



## Clinical trial results:

**A multicenter, single-arm, phase II study to evaluate the activity of pre-operative zoledronate in triple negative breast cancer patients, according to p53 level**

### Summary

EudraCT number	2014-004194-16
Trial protocol	IT
Global end of trial date	08 June 2018

### Results information

Result version number	v1 (current)
This version publication date	15 June 2022
First version publication date	15 June 2022

### Trial information

#### Trial identification

Sponsor protocol code	IRFMN-BRC-6591
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#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	Istituto di Ricerche Farmacologiche Mario Negri IRCCS
Sponsor organisation address	Via Mario Negri 2, Milan, Italy,
Public contact	Laboratorio di metodologia per la ricerca clinica, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, 039 0239014645, eliana.rulli@marionegri.it
Scientific contact	Laboratorio di metodologia per la ricerca clinica, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, 039 0239014645, eliana.rulli@marionegri.it

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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	17 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 June 2018
Global end of trial reached?	Yes
Global end of trial date	08 June 2018
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

The study is primarily aimed at assessing the anti-tumor activity of pre-operative zoledronate measured through its effect on the Ki67 proliferative surrogate biomarker, in patients with triple negative breast cancer selected according to the p53 expression (high vs low p53 expression).

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Italy: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

Notes:

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**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)	15
From 65 to 84 years	5
85 years and over	1

## Subject disposition

### Recruitment

Recruitment details:

Patients fulfilling the eligibility criteria will be registered using a centralized system and will receive a pre-operative, single administration of zol (4mg i.v.), 7 days before definitive breast surgery .

The interval between diagnostic core biopsy and study registration must be no more than 2 weeks.

### Pre-assignment

Screening details:

NA

### Period 1

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

### Arms

<b>Arm title</b>	Single arm
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Arm description:

Patients fulfilling the eligibility criteria will be registered using a centralized system and will receive a pre-operative, single administration of zol (4mg i.v.), 7 days before definitive breast surgery .

The interval between diagnostic core biopsy and study registration must be no more than 2 weeks.

Tumor tissue samples will be collected at diagnosis (core-biopsy) and at the time of definitive surgery.

Arm type	Experimental
Investigational medicinal product name	Zoledronate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients will receive a single, pre-operative dose of Zol (ATC code M05BA08) 4mg i.v., planned after TNBC diagnosis, 7 days before the scheduled definitive breast surgery.

<b>Number of subjects in period 1</b>	Single arm
Started	21
Completed	21

## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	21	21	
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)	15	15	
From 65-84 years	5	5	
85 years and over	1	1	
Age continuous			
Units: years			
median	60.3		
inter-quartile range (Q1-Q3)	50.2 to 67.0	-	
Gender categorical			
Units: Subjects			
Female	21	21	

### Subject analysis sets

Subject analysis set title	All subjects
Subject analysis set type	Full analysis
Subject analysis set description: The All Subjects Analysis Set included all participants who provided informed consent and who were enrolled in the study.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety Analysis Set included all subjects who provided informed consent, who were enrolled in the study, who had no major violations of eligibility criteria, and who received the dose of study treatment	
Subject analysis set title	PP1
Subject analysis set type	Per protocol
Subject analysis set description: The PP analysis set included all patients registered who had received the dose of study treatment and who had undergone the definitive breast surgery, without major eligibility criteria or study conduction violations and with p53 level < 30%.	
Subject analysis set title	PP2
Subject analysis set type	Per protocol

Subject analysis set description:

The PP analysis set included all patients registered who had received the dose of study treatment and who had undergone the definitive breast surgery, without major eligibility criteria or study conduct violations and with p53 level  $\geq 30\%$ .

Reporting group values	All subjects	Safety	PP1
Number of subjects	21	20	8
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	14	14
From 65-84 years	5	5	5
85 years and over	1	1	1
Age continuous Units: years			
median	60.3	61.2	61.2
inter-quartile range (Q1-Q3)	50.2 to 67.0	52.5 to 71.6	52.5 to 71.6
Gender categorical Units: Subjects			
Female	21	20	20

Reporting group values	PP2		
Number of subjects	8		
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			
median			
inter-quartile range (Q1-Q3)			
Gender categorical Units: Subjects			
Female			

## End points

### End points reporting groups

Reporting group title	Single arm
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Reporting group description:

Patients fulfilling the eligibility criteria will be registered using a centralized system and will receive a pre-operative, single administration of zol (4mg i.v.), 7 days before definitive breast surgery .

The interval between diagnostic core biopsy and study registration must be no more than 2 weeks.

Tumor tissue samples will be collected at diagnosis (core-biopsy) and at the time of definitive surgery.

Subject analysis set title	All subjects
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Subject analysis set type	Full analysis
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Subject analysis set description:

The All Subjects Analysis Set included all participants who provided informed consent and who were enrolled in the study.

Subject analysis set title	Safety
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The Safety Analysis Set included all subjects who provided informed consent, who were enrolled in the study, who had no major violations of eligibility criteria, and who received the dose of study treatment

Subject analysis set title	PP1
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Subject analysis set type	Per protocol
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Subject analysis set description:

The PP analysis set included all patients registered who had received the dose of study treatment and who had undergone the definitive breast surgery, without major eligibility criteria or study conduction violations and with p53 level < 30%.

Subject analysis set title	PP2
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Subject analysis set type	Per protocol
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Subject analysis set description:

The PP analysis set included all patients registered who had received the dose of study treatment and who had undergone the definitive breast surgery, without major eligibility criteria or study conduction violations and with p53 level  $\geq$  30%.

### Primary: Proportion of responder patients at surgery

End point title	Proportion of responder patients at surgery
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End point description:

Primary endpoint of the study is the proportion of responder patients, defined as those with at least 30% reduction in Ki67 at surgery with respect to core-biopsy analysis.

End point type	Primary
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End point timeframe:

Surgery with respect to core-biopsy evaluation

End point values	PP1	PP2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	7		
Units: Patients	3	1		

## Statistical analyses

Statistical analysis title	Proportion of responder patients
Statistical analysis description: Proportion of responder patients, defined as those with at least 30% reduction in Ki67 at surgery with respect to core-biopsy analysis, will be presented as point estimate and 95% confidence intervals (95% CIs) for each group.	
Comparison groups	PP1 v PP2
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Proportion of responder
Point estimate	42.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.9
upper limit	81.6

Statistical analysis title	Proportion of responder patients
Statistical analysis description: Proportion of responder patients, defined as those with at least 30% reduction in Ki67 at surgery with respect to core-biopsy analysis, will be presented as point estimate and 95% confidence intervals (95% CIs) for each group.	
Comparison groups	PP2 v PP1
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Proportion of responder
Point estimate	14.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	57.9

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the AE form.

All AEs, regardless of relationship to study drug, will be reported until 30 days after the dose of study drug.

Assessment type	Systematic
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### Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	4.0

### Reporting groups

Reporting group title	Overall
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Reporting group description: -

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 21 (14.29%)		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		



Aphthous ulcer subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 July 2016	PRINCIPAL CHANGES: 1. DRUG CHANGE -> possibility to use generic Zoledronato 2. STUDY PROCEDURE-> change in the length of the study 3. CONTACTS -> changes regarding study referents 4. CENTERS -> change PI in a centre 5. STUDY PROCEDURE-> change in the centers number 6. CONTRACT -> change in the contract between Sponsor and centers
04 September 2017	PRINCIPAL CHANGES: 1. STUDY PROCEDURE: change in the centralized laboratory 2. STUDY PROCEDURE: change in a metodological procedure 3. STUDY PROCEDURE: changes in the administrative procedure 4. IMPD changes 5 and 6 CONTACTS: changes regarding study referents

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported