Clinical trial results:
A Randomized Phase 4 Study Comparing 2 Intravenous Temsirolimus (TEMSR) Regimens in Subjects With Relapsed, Refractory Mantle Cell Lymphoma

Summary

EudraCT number	2009-015498-11
Trial protocol	BE FR HU DE IT BG CZ
Global end of trial date	

Results information

Result version number	v1
This version publication date	26 November 2016
First version publication date	26 November 2016

Trial information

Trial identification

Sponsor protocol code	3066K1-4438/B1771007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01180049
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 East 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021 x, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021 x, ClinicalTrials.gov_Inquiries@pfizer.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	Interim
Date of interim/final analysis	12 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 November 2015
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

Estimate independently assessed PFS in subjects with relapsed, refractory MCL.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed; in particular, those affording greater protection to the safety of study participants.
Participants were further followed up for every 3 months after last dose of TEMSR up to 3.5 years.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 March 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 23
Country: Number of subjects enrolled	Czech Republic: 10
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	90
EEA total number of subjects	52

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	38
From 65 to 84 years	50
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 25 centers in Europe, the Russian Federation, the Republic of Korea, Australia, and the United States of America.

Pre-assignment

Screening details:

All enrolled participants from 25 centers were included in the trial.

Period 1

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

Blinding implementation details:

The study was not blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	TEMSR 175/75 mg

Arm description:

Partcipants had received desipramine 50 mg one week prior to the first dose of temsirolimus (TEMSR). An additional desipramine 50 mg was administered again approximately 30 min prior to every first dose of TEMSR on Day 1. Participants then received 175 mg intravenously (IV) once weekly for the first 3 weeks and followed by 75 mg once weekly thereafter.

Arm type	Experimental
Investigational medicinal product name	Temsirolimus (TEMSR)
Investigational medicinal product code	PF-05208748
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Treatment was administered once weekly (IV dosing). In the test group, TEMSR was administered as 175 mg IV once weekly for the first 3 weeks followed by 75 mg once weekly thereafter. In the comparator group, TEMSR was administered as 75 mg IV once weekly.

Arm title	TEMSR 75 mg

Arm description:

Partcipants had received desipramine 50 mg one week prior to the first dose of TEMSR. An additional desipramine 50 mg was administered again approximately 30 min prior to every first dose of TEMSR on Day 1. Participants then received TEMSR 75 mg IV once weekly.

Arm type	Active comparator
Investigational medicinal product name	Temsirolimus (TEMSR)
Investigational medicinal product code	PF-05208748
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Treatment was administered once weekly (IV dosing). TEMSR was administered as 75 mg once weekly.

Number of subjects in period 1	TEMSR 175/75 mg	TEMSR 75 mg
Started	47	43
Treated	47	42
Completed	0	0
Not completed	47	43
Death	23	28
Enrolled to Another Clinical Trial	1	1
Lost to follow-up	-	1
Treatment ongoing (Data cut-off date: 12 Nov 2015)	18	10
Participant Refused Follow Up	5	3

Baseline characteristics

Reporting groups	
Reporting group title	TEMSR 175/75 mg
Reporting group description:	
Partcipants had received desipramine 50 mg one week prior to the first dose of temsirolimus (TEMSR). An additional desipramine 50 mg was administered again approximately 30 min prior to every first dose of TEMSR on Day 1. Participants then received 175 mg intravenously (IV) once weekly for the first 3 weeks and followed by 75 mg once weekly thereafter.	
Reporting group title	TEMSR 75 mg
Reporting group description:	
Partcipants had received desipramine 50 mg one week prior to the first dose of TEMSR. An additional desipramine 50 mg was administered again approximately 30 min prior to every first dose of TEMSR on Day 1. Participants then received TEMSR 75 mg IV once weekly.	

Reporting group values	TEMSR 175/75 mg	TEMSR 75 mg	Total
Number of subjects	47	43	90
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)	21	17	38
From 65-84 years	26	26	52
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	67	66.3	
standard deviation	± 8.49	± 8.47	-
Gender, Male/Female Units: Participants			
Female	13	7	20
Male	34	36	70

End points

End points reporting groups

Reporting group title	TEMSR 175/75 mg

Reporting group description:

Partcipants had received desipramine 50 mg one week prior to the first dose of temsirolimus (TEMSR). An additional desipramine 50 mg was administered again approximately 30 min prior to every first dose of TEMSR on Day 1. Participants then received 175 mg intravenously (IV) once weekly for the first 3 weeks and followed by 75 mg once weekly thereafter.

Reporting group title	TEMSR 75 mg

Reporting group description:

Partcipants had received desipramine 50 mg one week prior to the first dose of TEMSR. An additional desipramine 50 mg was administered again approximately 30 min prior to every first dose of TEMSR on Day 1. Participants then received TEMSR 75 mg IV once weekly.

Subject analysis set title	Intention to treat (ITT) population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The analysis was done on ITT population which included all participants who were randomized, with study drug assignment designated according to initial randomization, regardless of whether participants received study drug or received a different drug dose from that to which they were randomized.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

Analysis was done on safety population which included any participant who received at least 1 dose of TEMSR was included in the evaluation for safety.

Primary: Independently assessed Progression-free survival (PFS)

End point title	Independently assessed Progression-free survival (PFS)

End point description:

PFS is defined as the time from randomization to first documentation of disease progression by the independent assessor or to death due to any cause, whichever occurred first. PFS = (earliest date of progression or death due to any cause- randomization date+1)/30.4. Participants who were alive and progression-free at the time of analysis were censored on the date of last assessment; participants without adequate baseline assessment or without post-baseline assessments were censored on the randomization date; participants who died or progressed after 2 or more missed visits were censored on the date of last tumor assessment prior to the missing visit; and participants who started new anti-cancer therapy prior to death or progression were censored on the date of last tumor assessment prior to the start of anti-tumor treatment.

End point type	Primary

End point timeframe:

From randomization date to the date of first documentation of progression or death (average follow up done for 15 months)

End point values	TEMSR 175/75 mg	TEMSR 75 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	43		
Units: Months				
median (confidence interval 80%)	4.3 (3.3 to 6.4)	4.5 (2.7 to 4.9)		

Statistical analyses

Statistical analysis title	TEMSR 175/75 group vs. TEMSR 75 group
Statistical analysis description:	
Hazard ratio of TEMSR 175/75 mg vs. TEMSR 75 mg with 80% CI is estimated in unstratified Cox regression model.	
Comparison groups	TEMSR 175/75 mg v TEMSR 75 mg
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.731
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.52
upper limit	1.027

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS is defined as the time from the date of randomization to the date of death due to any cause.	
End point type	Secondary
End point timeframe:	
From randomization date until death (average follow up done for 18.6 months)	

End point values	TEMSR 175/75 mg	TEMSR 75 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	43		
Units: Months				
median (confidence interval 80%)	18.7 (7.5 to 48.2)	11 (6.3 to 16.2)		

Statistical analyses

Statistical analysis title	TEMSR 175/75 mg vs. TEMSR 75 mg
Statistical analysis description:	
Hazard ratio of TEMSR 175/75 mg vs. TEMSR 75 mg with 80% CI was estimated in unstratified Cox regression model.	
Comparison groups	TEMSR 175/75 mg v TEMSR 75 mg

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.681
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.472
upper limit	0.982

Secondary: Independent assessment - Objective Response Rate (ORR = CR + PR)

End point title	Independent assessment - Objective Response Rate (ORR = CR + PR)

End point description:

ORR is defined as the percentage of participants with confirmed complete response (CR) or confirmed partial response (PR) according to the Cheson Criteria relative to all randomized Participants. Participants who did not have on-study radiographic tumor re-evaluation or who died, progressed or dropped out for any reason prior to reaching a CR or PR were counted as non--responders in the assessment of ORR.

End point type	Secondary

End point timeframe:

From randomization date until end of treatment (average follow up done for 15 months)

End point values	TEMSR 175/75 mg	TEMSR 75 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	43		
Units: Percentage of participants				
number (confidence interval 80%)	27.7 (19.1 to 37.7)	20.9 (13 to 31)		

Statistical analyses

Statistical analysis title	TEMSR 175/75 mg vs. TEMSR 75 mg

Statistical analysis description:

Independent assessment- Difference (%) TEMSR 175/75 mg – TEMSR 75 mg (80% CI)

Comparison groups	TEMSR 175/75 mg v TEMSR 75 mg
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in arms
Point estimate	6.7

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-6.9
upper limit	20.3

Secondary: Investigator's assessment ORR (ORR = CR + PR)

End point title	Investigator's assessment ORR (ORR = CR + PR)

End point description:

ORR is defined as the percentage of participants with confirmed CR or PR according to the Cheson Criteria relative to all randomized Participants. Participants who did not have on-study radiographic tumor re-evaluation or who died, progressed or dropped out for any reason prior to reaching a CR or PR were counted as non-responders in the assessment of ORR.

End point type	Secondary

End point timeframe:

From randomization date until end of treatment (average follow up done for 15 months)

End point values	TEMSR 175/75 mg	TEMSR 75 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	43		
Units: Percentage of participants				
number (confidence interval 80%)	31.9 (22.9 to 42.2)	18.6 (11.1 to 28.5)		

Statistical analyses

Statistical analysis title	TEMSR 175/75 mg vs. TEMSR 75 mg

Statistical analysis description:

Investigator's assessment- Difference (%)TEMSR 175/75 mg – TEMSR 75 mg (80% CI)

Comparison groups	TEMSR 175/75 mg v TEMSR 75 mg
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference between arms
Point estimate	13.3
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.4
upper limit	26.7

Secondary: Investigator assessed PFS

End point title	Investigator assessed PFS

End point description:

PFS is defined as the time from randomization to first documentation of disease progression by the independent assessor or to death due to any cause, whichever occurred first. PFS = (earliest date of progression or death due to any cause- randomization date+1)/30.4. Participants who were alive and progression-free at the time of analysis were censored on the date of last assessment; participants without adequate baseline assessment or without post-baseline assessments were censored on the randomization date; participants who died or progressed after 2 or more missed visits were censored on the date of last tumor assessment prior to the missing visit; and participants who started new anti-cancer therapy prior to death or progression were censored on the date of last tumor assessment prior to the start of anti-tumor treatment.

End point type	Secondary

End point timeframe:

From randomization date to the date of first documentation of progression or death (average follow up done for 15 months)

End point values	TEMSR 175/75 mg	TEMSR 75 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	43		
Units: Percentage of participants				
median (confidence interval 80%)	4.7 (2.7 to 8.3)	3.9 (2.8 to 4.7)		

Statistical analyses

Statistical analysis title	TEMSR 175/75 mg vs. TEMSR 75 mg

Statistical analysis description:

Hazard ratio of TEMSR 175/75 mg vs. TEMSR 75 mg with 80% CI was estimated in unstratified Cox regression model.

Comparison groups	TEMSR 175/75 mg v TEMSR 75 mg
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.646
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.453
upper limit	0.922

Secondary: Percentage of participants with treatment-emergent infection- related AEs

End point title	Percentage of participants with treatment-emergent infection-related AEs

End point description:

To assess the safety through percentages of participants with treatment-emergent infection- related AEs (Grade 2 or Higher). TEAE: Treatment start date ≤ adverse event start date or adverse event worsened

with respect to grade after treatment started

End point type	Secondary

End point timeframe:

Treatment start date ≤ AEs start date or AE worsened with respect to grade after treatment started (from first dose until within 30 days of last TEMSR infusion)

End point values	TEMSR 175/75 mg	TEMSR 75 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	42[1]		
Units: Percentage of participants				
number (not applicable)				
Any adverse events	25.5	23.8		
Pneumonia	12.8	19		
Bronchitis	8.5	2.4		
Infection	6.4	2.4		
Herpes simplex	2.1	2.4		
Oral candidiasis	2.1	0		
Sepsis	0	2.4		

Notes:

[1] - subject withdrawal- 1

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with treatment-emergent bleeding-related AEs

End point title	Percentage of participants with treatment-emergent bleeding-related AEs

End point description:

To assess the safety through percentage of participants with treatment-emergent bleeding-related AEs (Grade 2 or Higher). TEAE: Treatment start date ≤ adverse event start date or adverse event worsened with respect to grade after treatment started

End point type	Secondary

End point timeframe:

Treatment start date ≤ AEs start date or AE worsened with respect to grade after treatment started (from first dose until within 30 days of last TEMSR infusion)

End point values	TEMSR 175/75 mg	TEMSR 75 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	42[2]		
Units: Percentage of participants				
number (not applicable)				
Any adverse events	12.8	2.4		
Epistaxis	10.6	2.4		
Ecchymosis	2.1	0		

Notes:
[2] - Subject withdrawal- 01

Statistical analyses

No statistical analyses for this end point

Secondary: Quantify the potential effect of TEMSR on AUC and Cmax

End point title	Quantify the potential effect of TEMSR on AUC and Cmax

End point description:

Potential TEMSR effects were investigated by calculating the ratio of AUCs with and without concomitant TEMSR from the model-estimated effect of TEMSR on apparent clearance (CL/F) values and using individual ratios of observed Cmax values with and without concomitant temsirolimus, for both parent and metabolite. The AUC mean ratio was calculated as 1 / mean shift on apparent clearance from TEMSR, and the 90% CI of the AUC ratios was calculated as 1 / 90% CI of the shift on apparent clearance from TEMSR. AUC: Area under plasma concentration-time curve from time zero to infinity Cmax: Characterization of maximum observed plasma concentration

End point type	Secondary

End point timeframe:

From one week predose (Day -7, -4hr, -8hr, -48hr) upto 2 weeks post dose (4hr, 8hr, 48hr and Day 8)

End point values	TEMSR 175/75 mg	TEMSR 75 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	43		
Units: Ratio				
arithmetic mean (confidence interval 90%)				
AUC	1 (0.965 to 1.11)	0.98 (0.87 to 1.12)		
Cmax	0.828 (0.758 to 0.898)	0.779 (0.7005 to 0.857)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment start date ≤ AEs start date or AE worsened with respect to grade after treatment started (from first dose until within 30 days of last TEMSR infusion)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	TEMSR 175/75 mg

Reporting group description:

Partcipants had received desipramine 50 mg one week prior to the first dose of temsirolimus (TEMSR). An additional desipramine 50 mg was administered again approximately 30 min prior to every first dose of TEMSR on Day 1. Participants then received 175 mg intravenously (IV) once weekly for the first 3 weeks and followed by 75 mg once weekly thereafter.

Reporting group title	TEMSR 75 mg

Reporting group description:

Partcipants had received desipramine 50 mg one week prior to the first dose of TEMSR. An additional desipramine 50 mg was administered again approximately 30 min prior to every first dose of TEMSR on Day 1. Participants then received TEMSR 75 mg IV once weekly.

Serious adverse events	TEMSR 175/75 mg	TEMSR 75 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 47 (57.45%)	31 / 42 (73.81%)	
number of deaths (all causes)	23	28	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			

subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Disease progression			
subjects affected / exposed	9 / 47 (19.15%)	9 / 42 (21.43%)	
occurrences causally related to treatment / all	0 / 9	0 / 11	
deaths causally related to treatment / all	0 / 9	0 / 11	
Mucosal inflammation			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 47 (8.51%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			

subjects affected / exposed	1 / 47 (2.13%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 47 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 47 (2.13%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Hallucination			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemoglobin			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcus test positive			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 47 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			

subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 47 (4.26%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 47 (2.13%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	5 / 5	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric disorder			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 47 (4.26%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeria sepsis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 47 (10.64%)	8 / 42 (19.05%)	
occurrences causally related to treatment / all	5 / 8	4 / 10	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	2 / 47 (4.26%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 47 (2.13%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster virus infection			

subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral skin infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 47 (0.00%)	3 / 42 (7.14%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	TEMSR 175/75 mg	TEMSR 75 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 47 (95.74%)	41 / 42 (97.62%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 47 (6.38%)	0 / 42 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 47 (10.64%)	4 / 42 (9.52%)	
occurrences (all)	6	5	
Chest discomfort			
subjects affected / exposed	1 / 47 (2.13%)	4 / 42 (9.52%)	
occurrences (all)	2	4	
Fatigue			
subjects affected / exposed	11 / 47 (23.40%)	13 / 42 (30.95%)	
occurrences (all)	23	19	
Oedema peripheral			
subjects affected / exposed	8 / 47 (17.02%)	8 / 42 (19.05%)	
occurrences (all)	12	24	
Pyrexia			
subjects affected / exposed	13 / 47 (27.66%)	9 / 42 (21.43%)	
occurrences (all)	18	9	
Mucosal inflammation			
subjects affected / exposed	3 / 47 (6.38%)	5 / 42 (11.90%)	
occurrences (all)	4	8	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 47 (14.89%)	8 / 42 (19.05%)	
occurrences (all)	16	11	
Dyspnoea			
subjects affected / exposed	10 / 47 (21.28%)	13 / 42 (30.95%)	
occurrences (all)	10	17	
Dyspnoea exertional			

subjects affected / exposed	3 / 47 (6.38%)	5 / 42 (11.90%)	
occurrences (all)	4	5	
Epistaxis			
subjects affected / exposed	12 / 47 (25.53%)	8 / 42 (19.05%)	
occurrences (all)	18	12	
Oropharyngeal pain			
subjects affected / exposed	1 / 47 (2.13%)	3 / 42 (7.14%)	
occurrences (all)	1	3	
Pneumonitis			
subjects affected / exposed	3 / 47 (6.38%)	1 / 42 (2.38%)	
occurrences (all)	5	1	
Psychiatric disorders			
Initial insomnia			
subjects affected / exposed	0 / 47 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Insomnia			
subjects affected / exposed	4 / 47 (8.51%)	0 / 42 (0.00%)	
occurrences (all)	8	0	
Investigations			
Blood pressure increased			
subjects affected / exposed	3 / 47 (6.38%)	0 / 42 (0.00%)	
occurrences (all)	3	0	
Platelet count decreased			
subjects affected / exposed	6 / 47 (12.77%)	2 / 42 (4.76%)	
occurrences (all)	12	6	
Weight decreased			
subjects affected / exposed	3 / 47 (6.38%)	6 / 42 (14.29%)	
occurrences (all)	3	7	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 47 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 47 (0.00%)	4 / 42 (9.52%)	
occurrences (all)	0	6	

Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 47 (2.13%)	4 / 42 (9.52%)	
occurrences (all)	1	4	
Headache			
subjects affected / exposed	5 / 47 (10.64%)	2 / 42 (4.76%)	
occurrences (all)	8	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 47 (21.28%)	13 / 42 (30.95%)	
occurrences (all)	27	37	
Leukopenia			
subjects affected / exposed	5 / 47 (10.64%)	2 / 42 (4.76%)	
occurrences (all)	18	4	
Neutropenia			
subjects affected / exposed	16 / 47 (34.04%)	11 / 42 (26.19%)	
occurrences (all)	32	39	
Thrombocytopenia			
subjects affected / exposed	32 / 47 (68.09%)	24 / 42 (57.14%)	
occurrences (all)	134	163	
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 47 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 47 (6.38%)	6 / 42 (14.29%)	
occurrences (all)	3	6	
Constipation			
subjects affected / exposed	6 / 47 (12.77%)	5 / 42 (11.90%)	
occurrences (all)	6	5	
Diarrhoea			
subjects affected / exposed	17 / 47 (36.17%)	12 / 42 (28.57%)	
occurrences (all)	22	20	
Mouth ulceration			
subjects affected / exposed	3 / 47 (6.38%)	3 / 42 (7.14%)	
occurrences (all)	3	3	

Nausea			
subjects affected / exposed	6 / 47 (12.77%)	9 / 42 (21.43%)	
occurrences (all)	7	12	
Stomatitis			
subjects affected / exposed	6 / 47 (12.77%)	4 / 42 (9.52%)	
occurrences (all)	7	5	
Vomiting			
subjects affected / exposed	2 / 47 (4.26%)	3 / 42 (7.14%)	
occurrences (all)	2	3	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	4 / 47 (8.51%)	5 / 42 (11.90%)	
occurrences (all)	6	10	
Erythema			
subjects affected / exposed	0 / 47 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Night sweats			
subjects affected / exposed	0 / 47 (0.00%)	5 / 42 (11.90%)	
occurrences (all)	0	6	
Onychoclasis			
subjects affected / exposed	4 / 47 (8.51%)	1 / 42 (2.38%)	
occurrences (all)	5	2	
Pruritus			
subjects affected / exposed	3 / 47 (6.38%)	3 / 42 (7.14%)	
occurrences (all)	3	4	
Rash			
subjects affected / exposed	8 / 47 (17.02%)	6 / 42 (14.29%)	
occurrences (all)	10	11	
Skin lesion			
subjects affected / exposed	0 / 47 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	8	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 47 (6.38%)	1 / 42 (2.38%)	
occurrences (all)	4	1	
Pain in extremity			

subjects affected / exposed	1 / 47 (2.13%)	3 / 42 (7.14%)	
occurrences (all)	1	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 47 (8.51%)	1 / 42 (2.38%)	
occurrences (all)	8	1	
Herpes simplex			
subjects affected / exposed	3 / 47 (6.38%)	2 / 42 (4.76%)	
occurrences (all)	3	2	
Infection			
subjects affected / exposed	3 / 47 (6.38%)	1 / 42 (2.38%)	
occurrences (all)	3	1	
Nasopharyngitis			
subjects affected / exposed	3 / 47 (6.38%)	1 / 42 (2.38%)	
occurrences (all)	9	1	
Pneumonia			
subjects affected / exposed	2 / 47 (4.26%)	3 / 42 (7.14%)	
occurrences (all)	3	3	
Rhinitis			
subjects affected / exposed	3 / 47 (6.38%)	1 / 42 (2.38%)	
occurrences (all)	4	1	
Skin infection			
subjects affected / exposed	3 / 47 (6.38%)	1 / 42 (2.38%)	
occurrences (all)	3	2	
Upper respiratory tract infection			
subjects affected / exposed	8 / 47 (17.02%)	10 / 42 (23.81%)	
occurrences (all)	19	11	
Urinary tract infection			
subjects affected / exposed	3 / 47 (6.38%)	3 / 42 (7.14%)	
occurrences (all)	3	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 47 (10.64%)	8 / 42 (19.05%)	
occurrences (all)	6	9	
Diabetes mellitus			

subjects affected / exposed	2 / 47 (4.26%)	4 / 42 (9.52%)	
occurrences (all)	2	4	
Hypercholesterolaemia			
subjects affected / exposed	3 / 47 (6.38%)	3 / 42 (7.14%)	
occurrences (all)	5	4	
Hyperglycaemia			
subjects affected / exposed	3 / 47 (6.38%)	4 / 42 (9.52%)	
occurrences (all)	6	4	
Hypertriglyceridaemia			
subjects affected / exposed	4 / 47 (8.51%)	5 / 42 (11.90%)	
occurrences (all)	13	6	
Hypoalbuminaemia			
subjects affected / exposed	2 / 47 (4.26%)	4 / 42 (9.52%)	
occurrences (all)	2	4	
Hypokalaemia			
subjects affected / exposed	6 / 47 (12.77%)	8 / 42 (19.05%)	
occurrences (all)	12	10	
Hypophosphataemia			
subjects affected / exposed	3 / 47 (6.38%)	3 / 42 (7.14%)	
occurrences (all)	3	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2010	Introduction of additional exclusion criteria regarding significant medical illness and abnormal laboratory findings, hypersensitivity to TEMSR and its metabolites, hypersensitivity to polysorbate 80 or other components of TEMSR formulation, hypersensitivity to antihistamines, and subjects who cannot receive antihistamines for other medical reasons.
20 March 2012	• Incorporation of updated Pfizer protocol template language from legacy Wyeth; • Clarifications to eligibility criteria, concomitant medications, and AEs of interest; • Modification of required procedures.
30 September 2014	• Modification of inclusion criteria value for total bilirubin and addition of a dose modification guideline to account for subjects with mild hepatic impairment per the updated Investigator Drug Brochure in September 2014; • Removal of the requirement for desipramine substudy and supporting PK sample collection, including CYP2D6 screening genotype sample, based on feedback from EMA in September 2014 confirming that results of interim PK analysis were acceptable and no further PK sampling was required; • Minor additions and modifications to align with the sponsor's standard protocol template and standard policies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported