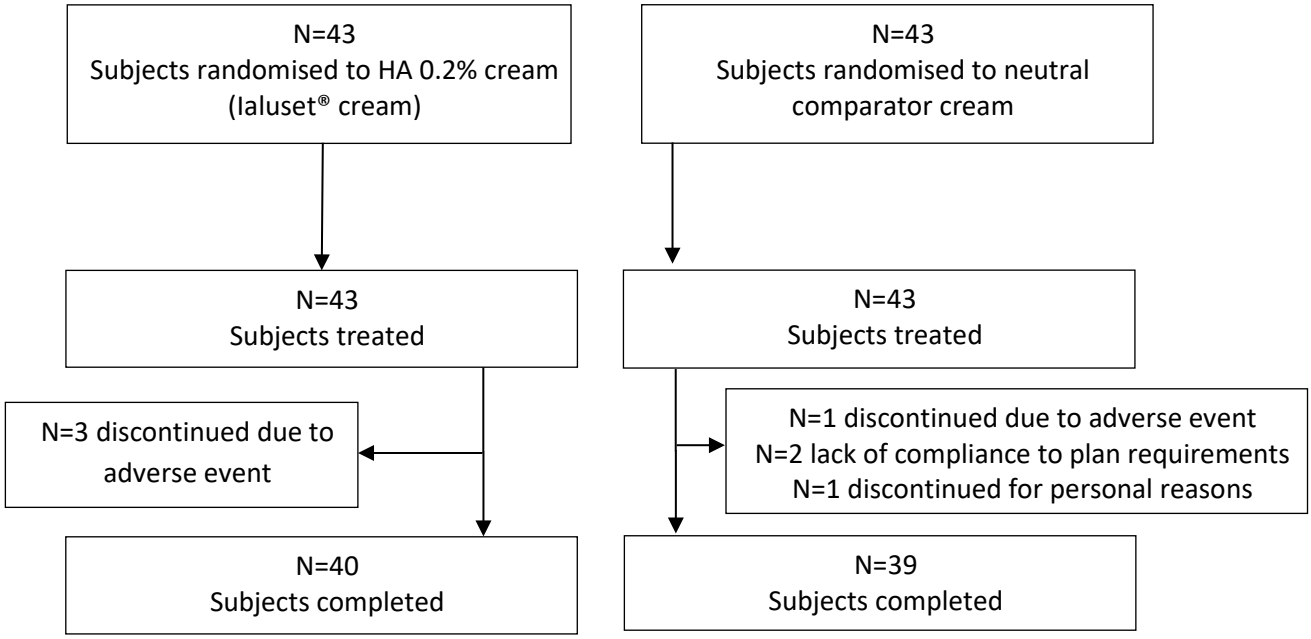
Participant flow



Baseline characteristics

Demographic data	Intention to treat and safety set N=86	Per protocol set N=76
Age (years)		
Mean ± standard deviation	64.1±11.9	64.6±12.0
Median (range)	65.0 (36 – 84)	65.0 (36 – 84)
Body weight (kg)		
Mean ± standard deviation	68.55±12.62	68.35±13.12
Range	66.50 (44.0 – 104.0)	66.00 (44.0 – 104.0)
Height (m)		
Mean ± standard deviation	1.639±0.070*	1.637±0.071**
Median (range)	1.650 (1.45 – 1.78)*	1.640 (1.45 – 1.78)**
Body Mass Index (kg/m^2)		
Mean ± standard deviation	25.680±4.552*	25.687±4.732**
Median (range)	25.155 (17.30 – 40.90)*	25.055 (17.30 – 40.90)**
Race		
White – n (%)	84 (97.7%)	74 (97.4%)
Native Hawaiian or other Pacific Islander– n (%)	1 (1.2%)	1 (1.3%)
Hispanic – n (%)	1 (1.2%)	1 (1.3%)

**: N=84; **: N=74*

LRT fractionation plan

Treatment group			HA 0.2% cream N=43	Neutral comparator N=43	Overall N=86
LRT fractionation plan	Hypofractionation	n (%)	24 (55.8)	26 (60.5)	50 (58.1)
	Conventional fractionation with boost		7 (16.3)	12 (27.9)	19 (22.1)
	Conventional fractionation		12 (27.9)	5 (11.6)	17 (19.8)
LRT total dose (Gy)		mean ± SD	49.4±11.1	49.6±12.1	49.5±11.6
Area to be irradiated (cm^2)			262.5±115.2	268.0±76.7	265.3±97.3
Total amount of cream applied (g)			199.5±53.7	205.8±67.1	n.a.

Outcome measures

Primary outcome:

Proportion of subjects with RTOG Grade >=2 at End of Treatment (EOT), stratified by LRT fractionation plan - Intention-to-treat set

LRT Fractionation plan	RTOG Grade >=2 at EOT	0.2% HA cream n (%)	Placebo cream n (%)	CMH Test p-value*
Conventional Fractionation	Yes	4 (21.1)	6 (35.3)	0.3477
	No	15 (78.9)	11 (64.7)	
Hypofractionation	Yes	0 (0.0)	0 (0.0)	
	No	24 (100.0)	26 (100.0)	

*Cochran-Mantel-Haenszel test for General Association

Secondary outcomes:

Proportion of subjects with RTOG Grade >=1 at any visit, stratified by LRT fractionation plan - Intention-to-treat set

LRT Fractionation plan	RTOG Grade >=2 at EOT	0.2% HA cream n (%)	Placebo cream n (%)	CMH Test p-value*
Conventional Fractionation	Yes	18 (94.7)	15 (88.2)	0.4725
	No	1 (5.3)	2 (11.8)	
Hypofractionation	Yes	10 (41.7)	15 (57.7)	
	No	14 (58.3)	11 (42.3)	

*Cochran-Mantel-Haenszel test for General Association

Time to reach a RTOG Grade>=1 skin reaction [days] - Intention-to-treat set

LRT Fractionation plan:	0.2% HA cream N=19	Placebo cream N=17	p-value*
Conventional Fractionation			
Median (Inter Quartile Range)(Days)	46.0 (43.0, 57.0)	47.0 (36.5, 57.0)	0.4725
Freedom from event (95% CI) at EOT visit (%)	18.95 (5.03, 39.62)	12.50 (2.07, 32.80)	
Hypofractionation			
Median (Inter Quartile Range) (Days)	37.0 (34.0, NC)	36.0 (35.0, 38.0)	0.7770
Freedom from event (95% CI) at EOT visit (%)	73.53 (50.07, 87.22)	80.22 (58.75, 91.27)	

* Log-rank test

Patient's self-perceived level of discomfort at the irradiated site - Intention-to-treat set.

Time	HA 0.2% cream N=43		Neutral comparator N=43	
	Conventional fractionation N=19	Hypofractionation N=24	Conventional fractionation N=17	Hypofractionation N=26
Week 1	6.5±17.3	8.5±13.7	4.0±7.1	7.5±17.2
Week 2	6.7±14.3	8.3±14.6	7.4±11.0	12.0±15.3
Week 3	14.8±17.9		13.1±19.3	
Week 4	20.0±20.2		13.1±21.3	
Week 5	29.2±27.5		23.8±26.4	
EOT	35.4±30.9	6.4±13.1	20.2±20.8	19.5±19.4
EOS	26.3±31.1	11.9±19.0	13.8±19.1	17.3±20.6

EOT: End of treatment; EOS: End of study

SF-36 Questionnaire Total Score over time - Intention-to-treat set.

	HA 0.2% cream		Neutral comparator	
Time point of Assessment	**Conventional fractionation**	**Hypofractionation**	**Conventional fractionation**	**Hypofractionation**
	Mean (SD)			
Screening	68.3 (19.1)	74.0 (13.6)	61.3 (16.4)	67.1 (18.7)
Start of LRT	65.8 (14.6)	72.5 (9.40)	67.8 (16.0)	68.7 (19.9)
End of Treatment	67.6 (13.9)	73.1 (12.3)	65.8 (17.2)	66.9 (19.7)
End of Study	66.3 (16.1)	74.8 (14.5)	61.8 (15.3)	67.7 (22.0)

Overall Treatment Efficacy evaluated by the Investigator at End of Study (EOS), stratified by LRT fractionation plan - Intention-to-treat set

LRT Fractionation plan	Overall Efficacy	0.2% HA cream n (%)	Placebo cream n (%)	CMH Test p-value*
Conventional Fractionation	None	1 (5.3)	0 (0.0)	
	Poor	1 (5.3)	1 (5.9)	
	Fair	0 (0.0)	1 (5.9)	
	Good	7 (36.8)	6 (35.3)	
	Excellent	7 (36.8)	4 (23.5)	
	(missing)	3 (15.8)	5 (29.4)	
				0.4537
Hypofractionation	None	1 (4.2)	0 (0.0)	
	Poor	0 (0.0)	0 (0.0)	
	Fair	3 (12.5)	3 (11.5)	
	Good	11 (45.8)	14 (53.8)	
	Excellent	8 (33.3)	4 (15.4)	
	(missing)	1 (4.2)	5 (19.2)	

*Cochran-Mantel-Haenszel test for General Association

Overall Treatment Satisfaction evaluated by the Subject at End of Study (EOS), stratified by LRT fractionation plan - Intention-to-treat set.

LRT Fractionation plan	Overall Efficacy	0.2% HA cream n (%)	Placebo cream n (%)	CMH Test p-value*
Conventional Fractionation	None	0 (0.0)	0 (0.0)	
	Poor	0 (0.0)	1 (5.9)	
	Fair	1 (5.3)	1 (5.9)	
	Good	7 (36.8)	7 (41.2)	
	Excellent	5 (26.3)	2 (11.8)	
	(missing)	6 (31.6)	7 (41.2)	
				0.4924
Hypofractionation	None	0 (0.0)	0 (0.0)	
	Poor	1 (4.2)	1 (3.8)	
	Fair	3 (12.5)	1 (3.8)	
	Good	11 (45.8)	13 (50.0))	
	Excellent	6 (25.0)	8 (30.8)	
	(missing)	3 (12.5	3 (11.5)	

*Cochran-Mantel-Haenszel test for General Association

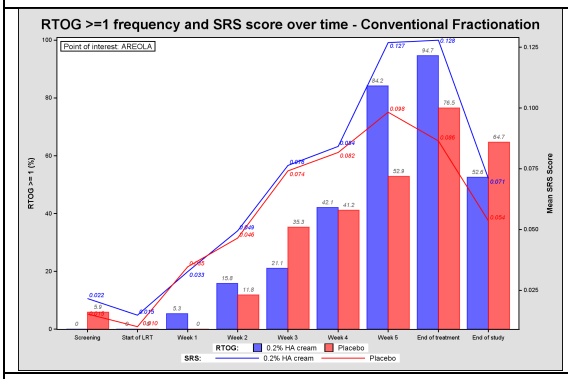
Coherence between SRS scores and RTOG scores at 4 specific points - Intention-to-treat set

Area	Goodness of fit R2
Areola	0.2242
Axilla	0.3133
Infra-mammary fold	0.2704
Inner midline	0.2805

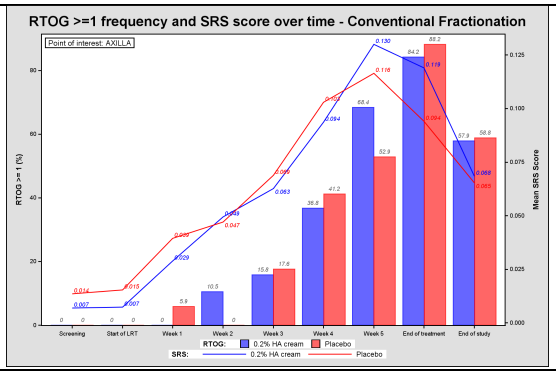
Dermal Toxicity Assessment of 4 Specific Points by means of SRS Score (LINES) and RTOG Score (BARS), over time.

Conventional fractionation: RTOG >=1 frequency (BLUE Bars: 0.2% HA; RED bars: Placebo) and SRS score (BLUE Line: 0.2% HA; RED Line: Placebo) over time - Intention to treat set

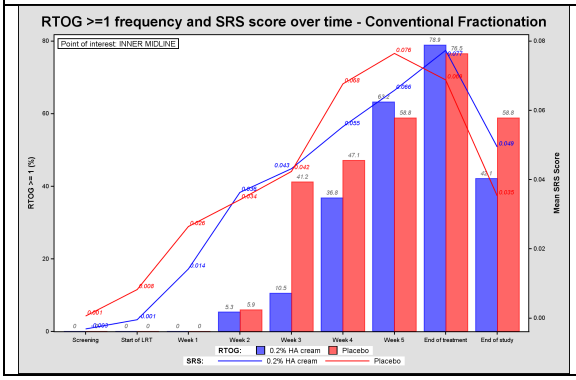
Areola



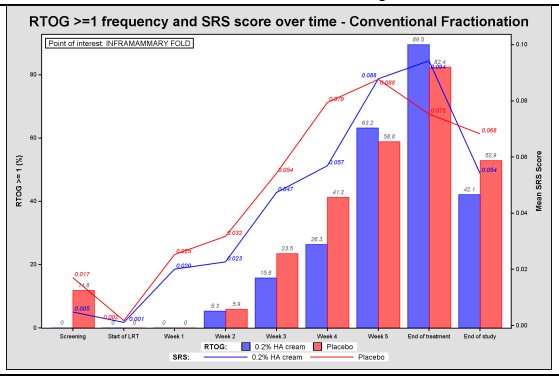
Axilla



Inner Midline

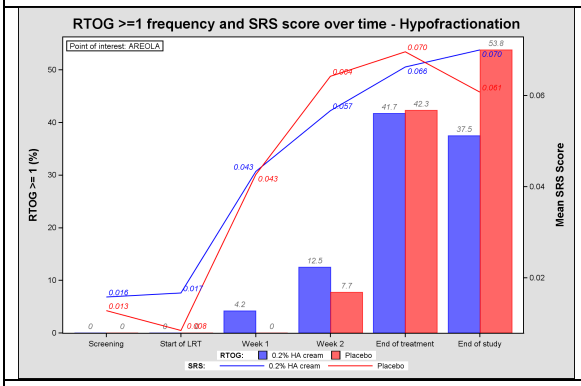


Inframammary fold

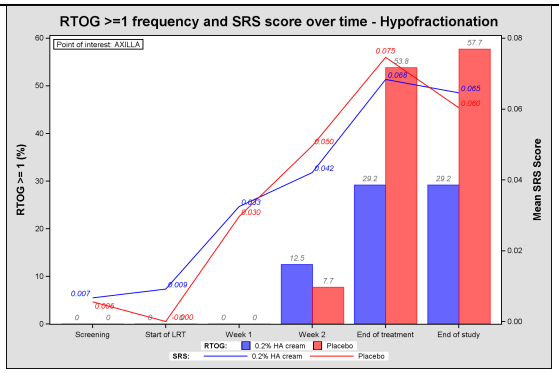


Hypofractionation: RTOG >=1 frequency (BLUE Bars: 0.2% HA; RED bars: Placebo) and SRS score (BLUE Line: 0.2% HA; RED Line: Placebo) over time - Intention to treat set

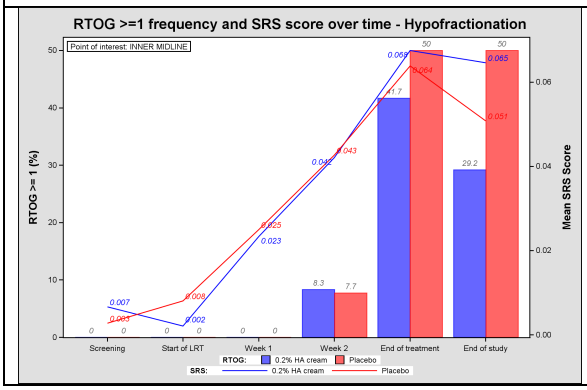
Areola



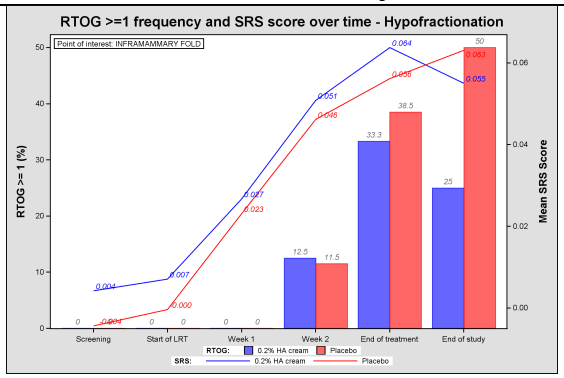
Axilla



Inner Midline



Inframammary fold



Adverse events

Number of treatment-emergent adverse events (TEAEs) and number and percentage of subjects with TEAEs by treatment group, system organ class (SOC) and preferred term (PT) are summarised in the table below. Safety set N=86

MedDRA description SOC and PT term	HA 0.2% cream N=43		Neutral comparator N=43	
	AEs n	Subjects n (%)	AEs n	Subjects n (%)
Total number of AEs and of subjects with at least one AE	**70**	**35 (81.4)**	**73**	**33 (76.7)**
General disorders and administration site conditions	**63**	**34 (79.1)**	**55**	**31 (72.1)**
Application site erythema	56	34 (79.1)	51	31 (72.1)
Application site pruritus	1	1 (2.3)	2	2 (4.7)
Application site pain	1	1 (2.3)	1	1 (2.3)
Application site discolouration	1	1 (2.3)	0	0
Application site eczema	0	0	1	1 (2.3)
Application site vesicles	1	1 (2.3)	0	0
Axillary pain	1	1 (2.3)	0	0
Fatigue	1	1 (2.3)	0	0
Pyrexia	1	1 (2.3)	0	0
Infections and infestations	**1**	**1 (2.3)**	**7**	**6 (14.0)**
Folliculitis	0	0	3	3 (7.0)
Abscess jaw	0	0	1	1 (2.3)
Bronchitis	0	0	1	1 (2.3)
Influenza	1	1 (2.3)	0	0
Rhinitis	0	0	1	1 (2.3)
Urinary tract infection	0	0	1	1 (2.3)
Musculoskeletal and connective tissue disorders	**2**	**2 (4.7)**	**2**	**2 (4.7)**
Musculoskeletal pain	1	1 (2.3)	1	1 (2.3)
Bone pain	1	1 (2.3)	0	0
Spinal pain	0	0	1	1 (2.3)
Reproductive system and breast disorders	**1**	**1 (2.3)**	**2**	**2 (4.7)**
Breast pain	1	1 (2.3)	2	2 (4.7)
Skin and subcutaneous tissue disorders	**1**	**1 (2.3)**	**2**	**2 (4.7)**
Dermatitis	0	0	1	1 (2.3)
Pruritus	0	0	1	1 (2.3)
Skin oedema	1	1 (2.3)	0	0
Gastrointestinal disorders	**1**	**1 (2.3)**	**2**	**1 (2.3)**
Nausea	1	1 (2.3)	1	1 (2.3)
Vomiting	0	0	1	1 (2.3)
Injury, poisoning and procedural complications	**0**	**0**	**2**	**2 (4.7)**
Radiation dysphagia	0	0	1	1 (2.3)
Toxicity to various agents	0	0	1	1 (2.3)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**0**	**0**	**1**	**1 (2.3)**
Melanocytic naevus	0	0	1	1 (2.3)
Psychiatric disorders	**1**	**1 (2.3)**	**0**	**0**
Insomnia	1	1 (2.3)	0	0

An overview of the TEAEs which occurred during the study and of the number of subjects who experienced TEAEs is presented in the table below. Safety set N=86

Category	**HA 0.2% cream N=43**		**Neutral comparator N=43**		**Overall N=86**	
	n AEs	**n (%) Subjects**	**n AEs**	**n (%) Subjects**	**n AEs**	**n (%) Subjects**
All adverse events	70	35 (81.4)	73	33 (76.7)	143	68 (79.1)
Adverse device effects	0	0	0	0	0	0
Skin reactions due to local radiotherapy	57	33 (76.7)	59	33 (76.7)	116	66 (76.7)
Serious adverse events	0	0	0	0	0	0
Leading to discontinuation	5	3 (7.0)	1	1 (2.3)	6	4 (4.7)