Clinical trial results:
A Randomized, Double-Blind, Double Dummy, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy of LF-PB 10 mg, 20 mg, and 30 mg to Treat Lymphorrhea Post Axillary Dissection in Breast Cancer

Summary

EudraCT number	2012-000114-10
Trial protocol	IT
Global end of trial date	30 September 2014

Results information

Result version number	v1 (current)
This version publication date	09 October 2019
First version publication date	09 October 2019

Trial information

Trial identification

Sponsor protocol code	LF-PB/11/04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01754285
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chemi S.p.A
Sponsor organisation address	Via dei Lavoratori, 54, Cinisello Balsamo, Italy, 20092
Public contact	Clinical Trial Transparency Manager, Chemi S.p.A. , Chemi S.p.A., 0039 02 64431, info@chemi.com
Scientific contact	Clinical Trial Transparency Manager, Chemi S.p.A. , Chemi S.p.A., 0039 02 6443 1, info@chemi.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	19 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 May 2014
Global end of trial reached?	Yes
Global end of trial date	30 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of the extended release of octreotide (LF-PB) 10 mg, 20 mg, and 30 mg on time to resolution of lymphorrhea
To evaluate safety and tolerability of LF-PB 10 mg, 20 mg, and 30 mg

Protection of trial subjects:

Informed consent was obtained before a patient was enrolled in the study and before the commencement of any protocol-driven activities. The investigator met with the patient and explained the study in sufficient detail to permit an informed decision to participate. The trial was performed in accordance International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and applicable local regulatory requirements and laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 November 2012
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	Italy: 114
Worldwide total number of subjects	114
EEA total number of subjects	114

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)	82
From 65 to 84 years	32

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Female patients aged 18 to 80 years inclusive, diagnosed with BC who underwent breast surgery with ALND, body mass index (BMI) ≥18 kg/m2.

Pre-assignment

Screening details:

Randomization was stratified and balanced by surgery in "conservative surgery + dissection surgery without mammary prosthesis placement (Type I)" versus "dissection surgery with mammary prosthesis placement (Type II)

Period 1

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

Blinding implementation details:

The study was blinded to patients, investigators, and the sponsor. In order to assure/maintain the blind, a double-dummy technique was used.

Arms

Are arms mutually exclusive?	Yes
Arm title	LF-PB 10 mg

Arm description:

LF-PB extended-release of octreotide at dose of 10 mg was given as 2 separate bolus IM injections of 1 mL

Arm type	Experimental
Investigational medicinal product name	LF-PB
Investigational medicinal product code	
Other name	extended-release octreotide
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intramuscular use

Dosage and administration details:

LF-PB was administered as 2 separate bolus IM injections of 1 mL. LF-PB 10 mg: 2 injections = placebo + LF-PB 10 mg.
1 injection of LF-PB 10 mg/mL (obtained by reconstituting an octreotide 10 mg red-capped vial) and 1 injection of placebo for LF-PB 20 mg/mL
(obtained by reconstituting a placebo 20 mg brown-capped vial).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intramuscular use

Dosage and administration details:

Placebo for LF-PB 10 mg octreotide/vial: a vial of lyophilized purified soybean lecithin (10 mg/vial) and hydroxypropyl-beta-cyclodextrin (5 mg/vial).
Placebo was given as 2 separate bolus IM injections of 1 mL.

Arm title	LF-PB 20 mg

Arm description:

LF-PB extended-release of octreotide at dose of 20 mg was given as 2 separate bolus IM injections of 1 mL

Arm type	Experimental

Investigational medicinal product name	LF-PB
Investigational medicinal product code	
Other name	extended-release octreotide
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intramuscular use

Dosage and administration details:

LF-PB was administered as 2 separate bolus IM injections of 1 mL. LF-PB 20 mg: 2 injections = placebo + LF-PB 20 mg.
1 injection of placebo for LF-PB 10 mg/mL (obtained by reconstituting a placebo 10 mg red-capped vial) and 1 injection of LF-PB 20 mg/mL (obtained by reconstituting an octreotide 20 mg brown-capped vial).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intramuscular use

Dosage and administration details:

Placebo for LF-PB 20 mg octreotide/vial: a vial of lyophilized purified soybean lecithin (10 mg/vial) and hydroxypropyl-beta-cyclodextrin (5 mg/vial). Placebo was
given as 2 separate bolus IM injections of 1 mL.

Arm title	LF-PB 30 mg

Arm description:

LF-PB extended-release of octreotide at dose of 30 mg was given as 2 separate bolus IM injections of 1 mL.

Arm type	Experimental
Investigational medicinal product name	LF-PB
Investigational medicinal product code	
Other name	extended-release octreotide
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intramuscular use

Dosage and administration details:

LF-PB was administered as 2 separate bolus IM injections of 1 mL. LF-PB 30 mg: 2 injections = LF-PB 10 mg + LF-PB 20 mg
1 injection of LF-PB 10 mg/mL (obtained by reconstituting an octreotide 10 mg red-capped vial) and 1 injection of LF-PB 20 mg/mL (obtained by reconstituting an octreotide 20 mg brown-capped vial).

Arm title	Placebo

Arm description:

Placebo for LF-PB 10 mg octreotide/vial and 20 mg octreotide/vial was given as 2 separate bolus IM injections of 1 mL

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intramuscular use

Dosage and administration details:

2 injections of placebo given as 1 injection of placebo for LF-PB 10 mg/mL (obtained by reconstituting a placebo 10 mg red-capped vial) and 1 injection
of placebo for LF-PB 20 mg/mL (obtained by reconstituting a placebo 20 mg brown-capped vial).

Number of subjects in period 1	LF-PB 10 mg	LF-PB 20 mg	LF-PB 30 mg
Started	29	29	28
Completed	29	27	28
Not completed	0	2	0
Consent withdrawn by subject	-	1	-
Lost to follow-up	-	1	-

Number of subjects in period 1	Placebo
Started	28
Completed	28
Not completed	0
Consent withdrawn by subject	-
Lost to follow-up	-

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	114	114	
Age categorical			
Age <65 subjects 82 (71.9%) Age >=65 subjects 32 (28.1%)			
Units: Subjects			
Adults (18-64 years)	82	82	
From 65 to 80 years	32	32	
Age continuous			
Units: years			
arithmetic mean	55.9		
standard deviation	± 12.08	-	
Gender categorical			
All females			
Units: Subjects			
Female	114	114	

Subject analysis sets

Subject analysis set title	LF-PB 10 mg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population included all patients who were enrolled and randomized into the treatment groups. The evaluable population included all patients who received the due dose of LF-PB or placebo and had at least 1 post-baseline disease assessment (duration of lymphorrhea or volume of lymph).

Subject analysis set title	LF-PB 20 mg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population included all patients who were enrolled and randomized into the treatment groups. The evaluable population included all patients who received the due dose of LF-PB or placebo and had at least 1 post-baseline disease assessment (duration of lymphorrhea or volume of lymph).

Subject analysis set title	LF-PB 30 mg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population included all patients who were enrolled and randomized into the treatment groups. The evaluable population included all patients who received the due dose of LF-PB or placebo and had at least 1 post-baseline disease assessment (duration of lymphorrhea or volume of lymph).

Subject analysis set title	Placebo - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population included all patients who were enrolled and randomized into the treatment groups. The evaluable population included all patients who received the due dose of LF-PB or

placebo and had at least 1 post-baseline disease assessment (duration of lymphorrhea or volume of lymph).

Subject analysis set title	LF-PB 10 mg - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population included 112 patients who received the due dose of LF-PB or placebo and had no major protocol violations; the 2 patients omitted from the PP group had major protocol violations.

Subject analysis set title	LF-PB 20 mg - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population included 112 patients who received the due dose of LF-PB or placebo and had no major protocol violations; the 2 patients omitted from the PP group had major protocol violations.

Subject analysis set title	LF-PB 30 mg - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population included 112 patients who received the due dose of LF-PB or placebo and had no major protocol violations; the 2 patients omitted from the PP group had major protocol violations.

Subject analysis set title	Placebo - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population included 112 patients who received the due dose of LF-PB or placebo and had no major protocol violations; the 2 patients omitted from the PP group had major protocol violations.

Subject analysis set title	LF-PB 10 mg - PK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pk population

Subject analysis set title	LF-PB 20 mg - PK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PK population

Subject analysis set title	LF-PB 30 mg - PK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PK population

Reporting group values	LF-PB 10 mg - ITT	LF-PB 20 mg - ITT	LF-PB 30 mg - ITT
Number of subjects	29	29	28
Age categorical			
Age <65 subjects 82 (71.9%) Age >=65 subjects 32 (28.1%)			
Units: Subjects			
Adults (18-64 years)	18	19	23
From 65 to 80 years	11	10	5
Age continuous			
Units: years			
arithmetic mean	57.6	59.4	52.7
standard deviation	± 12.81	± 10.11	± 11.48
Gender categorical			
All females			
Units: Subjects			

Female	29	29	28

Reporting group values	Placebo - ITT	LF-PB 10 mg - PP	LF-PB 20 mg - PP
Number of subjects	28	29	28
Age categorical			
Age <65 subjects 82 (71.9%) Age >=65 subjects 32 (28.1%)			
Units: Subjects			
Adults (18-64 years)	22	18	19
From 65 to 80 years	6	11	9
Age continuous			
Units: years			
arithmetic mean	53.7		
standard deviation	± 13.06	±	±
Gender categorical			
All females			
Units: Subjects			
Female	28	29	28

Reporting group values	LF-PB 30 mg - PP	Placebo - PP	LF-PB 10 mg - PK
Number of subjects	27	28	27
Age categorical			
Age <65 subjects 82 (71.9%) Age >=65 subjects 32 (28.1%)			
Units: Subjects			
Adults (18-64 years)	23	22	
From 65 to 80 years	4	6	
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
All females			
Units: Subjects			
Female	27	28	

Reporting group values	LF-PB 20 mg - PK	LF-PB 30 mg - PK	
Number of subjects	28	28	
Age categorical			
Age <65 subjects 82 (71.9%) Age >=65 subjects 32 (28.1%)			
Units: Subjects			
Adults (18-64 years)			
From 65 to 80 years			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	

Gender categorical			
All females			
Units: Subjects			
Female			

End points

End points reporting groups

Reporting group title	LF-PB 10 mg
Reporting group description:	
LF-PB extended-release of octreotide at dose of 10 mg was given as 2 separate bolus IM injections of 1 mL	
Reporting group title	LF-PB 20 mg
Reporting group description:	
LF-PB extended-release of octreotide at dose of 20 mg was given as 2 separate bolus IM injections of 1 mL	
Reporting group title	LF-PB 30 mg
Reporting group description:	
LF-PB extended-release of octreotide at dose of 30 mg was given as 2 separate bolus IM injections of 1 mL.	
Reporting group title	Placebo
Reporting group description:	
Placebo for LF-PB 10 mg octreotide/vial and 20 mg octreotide/vial was given as 2 separate bolus IM injections of 1 mL	
Subject analysis set title	LF-PB 10 mg - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population included all patients who were enrolled and randomized into the treatment groups. The evaluable population included all patients who received the due dose of LF-PB or placebo and had at least 1 post-baseline disease assessment (duration of lymphorrhea or volume of lymph).	
Subject analysis set title	LF-PB 20 mg - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population included all patients who were enrolled and randomized into the treatment groups. The evaluable population included all patients who received the due dose of LF-PB or placebo and had at least 1 post-baseline disease assessment (duration of lymphorrhea or volume of lymph).	
Subject analysis set title	LF-PB 30 mg - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population included all patients who were enrolled and randomized into the treatment groups. The evaluable population included all patients who received the due dose of LF-PB or placebo and had at least 1 post-baseline disease assessment (duration of lymphorrhea or volume of lymph).	
Subject analysis set title	Placebo - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population included all patients who were enrolled and randomized into the treatment groups. The evaluable population included all patients who received the due dose of LF-PB or placebo and had at least 1 post-baseline disease assessment (duration of lymphorrhea or volume of lymph).	
Subject analysis set title	LF-PB 10 mg - PP
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population included 112 patients who received the due dose of LF-PB or placebo and had no major protocol violations; the 2 patients omitted from the PP group had major protocol violations.	
Subject analysis set title	LF-PB 20 mg - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population included 112 patients who received the due dose of LF-PB or placebo and had no major protocol violations; the 2 patients omitted from the PP group had major protocol violations.

Subject analysis set title	LF-PB 30 mg - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population included 112 patients who received the due dose of LF-PB or placebo and had no major protocol violations; the 2 patients omitted from the PP group had major protocol violations.

Subject analysis set title	Placebo - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population included 112 patients who received the due dose of LF-PB or placebo and had no major protocol violations; the 2 patients omitted from the PP group had major protocol violations.

Subject analysis set title	LF-PB 10 mg - PK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pk population

Subject analysis set title	LF-PB 20 mg - PK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PK population

Subject analysis set title	LF-PB 30 mg - PK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PK population

Primary: Duration of lymphorrhea

End point title	Duration of lymphorrhea

End point description:

Duration of lymphorrhea was evaluated by collecting lymph by a drain placed in the axillary fossa during the first 15 days after surgery. At the resolution of lymphorrhea or, in any case, 15 days after surgery, the drain was removed.
On the first day, the drain was emptied and the lymph discarded. From that moment, the pocket drain containing lymph was emptied at the same time of the day into a graduated container. If the volume of lymph collected was ≥50 mL the patient discarded the lymph. If it was <50 mL, the patient kept the lymph in the graduated container, covered the container with the provided cap, and stored it in the refrigerator.
If the following day the volume was still <50 mL, the same procedure was followed and the 2 containers were taken to the site to allow the investigator to confirm the lymphorrhea resolution.
If the volume on the 2nd day was ≥50 mL, the patient discarded all the lymph and continued the daily collection.

End point type	Primary

End point timeframe:

Throughout the 12-week study: Day 1 (first day after surgery), Discharge (Visit 2), Visit 3-6 (2 times a week until Day 15 after surgery), Day 22 (Visit 7), Day 29 (Visit 8), Day 56 (Visit 9), Day 84 (Visit 10).

End point values	LF-PB 10 mg - ITT	LF-PB 20 mg - ITT	LF-PB 30 mg - ITT	Placebo - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	29	28	28
Units: days				
median (confidence interval 95%)	9.0 (6.0 to 13.0)	8.0 (5.0 to 14.0)	7.0 (6.0 to 12.0)	6.0 (5.0 to 7.0)

Statistical analyses

Statistical analysis title	LF-PB 10 mg vs Placebo

Statistical analysis description:

This is a primary analysis of the primary efficacy endpoint

Comparison groups	LF-PB 10 mg - ITT v Placebo - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.2502
Method	Logrank

Notes:

[1] - The duration of lymphorrhea was evaluated using the Kaplan-Meier method and comparisons among the treatment groups were performed using log-rank test.

Statistical analysis title	LF-PB 20 mg vs Placebo

Statistical analysis description:

This is a primary analysis of the primary efficacy endpoint.

Comparison groups	LF-PB 20 mg - ITT v Placebo - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.2152
Method	Logrank

Notes:

[2] - The duration of lymphorrhea was evaluated using the Kaplan-Meier method and comparisons among the treatment groups were performed using log-rank test.

Statistical analysis title	LF-PB 30 mg vs Placebo

Statistical analysis description:

This is a primary analysis of the primary efficacy endpoint.

Comparison groups	LF-PB 30 mg - ITT v Placebo - ITT
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.4637
Method	Logrank

Notes:

[3] - The duration of lymphorrhea was evaluated using the Kaplan-Meier method and comparisons among the treatment groups were performed using log-rank test.

Statistical analysis title	LF-PB 20 mg vs LF-PB 10 mg

Statistical analysis description:

This is a primary analysis of the primary efficacy endpoint.

Comparison groups	LF-PB 10 mg - ITT v LF-PB 20 mg - ITT
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.5453
Method	Logrank

Notes:

[4] - The duration of lymphorrhea was evaluated using the Kaplan-Meier method and comparisons among the treatment groups were performed using log-rank test.

Statistical analysis title	LF-PB 30 mg vs LF-PB 10 mg

Statistical analysis description:

This is a primary analysis of the primary efficacy endpoint.

Comparison groups	LF-PB 10 mg - ITT v LF-PB 30 mg - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.4815
Method	Logrank

Notes:

[5] - The duration of lymphorrhea was evaluated using the Kaplan-Meier method and comparisons among the treatment groups were performed using log-rank test.

Statistical analysis title	LF-PB 30 mg vs LF-PB 20 mg

Statistical analysis description:

This is a primary analysis of the primary efficacy endpoint.

Comparison groups	LF-PB 30 mg - ITT v LF-PB 20 mg - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.2424
Method	Logrank

Notes:

[6] - The duration of lymphorrhea was evaluated using the Kaplan-Meier method and comparisons among the treatment groups were performed using log-rank test.

Secondary: Daily volume of lymph collected when drain is in place

End point title	Daily volume of lymph collected when drain is in place

End point description:

the daily volume of lymph collected when the drain was in place is reported daily by the patient.
Only data of the 2nd and the 15th Days are reported. For the full timepoints data see the table attached

End point type	Secondary

End point timeframe:

Daily From Day 1 (first day after surgery) until Day 15 (when the drain is removed)

End point values	LF-PB 10 mg - ITT	LF-PB 20 mg - ITT	LF-PB 30 mg - ITT	Placebo - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29[7]	29[8]	28[9]	28[10]
Units: mL				
arithmetic mean (standard deviation)				
Day 2	118.6 (± 68.70)	105.7 (± 68.25)	98.8 (± 52.77)	91.1 (± 55.68)
Day 15	68.0 (± 23.87)	67.5 (± 23.30)	92.5 (± 29.86)	70.0 (± 55.83)

Notes:

[7] - n=5 at Day 15

[8] - n=8 at Day 15

[9] - n=4 at Day 15

[10] - n=4 at Day 15

Attachments (see zip file)	Daily volume of lymph/Daily Volume (mL) of Lymph-all

Statistical analyses

Statistical analysis title	LF-PB 10 mg vs Placebo
Comparison groups	LF-PB 10 mg - ITT v Placebo - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.0827
Method	ANCOVA

Notes:

[11] - For secondary efficacy endpoints, the daily volume of lymph collected was analyzed using a mixed model repeated measures (MMRM) approach. The model included treatment group, surgery type, site (pooled), time, and treatment by time interaction as fixed effects. A continuous covariate for number of removed lymph nodes was also included.

Statistical analysis title	LF-PB 20 mg vs Placebo
Comparison groups	Placebo - ITT v LF-PB 20 mg - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.0802
Method	ANCOVA

Notes:

[12] - For secondary efficacy endpoints, the daily volume of lymph collected was analyzed using a mixed model repeated measures (MMRM) approach. The model included treatment group, surgery type, site (pooled), time, and treatment by time interaction as fixed effects. A continuous covariate for the number of removed
lymph nodes was also included.

Statistical analysis title	LF-PB 30 mg vs Placebo
Comparison groups	Placebo - ITT v LF-PB 30 mg - ITT
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.1428
Method	ANCOVA

Notes:

[13] - For secondary efficacy endpoints, the daily volume of lymph collected was analyzed using a mixed model repeated measures (MMRM) approach. The model included treatment group, surgery type, site (pooled), time, and treatment by time interaction as fixed effects. A continuous covariate for number of removed
lymph nodes was also included.

Statistical analysis title	LF-PB 20 mg vs LF-PB 10 mg
Comparison groups	LF-PB 20 mg - ITT v LF-PB 10 mg - ITT
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.9504
Method	ANCOVA

Notes:

[14] - For secondary efficacy endpoints, the daily volume of lymph collected was analyzed using a mixed model repeated measures (MMRM) approach. The model included treatment group, surgery type, site (pooled), time, and
treatment by time interaction as fixed effects. A continuous covariate for number of removed
lymph nodes was also included.

Statistical analysis title	LF-PB 30 mg vs LF-PB 10 mg
Comparison groups	LF-PB 10 mg - ITT v LF-PB 30 mg - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.751
Method	ANCOVA
Confidence interval	
level	95 %

Notes:

[15] - For secondary efficacy endpoints, the daily volume of lymph collected was analyzed using a mixed model repeated measures (MMRM) approach. The model included treatment group, surgery type, site (pooled), time, and
treatment by time interaction as fixed effects. A continuous covariate for number of removed
lymph nodes was also included.

Statistical analysis title	LF-PB 30 mg vs LF-PB 20 mg
Comparison groups	LF-PB 30 mg - ITT v LF-PB 20 mg - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.7192
Method	ANCOVA
Confidence interval	
sides	2-sided

Notes:

[16] - For secondary efficacy endpoints, the daily volume of lymph collected was analyzed using a mixed model repeated measures (MMRM) approach. The model included treatment group, surgery type, site (pooled), time, and
treatment by time interaction as fixed effects. A continuous covariate for number of removed
lymph nodes was also included.

Secondary: Time to drain removal

End point title	Time to drain removal

End point description:

Time to drain removal is defined as: Date of drain removal – surgery date.

In the situation where the patient had the drain removed for another reason other than lymphorrhea resolution and the patient had not reached day 15 at the time of removal, the patient was included in the analysis as not having had the event (drain removal) and was censored at the time the drain was removed.

End point type	Secondary

End point timeframe:

From Day 0 (day of surgery) to day of drain removal.

End point values	LF-PB 10 mg - ITT	LF-PB 20 mg - ITT	LF-PB 30 mg - ITT	Placebo - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	27	27	26
Units: days				
median (confidence interval 95%)	10.0 (7.0 to 14.0)	9.0 (7.0 to 13.0)	8.5 (7.0 to 13.0)	7.0 (6.0 to 8.0)

Statistical analyses

Statistical analysis title	LF-PB 10 mg vs Placebo
Comparison groups	Placebo - ITT v LF-PB 10 mg - ITT
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.0652
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.554
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.269
upper limit	1.038

Notes:

[17] - Time to drain removal was analyzed using a Cox proportional hazards regression with the following covariates: number of removed lymph nodes, treatment group, surgery type and site (pooled).

Statistical analysis title	LF-PB 20 mg vs Placebo
Comparison groups	Placebo - ITT v LF-PB 20 mg - ITT
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.2071
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.668

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.357
upper limit	1.25

Notes:

[18] - Time to drain removal was analyzed using a Cox proportional hazards regression with the following covariates: number of removed lymph nodes, treatment group, surgery type and site (pooled).

Statistical analysis title	LF-PB 30 mg vs Placebo
Comparison groups	Placebo - ITT v LF-PB 30 mg - ITT
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.5151
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.818
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.446
upper limit	1.5

Notes:

[19] - Time to drain removal was analyzed using a Cox proportional hazards regression with the following covariates: number of removed lymph nodes, treatment group, surgery type and site (pooled).

Statistical analysis title	LF-PB 20 mg vs LF-PB 10 mg
Comparison groups	LF-PB 10 mg - ITT v LF-PB 20 mg - ITT
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.5081
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.205
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.693
upper limit	2.097

Notes:

[20] - Time to drain removal was analyzed using a Cox proportional hazards regression with the following covariates: number of removed lymph nodes, treatment group, surgery type and site (pooled).

Statistical analysis title	LF-PB 30 mg vs LF-PB 10 mg
Comparison groups	LF-PB 10 mg - ITT v LF-PB 30 mg - ITT

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.178
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.476
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.838
upper limit	2.599

Notes:

[21] - Time to drain removal was analyzed using a Cox proportional hazards regression with the following covariates: number of removed lymph nodes, treatment group, surgery type and site (pooled).

Statistical analysis title	LF-PB 30 mg vs LF-PB 20 mg
Comparison groups	LF-PB 20 mg - ITT v LF-PB 30 mg - ITT
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.4889
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.224
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	2.17

Notes:

[22] - Time to drain removal was analyzed using a Cox proportional hazards regression with the following covariates: number of removed lymph nodes, treatment group, surgery type and site (pooled).

Secondary: Percentage of responders at Day 4 after surgery

End point title	Percentage of responders at Day 4 after surgery

End point description:

Responders are patients for whom lymphorrhea was reduced to <50 mL in 2 consecutive daily collections.

End point type	Secondary

End point timeframe:

Day 4 after surgery

End point values	LF-PB 10 mg - ITT	LF-PB 20 mg - ITT	LF-PB 30 mg - ITT	Placebo - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	29	28	28
Units: percentage				
number (not applicable)				
Yes	28.6	17.2	24.1	25.0
No	71.4	82.8	75.9	75.0

Statistical analyses

Statistical analysis title	LF-PB 10 mg vs Placebo
Comparison groups	LF-PB 10 mg - ITT v Placebo - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.1578
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.341
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.077
upper limit	1.517

Notes:

[23] - The percentage of responders at Day 4 was analyzed using logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Statistical analysis title	LF-PB 20 mg vs Placebo
Comparison groups	Placebo - ITT v LF-PB 20 mg - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.5659
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.664
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.164
upper limit	2.684

Notes:

[24] - The percentage of responders at Day 4 was analyzed using logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Statistical analysis title	LF-PB 30 mg vs Placebo
Comparison groups	Placebo - ITT v LF-PB 30 mg - ITT

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.6439
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.729
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.191
upper limit	2.78

Notes:

[25] - The percentage of responders at Day 4 was analyzed using logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Statistical analysis title	LF-PB 20 mg vs LF-PB 10 mg
Comparison groups	LF-PB 10 mg - ITT v LF-PB 20 mg - ITT
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.3617
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.946
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.465
upper limit	8.135

Notes:

[26] - The percentage of responders at Day 4 was analyzed using logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Statistical analysis title	LF-PB 30 mg vs LF-PB 10 mg
Comparison groups	LF-PB 10 mg - ITT v LF-PB 30 mg - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.308
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.136
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.496
upper limit	9.196

Notes:

[27] - The percentage of responders at Day 4 was analyzed using logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Statistical analysis title	LF-PB 30 mg vs LF-PB 20 mg
Comparison groups	LF-PB 30 mg - ITT v LF-PB 20 mg - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.8949
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.098
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.275
upper limit	4.388

Notes:

[28] - The percentage of responders at Day 4 was analyzed using logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Secondary: Percentage of responders at 1 week after surgery

End point title	Percentage of responders at 1 week after surgery

End point description:

Responders are patients for whom lymphorrhea was reduced to <50 mL in 2 consecutive daily collections.

End point type	Secondary

End point timeframe:

at 1 week after surgery

End point values	LF-PB 10 mg - ITT	LF-PB 20 mg - ITT	LF-PB 30 mg - ITT	Placebo - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	29	28	28
Units: percentage				
number (not applicable)				
Yes	44.8	48.3	53.6	75.0
No	55.2	51.7	46.4	25.0

Statistical analyses

Statistical analysis title	LF-PB 10 mg vs Placebo
Comparison groups	LF-PB 10 mg - ITT v Placebo - ITT

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.0168
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.207
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.057
upper limit	0.752

Notes:

[29] - Percentage of responders at 1 week was analyzed by logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Statistical analysis title	LF-PB 20 mg vs Placebo
Comparison groups	Placebo - ITT v LF-PB 20 mg - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.0565
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.298
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.086
upper limit	1.034

Notes:

[30] - Percentage of responders at 1 week was analyzed by logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Statistical analysis title	LF-PB 30 mg vs Placebo
Comparison groups	Placebo - ITT v LF-PB 30 mg - ITT
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.1053
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.357
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.102
upper limit	1.242

Notes:

[31] - Percentage of responders at 1 week was analyzed by logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Statistical analysis title	LF-PB 20 mg vs LF-PB 10 mg
Comparison groups	LF-PB 20 mg - ITT v LF-PB 10 mg - ITT
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	= 0.5243
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.439
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.469
upper limit	4.414

Notes:

[32] - Percentage of responders at 1 week was analyzed by logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Statistical analysis title	LF-PB 30 mg vs LF-PB 10 mg
Comparison groups	LF-PB 10 mg - ITT v LF-PB 30 mg - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.3491
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.724
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.551
upper limit	5.392

Notes:

[33] - Percentage of responders at 1 week was analyzed by logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Statistical analysis title	LF-PB 30 mg vs LF-PB 20 mg
Comparison groups	LF-PB 30 mg - ITT v LF-PB 20 mg - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.7579
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.198

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	3.778

Notes:

[34] - Percentage of responders at 1 week was analyzed by logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Secondary: Percentage of responders at drain removal

End point title	Percentage of responders at drain removal

End point description:

Responders are patients for whom lymphorrhea was reduced to <50 mL in 2 consecutive daily collections.

End point type	Secondary

End point timeframe:

At Day 15

End point values	LF-PB 10 mg - ITT	LF-PB 20 mg - ITT	LF-PB 30 mg - ITT	Placebo - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	29	28	28
Units: Percentage				
number (not applicable)				
Yes	79.3	69.0	85.7	89.3
No	20.7	31.0	14.3	10.7

Statistical analyses

Statistical analysis title	LF-PB 10 mg vs Placebo
Comparison groups	Placebo - ITT v LF-PB 10 mg - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.2019
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.352
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.071
upper limit	1.75

Notes:

[35] - Percentage of responders at drain removal was analyzed by logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Statistical analysis title	LF-PB 20 mg vs Placebo
Comparison groups	Placebo - ITT v LF-PB 20 mg - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.0387
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.195
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.042
upper limit	0.919

Notes:

[36] - Percentage of responders at drain removal was analyzed by logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Statistical analysis title	LF-PB 30 mg vs Placebo
Comparison groups	Placebo - ITT v LF-PB 30 mg - ITT
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.7929
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.151
upper limit	4.233

Notes:

[37] - Percentage of responders at drain removal was analyzed by logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Statistical analysis title	LF-PB 20 mg vs LF-PB 10 mg
Comparison groups	LF-PB 20 mg - ITT v LF-PB 10 mg - ITT
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.3678
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.555
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.154
upper limit	1.999

Notes:

[38] - Percentage of responders at drain removal was analyzed by logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Statistical analysis title	LF-PB 30 mg vs LF-PB 10 mg
Comparison groups	LF-PB 10 mg - ITT v LF-PB 30 mg - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	= 0.2731
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.272
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.524
upper limit	9.864

Notes:

[39] - Percentage of responders at drain removal was analyzed by logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Statistical analysis title	LF-PB 30 mg vs LF-PB 20 mg
Comparison groups	LF-PB 30 mg - ITT v LF-PB 20 mg - ITT
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.0557
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.095
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.966
upper limit	17.35

Notes:

[40] - Percentage of responders at drain removal was analyzed by logistic regression with the following explanatory variables: number of the removed lymph
nodes, treatment group, surgery type, and site (pooled).

Secondary: Percentage of patients with complications related to lymphorrea

End point title	Percentage of patients with complications related to lymphorrea

End point description:

A Cochran-Armitage test was used to detect if there was an association between increasing dose level of LF-PB and number of patients reporting complications related to lymphorrhea.

End point type	Secondary

End point timeframe:

Throughout the 12-week study: Day 1 (first day after surgery), Discharge (Visit 2), Visit 3-6 (2 times a week until Day 15 after surgery), Day 22 (Visit 7), Day 29 (Visit 8), Day 56 (Visit 9), Day 84 (Visit 10).

End point values	LF-PB 10 mg - ITT	LF-PB 20 mg - ITT	LF-PB 30 mg - ITT	Placebo - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	29	28	28
Units: percentage				
number (not applicable)				
Yes	0.0	0.0	3.6	0.0
No	100.0	100.0	96.4	100.0

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax

End point title	Cmax

End point description:

Cmax = maximal plasma concentration

End point type	Secondary

End point timeframe:

Throughout the 12-week study: Day 0 (surgery), Day 1 (first day after surgery), Discharge (Visit 2), Visit 3-6 (2 times a week until Day 15 after surgery), Day 22 (Visit 7), Day 29 (Visit 8).

End point values	LF-PB 10 mg - PK	LF-PB 20 mg - PK	LF-PB 30 mg - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27	28	28	
Units: ng/mL				
arithmetic mean (standard deviation)	3.36 (± 2.56)	10.9 (± 7.17)	11.3 (± 5.27)	

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax

End point title	Tmax

End point description:

tmax = time of maximum plasma concentration

End point type	Secondary

End point timeframe:

Throughout the 12-week study: Day 0 (surgery), Day 1 (first day after surgery), Discharge (Visit 2), Visit 3-6 (2 times a week until Day 15 after surgery), Day 22 (Visit 7), Day 29 (Visit 8).

End point values	LF-PB 10 mg - PK	LF-PB 20 mg - PK	LF-PB 30 mg - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27	28	28	
Units: hours				
median (full range (min-max))	6 (2.95 to 207)	24 (0 to 168)	6 (3 to 141)	

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast

End point title	AUClast

End point description:

AUClast = area under the plasma concentration time up to the last detectable concentration

End point type	Secondary

End point timeframe:

Throughout the 12-week study: Day 0 (surgery), Day 1 (first day after surgery), Discharge (Visit 2), Visit 3-6 (2 times a week until Day 15 after surgery), Day 22 (Visit 7), Day 29 (Visit 8).

End point values	LF-PB 10 mg - PK	LF-PB 20 mg - PK	LF-PB 30 mg - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27	28	28	
Units: nghr/mL				
arithmetic mean (standard deviation)	495 (± 260)	1310 (± 593)	1480 (± 542)	

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-inf

End point title	AUC0-inf

End point description:

AUC∞ = area under the concentration-time curve up to the last quantified measurement

End point type	Secondary

End point timeframe:

Throughout the 12-week study: Day 0 (surgery), Day 1 (first day after surgery), Discharge (Visit 2), Visit 3-6 (2 times a week until Day 15 after surgery), Day 22 (Visit 7), Day 29 (Visit 8).

End point values	LF-PB 10 mg - PK	LF-PB 20 mg - PK	LF-PB 30 mg - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	14	22	24	
Units: ng*hour/mL				
arithmetic mean (standard deviation)	548 (± 214)	1400 (± 570)	1580 (± 547)	

Statistical analyses

No statistical analyses for this end point

Secondary: t1/2z

End point title	t1/2z

End point description:

t1/2z = apparent terminal half-life

End point type	Secondary

End point timeframe:

Throughout the 12-week study: Day 0 (surgery), Day 1 (first day after surgery), Discharge (Visit 2), Visit 3-6 (2 times a week until Day 15 after surgery), Day 22 (Visit 7), Day 29 (Visit 8).

End point values	LF-PB 10 mg - PK	LF-PB 20 mg - PK	LF-PB 30 mg - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	14	22	24	
Units: hours				
arithmetic mean (standard deviation)	72.5 (± 39.3)	91.1 (± 51.0)	92.4 (± 63.7)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the study, from Screening to Visit 1/Early Termination visit for patients who discontinued early.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	LF-PB 10 mg - Safety population
Reporting group description:	
The safety population included patients who have received at least one dose of the trial treatment.	
Reporting group title	LF-PB 20 mg - Safety population
Reporting group description:	
The safety population included patients who have received at least one dose of the trial treatment.	
Reporting group title	LF-PB 30 mg -Safety population
Reporting group description:	
The safety population included patients who have received at least one dose of the trial treatment.	
Reporting group title	Placebo - Safety population
Reporting group description:	
The safety population included patients who have received at least one dose of the trial treatment.	

Serious adverse events	LF-PB 10 mg - Safety population	LF-PB 20 mg - Safety population	LF-PB 30 mg -Safety population
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 29 (3.45%)	1 / 29 (3.45%)	2 / 28 (7.14%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Incision site haemorrhage			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo - Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 28 (10.71%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Incision site haemorrhage			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Multi-organ failure			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	LF-PB 10 mg - Safety population	LF-PB 20 mg - Safety population	LF-PB 30 mg -Safety population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 29 (58.62%)	20 / 29 (68.97%)	14 / 28 (50.00%)
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	2 / 29 (6.90%)	3 / 29 (10.34%)	5 / 28 (17.86%)
occurrences (all)	2	4	8
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 29 (3.45%)	1 / 29 (3.45%)	3 / 28 (10.71%)
occurrences (all)	1	1	4
Injury, poisoning and procedural complications			
Post procedural haematoma			
subjects affected / exposed	2 / 29 (6.90%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Procedural pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	2 / 28 (7.14%)
occurrences (all)	0	1	2
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Lymphoedema			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 29 (3.45%)	1 / 28 (3.57%)
occurrences (all)	1	1	2
Hyperpyrexia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	2 / 28 (7.14%)
occurrences (all)	0	2	2
Injection site erythema			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	4 / 29 (13.79%)	2 / 29 (6.90%)	3 / 28 (10.71%)
occurrences (all)	4	2	3
Pyrexia			

subjects affected / exposed	2 / 29 (6.90%)	3 / 29 (10.34%)	0 / 28 (0.00%)
occurrences (all)	2	4	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Diarrhoea			
subjects affected / exposed	3 / 29 (10.34%)	7 / 29 (24.14%)	2 / 28 (7.14%)
occurrences (all)	3	8	3
Nausea			
subjects affected / exposed	3 / 29 (10.34%)	3 / 29 (10.34%)	1 / 28 (3.57%)
occurrences (all)	5	4	1
Vomiting			
subjects affected / exposed	2 / 29 (6.90%)	1 / 29 (3.45%)	1 / 28 (3.57%)
occurrences (all)	2	1	1
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Postoperative wound infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	3
Urinary tract infection			
subjects affected / exposed	2 / 29 (6.90%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	2 / 29 (6.90%)	2 / 29 (6.90%)	1 / 28 (3.57%)
occurrences (all)	2	2	1

Non-serious adverse events	Placebo - Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 28 (64.29%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	6		
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	5		
Injury, poisoning and procedural complications			
Post procedural haematoma			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	6		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Lymphoedema			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	5		
Hyperpyrexia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Injection site erythema			

subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Injection site pain			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	7		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	7 / 28 (25.00%)		
occurrences (all)	8		
Vomiting			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Influenza			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Postoperative wound infection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		

Urinary tract infection subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 September 2012	The original protocol (Version 1, Dated 02 Jul 2012) was amended on 06 Sep 2012 (Version 2) to include the following changes. •Following guidance from coordinating EC, the evaluation of the safety and tolerability of LF-PB was updated as primary rather than secondary objective. •Exclusion criteria #8 was removed from the protocol as this criteria was appropriate for the oral medication but not for drugs with subcutaneous administration. Furthermore, the diseases already listed in the protocol were the most important. •Per coordinating EC's suggestions to include additional information about the safety of study drug, a new section, Background Information, on the safety of LF-PB in clinical trials, available as of September 2012, was included in the protocol. •To clarify the procedures that occur prior to and following surgery, Visit 1 was divided into 2 visits: randomization (Day 0) and Visit 1 (Day 1). •To obtain additional safety data on LF-PB, liver function tests were updated to include total bilirubin, AST, and ALT. •Section 3.3.7, Prior and Concomitant Illnesses and Treatments, was updated to clarify that chemotherapy cannot be initiated until resolution of lymphorrhea per the protocol definition. •The protocol was updated to also clarify that the patients should collect lymph from drain throughout the period prior to Day 15 regardless of date of discharge and that the duration of lymphorrhea persists when the volume of lymph is ≥50 mL rather than>50 mL.
12 February 2013	The protocol dated 06 Sep 2012 (Version 2) was amended on 12 Feb 2013 (Version 3.0) to include the following major changes: •The Exclusion Criteria in the synopsis and main body was elaborated as follows for clarity: Criterion 1 - Presence of any of the following conditions: a. Previous axillary surgery on the same armpit undergoing surgery in this study b. Previous chemotherapy or radiotherapy within 5 years from study drug administration c. Recurrent BC on the same breast undergoing surgery in this study d. Hypothyroidism. If a patient is being administered Euritox/Levothyroxine (or analogues) and levels of T3, T4, and TSH are confirmed to be within the normal ranges at screening, the patient can be enrolled in this study. Criterion 2 - History of radiotherapy on the breast or armpit undergoing surgery in this study Criterion 9 - Corticosteroid treatment on a long-term basis. Acute use of corticosteroids to prevent hypersensitivity reactions before surgery is not considered an exclusion criterion.

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.

No limitations or caveats to this summary of results.

Notes: