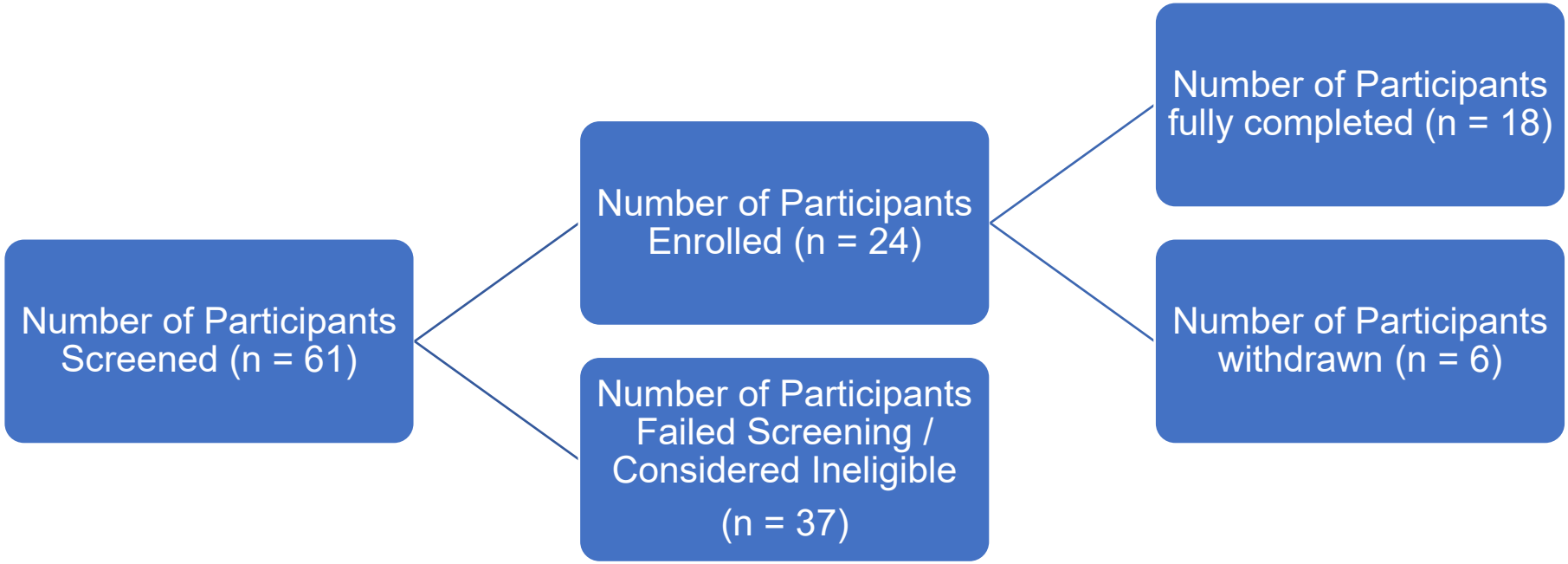
Participant Flow



Baseline Characteristics

Table 11.2.1 Summary of Participant Demographics (Safety Set) – Part 1a

Parameter	Statistic	Overall (N=10)
Height (m)	Mean	1.684
	SD	0.0696
Weight (kg)	Mean	72.07
	SD	11.969
BMI (kg/m^2)	Mean	25.25
	SD	2.341
Age at Informed Consent (yrs)	Mean	38.0
	SD	10.71
Gender:		
Male	n (%)	5 (50.0)
Female	n (%)	5 (50.0)
Race:		
Black	n (%)	1 (10.0)
Asian	n (%)	1 (10.0)
White	n (%)	8 (80.0)
Mixed	n (%)	0
Other	n (%)	0

Treatment: A single dose of adrenaline from ADD008 placed sublingually for 3 minutes (Test) or from EpiPen® Auto Injector Injector IM (Reference) over 6 treatment periods in an ascending dose sequence.
Percentages are based on the total number of participants in the Safety Set.
BMI = body mass index, IM = intramuscular
Data Source: Table 14.1.2.1

Table 11.2.2 Summary of Participant Demographics (Safety Set) – Part 1b

Parameter	Statistic	Overall (N=14)
Height (m)	Mean	1.772
	SD	0.0521
Weight (kg)	Mean	82.40
	SD	9.245
BMI (kg/m^2)	Mean	26.23
	SD	2.697
Age at Informed Consent (yrs)	Mean	39.0
	SD	9.72
Gender:		
Male	n (%)	12 (85.7)
Female	n (%)	2 (14.3)
Race:		
Black	n (%)	1 (7.1)
Asian	n (%)	0
White	n (%)	13 (92.9)
Mixed	n (%)	0
Other	n (%)	0

Treatment: A single dose of adrenaline from ADD008 placed sublingually for 20 minutes (Test) or from EpiPen® Auto Injector Injector IM (Reference) over 6 treatment periods in an ascending dose sequence.
Percentages are based on the total number of participants in the Safety Set.
BMI = body mass index, IM = intramuscular
Data Source: Table 14.1.2.1

Outcome Measures

Table 11.4.1 Summary of Derived Plasma Adrenaline (Baseline-Corrected) PK Parameters (PK Set) – Part 1a

Treatment	Summary Statistic	t_{lag} (min)	C_0 (pg/mL)	C_{max} (pg/mL)	T_{max} (min)	T_{max1} (min)	$t_{1/2}$ (min)	AUC_{0-10} (min*pg/mL)	AUC_{0-20} (min*pg/mL)	AUC_{0-30} (min*pg/mL)	AUC_{0-t} (min*pg/mL)	AUC_{0-inf} (min*pg/mL)	$AUC_{\%extrap}$ (%)
0.3 mg EpiPen (N=10)	n	10	10	10	10	10	4	9	10	10	10	4	4
	Geo. Mean	2.0[1]	33.7	431	15.0[1]	6.0[1]	106[2]	1950	3970	6150	16200	31400	40.9
	Geo. CV%	(0-10.0)[1]	NC	93.3	(2.0 – 30.0)[1]	(2.0 – 15.0)[1]	(100)[2]	96.7	56.0	41.3	70.6	88.6	15.6
2 mg ADD008 (N=9)	n	9	9	9	9	1	0	0	0	0	1	0	0
	Geo. Mean	0[1]	NC	132	0[1]	2.0[1]	NC[2]	NC	NC	NC	368	NC	NC
	Geo. CV%	(0 - 0)[1]	NC	NC	(0 – 2.0)[1]	(2.0 – 2.0)[1]	(NC)[2]	NC	NC	NC	NC	NC	NC
5 mg ADD008 (N=10)	n	10	10	10	10	2	0	1	2	2	2	0	0
	Geo. Mean	0[1]	NC	181	0[1]	9.5[1]	NC[2]	443	751	2050	4670	NC	NC
	Geo. CV%	(0 – 12.0)[1]	NC	28.4	(0 – 30.0)[1]	(4.0 – 15.0)[1]	(NC)[2]	NC	77.9	39.6	314.3	NC	NC
10 mg ADD008 (N=9)	n	9	9	9	9	1	0	0	1	2	4	0	0
	Geo. Mean	0[1]	NC	197	0[1]	12.0[1]	NC[2]	NC	1260	1970	10200	NC	NC
	Geo. CV%	(0 – 120)[1]	NC	81.3	(0 – 240)[1]	(12.0 – 12.0)[1]	(NC)[2]	NC	NC	220.7	104.6	NC	NC
20 mg ADD008 (N=9)	n	9	9	9	9	2	0	1	2	3	6	0	0
	Geo. Mean	12.0[1]	NC	214	60.0[1]	9.5[1]	NC[2]	482	717	1070	23000	NC	NC
	Geo. CV%	(0 – 120)[1]	NC	93.3	(0 – 240)[1]	(4.0 – 15.0)[1]	(NC)[2]	NC	7.3	63.7	75.1	NC	NC
30 mg ADD008 (N=9)	n	9	9	9	9	1	0	1	1	2	5	0	0
	Geo. Mean	4.0[1]	NC	185	20.0[1]	6.0[1]	NC[2]	217	929	1410	10000	NC	NC
	Geo. CV%	(0 – 120)[1]	NC	109.2	(0 – 240)[1]	(6.0 -6.0)[1]	(NC)[2]	NC	NC	62.1	276.3	NC	NC

[1] = Median (min—max) for t_{lag}, t_{max} and t_{max1}

[2] = Mean (SD) for $t_{1/2}$

Treatment: A single dose of adrenaline from ADD008 placed sublingually for 3 minutes (Test) or from EpiPen® Auto Injector IM (Reference) over 6 treatment periods in an ascending dose sequence.

LLOQ = 99.75 pg/mL. Values below LLOQ imputed as LLOQ/2 at pre-dose and for time points prior to the first quantifiable concentration, and missing for subsequent post-dose time points. Any negative results occurring as a result of baseline-correction were set to 0.

IM = intramuscular, LLOQ = lower limit of quantitation, NC = Non-calculable.

Data Source: Table 14.4.2.1

Table 11.4.4 Summary of Derived Plasma Adrenaline (Baseline-Corrected) PK Parameters (PK Set) – Part 1b

Treatment	Summary Statistic	t_{lag} (min)	C_0 (pg/mL)	C_{max} (pg/mL)	T_{max} (min)	T_{max1} (min)	$t_{1/2}$ (min)	AUC_{0-10} (min*pg/mL)	AUC_{0-20} (min*pg/mL)	AUC_{0-30} (min*pg/mL)	AUC_{0-t} (min*pg/mL)	AUC_{0-inf} (min*pg/mL)	$AUC_{\%extrap}$ (%)
0.3 mg EpiPen (N=9)	n	9	9	9	9	8	1	6	5	5	8	1	1
	Geo. Mean	2.0[1]	36.7	337	6.0[1]	6.0[1]	15.6[2]	2250	5620	8210	3340	9770	27.2
	Geo. CV%	(0 – 4.0)[1]	NC	82.1	(0 – 30.0)[1]	(4.0 – 10.0)[1]	(NC)[2]	77.3	41.5	33.6	375.1	NC	NC
2 mg ADD008 (N=10)	n	10	10	10	10	0	0	0	0	0	0	0	0
	Geo. Mean	0[1]	NC	NC	0[1]	NC[1]	NC[2]	NC	NC	NC	NC	NC	NC
	Geo. CV%	(0-0)[1]	NC	NC	(0-0)[1]	(NC)[1]	(NC)[2]	NC	NC	NC	NC	NC	NC
5 mg ADD008 (N=10)	n	10	10	10	10	0	0	0	0	0	0	0	0
	Geo. Mean	0[1]	NC	NC	0[1]	NC[1]	NC[2]	NC	NC	NC	NC	NC	NC
	Geo. CV%	(0-0)[1]	NC	NC	(0-0)[1]	(NC)[1]	(NC)[2]	NC	NC	NC	NC	NC	NC
10 mg ADD008 (N=10)	n	10	10	10	10	1	0	1	1	0	1	0	0
	Geo. Mean	0[1]	37.3	74.6	0[1]	10.0[1]	NC[2]	149	1410	NC	1410	NC	NC
	Geo. CV%	(0 – 8.0)[1]	NC	127.4	(0 – 10.0)[1]	(10.0 – 10.0)[1]	(NC)[2]	NC	NC	NC	NC	NC	NC
20 mg ADD008 (N=10)	n	10	10	10	10	1	0	0	1	2	2	0	0
	Geo. Mean	0[1]	NC	208	0[1]	15.0[1]	NC[2]	NC	1270	1620	24300	NC	NC
	Geo. CV%	(0 – 20.0)[1]	NC	35.2	(0 – 60.0)[1]	(15.0 – 15.0)[1]	(NC)[2]	NC	NC	85.5	90.1	NC	NC
30 mg ADD008 (N=10)	n	10	10	10	10	5	0	5	6	6	6	0	0
	Geo. Mean	0[1]	74.0	140	2.0[1]	12.0[1]	NC[2]	407	1250	2140	9240	NC	NC
	Geo. CV%	(0 – 12.0)[1]	NC	57.9	(0 – 240.0)[1]	(4.0 – 15.0)[1]	(NC)[2]	96.2	50.3	53.4	71.2	NC	NC

[1] = Median (min—max) for t_{lag}, t_{max} and t_{max1}

[2] = Mean (SD) for $t_{1/2}$

Treatment: A single dose of adrenaline from ADD008 placed sublingually for 3 minutes (Test) or from EpiPen® Auto Injector IM (Reference) over 6 treatment periods in an ascending dose sequence.

LLOQ = 99.16 pg/mL. Values below LLOQ imputed as LLOQ/2 at pre-dose and for time points prior to the first quantifiable concentration, and missing for subsequent post-dose time points. Any negative results occurring as a result of baseline-correction were set to 0.

IM = intramuscular, LLOQ = lower limit of quantitation, NC = Non-calculable.

Data Source: Table 14.4.2.1

Adverse Events

There were no severe TEAEs, SAEs or deaths during Part 1a or Part 1b of the study.

Part 1a: A total of 44 TEAEs were reported by 10 (100%) participants. All participants reported mild events considered of reasonable possible relationship to the IMP.

A higher percentage of participants reported TEAEs in the ADD008 treatment groups when compared to EpiPen® (100% vs 20%). This increase was dose-related and driven by a higher incidence of gastrointestinal disorders with increasing doses of ADD008. Indeed, the most common events overall were nausea (80% of participants), abdominal discomfort (70% of participants) and vomiting (70% of participants), only observed in the ADD008 treatment groups, all reported mild events considered related to IMP.

There was 1 withdrawal due to AEs during Part 1a. Drug was withdrawn from 1 participant (1005) in Part 1a for positive COVID test (mild, no relationship to IMP). The participant recovered from the event.

Part 1b: A total of 38 TEAEs were reported by 11 (78.6%) participants. The majority were mild and of reasonable possible relationship to the IMP.

A higher percentage of participants reported TEAEs in the ADD008 treatment groups when compared to EpiPen® (78.6% vs 14.3%). This increase was dose-related from 5 to 20 mg and driven by a higher incidence of gastrointestinal disorders with increasing doses of ADD008. At the 30 mg dose level, incidence of gastrointestinal TEAEs remained high at 70% participants, but lower than that observed at the 20 mg dose level (90% participants). Indeed, the most common events overall were abdominal discomfort (57.1% participants), vomiting (50% participants) and nausea (35.7% participants), only observed in the ADD008 treatment groups, all participants reported mild events considered related to IMP.

There was 1 withdrawal due to AEs during Part 1b of the study. Drug was withdrawn from 1 participant (1019) in Part 1b for influenza-like illness (moderate, no relationship to IMP). The participant recovered.

Table 12.2.1 Overall Summary of TEAEs by Severity and Relationship (Safety Set) – Part 1a

	0.3 mg EpiPen (N=10)	2 mg ADD008 (N=9)	5 mg ADD008 (N=10)	10 mg ADD008 (N=9)	20 mg ADD008 (N=9)	30 mg ADD008 (N=9)	ADD008 Overall (N=10)	Overall (N=10)
Number of TEAEs	3	0	7	7	11	16	41	44
Number of Study Drug-Related TEAEs[a]	1	0	5	7	11	16	39	40
Number (%) of participants reporting at least one:								
TEAE	2 (20.0)	0	4 (40.0)	4 (44.4)	8 (88.9)	9 (100.0)	10 (100.0)	10 (100.0)
Serious TEAE	0	0	0	0	0	0	0	0
TEAE Leading to Withdrawal	0	0	0	0	0	0	0	0
TEAE Leading to Death	0	0	0	0	0	0	0	0
Number (%) of participants with TEAE by severity:								
Mild	2 (20.0)	0	4 (40.0)	4 (44.4)	8 (88.9)	9 (100.0)	10 (100.0)	10 (100.0)
Moderate	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Number (%) of participants with TEAE by relationship to study drug:								
Reasonable Possibility	1 (10.0)	0	4 (40.0)	4 (44.4)	8 (88.9)	9 (100.0)	10 (100.0)	10 (100.0)
No Reasonable Possibility	1 (10.0)	0	0	0	0	0	0	0

Treatment: A single dose of adrenaline from ADD008 placed sublingually for 3 minutes (Test) or from EpiPen® Auto Injector IM (Reference) over 6 treatment periods in an ascending dose sequence.

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.
[a] Study Drug-Related defined as a causality of Reasonable Possibility.

IM = intramuscular, 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) – Part 1b

	0.3 mg EpiPen (N=14)	2 mg ADD008 (N=10)	5 mg ADD008 (N=10)	10 mg ADD008 (N=10)	20 mg ADD008 (N=10)	30 mg ADD008 (N=10)	ADD008 Overall (N=14)	Overall (N=14)
Number of TEAEs	2	2	1	6	18	9	36	38
Number of Study Drug-Related TEAEs[a]	1	1	1	6	14	8	30	31
Number (%) of participants reporting at least one:								
TEAE	2 (14.3)	2 (20.0)	1 (10.0)	4 (40.0)	9 (90.0)	7 (70.0)	11 (78.6)	11 (78.6)
Serious TEAE	0	0	0	0	0	0	0	0
TEAE Leading to Withdrawal	0	0	0	0	0	0	0	0
TEAE Leading to Death	0	0	0	0	0	0	0	0
Number (%) of participants with TEAE by severity:								
Mild	1 (7.1)	2 (20.0)	1 (10.0)	4 (40.0)	8 (80.0)	7 (70.0)	10 (71.4)	9 (64.3)
Moderate	1 (7.1)	0	0	0	1 (10.0)	0	1 (7.1)	2 (14.3)
Severe	0	0	0	0	0	0	0	0
Number (%) of participants with TEAE by relationship to study drug:								
Reasonable Possibility	1 (7.1)	1 (10.0)	1 (10.0)	4 (40.0)	9 (90.0)	7 (70.0)	11 (78.6)	11 (78.6)
No Reasonable Possibility	1 (7.1)	1 (10.0)	0	0	0	0	0	0

Treatment: A single dose of adrenaline from ADD008 placed sublingually for 20 minutes (Test) or from EpiPen® Auto Injector IM (Reference) over 6 treatment periods in an ascending dose sequence.

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.
[a] Study Drug-Related defined as a causality of Reasonable Possibility.

IM = intramuscular, TEAE = treatment emergent adverse event

Data Source: Table 14.3.1.1

Table 12.2.3 TEAEs in each Treatment Group by System Organ Class and Preferred Term (Safety Set) – Part 1a

	Number (%) of Participants							
SYSTEM ORGAN CLASS Preferred Term	**0.3 mg EpiPen (N=10)**	**2 mg ADD008 (N=9)**	**5 mg ADD008 (N=10)**	**10 mg ADD008 (N=9)**	**20 mg ADD008 (N=9)**	**30 mg ADD008 (N=9)**	**ADD008 Overall (N=10)**	**Overall (N=10)**
Number (%) of participants reporting at least one TEAE:	2 (20.0)	0	4 (40.0)	4 (44.4)	8 (88.9)	9 (100.0)	10 (100.0)	10 (100.0)
GASTROINTESTINAL DISORDERS:	**1 (10.0)**	**0 (0.0)**	**3 (30.0)**	**4 (44.4)**	**8 (88.9)**	**9 (100.0)**	**10 (100.0)**	**10 (100.0)**
Abdominal Discomfort	0 (0.0)	0 (0.0)	1 (10.0)	1 (11.1)	5 (55.6)	6 (66.7)	7 (70.0)	7 (70.0)
Nausea	0 (0.0)	0 (0.0)	3 (30.0)	4 (44.4)	3 (33.3)	4 (44.4)	8 (80.0)	8 (80.0)
Tongue Induration	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	2 (22.2)	5 (55.6)	7 (70.0)	7 (70.0)
INFECTIONS AND INFESTATIONS:	**1 (10.0)**	**0 (0.0)**	**1 (10.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (10.0)**	**2 (20.0)**
Gastroenteritis	1 (10.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	2 (20.0)
INVESTIGATIONS:	**0 (0.0)**	**0 (0.0)**	**1 (10.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (10.0)**	**1 (10.0)**
SARS-COV-2 Test Positive	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (10.0)
NERVOUS SYSTEM DISORDERS:	**1 (10.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (10.0)**
Dizziness	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS:	**0 (0.0)**	**0 (0.0)**	**1 (10.0)**	**0 (0.0)**	**1 (11.1)**	**0 (0.0)**	**2 (20.0)**	**2 (20.0)**
Oropharyngeal Discomfort	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	1 (11.1)	0 (0.0)	2 (20.0)	2 (20.0)

Treatment: A single dose of adrenaline from ADD008 placed sublingually for 3 minutes (Test) or from EpiPen® Auto Injector IM (Reference) over 6 treatment periods in an ascending dose sequence.
A participant is counted only once per SOC and preferred term within a treatment.

Percentages calculated from the number of participants in the Safety Set within a treatment.
MedDRA version 27.0.

IM = intramuscular, MedDRA = Medical Dictionary for Regulatory Activities, SOC = system organ class

Data Source: Table 14.3.1.1, Table 14.3.1.2

Table 12.2.4 TEAEs in each Treatment Group by System Organ Class and Preferred Term (Safety Set) – Part 1b

	Number (%) of Participants							
SYSTEM ORGAN CLASS Preferred Term	**0.3 mg EpiPen (N=14)**	**2 mg ADD008 (N=10)**	**5 mg ADD008 (N=10)**	**10 mg ADD008 (N=10)**	**20 mg ADD008 (N=10)**	**30 mg ADD008 (N=10)**	**ADD008 Overall (N=14)**	**Overall (N=14)**
Number (%) of participants reporting at least one TEAE:	2 (14.3)	2 (20.0)	1 (10.0)	4 (40.0)	9 (90.0)	7 (70.0)	11 (78.6)	11 (78.6)
GASTROINTESTINAL DISORDERS:	**0 (0.0)**	**1 (10.0)**	**1 (10.0)**	**4 (40.0)**	**9 (90.0)**	**7 (70.0)**	**11 (78.6)**	**11 (78.6)**
Abdominal Discomfort	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	7 (70.0)	2 (20.0)	8 (57.1)	8 (57.1)
Nausea	0 (0.0)	1 (10.0)	1 (10.0)	3 (30.0)	3 (30.0)	1 (10.0)	5 (35.7)	5 (35.7)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	2 (20.0)	3 (30.0)	5 (50.0)	7 (50.0)	7 (50.0)
GENERAL DISORDERS & ADMINISTRATION SITE CONDITIONS:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (10.0)**	**0 (0.0)**	**1 (7.1)**	**1 (7.1)**
Influenza Like Illness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	1 (7.1)	1 (7.1)
MUSCULOSKELETAL & CONNECTIVE TISSUE DISORDERS:	**0 (0.0)**	**1 (10.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (7.1)**	**1 (7.1)**
Myalgia	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (7.1)
NERVOUS SYSTEM DISORDERS:	**2 (14.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (10.0)**	**1 (10.0)**	**2 (14.3)**	**4 (28.6)**
Headache	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (10.0)	2 (14.3)	3 (21.4)
Tremor	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (10.0)**	**0 (0.0)**	**1 (7.1)**	**1 (7.1)**
Cough	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	1 (7.1)	1 (7.1)
VASCULAR DISORDERS:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (10.0)**	**0 (0.0)**	**1 (7.1)**	**1 (7.1)**
Hyperaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	1 (7.1)	1 (7.1)

Treatment: A single dose of adrenaline from ADD008 placed sublingually for 20 minutes (Test) or from EpiPen® Auto Injector IM (Reference) over 6 treatment periods in an ascending dose sequence.
A participant is counted only once per SOC and preferred term within a treatment.

Percentages calculated from the number of participants in the Safety Set within a treatment.
MedDRA version 27.0.

IM = intramuscular, MedDRA = Medical Dictionary for Regulatory Activities, SOC = system organ class

Data Source: Table 14.3.1.1, Table 14.3.1.2