) for each body system or assessment will be presented by visit and treatment group for the Safety and Randomized Safety Populations.

7.7.7. Laboratory Parameters

Clinical laboratory parameters for serum chemistry, hematology, and urinalysis will be summarized descriptively for each study visit. Mean and mean change from baseline values will be presented for each study visit. Change from baseline will be calculated as the Visit 4/ET measurement minus the baseline measurement. If either the baseline or Visit 4/ET value is missing, the observation will not be included in the change from baseline summary. The last value at post-baseline visits will be used for summaries.

Each laboratory result will be classified as low (L), normal (N), and high (H) at each visit according to the laboratory-supplied normal range. The shift from baseline will be presented. Potentially clinically significant (PCS) laboratory abnormalities will be identified using standardized criteria in Appendix 1 prior to database lock and will be presented by for each treatment group. Additional displays of PCS may be presented.

Baseline values are the last available values collected prior to the test-dose.

7.7.8. Vital Signs and Oxygen Saturation

Vital signs (systolic and diastolic blood pressure, pulse, respiration rate, temperature) will be summarized descriptively for each study visit and time point and presented graphically (excluding temperature) for each Visit 2 time point. Mean and mean change from baseline values will be presented for each study visit and time point, excluding temperature. Change from baseline will be calculated as post-baseline measurement minus baseline measurement. If either the baseline or post-baseline value is missing, the observation will not be included in the change from baseline summary. Baseline values are the last available values before Test-Dose administration.

Descriptive statistics and graphical presentations will be used to present results by visit and time point for oxygen saturation for the Safety Population.

The number of subjects meeting the following criteria will be presented by treatment group, by visit, and by time point:

- < 8 breaths per minute after study drug administration
- > 24 breaths per minute after study drug administration
- systolic blood pressure < 85 mm Hg
- a change from baseline in systolic pressure ≥ 40 mm Hg

- diastolic blood pressure < 50 mm Hg
- a change from baseline in diastolic pressure ≥ 30 mm Hg
- Pulse rate > 120 beats per minute
- Pulse rate < 50 beats per minute
- a change from baseline in heart rate ≥ 40 beats per minute
- oxygen saturation < 90%

The caregiver-recorded respiration rate from the Comparative Phase will be presented using descriptive statistics at 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours by treatment group and overall total for the Randomized Safety Population. The number of subjects who have < 8 and > 24 breaths per minute will be presented by time point, treatment group, and overall total.

7.7.9. Electrocardiogram (ECG)

Electrocardiogram (ECG) parameters (heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval) will be summarized descriptively for each scheduled visit and time point collected for the Safety Population. Mean and mean change from baseline values at Visit 2 will be presented. Change from baseline will be calculated as post-baseline measurement minus baseline measurement. If either the baseline or post-baseline value is missing, the observation will not be included in the change from baseline summary. In addition, counts and percentages for ECG diagnosis (normal or abnormal) at each study visit and time point will also be presented. If the diagnosis was abnormal, counts and percentages for clinical significance will be presented. Baseline values are the last available values before Test-Dose administration.

The number of subjects meeting the following criteria will be presented by treatment group for the Safety Population:

- QTcF interval > 450 msec for males and > 470 msec for females

8. OTHER PLANNED ANALYSES

8.1. Pharmacokinetic (PK) Analyses

Pharmacokinetic parameters for individual plasma concentrations will be calculated using a standard non-compartmental approach using appropriate validated PK software (WinNonlin Enterprise version 5.2 or higher). The following PK parameters of midazolam and 1-hydroxymidazolam will be calculated from data obtained for the PK Population:

- $AUC_{0\text{-last}}$ – the area under the plasma concentration-time curve from time 0 to the last measurable concentration. Estimation by the linear-up/log-down trapezoidal method is preferred.
- $AUC_{0\text{-}x}$ – the area under the plasma concentration-time curve from time 0 to time x, where x =1, 2 and 4 hours.
- C_{max} – the maximum plasma concentration
- t_{max} – the time to reach the maximum plasma concentration

- t_{lag} – the time before the first measurable plasma concentration

Due to the limited length of the PK sampling schedule (out to a maximum of 4 hrs post dose), it is unlikely that sufficient samples will be available for estimation of the terminal rate constant (λ_z). Thus, λ_z and associated PK parameters (viz. terminal half-life, $AUC_{0-\infty}$, CL/F and V_z/F) will not be calculated *a priori*. If supported by the data, additional PK parameters may be calculated after discussion with the Sponsor.

Pre-dose concentration values reported as below the limit of quantification (BLQ) and missing pre-dose values will be treated as "0" and listed as BLQ. A series of BLQ values that includes the pre-dose time point will also be treated as "0" and listed as BLQ. All other BLQ values will be set to missing. Actual sampling times will be used in the calculations of PK parameters.

With the exception of t_{max} and t_{lag}, descriptive statistics by treatment group will include the number of observations (N), mean, standard deviation (SD), coefficient of variation (CV%), geometric mean, and geometric CV%, as well as median, minimum, and maximum for the PK variables. Summary statistics for t_{max} and t_{lag} will be limited to N, minimum, maximum and median. In addition, summary of PK variables stratified by AED inducer status as well as figures of Midazolam and 1-OH Midazolam concentrations on linear and semi-log scales will also be presented.

A covariate analysis that examines the effect of continuous (age, weight) and, if supported, categorical (gender, race, and age group [adult vs adolescent]) demographic variables on the PK parameters may be conducted.

8.2. Pharmacokinetic/Pharmacodynamic Variables and Analyses

Correlations between PK/PD data from the test dose may be evaluated. If conducted, the PK/PD analysis may include correlating the plasma midazolam plus 1-hydroxymidazolam concentrations to respiratory rate, BP, HR, O_2 saturation, and/or sedation based on OAA/S scores. Regression analysis may be used describe the PK/PD relationship, if one exists. For those PD measurements found to correlate to plasma concentrations, the influence of covariates such as gender, AED inducer status, weight, BMI, race, and age group may be explored.

9. CHANGES TO THE PLANNED ANALYSIS

Since the last submission of the P261-401 Statistical Analysis Plan (v2.4) to the FDA (S-0150, 03 March 2015), the following changes were made to the plan (v2.5-v2.9):

- The Brief Smell Identification Test (B-SIT) was added to the list of safety objectives. The plan for analysis of B-SIT data was also added. These changes were made to reflect the changes implemented in Protocol Amendment 4, 20 May 2015.
- The procedures to be completed at Visits 1, 4, and on the monthly telephone follow-up calls between Visit 3 and Visit 4 were updated to add collection of the number of calls to EMS and ER visits for a seizure cluster or other seizure emergency prior to Visit 1 and during the study. This change was made to reflect the changes implemented in Protocol Amendment 4, 20 May 2015.

- The process for reviewing CSR Reportable protocol deviations and exclusions prior to database lock was clarified to determine if any subject should be excluded from specific analysis populations.
- The subgroup analyses of the primary and secondary endpoints were further clarified to examine consistency as follows:
  - The time-frame around the use of enzyme-inducing AEDs was defined as within 14 days before study drug administration. Population PK modeling of deinduction times for strong CYP3A4 inducers, including carbamazepine, indicates a deinduction half-life following discontinuation of approximately 3 – 4 days with return to baseline function occurring within approximately 14 days following discontinuation of dosing. Based on these estimates, a subject should be classified as "induced" if they have received an enzyme-inducing AED ≤ 14 days prior to administration of USL261.
  - The weight will be categorized based on the median weight for the safety population (< median weight and ≥ median weight). This categorization based on the median weight was chosen to be representative of the population studied.
  - The BMI will be categorized as underweight/normal (< 25), overweight (≥25 to <30), and obese 1-3 categories combined (≥ 30). This categorization was based on standard BMI categories.
  - The subgroups frequency of seizure clusters and benzodiazepine use was removed as these subgroups are based on historic data and may not represent the seizure cluster frequency or benzodiazepine use relative to administration of study drug in the Comparative Phase.
  - The subgroups seizure types (generalized and focal) and seizure etiology were removed.
- For subjects who were rescreened and underwent two Test Dose Visits, baseline will be defined as the last available values before the later Test Dose administration. This clarification was provided to prespecify how baseline is defined in a unique situation.
- An additional exploratory efficacy analysis, "treatment success of all doses of study drug," was included in the plan. This exploratory analysis was added to assess the Treatment Success of the first dose and Treatment Success of the second dose (taken within 6 hours) during the Comparative Phase.
- The definition of a treatment-emergent adverse event (TEAE) in the Test Dose Phase and in the Comparative Phase was clarified. This clarification was made to clearly define the phase in which TEAEs will be reported. However, it does not impact the definition of a TEAE or the total TEAEs reported.
- The AEs of special interest (AESI) and abuse-related AEs were defined.
- Additional detail for the calculation of the following PD parameters: OAA/S sum score, $AUEC_{0-t,}$ $AUEC_{0-x}$, and E_{max} was added.

- An early study termination analysis unrelated to study success or futility was added in the event that the trial has not crossed a boundary for early success or early futility and yet is stopped early before reaching the pre-specified maximum sample size of 240 subjects.

10. MOCK TABLES, FIGURES, AND DATA LISTINGS

The mock TLGs will be provided in a separate document.

11. REFERENCES

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APPENDIX 1. POTENTIALLY CLINICALLY SIGNIFICANT LABORATORY VALUES

Table 8: Potentially Clinically Significant Laboratory Values

Variable	Units	Values Low	High
Haematology			
Haemoglobin	g/L	< 100	Not applicable
	g/L	> 20 decrease from baseline	> 20 increase above ULN
Lymphocytes (Absolute)	10^9/L	< 0.8	Not applicable
Neutrophils (Absolute)	10^9/L	< 1.5	Not applicable
Platelet count	10^9/L	< 75	Not applicable
White blood cell (WBC) count	10^9/L	< 3	Not applicable
Serum Chemistry			
Albumin	g/L	< 30	Not applicable
Alkaline phosphotase (AP)	U/L	Not applicable	> 2.5xULN
Alanine aminotransferase (ALT) Grade 1	U/L	Not applicable	> ULN & ≤ 3xULN
Alanine aminotransferase (ALT) Grade 2	U/L	Not applicable	> 3xULN & ≤ 5xULN
Alanine aminotransferase (ALT) Grade 3	U/L	Not applicable	> 5xULN & ≤ 20xULN
Alanine aminotransferase (ALT) Grade 4	U/L	Not applicable	> 20xULN
Aspartate aminotransferase (AST) Grade 1	U/L	Not applicable	> ULN & ≤ 3xULN
Aspartate aminotransferase (AST) Grade 2	U/L	Not applicable	> 3xULN & ≤ 5xULN
Aspartate aminotransferase (AST) Grade 3	U/L	Not applicable	> 5xULN & ≤ 20xULN
Aspartate aminotransferase (AST) Grade 4	U/L	Not applicable	> 20xULN
Bicarbonate	mmol/L	≤ 15.9	Not applicable
Calcium	mmol/L	< 2	> 2.9
Cholesterol (Total)	mmol/L	Not applicable	> 7.75
Creatinine	umol/L	Not applicable	> 1.5xULN
	umol/L	Not applicable	> 2x baseline
Gamma glutamyl transferase (GGT)	U/L	Not applicable	> 2.5xULN
Glucose	mmol/L	< 3.0	> 8.9
Phosphorus	mmol/L	< 0.8	Not applicable
Potassium	mmol/L	< 3.0	> 5.5
Sodium	mmol/L	< 130	> 150
Total Bilirubin	umol/L	Not applicable	> 1.5xULN
Triglycerides	mmol/L	Not applicable	> 3.42

Abbreviation: ULN=Upper Limit of Normal

APPENDIX 2. CLASSIFICATION OF ENZYME INDUCING AEDS

Note – The AEDs represented in Table 9 and Table 10 do not represent an exhaustive list. Additional AEDs not listed need to be reviewed and assigned.

Table 9: Listing of Non-Enzyme Inducing AEDs

AED name	Reference
Acetazolamide	[1]
Chloral Hydrate	[2]
Chlorazepate	[3]
Clonazepam	[4]
Diazepam	[5]
Ethosuximide	[6]
Gabapentin	[7]
Lacosamide	[8]
Lamotrigine	[9]
Levetiracetam	[10]
Lorazepam	[11]
Midazolam	[12]
Oxazepam	[13]
Perampanel	[14]
Pregabalin	[15]
Retigabine (ezogabine)	[16]
Tiagabine	[17]
Valproic Acid, Valproate, Divalproex Sodium	[18]
Vigabatrin	[6]
Zonisamide	[19]

Table 10: List of Enzyme Inducing AEDs

AED name	Strength of inducer[a]	Reference
Carbamazepine	Strong	[20]
Clobazam	Weak	[21]
Eslicarbazepine	Weak (borderline moderate)	[22]
Ethotoin	Strong (assumed from *in vitro* induction vs. phenytoin)	[23]
Felbamate	Weak	[24]
Mephenytoin	Strong (assumed from *in vitro* induction vs. phenytoin)	[23]
Oxcarbazepine	Weak (borderline moderate)	[25]
Phenobarbital	Strong	[26, 27]
Phenytoin	Strong	[20]
Primidone	Strong (via phenobarbital major metabolite)	[26, 27]
Rufinamide	Weak	[20]
Topiramate	Weak (only at doses > 200 mg/day)	[28]

[a] Based on decrease in AUC of CYP3A4 substrate [20]: Weak = 20 – 50% decrease, Moderate = 50 – 80% decrease, Strong = ≥ 80% decrease

Washout period required for deinduction following discontinuation of inducing AEDs.

Population PK modeling of deinduction times for strong CYP3A4 inducers, including carbamazepine, indicates a deinduction half-life following discontinuation of approximately 3-4 days with return to baseline function occurring within approximately 14 days following discontinuation of dosing [29-32]. Based on these estimates, a subject should be classified as "induced" if they have received an enzyme-inducing AED ≤ 14 days prior to administration of USL261.

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APPENDIX 3. LIST OF AE TERMS OF SPECIAL INTEREST

Table 11: Abuse-related AEs (MedDRA Preferred Term)

Drug Abuse, Dependence, Withdrawal and Substance-Related Disorders, Including Diversion	
Accidental death	Multiple drug overdose intentional
Accidental overdose	Nasal necrosis
Accidental poisoning	Nasal septum perforation
Dependence	Nasal septum ulceration
Drug abuser	Needle track marks
Drug administered at inappropriate site	Neonatal complications of substance abuse
Drug dependence	Overdose
Drug detoxification	Poisoning
Drug diversion	Polysubstance dependence
Drug tolerance	Prescription form tampering
Drug tolerance increased	Product tampering
Drug toxicity	Product used for unknown indication
Drug Withdrawal	Rebound effect
Drug withdrawal convulsions	Substance abuse
Drug withdrawal headache	Substance abuser
Drug withdrawal syndrome	Substance use
Intentional drug misuse	Substance-induced mood disorder
Intentional overdose	Substance-induced psychotic disorder
Multiple drug overdose	Treatment noncompliance
Multiple drug overdose accidental	Withdrawal Syndrome
Euphoria-related Terms	
Dizziness	Feeling drunk
Elevated mood	Feeling of relaxation
Euphoric mood	Inappropriate affect
Feeling abnormal	
CNS Depressant Effects	
Fatigue	Sluggishness
Lethargy	Somnolence
Sedation	Stupor
Stimulation and Anxiety Symptoms	
Agitation	Hypervigilance
Anxiety	Nervousness
Energy increased	Psychomotor hyperactivity
Feeling jittery	Restlessness
Perceptual Disturbances/Psychotomimetic Effects	
Abnormal dreams	Hallucinations, mixed
Acute psychosis	Hostility
Aggression	Hypoaesthesia
Alice in wonderland syndrome	Ideas of reference
Altered state of consciousness	Illogical thinking
Altered visual depth perception	Illusion

Anger	Incoherent
Communication disorder	Indifference
Confusional state	Jamais vu
Consciousness fluctuating	Loose associations
Déjà vu	Magical thinking
Delirium	Muscle rigidity
Delusion	Nightmare
Depersonalisation	Paraesthesia
Derailment	Paranoia
Derealisation	Paroxysmal perceptual alteration
Disinhibition	Psychotic disorder
Disorientation	Reactive psychosis
Dissociation	Sensory disturbance
Dissociative disorder	Sensory level abnormal
Dissociative identity disorder	Somatic delusion
Dysarthria	Somatic hallucination
Fear	Staring
Flashback	Suspiciousness
Flight of ideas	Tangentiality
Formication	Thinking abnormal
Hallucination	Thought blocking
Hallucination, auditory	Thought broadcasting
Hallucination, olfactory	Thought insertion
Hallucination, synaesthetic	Thought withdrawal
Hallucination, tactile	Transient psychosis
Hallucination, visual	
Mood Disorders and Disturbances	
Abnormal behaviour	Asocial behaviour
Affective disorder	Attention-seeking behaviour
Affect lability	Belligerence
Depressed mood	Blunted affect
Depression	Compulsions
Emotional disorder	Confusional arousal
Emotional distress	Disturbance in social behaviour
Impatience	Feeling of despair
Mood altered	Flat effect
Mood swings	Impulsive behaviour
Personality change	Mania
Anhedonia	Panic attack
Antisocial behaviour	Panic reaction
Apathy	Parasomnia
Mental and Cognitive Impairment	
Amnesia	Mental disorder
Cognitive disorder	Mental status changes
Disturbance in attention	Paramnesia

Memory impairment	Psychomotor retardation
Mental impairment	Retrograde amnesia
Psychomotor skills impaired	Transient global amnesia
Amnestic disorder	Impaired driving ability
Anterograde amnesia	Impaired reasoning
Balance disorder	Dyslogia
Coordination abnormal	Bradyphrenia
Executive dysfunction	Confabulation
Judgement impaired	

Table 12: AEs Related to Acute Central Respiratory Depression (SMQ)

System Organ Class	Preferred Term	Lowest Level Term
Acute central respiratory depression (SMQ)		
Cardiac disorders	Cyanosis	Acrocyanosis
Cardiac disorders	Cardiac arrest	Arrest cardiac
Cardiac disorders	Cardiac arrest	Asystole
Cardiac disorders	Cardiac arrest	Asystolia
Cardiac disorders	Cardiac arrest	Asystolic
Cardiac disorders	Cyanosis	Blue lips
Cardiac disorders	Cardiac arrest	Cardiac arrest
Cardiac disorders	Cardiac arrest	Cardiac arrest transient
Cardiac disorders	Cardio-respiratory arrest	Cardio-respiratory arrest
Cardiac disorders	Cardio-respiratory arrest	Cardiopulmonary arrest
Cardiac disorders	Cardiac arrest	Congestive cardioplegia
Cardiac disorders	Cyanosis	Cyanosed
Cardiac disorders	Cyanosis	Cyanosis
Cardiac disorders	Cyanosis	Cyanosis NOS
Cardiac disorders	Cyanosis	Cyanosis of lip
Cardiac disorders	Cyanosis	Cyanosis peripheral
Cardiac disorders	Cyanosis	Cyanotic
Cardiac disorders	Cardiac arrest	Heart arrest
Cardiac disorders	Cardiac arrest	Hypoxic arrest
Cardiac disorders	Cyanosis	Lips cyanosed
Cardiac disorders	Cyanosis	Nails cyanosed
Cardiac disorders	Cardiac arrest	Standstill cardiac
Cardiac disorders	Cardiopulmonary failure	Cardio-respiratory failure
Cardiac disorders	Cardio-respiratory distress	Cardio-respiratory distress
Cardiac disorders	Cardiopulmonary failure	Cardiopulmonary insufficiency
Cardiac disorders	Cardiopulmonary failure	Cardiopulmonary failure
Cardiac disorders	Cyanosis	Circumoral cyanosis

System Organ Class	Preferred Term	Lowest Level Term
Acute central respiratory depression (SMQ)		
Cardiac disorders	Cyanosis	Cyanosis aggravated
Infections and infestations	Severe acute respiratory syndrome	Severe acute respiratory syndrome
Infections and infestations	Severe acute respiratory syndrome	SARS
Injury, poisoning and procedural complications	Respiratory fume inhalation disorder	Respiratory fume inhalation disorder NOS
Injury, poisoning and procedural complications	Respiratory fume inhalation disorder	Upper respiratory inflammation due to fumes and vapors
Injury, poisoning and procedural complications	Respiratory fume inhalation disorder	Upper respiratory inflammation due to fumes and vapours
Injury, poisoning and procedural complications	Respiratory fume inhalation disorder	Smoke inhalation
Injury, poisoning and procedural complications	Respiratory fume inhalation disorder	Respiratory fume inhalation disorder
Injury, poisoning and procedural complications	Postoperative respiratory failure	Postoperative respiratory failure
Investigations	Blood gases abnormal	ABGs abnormal
Investigations	Blood gases abnormal	Abnormal arterial blood gases
Investigations	Breath sounds abnormal	Abnormal chest sounds
Investigations	Breath sounds abnormal	Abnormal chest sounds NOS
Investigations	Blood gases abnormal	Blood gases abnormal
Investigations	Blood gases abnormal	Blood gases NOS abnormal
Investigations	Blood pH abnormal	Blood pH abnormal
Investigations	Blood pH decreased	Blood pH decreased
Investigations	Breath sounds abnormal	Breath sounds decreased
Investigations	Respiratory rate decreased	Breathing rate slowed
Investigations	Respiratory rate decreased	Breathing slowed
Investigations	Breath sounds abnormal	Diminished lung sounds
Investigations	Blood pH decreased	Low pH
Investigations	Oxygen saturation abnormal	Oxygen saturation abnormal
Investigations	Oxygen saturation decreased	Oxygen saturation decreased
Investigations	Oxygen saturation decreased	Oxygen saturation low
Investigations	PO2 abnormal	Oxygen tension abnormal NOS
Investigations	PO2 decreased	Oxygen tension decreased
Investigations	PCO2 decreased	Partial pressure CO2 decreased
Investigations	PO2 abnormal	Partial pressure O2 abnormal NOS
Investigations	PO2 decreased	Partial pressure O2 decreased
Investigations	PCO2 decreased	PCO2 decreased
Investigations	Blood pH decreased	pH decreased
Investigations	Blood pH decreased	pH reduced
Investigations	Blood pH decreased	Plasma pH decreased

System Organ Class	Preferred Term	Lowest Level Term
Acute central respiratory depression (SMQ)		
Investigations	PO2 abnormal	PO2 abnormal NOS
Investigations	PO2 decreased	PO2 decreased
Investigations	PCO2 decreased	Reduced CO2 tension
Investigations	Respiratory rate decreased	Respiration rate decreased
Investigations	Respiratory rate decreased	Respiratory rate decreased
Investigations	Respiratory rate decreased	Respiratory rate low
Investigations	Breath sounds abnormal	Respiratory sounds decreased
Investigations	Blood pH decreased	Serum pH decreased
Investigations	Oxygen saturation abnormal	Oximetry abnormal
Investigations	Oxygen saturation decreased	Oximetry decreased
Investigations	Blood pH decreased	Arterial blood pH decreased
Investigations	Blood pH decreased	Venous blood pH decreased
Investigations	PCO2 abnormal	PCO2 abnormal
Investigations	Breath sounds abnormal	Abnormal chest sound
Investigations	PO2 abnormal	PO2 abnormal
Investigations	Breath sounds absent	Breath sounds absent
Investigations	Breath sounds abnormal	Breath sounds abnormal
Investigations	Breath sounds abnormal	Vesicular breathing abnormal
Investigations	Venous oxygen saturation decreased	Mixed venous blood saturation decreased
Investigations	Venous oxygen saturation abnormal	Mixed venous blood saturation abnormal
Investigations	Venous oxygen saturation decreased	SvO2 decreased
Investigations	Venous oxygen saturation abnormal	SvO2 abnormal
Investigations	Capnogram abnormal	Capnogram abnormal
Investigations	End-tidal CO2 abnormal	End-tidal CO2 abnormal
Investigations	End-tidal CO2 decreased	End-tidal CO2 decreased
Investigations	Alveolar oxygen partial pressure decreased	Alveolar oxygen partial pressure decreased
Investigations	Alveolar oxygen partial pressure abnormal	Alveolar oxygen partial pressure abnormal
Investigations	Venous oxygen partial pressure decreased	Venous oxygen partial pressure decreased
Investigations	Venous oxygen partial pressure abnormal	Venous oxygen partial pressure abnormal
Investigations	Venous oxygen saturation decreased	Venous oxygen saturation decreased
Investigations	Venous oxygen saturation abnormal	Venous oxygen saturation abnormal
Investigations	Oxygen saturation decreased	Arterial oxygen saturation decreased
Investigations	Oxygen saturation abnormal	Arterial oxygen saturation abnormal

System Organ Class	Preferred Term	Lowest Level Term
Acute central respiratory depression (SMQ)		
Investigations	PO2 decreased	Arterial oxygen partial pressure decreased
Investigations	PO2 abnormal	Arterial oxygen partial pressure abnormal
Investigations	PO2 decreased	PaO2 decreased
Investigations	PO2 abnormal	PaO2 abnormal
Investigations	Breath sounds abnormal	Coarse breath sounds
Nervous system disorders	Central-alveolar hypoventilation	Central-alveolar hypoventilation
Nervous system disorders	Hypercapnic coma	Hypercapnic coma
Psychiatric disorders	Breath holding	Breath holding
Psychiatric disorders	Breath holding	Breath holding attack
Psychiatric disorders	Breath holding	Breath holding spells
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	A.R.D.S.
Respiratory, thoracic and mediastinal disorders	Respiratory acidosis	Acidosis respiratory
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	Acute on chronic respiratory failure
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	Acute respiratory distress syndrome
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	Acute respiratory failure
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	Adult RDS
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	Adult respiratory distress syndrome
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	Adult respiratory stress syndrome
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Air hunger
Respiratory, thoracic and mediastinal disorders	Anoxia	Anoxia
Respiratory, thoracic and mediastinal disorders	Apnoea	Apnea
Respiratory, thoracic and mediastinal disorders	Apnoea	Apnoea
Respiratory, thoracic and mediastinal disorders	Apnoeic attack	Apnoea attack
Respiratory, thoracic and mediastinal disorders	Apnoeic attack	Apnoeic attack
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	ARDS

System Organ Class	Preferred Term	Lowest Level Term
Acute central respiratory depression (SMQ)		
Respiratory, thoracic and mediastinal disorders	Respiratory arrest	Arrest pulmonary
Respiratory, thoracic and mediastinal disorders	Respiratory arrest	Arrest respiratory
Respiratory, thoracic and mediastinal disorders	Asphyxia	Asphyxia
Respiratory, thoracic and mediastinal disorders	Asphyxia	Asphyxiation
Respiratory, thoracic and mediastinal disorders	Bradypnoea	Bradypnea
Respiratory, thoracic and mediastinal disorders	Bradypnoea	Bradypnoea
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Breath shortness
Respiratory, thoracic and mediastinal disorders	Hypopnoea	Breathing abnormally shallow
Respiratory, thoracic and mediastinal disorders	Respiratory arrest	Breathing arrested
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Breathing difficult
Respiratory, thoracic and mediastinal disorders	Hypopnoea	Breathing shallow
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Breathlessness
Respiratory, thoracic and mediastinal disorders	Hypercapnia	Carbon dioxide narcosis
Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Central sleep apnoea syndrome
Respiratory, thoracic and mediastinal disorders	Cheyne-Stokes respiration	Cheyne-Stokes respiration
Respiratory, thoracic and mediastinal disorders	Cyanosis central	Cyanosis central
Respiratory, thoracic and mediastinal disorders	Respiratory depression	Depression respiratory
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Difficulty breathing
Respiratory, thoracic and mediastinal disorders	Respiratory distress	Distress respiratory
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Dyspnea
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Dyspnea exacerbated
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Dyspnoea

System Organ Class	Preferred Term	Lowest Level Term
Acute central respiratory depression (SMQ)		
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Dyspnoea exacerbated
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Dyspnoea NOS
Respiratory, thoracic and mediastinal disorders	Respiratory failure	Failure respiratory
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Gasping
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Hunger air
Respiratory, thoracic and mediastinal disorders	Hypercapnia	Hypercapnia
Respiratory, thoracic and mediastinal disorders	Hypercapnia	Hypercapnic
Respiratory, thoracic and mediastinal disorders	Hypercapnia	Hypercarbia
Respiratory, thoracic and mediastinal disorders	Hypopnoea	Hypopnea
Respiratory, thoracic and mediastinal disorders	Hypopnoea	Hypopnoea
Respiratory, thoracic and mediastinal disorders	Hypoventilation	Hypoventilation
Respiratory, thoracic and mediastinal disorders	Hypoxia	Hypoxaemia
Respiratory, thoracic and mediastinal disorders	Hypoxia	Hypoxemia
Respiratory, thoracic and mediastinal disorders	Hypoxia	Hypoxia
Respiratory, thoracic and mediastinal disorders	Hypoxia	Hypoxic
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Increased shortness of breath
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Increased work of breathing
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Labored breathing
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Laboured breathing
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Laboured respiration
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Marked inactivity of chest wall on inspiratory effort
Respiratory, thoracic and mediastinal disorders	Hypercapnia	Narcosis carbon dioxide

System Organ Class	Preferred Term	Lowest Level Term
Acute central respiratory depression (SMQ)		
Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Obstructive sleep apnoea syndrome
Respiratory, thoracic and mediastinal disorders	Orthopnoea	Orthopnea
Respiratory, thoracic and mediastinal disorders	Orthopnoea	Orthopnoea
Respiratory, thoracic and mediastinal disorders	Respiratory arrest	Pulmonary arrest
Respiratory, thoracic and mediastinal disorders	Respiratory gas exchange disorder	Resp gas exchange disorder NOS
Respiratory, thoracic and mediastinal disorders	Respiration abnormal	Respiration abnormal
Respiratory, thoracic and mediastinal disorders	Cheyne-Stokes respiration	Respiration biot-type
Respiratory, thoracic and mediastinal disorders	Cheyne-Stokes respiration	Respiration Cheyne-Stokes-type
Respiratory, thoracic and mediastinal disorders	Respiratory depression	Respiration depressed
Respiratory, thoracic and mediastinal disorders	Respiratory failure	Respiration failure
Respiratory, thoracic and mediastinal disorders	Respiratory disorder	Respiration irregularity
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Respiration labored
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Respiration labored
Respiratory, thoracic and mediastinal disorders	Hypopnoea	Respiration spontaneous decreased
Respiratory, thoracic and mediastinal disorders	Respiratory disorder	Respiratory abnormality, unspecified
Respiratory, thoracic and mediastinal disorders	Respiratory acidosis	Respiratory acidosis
Respiratory, thoracic and mediastinal disorders	Respiratory arrest	Respiratory arrest
Respiratory, thoracic and mediastinal disorders	Respiratory depression	Respiratory depression
Respiratory, thoracic and mediastinal disorders	Respiratory depth decreased	Respiratory depth decreased
Respiratory, thoracic and mediastinal disorders	Respiratory disorder	Respiratory disorder
Respiratory, thoracic and mediastinal disorders	Respiratory disorder	Respiratory disorder NOS
Respiratory, thoracic and mediastinal disorders	Respiratory distress	Respiratory distress

System Organ Class	Preferred Term	Lowest Level Term
Acute central respiratory depression (SMQ)		
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	Respiratory distress syndrome adult
Respiratory, thoracic and mediastinal disorders	Respiratory disorder	Respiratory dysfunction NOS
Respiratory, thoracic and mediastinal disorders	Respiratory failure	Respiratory failure
Respiratory, thoracic and mediastinal disorders	Respiratory gas exchange disorder	Respiratory gas exchange disorder NOS
Respiratory, thoracic and mediastinal disorders	Respiratory failure	Respiratory insufficiency
Respiratory, thoracic and mediastinal disorders	Respiratory paralysis	Respiratory paralysis
Respiratory, thoracic and mediastinal disorders	Respiratory disorder	Respiratory rhythm disorder
Respiratory, thoracic and mediastinal disorders	Respiratory disorder	Respiratory system disorder
Respiratory, thoracic and mediastinal disorders	Hypercapnia	Retention carbon dioxide
Respiratory, thoracic and mediastinal disorders	Hypopnoea	Shallow breathing
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	Shock lung
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Short of breath
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Shortness of breath
Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Sleep apnea
Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Sleep apnea syndrome
Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Sleep apnoea
Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Sleep apnoea syndrome
Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Sleep apnoea syndromes
Respiratory, thoracic and mediastinal disorders	Asphyxia	Strangulation
Respiratory, thoracic and mediastinal disorders	Asphyxia	Suffocation
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	Surfactant deficiency syndrome adult
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	Syndrome adult respiratory distress

System Organ Class	Preferred Term	Lowest Level Term
Acute central respiratory depression (SMQ)		
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	Syndrome respiratory distress adult
Respiratory, thoracic and mediastinal disorders	Respiratory disorder	Unspecified disease of respiratory system
Respiratory, thoracic and mediastinal disorders	Hypoventilation	Ventilation difficult
Respiratory, thoracic and mediastinal disorders	Respiratory failure	Ventilatory failure
Respiratory, thoracic and mediastinal disorders	Respiration abnormal	Respiratory sighs
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	Acute respiratory decompensation
Respiratory, thoracic and mediastinal disorders	Respiration abnormal	Respiration abnormal NOS
Respiratory, thoracic and mediastinal disorders	Respiratory failure	Pulmonary failure
Respiratory, thoracic and mediastinal disorders	Asphyxia	Injury asphyxiation
Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Apnoea syndrome
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Labored respiration
Respiratory, thoracic and mediastinal disorders	Apnoeic attack	Apnea attack
Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Apnea syndrome
Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Central sleep apnea syndrome
Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Obstructive sleep apnea syndrome
Respiratory, thoracic and mediastinal disorders	Orthopnoea	Supine dyspnea
Respiratory, thoracic and mediastinal disorders	Orthopnoea	Supine dyspnea
Respiratory, thoracic and mediastinal disorders	Respiratory failure	Hypercapnic respiratory failure
Respiratory, thoracic and mediastinal disorders	Respiratory gas exchange disorder	Respiratory gas exchange disorder
Respiratory, thoracic and mediastinal disorders	Respiratory failure	Restrictive respiratory insufficiency
Respiratory, thoracic and mediastinal disorders	Apnoeic attack	Apneic attack
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Acute dyspnea

System Organ Class	Preferred Term	Lowest Level Term
Acute central respiratory depression (SMQ)		
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Acute dyspnea
Respiratory, thoracic and mediastinal disorders	Cyanosis central	Cyanosis central aggravated
Respiratory, thoracic and mediastinal disorders	Respiratory failure	Respiratory failure aggravated
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	Acute respiratory insufficiency
Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Hypopnea syndrome
Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Hypopnoea syndrome
Respiratory, thoracic and mediastinal disorders	Hypoventilation	Alveolar hypoventilation
Surgical and medical procedures	Oxygen supplementation	Oxygen supplementation

Table 13: AEs Related to Route of Administration-Oral Soft Tissue Conditions (HLT)

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration : Oral Soft Tissue Conditions (HLT)		
Gastrointestinal disorders	Angina bullosa haemorrhagica	Angina bullosa haemorrhagica
Gastrointestinal disorders	Angina bullosa haemorrhagica	Angina bullosa hemorrhagica
Gastrointestinal disorders	Aphthous stomatitis	Aphthous stoma
Gastrointestinal disorders	Aphthous stomatitis	Aphthous stomatitis
Gastrointestinal disorders	Aphthous stomatitis	Aphthous ulcer
Gastrointestinal disorders	Aphthous stomatitis	Buccal mucosa aphthous ulceration
Gastrointestinal disorders	Aphthous stomatitis	Canker sores oral
Gastrointestinal disorders	Aphthous stomatitis	Oral aphthae
Gastrointestinal disorders	Aphthous stomatitis	Stomatitis aphthous
Gastrointestinal disorders	Aphthous stomatitis	Stomatitis ulcerative aphthous
Gastrointestinal disorders	Aphthous stomatitis	Ulcer aphthous
Gastrointestinal disorders	Aphthous stomatitis	Ulcer aphthous oral
Gastrointestinal disorders	Aphthous stomatitis	Ulcers aphthous oral
Gastrointestinal disorders	Aphthous stomatitis	Canker sore lip
Gastrointestinal disorders	Aphthous stomatitis	Aphthous ulcer recurrent
Gastrointestinal disorders	Aphthous stomatitis	Aphtha
Gastrointestinal disorders	Buccal mucosal roughening	Roughness oral
Gastrointestinal disorders	Buccal mucosal roughening	Buccal mucosal roughening
Gastrointestinal disorders	Buccal mucosal roughening	Rough mouth
Gastrointestinal disorders	Burning mouth syndrome	Burning mouth syndrome

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration : Oral Soft Tissue Conditions (HLT)		
Gastrointestinal disorders	Chapped lips	Lip rough
Gastrointestinal disorders	Chapped lips	Chapped lips
Gastrointestinal disorders	Chapped lips	Cracked lips
Gastrointestinal disorders	Cheilitis	Angular cheilitis
Gastrointestinal disorders	Cheilitis	Angular stomatitis
Gastrointestinal disorders	Cheilitis	Cheilitis
Gastrointestinal disorders	Cheilitis	Lip redness
Gastrointestinal disorders	Cheilitis	Desquamative cheilitis
Gastrointestinal disorders	Cheilitis	Rash lips
Gastrointestinal disorders	Cheilitis	Irritation lips
Gastrointestinal disorders	Cheilitis	Raw lips
Gastrointestinal disorders	Cheilitis	Redness corner of mouth
Gastrointestinal disorders	Cheilitis	Inflammation lips
Gastrointestinal disorders	Cheilitis	Soreness corner mouth
Gastrointestinal disorders	Cheilitis	Sores lip
Gastrointestinal disorders	Cheilitis	Perleche
Gastrointestinal disorders	Cheilitis	Angular cheilosis
Gastrointestinal disorders	Cheilitis granulomatosa	Cheilitis granulomatosa
Gastrointestinal disorders	Cheilosis	Cheilosis
Gastrointestinal disorders	Contact stomatitis	Contact stomatitis
Gastrointestinal disorders	Enlarged uvula	Enlarged uvula
Gastrointestinal disorders	Gingival blister	Gingival blister
Gastrointestinal disorders	Gingival blister	Blisters gum
Gastrointestinal disorders	Gingival oedema	Gingival oedema
Gastrointestinal disorders	Gingival oedema	Oedema gum
Gastrointestinal disorders	Gingival oedema	Gingival edema
Gastrointestinal disorders	Gingival oedema	Edema gum
Gastrointestinal disorders	Gingival pruritus	Gingival pruritus
Gastrointestinal disorders	Gingival pruritus	Itching gum
Gastrointestinal disorders	Gingival swelling	Gingival swelling
Gastrointestinal disorders	Gingival swelling	Gum swelling
Gastrointestinal disorders	Hypoaesthesia oral	Anaesthesia lip
Gastrointestinal disorders	Hypoaesthesia oral	Anaesthesia mouth
Gastrointestinal disorders	Hypoaesthesia oral	Anaesthesia oral mucosa
Gastrointestinal disorders	Hypoaesthesia oral	Anaesthesia tongue
Gastrointestinal disorders	Hypoaesthesia oral	Hypoaesthesia oral NOS
Gastrointestinal disorders	Hypoaesthesia oral	Hypoaesthesia tongue
Gastrointestinal disorders	Hypoaesthesia oral	Numbness circumoral

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration : Oral Soft Tissue Conditions (HLT)		
Gastrointestinal disorders	Hypoaesthesia oral	Numbness of mouth angular
Gastrointestinal disorders	Hypoaesthesia oral	Numbness of tongue
Gastrointestinal disorders	Hypoaesthesia oral	Numbness oral
Gastrointestinal disorders	Hypoaesthesia oral	Numbness perioral
Gastrointestinal disorders	Hypoaesthesia oral	Oral mucosal anaesthesia
Gastrointestinal disorders	Hypoaesthesia oral	Perioral numbness
Gastrointestinal disorders	Hypoaesthesia oral	Tongue sensation loss of
Gastrointestinal disorders	Hypoaesthesia oral	Tongue tip numbness of
Gastrointestinal disorders	Hypoaesthesia oral	Hypoaesthesia lips
Gastrointestinal disorders	Hypoaesthesia oral	Hypoaesthesia gingival
Gastrointestinal disorders	Hypoaesthesia oral	Numbness mouth
Gastrointestinal disorders	Hypoaesthesia oral	Numb mouth
Gastrointestinal disorders	Hypoaesthesia oral	Numb lips
Gastrointestinal disorders	Hypoaesthesia oral	Numbness lips
Gastrointestinal disorders	Hypoaesthesia oral	Hypoaesthesia gum
Gastrointestinal disorders	Hypoaesthesia oral	Numbness gum
Gastrointestinal disorders	Hypoaesthesia oral	Numbness gingival
Gastrointestinal disorders	Hypoaesthesia oral	Hypoesthesia gingival
Gastrointestinal disorders	Hypoaesthesia oral	Hypoesthesia lips
Gastrointestinal disorders	Hypoaesthesia oral	Hypoesthesia oral
Gastrointestinal disorders	Hypoaesthesia oral	Hypoesthesia tongue
Gastrointestinal disorders	Hypoaesthesia oral	Hypoaesthesia oral
Gastrointestinal disorders	Hypoaesthesia oral	Hypoesthesia gum
Gastrointestinal disorders	Hypoaesthesia oral	Anesthesia lip
Gastrointestinal disorders	Hypoaesthesia oral	Anesthesia mouth
Gastrointestinal disorders	Hypoaesthesia oral	Anesthesia oral mucosa
Gastrointestinal disorders	Hypoaesthesia oral	Anesthesia tongue
Gastrointestinal disorders	Leukoplakia oral	Leukoplakia of mouth
Gastrointestinal disorders	Leukoplakia oral	Leukoplakia of oral mucosa, including tongue
Gastrointestinal disorders	Leukoplakia oral	Leukoplakia oral
Gastrointestinal disorders	Leukoplakia oral	Leukoplakia oral NOS
Gastrointestinal disorders	Leukoplakia oral	Oral leukoplakia NOS
Gastrointestinal disorders	Leukoplakia oral	Leukoplakia buccalis
Gastrointestinal disorders	Leukoplakia oral	Leukoplakia labialis
Gastrointestinal disorders	Leukoplakia oral	Leukoplakia lingualis
Gastrointestinal disorders	Leukoplakia oral	Leukoplakia of oral mucosa, incl tongue
Gastrointestinal disorders	Leukoplakia oral	Leukoplakia tongue

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration : Oral Soft Tissue Conditions (HLT)		
Gastrointestinal disorders	Lip blister	Blister of lip
Gastrointestinal disorders	Lip blister	Lip blister
Gastrointestinal disorders	Lip blister	Blister lip
Gastrointestinal disorders	Lip discolouration	Lip colour altered
Gastrointestinal disorders	Lip discolouration	Lip discolouration
Gastrointestinal disorders	Lip discolouration	Lip color altered
Gastrointestinal disorders	Lip discolouration	Lip discoloration
Gastrointestinal disorders	Lip disorder	Lip disorder NOS
Gastrointestinal disorders	Lip disorder	Lip disorder
Gastrointestinal disorders	Lip disorder	Bumps lip
Gastrointestinal disorders	Lip erosion	Lip erosion
Gastrointestinal disorders	Lip exfoliation	Lip sloughing
Gastrointestinal disorders	Lip exfoliation	Peeling lips
Gastrointestinal disorders	Lip exfoliation	Lip exfoliation
Gastrointestinal disorders	Lip haematoma	Lip haematoma
Gastrointestinal disorders	Lip haematoma	Lip hematoma
Gastrointestinal disorders	Lip haemorrhage	Lip haemorrhage
Gastrointestinal disorders	Lip haemorrhage	Hemorrhage lips
Gastrointestinal disorders	Lip haemorrhage	Bleeding lips
Gastrointestinal disorders	Lip haemorrhage	Lip hemorrhage
Gastrointestinal disorders	Lip haemorrhage	Haemorrhage lips
Gastrointestinal disorders	Lip haemorrhage	Lip bleeding
Gastrointestinal disorders	Lip oedema	Edema lip
Gastrointestinal disorders	Lip oedema	Lip edema
Gastrointestinal disorders	Lip oedema	Lip oedema
Gastrointestinal disorders	Lip oedema	Oedema lip
Gastrointestinal disorders	Lip pain	Lip pain
Gastrointestinal disorders	Lip pain	Lip sore
Gastrointestinal disorders	Lip pain	Lip soreness
Gastrointestinal disorders	Lip pain	Tender lips
Gastrointestinal disorders	Lip pain	Stinging lips
Gastrointestinal disorders	Lip pain	Sensitive lips
Gastrointestinal disorders	Lip pruritus	Lip pruritus
Gastrointestinal disorders	Lip swelling	Lip swelling
Gastrointestinal disorders	Lip swelling	Lips swelling non-specific
Gastrointestinal disorders	Lip swelling	Swelling lips
Gastrointestinal disorders	Lip swelling	Swelling of lips
Gastrointestinal disorders	Lip swelling	Swollen lips

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration : Oral Soft Tissue Conditions (HLT)		
Gastrointestinal disorders	Lip ulceration	Lip ulcer
Gastrointestinal disorders	Lip ulceration	Lip ulceration
Gastrointestinal disorders	Lip ulceration	Ulcer lip
Gastrointestinal disorders	Melanoplakia oral	Melanoplakia oral
Gastrointestinal disorders	Mouth haemorrhage	Hemorrhage mouth
Gastrointestinal disorders	Mouth haemorrhage	Hemorrhage of mouth
Gastrointestinal disorders	Mouth haemorrhage	Hemorrhage oral
Gastrointestinal disorders	Mouth haemorrhage	Mouth haemorrhage
Gastrointestinal disorders	Mouth haemorrhage	Mouth hemorrhage
Gastrointestinal disorders	Mouth haemorrhage	Oral haemorrhage
Gastrointestinal disorders	Mouth haemorrhage	Oral hemorrhage
Gastrointestinal disorders	Mouth haemorrhage	Oral mucosa bleeding
Gastrointestinal disorders	Mouth haemorrhage	Oral mucosa ecchymosis
Gastrointestinal disorders	Mouth haemorrhage	Oral mucosal petechiae
Gastrointestinal disorders	Mouth haemorrhage	Petechiae oral mucosa
Gastrointestinal disorders	Mouth haemorrhage	Bleeding mouth
Gastrointestinal disorders	Mouth haemorrhage	Haemorrhage mouth
Gastrointestinal disorders	Mouth haemorrhage	Haemorrhage of mouth
Gastrointestinal disorders	Mouth haemorrhage	Haemorrhage oral
Gastrointestinal disorders	Mouth haemorrhage	Mouth bleeding
Gastrointestinal disorders	Mouth ulceration	Buccal mucosa ulceration
Gastrointestinal disorders	Mouth ulceration	Buccal ulceration
Gastrointestinal disorders	Mouth ulceration	Mouth ulcer
Gastrointestinal disorders	Mouth ulceration	Mouth ulceration
Gastrointestinal disorders	Mouth ulceration	Oral ulceration
Gastrointestinal disorders	Mouth ulceration	Stomatitis ulcerative
Gastrointestinal disorders	Mouth ulceration	Ulcer buccal
Gastrointestinal disorders	Mouth ulceration	Ulcer mouth
Gastrointestinal disorders	Mouth ulceration	Ulceration mouth
Gastrointestinal disorders	Mouth ulceration	Ulceration of mouth
Gastrointestinal disorders	Mouth ulceration	Ulcerative stomatitis
Gastrointestinal disorders	Mouth ulceration	Ulcerative stomatitis, acute
Gastrointestinal disorders	Mouth ulceration	Mouth ulceration aggravated
Gastrointestinal disorders	Odynophagia	Odynophagia
Gastrointestinal disorders	Odynophagia	Swallowing painful
Gastrointestinal disorders	Oedema mouth	Edema of mouth
Gastrointestinal disorders	Oedema mouth	Oedema mouth
Gastrointestinal disorders	Oedema mouth	Oral mucosa swollen

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration : Oral Soft Tissue Conditions (HLT)		
Gastrointestinal disorders	Oedema mouth	Swollen mouth
Gastrointestinal disorders	Oedema mouth	Edema mouth
Gastrointestinal disorders	Oedema mouth	Oedema of mouth
Gastrointestinal disorders	Oral discharge	Oral discharge
Gastrointestinal disorders	Oral discomfort	Burning oral sensation
Gastrointestinal disorders	Oral discomfort	Discomfort in mouth
Gastrointestinal disorders	Oral discomfort	Lip burning sensation of
Gastrointestinal disorders	Oral discomfort	Oral cavity discomfort
Gastrointestinal disorders	Oral discomfort	Oral discomfort
Gastrointestinal disorders	Oral discomfort	Oral hot feeling
Gastrointestinal disorders	Oral discomfort	Burning corner of mouth
Gastrointestinal disorders	Oral discomfort	Burning lips
Gastrointestinal disorders	Oral discomfort	Burning mouth
Gastrointestinal disorders	Oral disorder	Oral soft tissue disorder NOS
Gastrointestinal disorders	Oral disorder	Oral mucosal disorder
Gastrointestinal disorders	Oral disorder	Oral lesion
Gastrointestinal disorders	Oral disorder	Oral soft tissue disorder
Gastrointestinal disorders	Oral disorder	Oral disorder
Gastrointestinal disorders	Oral disorder	Mouth bump
Gastrointestinal disorders	Oral dysaesthesia	Dysesthesia of lips
Gastrointestinal disorders	Oral dysaesthesia	Dysesthesia of tongue
Gastrointestinal disorders	Oral dysaesthesia	Oral dysaesthesia
Gastrointestinal disorders	Oral dysaesthesia	Oral dysesthesia
Gastrointestinal disorders	Oral dysaesthesia	Dysaesthesia of lips
Gastrointestinal disorders	Oral dysaesthesia	Dysaesthesia of tongue
Gastrointestinal disorders	Oral dysaesthesia	Vincent's symptom
Gastrointestinal disorders	Oral leukoedema	Oral leukoedema
Gastrointestinal disorders	Oral lichen planus	Oral lichen planus
Gastrointestinal disorders	Oral mucosa atrophy	Oral mucosa atrophy
Gastrointestinal disorders	Oral mucosa erosion	Oral mucosa erosion
Gastrointestinal disorders	Oral mucosal blistering	Blistering of mouth
Gastrointestinal disorders	Oral mucosal blistering	Oral mucosa blister
Gastrointestinal disorders	Oral mucosal blistering	Oral mucosa blistering
Gastrointestinal disorders	Oral mucosal blistering	Oral mucosal blistering
Gastrointestinal disorders	Oral mucosal discolouration	Oral mucosa discolouration
Gastrointestinal disorders	Oral mucosal discolouration	Oral mucosal discolouration
Gastrointestinal disorders	Oral mucosal discolouration	Oral mucosal discoloration
Gastrointestinal disorders	Oral mucosal eruption	Oral mucosal eruption

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration : Oral Soft Tissue Conditions (HLT)		
Gastrointestinal disorders	Oral mucosal erythema	Oral mucosa redness
Gastrointestinal disorders	Oral mucosal erythema	Oral redness
Gastrointestinal disorders	Oral mucosal erythema	Redness mouth
Gastrointestinal disorders	Oral mucosal erythema	Oral mucosal erythema
Gastrointestinal disorders	Oral mucosal erythema	Palatal erythema
Gastrointestinal disorders	Oral mucosal exfoliation	Oral mucosal sloughing
Gastrointestinal disorders	Oral mucosal exfoliation	Sloughing of buccal mucosa
Gastrointestinal disorders	Oral mucosal exfoliation	Sloughing of mouth
Gastrointestinal disorders	Oral mucosal exfoliation	Gingival sloughing
Gastrointestinal disorders	Oral mucosal exfoliation	Peeling mouth
Gastrointestinal disorders	Oral mucosal exfoliation	Desquamation mouth
Gastrointestinal disorders	Oral mucosal exfoliation	Sloughing gums
Gastrointestinal disorders	Oral mucosal exfoliation	Sloughing gingival
Gastrointestinal disorders	Oral mucosal exfoliation	Peeling gingival
Gastrointestinal disorders	Oral mucosal exfoliation	Peeling gum
Gastrointestinal disorders	Oral mucosal exfoliation	Desquamation gum
Gastrointestinal disorders	Oral mucosal exfoliation	Desquamation gingival
Gastrointestinal disorders	Oral mucosal exfoliation	Oral mucosal exfoliation
Gastrointestinal disorders	Oral mucosal hypertrophy	Oral mucosal hypertrophy
Gastrointestinal disorders	Oral pain	Mouth pain
Gastrointestinal disorders	Oral pain	Oral angular pain
Gastrointestinal disorders	Oral pain	Oral mucosa pain
Gastrointestinal disorders	Oral pain	Oral pain
Gastrointestinal disorders	Oral pain	Pain mouth
Gastrointestinal disorders	Oral pain	Pain oral
Gastrointestinal disorders	Oral pain	Sore mouth
Gastrointestinal disorders	Oral pain	Sensitive mouth
Gastrointestinal disorders	Oral pain	Tender mouth
Gastrointestinal disorders	Oral pain	Stinging mouth
Gastrointestinal disorders	Oral pain	Soreness roof of mouth
Gastrointestinal disorders	Oral papule	Oral papule
Gastrointestinal disorders	Oral pruritus	Intraoral pruritus
Gastrointestinal disorders	Oral pruritus	Itching mouth
Gastrointestinal disorders	Oral pruritus	Oral pruritus
Gastrointestinal disorders	Oral submucosal fibrosis	Oral submucosal fibrosis
Gastrointestinal disorders	Oral submucosal fibrosis	Oral submucous fibrosis, including of tongue
Gastrointestinal disorders	Oral submucosal fibrosis	Oral submucous fibrosis, incl of tongue

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration : Oral Soft Tissue Conditions (HLT)		
Gastrointestinal disorders	Oral toxicity	Oral toxicity
Gastrointestinal disorders	Palatal disorder	Palatal disorder
Gastrointestinal disorders	Palatal disorder	Palatal lesion
Gastrointestinal disorders	Palatal disorder	Palatal nodule
Gastrointestinal disorders	Palatal disorder	Soft palate disorder
Gastrointestinal disorders	Palatal dysplasia	Palatal dysplasia
Gastrointestinal disorders	Palatal oedema	Palatine arch swollen
Gastrointestinal disorders	Palatal oedema	Oedema uvula
Gastrointestinal disorders	Palatal oedema	Edema uvula
Gastrointestinal disorders	Palatal oedema	Palatal oedema
Gastrointestinal disorders	Palatal oedema	Palatal edema
Gastrointestinal disorders	Palatitis	Palatitis
Gastrointestinal disorders	Paraesthesia oral	Circumoral paresthesia
Gastrointestinal disorders	Paraesthesia oral	Mouth paresthesia
Gastrointestinal disorders	Paraesthesia oral	Paraesthesia circumoral
Gastrointestinal disorders	Paraesthesia oral	Paraesthesia mouth
Gastrointestinal disorders	Paraesthesia oral	Paraesthesia oral NOS
Gastrointestinal disorders	Paraesthesia oral	Paraesthesia tongue
Gastrointestinal disorders	Paraesthesia oral	Paresthesia circumoral
Gastrointestinal disorders	Paraesthesia oral	Paresthesia mouth
Gastrointestinal disorders	Paraesthesia oral	Tongue abnormal feeling of
Gastrointestinal disorders	Paraesthesia oral	Paraesthesia lips
Gastrointestinal disorders	Paraesthesia oral	Paraesthesia gingival
Gastrointestinal disorders	Paraesthesia oral	Tingling mouth
Gastrointestinal disorders	Paraesthesia oral	Tingling lips
Gastrointestinal disorders	Paraesthesia oral	Paresthesia lips
Gastrointestinal disorders	Paraesthesia oral	Tingling tongue
Gastrointestinal disorders	Paraesthesia oral	Tingling gum
Gastrointestinal disorders	Paraesthesia oral	Tingling gingival
Gastrointestinal disorders	Paraesthesia oral	Paraesthesia gum
Gastrointestinal disorders	Paraesthesia oral	Paresthesia gingival
Gastrointestinal disorders	Paraesthesia oral	Paresthesia gum
Gastrointestinal disorders	Paraesthesia oral	Paresthesia oral
Gastrointestinal disorders	Paraesthesia oral	Paresthesia tongue
Gastrointestinal disorders	Paraesthesia oral	Paraesthesia oral
Gastrointestinal disorders	Paraesthesia oral	Perioral tingling
Gastrointestinal disorders	Paraesthesia oral	Perioral paraesthesia
Gastrointestinal disorders	Paraesthesia oral	Perioral paresthesia

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration : Oral Soft Tissue Conditions (HLT)		
Gastrointestinal disorders	Pigmentation buccal	Pigmentation buccal
Gastrointestinal disorders	Pigmentation lip	Lip pigmental spot
Gastrointestinal disorders	Pigmentation lip	Lip pigmentation
Gastrointestinal disorders	Pigmentation lip	Pigmentation lip
Gastrointestinal disorders	Pyostomatitis vegetans	Pyostomatitis vegetans
Gastrointestinal disorders	Stomatitis	Buccal inflammation
Gastrointestinal disorders	Stomatitis	Mouth irritation
Gastrointestinal disorders	Stomatitis	Mucositis oral
Gastrointestinal disorders	Stomatitis	Stomatitis
Gastrointestinal disorders	Stomatitis	Sores mouth
Gastrointestinal disorders	Stomatitis	Sores roof of mouth
Gastrointestinal disorders	Stomatitis	Raw mouth
Gastrointestinal disorders	Stomatitis	Irritation roof of mouth
Gastrointestinal disorders	Stomatitis	Chapped mouth
Gastrointestinal disorders	Stomatitis	Inflammation of mouth
Gastrointestinal disorders	Stomatitis	Mouth broke out
Gastrointestinal disorders	Stomatitis	Inflammation under tongue
Gastrointestinal disorders	Stomatitis	Oral mucosal irritation
Gastrointestinal disorders	Stomatitis	Vesicular stomatitis
Gastrointestinal disorders	Stomatitis	Gingivostomatitis
Gastrointestinal disorders	Stomatitis	Pseudomembranous stomatitis
Gastrointestinal disorders	Stomatitis haemorrhagic	Stomatitis haemorrhagic
Gastrointestinal disorders	Stomatitis haemorrhagic	Stomatitis hemorrhagic
Gastrointestinal disorders	Stomatitis necrotising	Cancrum oris
Gastrointestinal disorders	Stomatitis necrotising	Mouth necrosis
Gastrointestinal disorders	Stomatitis necrotising	Necrosis mouth
Gastrointestinal disorders	Stomatitis necrotising	Noma
Gastrointestinal disorders	Stomatitis necrotising	Stomatitis necrotising
Gastrointestinal disorders	Stomatitis necrotising	Stomatitis necrotizing
Gastrointestinal disorders	Uvulitis	Uvulitis

Table 14: AEs Related to Route of Administration-Respiratory Disorders NEC (HLT)

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Respiratory Disorders NEC (HLT)		
Respiratory, thoracic and mediastinal disorders	Allergic cough	Allergic cough
Respiratory, thoracic and mediastinal disorders	Choking	Choked on food

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Respiratory Disorders NEC (HLT)		
Respiratory, thoracic and mediastinal disorders	Choking	Choking
Respiratory, thoracic and mediastinal disorders	Choking	Choke on medication
Respiratory, thoracic and mediastinal disorders	Choking sensation	Choking sensation
Respiratory, thoracic and mediastinal disorders	Choking sensation	Choking sensation (excl psychogenic and dysphagia)
Respiratory, thoracic and mediastinal disorders	Choking sensation	Pharynx closed sensation of
Respiratory, thoracic and mediastinal disorders	Choking sensation	Pharynx strangled sensation of
Respiratory, thoracic and mediastinal disorders	Cough	Cough
Respiratory, thoracic and mediastinal disorders	Cough	Cough increased
Respiratory, thoracic and mediastinal disorders	Cough	Cough nonproductive
Respiratory, thoracic and mediastinal disorders	Cough	Cough resembling asthma
Respiratory, thoracic and mediastinal disorders	Cough	Coughing
Respiratory, thoracic and mediastinal disorders	Cough	Dry cough
Respiratory, thoracic and mediastinal disorders	Cough	Irritant cough
Respiratory, thoracic and mediastinal disorders	Cough	Irritative cough
Respiratory, thoracic and mediastinal disorders	Cough	Nocturnal cough
Respiratory, thoracic and mediastinal disorders	Cough	Persistent dry cough
Respiratory, thoracic and mediastinal disorders	Cough	Persistent non-productive cough
Respiratory, thoracic and mediastinal disorders	Cough	Cough aggravated
Respiratory, thoracic and mediastinal disorders	Cough	Coughing after drug inhalation
Respiratory, thoracic and mediastinal disorders	Cough	Drug-induced cough
Respiratory, thoracic and mediastinal disorders	Cough	Smoker's cough
Respiratory, thoracic and mediastinal disorders	Cough	Paroxysmal cough

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Respiratory Disorders NEC (HLT)		
Respiratory, thoracic and mediastinal disorders	Cough	Acute cough
Respiratory, thoracic and mediastinal disorders	Cough	Chronic cough
Respiratory, thoracic and mediastinal disorders	Cough	Persistent cough
Respiratory, thoracic and mediastinal disorders	Cough	Painful cough
Respiratory, thoracic and mediastinal disorders	Cough	Cough ineffective
Respiratory, thoracic and mediastinal disorders	Cough	Cough weak
Respiratory, thoracic and mediastinal disorders	Cough decreased	Cough decreased
Respiratory, thoracic and mediastinal disorders	Dry throat	Dry throat
Respiratory, thoracic and mediastinal disorders	Dry throat	Pharynx dry
Respiratory, thoracic and mediastinal disorders	Dry throat	Throat dry
Respiratory, thoracic and mediastinal disorders	Dysphonia	Distorted voice
Respiratory, thoracic and mediastinal disorders	Dysphonia	Disturbance in loudness
Respiratory, thoracic and mediastinal disorders	Dysphonia	Dysphonia
Respiratory, thoracic and mediastinal disorders	Dysphonia	Hoarse voice
Respiratory, thoracic and mediastinal disorders	Dysphonia	Hoarseness
Respiratory, thoracic and mediastinal disorders	Dysphonia	Hoarseness of voice
Respiratory, thoracic and mediastinal disorders	Dysphonia	Phonation difficulty
Respiratory, thoracic and mediastinal disorders	Dysphonia	Resonance disorder
Respiratory, thoracic and mediastinal disorders	Dysphonia	Vocal tone disorder
Respiratory, thoracic and mediastinal disorders	Dysphonia	Vocal volume disorder
Respiratory, thoracic and mediastinal disorders	Dysphonia	Voice alteration
Respiratory, thoracic and mediastinal disorders	Dysphonia	Voice disturbance

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Respiratory Disorders NEC (HLT)		
Respiratory, thoracic and mediastinal disorders	Dysphonia	Voice disturbance, unspecified
Respiratory, thoracic and mediastinal disorders	Dysphonia	Voice lowered
Respiratory, thoracic and mediastinal disorders	Dysphonia	Hypophonia
Respiratory, thoracic and mediastinal disorders	Dysphonia	Rhinolalia
Respiratory, thoracic and mediastinal disorders	Haemoptysis	Blood streaked sputum
Respiratory, thoracic and mediastinal disorders	Haemoptysis	Coughing blood
Respiratory, thoracic and mediastinal disorders	Haemoptysis	Haemoptysis
Respiratory, thoracic and mediastinal disorders	Haemoptysis	Hemoptysis
Respiratory, thoracic and mediastinal disorders	Haemoptysis	Sputum bloody
Respiratory, thoracic and mediastinal disorders	Hiccups	Hiccough
Respiratory, thoracic and mediastinal disorders	Hiccups	Hiccup
Respiratory, thoracic and mediastinal disorders	Hiccups	Hiccups
Respiratory, thoracic and mediastinal disorders	Hiccups	Singultation
Respiratory, thoracic and mediastinal disorders	Hiccups	Singultous
Respiratory, thoracic and mediastinal disorders	Hiccups	Singultus
Respiratory, thoracic and mediastinal disorders	Hiccups	Intractable hiccups
Respiratory, thoracic and mediastinal disorders	Increased bronchial secretion	Airway secretion excessive
Respiratory, thoracic and mediastinal disorders	Increased bronchial secretion	Bronchial secretion excessive
Respiratory, thoracic and mediastinal disorders	Increased bronchial secretion	Bronchorrhea
Respiratory, thoracic and mediastinal disorders	Increased bronchial secretion	Bronchorrhoea
Respiratory, thoracic and mediastinal disorders	Increased bronchial secretion	Excessive bronchial secretion
Respiratory, thoracic and mediastinal disorders	Increased bronchial secretion	Tracheo-bronchial secretion excess

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Respiratory Disorders NEC (HLT)		
Respiratory, thoracic and mediastinal disorders	Increased bronchial secretion	Increased bronchial secretion
Respiratory, thoracic and mediastinal disorders	Increased upper airway secretion	Throat secretion increased
Respiratory, thoracic and mediastinal disorders	Increased upper airway secretion	Phlegm
Respiratory, thoracic and mediastinal disorders	Increased upper airway secretion	Increased upper airway secretion
Respiratory, thoracic and mediastinal disorders	Increased viscosity of bronchial secretion	Sputum viscosity increased
Respiratory, thoracic and mediastinal disorders	Increased viscosity of bronchial secretion	Increased viscosity of bronchial secretion
Respiratory, thoracic and mediastinal disorders	Increased viscosity of nasal secretion	Increased viscosity of nasal secretion
Respiratory, thoracic and mediastinal disorders	Increased viscosity of nasal secretion	Thick nasal mucus
Respiratory, thoracic and mediastinal disorders	Laryngeal discomfort	Laryngeal discomfort
Respiratory, thoracic and mediastinal disorders	Laryngeal discomfort	Pharyngolaryngeal discomfort
Respiratory, thoracic and mediastinal disorders	Laryngeal pain	Laryngeal pain
Respiratory, thoracic and mediastinal disorders	Laryngeal pain	Larynx burning pain of
Respiratory, thoracic and mediastinal disorders	Laryngeal pain	Larynx pain
Respiratory, thoracic and mediastinal disorders	Laryngeal pain	Pharyngolaryngeal pain
Respiratory, thoracic and mediastinal disorders	Mouth breathing	Jaw breathing
Respiratory, thoracic and mediastinal disorders	Mouth breathing	Mouth breathing
Respiratory, thoracic and mediastinal disorders	Nasal discharge discolouration	Nasal discharge discolouration
Respiratory, thoracic and mediastinal disorders	Nasal discharge discolouration	Nasal discharge discoloration
Respiratory, thoracic and mediastinal disorders	Nasal discomfort	Discomfort in nose
Respiratory, thoracic and mediastinal disorders	Nasal discomfort	Nasal burning
Respiratory, thoracic and mediastinal disorders	Nasal discomfort	Nasal cavity strange sensation of
Respiratory, thoracic and mediastinal disorders	Nasal discomfort	Nasal irritation

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Respiratory Disorders NEC (HLT)		
Respiratory, thoracic and mediastinal disorders	Nasal discomfort	Nasal itching
Respiratory, thoracic and mediastinal disorders	Nasal discomfort	Nasal passage irritation
Respiratory, thoracic and mediastinal disorders	Nasal discomfort	Nasal soreness
Respiratory, thoracic and mediastinal disorders	Nasal discomfort	Sore nose
Respiratory, thoracic and mediastinal disorders	Nasal discomfort	Nasal discomfort
Respiratory, thoracic and mediastinal disorders	Nasal flaring	Nasal flaring
Respiratory, thoracic and mediastinal disorders	Nasal obstruction	Nasal obstruction
Respiratory, thoracic and mediastinal disorders	Nasal obstruction	Nasal obstruction increased
Respiratory, thoracic and mediastinal disorders	Nasopharyngeal reflux	Nasopharyngeal reflux
Respiratory, thoracic and mediastinal disorders	Nocturnal dyspnoea	Nocturnal dyspnoea
Respiratory, thoracic and mediastinal disorders	Nocturnal dyspnoea	Nocturnal dyspnea
Respiratory, thoracic and mediastinal disorders	Oropharyngeal blistering	Oropharyngeal blistering
Respiratory, thoracic and mediastinal disorders	Oropharyngeal discomfort	Pharynx discomfort
Respiratory, thoracic and mediastinal disorders	Oropharyngeal discomfort	Pharynx ill sensation of
Respiratory, thoracic and mediastinal disorders	Oropharyngeal discomfort	Pharynx strange sensation of
Respiratory, thoracic and mediastinal disorders	Oropharyngeal discomfort	Oropharyngeal discomfort
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Pain pharynx
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Pain throat
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Sore throat
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Sore throat NOS
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Throat pain
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Throat sore

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Respiratory Disorders NEC (HLT)		
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Chronic sore throat
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Oropharyngeal pain
Respiratory, thoracic and mediastinal disorders	Oropharyngeal plaque	Mouth plaque
Respiratory, thoracic and mediastinal disorders	Oropharyngeal plaque	Plaque mouth
Respiratory, thoracic and mediastinal disorders	Oropharyngeal plaque	Oropharyngeal plaque
Respiratory, thoracic and mediastinal disorders	Oropharyngeal scar	Oropharyngeal scar
Respiratory, thoracic and mediastinal disorders	Paranasal sinus discomfort	Paranasal sinus discomfort
Respiratory, thoracic and mediastinal disorders	Productive cough	Productive cough
Respiratory, thoracic and mediastinal disorders	Productive cough	Sputum
Respiratory, thoracic and mediastinal disorders	Productive cough	Expectoration
Respiratory, thoracic and mediastinal disorders	Respiratory tract oedema	Respiratory tract oedema
Respiratory, thoracic and mediastinal disorders	Respiratory tract oedema	Airway oedema
Respiratory, thoracic and mediastinal disorders	Respiratory tract oedema	Airway edema
Respiratory, thoracic and mediastinal disorders	Respiratory tract oedema	Respiratory tract edema
Respiratory, thoracic and mediastinal disorders	Rhinalgia	Nasal stinging
Respiratory, thoracic and mediastinal disorders	Rhinalgia	Stinging of nose
Respiratory, thoracic and mediastinal disorders	Rhinalgia	Rhinalgia
Respiratory, thoracic and mediastinal disorders	Rhinalgia	Nasal pain
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	Nasal discharge
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	Nasal discharge watery excessive
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	Rhinorrhea
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	Rhinorrhoea

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Respiratory Disorders NEC (HLT)		
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	Runny nose
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	Nasal mucus increased
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	Mucus nasal increased
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	Gustatory rhinorrhoea
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	Sniffles
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	Gustatory rhinorrhea
Respiratory, thoracic and mediastinal disorders	Sneezing	Paroxysmal sneeze
Respiratory, thoracic and mediastinal disorders	Sneezing	Sneezing
Respiratory, thoracic and mediastinal disorders	Sneezing	Sneezing excessive
Respiratory, thoracic and mediastinal disorders	Snoring	Snore
Respiratory, thoracic and mediastinal disorders	Snoring	Snoring
Respiratory, thoracic and mediastinal disorders	Sputum decreased	Sputum decreased
Respiratory, thoracic and mediastinal disorders	Sputum discoloured	Sputum discolored
Respiratory, thoracic and mediastinal disorders	Sputum discoloured	Sputum discoloured
Respiratory, thoracic and mediastinal disorders	Sputum increased	Sputum excretion increased
Respiratory, thoracic and mediastinal disorders	Sputum increased	Sputum increased
Respiratory, thoracic and mediastinal disorders	Sputum retention	Sputum excretion difficulty
Respiratory, thoracic and mediastinal disorders	Sputum retention	Sputum expectoration difficult
Respiratory, thoracic and mediastinal disorders	Sputum retention	Sputum sticking sensation of
Respiratory, thoracic and mediastinal disorders	Sputum retention	Sputum retention
Respiratory, thoracic and mediastinal disorders	Suffocation feeling	Suffocation feeling
Respiratory, thoracic and mediastinal disorders	Throat irritation	Burning in throat

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Respiratory Disorders NEC (HLT)		
Respiratory, thoracic and mediastinal disorders	Throat irritation	Local throat irritation
Respiratory, thoracic and mediastinal disorders	Throat irritation	Pharyngo-oral irritation
Respiratory, thoracic and mediastinal disorders	Throat irritation	Pharynx burning sensation of
Respiratory, thoracic and mediastinal disorders	Throat irritation	Pharynx irritated sensation of
Respiratory, thoracic and mediastinal disorders	Throat irritation	Pharynx itchy sensation of
Respiratory, thoracic and mediastinal disorders	Throat irritation	Throat burning sensation of
Respiratory, thoracic and mediastinal disorders	Throat irritation	Throat irritation
Respiratory, thoracic and mediastinal disorders	Throat irritation	Itchy throat
Respiratory, thoracic and mediastinal disorders	Throat lesion	Throat lesion
Respiratory, thoracic and mediastinal disorders	Throat tightness	Constriction throat
Respiratory, thoracic and mediastinal disorders	Throat tightness	Throat constriction
Respiratory, thoracic and mediastinal disorders	Throat tightness	Throat tightness
Respiratory, thoracic and mediastinal disorders	Upper airway necrosis	Upper airway necrosis
Respiratory, thoracic and mediastinal disorders	Upper airway obstruction	Upper airway obstruction
Respiratory, thoracic and mediastinal disorders	Upper airway resistance syndrome	Upper airway resistance syndrome
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract congestion	Upper respiratory tract congestion
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract inflammation	Upper respiratory tract inflammation
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract inflammation	Acute upper respiratory tract inflammation
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract irritation	Upper respiratory tract irritation
Respiratory, thoracic and mediastinal disorders	Upper-airway cough syndrome	Posterior nasal drip
Respiratory, thoracic and mediastinal disorders	Upper-airway cough syndrome	Postnasal drip
Respiratory, thoracic and mediastinal disorders	Upper-airway cough syndrome	Chronic post nasal drip

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Respiratory Disorders NEC (HLT)		
Respiratory, thoracic and mediastinal disorders	Upper-airway cough syndrome	Upper-airway cough syndrome
Respiratory, thoracic and mediastinal disorders	Yawning	Yawn
Respiratory, thoracic and mediastinal disorders	Yawning	Yawning
Respiratory, thoracic and mediastinal disorders	Yawning	Yawning excessive

Table 15: AEs Related to Route of Administration-Upper Respiratory Tract Disorders (HLT) (Exclude Infections)

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Upper Respiratory Tract Disorders (HLT) (Exclude Infections)		
Respiratory, thoracic and mediastinal disorders	Adductor vocal cord weakness	Adductor vocal cord weakness
Respiratory, thoracic and mediastinal disorders	Adenoidal disorder	Adenoidal disorder
Respiratory, thoracic and mediastinal disorders	Adenoidal hypertrophy	Adenoid vegetations
Respiratory, thoracic and mediastinal disorders	Adenoidal hypertrophy	Adenoidal hypertrophy
Respiratory, thoracic and mediastinal disorders	Allergic pharyngitis	Allergic pharyngitis
Respiratory, thoracic and mediastinal disorders	Allergic sinusitis	Allergic sinusitis
Respiratory, thoracic and mediastinal disorders	Allergic sinusitis	Seasonal sinusitis
Respiratory, thoracic and mediastinal disorders	Chronic eosinophilic rhinosinusitis	Chronic eosinophilic rhinosinusitis
Respiratory, thoracic and mediastinal disorders	Chronic hyperplastic eosinophilic sinusitis	Chronic hyperplastic eosinophilic sinusitis
Respiratory, thoracic and mediastinal disorders	Croup noninfectious	Croup noninfectious
Respiratory, thoracic and mediastinal disorders	Dysaesthesia pharynx	Dysaesthesia pharynx
Respiratory, thoracic and mediastinal disorders	Dysaesthesia pharynx	Dysesthesia pharynx
Respiratory, thoracic and mediastinal disorders	Dysaesthesia pharynx	Laryngopharyngeal dysesthesia

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Upper Respiratory Tract Disorders (HLT) (Exclude Infections)		
Respiratory, thoracic and mediastinal disorders	Dysaesthesia pharynx	Laryngopharyngeal dysaesthesia
Respiratory, thoracic and mediastinal disorders	Eosinophilic rhinitis	Eosinophilic rhinitis
Respiratory, thoracic and mediastinal disorders	Epiglottic cyst	Epiglottic cyst
Respiratory, thoracic and mediastinal disorders	Epiglottic erythema	Epiglottic erythema
Respiratory, thoracic and mediastinal disorders	Epiglottic mass	Epiglottic mass
Respiratory, thoracic and mediastinal disorders	Epiglottic oedema	Epiglottic oedema
Respiratory, thoracic and mediastinal disorders	Epiglottic oedema	Epiglottic edema
Respiratory, thoracic and mediastinal disorders	Epiglottis ulcer	Epiglottis ulcer
Respiratory, thoracic and mediastinal disorders	Epistaxis	Bleeding nose
Respiratory, thoracic and mediastinal disorders	Epistaxis	Epistaxis
Respiratory, thoracic and mediastinal disorders	Epistaxis	Haemorrhage nasal
Respiratory, thoracic and mediastinal disorders	Epistaxis	Hemorrhage nasal
Respiratory, thoracic and mediastinal disorders	Epistaxis	Nasal bleeding
Respiratory, thoracic and mediastinal disorders	Epistaxis	Nasal mucus blood tinged
Respiratory, thoracic and mediastinal disorders	Epistaxis	Nose bleed
Respiratory, thoracic and mediastinal disorders	Epistaxis	Nose bleeds
Respiratory, thoracic and mediastinal disorders	Epistaxis	Nosebleed
Respiratory, thoracic and mediastinal disorders	Epistaxis	Chronic epistaxis
Respiratory, thoracic and mediastinal disorders	Intranasal hypoaesthesia	Intranasal numbness
Respiratory, thoracic and mediastinal disorders	Intranasal hypoaesthesia	Intranasal hypoaesthesia

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Upper Respiratory Tract Disorders (HLT) (Exclude Infections)		
Respiratory, thoracic and mediastinal disorders	Intranasal hypoaesthesia	Intranasal hypoesthesia
Respiratory, thoracic and mediastinal disorders	Intranasal paraesthesia	Intranasal paraesthesia
Respiratory, thoracic and mediastinal disorders	Intranasal paraesthesia	Intranasal paresthesia
Respiratory, thoracic and mediastinal disorders	Laryngeal cyst	Laryngeal cyst
Respiratory, thoracic and mediastinal disorders	Laryngeal disorder	Laryngeal disorder NOS
Respiratory, thoracic and mediastinal disorders	Laryngeal disorder	Unspecified disease of larynx
Respiratory, thoracic and mediastinal disorders	Laryngeal disorder	Laryngeal disorder
Respiratory, thoracic and mediastinal disorders	Laryngeal dyspnoea	Laryngeal dyspnoea
Respiratory, thoracic and mediastinal disorders	Laryngeal dyspnoea	Laryngeal dyspnea
Respiratory, thoracic and mediastinal disorders	Laryngeal erythema	Laryngeal erythema
Respiratory, thoracic and mediastinal disorders	Laryngeal haematoma	Laryngeal haematoma
Respiratory, thoracic and mediastinal disorders	Laryngeal haematoma	Laryngeal hematoma
Respiratory, thoracic and mediastinal disorders	Laryngeal haematoma	Glottic haematoma
Respiratory, thoracic and mediastinal disorders	Laryngeal haematoma	Glottic hematoma
Respiratory, thoracic and mediastinal disorders	Laryngeal haemorrhage	Laryngeal haemorrhage
Respiratory, thoracic and mediastinal disorders	Laryngeal haemorrhage	Laryngeal hemorrhage
Respiratory, thoracic and mediastinal disorders	Laryngeal haemorrhage	Laryngeal bleeding
Respiratory, thoracic and mediastinal disorders	Laryngeal hypertrophy	Laryngeal hypertrophy
Respiratory, thoracic and mediastinal disorders	Laryngeal infiltration	Laryngeal infiltration NOS
Respiratory, thoracic and mediastinal disorders	Laryngeal infiltration	Laryngeal infiltration

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Upper Respiratory Tract Disorders (HLT) (Exclude Infections)		
Respiratory, thoracic and mediastinal disorders	Laryngeal inflammation	Laryngeal inflammation
Respiratory, thoracic and mediastinal disorders	Laryngeal inflammation	Laryngeal mucositis
Respiratory, thoracic and mediastinal disorders	Laryngeal leukoplakia	Laryngeal leukoplakia
Respiratory, thoracic and mediastinal disorders	Laryngeal leukoplakia	Laryngeal leucoplakia
Respiratory, thoracic and mediastinal disorders	Laryngeal mass	Laryngeal mass
Respiratory, thoracic and mediastinal disorders	Laryngeal necrosis	Laryngeal necrosis
Respiratory, thoracic and mediastinal disorders	Laryngeal necrosis	Laryngeal chondronecrosis
Respiratory, thoracic and mediastinal disorders	Laryngeal obstruction	Laryngeal obstruction
Respiratory, thoracic and mediastinal disorders	Laryngeal obstruction	Subglottic obstruction
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Edema glottis
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Edema larynx
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Edema of larynx
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Edema vocal cord
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Glottic edema
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Glottic oedema
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Laryngeal edema
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Laryngeal oedema
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Larynx edema
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Larynx oedema
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Oedema of larynx

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Upper Respiratory Tract Disorders (HLT) (Exclude Infections)		
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Subglottic edema
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Subglottic oedema
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Vocal cord edema
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Vocal cord oedema
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Oedema glottis
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Oedema larynx
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Oedema vocal cord
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Aryepiglottis edema
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Aryepiglottis oedema
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Acute laryngeal edema
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	Acute laryngeal oedema
Respiratory, thoracic and mediastinal disorders	Laryngeal polyp	Laryngeal polyp
Respiratory, thoracic and mediastinal disorders	Laryngeal stenosis	Laryngeal stenosis
Respiratory, thoracic and mediastinal disorders	Laryngeal stenosis	Laryngeal stricture
Respiratory, thoracic and mediastinal disorders	Laryngeal stenosis	Stenosis of larynx
Respiratory, thoracic and mediastinal disorders	Laryngeal stenosis	Subglottic stenosis
Respiratory, thoracic and mediastinal disorders	Laryngeal stenosis	Supraglottic stenosis
Respiratory, thoracic and mediastinal disorders	Laryngeal ulceration	Laryngeal ulceration
Respiratory, thoracic and mediastinal disorders	Laryngeal ulceration	Larynx ulcer
Respiratory, thoracic and mediastinal disorders	Laryngeal ulceration	Larynx ulceration

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Upper Respiratory Tract Disorders (HLT) (Exclude Infections)		
Respiratory, thoracic and mediastinal disorders	Laryngeal ventricle prolapse	Laryngeal ventricle prolapse
Respiratory, thoracic and mediastinal disorders	Laryngitis allergic	Laryngitis allergic
Respiratory, thoracic and mediastinal disorders	Laryngospasm	Glottic spasm
Respiratory, thoracic and mediastinal disorders	Laryngospasm	Laryngeal spasm
Respiratory, thoracic and mediastinal disorders	Laryngospasm	Laryngismus
Respiratory, thoracic and mediastinal disorders	Laryngospasm	Laryngospasm
Respiratory, thoracic and mediastinal disorders	Laryngospasm	Larynx muscle hypersensitive
Respiratory, thoracic and mediastinal disorders	Laryngospasm	Spasm glottis
Respiratory, thoracic and mediastinal disorders	Laryngospasm	Spasm larynx
Respiratory, thoracic and mediastinal disorders	Larynx irritation	Larynx irritation
Respiratory, thoracic and mediastinal disorders	Larynx irritation	Larynx itching
Respiratory, thoracic and mediastinal disorders	Maxillary sinus pseudocyst	Maxillary sinus pseudocyst
Respiratory, thoracic and mediastinal disorders	Nasal cavity mass	Nasal cavity mass
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Congestion nasal
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Nasal congestion
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Nasal stuffiness
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Nose congestion
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Rhinitis medicamentosa
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Rhinitis medicamentous
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Nasal mucosal swelling

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Upper Respiratory Tract Disorders (HLT) (Exclude Infections)		
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Chronic nasal congestion
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Acute nasal congestion
Respiratory, thoracic and mediastinal disorders	Nasal cyst	Nasal cyst
Respiratory, thoracic and mediastinal disorders	Nasal cyst	Intranasal cyst
Respiratory, thoracic and mediastinal disorders	Nasal disorder	Nasal disorder NOS
Respiratory, thoracic and mediastinal disorders	Nasal disorder	Nasal disorder
Respiratory, thoracic and mediastinal disorders	Nasal dryness	Dry nose
Respiratory, thoracic and mediastinal disorders	Nasal dryness	Nasal dryness
Respiratory, thoracic and mediastinal disorders	Nasal dryness	Nose dry feeling of
Respiratory, thoracic and mediastinal disorders	Nasal dryness	Nose dryness
Respiratory, thoracic and mediastinal disorders	Nasal inflammation	Nasal inflammation
Respiratory, thoracic and mediastinal disorders	Nasal inflammation	Nasal septal inflammation
Respiratory, thoracic and mediastinal disorders	Nasal inflammation	Nasal mucosal inflammation
Respiratory, thoracic and mediastinal disorders	Nasal mucosa atrophy	Nasal mucosa atrophy
Respiratory, thoracic and mediastinal disorders	Nasal mucosal discolouration	Nasal mucosal discolouration
Respiratory, thoracic and mediastinal disorders	Nasal mucosal discolouration	Nasal mucosal discoloration
Respiratory, thoracic and mediastinal disorders	Nasal mucosal discolouration	Nasal mucosal pallor
Respiratory, thoracic and mediastinal disorders	Nasal mucosal disorder	Nasal mucosal disorder NOS
Respiratory, thoracic and mediastinal disorders	Nasal mucosal disorder	Nasal mucosal disorder
Respiratory, thoracic and mediastinal disorders	Nasal mucosal disorder	Nasal mucosal erythema

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Upper Respiratory Tract Disorders (HLT) (Exclude Infections)		
Respiratory, thoracic and mediastinal disorders	Nasal mucosal disorder	Nasal mucosal hyperaemia
Respiratory, thoracic and mediastinal disorders	Nasal mucosal disorder	Nasal mucosal ulcer
Respiratory, thoracic and mediastinal disorders	Nasal mucosal disorder	Nasal mucosal hyperemia
Respiratory, thoracic and mediastinal disorders	Nasal mucosal hypertrophy	Nasal mucosal hypertrophy
Respiratory, thoracic and mediastinal disorders	Nasal necrosis	Nasal mucosal necrosis
Respiratory, thoracic and mediastinal disorders	Nasal necrosis	Nasal necrosis
Respiratory, thoracic and mediastinal disorders	Nasal necrosis	Necrosis nasal
Respiratory, thoracic and mediastinal disorders	Nasal necrosis	Nasal septal mucosa necrosis
Respiratory, thoracic and mediastinal disorders	Nasal odour	Nasal odour
Respiratory, thoracic and mediastinal disorders	Nasal odour	Nasal odor
Respiratory, thoracic and mediastinal disorders	Nasal oedema	Nasal oedema
Respiratory, thoracic and mediastinal disorders	Nasal oedema	Nose edema
Respiratory, thoracic and mediastinal disorders	Nasal oedema	Nose oedema
Respiratory, thoracic and mediastinal disorders	Nasal oedema	Nasal turbinate edema
Respiratory, thoracic and mediastinal disorders	Nasal oedema	Nasal edema
Respiratory, thoracic and mediastinal disorders	Nasal oedema	Nasal turbinate oedema
Respiratory, thoracic and mediastinal disorders	Nasal polyps	Nasal polyp
Respiratory, thoracic and mediastinal disorders	Nasal polyps	Nasal polyps
Respiratory, thoracic and mediastinal disorders	Nasal polyps	Polyp of nasal cavity
Respiratory, thoracic and mediastinal disorders	Nasal polyps	Polyps nasal

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Upper Respiratory Tract Disorders (HLT) (Exclude Infections)		
Respiratory, thoracic and mediastinal disorders	Nasal polyps	Unspecified nasal polyp
Respiratory, thoracic and mediastinal disorders	Nasal polyps	Hyperplastic nasal polyp
Respiratory, thoracic and mediastinal disorders	Nasal polyps	Choanal polyp
Respiratory, thoracic and mediastinal disorders	Nasal septum disorder	Nasal septum disorder
Respiratory, thoracic and mediastinal disorders	Nasal septum disorder	Nasal septum disorder NOS
Respiratory, thoracic and mediastinal disorders	Nasal septum disorder	Nasal septal erythema
Respiratory, thoracic and mediastinal disorders	Nasal septum perforation	Nasal septum perforation
Respiratory, thoracic and mediastinal disorders	Nasal septum perforation	Perforation nasal septum
Respiratory, thoracic and mediastinal disorders	Nasal septum ulceration	Nasal septum ulceration
Respiratory, thoracic and mediastinal disorders	Nasal turbinate abnormality	Nasal turbinate abnormality
Respiratory, thoracic and mediastinal disorders	Nasal turbinate hypertrophy	Hypertrophy of nasal turbinates
Respiratory, thoracic and mediastinal disorders	Nasal turbinate hypertrophy	Nasal turbinate hypertrophy
Respiratory, thoracic and mediastinal disorders	Nasal turbinate hypertrophy	Concha bullosa
Respiratory, thoracic and mediastinal disorders	Nasal ulcer	Nasal ulcer
Respiratory, thoracic and mediastinal disorders	Oropharyngeal spasm	Oropharyngeal spasm
Respiratory, thoracic and mediastinal disorders	Oropharyngeal spasm	Spasm oropharyngeal
Respiratory, thoracic and mediastinal disorders	Oropharyngeal swelling	Oropharyngeal swelling
Respiratory, thoracic and mediastinal disorders	Paranasal cyst	Paranasal sinus mucocoele
Respiratory, thoracic and mediastinal disorders	Paranasal cyst	Paranasal cyst
Respiratory, thoracic and mediastinal disorders	Paranasal cyst	Paranasal sinus mucocele

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Upper Respiratory Tract Disorders (HLT) (Exclude Infections)		
Respiratory, thoracic and mediastinal disorders	Paranasal sinus haematoma	Maxillary sinus haematoma
Respiratory, thoracic and mediastinal disorders	Paranasal sinus haematoma	Maxillary sinus hematoma
Respiratory, thoracic and mediastinal disorders	Paranasal sinus haematoma	Paranasal sinus haematoma
Respiratory, thoracic and mediastinal disorders	Paranasal sinus haematoma	Paranasal sinus hematoma
Respiratory, thoracic and mediastinal disorders	Paranasal sinus hypersecretion	Paranasal sinus hypersecretion
Respiratory, thoracic and mediastinal disorders	Paranasal sinus hypersecretion	Nasal sinus discharge
Respiratory, thoracic and mediastinal disorders	Paranasal sinus mucosal hypertrophy	Paranasal sinus mucosal hypertrophy
Respiratory, thoracic and mediastinal disorders	Paranasal sinus necrosis	Paranasal sinus necrosis
Respiratory, thoracic and mediastinal disorders	Pharyngeal cyst	Pharyngeal cyst
Respiratory, thoracic and mediastinal disorders	Pharyngeal disorder	Pharyngeal disorder NOS
Respiratory, thoracic and mediastinal disorders	Pharyngeal disorder	Unspecified disease of pharynx
Respiratory, thoracic and mediastinal disorders	Pharyngeal disorder	Nasopharyngeal disorder
Respiratory, thoracic and mediastinal disorders	Pharyngeal disorder	Pharyngeal disorder
Respiratory, thoracic and mediastinal disorders	Pharyngeal dyskinesia	Pharyngeal dyskinesia
Respiratory, thoracic and mediastinal disorders	Pharyngeal enanthema	Pharyngeal enanthema
Respiratory, thoracic and mediastinal disorders	Pharyngeal erosion	Pharyngeal erosion
Respiratory, thoracic and mediastinal disorders	Pharyngeal erythema	Pharynx redness of
Respiratory, thoracic and mediastinal disorders	Pharyngeal erythema	Red throat
Respiratory, thoracic and mediastinal disorders	Pharyngeal erythema	Pharyngeal erythema
Respiratory, thoracic and mediastinal disorders	Pharyngeal erythema	Uvular erythema

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Upper Respiratory Tract Disorders (HLT) (Exclude Infections)		
Respiratory, thoracic and mediastinal disorders	Pharyngeal exudate	Pharyngeal exudate
Respiratory, thoracic and mediastinal disorders	Pharyngeal fistula	Pharyngeal fistula
Respiratory, thoracic and mediastinal disorders	Pharyngeal haematoma	Pharyngeal haematoma
Respiratory, thoracic and mediastinal disorders	Pharyngeal haematoma	Pharyngeal hematoma
Respiratory, thoracic and mediastinal disorders	Pharyngeal haemorrhage	Haemorrhage from throat
Respiratory, thoracic and mediastinal disorders	Pharyngeal haemorrhage	Haemorrhage pharyngeal
Respiratory, thoracic and mediastinal disorders	Pharyngeal haemorrhage	Hemorrhage from throat
Respiratory, thoracic and mediastinal disorders	Pharyngeal haemorrhage	Pharyngeal haemorrhage
Respiratory, thoracic and mediastinal disorders	Pharyngeal haemorrhage	Hemorrhage pharyngeal
Respiratory, thoracic and mediastinal disorders	Pharyngeal haemorrhage	Pharyngeal hemorrhage
Respiratory, thoracic and mediastinal disorders	Pharyngeal haemorrhage	Oropharyngeal hemorrhage
Respiratory, thoracic and mediastinal disorders	Pharyngeal haemorrhage	Oropharyngeal haemorrhage
Respiratory, thoracic and mediastinal disorders	Pharyngeal haemorrhage	Pharyngeal bleeding
Respiratory, thoracic and mediastinal disorders	Pharyngeal hypertrophy	Pharyngeal hypertrophy
Respiratory, thoracic and mediastinal disorders	Pharyngeal hypoaesthesia	Pharyngeal hypoaesthesia
Respiratory, thoracic and mediastinal disorders	Pharyngeal hypoaesthesia	Numbness throat
Respiratory, thoracic and mediastinal disorders	Pharyngeal hypoaesthesia	Pharyngeal hypoesthesia
Respiratory, thoracic and mediastinal disorders	Pharyngeal inflammation	Pharyngeal inflammation
Respiratory, thoracic and mediastinal disorders	Pharyngeal inflammation	Pharyngeal mucositis
Respiratory, thoracic and mediastinal disorders	Pharyngeal lesion	Pharyngeal lesion

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Upper Respiratory Tract Disorders (HLT) (Exclude Infections)		
Respiratory, thoracic and mediastinal disorders	Pharyngeal leukoplakia	Pharyngeal leukoplakia
Respiratory, thoracic and mediastinal disorders	Pharyngeal mass	Pharyngeal mass
Respiratory, thoracic and mediastinal disorders	Pharyngeal mucosa atrophy	Pharyngeal mucosa atrophy
Respiratory, thoracic and mediastinal disorders	Pharyngeal necrosis	Pharyngeal necrosis
Respiratory, thoracic and mediastinal disorders	Pharyngeal oedema	Edema pharynx
Respiratory, thoracic and mediastinal disorders	Pharyngeal oedema	Oedema pharynx
Respiratory, thoracic and mediastinal disorders	Pharyngeal oedema	Pharyngeal oedema
Respiratory, thoracic and mediastinal disorders	Pharyngeal oedema	Pharynx edema
Respiratory, thoracic and mediastinal disorders	Pharyngeal oedema	Throat edema
Respiratory, thoracic and mediastinal disorders	Pharyngeal oedema	Throat oedema
Respiratory, thoracic and mediastinal disorders	Pharyngeal oedema	Throat swelling
Respiratory, thoracic and mediastinal disorders	Pharyngeal oedema	Throat swelling non-specific
Respiratory, thoracic and mediastinal disorders	Pharyngeal oedema	Throat swelling NOS
Respiratory, thoracic and mediastinal disorders	Pharyngeal oedema	Pharyngeal edema
Respiratory, thoracic and mediastinal disorders	Pharyngeal oedema	Pharynx oedema
Respiratory, thoracic and mediastinal disorders	Pharyngeal polyp	Pharyngeal polyp
Respiratory, thoracic and mediastinal disorders	Pharyngeal stenosis	Pharyngeal stenosis
Respiratory, thoracic and mediastinal disorders	Pharyngeal ulceration	Pharyngeal ulceration
Respiratory, thoracic and mediastinal disorders	Reflux laryngitis	Laryngopharyngeal reflux
Respiratory, thoracic and mediastinal disorders	Reflux laryngitis	Reflux laryngitis

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Upper Respiratory Tract Disorders (HLT) (Exclude Infections)		
Respiratory, thoracic and mediastinal disorders	Rhinitis allergic	Allergic rhinitis
Respiratory, thoracic and mediastinal disorders	Rhinitis allergic	Allergic rhinitis (excl hay fever)
Respiratory, thoracic and mediastinal disorders	Rhinitis allergic	Atopic rhinitis
Respiratory, thoracic and mediastinal disorders	Rhinitis allergic	Rhinitis allergic
Respiratory, thoracic and mediastinal disorders	Rhinitis allergic	Rhinitis allergic atopic
Respiratory, thoracic and mediastinal disorders	Rhinitis allergic	Rhinitis allergic NOS
Respiratory, thoracic and mediastinal disorders	Rhinitis atrophic	Atrophic rhinitis
Respiratory, thoracic and mediastinal disorders	Rhinitis atrophic	Ozena
Respiratory, thoracic and mediastinal disorders	Rhinitis atrophic	Rhinitis atrophic
Respiratory, thoracic and mediastinal disorders	Rhinitis atrophic	Dry rhinitis
Respiratory, thoracic and mediastinal disorders	Rhinitis hypertrophic	Rhinitis hypertrophic
Respiratory, thoracic and mediastinal disorders	Rhinitis perennial	Perennial allergic rhinitis
Respiratory, thoracic and mediastinal disorders	Rhinitis perennial	Perennial rhinitis
Respiratory, thoracic and mediastinal disorders	Rhinitis perennial	Rhinitis perennial
Respiratory, thoracic and mediastinal disorders	Rhinitis seasonal	Allergic rhinitis due to pollen
Respiratory, thoracic and mediastinal disorders	Rhinitis seasonal	Rhinitis seasonal
Respiratory, thoracic and mediastinal disorders	Rhinitis seasonal	Seasonal allergic rhinitis
Respiratory, thoracic and mediastinal disorders	Rhinitis seasonal	Seasonal rhinitis
Respiratory, thoracic and mediastinal disorders	Rhinitis ulcerative	Rhinitis ulcerative
Respiratory, thoracic and mediastinal disorders	Rhinolithiasis	Rhinolithiasis

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Upper Respiratory Tract Disorders (HLT) (Exclude Infections)		
Respiratory, thoracic and mediastinal disorders	Rhinolithiasis	Nasal calculus
Respiratory, thoracic and mediastinal disorders	Sinus congestion	Nasal sinus congestion
Respiratory, thoracic and mediastinal disorders	Sinus congestion	Sinus congestion
Respiratory, thoracic and mediastinal disorders	Sinus disorder	Sinus disorder NOS
Respiratory, thoracic and mediastinal disorders	Sinus disorder	Sinus disorder
Respiratory, thoracic and mediastinal disorders	Sinus perforation	Perforation of sinus
Respiratory, thoracic and mediastinal disorders	Sinus perforation	Sinus perforation
Respiratory, thoracic and mediastinal disorders	Sinus polyp	Antral polyp (of maxillary sinus)
Respiratory, thoracic and mediastinal disorders	Sinus polyp	Maxillary sinus polyp
Respiratory, thoracic and mediastinal disorders	Sinus polyp	Sinus polyp
Respiratory, thoracic and mediastinal disorders	Sinus polyp degeneration	Polypoid sinus degeneration
Respiratory, thoracic and mediastinal disorders	Sinus polyp degeneration	Sinus polyp degeneration
Respiratory, thoracic and mediastinal disorders	Sinusitis noninfective	Sinusitis noninfective
Respiratory, thoracic and mediastinal disorders	Stridor	Stridor
Respiratory, thoracic and mediastinal disorders	Stridor	Stridor inspiratory
Respiratory, thoracic and mediastinal disorders	Tonsillar atrophy	Tonsillar atrophy
Respiratory, thoracic and mediastinal disorders	Tonsillar atrophy	Submerged tonsil
Respiratory, thoracic and mediastinal disorders	Tonsillar disorder	Chronic tonsillar disease
Respiratory, thoracic and mediastinal disorders	Tonsillar disorder	Tonsillar disorder
Respiratory, thoracic and mediastinal disorders	Tonsillar disorder	Cryptic tonsil

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Upper Respiratory Tract Disorders (HLT) (Exclude Infections)		
Respiratory, thoracic and mediastinal disorders	Tonsillar haemorrhage	Tonsillar haemorrhage
Respiratory, thoracic and mediastinal disorders	Tonsillar haemorrhage	Tonsillar hemorrhage
Respiratory, thoracic and mediastinal disorders	Tonsillar haemorrhage	Tonsillar bleeding
Respiratory, thoracic and mediastinal disorders	Tonsillar hypertrophy	Tonsillar hypertrophy
Respiratory, thoracic and mediastinal disorders	Tonsillar hypertrophy	Enlarged tonsils
Respiratory, thoracic and mediastinal disorders	Tonsillar inflammation	Tonsillar inflammation
Respiratory, thoracic and mediastinal disorders	Tonsillar ulcer	Tonsillar ulcer
Respiratory, thoracic and mediastinal disorders	Tonsillolith	Tonsillolith
Respiratory, thoracic and mediastinal disorders	Vasomotor rhinitis	Vasomotor rhinitis
Respiratory, thoracic and mediastinal disorders	Velopharyngeal incompetence	Velopharyngeal incompetence
Respiratory, thoracic and mediastinal disorders	Vocal cord atrophy	Vocal cord atrophy
Respiratory, thoracic and mediastinal disorders	Vocal cord cyst	Vocal cord cyst
Respiratory, thoracic and mediastinal disorders	Vocal cord disorder	Vocal cord disorder NOS
Respiratory, thoracic and mediastinal disorders	Vocal cord disorder	Vocal cord dysfunction
Respiratory, thoracic and mediastinal disorders	Vocal cord disorder	Vocal cord disorder
Respiratory, thoracic and mediastinal disorders	Vocal cord inflammation	Vocal cord inflammation
Respiratory, thoracic and mediastinal disorders	Vocal cord leukoplakia	Vocal cord leukoplakia
Respiratory, thoracic and mediastinal disorders	Vocal cord polyp	Polyp of vocal cord
Respiratory, thoracic and mediastinal disorders	Vocal cord polyp	Vocal cord polyp
Respiratory, thoracic and mediastinal disorders	Vocal cord thickening	Singers nodules

System Organ Class	Preferred Term	Lowest Level Term
Route of Administration: Upper Respiratory Tract Disorders (HLT) (Exclude Infections)		
Respiratory, thoracic and mediastinal disorders	Vocal cord thickening	Vocal cord thickening
Respiratory, thoracic and mediastinal disorders	Vocal cord thickening	Vocal cord nodule

Table 16: AEs Related to Taste and Smell Disorders (SMQ)

System Organ Class	Preferred Term	Lowest Level Term
Taste and Smell Disorders (SMQ)		
Nervous system disorders	Dysgeusia	After taste
Nervous system disorders	Ageusia	Ageusia
Nervous system disorders	Parosmia	Altered smell sensation
Nervous system disorders	Anosmia	Anosmia
Nervous system disorders	Dysgeusia	Dysgeusia
Nervous system disorders	Parosmia	Dysosmia
Nervous system disorders	Parosmia	Dysosmia NOS
Nervous system disorders	Parosmia	Faint odor of sulfur
Nervous system disorders	Hypogeusia	Gustatory sense diminished
Psychiatric disorders	Hallucination, gustatory	Hallucination gustatory
Psychiatric disorders	Hallucination, olfactory	Hallucination olfactory
Psychiatric disorders	Hallucination, gustatory	Hallucination, gustatory
Psychiatric disorders	Hallucination, olfactory	Hallucination, olfactory
Nervous system disorders	Parosmia	Hyperosmia
Nervous system disorders	Hypogeusia	Hypogeusia
Nervous system disorders	Anosmia	Loss of smell
Nervous system disorders	Ageusia	Loss of taste
Psychiatric disorders	Hallucination, olfactory	Olfactory hallucination
Nervous system disorders	Dysgeusia	Parageusia
Nervous system disorders	Parosmia	Parosmia
Nervous system disorders	Parosmia	Perversion olfactory
Nervous system disorders	Parosmia	Smell alteration
Nervous system disorders	Parosmia	Smell change
Nervous system disorders	Anosmia	Smell loss
Nervous system disorders	Parosmia	Smell perversion
Nervous system disorders	Parosmia	Smelly sensation
Nervous system disorders	Parosmia	Strange smell sensation
Nervous system disorders	Dysgeusia	Taste abnormality
Nervous system disorders	Ageusia	Taste absent

System Organ Class	Preferred Term	Lowest Level Term
Taste and Smell Disorders (SMQ)		
Nervous system disorders	Dysgeusia	Taste alteration
Nervous system disorders	Dysgeusia	Taste altered
Nervous system disorders	Dysgeusia	Taste bitter
Nervous system disorders	Dysgeusia	Taste bitter-salty
Nervous system disorders	Dysgeusia	Taste changed
Nervous system disorders	Hypogeusia	Taste diminished
Nervous system disorders	Dysgeusia	Taste disturbance
Nervous system disorders	Dysgeusia	Taste garlic
Nervous system disorders	Ageusia	Taste loss
Nervous system disorders	Dysgeusia	Taste metallic
Nervous system disorders	Dysgeusia	Taste peculiar
Nervous system disorders	Dysgeusia	Taste perversion
Nervous system disorders	Dysgeusia	Taste salty
Nervous system disorders	Dysgeusia	Taste sour
Nervous system disorders	Dysgeusia	Taste sweet
Nervous system disorders	Dysgeusia	Bilious taste
Nervous system disorders	Parosmia	Cacosmia
Nervous system disorders	Hyposmia	Hyposmia
Nervous system disorders	Parosmia	Faint odour of sulfur
Nervous system disorders	Olfactory nerve disorder	Olfactory nerve disorder
Investigations	Olfactory test abnormal	Olfactory test abnormal
Investigations	Olfactory test abnormal	Olfactory acuity test abnormal
Nervous system disorders	Hyposmia	Diminished sense of smell
Investigations	Gustometry abnormal	Gustometry abnormal
General disorders and administration site conditions	Product taste abnormal	Medication after taste
Nervous system disorders	Parosmia	Phantosmia
Nervous system disorders	Parosmia	Olfactism
Nervous system disorders	Hypergeusia	Hypergeusia
Nervous system disorders	Dysgeusia	Chalky taste

Table 17: AEs Related to Depression and Suicidality/Self-Injury-Depression (SMQ) (Exclude Suicide/Self-Injury)

Preferred Term	Lowest Level Term
Depression and Suicide/Self-Injury: Depression (SMQ) (Exclude Suicide/Self-Injury)	
Activation syndrome	Activation syndrome
Adjustment disorder with depressed mood	Adjustment disorder with depressed mood

Preferred Term	Lowest Level Term
Depression and Suicide/Self-Injury: Depression (SMQ) (Exclude Suicide/Self-Injury)	
Adjustment disorder with depressed mood	Adjustment reaction with brief depressive reaction
Adjustment disorder with depressed mood	Adjustment reaction with prolonged depressive reaction
Adjustment disorder with mixed anxiety and depressed mood	Adjustment disorder with mixed anxiety and depressed mood
Agitated depression	Agitated depression
Agitated depression	Depression agitated
Anhedonia	Anhedonia
Anhedonia	Loss of all pleasure
Antidepressant therapy	Antidepressant therapy
Childhood depression	Childhood depression
Decreased interest	Decreased interest
Decreased interest	Loss of all interest
Decreased interest	Loss of interest
Decreased interest	Reduced interest in usual activities
Depressed mood	Chronic depressive mood
Depressed mood	Dejection emotional
Depressed mood	Depressed mood
Depressed mood	Emotional dejection
Depressed mood	Feeling blue
Depressed mood	Feeling down
Depressed mood	Feeling sad
Depressed mood	Low mood
Depressed mood	Mood depression
Depressed mood	Mood depressions
Depressed mood	Unhappiness
Depression	Acute depression
Depression	Anxiety depression
Depression	Anxiodepressive syndrome
Depression	Anxious depression
Depression	Atypical depressive disorder
Depression	Brief depressive reaction
Depression	Chronic depression
Depression	Depressed reaction
Depression	Depressed state
Depression	Depression
Depression	Depression aggravated
Depression	Depression functional
Depression	Depression mental

Preferred Term	Lowest Level Term
Depression and Suicide/Self-Injury: Depression (SMQ) (Exclude Suicide/Self-Injury)	
Depression	Depression NOS
Depression	Depression reactive
Depression	Depression worsened
Depression	Depressive disorder
Depression	Depressive episode
Depression	Depressive illness
Depression	Depressive reaction
Depression	Depressive state
Depression	Depressive stupor
Depression	Exogenous depression
Depression	Mixed anxiety & depressive
Depression	Reactive depression
Depression	Recurrent depressive disorder
Depression	Unipolar depression
Depression	Unipolar depressive illness
Depression postoperative	Depression postoperative
Depression postoperative	Postoperative depression
Depressive symptoms	Depressive symptoms
Depressive symptoms	Depressive symptoms aggravvated
Dysphoria	Dysphoria
Dysthymic disorder	Chronic depressive personality disorder
Dysthymic disorder	Depression neurotic
Dysthymic disorder	Depressive neurosis
Dysthymic disorder	Depressive personality disorder
Dysthymic disorder	Dysthymia
Dysthymic disorder	Dysthymic disorder
Dysthymic disorder	Neurotic depression
Electroconvulsive therapy	Bilateral ECT
Electroconvulsive therapy	ECT
Electroconvulsive therapy	ECT (electro-convulsive therapy)
Electroconvulsive therapy	Electroconvulsive therapy
Electroconvulsive therapy	Modified ECT
Electroconvulsive therapy	Unilateral ECT
Electroconvulsive therapy	Unmodified ECT
Feeling guilty	Feeling guilty
Feeling guilty	Feeling remorse
Feeling of despair	Feeling of despair
Feelings of worthlessness	Feelings of worthlessness

Preferred Term	Lowest Level Term
Depression and Suicide/Self-Injury: Depression (SMQ) (Exclude Suicide/Self-Injury)	
Major depression	Depression endogenous
Major depression	Depression psychotic
Major depression	Depressive type psychosis
Major depression	Endogenous depression
Major depression	Involutional depression
Major depression	Involutional melancholia
Major depression	Major depression
Major depression	Major depressive disorder aggravated
Major depression	Major depressive disorder NOS
Major depression	Major depressive disorder with melancholic features
Major depression	Major depressive disorder, recurrent episode
Major depression	Major depressive disorder, recurrent episode, in full remission
Major depression	Major depressive disorder, single episode
Major depression	Major depressive disorder, single episode in full remission
Major depression	Major depressive illness
Major depression	Melancholia
Major depression	Melancholic depression
Major depression	Psychosis depressive
Major depression	Psychotic depression
Menopausal depression	Depression perimenopausal
Menopausal depression	Depression postmenopausal
Menopausal depression	Menopausal depression
Menopausal depression	Postmenopausal depression
Post stroke depression	Post stroke depression
Postictal depression	Postictal depression
Postpartum depression	Baby blues
Postpartum depression	Depression puerperal
Postpartum depression	Postnatal blues
Postpartum depression	Postnatal depression (excl psychosis)
Postpartum depression	Postpartum depression
Postpartum depression	Puerperal depression
Postpartum depression	Transitory postpartum mood disturbance
Affect lability	Affect lability
Affect lability	Affective incontinence
Affect lability	Emotional incontinence
Affect lability	Emotional instability
Affect lability	Emotional lability

Preferred Term	Lowest Level Term
Depression and Suicide/Self-Injury: Depression (SMQ) (Exclude Suicide/Self-Injury)	
Affect lability	Instability emotional
Affect lability	Labile affect
Affect lability	Lability emotional
Affect lability	Mental lability symptom
Affect lability	Pseudobulbar affect
Alcohol abuse	Alcohol abuse
Alcohol abuse	Alcohol abuse chronic
Alcohol abuse	Alcohol abuse, continuous drinking behavior
Alcohol abuse	Alcohol abuse, continuous drinking behaviour
Alcohol abuse	Alcohol abuse, episodic drinking behavior
Alcohol abuse	Alcohol abuse, episodic drinking behaviour
Alcohol abuse	Alcohol abuse, in remission
Alcohol abuse	Alcohol abuse, unspecified drinking behavior
Alcohol abuse	Alcohol abuse, unspecified drinking behaviour
Alcohol abuse	Nondependent abuse of alcohol
Alcohol poisoning	Acute alcoholic intoxication
Alcohol poisoning	Acute alcoholic intoxication in alcoholism, continuous drinking behavior
Alcohol poisoning	Acute alcoholic intoxication in alcoholism, continuous drinking behaviour
Alcohol poisoning	Acute alcoholic intoxication in alcoholism, episodic drinking behavior
Alcohol poisoning	Acute alcoholic intoxication in alcoholism, episodic drinking behaviour
Alcohol poisoning	Acute alcoholic intoxication in alcoholism, in remission
Alcohol poisoning	Acute alcoholic intoxication in alcoholism, unspecified drinking behavior
Alcohol poisoning	Acute alcoholic intoxication in alcoholism, unspecified drinking behaviour
Alcohol poisoning	Alcohol intoxication
Alcohol poisoning	Alcohol intoxication acute
Alcohol poisoning	Alcohol intoxication, acute
Alcohol poisoning	Alcohol poisoning
Alcohol poisoning	Drunkenness
Alcohol poisoning	Toxic effect of alcohol
Alcohol poisoning	Toxic effect of ethyl alcohol
Alcohol poisoning	Toxic effect of fusel oil
Alcohol poisoning	Toxic effect of isopropyl alcohol
Alcohol poisoning	Toxic effect of methyl alcohol

Preferred Term	Lowest Level Term
Depression and Suicide/Self-Injury: Depression (SMQ) (Exclude Suicide/Self-Injury)	
Alcohol poisoning	Toxic effect of unspecified alcohol
Alcohol problem	Alcohol problem
Alcohol problem	Alcohol problem NOS
Alcohol rehabilitation	Alcohol rehabilitation
Alcoholism	Alcohol addiction
Alcoholism	Alcohol craving
Alcoholism	Alcohol dependence syndrome
Alcoholism	Alcoholic relapse
Alcoholism	Alcoholism
Alcoholism	Alcoholism (excl psychosis)
Alcoholism	Chronic alcoholism
Alcoholism	Dipsomania
Apathy	Ambition loss of
Apathy	Apathy
Apathy	Avolition
Apathy	Initiative loss of
Apathy	Lack of motivation
Apathy	Loss of ambition
Apathy	Loss of initiative
Blunted affect	Affective blunting
Blunted affect	Blunted affect
Constricted affect	Constricted affect
Constricted affect	Restricted affect
Crying	Crying
Crying	Crying abnormal
Crying	Crying uncontrollable
Crying	High-pitched crying
Crying	Inconsolable crying
Crying	Persistent crying
Crying	Uncontrollable crying
Crying	Weeping
Crying	Weepy
Disturbance in attention	Attention concentration difficulty
Disturbance in attention	Attention impaired
Disturbance in attention	Attentiveness decreased
Disturbance in attention	Concentration (mental) abnormal
Disturbance in attention	Concentration ability impaired
Disturbance in attention	Concentration impaired

Preferred Term	Lowest Level Term
Depression and Suicide/Self-Injury: Depression (SMQ) (Exclude Suicide/Self-Injury)	
Disturbance in attention	Concentration impairment
Disturbance in attention	Concentration loss
Disturbance in attention	Disturbance in attention
Disturbance in attention	Impairment of attention
Disturbance in attention	Mental concentration decreased
Disturbance in attention	Mental concentration difficult
Disturbance in attention	Mental concentration difficulty
Disturbance in attention	Mental concentration impaired
Disturbance in attention	Poor concentration
Disturbance in attention	Simple disturbance of activity and attention
Disturbance in attention	Vigilance decreased
Dyssomnia	Dysfunctions associated with sleep stages or arousal from sleep
Dyssomnia	Dyssomnia
Dyssomnia	Dyssomnia NOS
Emotional distress	Embarrassment
Emotional distress	Emotional distress
Emotional distress	Humiliation
Emotional distress	Mental distress
Emotional distress	Suffering
Emotional poverty	Emotional poverty
Emotional poverty	Emotional withdrawal
Emotional poverty	Lack of feeling emotions
Emotional poverty	Poverty emotional
Emotional poverty	Withdrawal emotional
Hypersomnia	Hypersomnia
Hypersomnia	Idiopathic hypersomnia
Hypersomnia	Persistent disorder of initiating or maintaining wakefulness
Hypersomnia	Primary hypersomnia
Hypersomnia	Sleep excessive
Hypersomnia	Transient disorder of initiating or maintaining wakefulness
Hyposomnia	Hyposomnia
Impaired self-care	Impaired self-care
Initial insomnia	Initial insomnia
Initial insomnia	Trouble falling asleep
Intentional product misuse	Intentional drug misuse
Intentional product misuse	Intentional misuse

Preferred Term	Lowest Level Term
Depression and Suicide/Self-Injury: Depression (SMQ) (Exclude Suicide/Self-Injury)	
Intentional product misuse	Intentional misuse by dose change
Intentional product misuse	Intentional misuse in dosing frequency
Intentional product misuse	Intentional product misuse
Intentional product use issue	Intentional dose decrease
Intentional product use issue	Intentional dose increase
Intentional product use issue	Intentional product use issue
Intentional product use issue	Intentional use beyond labeled administration duration
Intentional product use issue	Intentional use beyond labeled duration
Intentional product use issue	Intentional use beyond labelled administration duration
Intentional product use issue	Intentional use beyond labelled duration
Intentional product use issue	Intentional use by incorrect route
Intentional product use issue	Intentional use for unlabeled indication
Intentional product use issue	Intentional use for unlabelled indication
Listless	Listless
Listless	Listlessness
Maternal use of illicit drugs	Maternal use of illicit drugs
Memory impairment	Forgetfulness
Memory impairment	Hypomnesia
Memory impairment	Memory deficit
Memory impairment	Memory disturbance
Memory impairment	Memory disturbance (excl dementia)
Memory impairment	Memory impaired
Memory impairment	Memory impairment
Memory impairment	Short-term memory impairment
Middle insomnia	Arousal night
Middle insomnia	Middle insomnia
Middle insomnia	Nocturnal awakening
Middle insomnia	Sleep maintenance insomnia
Mood altered	Affect alteration
Mood altered	Affect altered
Mood altered	Altered mood
Mood altered	Bad mood
Mood altered	Mood alteration NOS
Mood altered	Mood altered
Mood altered	Mood change
Mood swings	Mood swings
Mood swings	Mood variable
Morose	Morose

Preferred Term	Lowest Level Term
Depression and Suicide/Self-Injury: Depression (SMQ) (Exclude Suicide/Self-Injury)	
Morose	Moroseness
Negative thoughts	Negative thoughts
Neglect of personal appearance	Appearance personal neglect of
Neglect of personal appearance	Neglect of person appearance
Neglect of personal appearance	Neglect of personal appearance
Neglect of personal appearance	Personal appearance neglect of
Poor quality sleep	Light sleep
Poor quality sleep	Poor quality sleep
Poor quality sleep	Poor sleep
Poor quality sleep	Sleep restless
Poor quality sleep	Sleep unwell
Poor quality sleep	Wakefulness
Psychomotor hyperactivity	Activity motor exaggerated
Psychomotor hyperactivity	Behavior hyperactive
Psychomotor hyperactivity	Behaviour hyperactive
Psychomotor hyperactivity	Hyperactive
Psychomotor hyperactivity	Hyperactivity
Psychomotor hyperactivity	Increased activity
Psychomotor hyperactivity	Irritable hyperkinesis
Psychomotor hyperactivity	Motor activity exaggerated
Psychomotor hyperactivity	Muscular hyperactivity
Psychomotor hyperactivity	Overactive
Psychomotor hyperactivity	Overactivity
Psychomotor hyperactivity	Psychomotor agitation
Psychomotor hyperactivity	Psychomotor excitability
Psychomotor hyperactivity	Psychomotor hyperactivity
Psychomotor retardation	Psychomotor retardation
Psychosocial support	Psychosocial counseling
Psychosocial support	Psychosocial support
Psychotherapy	Art therapy
Psychotherapy	Cognitive psychotherapy
Psychotherapy	Couples psychotherapy
Psychotherapy	Family psychotherapy
Psychotherapy	Group psychotherapy
Psychotherapy	Hippotherapy
Psychotherapy	Interpersonal psychotherapy
Psychotherapy	Play therapy
Psychotherapy	Psychotherapy

Preferred Term	Lowest Level Term
Depression and Suicide/Self-Injury: Depression (SMQ) (Exclude Suicide/Self-Injury)	
Psychotherapy	Supportive psychotherapy
Self esteem decreased	Self esteem decreased
Substance-induced mood disorder	Stimulant-induced mood disorder
Substance-induced mood disorder	Substance-induced mood disorder
Tearfulness	Tearfulness
Terminal insomnia	Awakening early
Terminal insomnia	Early morning awakening
Terminal insomnia	Terminal insomnia

Table 18: AEs Related to Depression and Suicidality/Self-Injury-Suicide/Self-Injury (SMQ)

Preferred Term	Lowest Level Term
Depression and Suicide/Self-Injury: Suicide/Self-Injury (SMQ)	
Columbia suicide severity rating scale abnormal	Columbia suicide severity rating scale abnormal
Completed suicide	Accomplished suicide
Completed suicide	Completed suicide
Completed suicide	Suicide
Completed suicide	Suicide (accomplished)
Depression suicidal	Depression suicidal
Depression suicidal	Suicidal depression
Intentional overdose	Deliberate overdose
Intentional overdose	Drug overdose deliberate self-inflicted
Intentional overdose	Intentional overdose
Intentional overdose	Multiple drug overdose intentional
Intentional overdose	Non-accidental overdose
Intentional overdose	Overdose deliberate self-inflicted
Intentional overdose	Overdose intentional
Intentional self-injury	Deliberate self-harm
Intentional self-injury	Deliberate self-injury
Intentional self-injury	Intentional self-injury
Intentional self-injury	Parasuicide
Intentional self-injury	Repeated parasuicide
Intentional self-injury	Self inflicted laceration
Intentional self-injury	Self mutilation
Attempted suicide	Deliberate poisoning
Attempted suicide	Poisoning deliberate
Poisoning deliberate	Poisoning deliberate

Preferred Term	Lowest Level Term
Depression and Suicide/Self-Injury: Suicide/Self-Injury (SMQ)	
Poisoning deliberate	Poisoning deliberate self-inflicted
Self injurious behaviour	Self injurious behavior
Self injurious behaviour	Self injurious behavior without suicidal intent
Self injurious behaviour	Self injurious behaviour
Self injurious behaviour	Self injurious behaviour without suicidal intent
Self-injurious ideation	Self-injurious ideation
Self-injurious ideation	Thoughts of self harm
Suicidal behaviour	Preparatory actions toward imminent suicidal behavior
Suicidal behaviour	Preparatory actions toward imminent suicidal behaviour
Suicidal behaviour	Suicidal behavior
Suicidal behaviour	Suicidal behaviour
Suicidal behaviour	Suicide gesture
Suicidal ideation	Active suicidal ideation
Suicidal ideation	Death wishes
Suicidal ideation	Life weariness
Suicidal ideation	Passive suicidal ideation
Suicidal ideation	Suicidal ideation
Suicidal ideation	Suicidal intention
Suicidal ideation	Suicidal plans
Suicidal ideation	Suicidal tendency
Suicide attempt	Attempted suicide
Suicide attempt	Suicide attempt
Suicide attempt	Suicide attempt other than overdose
Suicide attempt	Unsuccessful suicide