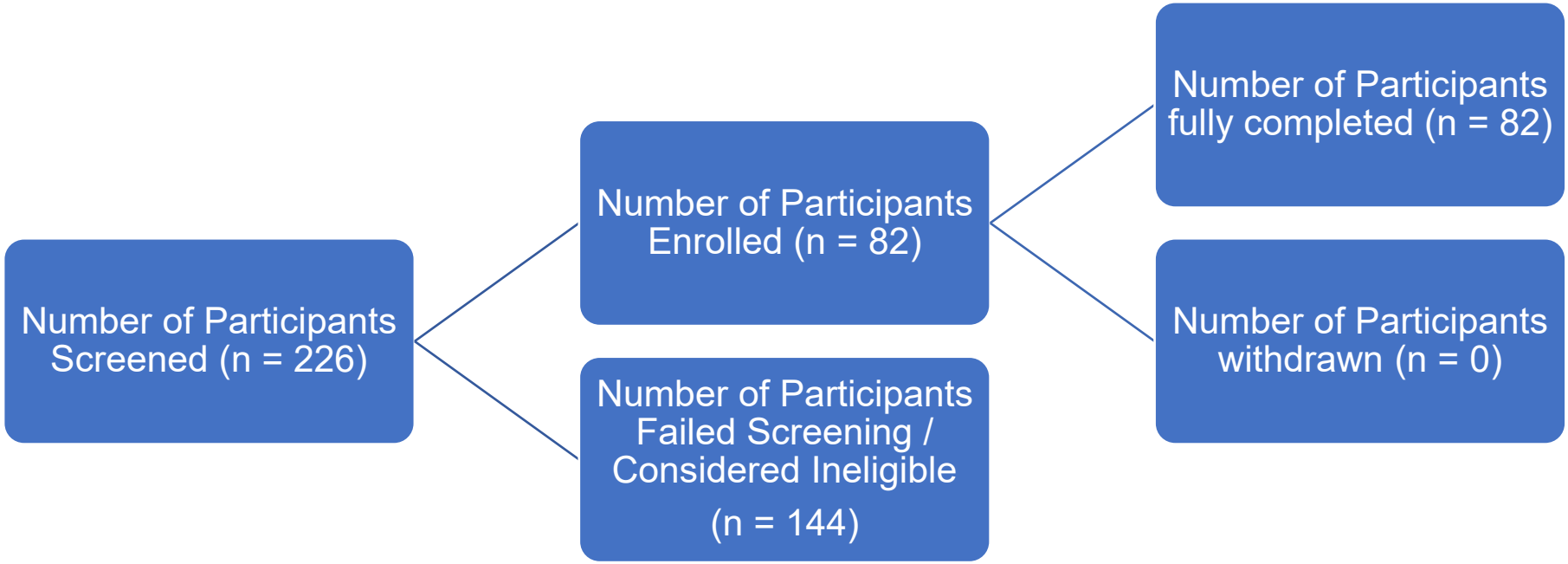
Participant Flow



Baseline Characteristics

Table 11.2.1 Summary of Participant Demographics (Safety Set) – Single Ascending Dose

Parameter	Statistic	Placebo (Swallow) (N=8)	Placebo (Mouth-hold) (N=6)	C1: KH-001 0.5 mg (N=6)	C 2: KH-001 2.5 mg (N=6)	C3: KH-001 12.5 mg (N=6)	C4: KH-001 62.5 mg (N=6)	C5: KH-001 5 mg (N=6)	C6: KH-001 7.5 mg (N=6)	C7: KH-001 15 mg (N=6)	KH-001 Overall (N=42)	Overall (N=56)
Height (m)	N	8	6	6	6	6	6	6	6	6	42	56
	Mean	1.808	1.770	1.802	1.787	1.787	1.828	1.833	1.758	1.745	1.791	1.791
	SD	0.0759	0.0518	0.0354	0.0809	0.0528	0.0527	0.0650	0.0483	0.0501	0.0608	0.0618
Weight (kg)	N	8	6	6	6	6	6	6	6	6	42	56
	Mean	86.39	83.25	79.60	76.67	80.18	81.97	89.57	77.43	79.83	80.75	81.82
	SD	7.844	10.321	13.744	8.772	8.781	16.171	4.925	6.702	9.626	10.462	10.161
BMI (kg/m^2)	N	8	6	6	6	6	6	6	6	6	42	56
	Mean	26.471	26.515	24.460	24.042	25.245	24.503	26.665	25.093	26.173	25.169	25.499
	SD	2.1848	2.6775	3.6754	2.4943	3.6677	4.5086	1.2138	2.6043	2.4712	3.0130	2.8914
Age (yrs)	N	8	6	6	6	6	6	6	6	6	42	56
	Mean	40.5	28.5	32.7	40.2	34.0	33.3	39.7	43.2	29.2	36.0	35.9
	SD	8.25	9.38	9.29	11.97	12.03	13.60	13.52	13.63	10.59	12.20	11.69
Gender:												
Male	N (%)	8 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	42 (100.0)	56 (100.0)
Ethnicity:												
Not Hispanic or Latino	N (%)	8 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	5 (83.3)	6 (100.0)	6 (100.0)	41 (97.6)	55 (98.2)
Hispanic or Latino	N (%)	0	0	0	0	0	0	1 (16.7)	0	0	1 (2.4)	1 (1.8)
Race:												
Black Or African American	N (%)	0	0	2 (33.3)	0	1 (16.7)	0	0	0	2 (33.3)	5 (11.9)	5 (8.9)
Asian	N (%)	0	1 (16.7)	0	0	0	1 (16.7)	0	1 (16.7)	0	2 (4.8)	3 (5.4)
White	N (%)	8 (100.0)	5 (83.3)	4 (66.7)	6 (100.0)	5 (83.3)	5 (83.3)	5 (83.3)	4 (66.7)	4 (66.7)	33 (78.6)	46 (82.1)
Mixed	N (%)	0	0	0	0	0	0	1 (16.7)	1 (16.7)	0	2 (4.8)	2 (3.6)

Treatment: Single dose of KH-001 besylate oral solution or placebo in the fasted state, administered using the 3-minute mouth-holding method for Cohort 5 onwards. Percentages calculated from the number of participants in the Safety Set within a treatment group.
BMI = body mass index, C = cohort SD = standard deviation
Data Source: Table 14.1.2.1

Table 11.2.2 Summary of Participant Demographics (Safety Set) – Multiple Ascending Dose

Parameter	Statistic	Placebo (N=6)	C1: KH-001 10 mg (N=6)	C2: KH-001 12.5 mg (N=6)	KH-001 Overall (N=12)	Overall (N=18)
Height (m)	N	6	6	6	12	18
	Mean	1.838	1.762	1.762	1.762	1.787
	SD	0.0898	0.0387	0.0578	0.0469	0.0719
Weight (kg)	N	6	6	6	12	18
	Mean	89.25	80.15	81.13	80.64	83.51
	SD	9.958	11.315	8.113	9.401	10.188
BMI (kg/m^2)	N	6	6	6	12	18
	Mean	26.367	25.753	26.237	25.995	26.119
	SD	1.3512	2.8233	3.3138	2.9459	2.4869
Age (yrs)	N	6	6	6	12	18
	Mean	35.0	33.8	36.0	34.9	34.9
	SD	11.92	8.98	9.78	9.02	9.72
Gender: Male	N (%)	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	18 (100.0)
Ethnicity: Not Hispanic or Latino	N (%)	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	18 (100.0)
Race: White	N (%)	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	18 (100.0)

Treatment: Once daily dosing of KH-001 besylate oral solution or placebo administered using the 3-minute mouth- holding method, in the fasted state for 5 days.Percentages calculated from the number of dosed participants within a treat ment group. BMI = body mass index, C = cohort SD = standard deviation
Data Source: Table 14.1.2.1

Table 11.2.3 Summary of Participant Demographics (Safety Set) – Formulation Effect

Parameter	Statistic	Overall (N=8)
Height (m)	N	8
	Mean	1.740
	SD	0.0460
Weight (kg)	N	8
	Mean	83.61
	SD	8.228
BMI (kg/m^2)	N	8
	Mean	27.568
	SD	1.7383
Age (yrs)	N	8
	Mean	40.6
	SD	8.33
Gender: Male	N (%)	8 (100.0)
Ethnicity: Not Hispanic Or Latino	N (%)	8 (100.0)
Race: White	N (%)	8 (100.0)

Treatment: Single ascending dose of KH-001 besylate ODT administered over two treatment periods in the fasted state. Percentages calculated from the number of dosed participants within a treatment group.
BMI = body mass index. ODT = orodispersible tablet, SD = standard deviation
Data Source: Table 14.1.2.1

Outcome Measures

Table 11.4.1 Derived KH-001 PK Parameters (PK Set) – Single Ascending Dose

Treatment	Summary Statistic	C_{max} (ng/mL)	T_{max} (h)[1]	$AUC_{(0-t)}$ (h*ng/mL)
Cohort 3:	N	6	6	6
12.5 mg	Geo. Mean	0.495	0.5	0.401
KH-001 (N=6)	Geo. CV%	42.6	(0.25-1.0)	47.3
Cohort 4:	N	6	6	6
62.5 mg	Geo. Mean	1.27	0.5	1.84
KH-001 (N=6)	Geo. CV%	70.4	(0.25-1.0)	32.3
Cohort 5:	N	6	6	6
5 mg	Geo. Mean	2.41	0.25	1.78
KH-001 (N=6)	Geo. CV%	66.4	(0.208-0.5)	47.1
Cohort 6:	N	6	6	6
7.5 mg	Geo. Mean	2.84	0.375	2.72
KH-001 (N=6)	Geo. CV%	87.4	(0.25-0.53)	40.8
Cohort 7:	N	6	6	6
15 mg	Geo. Mean	4.74	0.25	3.78
KH-001 (N=6)	Geo. CV%	45.9	(0.125-0.5)	31.2

Treatment: Single dose of KH-001 besylate oral solution or placebo in the fasted state, administered using the 3-minute mouth-holding method for Cohort 5 onwards.
Plasma KH-001 concentrations for Cohorts 1 and 2 are not presented due to having no quantifiable plasma concentrations reported.
Data Source: Table 14.4.2.1

Table 11.4.11 Derived KH-001 PK Parameters (PK Set) – Multiple Ascending Dose

Day 1:

Treatment	Summary Statistic	C_{max} (ng/mL)	T_{max} (h)[1]	$AUC_{(0\text{-}tau)}$ (h*ng/mL)
Cohort 1: **10 mg KH-001 (N=6)**	N Geo. Mean Geo. CV%	6 3.69 88.8	6 0.250 (0.250-0.50)	6 2.93 54.6
Cohort 2: **12.5 mg KH-001 (N=6)**	N Geo. Mean Geo. CV%	6 3.95 57.7	6 0.229 (0.167- 0.50)	6 3.12 54.9

Day 5:

Treatment	Summary Statistic	C_{max} (ng/mL)	T_{max} (h)[1]	$AUC_{(0\text{-}t)}$ (h*ng/mL)
Cohort 1: **10 mg KH-001 (N=6)**	N Geo. Mean Geo. CV%	6 2.58 57.9	6 0.375 (0.208-0.517)	6 2.36 31.8
Cohort 2: **12.5 mg KH-001 (N=6)**	N Geo. Mean Geo. CV%	6 2.41 72.6	6 0.375 (0.250-0.517)	6 2.10 87.5

Treatment: Once daily dosing of KH-001 besylate oral solution or placebo administered using the 3-minute mouth-holding method, in the fasted state for 5 days.
Data Source: Table 14.4.2.1, Table 14.4.2.2

Table 11.4.21 Derived KH-001 PK Parameters (PK Set) - Formulation Effect

Treatment	Summary Statistic	C_{max} (ng/mL)	T_{max} (h)[1]	$AUC_{(0-t)}$ (h*ng/mL)
KH-001 5 mg (N=8))	N	8	8	8
	Geo. Mean	3.90	0.188	2.25
	Geo. CV%	61.1	(0.167-0.25)	49.9
KH-001 10 mg (N=8)	N	8	8	8
	Geo. Mean	8.73	0.208	4.72
	Geo. CV%	62.3	(0.125-0.50)	53.5

Treatment: Single ascending dose of KH-001 besylate ODT administered over two treatment periods in the fasted state.
Data Source: Table 14.4.2.1

Adverse Events

There were no SAEs, severe TEAEs or TEAEs leading to death or withdrawal during the study. In addition, it is noted that there were no clinically significant changes from baseline with respect to any of the primary safety endpoints i.e., laboratory safety testing, vital signs or ECG.

Single Ascending Dose (SAD): A total of 16 TEAEs were reported by 13 (23.2%) participants. All were mild, with the highest percentage of participants (16.1%) reporting events that were considered to be of reasonable possible relationship to IMP. The most commonly reported related (of reasonable possible relationship to IMP) TEAE was nausea (7.1%) followed by vomiting (5.4%), dizziness (3.6%), and pre-syncope (3.6%).

In the immediate swallow cohorts (Cohorts 1 to 4), a higher % of participants reported TEAEs at the 62.5 mg dose level when compared to placebo, 0.5, 2,5 and 12.5 mg doses (66.7% vs 12.5%, 33.3%, 0%, 16.7% respectively). This is likely driven by the increased incidence of related gastrointestinal events (nausea and vomiting) in this cohort. It should also be noted that vomiting events were only observed in the immediate swallow cohorts.

In the 3-minute mouth-hold cohorts (Cohort 5 onwards), a higher % of participants reported TEAEs at the 15 mg dose level when compared to placebo, 5 and 7.5 mg dose levels (83.3% vs 0% (for 5 and 7.5 mg doses respectively). This is likely driven by the increased incidence of related gastrointestinal events (nausea) and nervous system disorders (dizziness and pre-syncope) in this cohort. It should also be noted that related nervous system disorders events were only observed in the 3-minute mouth-hold cohorts. All events resolved.

Multiple Ascending Dose (MAD): A total of 7 TEAEs were reported by 5 (27.8%) participants. All were mild or moderate (moderate events had no reasonable possible relationship to IMP), with the highest percentage of participants (16.7%) reporting events that were considered to be of no reasonable possible relationship to IMP. The most commonly reported related (of reasonable possible relationship to IMP) TEAE was dizziness (11.1%), followed by nausea (5.6%) and somnolence (5.6%). There were no treatment or dose-related trends/changes in any TEAE profile with the oral solution of KH-001. All events resolved.

Formulation Effect: A total of 4 TEAEs were reported by 3 (37.5%) participants. All were mild or moderate (moderate events had no reasonable possible relationship to IMP), with the highest percentage of participants (25.0%) reporting events that were considered to be of reasonable possible relationship to IMP. Nausea and dizziness were the only related (of reasonable possible relationship to IMP) TEAEs reported, each was reported by 1 (12.5%) participant overall. There were no dose-related trends/changes in any TEAE profile with the ODT formulation of KH-001. All events resolved.

Table 12.2.1 Overall Summary of TEAEs by Severity and Relationship (Safety Set) – Single Ascending Dose

	Placebo (Swallow) (N=8)	Placebo (Mouth-hold) (N=6)	C1: KH-001 0.5 mg (N=6)	C2: KH-001 2.5 mg (N=6)	C3: KH-001 12.5 mg (N=6)	C4: KH-001 62.5 mg (N=6)	C5: KH-001 5 mg (N=6)	C6: KH-001 7.5 mg (N=6)	C7: KH-001 15 mg (N=6)	KH-001 Overall (N=42)	Overall (N=56)
Number of TEAEs	1	0	2	0	1	5	0	0	7	15	16
Number of Study Drug-Related TEAEs	0	0	0	0	1	4	0	0	6	11	11
Number (%) of participants reporting at least one:											
TEAE	1 (12.5)	0	2 (33.3)	0	1 (16.7)	4 (66.7)	0	0	5 (83.3)	12 (28.6)	13 (23.2)
Serious TEAE	0	0	0	0	0	0	0	0	0	0	0
TEAE Leading to Withdrawal	0	0	0	0	0	0	0	0	0	0	0
TEAE Leading to Death	0	0	0	0	0	0	0	0	0	0	0
Number (%) of participants with TEAE by severity:											
Mild	1 (12.5)	0	2 (33.3)	0	1 (16.7)	4 (66.7)	0	0	5 (83.3)	12 (28.6)	13 (23.2)
Moderate	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0
Number (%) of participants with TEAE by relationship to study drug:											
Reasonable Possibility	0	0	0	0	1 (16.7)	4 (66.7)	0	0	4 (66.7)	9 (21.4)	9 (16.1)
No Reasonable Possibility	1 (12.5)	0	2 (33.3)	0	0	1 (16.7)	0	0	1 (16.7)	4 (9.5)	5 (8.9)

Treatment: Single dose of KH-001 besylate oral solution or placebo in the fasted state, administered using the 3-minute mouth-holding method for Cohort 5 onwards. A participant with multiple adverse events is counted only once at the maximum level of severity or the strongest relationship to study drug within a treatment.
Percentages calculated from the number of participants in the Safety Set within a treatment group. Study drug-related defined as having a relationship of Reasonable Possibility.
C = cohort, TEAE = treatment-emergent adverse event
Data Source: Table 14.3.1.1

Table 12.2.2 Overall Summary of TEAEs by Severity and Relationship (Safety Set) – Multiple Ascending Dose

	Placebo (N=6)	C1: KH-001 10 mg (N=6)	C2: KH-001 12.5 mg (N=6)	KH-001 Overall (N=12)	Overall (N=18)
Number of TEAEs	2	0	5	5	7
Number of Study Drug-Related TEAEs	0	0	4	4	4
Number (%) of participants reporting at least one:					
TEAE	2 (33.3)	0	3 (50.0)	3 (25.0)	5 (27.8)
Serious TEAE	0	0	0	0	0
TEAE Leading to Withdrawal	0	0	0	0	0
TEAE Leading to Death	0	0	0	0	0
Number (%) of participants with TEAE by severity:					
Mild	2 (33.3)	0	2 (33.3)	2 (16.7)	4 (22.2)
Moderate	0	0	1 (16.7)	1 (8.3)	1 (5.6)
Severe	0	0	0	0	0
Number (%) of participants with TEAE by relationship to study drug:					
Reasonable Possibility	0	0	2 (33.3)	2 (16.7)	2 (11.1)
No Reasonable Possibility	2 (33.3)	0	1 (16.7)	1 (8.3)	3 (16.7)

Treatment: Once daily dosing of KH-001 besylate oral solution or placebo administered using the 3-minute mouth-holding method, in the fasted state for 5 days. A participant with multiple adverse events is counted only once at the maximum level of severity or the strongest relationship to study drug within a treatment. Percentages calculated from the number of participants in the Safety Set within a treatment group.
Study drug-related defined as having a relationship of Reasonable Possibility. C = cohort, TEAE = treatment-emergent adverse event
Data Source: Table 14.3.1.1

Table 12.2.3 Overall Summary of TEAEs by Severity and Relationship (Safety Set) – Formulation Effect

	KH-001 5 mg (N=8)	KH-001 10 mg (N=8)	Overall (N=8)
Number of TEAEs	2	2	4
Number of Study Drug-Related TEAEs	2	1	3
Number (%) of participants reporting at least one:			
TEAE	2 (25.0)	2 (25.0)	3 (37.5)
Serious TEAE	0	0	0
TEAE Leading to Withdrawal	0	0	0
TEAE Leading to Death	0	0	0
Number (%) of participants with TEAE by severity:			
Mild	2 (25.0)	1 (12.5)	2 (25.0)
Moderate	0	1 (12.5)	1 (12.5)
Severe	0	0	0
Number (%) of participants with TEAE by relationship to study drug:			
Reasonable Possibility	2 (25.0)	1 (12.5)	2 (25.0)
No Reasonable Possibility	0	1 (12.5)	1 (12.5)

Treatment: Single ascending dose of KH-001 besylate ODT administered over two treatment periods in the fasted state.
A participant with multiple adverse events is counted only once at the maximum level of severity or the strongest relationship to study drug within a treatment. Percentages calculated from the number of participants in the Safety Set within a treatment.
Study drug-related defined as having a relationship of Reasonable Possibility. ODT = orodispersible tablet, TEAE = treatment-emergent adverse events
Data Source: Table 14.3.1.1