



Clinical trial results:

Prospective, explorative trial for the detection of circulating cell-free tumor DNA in the plasma of patients with gastrointestinal stromal tumors (GIST) harboring activating mutations of CKIT or PDGFRA pre/post surgery or pre/under treatment with a tyrosine kinase inhibitor or progressive disease irrespective of current or planned Treatment. An open-label, non-randomized, multicenter phase IIIb clinical trial

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2011-002544-27 |
| Trial protocol | DE |
| Global end of trial date | 14 October 2015 |

Results information

| | |
|-----------------------------------|----------------------------------------------------------|
| Result version number | v1 (current) |
| This version publication date | 13 September 2020 |
| First version publication date | 13 September 2020 |
| Summary attachment (see zip file) | GIST-Clinical_Cancer_Research (CF-DNA-GIST_IJC_2019.pdf) |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | CSTI571BDE78T |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01462994 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name | Technische Universität München, Fakultät für Medizin |
| Sponsor organisation address | Ismaninger Str. 22, München, Germany, 81675 |
| Public contact | Professor Dr. med. Nikolas von Bubnoff , Klinikum rechts der Isar, Klinik und Poliklinik für Innere Medizin III , +49 761 270 33210, |
| Scientific contact | Professor Dr. med. Nikolas von Bubnoff , Klinikum rechts der Isar, Klinik und Poliklinik für Innere Medizin III , +49 761 270 33210, nikolas.bubnoff@uniklinik-freiburg.de |

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 | 12 October 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 14 October 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 October 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Goal of the study is to investigate whether tumor-specific CKIT or PDGFRA DNA fragments can be detected and quantified in the plasma of patients with active GIST as defined as GIST lesions that can be measured by diagnostic imaging.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance the ethical principles of Good Clinical Practice (GCP). Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. The study was regularly monitored by the Sponsor and all investigators connected to the study were GCP trained.

Background therapy:

Medical treatment will be given according to the clinical trial centers' routine with TKI such as imatinib or sunitinib. The medication is standard medication, which can vary between study centers. The information on which medication is administered, dose and duration of medical treatment will be collected and captured on the CRF at baseline and each time the patient presents in the hospital for follow-up visits.

Evidence for comparator:

n.a.

| | |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment | 24 January 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 35 |
| Worldwide total number of subjects | 35 |
| EEA total number of subjects | 35 |

Notes:

Subjects enrolled per age group

| | |
|-------------------------------------------|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

| | |
|------------------------------------------|----|
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 22 |
| From 65 to 84 years | 13 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted multicentric single-centre in Germany between 24.01.2012 (first patient recruited) and 14.10.2015 (last patient completed).

Pre-assignment

Screening details:

During screening it will be assessed whether the patient meets all inclusion and no exclusion criteria. Each patient screened will be captured on the subject screening list. Patients were enrolled to the study, if eligibility was confirmed. After Screening, a total of 35 patients were included in the study.

Period 1

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

Blinding implementation details:

This is a single-arm not blinded study.

Arms

| | |
|-----------|------------|
| Arm title | GIST trial |
|-----------|------------|

Arm description:

Single arm for detection of circulating tumor DNA in the plasma of patients with GIST pre/post surgery and pre/under neoadjuvant or palliative medical treatment with a tyrosinase inhibitors (TKI) like imatinib or sunitinib or in progressive disease irrespective of therapy.

| | |
|----------------------------------------|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Imatinib |
| Investigational medicinal product code | CAS 152459-95-5 |
| Other name | SUB25387 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

400 mg /day for 12 months

| | |
|----------------------------------------|---------------|
| Investigational medicinal product name | Sunitinib |
| Investigational medicinal product code | 557795-19-4 |
| Other name | SUB22321 |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

50 mg per day for 4 weeks

| Number of subjects in period 1 | GIST trial |
|--------------------------------|------------|
| Started | 35 |
| Completed | 11 |
| Not completed | 24 |
| Adverse event, serious fatal | 5 |

| | |
|------------------------------|---|
| Consent withdrawn by subject | 8 |
| Developed NSCLC | 1 |
| Organizational reasons | 3 |
| Lost to follow-up | 4 |
| Protocol deviation | 3 |

Baseline characteristics

Reporting groups

| | |
|------------------------------|---------------|
| Reporting group title | Overall Trial |
| Reporting group description: | |
| Single Arm | |

| Reporting group values | Overall Trial | Total | |
|----------------------------------------------------|---------------|-------|--|
| Number of subjects | 35 | 35 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 22 | 22 | |
| From 65-84 years | 13 | 13 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 55.2 | | |
| standard deviation | ± 12.8 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 16 | 16 | |
| Male | 19 | 19 | |

Subject analysis sets

| | |
|----------------------------|--------------------|
| Subject analysis set title | ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Eight patients were excluded from the ITT set due to missing baseline plasma samples. Another two patients were excluded from the ITT set since they showed no measureable lesions at baseline (due to no CT/MRI).

| Reporting group values | ITT | | |
|----------------------------------------------------|-----|--|--|
| Number of subjects | 25 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 22 | | |
| From 65-84 years | 13 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 61,9 | | |
| standard deviation | ± | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 12 | | |
| Male | 13 | | |

End points

End points reporting groups

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Reporting group title | GIST trial |
| Reporting group description: Single arm for detection of circulating tumor DNA in the plasma of patients with GIST pre/post surgery and pre/under neoadjuvant or palliative medical treatment with a tyrosinase inhibitors (TKI) like imatinib or sunitinib or in progressive disease irrespective of therapy. | |
| Subject analysis set title | ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Eight patients were excluded from the ITT set due to missing baseline plasma samples. Another two patients were excluded from the ITT set since they showed no measurable lesions at baseline (due to no CT/MRI). | |

Primary: Detection of tumor-specific DNA

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title | Detection of tumor-specific DNA |
| End point description: Percentage of patients with histologically proven GIST, measurable lesions in imaging, and activating CKIT and PDGFRA mutation, where detection of tumor-specific DNA encoding for mutated CKIT or PDGFRA is possible in the plasma at least at one time point. The detection rate was 64% with exact 95%CI of (42.5%, 82.0%). | |
| End point type | Primary |
| End point timeframe: Throughout the study (up to 2 years) | |

| End point values | GIST trial | ITT | ITT | |
|-----------------------------|-------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 25 ^[1] | 25 | 25 | |
| Units: Patients | | | | |
| Detection possible | 16 | 16 | 16 | |
| Detection not possible | 9 | 9 | 9 | |

Notes:

[1] - This analysis was performed on the ITT set.

Statistical analyses

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Statistical analysis title | Detection Rate |
| Statistical analysis description: The detection rate for the primary endpoint was 64.0% and the two-sided exact 95% CI was (42.5%, 82.0%). | |
| Comparison groups | ITT v ITT |
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| Parameter estimate | Detection rate |
| Point estimate | 0.64 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.425 |
| upper limit | 0.82 |

Notes:

[2] - Detection rate in the primary endpoint including exact 95% CI.

Secondary: Amount of tumor

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| End point title | Amount of tumor |
| End point description: The Spearman's correlation coefficient between the amount of tumor specific CKIT or PDGFRA DNA in plasma samples and the amount of tumor as assessed by diagnostic imaging was 0.187 (p=0.044). | |
| End point type | Secondary |
| End point timeframe: Throughout the study. | |

| End point values | GIST trial | ITT | | |
|--------------------------------------|-------------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 25 ^[3] | | | |
| Units: millimeter | | | | |
| arithmetic mean (standard deviation) | 77.1 (± 61.1) | 77.1 (± 61.1) | | |

Notes:

[3] - This endpoint was analyzed on the ITT set.

Statistical analyses

No statistical analyses for this end point

Secondary: Response to therapy

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| End point title | Response to therapy |
| End point description: Response was coded in increasing manner starting with complete response. The Spearman correlation coefficient between the amount of tumor specific CKIT or PDGFRA DNA in plasma samples and the response to therapy (surgery and/or therapy with a TKI) as assessed by diagnostic imaging was 0.092 (p=0.269). Differences in the amount of tumor-DNA measured for patients with response and progression could not be shown (Mann-Whitney U test: p=0.549). | |
| End point type | Secondary |
| End point timeframe: Throughout the study | |

| End point values | GIST trial | ITT | | |
|--------------------------------------|-------------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 25 ^[4] | | | |
| Units: Response | | | | |
| arithmetic mean (standard deviation) | 2.88 (± 1.17) | 2.88 (± 1.17) | | |

Notes:

[4] - This endpoint was calculated on the ITT set.

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse or progression

| | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| End point title | Relapse or progression |
| End point description: | |
| Relapse or progression =1, else 0. The variable was used for calculation of Spearman's correlation coefficient (0.050; p=0.551) between the amount of tumor specific CKIT or PDGFRA DNA in plasma samples and relapse or progression of disease as assessed by diagnostic imaging showed no correlation between the variables. | |
| End point type | Secondary |
| End point timeframe: | |
| Throughout the trial | |

| End point values | GIST trial | ITT | | |
|--------------------------------------|-------------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 25 ^[5] | | | |
| Units: Relapse | | | | |
| arithmetic mean (standard deviation) | 0.42 (± 0.50) | 0.42 (± 0.50) | | |

Notes:

[5] - This analysis was performed on the ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor flair

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| End point title | Tumor flair |
| End point description: | |
| The percentage of patients with transient increase of tumor specific CKIT or PDGFRA DNA in the plasma („tumor flare“) after starting a medical treatment with a TKI was calculated. This percentage is 0%, as no such patients existed. This calculation was done on the subset of 8 patients who did not have TKI at screening, but received it during study conduct and who have L-PCR measurements both pre and (1-5 days) post TKI. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 5 days post TKI. | |

| End point values | GIST trial | ITT | | |
|-----------------------------|------------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 8 ^[6] | 25 | | |
| Units: Patients | | | | |
| tumor flair | 0 | 0 | | |
| no tumor flair | 8 | 8 | | |

Notes:

[6] - This analysis was done on the set of 8 patients who did not have TKI at screening.

Statistical analyses

No statistical analyses for this end point

Secondary: Sensitivity of L-PCR

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| End point title | Sensitivity of L-PCR |
| End point description: | |
| Comparison of the sensitivity of L-PCR for specific CKIT or PGDFRA mutations: sensitivity, specificity, PPR, NPR, and accuracy were calculated using diagnostic imaging as a "gold standard". All available time points were used. Sensitivity was 71.9%, specificity was 28.0%, PPR was 43.8%, NPR was 56.1%, accuracy was 47.3%. As only two patients had mutations in exon 9 and one patient in PDGFRA18, this analysis does not distinguish between the different types of mutations. | |
| End point type | Secondary |
| End point timeframe: | |
| Throughout the study | |

| End point values | GIST trial | ITT | | |
|------------------------------|-------------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 25 ^[7] | | | |
| Units: Lab tests | | | | |
| Lab negative and no response | 46 | 46 | | |
| Lab negative but response | 59 | 59 | | |
| Lab positive but no response | 18 | 18 | | |
| Lab positive and response | 23 | 23 | | |

Notes:

[7] - 146 valid lab/response pairs were available for analysis resulting from 25 patients

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Study duration

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 15 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall trial |
|-----------------------|---------------|

Reporting group description: -

| Serious adverse events | Overall trial | | |
|---------------------------------------------------------------------|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 35 (17.14%) | | |
| number of deaths (all causes) | 5 | | |
| number of deaths resulting from adverse events | 5 | | |
| Investigations | | | |
| ECOG performance status worsened | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasm | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|------------------------------------------------------|-----------------|--|--|
| Cardiac disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 5 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatotoxicity | | | |

| | | | |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Jaundice | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| | | | |
|-------------------------------------------------------|------------------|--|--|
| Non-serious adverse events | Overall trial | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 19 / 35 (54.29%) | | |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration | | | |

| | | | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|--|--|
| site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) | 3 / 35 (8.57%) 3 4 / 35 (11.43%) 4 | | |
| Eye disorders Periorbital oedema subjects affected / exposed occurrences (all) | 5 / 35 (14.29%) 6 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) | 8 / 35 (22.86%) 11 2 / 35 (5.71%) 2 2 / 35 (5.71%) 2 4 / 35 (11.43%) 4 | | |
| Skin and subcutaneous tissue disorders Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all) Alopecia subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) | 6 / 35 (17.14%) 6 2 / 35 (5.71%) 2 2 / 35 (5.71%) 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported