Clinical trial results:
Evaluating the Long-Term Outcomes and Durability of Effect Following Treatment with Cladribine Tablets for Multiple Sclerosis: An Exploratory Phase IV Ambispective Study of Patients Who Previously Participated in the CLARITY/CLARITY-EXT and ORACLE MS Clinical Trials

Summary

EudraCT number	2019-000069-19
Trial protocol	CZ SE PT EE BG AT LT BE PL ES HR IT RO
Global end of trial date	13 May 2021

Results information

Result version number	v2 (current)
This version publication date	16 June 2022
First version publication date	10 March 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	MS700568_0026

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03961204
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Healthcare KGaA, Darmstadt, Germany
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Center, Merck Healthcare KGaA,Darmstadt, Germany, +49 6151 72 5200, service@merckgroup.com
Scientific contact	Communication Center, Merck Healthcare KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.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	13 May 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to explore the long-term outcomes, durability of effect, and real world treatment patterns in subjects previously participating in the Phase 3 oral cladribine in first clinical demyelinating event (ORACLE MS) and Oral Cladribine in subjects with relapsing remitting multiple sclerosis (RRMS), extension study (CLARITY/CLARITY-EXT) clinical trials with the study number of 28821 (NCT00725985), 25643 (NCT00213135) and 27820 (NCT00641537) respectively.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 August 2019
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	United States: 17
Country: Number of subjects enrolled	Canada: 29
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Italy: 68
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Bulgaria: 40
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Czechia: 73

Country: Number of subjects enrolled	Estonia: 31
Country: Number of subjects enrolled	Georgia: 9
Country: Number of subjects enrolled	Lithuania: 7
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Romania: 15
Country: Number of subjects enrolled	Serbia: 22
Country: Number of subjects enrolled	Ukraine: 21
Country: Number of subjects enrolled	Russian Federation: 182
Country: Number of subjects enrolled	Lebanon: 7
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Tunisia: 19
Worldwide total number of subjects	662
EEA total number of subjects	332

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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	662
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 662 subjects were enrolled in this trial at different sites in United States and Europe.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Cohort A

Arm description:

Subjects previously enrolled in parent studies CLARITY (NCT00213135), CLARITY-EXT (NCT00641537), ORACLE (NCT00725985) and had received Cladribine tablet and Placebo were invited up to 2 visit for follow-up/data collection.

Arm type	No intervention
Investigational medicinal product name	Cladribine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

No study treatment was administered as part of this study

Number of subjects in period 1	Cohort A
Started	662
Completed	655
Not completed	7
Consent withdrawn by subject	2
Not Specified	1
Lost to follow-up	3
Missing	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A
Reporting group description:	
Subjects previously enrolled in parent studies CLARITY (NCT00213135), CLARITY-EXT (NCT00641537), ORACLE (NCT00725985) and had received Cladribine tablet and Placebo were invited up to 2 visit for follow-up/data collection.	

Reporting group values	Cohort A	Total	
Number of subjects	662	662	
Age categorical Units:			
Age Continuous Units: Years			
arithmetic mean	49.3		
standard deviation	± 10.32	-	
Sex: Female, Male Units: Participants			
Female	444	444	
Male	218	218	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	8	8	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	3	3	
White	645	645	
More than one race	6	6	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Cohort A

Reporting group description:

Subjects previously enrolled in parent studies CLARITY (NCT00213135), CLARITY-EXT (NCT00641537), ORACLE (NCT00725985) and had received Cladribine tablet and Placebo were invited up to 2 visit for follow-up/data collection.

Primary: Percentage of Subjects Using Wheelchair or Being Bedridden Assessed by Expanded Disability Status Scale (EDSS) Score 7.0 or Higher

End point title	Percentage of Subjects Using Wheelchair or Being Bedridden Assessed by Expanded Disability Status Scale (EDSS) Score 7.0 or Higher[1]

End point description:

EDSS scores range from 0.0 (normal) to 10.0 (dead). EDDS is a scale from 0-10 that evaluates a person with Multiple Sclerosis (MS) disability/neurologic function level where 0=normal and 10=death due to MS. Score of 7.0 is defined as unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day. Score of 8.0 is defined as Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms. FAS included all subjects participating in CLASSIC study [randomized in CLARITY and have received ≥ 1 course of IMP (Cladribine Tablets or placebo) or subjects randomized in ORACLE study and have received ≥ 1 course of IMP]. Here, "Number of subjects analyzed", signifies those subjects who were evaluable for this outcome measure.

End point type	Primary

End point timeframe:

3 months prior to study visit 1. Retrospectively from end of parent study (NCT00213135, NCT00641537 and NCT00725985) to study visit 1 (study visit 1 occurred up to 3 months from screening)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics was planned for this endpoint.

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	636			
Units: percentage of participant				
number (confidence interval 95%)	8.2 (6.2 to 10.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical and Demographic Characteristic: Age, Disease Duration

End point title	Clinical and Demographic Characteristic: Age, Disease Duration

End point description:

Clinical and demographic characteristics including age & disease duration is reported in form of long term responders (LTR) & non-responder (NR). Here LTR is defined as study subjects not requiring DMD 4 years or later following their last dose of IMP, and who did not demonstrate any evidence of disease

reactivation based on Investigator assessment of clinical & imaging outcomes. NR is defined as study subjects requiring DMD < 4 years following their last dose of IMP or who demonstrate any evidence of disease reactivation based on Investigator assessment of clinical & imaging outcomes. Full analysis set population was included. Here, "Number of subjects analyzed", signifies those subjects who were evaluable for this outcome measure. Here n=Number analyzed, signifies those subjects who were evaluable for this outcome measure for specified categories.

End point type	Secondary

End point timeframe:

At study visit 1, occurred up to 3 months from screening (Retrospective analysis of medical record of parent study-NCT00213135, NCT00641537 and NCT00725985)

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	627			
Units: years				
arithmetic mean (standard deviation)				
Long-term responders (LTR): Age at SV 1 (n= 378)	50.5 (± 10.65)			
Non-responders (NR): Age at SV1 (n=249)	47.1 (± 9.47)			
LTR: Disease duration (n= 330)	19.82 (± 9.161)			
NR: Disease duration (n=226)	16.82 (± 8.321)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Expanded Disability Status Scale (EDSS) Score 6.0 or Higher

End point title	Percentage of Subjects With Expanded Disability Status Scale (EDSS) Score 6.0 or Higher

End point description:

EDDS is a scale from 0-10 that evaluates a person with MS disability/neurologic function level where 0= normal and 10= death due to MS. Score of 6.0 is defined as "intermittent or unilateral constant assistance (cane, crutch and brace) required to walk about 100 meters with or without resting". FAS included all subjects participating in CLASSIC study [randomized in CLARITY and have received ≥ 1 course of IMP (Cladribine Tablets or placebo) or subjects randomized in ORACLE study and have received ≥ 1 course of IMP].

End point type	Secondary

End point timeframe:

At study visit 1. Retrospectively after last IMP administration from parent study (NCT00213135, NCT00641537 and NCT00725985) to study visit 1 (study visit 1 occurred up to 3 months from screening)

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	662			
Units: percentage of participant				
number (confidence interval 95%)	13.9 (11.4 to 16.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects in Each Category of Clinical and Demographic Characteristics

End point title	Number of Subjects in Each Category of Clinical and Demographic Characteristics

End point description:

Clinical characteristics included gender, race, disease classification (RRMS, SPMS, unknown & no MS disease), Prior use of DMDs & high-disease activity (HAD) status, education level, and employment status. Number of subjects in each category of clinical characteristics were reported in form of long-term responder and non-responder. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure. Here n=Number analyzed, signifies those subjects who were evaluable for this outcome measure for specified categories.

End point type	Secondary

End point timeframe:

At study visit 1, occurred up to 3 months from screening (Retrospective analysis of medical record of parent study-NCT00213135, NCT00641537 and NCT00725985)

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	627			
Units: subjects				
Long term responder (LTR): Sex (Female) (n=378)	251			
LTR: Sex (Male) (n=378)	127			
Non-responder (NR): Sex (Female) (n=249)	171			
NR: Sex (Male) (n=249)	78			
LTR: Race (White) (n=378)	368			
NR: Race (White) (n=249)	244			
LTR: Race (Black or African American) (n=378)	1			
NR: Race (Black or African American) (n=249)	0			
LTR: Race (Asian) (n=378)	5			
NR: Race (Asian) (n=249)	3			
LTR: Race (Other) (n=378)	4			
NR: Race (Other) (n=249)	2			
LTR: Type of MS-RRMS (n=378)	259			
NR: Type of MS-RRMS (n=249)	173			
LTR: Type of MS-SPMS (n=378)	71			

NR: Type of MS-SPMS (n=249)	41			
LTR: Type of MS-Unknown (n=378)	0			
NR: Type of MS-Unknown (n=249)	14			
LTR: Type of MS-No MS disease (n=378)	48			
NR: Type of MS-No MS disease (n=249)	21			
LTR: Prior Use of DMDs (n=276)	57			
NR: Prior Use of DMDs (n=132)	33			
LTR:HDA Subjects (n=276)	83			
NR: HDA Subjects (n=132)	35			
LTR: Education level (Below 8 Years) (n=373)	19			
NR: Education level (Below 8 Years) (n=245)	16			
LTR: Education level (8 to 10 Years) (n=373)	73			
NR: Education level (8 to 10 Years) (n=245)	43			
LTR: Education level (10 to 15 Years) (n=373)	190			
NR: Education level (10 to 15 Years) (n=245)	130			
LTR: Education level (Over 15 Years) (n=373)	91			
NR: Education level (Over 15 Years) (n=245)	56			
LTR: Employment Status (with wages) (n=378)	160			
NR: Employment Status (with wages) (n=249)	122			
LTR: Employment Status (Self Employed) (n=378)	38			
NR: Employment Status (Self-Employed) (n=249)	17			
LTR:Employment (Out of Work > 1 year) (n=378)	12			
NR: Employment (Out of Work >1 year) (n=249)	13			
LTR:Employment (Out of Work < 1 year) (n=378)	4			
NR: Employment (Out of Work < 1 year) (n=249)	2			
LTR: Employment (A Homemaker) (n=378)	22			
NR: Employment (A Homemaker) (n=249)	24			
LTR: Employment Status (Retired) (n=378)	67			
NR: Employment Status (Retired) (n=249)	19			
LTR: Employment (Unable to work) (n=378)	48			
NR: Employment (Unable to work) (n=249)	26			
LTR:Employment (Not collected at site) (n=378)	3			
NR: Employment (Not collected at site) (n=249)	6			
LTR: Employment (Unknown/Not reported) (n=378)	24			

NR: Employment (Unknown/Not reported) (n=249)	20			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Characteristic: Expanded Disability Status Scale (EDSS) Score

End point title	Clinical Characteristic: Expanded Disability Status Scale (EDSS) Score

End point description:

EDSS is a scale based on standardized neurological examination which comprised of optic, brain stem, pyramidal, cerebellar, sensory & cerebral functions, as well as walking ability. EDSS scores range from 0.0 (normal) to 10.0 (dead). Clinical characteristics of EDSS score in form of long-term responders & non-responder was reported for at parent study baseline (based on retrospective data collection [based on chart review] at study visit 1) & study visit 1. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure. Here n=Number analyzed, signifies those subjects who were evaluable for this outcome measure for specified categories.

End point type	Secondary

End point timeframe:

At study visit 1, occurred up to 3 months from screening (Retrospective analysis of medical record of parent study-NCT00213135, NCT00641537 and NCT00725985)

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	627			
Units: score on a scale				
arithmetic mean (standard deviation)				
LTR:EDSS score at parent study baseline (n=378)	2.44 (± 1.292)			
NR: EDSS score at parent study baseline (n=249)	2.38 (± 1.251)			
LTR: EDSS score at study visit 1 (n=366)	3.23 (± 2.121)			
NR: EDSS score at study visit 1, (n=234)	3.32 (± 2.102)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Characteristic: Number of Relapses

End point title	Clinical Characteristic: Number of Relapses

End point description:

Relapse was defined as participant-reported symptoms & objectively observed signs typical of an acute inflammatory demyelinating event in CNS, developing acutely or sub-acutely with duration of at least 24 hours, in absence of fever or infection. Clinical characteristics of number of relapses during last year

before enrollment of parent study (it is reported based on retrospective data collection [based on chart review] at study visit 1) in the form of long-term responders (LTR) & non-responder (NR) was reported. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure. Here n=Number analyzed, signifies those subjects who were evaluable for this outcome measure for specified categories.

End point type	Secondary

End point timeframe:

At study visit 1, occurred up to 3 months from screening (Retrospective analysis of medical record of parent study-NCT00213135, NCT00641537 and NCT00725985)

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	408			
Units: Relapses				
arithmetic mean (standard deviation)				
LTR:Relapses before enrollment parent study(n=276)	1.3 (± 0.64)			
NR:Relapses before enrollment parent study (n=132)	1.3 (± 0.56)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of total T1-weighted (T1-W) Lesions

End point title	Number of total T1-weighted (T1-W) Lesions

End point description:

Total number of T1-W lesion were measured by Using magnetic resonance imaging (MRI) Scans. Here long term responder is defined as study participants not requiring DMD 4 years or later following their last dose of IMP in parent study. Non-responder is defined as study participants requiring DMD less than 4 years following their last dose of IMP in parent study. The MRI analysis population includes all FAS subjects who signed the MRI sub- study informed consent. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure and Here n=Number analyzed, signifies those subjects who were evaluable for this outcome measure for specified categories.

End point type	Secondary

End point timeframe:

At study visit 2, within 6 months from screening (Retrospective analysis of medical record of parent study-NCT00213135, NCT00641537 and NCT00725985)

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: lesions				
arithmetic mean (standard deviation)				
Long-term responder (n=20)	12.7 (± 8.97)			
Non-responder (n=19)	16.1 (± 10.90)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of total T2-weighted (T2-W) Lesions

End point title	Number of total T2-weighted (T2-W) Lesions

End point description:

Total number of T2-W lesion were measured by Using magnetic resonance imaging (MRI) Scans. Here long term responder is defined as study participants not requiring DMD 4 years or later following their last dose of IMP in parent study. Non-responder is defined as study participants requiring DMD less than 4 years following their last dose of IMP in parent study. The MRI analysis population includes all FAS subjects who signed the MRI sub- study informed consent. Number of subjects analyzed signifies number of subjects who were evaluable for this outcome measure. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure and Here n=Number analyzed, signifies those subjects who were evaluable for this outcome measure for specified categories.

End point type	Secondary

End point timeframe:

At study visit 2, within 6 months from screening (Retrospective analysis of medical record of parent study-NCT00213135, NCT00641537 and NCT00725985)

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: lesions				
arithmetic mean (standard deviation)				
Long-term responder (n=22)	20.2 (± 18.67)			
Non-responder (n=19)	25.1 (± 18.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: T1-weighted (T1-W) Lesion Volume

End point title	T1-weighted (T1-W) Lesion Volume

End point description:

T1-W lesion volume were measured by Using magnetic resonance imaging (MRI) Scans. Here long term responder is defined as study participants not requiring DMD 4 years or later following their last dose of IMP in parent study. Non-responder is defined as study participants requiring DMD less than 4 years following their last dose of IMP in parent study. The MRI analysis population includes all FAS subjects who signed the MRI sub- study informed consent. Number of subjects analyzed signifies number of subjects who were evaluable for this outcome measure. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure and Here n=Number analyzed, signifies those subjects who were evaluable for this outcome measure for specified categories.

End point type	Secondary

End point timeframe:

At study visit 2, within 6 months from screening (Retrospective analysis of medical record of parent study-NCT00213135, NCT00641537 and NCT00725985)

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: cubic centimeter (cm^3)				
arithmetic mean (standard deviation)				
Long-term responder (n=20)	1.655 (± 1.3953)			
Non-responder (n=18)	6.773 (± 6.4788)			

Statistical analyses

No statistical analyses for this end point

Secondary: T2-weighted (T2-W) Lesion Volume

End point title	T2-weighted (T2-W) Lesion Volume

End point description:

T2-W lesion volume were measured by Using magnetic resonance imaging (MRI) Scans. Here long term responder is defined as study participants not requiring DMD 4 years or later following their last dose of IMP in parent study. Non-responder is defined as study participants requiring DMD less than 4 years following their last dose of IMP in parent study. The MRI analysis population includes all FAS subjects who signed the MRI sub- study informed consent. Number of subjects analyzed signifies number of subjects who were evaluable for this outcome measure. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure and Here n=Number analyzed, signifies those subjects who were evaluable for this outcome measure for specified categories.

End point type	Secondary

End point timeframe:

At study visit 2, within 6 months from screening (Retrospective analysis of medical record of parent study-NCT00213135, NCT00641537 and NCT00725985)

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: cubic centimeter (cm^3)				
arithmetic mean (standard deviation)				
Long-term responder (n=22)	4.920 (± 6.7665)			
Non-responder (n=19)	14.664 (± 13.8109)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Brain Volume

End point title	Total Brain Volume

End point description:

Brain volume were measured by Using magnetic resonance imaging (MRI) Scans. Here long term responder is defined as study participants not requiring DMD 4 years or later following their last dose of IMP in parent study. Non-responder is defined as study participants requiring DMD less than 4 years following their last dose of IMP in parent study. The MRI analysis population includes all FAS subjects who signed the MRI sub- study informed consent. Number of subjects analyzed signifies number of subjects who were evaluable for this outcome measure. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure and Number analyzed refers to number of subjects evaluable for specified categories.

End point type	Secondary

End point timeframe:

At study visit 2, within 6 months from screening (Retrospective analysis of medical record of parent study-NCT00213135, NCT00641537 and NCT00725985)

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: cubic centimeter (cm^3)				
arithmetic mean (standard deviation)				
Long-term responder (n=21)	1472.559 (± 59.9500)			
Non-responder (n=18)	1417.431 (± 109.8668)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to study visit 2 (Up to approximately 6 months and Retrospective AEs data collection based on chart review of subjects from end of parent studies; NCT00213135, NCT00641537 and NCT00725985)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	Cohort A
Reporting group description:	
Subjects previously enrolled in parent studies CLARITY (NCT00213135), CLARITY-EXT (NCT00641537), ORACLE (NCT00725985) and had received Cladribine tablet and Placebo were invited up to 2 visit for follow-up/data collection.	

Serious adverse events	Cohort A		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 662 (0.15%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 662 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort A		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 662 (1.21%)		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 662 (0.15%)		
occurrences (all)	1		
Vascular disorders			

Flushing subjects affected / exposed occurrences (all)	1 / 662 (0.15%) 1		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	 2 / 662 (0.30%) 2 2 / 662 (0.30%) 2 1 / 662 (0.15%) 1		
Endocrine disorders Autoimmune thyroid disorder subjects affected / exposed occurrences (all)	 1 / 662 (0.15%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 1 / 662 (0.15%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 July 2020	There was updates in study design, objective and endpoint section, schedule of activities, exclusion criteria and adverse event section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported