



## Clinical trial results:

**A randomized, double blind, placebo-controlled, parallel, international multicenter study assessing the efficacy of S 066913 in patients with paroxysmal atrial fibrillation**

**Double-blind, International study AssessinG efficacy of S 066913 in paRoxysmal Atrial Fibrillation – IKur inhibitor (DIAGRAF - IKUR).**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2014-002333-63    |
| Trial protocol           | CZ SK SE DK NL PL |
| Global end of trial date | 06 September 2016 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 02 June 2017 |
| First version publication date | 02 June 2017 |

### Trial information

#### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | CL2-066913-002 |
|-----------------------|----------------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |                                                                                                                         |
|------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Institut de Recherches Internationales Servier (I.R.I.S.)                                                               |
| Sponsor organisation address | 50, rue Carnot, Suresnes, France, 92284                                                                                 |
| Public contact               | Clinical Studies Department, Institut de Recherches Internationales Servier, +33 0155724366, clinicaltrials@servier.com |
| Scientific contact           | Clinical Studies Department, Institut de Recherches Internationales Servier, +33 0155724366, 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 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |                   |
|------------------------------------------------------|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 06 September 2016 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 06 September 2016 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 06 September 2016 |
| Was the trial ended prematurely?                     | Yes               |

Notes:

## General information about the trial

Main objective of the trial:

Evaluation of the efficacy of three doses of S 66913 (5 mg, 25 mg and 100 mg o.d.) versus placebo administered for 4 weeks, on atrial fibrillation and/or atrial tachycardia burden (AF/AT burden) in patients with paroxysmal atrial fibrillation (PAF) who were potentially eligible for atrial fibrillation (AF) ablation and were implanted with insertable continuous cardiac rhythm monitoring (ICM) device. The study was divided into 3 periods: A pre-randomisation baseline period (Period 1) of at least 4 weeks during which the ICM was implanted and the eligibility according to ICM data and blood test results was assessed. A double-blind treatment period lasting 4 weeks (Period 2). A post-treatment and extended follow-up period (appears here as part of Period 2 for technical reasons) comprising visits WEND, FU1 and FU2 (6 months after FU1).

Protection of trial subjects:

This study was conducted in accordance with Good Clinical 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                          | 08 December 2014 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety           |
| Long term follow-up duration                              | 6 Months         |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Australia: 14         |
| Country: Number of subjects enrolled | Canada: 6             |
| Country: Number of subjects enrolled | Czech Republic: 13    |
| Country: Number of subjects enrolled | Germany: 1            |
| Country: Number of subjects enrolled | Netherlands: 1        |
| Country: Number of subjects enrolled | Poland: 19            |
| Country: Number of subjects enrolled | Russian Federation: 3 |
| Country: Number of subjects enrolled | Slovakia: 1           |
| Worldwide total number of subjects   | 58                    |
| EEA total number of subjects         | 35                    |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| 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)                      | 40 |
| From 65 to 84 years                       | 18 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Investigators were cardiologists having expertise in arrhythmology.

### Pre-assignment

Screening details:

The patients were adult male or female (non-childbearing potential), in sinus rhythm at selection visit, with at least one AF episode within the last 18 months and at least 2 other AF episodes within 30 days, prior to selection visit, indicated for AF ablation and eligible for ICM implantation (or having an approved ICM device).

### Period 1

|                              |                |
|------------------------------|----------------|
| Period 1 title               | Baseline       |
| Is this the baseline period? | Yes            |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

### Arms

|                                        |                             |
|----------------------------------------|-----------------------------|
| Arm title                              | All patients                |
| Arm description: -                     |                             |
| Arm type                               | ICM                         |
| Investigational medicinal product name | No IMP                      |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Implant, Transdermal system |
| Routes of administration               | Implantation                |

Dosage and administration details:

Insertable Continuous Monitoring (ICM) implantation .

|                                       |              |
|---------------------------------------|--------------|
| <b>Number of subjects in period 1</b> | All patients |
| Started                               | 58           |
| Completed                             | 58           |

### Period 2

|                              |                                   |
|------------------------------|-----------------------------------|
| Period 2 title               | DB treatment period + extended FU |
| Is this the baseline period? | No                                |
| Allocation method            | Randomised - controlled           |
| Blinding used                | Double blind                      |
| Roles blinded                | Subject, Investigator, Monitor    |

Blinding implementation details:

The study was double-blinded with active drugs and matching placebo supplied as identical tablets and

packaging.

## Arms

|                                                                                                                                                                                                           |                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| Are arms mutually exclusive?                                                                                                                                                                              | Yes            |
| <b>Arm title</b>                                                                                                                                                                                          | S 66913 5 mg   |
| Arm description: -                                                                                                                                                                                        |                |
| Arm type                                                                                                                                                                                                  | Experimental   |
| Investigational medicinal product name                                                                                                                                                                    | S 66913 5 mg   |
| Investigational medicinal product code                                                                                                                                                                    |                |
| Other name                                                                                                                                                                                                |                |
| Pharmaceutical forms                                                                                                                                                                                      | Tablet         |
| Routes of administration                                                                                                                                                                                  | Oral use       |
| Dosage and administration details:                                                                                                                                                                        |                |
| The treatment consisted of 3 tablets (2 big and 1 small, either could contain S 66913 5 mg or placebo) administered orally once daily during breakfast i.e. visually identical for each treatment arm.    |                |
| <b>Arm title</b>                                                                                                                                                                                          | S 66913 25 mg  |
| Arm description: -                                                                                                                                                                                        |                |
| Arm type                                                                                                                                                                                                  | Experimental   |
| Investigational medicinal product name                                                                                                                                                                    | S 66913 25 mg  |
| Investigational medicinal product code                                                                                                                                                                    |                |
| Other name                                                                                                                                                                                                |                |
| Pharmaceutical forms                                                                                                                                                                                      | Tablet         |
| Routes of administration                                                                                                                                                                                  | Oral use       |
| Dosage and administration details:                                                                                                                                                                        |                |
| The treatment consisted of 3 tablets (2 big and 1 small, either could contain S 66913 12.5 mg or placebo) administered orally once daily during breakfast i.e. visually identical for each treatment arm. |                |
| <b>Arm title</b>                                                                                                                                                                                          | S 66913 100 mg |
| Arm description: -                                                                                                                                                                                        |                |
| Arm type                                                                                                                                                                                                  | Experimental   |
| Investigational medicinal product name                                                                                                                                                                    | S 66913 100 mg |
| Investigational medicinal product code                                                                                                                                                                    |                |
| Other name                                                                                                                                                                                                |                |
| Pharmaceutical forms                                                                                                                                                                                      | Tablet         |
| Routes of administration                                                                                                                                                                                  | Oral use       |
| Dosage and administration details:                                                                                                                                                                        |                |
| The treatment consisted of 3 tablets (2 big and 1 small, either could contain S 66913 50 mg or placebo) administered orally once daily during breakfast i.e. visually identical for each treatment arm.   |                |
| <b>Arm title</b>                                                                                                                                                                                          | Placebo        |
| Arm description: -                                                                                                                                                                                        |                |
| Arm type                                                                                                                                                                                                  | Placebo        |
| Investigational medicinal product name                                                                                                                                                                    | Placebo        |
| Investigational medicinal product code                                                                                                                                                                    |                |
| Other name                                                                                                                                                                                                |                |
| Pharmaceutical forms                                                                                                                                                                                      | Tablet         |
| Routes of administration                                                                                                                                                                                  | Oral use       |
| Dosage and administration details:                                                                                                                                                                        |                |
| The treatment consisted of 3 tablets (2 big and 1 small) administered orally once daily during breakfast i.e. visually identical for each treatment arm.                                                  |                |

| <b>Number of subjects in period 2</b> | S 66913 5 mg | S 66913 25 mg | S 66913 100 mg |
|---------------------------------------|--------------|---------------|----------------|
| Started                               | 16           | 13            | 15             |
| Completed                             | 10           | 11            | 11             |
| Not completed                         | 6            | 2             | 4              |
| Other                                 | 1            | -             | -              |
| Study discontinuation                 | 5            | 1             | 4              |
| Protocol deviation                    | -            | 1             | -              |

| <b>Number of subjects in period 2</b> | Placebo |
|---------------------------------------|---------|
| Started                               | 14      |
| Completed                             | 11      |
| Not completed                         | 3       |
| Other                                 | -       |
| Study discontinuation                 | 3       |
| Protocol deviation                    | -       |

## Baseline characteristics

### Reporting groups

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

Reporting group description: -

| Reporting group values                                | All patients | Total |  |
|-------------------------------------------------------|--------------|-------|--|
| Number of subjects                                    | 58           | 58    |  |
| Age categorical                                       |              |       |  |
| Units: Subjects                                       |              |       |  |
| In utero                                              | 0            | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0            | 0     |  |
| Newborns (0-27 days)                                  | 0            | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0            | 0     |  |
| Children (2-11 years)                                 | 0            | 0     |  |
| Adolescents (12-17 years)                             | 0            | 0     |  |
| Adults (18-64 years)                                  | 40           | 40    |  |
| From 65-84 years                                      | 18           | 18    |  |
| 85 years and over                                     | 0            | 0     |  |
| Age continuous                                        |              |       |  |
| Units: years                                          |              |       |  |
| arithmetic mean                                       | 58.5         |       |  |
| standard deviation                                    | ± 10.2       | -     |  |
| Gender categorical                                    |              |       |  |
| Units: Subjects                                       |              |       |  |
| Female                                                | 16           | 16    |  |
| Male                                                  | 42           | 42    |  |
| AF/AT Burden                                          |              |       |  |
| Units: percent                                        |              |       |  |
| median                                                | 9.6          |       |  |
| inter-quartile range (Q1-Q3)                          | 2.7 to 20.4  | -     |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                              |                    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Reporting group title                                                                                                                                                                                                                                                        | All patients       |
| Reporting group description: -                                                                                                                                                                                                                                               |                    |
| Reporting group title                                                                                                                                                                                                                                                        | S 66913 5 mg       |
| Reporting group description: -                                                                                                                                                                                                                                               |                    |
| Reporting group title                                                                                                                                                                                                                                                        | S 66913 25 mg      |
| Reporting group description: -                                                                                                                                                                                                                                               |                    |
| Reporting group title                                                                                                                                                                                                                                                        | S 66913 100 mg     |
| Reporting group description: -                                                                                                                                                                                                                                               |                    |
| Reporting group title                                                                                                                                                                                                                                                        | Placebo            |
| Reporting group description: -                                                                                                                                                                                                                                               |                    |
| Subject analysis set title                                                                                                                                                                                                                                                   | Full Analysis Set  |
| Subject analysis set type                                                                                                                                                                                                                                                    | Intention-to-treat |
| Subject analysis set description:                                                                                                                                                                                                                                            |                    |
| In accordance with the intention-to-treat principle, all patients of the Randomized Set having taken at least one dose of IMP and with at least two evaluations of AF/AT burden on adjudicated data from ICM: one over baseline period and one over 4-week treatment period. |                    |

### Primary: AF/AT Burden

|                                                                                                                                                                           |                             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| End point title                                                                                                                                                           | AF/AT Burden <sup>[1]</sup> |
| End point description:                                                                                                                                                    |                             |
| The primary efficacy endpoint was the AF/AT burden derived from ICM device recording, expressed mainly as absolute change from baseline over the 4-week treatment period. |                             |
| End point type                                                                                                                                                            | Primary                     |
| End point timeframe:                                                                                                                                                      |                             |
| The AF/AT burden is calculated as the percentage time in AF and/or AT (including atrial flutter (AFL)) during the total observation period.                               |                             |

#### 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: Prematurely discontinued study treatment as a precautionary measure due to a non-clinical safety concern.

| End point values                      | S 66913 5 mg      | S 66913 25 mg     | S 66913 100 mg     | Placebo           |
|---------------------------------------|-------------------|-------------------|--------------------|-------------------|
| Subject group type                    | Reporting group   | Reporting group   | Reporting group    | Reporting group   |
| Number of subjects analysed           | 15                | 13                | 14                 | 14                |
| Units: percent                        |                   |                   |                    |                   |
| median (inter-quartile range (Q1-Q3)) | 0.1 (-1.4 to 2.3) | 0.5 (-4.4 to 1.8) | -0.3 (-3.1 to 0.5) | 0.7 (-2.1 to 6.6) |

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Double-blind 4 weeks period (W0-W4) for each group and post-treatment/extended follow-up period for patients who took at least one dose of study drug.

For FU, contact was established for 51 patients: 39 attended FU1; 37 attended FU2.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.0   |

### Reporting groups

|                                |                                       |
|--------------------------------|---------------------------------------|
| Reporting group title          | S 66913 5 mg                          |
| Reporting group description: - |                                       |
| Reporting group title          | S 66913 25 mg                         |
| Reporting group description: - |                                       |
| Reporting group title          | S 66913 100 mg                        |
| Reporting group description: - |                                       |
| Reporting group title          | Placebo                               |
| Reporting group description: - |                                       |
| Reporting group title          | FU after starting with S 66913 5 mg   |
| Reporting group description: - |                                       |
| Reporting group title          | FU after starting with S 66913 25 mg  |
| Reporting group description: - |                                       |
| Reporting group title          | FU after starting with S 66913 100 mg |
| Reporting group description: - |                                       |
| Reporting group title          | FU after starting with Placebo        |
| Reporting group description: - |                                       |

| Serious adverse events                            | S 66913 5 mg    | S 66913 25 mg  | S 66913 100 mg |
|---------------------------------------------------|-----------------|----------------|----------------|
| Total subjects affected by serious adverse events |                 |                |                |
| subjects affected / exposed                       | 2 / 16 (12.50%) | 1 / 13 (7.69%) | 0 / 14 (0.00%) |
| number of deaths (all causes)                     | 0               | 0              | 0              |
| number of deaths resulting from adverse events    | 0               | 0              | 0              |
| Injury, poisoning and procedural complications    |                 |                |                |
| Vascular pseudoaneurysm                           |                 |                |                |
| subjects affected / exposed                       | 0 / 16 (0.00%)  | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0          | 0 / 0          |
| Cardiac disorders                                 |                 |                |                |
| Atrial fibrillation                               |                 |                |                |

|                                                      |                |                |                |
|------------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                          | 1 / 16 (6.25%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac failure                                      |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 1 / 13 (7.69%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Sinus arrest                                         |                |                |                |
| subjects affected / exposed                          | 1 / 16 (6.25%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Non-cardiac chest pain                               |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye disorders                                        |                |                |                |
| Vitreous adhesions                                   |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders      |                |                |                |
| Dyspnoea                                             |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Pulmonary fibrosis                                   |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Bronchiectasis                                       |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Haematuria                                      |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Endocrine disorders                             |                |                |                |
| Hypothyroidism                                  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Influenza                                       |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Post procedural cellulitis                      |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bronchitis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| Serious adverse events                            | Placebo        | FU after starting with S 66913 5 mg | FU after starting with S 66913 25 mg |
|---------------------------------------------------|----------------|-------------------------------------|--------------------------------------|
| Total subjects affected by serious adverse events |                |                                     |                                      |
| subjects affected / exposed                       | 0 / 14 (0.00%) | 3 / 14 (21.43%)                     | 2 / 11 (18.18%)                      |
| number of deaths (all causes)                     | 0              | 0                                   | 0                                    |

|                                                      |                |                |                |
|------------------------------------------------------|----------------|----------------|----------------|
| number of deaths resulting from adverse events       | 0              | 0              | 0              |
| Injury, poisoning and procedural complications       |                |                |                |
| Vascular pseudoaneurysm                              |                |                |                |
| subjects affected / exposed                          | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                                    |                |                |                |
| Atrial fibrillation                                  |                |                |                |
| subjects affected / exposed                          | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac failure                                      |                |                |                |
| subjects affected / exposed                          | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Sinus arrest                                         |                |                |                |
| subjects affected / exposed                          | 0 / 14 (0.00%) | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Non-cardiac chest pain                               |                |                |                |
| subjects affected / exposed                          | 0 / 14 (0.00%) | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye disorders                                        |                |                |                |
| Vitreous adhesions                                   |                |                |                |
| subjects affected / exposed                          | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders      |                |                |                |
| Dyspnoea                                             |                |                |                |
| subjects affected / exposed                          | 0 / 14 (0.00%) | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Pulmonary fibrosis                              |                |                |                |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bronchiectasis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Haematuria                                      |                |                |                |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Endocrine disorders                             |                |                |                |
| Hypothyroidism                                  |                |                |                |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Influenza                                       |                |                |                |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Post procedural cellulitis                      |                |                |                |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bronchitis                                      |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                        | FU after starting with S 66913 100 mg | FU after starting with Placebo |  |
|------------------------------------------------------|---------------------------------------|--------------------------------|--|
| Total subjects affected by serious adverse events    |                                       |                                |  |
| subjects affected / exposed                          | 2 / 14 (14.29%)                       | 0 / 12 (0.00%)                 |  |
| number of deaths (all causes)                        | 0                                     | 0                              |  |
| number of deaths resulting from adverse events       | 0                                     | 0                              |  |
| Injury, poisoning and procedural complications       |                                       |                                |  |
| Vascular pseudoaneurysm                              |                                       |                                |  |
| subjects affected / exposed                          | 1 / 14 (7.14%)                        | 0 / 12 (0.00%)                 |  |
| occurrences causally related to treatment / all      | 0 / 1                                 | 0 / 0                          |  |
| deaths causally related to treatment / all           | 0 / 0                                 | 0 / 0                          |  |
| Cardiac disorders                                    |                                       |                                |  |
| Atrial fibrillation                                  |                                       |                                |  |
| subjects affected / exposed                          | 0 / 14 (0.00%)                        | 0 / 12 (0.00%)                 |  |
| occurrences causally related to treatment / all      | 0 / 0                                 | 0 / 0                          |  |
| deaths causally related to treatment / all           | 0 / 0                                 | 0 / 0                          |  |
| Cardiac failure                                      |                                       |                                |  |
| subjects affected / exposed                          | 0 / 14 (0.00%)                        | 0 / 12 (0.00%)                 |  |
| occurrences causally related to treatment / all      | 0 / 0                                 | 0 / 0                          |  |
| deaths causally related to treatment / all           | 0 / 0                                 | 0 / 0                          |  |
| Sinus arrest                                         |                                       |                                |  |
| subjects affected / exposed                          | 0 / 14 (0.00%)                        | 0 / 12 (0.00%)                 |  |
| occurrences causally related to treatment / all      | 0 / 0                                 | 0 / 0                          |  |
| deaths causally related to treatment / all           | 0 / 0                                 | 0 / 0                          |  |
| General disorders and administration site conditions |                                       |                                |  |
| Non-cardiac chest pain                               |                                       |                                |  |
| subjects affected / exposed                          | 0 / 14 (0.00%)                        | 0 / 12 (0.00%)                 |  |
| occurrences causally related to treatment / all      | 0 / 0                                 | 0 / 0                          |  |
| deaths causally related to treatment / all           | 0 / 0                                 | 0 / 0                          |  |
| Eye disorders                                        |                                       |                                |  |
| Vitreous adhesions                                   |                                       |                                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Dyspnoea                                        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pulmonary fibrosis                              |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bronchiectasis                                  |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Haematuria                                      |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Endocrine disorders                             |                |                |  |
| Hypothyroidism                                  |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Influenza                                       |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia                                       |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 14 (7.14%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Post procedural cellulitis                      |                |                |  |
| subjects affected / exposed                     | 1 / 14 (7.14%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bronchitis                                      |                |                |  |
| subjects affected / exposed                     | 1 / 14 (7.14%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | <b>S 66913 5 mg</b> | <b>S 66913 25 mg</b> | <b>S 66913 100 mg</b> |
|-------------------------------------------------------|---------------------|----------------------|-----------------------|
| Total subjects affected by non-serious adverse events |                     |                      |                       |
| subjects affected / exposed                           | 5 / 16 (31.25%)     | 1 / 13 (7.69%)       | 1 / 14 (7.14%)        |
| Vascular disorders                                    |                     |                      |                       |
| Orthostatic hypotension                               |                     |                      |                       |
| subjects affected / exposed                           | 1 / 16 (6.25%)      | 0 / 13 (0.00%)       | 0 / 14 (0.00%)        |
| occurrences (all)                                     | 1                   | 0                    | 0                     |
| General disorders and administration site conditions  |                     |                      |                       |
| Oedema peripheral                                     |                     |                      |                       |
| subjects affected / exposed                           | 0 / 16 (0.00%)      | 0 / 13 (0.00%)       | 0 / 14 (0.00%)        |
| occurrences (all)                                     | 0                   | 0                    | 0                     |
| Immune system disorders                               |                     |                      |                       |
| Food allergy                                          |                     |                      |                       |
| subjects affected / exposed                           | 0 / 16 (0.00%)      | 0 / 13 (0.00%)       | 0 / 14 (0.00%)        |
| occurrences (all)                                     | 0                   | 0                    | 0                     |
| Reproductive system and breast disorders              |                     |                      |                       |
| Prostatitis                                           |                     |                      |                       |
| subjects affected / exposed                           | 0 / 16 (0.00%)      | 0 / 13 (0.00%)       | 1 / 14 (7.14%)        |
| occurrences (all)                                     | 0                   | 0                    | 1                     |
| Respiratory, thoracic and mediastinal disorders       |                     |                      |                       |



|                                              |                |                |                |
|----------------------------------------------|----------------|----------------|----------------|
| Bronchiectasis                               |                |                |                |
| subjects affected / exposed                  | 1 / 16 (6.25%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all)                            | 1              | 0              | 0              |
| Pleural effusion                             |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all)                            | 0              | 0              | 0              |
| Cough                                        |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all)                            | 0              | 0              | 0              |
| Chronic obstructive pulmonary disease        |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all)                            | 0              | 0              | 0              |
| Obstructive airways disorder                 |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all)                            | 0              | 0              | 0              |
| Investigations                               |                |                |                |
| Electrocardiogram PR prolongation            |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 1 / 13 (7.69%) | 0 / 14 (0.00%) |
| occurrences (all)                            | 0              | 1              | 0              |
| International normalised ratio fluctuation   |                |                |                |
| subjects affected / exposed                  | 1 / 16 (6.25%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all)                            | 1              | 0              | 0              |
| Vital capacity decreased                     |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all)                            | 0              | 0              | 0              |
| Functional residual capacity increased       |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all)                            | 0              | 0              | 0              |
| Carbon monoxide diffusing capacity decreased |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all)                            | 0              | 0              | 0              |
| Total lung capacity decreased                |                |                |                |
| subjects affected / exposed                  | 0 / 16 (0.00%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all)                            | 0              | 0              | 0              |

|                                                                                         |                                                                 |                     |                     |
|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------|---------------------|---------------------|
| Expiratory reserve volume increased<br>subjects affected / exposed<br>occurrences (all) | Additional description: Residual volume of the lungs increased. |                     |                     |
|                                                                                         | 0 / 16 (0.00%)<br>0                                             | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |
| Cardiac disorders                                                                       |                                                                 |                     |                     |
| Bradycardia<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 16 (0.00%)<br>0                                             | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |
| Pericarditis<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 16 (0.00%)<br>0                                             | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |
| Atrial thrombosis<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 16 (0.00%)<br>0                                             | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |
| Nervous system disorders                                                                |                                                                 |                     |                     |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 16 (0.00%)<br>0                                             | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |
| Phrenic nerve paralysis<br>subjects affected / exposed<br>occurrences (all)             | 0 / 16 (0.00%)<br>0                                             | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |
| Facial paralysis<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 16 (0.00%)<br>0                                             | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |
| Gastrointestinal disorders                                                              |                                                                 |                     |                     |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 16 (0.00%)<br>0                                             | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |
| Gingival recession<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 16 (6.25%)<br>1                                             | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |
| Gastritis<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 16 (0.00%)<br>0                                             | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders                                                  |                                                                 |                     |                     |
| Rash pruritic<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 16 (0.00%)<br>0                                             | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |

|                                                                                                         |                     |                     |                     |
|---------------------------------------------------------------------------------------------------------|---------------------|---------------------|---------------------|
| Renal and urinary disorders<br>Pollakiuria<br>subjects affected / exposed<br>occurrences (all)          | 0 / 16 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |
| Infections and infestations<br>Cystitis escherichia<br>subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1 | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |
| Herpes zoster<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 16 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 16 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |
| Metabolism and nutrition disorders<br>Gout<br>subjects affected / exposed<br>occurrences (all)          | 1 / 16 (6.25%)<br>1 | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |

| <b>Non-serious adverse events</b>                                                                                                | Placebo             | FU after starting<br>with S 66913 5 mg | FU after starting<br>with S 66913 25 mg |
|----------------------------------------------------------------------------------------------------------------------------------|---------------------|----------------------------------------|-----------------------------------------|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed                                          | 3 / 14 (21.43%)     | 3 / 14 (21.43%)                        | 2 / 11 (18.18%)                         |
| Vascular disorders<br>Orthostatic hypotension<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 14 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0                    | 0 / 11 (0.00%)<br>0                     |
| General disorders and administration<br>site conditions<br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all) | 0 / 14 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0                    | 0 / 11 (0.00%)<br>0                     |
| Immune system disorders<br>Food allergy<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 14 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0                    | 0 / 11 (0.00%)<br>0                     |
| Reproductive system and breast<br>disorders<br>Prostatitis                                                                       |                     |                                        |                                         |

|                                                  |                     |                     |                     |
|--------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 14 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Respiratory, thoracic and mediastinal disorders  |                     |                     |                     |
| Bronchiectasis                                   |                     |                     |                     |
| subjects affected / exposed                      | 0 / 14 (0.00%)      | 0 / 14 (0.00%)      | 0 / 11 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Pleural effusion                                 |                     |                     |                     |
| subjects affected / exposed                      | 0 / 14 (0.00%)      | 0 / 14 (0.00%)      | 1 / 11 (9.09%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Cough                                            |                     |                     |                     |
| subjects affected / exposed                      | 0 / 14 (0.00%)      | 0 / 14 (0.00%)      | 0 / 11 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Chronic obstructive pulmonary disease            |                     |                     |                     |
| subjects affected / exposed                      | 0 / 14 (0.00%)      | 0 / 14 (0.00%)      | 0 / 11 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Obstructive airways disorder                     |                     |                     |                     |
| subjects affected / exposed                      | 0 / 14 (0.00%)      | 0 / 14 (0.00%)      | 0 / 11 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Investigations                                   |                     |                     |                     |
| Electrocardiogram PR prolongation                |                     |                     |                     |
| subjects affected / exposed                      | 0 / 14 (0.00%)      | 0 / 14 (0.00%)      | 0 / 11 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| International normalised ratio fluctuation       |                     |                     |                     |
| subjects affected / exposed                      | 0 / 14 (0.00%)      | 0 / 14 (0.00%)      | 0 / 11 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Vital capacity decreased                         |                     |                     |                     |
| subjects affected / exposed                      | 0 / 14 (0.00%)      | 0 / 14 (0.00%)      | 0 / 11 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Functional residual capacity increased           |                     |                     |                     |
| subjects affected / exposed                      | 0 / 14 (0.00%)      | 0 / 14 (0.00%)      | 0 / 11 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Carbon monoxide diffusing capacity decreased     |                     |                     |                     |
| subjects affected / exposed                      | 0 / 14 (0.00%)      | 0 / 14 (0.00%)      | 1 / 11 (9.09%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |

|                                                                                         |                                                                 |                     |                     |
|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------|---------------------|---------------------|
| Total lung capacity decreased<br>subjects affected / exposed<br>occurrences (all)       | 0 / 14 (0.00%)<br>0                                             | 0 / 14 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Expiratory reserve volume increased<br>subjects affected / exposed<br>occurrences (all) | Additional description: Residual volume of the lungs increased. |                     |                     |
|                                                                                         | 0 / 14 (0.00%)<br>0                                             | 0 / 14 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Cardiac disorders                                                                       |                                                                 |                     |                     |
| Bradycardia<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 14 (0.00%)<br>0                                             | 0 / 14 (0.00%)<br>0 | 1 / 11 (9.09%)<br>1 |
| Pericarditis<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 14 (0.00%)<br>0                                             | 0 / 14 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Atrial thrombosis<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 14 (0.00%)<br>0                                             | 1 / 14 (7.14%)<br>1 | 0 / 11 (0.00%)<br>0 |
| Nervous system disorders                                                                |                                                                 |                     |                     |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 14 (7.14%)<br>1                                             | 0 / 14 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Phrenic nerve paralysis<br>subjects affected / exposed<br>occurrences (all)             | 0 / 14 (0.00%)<br>0                                             | 0 / 14 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Facial paralysis<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 14 (0.00%)<br>0                                             | 0 / 14 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Gastrointestinal disorders                                                              |                                                                 |                     |                     |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 14 (7.14%)<br>1                                             | 0 / 14 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Gingival recession<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 14 (0.00%)<br>0                                             | 0 / 14 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Gastritis<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 14 (0.00%)<br>0                                             | 0 / 14 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders                                                  |                                                                 |                     |                     |

|                                                                                                         |                     |                     |                     |
|---------------------------------------------------------------------------------------------------------|---------------------|---------------------|---------------------|
| Rash pruritic<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 14 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Renal and urinary disorders<br>Pollakiuria<br>subjects affected / exposed<br>occurrences (all)          | 1 / 14 (7.14%)<br>1 | 0 / 14 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Infections and infestations<br>Cystitis escherichia<br>subjects affected / exposed<br>occurrences (all) | 0 / 14 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Herpes zoster<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 14 (7.14%)<br>1 | 0 / 14 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 14 (0.00%)<br>0 | 1 / 14 (7.14%)<br>1 | 1 / 11 (9.09%)<br>1 |
| Metabolism and nutrition disorders<br>Gout<br>subjects affected / exposed<br>occurrences (all)          | 0 / 14 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |

| <b>Non-serious adverse events</b>                                                                                                | FU after starting<br>with S 66913 100<br>mg | FU after starting<br>with Placebo |  |
|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|-----------------------------------|--|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed                                          | 3 / 14 (21.43%)                             | 3 / 12 (25.00%)                   |  |
| Vascular disorders<br>Orthostatic hypotension<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 14 (0.00%)<br>0                         | 0 / 12 (0.00%)<br>0               |  |
| General disorders and administration<br>site conditions<br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all) | 0 / 14 (0.00%)<br>0                         | 1 / 12 (8.33%)<br>1               |  |
| Immune system disorders<br>Food allergy<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 14 (7.14%)<br>1                         | 0 / 12 (0.00%)<br>0               |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Reproductive system and breast disorders        |                |                |  |
| Prostatitis                                     |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                               | 0              | 0              |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Bronchiectasis                                  |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                               | 0              | 0              |  |
| Pleural effusion                                |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                               | 0              | 0              |  |
| Cough                                           |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 1 / 12 (8.33%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Chronic obstructive pulmonary disease           |                |                |  |
| subjects affected / exposed                     | 1 / 14 (7.14%) | 0 / 12 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Obstructive airways disorder                    |                |                |  |
| subjects affected / exposed                     | 1 / 14 (7.14%) | 0 / 12 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Investigations                                  |                |                |  |
| Electrocardiogram PR prolongation               |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                               | 0              | 0              |  |
| International normalised ratio fluctuation      |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                               | 0              | 0              |  |
| Vital capacity decreased                        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 1 / 12 (8.33%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Functional residual capacity increased          |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 1 / 12 (8.33%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Carbon monoxide diffusing capacity decreased    |                |                |  |

|                                                                                         |                                                                 |                     |  |
|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                                        | 1 / 14 (7.14%)<br>1                                             | 0 / 12 (0.00%)<br>0 |  |
| Total lung capacity decreased<br>subjects affected / exposed<br>occurrences (all)       | 0 / 14 (0.00%)<br>0                                             | 1 / 12 (8.33%)<br>1 |  |
| Expiratory reserve volume increased<br>subjects affected / exposed<br>occurrences (all) | Additional description: Residual volume of the lungs increased. |                     |  |
|                                                                                         | 1 / 14 (7.14%)<br>1                                             | 0 / 12 (0.00%)<br>0 |  |
| Cardiac disorders                                                                       |                                                                 |                     |  |
| Bradycardia                                                                             |                                                                 |                     |  |
| subjects affected / exposed<br>occurrences (all)                                        | 0 / 14 (0.00%)<br>0                                             | 0 / 12 (0.00%)<br>0 |  |
| Pericarditis                                                                            |                                                                 |                     |  |
| subjects affected / exposed<br>occurrences (all)                                        | 1 / 14 (7.14%)<br>1                                             | 0 / 12 (0.00%)<br>0 |  |
| Atrial thrombosis                                                                       |                                                                 |                     |  |
| subjects affected / exposed<br>occurrences (all)                                        | 0 / 14 (0.00%)<br>0                                             | 0 / 12 (0.00%)<br>0 |  |
| Nervous system disorders                                                                |                                                                 |                     |  |
| Dizziness                                                                               |                                                                 |                     |  |
| subjects affected / exposed<br>occurrences (all)                                        | 0 / 14 (0.00%)<br>0                                             | 0 / 12 (0.00%)<br>0 |  |
| Phrenic nerve paralysis                                                                 |                                                                 |                     |  |
| subjects affected / exposed<br>occurrences (all)                                        | 1 / 14 (7.14%)<br>1                                             | 0 / 12 (0.00%)<br>0 |  |
| Facial paralysis                                                                        |                                                                 |                     |  |
| subjects affected / exposed<br>occurrences (all)                                        | 0 / 14 (0.00%)<br>0                                             | 1 / 12 (8.33%)<br>1 |  |
| Gastrointestinal disorders                                                              |                                                                 |                     |  |
| Diarrhoea                                                                               |                                                                 |                     |  |
| subjects affected / exposed<br>occurrences (all)                                        | 0 / 14 (0.00%)<br>0                                             | 0 / 12 (0.00%)<br>0 |  |
| Gingival recession                                                                      |                                                                 |                     |  |
| subjects affected / exposed<br>occurrences (all)                                        | 0 / 14 (0.00%)<br>0                                             | 0 / 12 (0.00%)<br>0 |  |
| Gastritis                                                                               |                                                                 |                     |  |



|                                                                                                                                                                                                                                                                               |                                                                           |                                                                           |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                              | 1 / 14 (7.14%)<br>1                                                       | 0 / 12 (0.00%)<br>0                                                       |  |
| Skin and subcutaneous tissue disorders<br>Rash pruritic<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                   | 1 / 14 (7.14%)<br>1                                                       | 0 / 12 (0.00%)<br>0                                                       |  |
| Renal and urinary disorders<br>Pollakiuria<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                | 0 / 14 (0.00%)<br>0                                                       | 0 / 12 (0.00%)<br>0                                                       |  |
| Infections and infestations<br>Cystitis escherichia<br>subjects affected / exposed<br>occurrences (all)<br><br>Herpes zoster<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 14 (0.00%)<br>0<br><br>0 / 14 (0.00%)<br>0<br><br>0 / 14 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0<br><br>0 / 12 (0.00%)<br>0<br><br>1 / 12 (8.33%)<br>1 |  |
| Metabolism and nutrition disorders<br>Gout<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                | 0 / 14 (0.00%)<br>0                                                       | 0 / 12 (0.00%)<br>0                                                       |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10 October 2014 | Amendment n°1 applicable in all countries: modification of selection criterion 1 regarding the inclusion of women of childbearing potential who were to be excluded. A pregnancy test was therefore no longer appropriate and birth control method was updated.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 27 January 2015 | Amendment n°3 applicable in all countries: interdiction of rosuvastatin (a BCRP substrate) as a precautionary measure.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 03 July 2015    | Amendment No. 4 applicable in all countries:<br>Clarification or modification of the study selection and inclusion criteria : <ul style="list-style-type: none"><li>- Selection criterion 3: Paroxysmal atrial fibrillation: sinus rhythm was to be recorded within maximum 7 days since the onset of this AF episode.</li><li>- Selection criterion 4: Paroxysmal AF could be documented by an ECG within 18 months to demonstrate the existence of the disease.</li><li>- Selection criterion 5: Wording for AF ablation slightly modified to allow countries to select patients according to local guideline (HRS/EHRA/ECAS, 2012; AHA/ACC/HRS, 2014).</li><li>- Non-selection criterion 17: Patients who had been treated for persistent atrial fibrillation were considered as eligible under certain circumstances.</li></ul> A precautionary measure concerning gastrointestinal events was added. |
| 30 October 2015 | Amendment No. 5 applicable in all countries: Addition of extended clinical follow-up further to the decision (in agreement with the DIAGRAF-IKUR study Executive Committee, the Data Monitoring Committee) to prematurely discontinue the study treatment in all patients as a precautionary measure for all randomized patients who received at least one dose of study treatment (either placebo or S066913). The follow-up consists of an initial visit and a second follow-up visit 6 months later.                                                                                                                                                                                                                                                                                                                                                                                                   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date              | Interruption                                                                                                                                                                                                                                                                                                                     | Restart date |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 30 September 2015 | The Sponsor decided, in agreement with the study Data Monitoring Committee and Executive Committee, to prematurely discontinue the study treatment as a precautionary measure and to implement a clinical follow-up period with two visits separated by 6 months in all patients having taken the study treatment at least once. | -            |

Notes:

### Limitations and caveats

None reported