Clinical trial results:
A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

Summary

EudraCT number	2013-000423-14
Trial protocol	SE DE IT FR DK
Global end of trial date	06 March 2019

Results information

Result version number	v1 (current)
This version publication date	15 August 2019
First version publication date	15 August 2019

Trial information

Trial identification

Sponsor protocol code	D1532C00065

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01843062
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Research and Development, Södertälje, Sweden, SE-151 85
Public contact	Global Clinical Lead, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 May 2018
Global end of trial reached?	Yes
Global end of trial date	06 March 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of selumetinib (75 milligrams [mg], orally, twice daily [BD]) in combination with adjuvant radioactive iodine (RAI) therapy, versus placebo and adjuvant RAI therapy, by assessment of complete remission rate at 18 months post-RAI treatment.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 34
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Sweden: 26
Country: Number of subjects enrolled	United States: 75
Worldwide total number of subjects	233
EEA total number of subjects	124

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	203
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study conducted between 27 Aug 2013 and 06 Mar 2019. 42 centres in 8 countries randomised patients in the study. A primary analysis was performed for the 18 months post-RAI treatment period with a data cut-off of 18 May 2018. All primary and secondary outcome measures were reported at the time of the primary analysis.

Pre-assignment

Screening details:

Eligible patients with differentiated thyroid cancer at high risk of primary treatment failure were randomly assigned (ratio 2:1), to receive selumetinib or placebo for approximately 5 weeks. All patients also received adjuvant RAI therapy (100 millicuries [mCi] single oral dose) and recombinant human thyroid stimulating hormone (rhTSH) injections.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Blinding implementation details:

The active and placebo capsules appeared identical and were presented in the same packaging to ensure blinding of the medication. All patients remained blinded until after the 18 months primary endpoint data analysis had been conducted.

Arms

Are arms mutually exclusive?	Yes
Arm title	Selumetinib 75 mg BD + RAI

Arm description:

Patients received selumetinib (75 mg, orally, BD), for a period of approximately 5 weeks. Selumetinib was to be started approximately 4 weeks prior to the planned day of RAI therapy administered as a single oral dose of 100 mCi. To stimulate iodide uptake, patients received a rhTSH injection for each of the 2 days immediately prior to RAI therapy.

Arm type	Experimental
Investigational medicinal product name	Selumetinib
Investigational medicinal product code	AZD6244
Other name	Selumetinib hydrogen sulphate, AZD6244 Hyd-Sulfate
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

3 capsules of 25 mg strength, orally BD, for approximately 5 weeks treatment period.

Arm title	Placebo + RAI

Arm description:

Patients received placebo capsules (to match selumetinib, orally BD), for a period of approximately 5 weeks. Placebo was to be started approximately 4 weeks prior to the planned day of RAI therapy administered as a single oral dose of 100 mCi. To stimulate iodide uptake, patients received a rhTSH injection for each of the 2 days immediately prior to RAI therapy.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

3 capsules of placebo to match selumetinib, orally BD, for approximately 5 weeks treatment period.

Number of subjects in period 1	Selumetinib 75 mg BD + RAI	Placebo + RAI
Started	155	78
Intention to treat (ITT) analysis set	155	78
Safety analysis set	154	77
BRAF/NRAS mutation positive analysis set	91 [1]	51 [2]
Ongoing at primary analysis data cut-off	134	71
Completed	133	69
Not completed	22	9
Adverse event, serious fatal	1	2
Consent withdrawn by subject	12	3
New treatment following progression	2	-
Adverse event, non-fatal	2	-
Pregnancy	1	-
Incorrect randomisation	1	-
Lost to follow-up	2	4
Protocol deviation	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This represents the number of subjects included in the BRAF/NRAS mutation positive analysis set and should therefore be viewed as a subgroup analysis set, as opposed to an intermediate milestone.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This represents the number of subjects included in the BRAF/NRAS mutation positive analysis set and should therefore be viewed as a subgroup analysis set, as opposed to an intermediate milestone.

Baseline characteristics

Reporting groups	
Reporting group title	Selumetinib 75 mg BD + RAI
Reporting group description:	
Patients received selumetinib (75 mg, orally, BD), for a period of approximately 5 weeks. Selumetinib was to be started approximately 4 weeks prior to the planned day of RAI therapy administered as a single oral dose of 100 mCi. To stimulate iodide uptake, patients received a rhTSH injection for each of the 2 days immediately prior to RAI therapy.	
Reporting group title	Placebo + RAI
Reporting group description:	
Patients received placebo capsules (to match selumetinib, orally BD), for a period of approximately 5 weeks. Placebo was to be started approximately 4 weeks prior to the planned day of RAI therapy administered as a single oral dose of 100 mCi. To stimulate iodide uptake, patients received a rhTSH injection for each of the 2 days immediately prior to RAI therapy.	

Reporting group values	Selumetinib 75 mg BD + RAI	Placebo + RAI	Total
Number of subjects	155	78	233
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	46.2	47.9	
standard deviation	± 14.20	± 14.67	-
Sex: Female, Male Units: Subjects			
Female	92	40	132
Male	63	38	101
Race Units: Subjects			
White	145	73	218
Black or African American	3	1	4
Asian	3	3	6
Other	4	1	5
Ethnicity Units: Subjects			
Hispanic or Latino	27	14	41
Not Hispanic or Latino	128	64	192

End points

End points reporting groups

Reporting group title	Selumetinib 75 mg BD + RAI

Reporting group description:

Patients received selumetinib (75 mg, orally, BD), for a period of approximately 5 weeks. Selumetinib was to be started approximately 4 weeks prior to the planned day of RAI therapy administered as a single oral dose of 100 mCi. To stimulate iodide uptake, patients received a rhTSH injection for each of the 2 days immediately prior to RAI therapy.

Reporting group title	Placebo + RAI

Reporting group description:

Patients received placebo capsules (to match selumetinib, orally BD), for a period of approximately 5 weeks. Placebo was to be started approximately 4 weeks prior to the planned day of RAI therapy administered as a single oral dose of 100 mCi. To stimulate iodide uptake, patients received a rhTSH injection for each of the 2 days immediately prior to RAI therapy.

Primary: Complete remission rate (expressed as percentage of patients in complete remission) at 18 months post-RAI treatment; ITT analysis set

End point title	Complete remission rate (expressed as percentage of patients in complete remission) at 18 months post-RAI treatment; ITT analysis set

End point description:

Patients were defined to be in complete remission if all of the following criteria were demonstrated: 1. Serum thyroglobulin (Tg) levels <1 nanograms / millilitre (ng/mL) during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis. 2. No confirmed evidence of thyroid cancer on neck ultrasound, as assessed by investigator site review. 3. No confirmed radiological evidence of thyroid cancer, as assessed by blinded independent central review. 4. No histopathological evidence of thyroid cancer on fine needle aspiration (FNA)/biopsy when performed, as assessed by investigator site review. 5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.
Analysis performed on the ITT analysis set which included all randomised patients. Patients who were randomised but did not subsequently go on to receive selumetinib/placebo were included in the ITT analysis set.

End point type	Primary

End point timeframe:

At 18 months post-RAI treatment

End point values	Selumetinib 75 mg BD + RAI	Placebo + RAI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	78		
Units: Percentage of participants				
number (not applicable)	40.0	38.5		

Statistical analyses

Statistical analysis title	Complete remission rate: ITT set

Statistical analysis description:

Selumetinib in combination with RAI was compared with placebo in combination with RAI. The analysis

was performed using a logistic regression model including treatment as the only covariate. An odds ratio >1 favours selumetinib in combination with RAI.

Comparison groups	Selumetinib 75 mg BD + RAI v Placebo + RAI
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8205 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.87

Notes:

[1] - The primary endpoint was to be considered statistically significant if the 2-sided p-value was less than 0.05. P-value and confidence intervals (CIs) were calculated using profile likelihood.

Secondary: Complete remission rate (expressed as percentage of patients in complete remission) at 18 months post-RAI treatment; subgroup analysis BRAF/NRAS mutation positive

End point title	Complete remission rate (expressed as percentage of patients in complete remission) at 18 months post-RAI treatment; subgroup analysis BRAF/NRAS mutation positive

End point description:

Patients were defined to be in complete remission if all of the following criteria were demonstrated: 1. Serum Tg levels <1 ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis. 2. No confirmed evidence of thyroid cancer on neck ultrasound, as assessed by investigator site review. 3. No confirmed radiological evidence of thyroid cancer, as assessed by blinded independent central review. 4. No histopathological evidence of thyroid cancer FNA/biopsy when performed, as assessed by investigator site review. 5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment. Analysis performed on the BRAF/NRAS mutation positive analysis set which included only those patients from the ITT population whose tumour samples were mutation positive for the oncogenes BRAF or NRAS.

End point type	Secondary

End point timeframe:

At 18 months post-RAI treatment

End point values	Selumetinib 75 mg BD + RAI	Placebo + RAI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	51		
Units: Percentage of participants				
number (not applicable)	37.4	41.2		

Statistical analyses

Statistical analysis title	Complete remission rate: BRAF/NRAS positive set

Statistical analysis description:

Selumetinib in combination with RAI was compared with placebo in combination with RAI. The analysis was performed using a logistic regression model including treatment as the only covariate. An odds ratio >1 favours selumetinib in combination with RAI.

Comparison groups	Selumetinib 75 mg BD + RAI v Placebo + RAI
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6549 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.73

Notes:

[2] - P-value and CIs were calculated using profile likelihood.

Secondary: Clinical remission rate (expressed as percentage of patients in clinical remission) at 18 months post-RAI treatment; ITT analysis set

End point title	Clinical remission rate (expressed as percentage of patients in clinical remission) at 18 months post-RAI treatment; ITT analysis set

End point description:

Patients were defined to be in clinical remission if all of the following criteria were demonstrated: 1. Serum Tg levels <1 ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis. 2. No confirmed evidence of thyroid cancer on neck ultrasound, as assessed by investigator site review. 3. No evidence of thyroid cancer on diagnostic whole body scan (WBS), as assessed by blinded independent central review. 4. No histopathological evidence of thyroid cancer on FNA/biopsy when performed to clarify equivocal ultrasound findings, as assessed by investigator site review. 5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.
Analysis performed on the ITT analysis set which included all randomised patients. Patients who were randomised but did not subsequently go on to receive selumetinib/placebo were included in the ITT analysis set.

End point type	Secondary

End point timeframe:

At 18 months post-RAI treatment

End point values	Selumetinib 75 mg BD + RAI	Placebo + RAI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	78		
Units: Percentage of participants				
number (not applicable)	40.0	38.5		

Statistical analyses

Statistical analysis title	Clinical remission rate: ITT set

Statistical analysis description:

Selumetinib in combination with RAI was compared with placebo in combination with RAI. The analysis was performed using a logistic regression model including treatment as the only covariate. An odds ratio >1 favours selumetinib in combination with RAI.

Comparison groups	Selumetinib 75 mg BD + RAI v Placebo + RAI
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8205 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.87

Notes:

[3] - P-value and CIs were calculated using profile likelihood.

Secondary: Clinical remission rate (expressed as percentage of patients in clinical remission) at 18 months post-RAI treatment; subgroup analysis BRAF/NRAS mutation positive

End point title	Clinical remission rate (expressed as percentage of patients in clinical remission) at 18 months post-RAI treatment; subgroup analysis BRAF/NRAS mutation positive

End point description:

Patients were defined to be in clinical remission if all of the following criteria were demonstrated: 1. Serum Tg levels <1 ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis. 2. No confirmed evidence of thyroid cancer on neck ultrasound, as assessed by investigator site review. 3. No evidence of thyroid cancer on diagnostic WBS, as assessed by blinded independent central review. 4. No histopathological evidence of thyroid cancer on FNA/biopsy when performed to clarify equivocal ultrasound findings, as assessed by investigator site review. 5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.
Analysis performed on the BRAF/NRAS mutation positive analysis set which included only those patients from the ITT population whose tumour samples were mutation positive for the oncogenes BRAF or NRAS.

End point type	Secondary

End point timeframe:

At 18 months post-RAI treatment

End point values	Selumetinib 75 mg BD + RAI	Placebo + RAI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	51		
Units: Percentage of participants				
number (not applicable)	37.4	41.2		

Statistical analyses

Statistical analysis title	Clinical remission rate: BRAF/NRAS positive set

Statistical analysis description:

Selumetinib in combination with RAI was compared with placebo in combination with RAI. The analysis was performed using a logistic regression model including treatment as the only covariate. An odds ratio >1 favours selumetinib in combination with RAI.

Comparison groups	Selumetinib 75 mg BD + RAI v Placebo + RAI
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6549 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.73

Notes:

[4] - P-value and CIs were calculated using profile likelihood.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Includes adverse events (AEs) with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of selumetinib/placebo. Overall timeframe for collection of AEs was up to 66 days from the first dose.

Adverse event reporting additional description:

Deaths (all causes) is reported for the ITT analysis set for the overall study period. Serious and Non-serious) AE data is reported for the safety analysis set (including all patients who received at least 1 dose of randomised treatment) for the 5-week treatment period plus 30-day follow-up phase.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Selumetinib 75mg BID

Reporting group description:

Description (Arm-group)

Reporting group title	Placebo 75mg BID

Reporting group description:

Description (Arm-group)

Serious adverse events	Selumetinib 75mg BID	Placebo 75mg BID	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 154 (4.55%)	0 / 77 (0.00%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events			
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 154 (0.65%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 154 (0.65%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric haemorrhage			

subjects affected / exposed	1 / 154 (0.65%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	2 / 154 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 154 (0.65%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Selumetinib 75mg BID	Placebo 75mg BID	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	141 / 154 (91.56%)	43 / 77 (55.84%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	31 / 154 (20.13%)	1 / 77 (1.30%)	
occurrences (all)	31	1	
Weight decreased			
subjects affected / exposed	0 / 154 (0.00%)	4 / 77 (5.19%)	
occurrences (all)	0	4	
Vascular disorders			
Hypertension			
subjects affected / exposed	20 / 154 (12.99%)	3 / 77 (3.90%)	
occurrences (all)	23	3	

Nervous system disorders			
Dysgeusia			
subjects affected / exposed	6 / 154 (3.90%)	4 / 77 (5.19%)	
occurrences (all)	6	4	
Headache			
subjects affected / exposed	8 / 154 (5.19%)	10 / 77 (12.99%)	
occurrences (all)	8	11	
Paraesthesia			
subjects affected / exposed	4 / 154 (2.60%)	4 / 77 (5.19%)	
occurrences (all)	4	4	
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	9 / 154 (5.84%)	0 / 77 (0.00%)	
occurrences (all)	9	0	
Fatigue			
subjects affected / exposed	44 / 154 (28.57%)	13 / 77 (16.88%)	
occurrences (all)	44	13	
Oedema peripheral			
subjects affected / exposed	30 / 154 (19.48%)	4 / 77 (5.19%)	
occurrences (all)	32	4	
Eye disorders			
Periorbital oedema			
subjects affected / exposed	8 / 154 (5.19%)	0 / 77 (0.00%)	
occurrences (all)	8	0	
Vision blurred			
subjects affected / exposed	16 / 154 (10.39%)	5 / 77 (6.49%)	
occurrences (all)	16	5	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	15 / 154 (9.74%)	3 / 77 (3.90%)	
occurrences (all)	15	3	
Diarrhoea			
subjects affected / exposed	68 / 154 (44.16%)	12 / 77 (15.58%)	
occurrences (all)	78	13	
Dry mouth			

subjects affected / exposed	15 / 154 (9.74%)	3 / 77 (3.90%)	
occurrences (all)	15	3	
Dyspepsia			
subjects affected / exposed	8 / 154 (5.19%)	1 / 77 (1.30%)	
occurrences (all)	8	1	
Nausea			
subjects affected / exposed	44 / 154 (28.57%)	8 / 77 (10.39%)	
occurrences (all)	44	10	
Stomatitis			
subjects affected / exposed	17 / 154 (11.04%)	4 / 77 (5.19%)	
occurrences (all)	18	4	
Vomiting			
subjects affected / exposed	14 / 154 (9.09%)	0 / 77 (0.00%)	
occurrences (all)	14	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 154 (1.95%)	4 / 77 (5.19%)	
occurrences (all)	3	4	
Skin and subcutaneous tissue disorders			
Rash follicular			
subjects affected / exposed	13 / 154 (8.44%)	0 / 77 (0.00%)	
occurrences (all)	13	0	
Rash macular			
subjects affected / exposed	12 / 154 (7.79%)	2 / 77 (2.60%)	
occurrences (all)	12	2	
Acne			
subjects affected / exposed	13 / 154 (8.44%)	2 / 77 (2.60%)	
occurrences (all)	13	2	
Dermatitis acneiform			
subjects affected / exposed	67 / 154 (43.51%)	4 / 77 (5.19%)	
occurrences (all)	70	4	
Dry skin			
subjects affected / exposed	12 / 154 (7.79%)	4 / 77 (5.19%)	
occurrences (all)	12	4	
Pruritus			

subjects affected / exposed	21 / 154 (13.64%)	3 / 77 (3.90%)	
occurrences (all)	21	3	
Rash maculo-papular			
subjects affected / exposed	19 / 154 (12.34%)	4 / 77 (5.19%)	
occurrences (all)	19	4	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 154 (0.65%)	4 / 77 (5.19%)	
occurrences (all)	1	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2013	• Additional safety assessments were added and blood volumes for clinical chemistry and haematology assessments were increased accordingly (Food and Drug Administration [FDA] request). • Inclusion criterion 13 was updated (clarification). • Text added to specify that all adverse events were to be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4 (clarification at FDA request). • BRAF/NRAS mutation status definitions were added (clarification). • Haematoxylin and eosin stained sections were to be prepared by the central laboratory (to ensure sample processing consistency).
15 July 2013	• Primary and secondary objectives were updated (FDA comments): efficacy in the genetic subgroup population of BRAF or NRAS mutation positive patients was considered a secondary objective (previously a co primary objective). It was also clarified that complete remission rate and clinical remission rate at 18 months were to be assessed in the ITT study population. Text describing the analysis of the primary endpoint was updated accordingly and further details of sensitivity analyses were added. Description of the Dunnett and Tamhane step-up procedure was removed as this was no longer applicable. • Exclusion criterion 7 was added (FDA request). • Text was added to clarify that archival tumour analyses may have included, but were not limited to, BRAF V600E and NRAS Q61R, Q61K and Q61L (FDA comments). • It was clarified that randomisation of 228 patients in a 2:1 ratio was expected to provide at least 80% power to show statistical significance for the primary endpoint (FDA comments).
01 July 2014	• The treatment plan was updated to clarify that if a patient suspended study drug (selumetinib or placebo) treatment for more than 14 days, they were no longer eligible to re-start treatment (to provide clear instruction on allowed study drug interruption). • It was clarified that the visit window for Visit 4, RAI treatment dose administration (Visit 5) and Visit 6 was +1 week (clarification). • Inclusion criterion 14 was updated (to specify the time frame for adequate organ function assessment). • Exclusion criteria 4, 10 and 22 were updated (to allow patient rescreening, enrolment of patients without external beam radiation therapy in the 6 months before randomisation and to specify the time frame for assessment of blood pressure and adequate organ function). • The maximum daily dose of vitamin E received from selumetinib/placebo was increased to 261.6 mg/day (new calculation). • Text added to allow re-screening. • Instructions on handling patients who had discontinued selumetinib/placebo were updated. • It was clarified that assessment of the percentage uptake in the thyroid bed was to be assessed by the local investigator site according to local clinical practice (to reflect the current situation in clinical practice). • Plasma clinical chemistry assessments and leucocyte differential count as a percentage were added (to allow local laboratories to perform clinical chemistry assessments in plasma). • Guidance for the management of visual symptoms was updated (retinal pigment epithelial detachment added). • Guidance for the management of patients with dyspnoea was updated (dyspnoea is an expected event of selumetinib; however, dyspnoea could also be the symptom of underlying serious lung conditions).

25 October 2018	• Study was to be terminated early and all randomised patients who had not yet completed their 3-year follow up were to instead have an end of study phone call. The wording of the 3-years post-RAI follow-up was changed to final study follow-up, in-line with the change. Reason: In the primary analysis (DCO date: 18 May 2018), the primary endpoint was not met and, consequently, collection of further data on efficacy endpoints was no longer considered relevant.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated early (based on the findings of the primary analysis at 18 months post-RAI treatment) and all randomised patients who had not yet completed their 3-year follow-up visit were instead to have an end of study phone call.

Notes: