



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:

Participants 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:

Participants 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:

Participants 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:

Participants 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:

Participants 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:

Participants 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. $PFS = (\text{earliest date of progression or death due to any cause} - \text{randomization date} + 1) / 30.4$. 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:

Participants 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:

Participants 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 | | | |

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

| | | | |
|--------------------------------------|------------------|------------------|--|
| 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 | |
| Onychoclasia | | | |
| 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 occurrences (all) | 1 / 47 (2.13%) 1 | 3 / 42 (7.14%) 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 | <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. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported