



Clinical trial results:

Phase I/II study of oral administration of S 49076 given in combination with gefitinib in patients with EGFR mutated advanced non-small-cell lung cancer who have progressed after treatment with EGFR tyrosine kinase inhibitor.

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2015-002646-31 |
| Trial protocol | ES HU DE |
| Global end of trial date | 07 November 2018 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 18 July 2019 |
| First version publication date | 18 July 2019 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | CL1-49076-003 |
|-----------------------|---------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Laboratorios Servier S.L. |
| Sponsor organisation address | Avenida de los Madronos, 33, Madrid, Spain, 28043 |
| Public contact | Dpto. Investigación y Desarrollo, Laboratorios Servier S.L., +34 917489014, itziar.fernandezgonzalez@servier.com |
| Scientific contact | Dpto. Investigación y Desarrollo, Laboratorios Servier S.L., +34 917489014, itziar.fernandezgonzalez@servier.com |
| Sponsor organisation name | Institut de Recherches Internationales Servier |
| Sponsor organisation address | 50 rue Carnot, Suresnes, France, 92284 |
| Public contact | Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.com |
| Scientific contact | Center for Therapeutic Innovation in Oncology, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.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 | No |

| |
|--------------------------------|
| 1901/2006 apply to this trial? |
|--------------------------------|

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 07 November 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 07 November 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 November 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and activity of S49076 in combination with gefitinib in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring activating Epidermal Growth Factor Receptor (EGFR) mutations, who had received clinical benefit and then progressed on an EGFR tyrosine kinase inhibitor (TKI) (erlotinib, gefitinib, icotinib, afatinib or dacomitinib).

Protection of trial subjects:

This study was conducted in accordance with Good Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 26 January 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 9 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---|
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 2 |
| Country: Number of subjects enrolled | Italy: 3 |
| Country: Number of subjects enrolled | Singapore: 3 |
| Country: Number of subjects enrolled | Spain: 3 |
| Country: Number of subjects enrolled | Taiwan: 3 |
| Worldwide total number of subjects | 14 |
| EEA total number of subjects | 6 |

Notes:

| Subjects enrolled per age group | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 9 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The investigators were specialists in Medical Oncology.

Pre-assignment

Screening details:

Male/female patients aged ≥ 18 years with locally advanced or metastatic stage IIIB/IV NSCLC with measurable tumour disease according to RECIST V1.1, having EGFR Mutation without T790M mutation; with AXL overexpression or MET amplification and/or MET overexpression, who had received clinical benefit, and then progressed on one single agent EGFR TKI

Period 1

| | |
|------------------------------|---------------------------------|
| Period 1 title | Phase I period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|---------|
| Arm title | S 49076 |
|-----------|---------|

Arm description:

Phase I / Dose-escalation part: patients received S49076 dose level of 500 mg or 600 mg in combination with fixed dose (250 mg) of gefitinib, orally once daily (q.d.), on a continuous schedule during 28-day cycles.

Cycles were repeated until disease progression, unacceptable toxicity, or investigator's/patient's decision.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | S 49076 |
| Investigational medicinal product code | S 49076 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Patients took either 5 or 6 tablets of S49076 100 mg once daily on a continuous dosing schedule, during a 28-day cycle.

Patients took one tablet of 250 mg of gefitinib (Non IMP), orally, once daily on a continuous dosing schedule, during a 28-day cycle.

| | |
|---------------------------------------|---------|
| Number of subjects in period 1 | S 49076 |
| Started | 14 |
| Completed | 11 |
| Not completed | 3 |
| Consent withdrawn by subject | 1 |
| Adverse event, non-fatal | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | S 49076 |
|-----------------------|---------|

Reporting group description:

Phase I / Dose-escalation part: patients received S49076 dose level of 500 mg or 600 mg in combination with fixed dose (250 mg) of gefitinib, orally once daily (q.d.), on a continuous schedule during 28-day cycles.

Cycles were repeated until disease progression, unacceptable toxicity, or investigator's/patient's decision.

| Reporting group values | S 49076 | Total | |
|------------------------|----------|-------|--|
| Number of subjects | 14 | 14 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 9 | 9 | |
| From 65-84 years | 5 | 5 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 60.9 | | |
| full range (min-max) | 35 to 72 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 8 | 8 | |
| Male | 6 | 6 | |

Subject analysis sets

| | |
|----------------------------|------------|
| Subject analysis set title | Safety Set |
|----------------------------|------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

The Safety Set consisted of 14 patients included in the study and who received at least one dose of S49076 or one dose of gefitinib.

| | |
|----------------------------|-------------------|
| Subject analysis set title | DLT Evaluable Set |
|----------------------------|-------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

All patients who took at least one dose of S49076 or one dose of gefitinib, and were evaluable for DLT (Dose-Limiting Toxicities) according to the DLT assessment at end of cycle 1.

A patient was not considered evaluable if:

- He/she definitely discontinued during first cycle for a reason other than DLT or
- He/she did not undergo a DLT assessment at the start of cycle 2 or
- He/she did not receive at least 85% (24 doses over 28) of S49076 doses, unless treatment was stopped for a DLT.
- He/she did not receive at least 85% (24 doses over 28) of gefitinib doses, unless treatment was stopped for a DLT.

| Reporting group values | Safety Set | DLT Evaluable Set | |
|------------------------|------------|-------------------|--|
| Number of subjects | 14 | 10 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 9 | | |
| From 65-84 years | 5 | | |

| | | | |
|----------------------|----------|--|--|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 60.9 | | |
| full range (min-max) | 35 to 72 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 8 | | |
| Male | 6 | | |

End points

End points reporting groups

| | |
|-----------------------|---------|
| Reporting group title | S 49076 |
|-----------------------|---------|

Reporting group description:

Phase I / Dose-escalation part: patients received S49076 dose level of 500 mg or 600 mg in combination with fixed dose (250 mg) of gefitinib, orally once daily (q.d.), on a continuous schedule during 28-day cycles.

Cycles were repeated until disease progression, unacceptable toxicity, or investigator's/patient's decision.

| | |
|----------------------------|------------|
| Subject analysis set title | Safety Set |
|----------------------------|------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

The Safety Set consisted of 14 patients included in the study and who received at least one dose of S49076 or one dose of gefitinib.

| | |
|----------------------------|-------------------|
| Subject analysis set title | DLT Evaluable Set |
|----------------------------|-------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

All patients who took at least one dose of S49076 or one dose of gefitinib, and were evaluable for DLT (Dose-Limiting Toxicities) according to the DLT assessment at end of cycle 1.

A patient was not considered evaluable if:

- He/she definitely discontinued during first cycle for a reason other than DLT or
- He/she did not undergo a DLT assessment at the start of cycle 2 or
- He/she did not receive at least 85% (24 doses over 28) of S49076 doses, unless treatment was stopped for a DLT.
- He/she did not receive at least 85% (24 doses over 28) of gefitinib doses, unless treatment was stopped for a DLT.

Primary: Recommended Phase II Dose (RP2D)

| | |
|-----------------|---|
| End point title | Recommended Phase II Dose (RP2D) ^[1] |
|-----------------|---|

End point description:

During the dose-escalation (Phase I of the study), two S49076 dose levels were tested in combination with fixed dose gefitinib : 500 mg and 600 mg once daily. DLT was assessed during cycle 1 according to a modified version of Continual Reassessment Method and stopping rules. One DLT at 600 mg (oral mucositis grade 3) was observed in the second cohort including 4 patients. At the end of dose escalation, no Maximum Tolerated Dose was reached, and the RP2D was defined as 600 mg once daily in combination with 250mg once daily of gefitinib.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

See the section description

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses required for this end point.

| | | | | |
|-----------------------------|----------------------|--|--|--|
| End point values | DLT Evaluable Set | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 10 | | | |
| Units: mg once daily | 600 | | | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Emergent adverse events on treatment were defined -as adverse events which occurred or worsen (in terms of severity) or became serious between the first S49076 or Gefitinib intake date and the last S49076 / Gefitinib intake date +28 days

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | 500 mg Group |
|-----------------------|--------------|

Reporting group description:

Phase I / Dose-escalation part: patients received fixed dose (250 mg) of gefitinib and S 49076 dose level of 500 mg orally once daily (q.d.), on a continuous schedule during 28-day cycles. Cycles were repeated until disease progression, unacceptable toxicity, or investigator's/patient's decision.

| | |
|-----------------------|--------------|
| Reporting group title | 600 mg Group |
|-----------------------|--------------|

Reporting group description:

Phase I / Dose-escalation part: patients received fixed dose (250 mg) of gefitinib and S 49076 dose level of 600 mg orally once daily (q.d.), on a continuous schedule during 28-day cycles. Cycles were repeated until disease progression, unacceptable toxicity, or investigator's/patient's decision.

| | |
|-----------------------|--------------|
| Reporting group title | All patients |
|-----------------------|--------------|

Reporting group description:

Phase I / Dose-escalation part: patients received fixed dose (250 mg) of gefitinib and S 49076 (dose level of 500 mg or 600 mg) orally once daily (q.d.), on a continuous schedule during 28-day cycles. Cycles were repeated until disease progression, unacceptable toxicity, or investigator's/patient's decision.

| Serious adverse events | 500 mg Group | 600 mg Group | All patients |
|---|----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | 6 / 10 (60.00%) | 9 / 14 (64.29%) |
| number of deaths (all causes) | 0 | 1 | 1 |
| number of deaths resulting from adverse events | 0 | 1 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 10 (20.00%) | 2 / 14 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Metastases to central nervous system | | | |

| | | | |
|--|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related thrombosis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug interaction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Delusion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hallucination | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Legionella test positive | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ulna fracture | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|----------------|
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 1 / 10 (10.00%) | 3 / 14 (21.43%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | 500 mg Group | 600 mg Group | All patients |
|--|-----------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 4 (100.00%) | 10 / 10 (100.00%) | 14 / 14 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Pyogenic granuloma | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Pallor | | | |

| | | | |
|---|---------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 10 (0.00%) 0 | 1 / 14 (7.14%) 1 |
| General disorders and administration site conditions | | | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 2 / 4 (50.00%) 2 | 4 / 10 (40.00%) 4 | 6 / 14 (42.86%) 6 |
| Asthenia subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 2 | 4 / 10 (40.00%) 4 | 5 / 14 (35.71%) 6 |
| Generalised oedema subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 1 / 10 (10.00%) 1 | 2 / 14 (14.29%) 2 |
| Catheter site oedema subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 10 (0.00%) 0 | 1 / 14 (7.14%) 1 |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 1 / 10 (10.00%) 2 | 1 / 14 (7.14%) 2 |
| Gait disturbance subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 10 (0.00%) 0 | 1 / 14 (7.14%) 1 |
| Malaise subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 10 (0.00%) 0 | 1 / 14 (7.14%) 1 |
| Peripheral swelling subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 1 / 10 (10.00%) 1 | 1 / 14 (7.14%) 1 |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 1 / 10 (10.00%) 1 | 1 / 14 (7.14%) 1 |
| Reproductive system and breast disorders | | | |
| Vulvovaginal inflammation subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 1 / 10 (10.00%) 1 | 1 / 14 (7.14%) 1 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--------------------------------------|-----------------|-----------------|-----------------|
| Epistaxis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 10 (10.00%) | 2 / 14 (14.29%) |
| occurrences (all) | 1 | 2 | 3 |
| Cough | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Lung infiltration | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 2 | 2 |
| Organising pneumonia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 4 / 4 (100.00%) | 1 / 10 (10.00%) | 5 / 14 (35.71%) |
| occurrences (all) | 4 | 1 | 5 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | 2 / 10 (20.00%) | 5 / 14 (35.71%) |
| occurrences (all) | 3 | 3 | 6 |
| Blood creatine increased | | | |

| | | | |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 10 (10.00%) | 2 / 14 (14.29%) |
| occurrences (all) | 1 | 1 | 2 |
| Blood albumin decreased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 2 | 2 |
| Body temperature increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Troponin I increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 2 | 0 | 2 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Skin abrasion | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Skin wound | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 1 / 10 (10.00%) 1 | 1 / 14 (7.14%) 1 |
| Cardiac disorders Ventricular extrasystoles subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 10 (0.00%) 0 | 1 / 14 (7.14%) 1 |
| Nervous system disorders Allodynia subjects affected / exposed occurrences (all) Central pain syndrome subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 | 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 | 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 2 | 2 / 10 (20.00%) 2 | 3 / 14 (21.43%) 4 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Mouth ulceration subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal distension | 3 / 4 (75.00%) 4 3 / 4 (75.00%) 3 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1 1 / 4 (25.00%) 3 | 4 / 10 (40.00%) 11 3 / 10 (30.00%) 4 2 / 10 (20.00%) 2 2 / 10 (20.00%) 3 1 / 10 (10.00%) 1 | 7 / 14 (50.00%) 15 6 / 14 (42.86%) 7 3 / 14 (21.43%) 3 3 / 14 (21.43%) 4 2 / 14 (14.29%) 4 |

| | | | |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Constipation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Hepatobiliary disorders | | | |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 2 / 10 (20.00%) | 3 / 14 (21.43%) |
| occurrences (all) | 1 | 4 | 5 |
| Yellow skin | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | 0 / 10 (0.00%) | 3 / 14 (21.43%) |
| occurrences (all) | 3 | 0 | 3 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 10 (20.00%) | 2 / 14 (14.29%) |
| occurrences (all) | 0 | 3 | 3 |
| rash | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 10 (20.00%) | 2 / 14 (14.29%) |
| occurrences (all) | 0 | 2 | 2 |
| Rash papular | | | |

| | | | |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 4 (50.00%) | 0 / 10 (0.00%) | 2 / 14 (14.29%) |
| occurrences (all) | 2 | 0 | 2 |
| Dry skin | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 2 | 2 |
| Erythema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Hair texture abnormal | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Onycholysis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 2 | 0 | 2 |
| Onychomadesis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Pigmentation disorder | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Skin fissures | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Skin ulcer | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Renal and urinary disorders | | | |
| Chromaturia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|---|----------------|-----------------|-----------------|
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 2 | 2 |
| Back pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Periarthritis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Infections and infestations | | | |
| Paronychia | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | 4 / 10 (40.00%) | 7 / 14 (50.00%) |
| occurrences (all) | 3 | 7 | 10 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 10 (20.00%) | 2 / 14 (14.29%) |
| occurrences (all) | 0 | 2 | 2 |
| Carbuncle | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|------------------------------------|----------------|-----------------|-----------------|
| Ear infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Genital herpes | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 2 | 2 |
| Herpes simplex | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Onychomycosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 3 / 10 (30.00%) | 5 / 14 (35.71%) |
| occurrences (all) | 4 | 3 | 7 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 10 (20.00%) | 2 / 14 (14.29%) |
| occurrences (all) | 0 | 2 | 2 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Hyponatraemia | | | |

| | | | |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 3 / 10 (30.00%) | 5 / 14 (35.71%) |
| occurrences (all) | 2 | 3 | 5 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 17 November 2015 | Update to the list of treatments prohibited and non-inclusion criteria (related to Investigator Brochure version 5): rosuvastatin is contraindicated. Addition of a new country (Japan) and new centres in the phase I part of the study Corrections of inconsistencies and clarifications |
| 27 January 2016 | Concerned Japan : update related to Pharmaceuticals and Medical Devices Agency request. |
| 19 April 2017 | Dacomitinib allowed as previous line. Palliative radiotherapy allowed up to 1 week prior to inclusion. A 2-week time window added between biopsy collection and inclusion. Clarification on the reporting of adverse events possibly related to disease progression. The period for LVEF reassessment in case of asymptomatic decreased has been lengthened from 2 to 3 weeks in case of relative LVEF decrease ≥ 10 units from baseline or absolute LVEF $\geq 40\%$ and $< 50\%$. Addition of herbal product as a prohibited concomitant treatment. |
| 04 June 2018 | Update of the list of prohibited treatments and non-inclusion criteria |
| 23 August 2018 | Definition of the end of the study and cancellation of the follow-up period |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|--------------|---|--------------|
| 04 July 2018 | During phase I, the observed frequency of AXL dysregulation was lower than expected. Additionally, the global anti-tumoral preliminary data did not suggest an increase of activity by adding S 49076 to gefitinib. These elements taken together have led the Sponsor not to initiate the phase II part of the study due to feasibility challenges. | - |

Notes:

Limitations and caveats

None reported