



Clinical trial results:

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

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2009-015498-11 |
| Trial protocol | BE FR HU DE IT BG CZ |
| Global end of trial date | 28 June 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v3 (current) |
| This version publication date | 09 June 2019 |
| First version publication date | 26 November 2016 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|------------------------|
| Sponsor protocol code | B1771007 (3066K1-4438) |
|-----------------------|------------------------|

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, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, 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 | Final |
| Date of interim/final analysis | 08 October 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 June 2018 |
| Was the trial ended prematurely? | 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 Conference 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 subjects.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 10 March 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Australia: 23 |
| Country: Number of subjects enrolled | Czech Republic: 12 |
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Germany: 2 |
| Country: Number of subjects enrolled | Italy: 12 |
| Country: Number of subjects enrolled | Korea, Republic of: 5 |
| Country: Number of subjects enrolled | Poland: 27 |
| Country: Number of subjects enrolled | Romania: 6 |
| Country: Number of subjects enrolled | Russian Federation: 7 |
| Country: Number of subjects enrolled | Serbia: 1 |
| Country: Number of subjects enrolled | United States: 4 |
| Worldwide total number of subjects | 101 |
| EEA total number of subjects | 61 |

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) | 40 |
| From 65 to 84 years | 58 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted at multiple centers from 10 Mar 2011 to 28 Jun 2018.

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:

Subjects 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. Subjects 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:

Subjects 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. Subjects 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 | 53 | 48 |
| Completed | 0 | 0 |
| Not completed | 53 | 48 |
| Death | 36 | 35 |
| Unspecified | 9 | 7 |
| Lost to follow-up | 8 | 6 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | TEMSR 175/75 mg |
|-----------------------|-----------------|

Reporting group description:

Subjects 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. Subjects 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:

Subjects 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. Subjects then received TEMSR 75 mg IV once weekly.

| Reporting group values | TEMSR 175/75 mg | TEMSR 75 mg | Total |
|--|-----------------|-------------|-------|
| Number of subjects | 53 | 48 | 101 |
| 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) | 22 | 18 | 40 |
| From 65-84 years | 29 | 29 | 58 |
| 85 years and over | 2 | 1 | 3 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 67.2 | 66.3 | |
| standard deviation | ± 9.11 | ± 8.36 | - |
| Gender, Male/Female | | | |
| Units: Participants | | | |
| Female | 15 | 8 | 23 |
| Male | 38 | 40 | 78 |

End points

End points reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | TEMSR 175/75 mg |
|-----------------------|-----------------|

Reporting group description:

Subjects 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. Subjects 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:

Subjects 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. Subjects 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 subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects 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 subject 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. $PFS = (\text{earliest date of progression or death due to any cause} - \text{randomization date} + 1) / 30.4$. Subjects who were alive and progression-free at the time of analysis were censored on the date of last assessment; subjects without adequate baseline assessment or without post-baseline assessments were censored on the randomization date; subjects 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 subjects 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. The analysis was done on ITT population which included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug dose from that to which they were randomized. Here, "Overall Number of Subjects Analyzed" signifies subjects who were evaluable for this end point. | |
| End point type | Secondary |
| End point timeframe: From randomization date until death due to any cause (average follow up done for 56.1 months) | |

| | | | | |
|----------------------------------|--------------------|--------------------|--|--|
| End point values | TEMSR 175/75 mg | TEMSR 75 mg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 53 | 48 | | |
| Units: Months | | | | |
| median (confidence interval 80%) | 10.9 (7.0 to 19.7) | 11.2 (6.6 to 18.1) | | |

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 | 101 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.778 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.568 |
| upper limit | 1.064 |

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 subjects with confirmed complete response (CR) or confirmed partial response (PR) according to the Cheson Criteria relative to all randomized subjects. Subjects 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 subjects | | | | |
| number (confidence interval 80%) | 27.7 (19.1 to 37.7) | 20.9 (13.0 to 31.0) | | |

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 subjects with confirmed CR or PR according to the Cheson Criteria relative to all randomized subjects. Subjects 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 subjects | | | | |
| 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. Subjects who were alive and progression-free at the time of analysis were censored on the date of last assessment; subjects without adequate baseline assessment or without post-baseline assessments were censored on the randomization date; subjects 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 subjects 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 subjects | | | | |
| 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 Subjects With Treatment-Emergent Infection- Related Adverse Events (AEs) With Grade 2 or Higher as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Treatment-Emergent Infection-Related Adverse Events (AEs) With Grade 2 or Higher as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) |
|-----------------|--|

End point description:

AE was any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. Treatment emergent adverse event=as an event that emerged during treatment period that was absent before treatment, or worsened during treatment period relative to pretreatment state. Treatment-emergent infection-related AEs included events: pneumonia, bronchitis, infection, herpes simplex, oral candidiasis and sepsis. Grading by NCI CTCAE Version 3.0.: Grade 1= mild; Grade 2= moderate; Grade 3= severe; Grade 4= life-threatening; urgent intervention indicated; Grade 5= death. Analysis was done on safety population which included any subject who received at least 1 dose of TEMSR.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From screening up to a maximum of 57.1 months

| End point values | TEMSR 175/75 mg | TEMSR 75 mg | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 53 | 47 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Pneumonia | 17.0 | 21.3 | | |
| Bronchitis | 7.5 | 2.1 | | |
| Infection | 5.7 | 2.1 | | |
| Herpes simplex | 3.8 | 2.1 | | |
| Oral candidiasis | 3.8 | 0 | | |
| Sepsis | 0 | 2.1 | | |
| Cellulitis | 1.9 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment-Emergent Bleeding-Related AEs With Grade 2 or Higher as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Treatment-Emergent Bleeding-Related AEs With Grade 2 or Higher as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) |
|-----------------|--|

End point description:

An AE was any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. Treatment emergent adverse event=as an event that emerged during treatment period that was absent before treatment, or worsened during treatment period relative to pretreatment state. Treatment-emergent bleeding related AEs included events: epistaxis and ecchymosis. AE were assessed according to maximum severity grading based on NCI CTCAE Version 4.03. Grade 1=mild; Grade 2=moderate; within normal limits. Grade 3=severe or medically significant but not immediately life-threatening; Grade 4=life-threatening or disabling; urgent intervention indicated; Grade 5=death. Analysis was done on safety population which included any subject who received at least 1 dose of TEMSR.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From screening up to a maximum of 57.1 months

| End point values | TEMSR 175/75 mg | TEMSR 75 mg | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 53 | 47 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Epistaxis | 13.2 | 2.1 | | |
| Ecchymosis | 1.9 | 0 | | |

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 | 1.00 (0.965 to 1.11) | 0.980 (0.870 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:

From screening up to a maximum of 57.1 months

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. However, what is presented are distinct events. An event may be categorized as serious in 1 subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event. Analysis was done on safety population which included any subject who received at least 1 dose of TEMSR.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | TEMSR 75 mg |
|-----------------------|-------------|

Reporting group description:

Subjects 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. Subjects then received TEMSR 75 mg IV once weekly.

| | |
|-----------------------|-----------------|
| Reporting group title | TEMSR 175/75 mg |
|-----------------------|-----------------|

Reporting group description:

Subjects 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. Subjects then received 175 mg intravenously (IV) once weekly for the first 3 weeks and followed by 75 mg once weekly thereafter.

| Serious adverse events | TEMSR 75 mg | TEMSR 175/75 mg | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 34 / 47 (72.34%) | 35 / 53 (66.04%) | |
| number of deaths (all causes) | 35 | 36 | |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |

| | | | |
|--|-----------------|------------------|--|
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Disease progression | | | |
| subjects affected / exposed | 9 / 47 (19.15%) | 10 / 53 (18.87%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 12 | 0 / 9 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 4 / 53 (7.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Hiccups | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 2 / 53 (3.77%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |

| | | | |
|--|----------------|----------------|--|
| Hallucination | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Eastern Cooperative Oncology Group performance status worsened | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoglobin | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcus test positive | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Human rhinovirus test positive | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Toxicity to various agents | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound dehiscence | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 2 / 53 (3.77%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Agranulocytosis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 2 / 53 (3.77%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 3 / 3 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute abdomen | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Ascites | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric disorder | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incarcerated inguinal hernia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ulcerative | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| 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 | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Chondrocalcinosis pyrophosphate | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Atypical pneumonia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 2 / 53 (3.77%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fungal infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Listeria sepsis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 9 / 47 (19.15%) | 7 / 53 (13.21%) | |
| occurrences causally related to treatment / all | 4 / 11 | 5 / 11 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 2 / 53 (3.77%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varicella zoster virus infection | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral skin infection | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Acidosis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decreased appetite | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 53 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | TEMSR 75 mg | TEMSR 175/75 mg | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 46 / 47 (97.87%) | 51 / 53 (96.23%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 3 / 53 (5.66%) | |
| occurrences (all) | 0 | 3 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 7 / 47 (14.89%) | 7 / 53 (13.21%) | |
| occurrences (all) | 11 | 9 | |
| Chest discomfort | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 4 / 47 (8.51%) | 1 / 53 (1.89%) | |
| occurrences (all) | 4 | 2 | |
| Fatigue | | | |
| subjects affected / exposed | 13 / 47 (27.66%) | 11 / 53 (20.75%) | |
| occurrences (all) | 19 | 24 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 8 / 47 (17.02%) | 9 / 53 (16.98%) | |
| occurrences (all) | 25 | 15 | |
| Pyrexia | | | |
| subjects affected / exposed | 11 / 47 (23.40%) | 13 / 53 (24.53%) | |
| occurrences (all) | 12 | 18 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 5 / 47 (10.64%) | 3 / 53 (5.66%) | |
| occurrences (all) | 8 | 4 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 9 / 47 (19.15%) | 8 / 53 (15.09%) | |
| occurrences (all) | 12 | 17 | |
| Dyspnoea | | | |
| subjects affected / exposed | 13 / 47 (27.66%) | 10 / 53 (18.87%) | |
| occurrences (all) | 17 | 10 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 5 / 47 (10.64%) | 3 / 53 (5.66%) | |
| occurrences (all) | 5 | 4 | |
| Epistaxis | | | |
| subjects affected / exposed | 9 / 47 (19.15%) | 14 / 53 (26.42%) | |
| occurrences (all) | 13 | 20 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 1 / 53 (1.89%) | |
| occurrences (all) | 3 | 1 | |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 4 / 53 (7.55%) | |
| occurrences (all) | 3 | 6 | |
| Psychiatric disorders | | | |

| | | | |
|---|----------------------|-----------------------|--|
| Initial insomnia subjects affected / exposed occurrences (all) | 3 / 47 (6.38%) 3 | 0 / 53 (0.00%) 0 | |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 4 / 53 (7.55%) 8 | |
| Investigations | | | |
| Blood pressure increased subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 3 / 53 (5.66%) 3 | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 2 / 47 (4.26%) 6 | 6 / 53 (11.32%) 12 | |
| Weight decreased subjects affected / exposed occurrences (all) | 6 / 47 (12.77%) 7 | 6 / 53 (11.32%) 7 | |
| Blood cholesterol increased subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 3 / 53 (5.66%) 6 | |
| Injury, poisoning and procedural complications | | | |
| Contusion subjects affected / exposed occurrences (all) | 3 / 47 (6.38%) 3 | 0 / 53 (0.00%) 0 | |
| Cardiac disorders | | | |
| Tachycardia subjects affected / exposed occurrences (all) | 4 / 47 (8.51%) 6 | 0 / 53 (0.00%) 0 | |
| Nervous system disorders | | | |
| Dysgeusia subjects affected / exposed occurrences (all) | 4 / 47 (8.51%) 4 | 2 / 53 (3.77%) 3 | |
| Headache subjects affected / exposed occurrences (all) | 3 / 47 (6.38%) 4 | 5 / 53 (9.43%) 8 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|-----------------------------|------------------|------------------|--|
| Anaemia | | | |
| subjects affected / exposed | 13 / 47 (27.66%) | 14 / 53 (26.42%) | |
| occurrences (all) | 37 | 32 | |
| Leukopenia | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 5 / 53 (9.43%) | |
| occurrences (all) | 4 | 18 | |
| Neutropenia | | | |
| subjects affected / exposed | 11 / 47 (23.40%) | 18 / 53 (33.96%) | |
| occurrences (all) | 39 | 34 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 28 / 47 (59.57%) | 37 / 53 (69.81%) | |
| occurrences (all) | 182 | 178 | |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 3 / 53 (5.66%) | |
| occurrences (all) | 1 | 3 | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 3 / 53 (5.66%) | |
| occurrences (all) | 1 | 5 | |
| Lymphopenia | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 2 / 53 (3.77%) | |
| occurrences (all) | 15 | 13 | |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 0 / 53 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 6 / 47 (12.77%) | 3 / 53 (5.66%) | |
| occurrences (all) | 6 | 3 | |
| Constipation | | | |
| subjects affected / exposed | 5 / 47 (10.64%) | 6 / 53 (11.32%) | |
| occurrences (all) | 5 | 6 | |
| Diarrhoea | | | |
| subjects affected / exposed | 14 / 47 (29.79%) | 19 / 53 (35.85%) | |
| occurrences (all) | 32 | 24 | |
| Mouth ulceration | | | |

| | | | |
|--|-----------------|------------------|--|
| subjects affected / exposed | 3 / 47 (6.38%) | 3 / 53 (5.66%) | |
| occurrences (all) | 3 | 3 | |
| Nausea | | | |
| subjects affected / exposed | 9 / 47 (19.15%) | 6 / 53 (11.32%) | |
| occurrences (all) | 12 | 7 | |
| Stomatitis | | | |
| subjects affected / exposed | 4 / 47 (8.51%) | 7 / 53 (13.21%) | |
| occurrences (all) | 5 | 8 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 2 / 53 (3.77%) | |
| occurrences (all) | 3 | 2 | |
| Aphthous ulcer | | | |
| subjects affected / exposed | 4 / 47 (8.51%) | 1 / 53 (1.89%) | |
| occurrences (all) | 4 | 3 | |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 5 / 47 (10.64%) | 5 / 53 (9.43%) | |
| occurrences (all) | 10 | 7 | |
| Erythema | | | |
| subjects affected / exposed | 4 / 47 (8.51%) | 0 / 53 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Night sweats | | | |
| subjects affected / exposed | 5 / 47 (10.64%) | 0 / 53 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Onychoclasia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 4 / 53 (7.55%) | |
| occurrences (all) | 2 | 5 | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 3 / 53 (5.66%) | |
| occurrences (all) | 4 | 3 | |
| Rash | | | |
| subjects affected / exposed | 8 / 47 (17.02%) | 10 / 53 (18.87%) | |
| occurrences (all) | 13 | 12 | |
| Skin lesion | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 1 / 53 (1.89%) | |
| occurrences (all) | 8 | 1 | |

| | | | |
|---|------------------|------------------|--|
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 3 / 53 (5.66%) | |
| occurrences (all) | 0 | 3 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 3 / 53 (5.66%) | |
| occurrences (all) | 1 | 4 | |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 1 / 53 (1.89%) | |
| occurrences (all) | 3 | 1 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 4 / 53 (7.55%) | |
| occurrences (all) | 1 | 8 | |
| Herpes simplex | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 4 / 53 (7.55%) | |
| occurrences (all) | 2 | 4 | |
| Infection | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 3 / 53 (5.66%) | |
| occurrences (all) | 1 | 3 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 3 / 53 (5.66%) | |
| occurrences (all) | 1 | 13 | |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 47 (8.51%) | 3 / 53 (5.66%) | |
| occurrences (all) | 4 | 4 | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 4 / 53 (7.55%) | |
| occurrences (all) | 1 | 5 | |
| Skin infection | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 3 / 53 (5.66%) | |
| occurrences (all) | 2 | 3 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 10 / 47 (21.28%) | 10 / 53 (18.87%) | |
| occurrences (all) | 14 | 28 | |

| | | | |
|---|-----------------------|-----------------------|--|
| Urinary tract infection subjects affected / exposed occurrences (all) | 3 / 47 (6.38%) 6 | 3 / 53 (5.66%) 3 | |
| Oral candidiasis subjects affected / exposed occurrences (all) | 2 / 47 (4.26%) 2 | 3 / 53 (5.66%) 3 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 8 / 47 (17.02%) 9 | 6 / 53 (11.32%) 8 | |
| Diabetes mellitus subjects affected / exposed occurrences (all) | 5 / 47 (10.64%) 5 | 2 / 53 (3.77%) 2 | |
| Hypercholesterolaemia subjects affected / exposed occurrences (all) | 5 / 47 (10.64%) 6 | 3 / 53 (5.66%) 5 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 5 / 47 (10.64%) 5 | 4 / 53 (7.55%) 7 | |
| Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 5 / 47 (10.64%) 6 | 6 / 53 (11.32%) 15 | |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 4 / 47 (8.51%) 4 | 2 / 53 (3.77%) 2 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 8 / 47 (17.02%) 10 | 8 / 53 (15.09%) 14 | |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 3 / 47 (6.38%) 4 | 3 / 53 (5.66%) 3 | |

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 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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. |
| 08 June 2017 | Terminated long-term follow-up. |

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.

Overall Survival was not collected for the intended duration as planned initially, no long term follow up was conducted according to amendment in protocol. Hence overall survival results were limited.

Notes: