



Clinical trial results:

Neoadjuvant study of targeting ROS1 in combination with endocrine therapy in invAsive Lobular carciNoma of the breast

Summary

EudraCT number	2019-004942-14
Trial protocol	BE FR
Global end of trial date	17 January 2025

Results information

Result version number	v1 (current)
This version publication date	29 July 2026
First version publication date	29 July 2026

Trial information

Trial identification

Sponsor protocol code	IJB-LOB-2019
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04551495
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut Jules Bordet
Sponsor organisation address	Rue Meylemeersch, 90, Anderlecht, Belgium, 1070
Public contact	Study Chair, Dr. Philippe Aftimos, +32 025413208, philippe.aftimos@hubruxelles.be
Scientific contact	CTC, Institut Jules Bordet, ROSALINE.ctc@hubruxelles.be

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	24 January 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 August 2024
Global end of trial reached?	Yes
Global end of trial date	17 January 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of endocrine therapy + entrectinib in women with ER-positive/HER2-negative early breast cancer of the lobular subtype

Protection of trial subjects:

An IDMC took place on the 16-Sep-22 and the IDMC had no objection to the continuation of the trial to stage II.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 January 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 37
Country: Number of subjects enrolled	France: 19
Worldwide total number of subjects	56
EEA total number of subjects	56

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)	44
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 08/01/2021 and 15/03/2024, participants were recruited in 10 participating sites in 2 countries (Belgium and France)

Pre-assignment

Screening details:

Once informed consent was signed, inclusion and exclusion criteria were double checked to identify any screening failure. They were reported in the trial registration tool.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Single arm trial
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Arm description:

This single arm, multi-center, phase 2 trial will include pre and post-menopausal women with ER-positive/HER2-negative early stage invasive lobular carcinoma of the breast to evaluate the effect of combining endocrine therapy with entrectinib. Surgery took place after at least 16 weeks of treatment, during week 18 (+ 7-day window).

Intervention information: Participants received four 28-day cycles of letrozole 2.5 mg daily in combination with entrectinib 600 mg daily. Pre-menopausal women received goserelin 3.6 mg every 28 days.

Surgery took place after at least 16 weeks of treatment, during week 18 (+ 7-day window).

Arm type	Experimental
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	Femara®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received four 28-day cycles of letrozole 2.5 mg daily in combination with entrectinib 600 mg daily. Pre-menopausal women received goserelin 3.6 mg every 28 days.

Investigational medicinal product name	Entrectinib
Investigational medicinal product code	
Other name	Rozlytrek
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants received four 28-day cycles of letrozole 2.5 mg daily in combination with entrectinib 600 mg daily. Pre-menopausal women received goserelin 3.6 mg every 28 days.

Investigational medicinal product name	Goserelin
Investigational medicinal product code	
Other name	Zoladex 3.6 mg Implant
Pharmaceutical forms	Implant in pre-filled syringe
Routes of administration	Injection

Dosage and administration details:

Participants received four 28-day cycles of letrozole 2.5 mg daily in combination with entrectinib 600 mg

daily. Pre-menopausal women received goserelin 3.6 mg every 28 days.

Number of subjects in period 1	Single arm trial
Started	56
Completed	49
Not completed	7
Consent withdrawn by subject	1
Ductal carcinoma found in baseline biopsy in addit	1
Adverse event, non-fatal	5

Baseline characteristics

Reporting groups

Reporting group title	Single arm trial
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Reporting group description:

This single arm, multi-center, phase 2 trial will include pre and post-menopausal women with ER-positive/HER2-negative early stage invasive lobular carcinoma of the breast to evaluate the effect of combining endocrine therapy with entrectinib. Surgery took place after at least 16 weeks of treatment, during week 18 (+ 7-day window).

Intervention information: Participants received four 28-day cycles of letrozole 2.5 mg daily in combination with entrectinib 600 mg daily. Pre-menopausal women received goserelin 3.6 mg every 28 days.

Surgery took place after at least 16 weeks of treatment, during week 18 (+ 7-day window).

Reporting group values	Single arm trial	Total	
Number of subjects	56	56	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	44	44	
From 65-84 years	12	12	
85 years and over	0	0	
Age continuous			
Units: years			
median	56		
standard deviation	± 9.68	-	
Gender categorical			
Units: Subjects			
Female	56	56	
Male	0	0	
Menopausal characteristics			
Units: Subjects			
Premenopausal	23	23	
Postmenopausal	33	33	
Tumor laterality			
Units: Subjects			
Bilateral	1	1	
Left	22	22	
Right	33	33	
Primary tumor location			
Units: Subjects			
Breast	56	56	
Invasive emboli/invasion			
Units: Subjects			

Yes	5	5	
No	48	48	
Unkown	3	3	
Multifocal tumor Units: Subjects			
Yes	13	13	
No	43	43	
Clinical Tumor Stage Units: Subjects			
T1c	1	1	
T2	28	28	
T3	27	27	
Clinical Tumor Stage Units: Subjects			
N0	35	35	
N1	21	21	
Clinical Stage (Cancer Characteristics) Units: Subjects			
IIA	20	20	
IIB	25	25	
IIIA	11	11	
Histological Grade Units: Subjects			
G1: well differentiated	7	7	
G2: Moderately differentiated	43	43	
G3: Poorly differentiated	5	5	
Missing	1	1	
ECOG at screening Units: Subjects			
Zero	45	45	
One	8	8	
Missing	3	3	
ECG at screening Units: Subjects			
Normal (clinical significance)	40	40	
Abnormal (clinical significance)	16	16	
Prior systemic therapies Units: Subjects			
Yes	0	0	
No	56	56	
Biomarker at screening - ER positive status Units: Subjects			
Yes	56	56	
No	0	0	
Biomarker at screening - PR (all PR were the same in all tested foci) Units: Subjects			
Yes	54	54	
No	2	2	
Biomarker at screening - HER2 IHC Units: Subjects			

Zero	23	23	
1+	20	20	
2+	13	13	
Biomarker at screening - KI67 Units: Subjects			
<20%	40	40	
>20%	11	11	
Missing	5	5	
Age at inclusion Units: year			
median	56		
full range (min-max)	35 to 78	-	
Biomarker at screening - PR Results Units: percent			
arithmetic mean	23.3		
standard deviation	± 30.43	-	

End points

End points reporting groups

Reporting group title	Single arm trial
Reporting group description: This single arm, multi-center, phase 2 trial will include pre and post-menopausal women with ER-positive/HER2-negative early stage invasive lobular carcinoma of the breast to evaluate the effect of combining endocrine therapy with entrectinib. Surgery took place after at least 16 weeks of treatment, during week 18 (+ 7-day window). Intervention information: Participants received four 28-day cycles of letrozole 2.5 mg daily in combination with entrectinib 600 mg daily. Pre-menopausal women received goserelin 3.6 mg every 28 days. Surgery took place after at least 16 weeks of treatment, during week 18 (+ 7-day window).	
Subject analysis set title	Evaluable Participants
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: all evaluable participants defined as participant : *who started the combined schedule of letrozole and entrectinib *who did not miss more than 18 days of entrectinib, to have a minimal dose of intensity of 85% *Who was surgically treated and *for whom he criteria for assessing RCB can be applied *For whom the RCB, ypTNM and loa-cally-assessed breast MRI (tumor objective response) data was collected)	

Primary: Observed proportion of residual cancer burden (0/1) estimated to be equal to 3% to the theoretical proportion of 15%

End point title	Observed proportion of residual cancer burden (0/1) estimated to be equal to 3% to the theoretical proportion of 15% ^[1]
End point description: The primary efficacy analysis tests the hypothesis of equality of observed proportion of residual cancer burden (0/1) estimated to be equal to 3% to the theoretical proportion of 15%. The study will then test the null hypothesis that the rate of RCB 0/1 is less or equal than 3% versus that this rate is greater than 3% with the desired power to be reached in case this rate is greater or equal than 15%. One-sided level of alpha =10% and bêta =10% have been used for sample size determination. The analyses are performed on the evaluable set (n = 41). We observe 0/41 participant with RCB equal to 0 or 1. Under the Simon's design, we cannot reject the null hypothesis because no patient had RCB « 0/1 ». Level of confidence interval is 90 % ; one side Parameter type is the proportion of residual cancer burden (0/1)	
End point type	Primary
End point timeframe: At surgery, after neoadjuvant treatment	

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: This is single arm study

End point values	Evaluable Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	41			
Units: Participants				
RCB 0/1	0			
RCB 2/3	41			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with pCR and axilla by local evaluation

End point title	Number of patients with pCR and axilla by local evaluation
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End point description:

The number of participants with pCR and axilla by local evaluation is 0/41

End point type	Secondary
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End point timeframe:

At surgery

End point values	Single arm trial	Evaluable Participants		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	56	41		
Units: Participants	56	41		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with best overall rate response

End point title	Number of participants with best overall rate response
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End point description:

There are 20/41 ($p = 0.4878$; 95% CI= [0.3348-0.6408], in percent 48.78%) patients with complete RECIST response evaluation or partial RECIST response evaluation.

End point type	Secondary
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End point timeframe:

At surgery

End point values	Single arm trial	Evaluable Participants		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	56	41		
Units: Participants	56	41		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first administration of study treatment until 30 days after the last administration of study treatments, all AEs should be reported.

From 31 days after last administration of study treatment, only SAEs related to study treatment must be reported

Adverse event reporting additional description:

If the participant receives goserelin during the screening period, the reporting of all SAEs starts at the goserelin administration date.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	28

Reporting groups

Reporting group title	Overall trial
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Reporting group description:

Overall trial

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 56 (7.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Enterococcal sepsis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 56 (1.79%)		
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	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 56 (98.21%)		
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Hot flush			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	10		
Hypotension			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Lymphocele			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Orthostatic hypotension			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Peripheral venous disease			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	12 / 56 (21.43%)		
occurrences (all)	12		
Face oedema			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	24 / 56 (42.86%)		
occurrences (all)	25		
Malaise			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
Mucosal inflammation			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Oedema			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	16 / 56 (28.57%)		
occurrences (all)	19		
Pain			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Swelling face			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Reproductive system and breast disorders			

Breast discharge subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Vulvovaginal dryness subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	5 / 56 (8.93%) 5		
Dysphonia subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Dyspnoea subjects affected / exposed occurrences (all)	11 / 56 (19.64%) 12		
Dyspnoea exertional subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2		
Hyperventilation subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Nasal inflammation subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Psychiatric disorders			
Affective disorder subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Confusional state subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Hallucination			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	3		
Irritability			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Libido decreased			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Mood altered			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Blood creatine increased			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
Hepatic enzyme increased			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Oxygen saturation decreased			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Troponin increased			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	5		
Injury, poisoning and procedural complications			
Breast injury			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Foot fracture			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Wrist fracture			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	2		
Nervous system disorders			
Ageusia			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
Allodynia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Amnesia			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Ataxia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Balance disorder			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	6		
Cognitive disorder			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
Disturbance in attention			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	6		
Dizziness			
subjects affected / exposed	10 / 56 (17.86%)		
occurrences (all)	11		
Dysaesthesia			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	9		
Dysarthria			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
Dysgeusia			
subjects affected / exposed	34 / 56 (60.71%)		
occurrences (all)	37		
Dyskinesia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	5		
Hyperaesthesia			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
Hypotonia			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Language disorder			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Memory impairment			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Migraine			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Neuralgia			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
Neuropathy peripheral			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	9		
Peripheral motor neuropathy			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	10		
Polyneuropathy			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Presyncope			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Restless legs syndrome			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
Taste disorder			

subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1 1 / 56 (1.79%) 1 1 / 56 (1.79%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	27 / 56 (48.21%) 29		
Eye disorders Eye pain subjects affected / exposed occurrences (all) Photopsia subjects affected / exposed occurrences (all) Vision blurred subjects affected / exposed occurrences (all) Visual impairment subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1 1 / 56 (1.79%) 1 2 / 56 (3.57%) 2 4 / 56 (7.14%) 4		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain lower	3 / 56 (5.36%) 3 3 / 56 (5.36%) 3		

subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
Cheilitis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	40 / 56 (71.43%)		
occurrences (all)	45		
Diarrhoea			
subjects affected / exposed	16 / 56 (28.57%)		
occurrences (all)	17		
Dry mouth			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
Dyspepsia			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Dysphagia			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	5		
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Hypoaesthesia oral			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	18 / 56 (32.14%)		
occurrences (all)	19		
Odynophagia			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Oral hyperaesthesia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Paraesthesia oral			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Saliva altered			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	10 / 56 (17.86%)		
occurrences (all)	11		
Tongue discomfort			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Pain of skin			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	7		
Rash			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	7		

Rash maculo-papular subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Sensitive skin subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Skin exfoliation subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Renal and urinary disorders			
Acute kidney injury subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2		
Dysuria subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2		
Renal failure subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4		
Renal impairment subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Urinary incontinence subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	21 / 56 (37.50%) 23		
Back pain subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2		
Muscle spasms subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3		
Muscular weakness			

subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	6		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	12 / 56 (21.43%)		
occurrences (all)	12		
Neck pain			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Pain in jaw			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Torticollis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Infections and infestations			
COVID-19			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	5		
Cystitis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Gastroenteritis viral			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Laryngitis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		

Pseudomonas infection subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Sinusitis subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Vaginal infection subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	6 / 56 (10.71%) 7		
Fluid retention subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3		
Hypercreatininaemia subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Hyperuricaemia subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
Increased appetite subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 April 2021	BELGIUM Site agreement initial IJB/UCL St Luc/GHDC/Ste Elisabeth Namur New/amended patient information sheet / informed consent (including addendum) v2.0 + addendum A New/amended protocol v1.3 *Summary of changes in resquest from ANSM & CPP *addition of triple ECG before start of C3 & C4 *modification IC5 & EC1, EC4,EC10, EC12
30 July 2021	BELGIUM Addition of at least a new site or a site whose LEC did not reply initially or moved site *Addition of a site: UZ Leuven Site agreement initial UZ Brussels/ UZ Gent Site agreement amdt1UZ Brussels/ GHDC/ Ste Elisabeth Namur/ UCL St Luc
29 November 2021	BELGIUM Addition of at least a new site or a site whose LEC did not reply initially or moved site *IJB address change
22 March 2022	FRANCE New/amended patient information sheet / informed consent (including addendum) *ICF v2.0 + Addendum A *ICF 1.2 *ICF Pregnancy v1.1 New/amended Reference Safety Information *IB entrectinib v11 *Labels letrozole + goserelin v2.0 New/amended protocol *Protocol v2.0: Change IC4, section 6. 4 Cf new IB Entrectinib v11, EC7 Synopsis v2.0 Carte urgence v2.0 Annual Study progress Report v1 Change IJB address in all docs
14 April 2022	BELGIUM New/amended Reference Safety Information *IB v11 *Labels v2.0 letrozole + goserelin New/amended patient information sheet / informed consent (including addendum) *ICF v3.0 + Addendum B FR, NL, EN + SoC *ICF 2.1 FR, NL, EN (notification) *ICF Pregnancy 1.1 FR, NL, EN New/amended protocol *Protocol v2.0 FR, NL, EN + SoC : Change IC4, section 6. 4 Cf new IB Entrectinib v11, EC7 Synopsis v2.0 FR, NL, EN Patient emergency cards v2.0 Annual study progress report Site contracts : UZ Leuven initial ; UZ Gent Change IJB address in all docs

24 January 2023	FRANCE New/amended patient diary *Patient diary v2.0 New/amended patient information sheet / informed consent (including addendum) *ICF v3.0 + Addendum C FR + SoC New/amended documents or information related to IMP or IMPD: IB v12 Changes in the logistics of the trial, which are NOT site-related (ex: lab, CRO etc) Change of PI – already approved site *Change of PI IGR: CV & GCP Dr Ribeiro New/amended protocol *Protocol v3.0 + SoC: Increase of the patients to enrol number & increase of the study duration following IDMC recommendation Synopsis v3.0 FR Insurance certificate
02 March 2023	BELGIUM New/amended protocol *Protocol v3.0 + SoC : Increase of the patients to enrol number & increase of the study duration following IDMC recommendation New/amended patient information sheet / informed consent (including addendum): ICF v4.0 + Addendum C FR, EN, NL + SoC New/amended other study documents *Synopsis v3.0 FR, EN, NL *Insurance certificat New/amended Reference Safety Information: IB v12 New/amended patient diary: Patient diary v2.0

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.

There were no limitations and caveats.

Notes: