A Phase Two, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of the Travelers' Diarrhea Vaccine System in Travelers to Asia

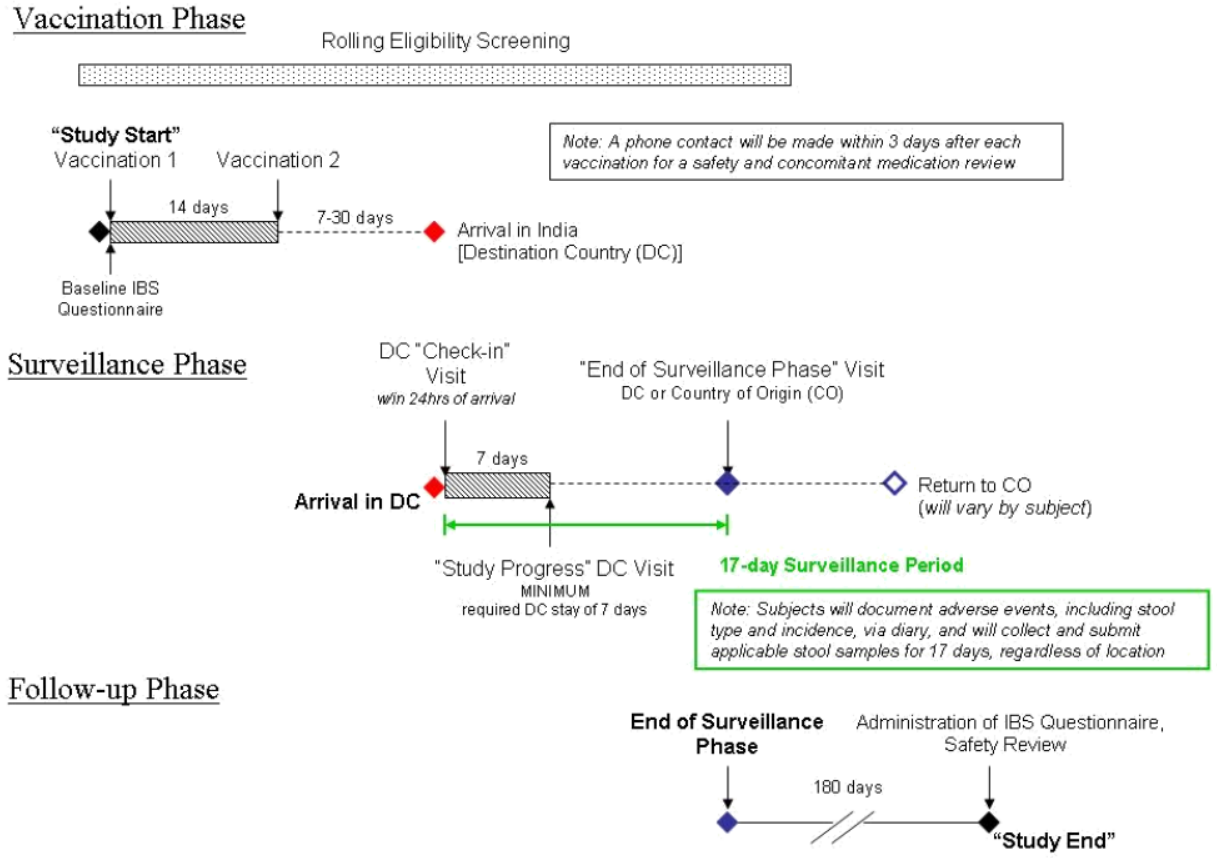
Protocol Number: ELT209
EudraCT number: 2009-015603-10
ClinicalTrials.gov id: NCT01040325

Sponsor: Intercell USA, Inc.
20 Firstfield Road
Gaithersburg, Maryland 20878

Name of Investigational Product: Heat-Labile Enterotoxin of *Escherichia coli*

Overall Study Design and Plan

Study ELT209 was a multicenter, randomized, double-blinded, placebo-controlled study designed to evaluate the efficacy of the TD Vaccine System in travelers to Asia. This pivotal field efficacy study was designed to enroll 716 eligible male and female subjects (18 to 64 years) and was conducted across multiple clinical sites in travelers beginning their study participation in the Country of Origin (CO) (UK and Germany), before traveling to the Destination Country (DC) (India) for surveillance. Two transcutaneous immunizations (skin preparation with the SPS:Buffer and LT or placebo patch application) were performed 14 days apart, on alternating deltoids by a clinician in the CO. Subjects received 37.5 micrograms (µg) LT or placebo patches according to randomized (1:1) group assignment. Patches were to be worn for six hours prior to removal by the subject.



Efficacy assessments were based on subject diary-reported diarrheal events and analysis of stool samples submitted during the Surveillance Phase for detection of ETEC and other co-pathogens. The primary endpoint of this study was to evaluate the incidence of VPO reported during the Surveillance Phase; a VPO was defined as a case of moderate/severe diarrhea in which LT, LT and ST or ST toxins (ETEC) were detected by either PCR or DNA hybridization (and no copathogen was detected) from diarrheal stool samples that were collected during the first diarrheal episode.

Main objective of the trial:
The primary objective of this study was to evaluate the efficacy of the TD Vaccine System to prevent moderate to severe ETEC disease in travelers to India.

Analysis Populations of Randomized Subjects

Analysis Populations	Group 1 (37.5µg LT) N=363 n (%)	Group 2 (Placebo) N=360 n (%)	Overall N=723 n (%)
Intent-to-Treat (ITT) [1]	363 (100)	360 (100)	723 (100)
Safety [2, 3]	362 (>99)	360 (100)	722 (>99)
Modified ITT (mITT) [4]	335 (92)	338 (94)	673 (93)
Per Protocol (PPP) [5]	299 (82)	304 (84)	603 (83)
Reasons for Exclusion from PPP [6]			
Did not receive two vaccinations	22 (6)	9 (3)	31 (4)
Received less than five hours exposure at either vaccination	17 (5)	10 (3)	27 (4)
Used antibiotics or antibacterials in DC [7]	11 (3)	14 (4)	25 (4)
Did not complete the "DC Check-in" Visit	10 (3)	14 (4)	24 (3)
Did not complete the first seven days of diary records in DC	6 (2)	7 (2)	13 (2)
Used antipropulsives in DC [7]	2 (<1)	2 (<1)	4 (<1)
Arrived in DC less than seven days after Vaccination 2	0 (0)	1 (<1)	1 (<1)
Vaccination error	1 (<1)	0 (0)	1 (<1)

Note: Percentages are based on the number of randomized subjects.
DC=Destination Country; N=Number of randomized subjects per group; n=Number of subjects in the category indicated per group.

[1] All consented, randomized subjects.
[2] All subjects who received at least one vaccination (active or placebo) as randomized.
[3] Subject 5010022 was excluded from the Safety Population due to vaccination
[4] All consented, randomized subjects who entered the DC within the study period.
[5] All subjects who were consented, randomized, received both study vaccinations as assigned, arrived in the DC, successfully attended the "DC Check-in" and "Study Progress" Visits, and completed the Surveillance Phase Diary information for each day up through the date of completion of the Study Progress Visit.
[6] A subject may have been counted more than once. Subjects were counted for each PPP exclusion criterion met.
[7] Use of antibiotics/antibacterials/antipropulsives in DC - For subjects who had a diarrheal episode, use was disallowed prior to the fourth stool sample. For subjects who did not have an episode, use was disallowed during DC visit.

Demographic Characteristics

	Safety Population [1]			mITT Population [2]			PPP [3]		
	Group 1 (37.5µg LT) N=362	Group 2 (Placebo) N=360	Overall N=722	Group 1 (37.5µg LT) N=335	Group 2 (Placebo) N=338	Overall N=673	Group 1 (37.5µg LT) N=299	Group 2 (Placebo) N=304	Overall N=603
Age (years) [4]									
Mean (SD)	32.0 (10.37)	31.7 (10.16)	31.9 (10.26)	32.1 (10.50)	31.9 (10.31)	32.0 (10.39)	32.3 (10.63)	32.1 (10.19)	32.2 (10.40)
Median	28.8	28.5	28.6	28.8	28.6	28.7	28.8	28.6	28.7
Min, Max	18, 63	19, 63	18, 63	18, 63	19, 63	18, 63	18, 63	19, 60	18, 63
Gender, n (%)									
Male	191 (53)	186 (52)	377 (52)	177 (53)	175 (52)	352 (52)	158 (53)	159 (52)	317 (53)
Female	171 (47)	174 (48)	345 (48)	158 (47)	163 (48)	321 (48)	141 (47)	145 (48)	286 (47)
Race, n (%) [5]									
Asian	39 (11)	37 (10)	76 (11)	35 (10)	34 (10)	69 (10)	29 (10)	31 (10)	60 (10)
Black	3 (<1)	4 (1)	7 (1)	3 (<1)	4 (1)	7 (1)	3 (1)	3 (1)	6 (1)
Caucasian	312 (86)	312 (87)	624 (86)	289 (86)	293 (87)	582 (87)	261 (87)	264 (87)	525 (87)
Other	7 (2)	7 (2)	14 (2)	7 (2)	7 (2)	14 (2)	5 (2)	6 (2)	11 (2)
Ethnicity, n (%) [5]									
Hispanic or Latino	6 (2)	7 (2)	13 (2)	6 (2)	6 (2)	12 (2)	4 (1)	6 (2)	10 (2)
Not Hispanic or Latino	355 (98)	353 (98)	708 (98)	328 (98)	332 (98)	660 (98)	294 (98)	298 (98)	592 (98)

	Safety Population [1]			mITT Population [2]			PPP [3]		
	Group 1 (37.5µg LT) N=362	Group 2 (Placebo) N=360	Overall N=722	Group 1 (37.5µg LT) N=335	Group 2 (Placebo) N=338	Overall N=673	Group 1 (37.5µg LT) N=299	Group 2 (Placebo) N=304	Overall N=603
Weight (kg) [6]									
Mean (SD)	74.00 (15.45)	72.04 (14.69)	73.02 (15.10)	73.89 (15.62)	72.18 (14.96)	73.04 (15.30)	74.04 (15.80)	72.15 (14.87)	73.09 (15.36)
Median	71.60	70.65	71.15	71.40	70.70	71.00	71.60	70.70	71.10
Min, Max	46.5, 181.0	42.0, 146.6	42.0, 181.0	46.5, 181.0	42.0, 146.6	42.0, 181.0	46.5, 181.0	42.0, 146.6	42.0, 181.0
Height (cm) [6]									
Mean (SD)	173.3 (12.15)	172.4 (10.51)	172.8 (11.36)	173.6 (12.10)	172.4 (10.41)	173.0 (11.29)	173.5 (12.27)	172.6 (10.26)	173.1 (11.30)
Median	174.0	173.0	173.0	174.0	173.0	173.0	174.0	173.0	174.0
Min, Max	69, 203	131, 205	69, 205	69, 203	131, 205	69, 205	69, 203	131, 205	69, 205

Note: Percentages are based on the number of subjects in the specified analysis population
kg=Kilogram; cm=Centimeter; SD=Standard deviation; Min=Minimum; Max=Maximum; N=Number of subjects in the specified analysis population per group; n=Number of subjects in the category indicated per group.
[1] All subjects who received at least one vaccination (active or placebo) as randomized.
[2] All consented, randomized subjects who entered the DC within the study period.
[3] All subjects who were consented, randomized, received both study vaccinations as assigned, arrived in the DC, successfully attended the "DC Check-in" and "Study Progress" Visits, and completed the Surveillance Phase Diary information for each day up through the date of completion of the Study Progress Visit.
[4] Age was calculated as an integer value indicating the number of full years passed since birth.
[5] Race and ethnicity data were not collected for Subject 6020065 (Group 1).
[6] Height and weight measurements were not taken for all subjects. Data are presented for those subjects with non-missing data.

Country of Origin and Destination City, Safety Population

	Group 1 (37.5µg LT) N=362	Group 2 (Placebo) N=360	Overall N=722
	n (%)	n (%)	n (%)
Country of Origin (CO)			
United Kingdom	264 (73)	247 (69)	511 (71)
Germany	98 (27)	113 (31)	211 (29)
Destination City [4]			
South Goa	119 (33)	113 (31)	232 (32)
North Goa	99 (27)	105 (29)	204 (28)
Delhi	83 (23)	95 (26)	178 (25)
Varanasi	19 (5)	13 (4)	32 (4)
Kolkata	14 (4)	12 (3)	26 (4)
No travel to Destination Country	28 (8)	22 (6)	50 (7)

[4] The destination city refers to the city in which the Destination Country (DC) Check-in Visit took place. Subjects frequently travelled throughout India and were seen at multiple DC study sites.

Duration (Hours) of Patch Exposure

	Safety Population [1]		mITT Population [2]		PPP [3]	
	Group 1 (37.5µg LT) N=362	Group 2 (Placebo) N=360	Group 1 (37.5µg LT) N=335	Group 2 (Placebo) N=338	Group 1 (37.5µg LT) N=299	Group 2 (Placebo) N=304
Vaccination 1						
Subjects Vaccinated, n	358	359	334	337	299	304
Patch Exposure (Hours)						
Mean (SD)	6.2 (0.49)	6.2 (0.45)	6.2 (0.49)	6.2 (0.45)	6.2 (0.47)	6.2 (0.44)
Median	6.1	6.1	6.1	6.1	6.1	6.1
Min, Max	3, 10	5, 9	3, 10	5, 9	5, 10	5, 9
Vaccination 2						
Subjects Vaccinated, n	334	348	326	334	299	304
Patch Exposure (Hours)						
Mean (SD)	6.3 (0.93)	6.2 (0.67)	6.3 (0.94)	6.2 (0.68)	6.3 (0.88)	6.3 (0.65)
Median	6.1	6.1	6.1	6.1	6.1	6.1
Min, Max	2, 15	4, 12	2, 15	4, 12	5, 15	5, 12

SD=Standard deviation; Min=Minimum; Max=Maximum; N=Number of subjects in the specified analysis population per group; n=Number of subjects in the category indicated per group.
[1] All subjects who received at least one vaccination (active or placebo) as randomized.
[2] All consented, randomized subjects who entered the DC within the study period.
[3] All subjects who were consented, randomized, received both study vaccinations as assigned, arrived in the DC, successfully attended the “DC Check-in” and “Study Progress” Visits, and completed the Surveillance Phase Diary information for each day up through the date of completion of the Study Progress Visit.

Primary Endpoint: Incidence of Vaccine Preventable Outcome [1] Diarrheal Episodes Experienced during the Surveillance Phase (First Episode Experienced), Per Protocol and mITT Populations

Analysis Population	Group 1 (37.5µg LT)		Group 2 (Placebo)		VE% [2]	VE 95% CI [3]	p-value [4]
	n/N (%)	95% CI	n/N (%)	95% CI			
Per Protocol Population	18/299 (6.0)	3.6, 9.3	18/304 (5.9)	3.5, 9.2	-1.34	-97.62, 48.04	1.0000
mITT Population	19/335 (5.7)	3.4, 8.7	19/338 (5.6)	3.4, 8.6	-0.90	-91.40, 46.82	1.0000

Note: All percentages are based on the number of subjects in the specified analysis population per group.
[1] All moderate/severe diarrheal cases (those with four or more unformed stools as the greatest frequency observed in any consecutive 24-hour period during a diarrheal episode) in which LT, LT and ST or ST toxins were detected by either PCR or DNA hybridization from diarrheal stool samples that were passed during the first diarrheal episode and were otherwise pathogen-free.
[2] Vaccination Efficacy (VE) defined as 100*(1-Pt/Pc) where Pt=fraction of cases in the LT Patch group and Pc=fraction of cases in the Placebo Patch group.
[3] Vaccine Efficacy 95% exact confidence interval for the ratio of two binomial proportions.
[4] Exact unconditional test of treatment equality (Barnard's).
CI=Confidence interval; mITT=Modified Intent-to-Treat; VE=Vaccine efficacy; N=Number of subjects in the specified analysis population per group; n= Number of subjects with one or more VPO diarrheal episode per group.

This study failed to meet the primary endpoint – VPO incidence was low and similar across treatment groups and analysis populations (PPP: 6.0% in LT Group, 5.9% in Placebo Group; mITT Population: 5.7% in LT Group, 5.6% in Placebo Group), with vaccine efficacy (VE) near zero (PPP: -1.34%; mITT Population: -0.90%) and p=1.0000.

Overall Summary of All Adverse Events, Safety Population

	Group 1 (37.5µg LT) N=362	Group 2 (Placebo) N=360	Overall N=722	
	n (%)	n (%)	n (%)	p-value [1]
Any adverse events [2]				
Number of adverse events	6127	2386	8513	---
Subjects with at least one adverse event	355 (98)	326 (91)	681 (94)	---
Subjects with a Grade 3 or higher adverse event	112 (31)	96 (27)	208 (29)	---
Subjects with a serious adverse event	8 (2)	4 (1)	12 (2)	---
Subjects with an adverse event leading to study withdrawal	4 (1)	0 (0)	4 (<1)	---

	Group 1 (37.5µg LT) N=362	Group 2 (Placebo) N=360	Overall N=722	
	n (%)	n (%)	n (%)	p-value [1]
Any local adverse events				
Number of adverse events	4237	555	4792	---
Subjects with at least one adverse event	349 (96)	232 (64)	581 (81)	**<0.0001**
Subjects with a Grade 3 or higher adverse event	75 (21)	43 (12)	118 (16)	**0.0017**
Subjects with a serious adverse event	0 (0)	0 (0)	0 (0)	---
Any systemic adverse events				
Number of adverse events	1890	1831	3721	---
Subjects with at least one adverse event	297 (82)	296 (82)	593 (82)	1.0000
Subjects with a Grade 3 or higher adverse event	52 (14)	65 (18)	117 (16)	0.1901
Subjects with a serious adverse event	8 (2)	4 (1)	12 (2)	0.3837

Note: 'n' denotes the number of subjects with the specified adverse event by vaccination. Percentages are based on the number of subjects in the Safety Population. A subject is counted once per category.
[1] Fisher's Exact Test
[2] Local and Systemic AEs
N=Number of subjects per group in the Safety Population; n=Number of subjects meeting the specified criteria

Incidence of Non-Solicited Systemic Adverse Events Reported in ≥2% of Subjects by Vaccination, Study Phase and Preferred Term, Safety Population

Preferred Term	Group 1 (37.5µg LT) n (%)	Group 2 (Placebo) n (%)
Vaccination Phase - Vaccination 1 [1]	**N=362**	**N=360**
Any non-solicited systemic adverse event	115 (32)	109 (30)
Diarrhoea	33 (9)	28 (8)
Headache	18 (5)	36 (10)
Nasopharyngitis	14 (4)	13 (4)
Fatigue	9 (3)	5 (1)
Dizziness	4 (1)	8 (2)
Vaccination Phase - Vaccination 2 [2]	**N=340**	**N=351**
Any non-solicited systemic adverse event	105 (31)	83 (24)
Diarrhoea	23 (7)	20 (6)
Headache	23 (7)	18 (5)
Dysmenorrhoea	9 (3)	6 (2)
Nasopharyngitis	6 (2)	7 (2)
Nausea	9 (3)	1 (<1)
Pain	8 (2)	1 (<1)
Fatigue	7 (2)	2 (<1)
Vomiting	7 (2)	0 (0)

Preferred Term	Group 1 (37.5µg LT) n (%)	Group 2 (Placebo) n (%)
Surveillance Phase [3]	**N=334**	**N=338**
Any non-solicited systemic adverse event	251 (75)	248 (73)
Diarrhoea	236 (71)	225 (67)
Fecal urgency	61 (18)	62 (18)
Abdominal pain	53 (16)	66 (20)
Headache	48 (14)	50 (15)
Nausea	38 (11)	42 (12)
Vomiting	19 (6)	25 (7)
Dehydration	5 (2)	21 (6)
Pyrexia	6 (2)	18 (5)
Nasopharyngitis	8 (2)	3 (<1)
Fatigue	1 (<1)	8 (2)
Constipation	1 (<1)	7 (2)
Follow-up Phase [4]	**N=320**	**N=331**
Any non-solicited systemic adverse event	32 (10)	38 (12)
Diarrhoea	6 (2)	9 (3)

Note: Percentages are based on the number of subjects in the Safety Population who were in the study during the specified phase. A subject is counted only once per category.

[1] Systemic adverse events that occurred following Vaccination 1 prior to Vaccination 2. Events of fever, malaise, headache, and unformed stools/diarrheal episodes were considered unsolicited events when reported more than seven days post-vaccination.

[2] Systemic adverse events that occurred following Vaccination 2 prior to the start of the Surveillance Phase. Events of fever, malaise, headache, and unformed stools/diarrheal episodes were considered unsolicited events when reported more than seven days post-vaccination.

[3] Systemic adverse events that occurred within the Surveillance Phase prior to the start of the Follow-up Phase.

[4] Systemic adverse events that occurred within the Follow-up Phase prior to the end of the study.

N=Number of subjects in the Safety Population who were in the study during the specified phase; n = Number of subjects meeting the specified criteria.

Incidence of Solicited Local Adverse Events by Vaccination, Safety Population

Local Adverse Event	Group 1 (37.5µg LT) n (%)	Group 2 (Placebo) n (%)
Vaccination 1[1]		
Subjects Vaccinated:	**N=362**	**N=360**
Erythema	322 (89)	174 (48)
Rash	314 (87)	36 (10)
Pruritus	289 (80)	29 (8)
Hyperpigmentation	177 (49)	7 (2)
Pain	94 (26)	18 (5)
Edema	6 (2)	2 (<1)
Hypopigmentation	6 (2)	0 (0)
Vaccination 2[2]		
Subjects Vaccinated:	**N=340**	**N=351**
Erythema	315 (93)	139 (40)
Rash	305 (90)	36 (10)
Pruritus	268 (79)	11 (3)
Hyperpigmentation	89 (26)	1 (<1)
Pain	58 (17)	7 (2)
Edema	12 (4)	0 (0)
Hypopigmentation	6 (2)	1 (<1)

Note: 'n' denotes the number of subjects with the specified local event by vaccination. Percentages are based on the number of subjects that received vaccination in each group.
[1] Local events occurring at the Vaccination 1 application site.
[2] Local events occurring at the Vaccination 2 application site.
N=Number of subjects per group in the Safety Population

Overall Summary of All Serious Adverse Events by System Organ Class and Preferred Term, Safety Population

System Organ Class Preferred Term	Group 1 LT Patch (37.5 µg) (N=362) n (%)	Group 2 Placebo Patch (N=360) n (%)	Overall (N=722) n (%)
No Serious Adverse Events	354 (97.8%)	356 (98.9%)	710 (98.3%)
All Serious Adverse Events	8 (2.2%)	4 (1.1%)	12 (1.7%)
Infections and infestations	3 (0.8%)	3 (0.8%)	6 (0.8%)
Diarrhoea infectious	0 (0.0%)	1 (0.3%)	1 (0.1%)
Gastric infection	0 (0.0%)	1 (0.3%)	1 (0.1%)
Gastroenteritis	0 (0.0%)	1 (0.3%)	1 (0.1%)
Gastroenteritis viral	0 (0.0%)	1 (0.3%)	1 (0.1%)
Hepatitis B	1 (0.3%)	0 (0.0%)	1 (0.1%)
Malaria	1 (0.3%)	0 (0.0%)	1 (0.1%)
Pyelonephritis	1 (0.3%)	0 (0.0%)	1 (0.1%)
Urinary tract infection	0 (0.0%)	1 (0.3%)	1 (0.1%)
Metabolism and nutrition disorders	1 (0.3%)	1 (0.3%)	2 (0.3%)
Dehydration	0 (0.0%)	1 (0.3%)	1 (0.1%)
Hyperglycaemia	1 (0.3%)	0 (0.0%)	1 (0.1%)
Hepatobiliary disorders	1 (0.3%)	0 (0.0%)	1 (0.1%)
Cholecystitis	1 (0.3%)	0 (0.0%)	1 (0.1%)
Injury, poisoning and procedural complications	0 (0.0%)	1 (0.3%)	1 (0.1%)
Radius fracture	0 (0.0%)	1 (0.3%)	1 (0.1%)
Nervous system disorders	1 (0.3%)	0 (0.0%)	1 (0.1%)
Coma	1 (0.3%)	0 (0.0%)	1 (0.1%)

Loss of consciousness	1 (0.3%)	0 (0.0%)	1 (0.1%)
Psychiatric disorders	1 (0.3%)	0 (0.0%)	1 (0.1%)
Mania	1 (0.3%)	0 (0.0%)	1 (0.1%)
Reproductive system and breast disorders	1 (0.3%)	0 (0.0%)	1 (0.1%)
Ovarian cyst	1 (0.3%)	0 (0.0%)	1 (0.1%)
Ovarian cyst torsion	1 (0.3%)	0 (0.0%)	1 (0.1%)
Vascular disorders	1 (0.3%)	0 (0.0%)	1 (0.1%)
Hypertension	1 (0.3%)	0 (0.0%)	1 (0.1%)