



## Clinical trial results:

### Prospective, Multicenter, Open-label Phase IV trial of Trifluridine/Tipiracil to Evaluate the Health-related Quality of Life in Patients with Metastatic Colorectal Cancer

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2017-000292-83   |
| Trial protocol           | DE               |
| Global end of trial date | 24 December 2020 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 11 January 2022 |
| First version publication date | 11 January 2022 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | Tallisur |
|-----------------------|----------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Servier Deutschland GmbH  |
| Sponsor organisation address | Elsenheimerstraße 53, München, Germany, 80687   |
| Public contact               | Dr. Timo Reisländer, Servier Deutschland GmbH, +49 (0)89 570 95 167, Timo.Reislaender@servier.com |
| Scientific contact           | Dr. Timo Reisländer, Servier Deutschland GmbH, +49 (0)89 570 95 167, Timo.Reislaender@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                       | 12 July 2021     |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 24 December 2020 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 24 December 2020 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effect of treatment with FTD/TPI on HRQoL as measured by EORTC QLQ-C30 (global health status/quality of life scale)

Protection of trial subjects:

The clinical study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in accordance with the International Council on Harmonisation (ICH) guideline for good clinical practice (GCP).

The investigator obtained written informed consent of a patient prior to any study-related procedures including the documentation of results of clinical routine procedures for study purposes as set forth in the ICH-GCP guidelines and the respective European Union's and national legislation. Subjects had the right to withdraw consent at any time and without giving any reasons without prejudice to his or her future medical care by the investigator or other medical health care personnel at the institution. The investigator discussed with the subject the most appropriate way to withdraw to ensure the subject's health.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable. To evaluate the effect of treatment with trifluridine/tipiracil on quality of life, a controlled study with best supportive care (BSC) was chosen and considered appropriate comparative treatment according to the advice from the German Federal Joint Committee (G-BA) on 29 September 2016.

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 22 September 2017 |
| Long term follow-up planned                               | Yes               |
| Long term follow-up rationale                             | Safety, Efficacy  |
| Long term follow-up duration                              | 12 Months         |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Germany: 195 |
| Worldwide total number of subjects   | 195          |
| EEA total number of subjects         | 195          |

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)                      | 76  |
| From 65 to 84 years                       | 116 |
| 85 years and over                         | 3   |

## Subject disposition

### Recruitment

Recruitment details:

The recruitment period of this clinical study lasted from 22 September 2017 (first patient registered) to 08 January 2019 (last patient registered). 202 patients were recruited to 44 study centres in Germany, 7 of which did not enter the treatment / close observation phase (2 deaths, 3 patient`s wish, 1 AE, 1 violation of selection criteria).

### Pre-assignment

Screening details:

Adult patients with histologically or cytologically confirmed UICC stage IV carcinoma of the colon or rectum with metastatic colorectal cancer, at least one measurable or non-measurable lesion as defined by RECIST version 1.1, any ECOG performance status, previously treated with or not considered candidates for available therapies.

### Period 1

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

Blinding implementation details:

Not applicable.

### Arms

|                              |                                  |
|------------------------------|----------------------------------|
| Are arms mutually exclusive? | Yes                              |
| <b>Arm title</b>             | FTD/TPI (trifluridine/tipiracil) |

Arm description:

FTD/TPI (starting dose 35 mg/m<sup>2</sup> BSA/dose) was taken orally twice daily (BID) on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as a benefit was observed or until unacceptable toxicity occurred.

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Trifluridine/tipiracil |
| Investigational medicinal product code |                        |
| Other name                             | Lonsurf (R)            |
| Pharmaceutical forms                   | Film-coated tablet     |
| Routes of administration               | Oral use               |

Dosage and administration details:

The daily FTD/TPI dosage was calculated according to the body surface area (BSA). FTD/TPI (starting dose 35 mg/m<sup>2</sup> BSA/dose) was taken orally twice daily (BID) on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as a benefit was observed or until unacceptable toxicity occurred. The dosage was not allowed to exceed 80 mg per dose. In case of haematological or non-haematological toxicities, criteria for dose interruption and dose modification applied. A maximum of 3 dose reduction levels (30 mg/m<sup>2</sup> BSA BID, 25 mg/m<sup>2</sup> BSA BID, and 20 mg/m<sup>2</sup> BSA BID) was permitted to a minimum dose of 20 mg/m<sup>2</sup> BID.

|                  |                            |
|------------------|----------------------------|
| <b>Arm title</b> | BSC (Best Supportive Care) |
|------------------|----------------------------|

Arm description:

Best supportive care, tailored to the patient`s individual needs.

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

| <b>Number of subjects in period 1</b> | <b>FTD/TPI<br/>(trifluridine/tipiracil)</b> | <b>BSC (Best<br/>Supportive Care)</b> |
|---------------------------------------|---|---------------------------------------|
| Started                               | 186   | 9                                     |
| Completed                             | 0   | 0                                     |
| Not completed                         | 186   | 9                                     |
| Disease progression (clinical)        | 23  | -                                     |
| Consent withdrawn by subject          | 12  | 1                                     |
| Physician decision                    | 6   | -                                     |
| Adverse event, non-fatal              | 25  | 1                                     |
| Death                                 | 10  | 3                                     |
| Patient non-compliance                | 1   | -                                     |
| Other / unknown                       | 10  | -                                     |
| Lost to follow-up                     | 2   | 1                                     |
| Start of further anti-tumour therapy  | -   | 2                                     |
| Protocol deviation                    | 2   | -                                     |
| Disease progression (RECIST 1.1)      | 95  | 1                                     |

## Baseline characteristics

### Reporting groups

|  |                                  |
|--|----------------------------------|
| Reporting group title  | FTD/TPI (trifluridine/tipiracil) |
| Reporting group description:   |                                  |
| FTD/TPI (starting dose 35 mg/m <sup>2</sup> BSA/dose) was taken orally twice daily (BID) on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as a benefit was observed or until unacceptable toxicity occurred. |                                  |
| Reporting group title  | BSC (Best Supportive Care)       |
| Reporting group description:   |                                  |
| Best supportive care, tailored to the patient's individual needs.  |                                  |

| Reporting group values  | FTD/TPI<br>(trifluridine/tipiracil) | BSC (Best<br>Supportive Care) | Total |
|---|-------------------------------------|-------------------------------|-------|
| Number of subjects  | 186                                 | 9                             | 195   |
| Age categorical   |                                     |                               |       |
| Units: Subjects   |                                     |                               |       |
| In utero  | 0                                   | 0                             | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks)   | 0                                   | 0                             | 0     |
| Newborns (0-27 days)  | 0                                   | 0                             | 0     |
| Infants and toddlers (28 days-23<br>months)   | 0                                   | 0                             | 0     |
| Children (2-11 years)   | 0                                   | 0                             | 0     |
| Adolescents (12-17 years)   | 0                                   | 0                             | 0     |
| Adults (18-64 years)  | 74                                  | 2                             | 76    |
| From 65-84 years  | 109                                 | 7                             | 116   |
| 85 years and over   | 3                                   | 0                             | 3     |
| Age continuous  |                                     |                               |       |
| Units: years  |                                     |                               |       |
| median  | 67.0                                | 78.0                          |       |
| full range (min-max)  | 40 to 88                            | 54 to 82                      | -     |
| Gender categorical  |                                     |                               |       |
| Units: Subjects   |                                     |                               |       |
| Female  | 69                                  | 4                             | 73    |
| Male  | 117                                 | 5                             | 122   |
| ECOG Performance Status   |                                     |                               |       |
| Units: Subjects   |                                     |                               |       |
| ECOG PS 0   | 72                                  | 0                             | 72    |
| ECOG PS 1   | 94                                  | 4                             | 98    |
| ECOG PS 2   | 18                                  | 3                             | 21    |
| ECOG PS 3   | 0                                   | 1                             | 1     |
| Unknown   | 2                                   | 1                             | 3     |
| Number of previous therapy lines of<br>mCRC   |                                     |                               |       |
| Only systemic anticancer therapies; a new therapy was defined as administration of a substance that was not part of the preceding therapy line. |                                     |                               |       |
| Units: Subjects   |                                     |                               |       |
| 0 previous therapy lines  | 8                                   | 2                             | 10    |
| 1 previous therapy line   | 23                                  | 1                             | 24    |
| 2 previous therapy lines  | 71                                  | 3                             | 74    |
| 3 previous therapy lines  | 49                                  | 0                             | 49    |

|                            |    |   |    |
|----------------------------|----|---|----|
| ≥ 4 previous therapy lines | 35 | 3 | 38 |
|----------------------------|----|---|----|

## Subject analysis sets

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type  | Full analysis           |

Subject analysis set description:

All enrolled patients who received at least one dose of FTD/TPI (Group A) or started the close observation period (Group B).

|                            |               |
|----------------------------|---------------|
| Subject analysis set title | FAS-C30       |
| Subject analysis set type  | Full analysis |

Subject analysis set description:

FAS HR QoL subset 1: Patients of the FAS who answered the baseline and at least one additional EORTC QLQ-C30 questionnaire between start of FTD/TPI treatment (Group A) or the start of the close observation period (Group B) and the end of treatment/close observation.

|                            |               |
|----------------------------|---------------|
| Subject analysis set title | FAS-EQ        |
| Subject analysis set type  | Full analysis |

Subject analysis set description:

FAS HR QoL subset 2: Patients of the FAS who answered the baseline and at least one additional EQ-5D-5L questionnaire between start of FTD/TPI treatment (Group A) or the start of the close observation period (Group B) and the end of treatment/close observation.

|                            |               |
|----------------------------|---------------|
| Subject analysis set title | FAS-C30 (pe)  |
| Subject analysis set type  | Full analysis |

Subject analysis set description:

FAS-C30 evaluable for the primary endpoint (pe): a subset of the FAS-C30 comprising all patients who received at least two cycles of FTD/TPI and who completed the baseline EORTC-QLQ-C30 questionnaire and at least one more questionnaire AFTER Cycle 1 (i.e., the earliest within two days before Day 1 of Cycle 2).

|                            |              |
|----------------------------|--------------|
| Subject analysis set title | Per protocol |
| Subject analysis set type  | Per protocol |

Subject analysis set description:

All patients of the FAS/SAF without any relevant violation of selection criteria; moreover, patients from two centres were excluded from the PP due to inspection findings.

| Reporting group values                             | Full Analysis Set (FAS) | FAS-C30 | FAS-EQ |
|--|-------------------------|---------|--------|
| Number of subjects                                 | 195                     | 129     | 128    |
| Age categorical<br>Units: Subjects                 |                         |         |        |
| In utero   |                         |         |        |
| Preterm newborn infants (gestational age < 37 wks) |                         |         |        |
| Newborns (0-27 days)                               |                         |         |        |
| Infants and toddlers (28 days-23 months)           |                         |         |        |
| Children (2-11 years)                              |                         |         |        |
| Adolescents (12-17 years)                          |                         |         |        |
| Adults (18-64 years)                               | 76                      |         |        |
| From 65-84 years                                   | 116                     |         |        |
| 85 years and over                                  | 3                       |         |        |
| Age continuous<br>Units: years<br>median           | 67.0                    |         |        |

|                      |          |  |  |
|----------------------|----------|--|--|
| full range (min-max) | 40 to 88 |  |  |
|----------------------|----------|--|--|

|   |     |  |  |
|---|-----|--|--|
| Gender categorical<br>Units: Subjects   |     |  |  |
| Female  | 73  |  |  |
| Male  | 122 |  |  |
| ECOG Performance Status<br>Units: Subjects  |     |  |  |
| ECOG PS 0   | 72  |  |  |
| ECOG PS 1   | 98  |  |  |
| ECOG PS 2   | 21  |  |  |
| ECOG PS 3   | 1   |  |  |
| Unknown   | 3   |  |  |
| Number of previous therapy lines of mCRC  |     |  |  |
| Only systemic anticancer therapies; a new therapy was defined as administration of a substance that was not part of the preceding therapy line. |     |  |  |
| Units: Subjects   |     |  |  |
| 0 previous therapy lines  | 10  |  |  |
| 1 previous therapy line   | 24  |  |  |
| 2 previous therapy lines  | 74  |  |  |
| 3 previous therapy lines  | 49  |  |  |
| ≥ 4 previous therapy lines  | 38  |  |  |

|   |              |              |  |
|---|--------------|--------------|--|
| <b>Reporting group values</b>   | FAS-C30 (pe) | Per protocol |  |
| Number of subjects  | 112          | 171          |  |
| Age categorical<br>Units: Subjects  |              |              |  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |              |              |  |
| Age continuous<br>Units: years<br>median<br>full range (min-max)  |              |              |  |
| Gender categorical<br>Units: Subjects   |              |              |  |
| Female  |              |              |  |
| Male  |              |              |  |
| ECOG Performance Status<br>Units: Subjects  |              |              |  |
| ECOG PS 0   |              |              |  |
| ECOG PS 1   |              |              |  |



|   |  |  |  |
|---|--|--|--|
| ECOG PS 2   |  |  |  |
| ECOG PS 3   |  |  |  |
| Unknown   |  |  |  |
| Number of previous therapy lines of mCRC  |  |  |  |
| Only systemic anticancer therapies; a new therapy was defined as administration of a substance that was not part of the preceding therapy line. |  |  |  |
| Units: Subjects   |  |  |  |
| 0 previous therapy lines  |  |  |  |
| 1 previous therapy line   |  |  |  |
| 2 previous therapy lines  |  |  |  |
| 3 previous therapy lines  |  |  |  |
| ≥ 4 previous therapy lines  |  |  |  |

## End points

### End points reporting groups

|  |                                  |
|--|----------------------------------|
| Reporting group title  | FTD/TPI (trifluridine/tipiracil) |
| Reporting group description:<br>FTD/TPI (starting dose 35 mg/m <sup>2</sup> BSA/dose) was taken orally twice daily (BID) on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as a benefit was observed or until unacceptable toxicity occurred.   |                                  |
| Reporting group title  | BSC (Best Supportive Care)       |
| Reporting group description:<br>Best supportive care, tailored to the patient's individual needs.  |                                  |
| Subject analysis set title   | Full Analysis Set (FAS)          |
| Subject analysis set type  | Full analysis                    |
| Subject analysis set description:<br>All enrolled patients who received at least one dose of FTD/TPI (Group A) or started the close observation period (Group B).  |                                  |
| Subject analysis set title   | FAS-C30                          |
| Subject analysis set type  | Full analysis                    |
| Subject analysis set description:<br>FAS HR QoL subset 1: Patients of the FAS who answered the baseline and at least one additional EORTC QLQ-C30 questionnaire between start of FTD/TPI treatment (Group A) or the start of the close observation period (Group B) and the end of treatment/close observation.  |                                  |
| Subject analysis set title   | FAS-EQ                           |
| Subject analysis set type  | Full analysis                    |
| Subject analysis set description:<br>FAS HR QoL subset 2: Patients of the FAS who answered the baseline and at least one additional EQ-5D-5L questionnaire between start of FTD/TPI treatment (Group A) or the start of the close observation period (Group B) and the end of treatment/close observation.   |                                  |
| Subject analysis set title   | FAS-C30 (pe)                     |
| Subject analysis set type  | Full analysis                    |
| Subject analysis set description:<br>FAS-C30 evaluable for the primary endpoint (pe): a subset of the FAS-C30 comprising all patients who received at least two cycles of FTD/TPI and who completed the baseline EORTC-QLQ-C30 questionnaire and at least one more questionnaire AFTER Cycle 1 (i.e., the earliest within two days before Day 1 of Cycle 2). |                                  |
| Subject analysis set title   | Per protocol                     |
| Subject analysis set type  | Per protocol                     |
| Subject analysis set description:<br>All patients of the FAS/SAF without any relevant violation of selection criteria; moreover, patients from two centres were excluded from the PP due to inspection findings.   |                                  |

### Primary: Rate of responders with unchanged or improved HRQoL

|   |   |
|---|---|
| End point title   | Rate of responders with unchanged or improved HRQoL |
| End point description:<br>Response was calculated as the mean of the score of the EORTC QLQ C30 global health status/quality of life scale (QL2) at all scheduled time points of HR-QoL analysis in the time interval from two days before start of Cycle 2 until the end of treatment/end of close observation compared to the baseline score of the global health status/quality of life (QL2) scale. The rate of responders was defined as the proportion of patients with response, i.e. improvement ( $\geq 10$ scores) or stabilization ( $> -10$ and $< 10$ scores) of the EORTC QLQ C30 global health status/ quality of life (QL2) score compared to the baseline score.<br><br>CAVE: Only the analyses in FAS-C30 (pe) are the primary endpoint of the study. |   |
| End point type  | Primary   |
| End point timeframe:<br>From two days before start of Cycle 2 until the end of treatment/end of close observation.  |   |

| End point values                                   | FTD/TPI<br>(trifluridine/tipi<br>racil) | BSC (Best<br>Supportive<br>Care) |  |  |
|--|---|----------------------------------|--|--|
| Subject group type                                 | Reporting group                         | Reporting group                  |  |  |
| Number of subjects analysed                        | 106 <sup>[1]</sup>                      | 6 <sup>[2]</sup>                 |  |  |
| Units: Response rate, %                            |   |                                  |  |  |
| number (confidence interval 95%)                   |   |                                  |  |  |
| FAS-C30 pe, Group A: 62/106                        | 58.5 (48.5 to 68.0)                     | 0 (0 to 0)                       |  |  |
| FAS-C30 pe, Group B: 3/6                           | 0 (0 to 0)                              | 50.0 (11.8 to 88.2)              |  |  |
| FAS-C30 pe, Group A, ECOG 0: 24/43                 | 55.8 (39.9 to 70.9)                     | 0 (0 to 0)                       |  |  |
| FAS-C30 pe, Group A, ECOG 1: 33/54                 | 61.1 (46.9 to 74.1)                     | 0 (0 to 0)                       |  |  |
| FAS-C30 pe, Group B, ECOG 1: 1/3                   | 0 (0 to 0)                              | 33.3 (0.8 to 90.6)               |  |  |
| FAS-C30 pe, Group A, ECOG 2-3: 4/8                 | 50.0 (15.7 to 84.3)                     | 0 (0 to 0)                       |  |  |
| FAS-C30 pe, Group B, ECOG 2-3: 1/2                 | 0 (0 to 0)                              | 50.0 (1.3 to 98.7)               |  |  |
| FAS-C30 pe, Grp. A, 0 prev. therapy lines: 4/6     | 66.7 (22.3 to 95.7)                     | 0 (0 to 0)                       |  |  |
| FAS-C30 pe, Grp. B, 0 prev. therapy lines: 1/1     | 0 (0 to 0)                              | 100.0 (2.5 to 100.0)             |  |  |
| FAS-C30 pe, Grp. A, 1-2 prev. therapy lines: 29/54 | 53.7 (39.6 to 67.4)                     | 0 (0 to 0)                       |  |  |
| FAS-C30 pe, Grp. B, 1-2 prev. therapy lines: 2/4   | 0 (0 to 0)                              | 50.0 (6.8 to 93.2)               |  |  |
| FAS-C30 pe, Grp. A, 2 prev. therapy lines: 23/42   | 54.8 (38.7 to 70.2)                     | 0 (0 to 0)                       |  |  |
| FAS-C30 pe, Grp. B, 2 prev. therapy lines: 1/3     | 0 (0 to 0)                              | 33.3 (0.8 to 90.6)               |  |  |
| FAS-C30 pe, Grp. A, > 2 prev. therapy lines: 29/46 | 63.0 (47.5 to 76.8)                     | 0 (0 to 0)                       |  |  |
| FAS-C30 pe, Grp. B, > 2 prev. therapy lines: 0/1   | 0 (0 to 0)                              | 0.0 (0 to 0)                     |  |  |
| PP pe, Group A: 56/96                              | 58.3 (47.8 to 68.3)                     | 0 (0 to 0)                       |  |  |
| PP pe, Group B: 3/6                                | 0 (0 to 0)                              | 50.0 (11.8 to 88.2)              |  |  |

Notes:

[1] - 106 in FAS-C30 pe; subgroup numbers identified in category headers.

[2] - 6 in FAS-C30 pe; subgroup numbers identified in category headers.

## Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | Primary endpoint analysis                                     |
| Statistical analysis description:  |   |
| Calculation of the 2-sided 95% confidence interval for the response rate separately for both groups. |   |
| Comparison groups  | FTD/TPI (trifluridine/tipiracil) v BSC (Best Supportive Care) |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 112                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | equivalence <sup>[3]</sup> |
| Parameter estimate                      | Confidence interval        |
| Point estimate                          | 58.5                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 48.5                       |
| upper limit                             | 68                         |

Notes:

[3] - A response rate of 45% ± 10% was assessed as appropriate in Group A (patients with ≥ 2 cycles FTD/TPI).

A response rate of 45% ± 20% was assessed as appropriate in Group B (patients with ≥ 2 cycles BSC).

Note: Number of patients needed was not achieved in Group B. Parameter estimate presented is estimate for Group A.

### Secondary: Progression-free survival (PFS)

|   |                                 |
|---|---------------------------------|
| End point title   | Progression-free survival (PFS) |
| End point description:  |                                 |
| PFS (based on RECIST version 1.1) was defined as the duration from the first administration of FTD/TPI (Group A) or Day 1 of observation Cycle 1 (Group B) to the day of radiological or clinical tumour progression or death of any cause, whichever came first. |                                 |
| Patients who were not known to have had a radiological or clinical progression were censored for PFS analysis at the last date they were known not to have experienced progression.   |                                 |
| End point type  | Secondary                       |

End point timeframe:

Patients were followed until the end of study, at least one year after start of FTD/TPI / close observation.

| End point values                 | FTD/TPI<br>(trifluridine/tipiracil) | BSC (Best<br>Supportive<br>Care) | Full Analysis<br>Set (FAS) | Per protocol         |
|----------------------------------|-------------------------------------|----------------------------------|----------------------------|----------------------|
| Subject group type               | Reporting group                     | Reporting group                  | Subject analysis set       | Subject analysis set |
| Number of subjects analysed      | 186                                 | 9                                | 195                        | 171                  |
| Units: months                    |                                     |                                  |                            |                      |
| median (confidence interval 95%) | 2.5 (2.1 to 2.9)                    | 3.7 (2.2 to 4.7)                 | 2.5 (2.2 to 3.1)           | 2.5 (2.1 to 3.2)     |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS)

|   |                       |
|---|-----------------------|
| End point title   | Overall Survival (OS) |
| End point description:  |                       |
| Duration from first administration of FTD/TPI (Group A) or Day 1 of observation Cycle 1 (Group B) to the day of death from any cause. |                       |
| Patients who were not known to have died were censored for OS analysis on the last day they were known to have been alive.            |                       |

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Patients were followed until the end of study, at least one year after start of FTD/TPI / close observation. |           |

| End point values                 | FTD/TPI<br>(trifluridine/tipi<br>racil) | BSC (Best<br>Supportive<br>Care) | Full Analysis<br>Set (FAS) | Per protocol         |
|----------------------------------|---|----------------------------------|----------------------------|----------------------|
| Subject group type               | Reporting group                         | Reporting group                  | Subject analysis set       | Subject analysis set |
| Number of subjects analysed      | 186                                     | 9                                | 195                        | 171                  |
| Units: months                    |   |                                  |                            |                      |
| median (confidence interval 95%) | 6.9 (6.1 to 8.3)                        | 4.7 (3.6 to 11.6)                | 6.8 (6.0 to 8.2)           | 6.8 (5.9 to 8.6)     |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Average EORTC QLQ-C30 scores

|                 |                              |
|-----------------|------------------------------|
| End point title | Average EORTC QLQ-C30 scores |
|-----------------|------------------------------|

End point description:

EORTC QLQ-C30 consists of the global health status (QL2) scale, the functional scales physical functioning (PF2), role functioning (RF2), emotional functioning (EF), cognitive functioning (CF), and social functioning (SF), and the symptom scales / items fatigue (FA), nausea and vomiting (NV), pain (PA), dyspnoea (DY), insomnia (SL), appetite loss (AP), constipation (CO), diarrhoea (DI), and financial difficulties (FI). For the global health status and functional scales higher scores (on a scale of 0 - 100) represent a higher QoL / higher/healthier level of functioning. For a symptom scale/item, higher scores represent a higher level of symptomatology/problems.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| At baseline, during and after treatment/close observation. After treatment includes all questionnaires completed at the end of treatment visit and during follow-up. Only questionnaires completed within prespecified time windows were considered. |           |

| End point values                     | FTD/TPI<br>(trifluridine/tipi<br>racil) | BSC (Best<br>Supportive<br>Care) |  |  |
|--------------------------------------|---|----------------------------------|--|--|
| Subject group type                   | Reporting group                         | Reporting group                  |  |  |
| Number of subjects analysed          | 123 <sup>[4]</sup>                      | 6 <sup>[5]</sup>                 |  |  |
| Units: Score points                  |   |                                  |  |  |
| arithmetic mean (standard deviation) |   |                                  |  |  |
| QL2 at baseline                      | 59.4 (± 20.5)                           | 50.0 (± 14.9)                    |  |  |
| QL2 during treatment                 | 54.2 (± 22.3)                           | 61.8 (± 31.0)                    |  |  |
| QL2 after treatment                  | 45.0 (± 25.1)                           | 52.8 (± 21.0)                    |  |  |
| PF2 at baseline                      | 65.1 (± 24.5)                           | 33.3 (± 34.8)                    |  |  |

|                      |               |               |  |  |
|----------------------|---------------|---------------|--|--|
| PF2 during treatment | 60.1 (± 25.2) | 43.3 (± 47.0) |  |  |
| PF2 after treatment  | 52.8 (± 28.5) | 39.7 (± 44.8) |  |  |
| RF2 at baseline      | 57.9 (± 31.6) | 25.0 (± 39.1) |  |  |
| RF2 during treatment | 51.8 (± 31.1) | 43.1 (± 51.0) |  |  |
| RF2 after treatment  | 39.5 (± 34.0) | 42.2 (± 51.8) |  |  |
| EF at baseline       | 67.7 (± 23.9) | 62.5 (± 35.3) |  |  |
| EF during treatment  | 66.8 (± 26.4) | 80.6 (± 21.2) |  |  |
| EF after treatment   | 63.5 (± 26.5) | 75.8 (± 29.7) |  |  |
| CF at baseline       | 79.2 (± 23.2) | 75.0 (± 23.0) |  |  |
| CF during treatment  | 76.2 (± 22.7) | 59.7 (± 37.8) |  |  |
| CF after treatment   | 74.6 (± 23.3) | 82.8 (± 9.2)  |  |  |
| SF at baseline       | 63.1 (± 30.7) | 61.1 (± 44.3) |  |  |
| SF during treatment  | 60.0 (± 31.5) | 68.1 (± 31.5) |  |  |
| SF after treatment   | 56.0 (± 33.7) | 76.7 (± 20.3) |  |  |
| FA at baseline       | 46.0 (± 27.0) | 72.2 (± 23.0) |  |  |
| FA during treatment  | 52.3 (± 26.9) | 56.5 (± 34.4) |  |  |
| FA after treatment   | 57.8 (± 30.6) | 61.7 (± 33.0) |  |  |
| NV at baseline       | 9.6 (± 19.1)  | 19.4 (± 19.5) |  |  |
| NV during treatment  | 14.1 (± 16.5) | 8.3 (± 16.7)  |  |  |
| NV after treatment   | 16.3 (± 20.5) | 8.6 (± 7.5)   |  |  |
| PA at baseline       | 34.3 (± 32.7) | 41.7 (± 27.4) |  |  |
| PA during treatment  | 43.7 (± 34.0) | 31.9 (± 25.0) |  |  |
| PA after treatment   | 47.2 (± 34.9) | 48.6 (± 35.4) |  |  |
| DY at baseline       | 29.8 (± 30.7) | 55.6 (± 34.4) |  |  |
| DY during treatment  | 38.3 (± 30.1) | 38.9 (± 43.0) |  |  |
| DY after treatment   | 43.7 (± 34.3) | 40.0 (± 43.7) |  |  |
| SL at baseline       | 30.1 (± 31.2) | 38.9 (± 25.1) |  |  |
| SL during treatment  | 36.8 (± 31.5) | 25.0 (± 31.9) |  |  |
| SL after treatment   | 40.9 (± 35.0) | 60.6 (± 47.2) |  |  |
| AP at baseline       | 29.8 (± 33.3) | 38.9 (± 49.1) |  |  |
| AP during treatment  | 39.2 (± 31.9) | 25.0 (± 50.0) |  |  |
| AP after treatment   | 42.0 (± 30.9) | 47.2 (± 33.7) |  |  |
| CO at baseline       | 18.9 (± 28.7) | 11.1 (± 17.2) |  |  |
| CO during treatment  | 19.5 (± 26.3) | 8.3 (± 16.7)  |  |  |
| CO after treatment   | 16.4 (± 23.6) | 8.9 (± 15.4)  |  |  |
| DI at baseline       | 19.4 (± 27.0) | 16.7 (± 27.9) |  |  |
| DI during treatment  | 19.5 (± 27.2) | 0.0 (± 0.0)   |  |  |
| DI after treatment   | 24.2 (± 27.6) | 10.6 (± 12.9) |  |  |
| FI at baseline       | 17.8 (± 27.2) | 5.6 (± 13.6)  |  |  |
| FI during treatment  | 19.9 (± 26.9) | 0.0 (± 0.0)   |  |  |
| FI after treatment   | 20.2 (± 26.5) | 0.0 (± 0.0)   |  |  |

Notes:

[4] - 123 in FAS-C30; 123 (121-123 per item) at BL, 92 (91-92) during, 55 (54-55) after treatment.

[5] - 6 in FAS-C30; 6 at baseline, 4 during treatment, 3 after treatment.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Average EQ-5D-5L index and EQ VAS scores

|                 |  |
|-----------------|--|
| End point title | Average EQ-5D-5L index and EQ VAS scores |
|-----------------|--|

**End point description:**

EQ-5D-5L consists of the EQ-5D descriptive system comprising 5 dimensions mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and the EQ 20 cm vertical visual analogue scale (VAS). EQ-5D-5L results are represented by an index value between 0 and 1 computed by the Crosswalk Index Value Calculator, where a higher value represents a higher level of problems; EQ VAS scores are presented as continuous parameter (0-100) where a high value represents a high health profile.

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

**End point timeframe:**

At baseline, during and after treatment/close observation. After treatment includes all questionnaires completed at the end of treatment visit and during follow-up. Only questionnaires completed within prespecified time windows were considered.

| End point values                     | FTD/TPI (trifluridine/tipiracil) | BSC (Best Supportive Care) |  |  |
|--------------------------------------|----------------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group                  | Reporting group            |  |  |
| Number of subjects analysed          | 122 <sup>[6]</sup>               | 6 <sup>[7]</sup>           |  |  |
| Units: score points                  |                                  |                            |  |  |
| arithmetic mean (standard deviation) |                                  |                            |  |  |
| EQ-5D-5L index at baseline           | 0.8 (± 0.2)                      | 0.7 (± 0.4)                |  |  |
| EQ-5D-5L index during treatment      | 0.7 (± 0.2)                      | 0.6 (± 0.4)                |  |  |
| EQ-5D-5L index after treatment       | 0.6 (± 0.3)                      | 0.5 (± 0.5)                |  |  |
| EQ VAS at baseline                   | 62.7 (± 20.0)                    | 65.0 (± 15.8)              |  |  |
| EQ VAS during treatment              | 58.1 (± 23.1)                    | 68.5 (± 26.1)              |  |  |
| EQ VAS after treatment               | 49.5 (± 27.1)                    | 61.9 (± 18.9)              |  |  |

**Notes:**

[6] - 122 in FAS-EQ; EQ-5D-5L index n=120 at BL, 86 during, 57 after treatment; VAS n=120, 90, and 57.

[7] - 6 in FAS-EQ; EQ-5D-5L index n=5 and VAS n=6 at BL; both n=4 during and n=3 after treatment.

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Time to deterioration of HR-QoL according to EORTC QLQ-C30 global health status QL2**

|                 |   |
|-----------------|---|
| End point title | Time to deterioration of HR-QoL according to EORTC QLQ-C30 global health status QL2 |
|-----------------|---|

**End point description:**

From day 1 of cycle 1 of treatment with FTD/TPI / close observation to first change of global health/quality of life scale of  $\leq -10$  scores compared to the baseline score.

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

**End point timeframe:**

From day 1 of cycle 1 of treatment with FTD/TPI / close observation to end of treatment / close observation (EoT) and end of follow-up (EoF), respectively.

| End point values                         | FTD/TPI<br>(trifluridine/tipi<br>racil) | BSC (Best<br>Supportive<br>Care) | FAS-C30                  |  |
|--|---|----------------------------------|--------------------------|--|
| Subject group type                       | Reporting group                         | Reporting group                  | Subject analysis set     |  |
| Number of subjects analysed              | 123 <sup>[8]</sup>                      | 6 <sup>[9]</sup>                 | 129 <sup>[10]</sup>      |  |
| Units: months                            |   |                                  |                          |  |
| median (confidence interval 95%)         |   |                                  |                          |  |
| until end of treatment/close observation | 84.0 (64.0 to<br>391.0)                 | 9999 (60.0 to<br>9999)           | 84.0 (64.0 to<br>391.0)  |  |
| until end of follow-up                   | 121.0 (84.0 to<br>172.0)                | 104.0 (60.0 to<br>9999)          | 121.0 (87.0 to<br>172.0) |  |

Notes:

[8] - 123 in FAS-C30. Deteriorations n=39 (31.7%) until EoT, n=63 (51.2%) until EoF.

[9] - 6 in FAS-C30. Deteriorations n=1 (16.7%) until EoT, n=2 (33.3%) until EoF.

[10] - N=40 deteriorations until EoT, n=65 (50.4%) deteriorations until EoF.

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Objective Response Rate (ORR)

|                 |                               |
|-----------------|-------------------------------|
| End point title | Objective Response Rate (ORR) |
|-----------------|-------------------------------|

End point description:

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Proportion of patients experiencing a response (complete [CR] or partial response [PR] based on RECIST version 1.1) in the period from start of Cycle 1 until the last administration of FTD/TPI (Group A) or close observation (Group B) plus 28 days.

| End point values            | FTD/TPI<br>(trifluridine/tipi<br>racil) | BSC (Best<br>Supportive<br>Care) | Full Analysis<br>Set (FAS) |  |
|-----------------------------|---|----------------------------------|----------------------------|--|
| Subject group type          | Reporting group                         | Reporting group                  | Subject analysis set       |  |
| Number of subjects analysed | 186                                     | 9                                | 195                        |  |
| Units: Responders           | 4                                       | 0                                | 4                          |  |

## Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first administration of FTD/TPI (Group A) or Day 1 of the close observation Cycle 1 (Group B) to 28 days after the last administration of FTD/TPI (Group A) or until the end of close observation (Group B)

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20.1   |

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | A: FTD/TPI (trifluridine/tipiracil) (SAF) |
|-----------------------|---|

Reporting group description:

FTD/TPI (starting dose 35 mg/m<sup>2</sup> BSA/dose) was taken orally twice daily (BID) on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as a benefit was observed or until unacceptable toxicity occurred.

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | B: BSC (Best Supportive Care) (SAF) |
|-----------------------|-------------------------------------|

Reporting group description:

Best supportive care, tailored to the patient`s individual needs.

| Serious adverse events  | A: FTD/TPI<br>(trifluridine/tipiracil)<br>(SAF) | B: BSC (Best<br>Supportive Care)<br>(SAF) |  |
|---|---|---|--|
| Total subjects affected by serious adverse events                   |   |   |  |
| subjects affected / exposed   | 83 / 186 (44.62%)                               | 5 / 9 (55.56%)                            |  |
| number of deaths (all causes)                                       | 147   | 7   |  |
| number of deaths resulting from adverse events                      | 25  | 1   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |   |  |
| Malignant ascites   |   |   |  |
| subjects affected / exposed   | 1 / 186 (0.54%)                                 | 0 / 9 (0.00%)                             |  |
| occurrences causally related to treatment / all                     | 0 / 1   | 0 / 0                                     |  |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0                                     |  |
| Malignant neoplasm progression                                      |   |   |  |
| subjects affected / exposed   | 23 / 186 (12.37%)                               | 1 / 9 (11.11%)                            |  |
| occurrences causally related to treatment / all                     | 0 / 23  | 0 / 1                                     |  |
| deaths causally related to treatment / all                          | 0 / 13  | 0 / 1                                     |  |
| Metastases to central nervous system                                |   |   |  |
| subjects affected / exposed   | 3 / 186 (1.61%)                                 | 0 / 9 (0.00%)                             |  |
| occurrences causally related to treatment / all                     | 0 / 3   | 0 / 0                                     |  |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0                                     |  |

|  |                 |                |  |
|--|-----------------|----------------|--|
| Metastases to lung                                   |                 |                |  |
| subjects affected / exposed                          | 3 / 186 (1.61%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 3           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0          |  |
| Metastases to spine                                  |                 |                |  |
| subjects affected / exposed                          | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Vascular disorders                                   |                 |                |  |
| Deep vein thrombosis                                 |                 |                |  |
| subjects affected / exposed                          | 0 / 186 (0.00%) | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Peripheral vascular disorder                         |                 |                |  |
| subjects affected / exposed                          | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| General disorders and administration site conditions |                 |                |  |
| Asthenia   |                 |                |  |
| subjects affected / exposed                          | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Fatigue  |                 |                |  |
| subjects affected / exposed                          | 2 / 186 (1.08%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all      | 1 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Multiple organ dysfunction syndrome                  |                 |                |  |
| subjects affected / exposed                          | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0          |  |
| Pain   |                 |                |  |
| subjects affected / exposed                          | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| Pyrexia   |                 |                |  |
| subjects affected / exposed                     | 2 / 186 (1.08%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| General physical health deterioration           |                 |                |  |
| subjects affected / exposed                     | 4 / 186 (2.15%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 3           | 0 / 0          |  |
| Reproductive system and breast disorders        |                 |                |  |
| Female genital tract fistula                    |                 |                |  |
| subjects affected / exposed                     | 0 / 186 (0.00%) | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1          |  |
| Respiratory, thoracic and mediastinal disorders |                 |                |  |
| Cough   |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Dyspnoea  |                 |                |  |
| subjects affected / exposed                     | 2 / 186 (1.08%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Hiccups   |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Pleural effusion                                |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| Pneumonitis                                     |                 |                |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Pulmonary embolism                              |                 |                |  |
| subjects affected / exposed                     | 2 / 186 (1.08%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| Stridor   |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Psychiatric disorders                           |                 |                |  |
| Insomnia  |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Investigations                                  |                 |                |  |
| Blood creatinine increased                      |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                 |                |  |
| Femoral neck fracture                           |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Gastroenteritis radiation                       |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Incisional hernia                               |                 |                |  |
| subjects affected / exposed                     | 0 / 186 (0.00%) | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |

|   |                 |               |  |
|---|-----------------|---------------|--|
| Urinary tract stoma complication<br>subjects affected / exposed | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0         |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0         |  |
| Cardiac disorders   |                 |               |  |
| Angina pectoris<br>subjects affected / exposed                  | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0         |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0         |  |
| Cardiac failure<br>subjects affected / exposed                  | 2 / 186 (1.08%) | 0 / 9 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 2           | 0 / 0         |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0         |  |
| Nervous system disorders  |                 |               |  |
| Coma hepatic<br>subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0         |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0         |  |
| Hepatic encephalopathy<br>subjects affected / exposed           | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0         |  |
| deaths causally related to<br>treatment / all                   | 0 / 1           | 0 / 0         |  |
| Monoparesis<br>subjects affected / exposed                      | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0         |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0         |  |
| Nervous system disorder<br>subjects affected / exposed          | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0         |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0         |  |
| Neuropathy peripheral<br>subjects affected / exposed            | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0         |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0         |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| Radiculopathy                                   |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Seizure   |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Syncope   |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Blood and lymphatic system disorders            |                 |                |  |
| Anaemia   |                 |                |  |
| subjects affected / exposed                     | 4 / 186 (2.15%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 5 / 5           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Febrile neutropenia                             |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Neutropenia                                     |                 |                |  |
| subjects affected / exposed                     | 2 / 186 (1.08%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Gastrointestinal disorders                      |                 |                |  |
| Abdominal pain                                  |                 |                |  |
| subjects affected / exposed                     | 0 / 186 (0.00%) | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Ascites   |                 |                |  |
| subjects affected / exposed                     | 2 / 186 (1.08%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| Diarrhoea                                       |                 |                |  |
| subjects affected / exposed                     | 3 / 186 (1.61%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Duodenal stenosis                               |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Gastric haemorrhage                             |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| Gastrointestinal haemorrhage                    |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| Ileus   |                 |                |  |
| subjects affected / exposed                     | 2 / 186 (1.08%) | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Intestinal perforation                          |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Large intestinal stenosis                       |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Mechanical ileus                                |                 |                |  |
| subjects affected / exposed                     | 2 / 186 (1.08%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Melaena   |                 |                |  |

|   |                 |               |  |
|---|-----------------|---------------|--|
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |
| Nausea  |                 |               |  |
| subjects affected / exposed                     | 2 / 186 (1.08%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |
| Oesophageal varices haemorrhage                 |                 |               |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |
| Pancreatitis chronic                            |                 |               |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |
| Proctitis                                       |                 |               |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |
| Subileus  |                 |               |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |
| Vomiting  |                 |               |  |
| subjects affected / exposed                     | 4 / 186 (2.15%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |
| Hepatobiliary disorders                         |                 |               |  |
| Bile duct stenosis                              |                 |               |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |
| Cholangitis                                     |                 |               |  |



|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 4 / 186 (2.15%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Cholestasis                                     |                 |                |  |
| subjects affected / exposed                     | 5 / 186 (2.69%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Hepatic failure                                 |                 |                |  |
| subjects affected / exposed                     | 2 / 186 (1.08%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0          |  |
| Blood bilirubin increased                       |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Renal and urinary disorders                     |                 |                |  |
| Acute kidney injury                             |                 |                |  |
| subjects affected / exposed                     | 4 / 186 (2.15%) | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 3 / 4           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| Bladder perforation                             |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Chronic kidney disease                          |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Renal failure                                   |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Urinary tract disorder                          |                 |                |  |

|   |                 |               |  |
|---|-----------------|---------------|--|
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |
| Urinary tract obstruction                       |                 |               |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |
| Musculoskeletal and connective tissue disorders |                 |               |  |
| Arthralgia                                      |                 |               |  |
| subjects affected / exposed                     | 2 / 186 (1.08%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |
| Pain in extremity                               |                 |               |  |
| subjects affected / exposed                     | 2 / 186 (1.08%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |
| Pathological fracture                           |                 |               |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |
| Infections and infestations                     |                 |               |  |
| Abdominal wall abscess                          |                 |               |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |
| Abscess   |                 |               |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0         |  |
| Arthritis infective                             |                 |               |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| Cholangitis infective                           |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Hepatic infection                               |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Infection                                       |                 |                |  |
| subjects affected / exposed                     | 3 / 186 (1.61%) | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Kidney infection                                |                 |                |  |
| subjects affected / exposed                     | 0 / 186 (0.00%) | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Ophthalmic herpes zoster                        |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Peritonitis bacterial                           |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Pneumonia                                       |                 |                |  |
| subjects affected / exposed                     | 3 / 186 (1.61%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| Pyelonephritis                                  |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Respiratory tract infection                     |                 |                |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Sepsis  |                 |                |  |
| subjects affected / exposed                     | 2 / 186 (1.08%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| Superinfection                                  |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Urinary tract infection                         |                 |                |  |
| subjects affected / exposed                     | 2 / 186 (1.08%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Urosepsis                                       |                 |                |  |
| subjects affected / exposed                     | 0 / 186 (0.00%) | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Vestibular neuronitis                           |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Wound abscess                                   |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Metabolism and nutrition disorders              |                 |                |  |
| Cachexia  |                 |                |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| Dehydration                                     |                 |                |  |

|   |                 |               |  |
|---|-----------------|---------------|--|
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |
| Hyperglycaemia                                  |                 |               |  |
| subjects affected / exposed                     | 1 / 186 (0.54%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         |  |

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

| Non-serious adverse events                            | A: FTD/TPI<br>(trifluridine/tipiracil)<br>(SAF)  | B: BSC (Best<br>Supportive Care)<br>(SAF) |  |
|---|--|---|--|
| Total subjects affected by non-serious adverse events |  |   |  |
| subjects affected / exposed                           | 170 / 186 (91.40%)   | 6 / 9 (66.67%)                            |  |
| Nervous system disorders                              |  |   |  |
| Polyneuropathy  | Additional description: Includes PTs polyneuropathy (n=8, FTD/TPI), neuropathy peripheral (n=1, FTD/TPI) and peripheral motor neuropathy (n=1, FTD/TPI). |   |  |
| subjects affected / exposed                           | 10 / 186 (5.38%)   | 0 / 9 (0.00%)                             |  |
| occurrences (all)                                     | 10   | 0   |  |
| Blood and lymphatic system disorders                  |  |   |  |
| Anaemia   | Additional description: Includes PTs anaemia (n=39, FTD/TPI; n=1, BSC) and haemoglobin decreased (n=4, FTD/TPI).   |   |  |
| subjects affected / exposed                           | 43 / 186 (23.12%)  | 1 / 9 (11.11%)                            |  |
| occurrences (all)                                     | 56   | 1   |  |
| Leukopenia  | Additional description: Includes PTs leukopenia (n=29, FTD/TPI) and white blood cell count decreased (n=8, FTD/TPI).                                     |   |  |
| subjects affected / exposed                           | 37 / 186 (19.89%)  | 0 / 9 (0.00%)                             |  |
| occurrences (all)                                     | 79   | 0   |  |
| Neutropenia   | Additional description: Includes PTs neutropenia (n=48, FTD/TPI) and neutrophil count decreased (n=8, FTD/TPI).  |   |  |
| subjects affected / exposed                           | 55 / 186 (29.57%)  | 0 / 9 (0.00%)                             |  |
| occurrences (all)                                     | 117  | 0   |  |
| General disorders and administration site conditions  |  |   |  |
| Fatigue   |  |   |  |
| subjects affected / exposed                           | 42 / 186 (22.58%)  | 2 / 9 (22.22%)                            |  |
| occurrences (all)                                     | 53   | 3   |  |
| Oedema  | Additional description: Includes PTs oedema (n=3, FTD/TPI) and oedema peripheral (n=17, FTD/TPI).  |   |  |

|   |   |                |  |
|---|---|----------------|--|
| subjects affected / exposed                     | 19 / 186 (10.22%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)                               | 22  | 0              |  |
| Pain  |   |                |  |
| subjects affected / exposed                     | 8 / 186 (4.30%)   | 2 / 9 (22.22%) |  |
| occurrences (all)                               | 9   | 2              |  |
| Pyrexia   |   |                |  |
| subjects affected / exposed                     | 16 / 186 (8.60%)  | 0 / 9 (0.00%)  |  |
| occurrences (all)                               | 24  | 0              |  |
| Gastrointestinal disorders                      |   |                |  |
| Abdominal pain                                  |   |                |  |
| subjects affected / exposed                     | 13 / 186 (6.99%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 14  | 1              |  |
| Ascites   |   |                |  |
| subjects affected / exposed                     | 9 / 186 (4.84%)   | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 13  | 1              |  |
| Constipation                                    |   |                |  |
| subjects affected / exposed                     | 22 / 186 (11.83%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)                               | 25  | 0              |  |
| Diarrhoea                                       |   |                |  |
| subjects affected / exposed                     | 38 / 186 (20.43%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)                               | 45  | 0              |  |
| Nausea  |   |                |  |
| subjects affected / exposed                     | 42 / 186 (22.58%)   | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 49  | 1              |  |
| Vomiting  |   |                |  |
| subjects affected / exposed                     | 24 / 186 (12.90%)   | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 32  | 1              |  |
| Respiratory, thoracic and mediastinal disorders |   |                |  |
| Dyspnoea  | Additional description: Includes PTs dyspnoea (n=16, FTD/TPI) and dyspnoea exertional (n=2, FTD/TPI). |                |  |
| subjects affected / exposed                     | 18 / 186 (9.68%)  | 0 / 9 (0.00%)  |  |
| occurrences (all)                               | 21  | 0              |  |
| Skin and subcutaneous tissue disorders          |   |                |  |
| Alopecia  |   |                |  |
| subjects affected / exposed                     | 13 / 186 (6.99%)  | 0 / 9 (0.00%)  |  |
| occurrences (all)                               | 13  | 0              |  |
| Infections and infestations                     |   |                |  |

|  |                         |                    |  |
|--|-------------------------|--------------------|--|
| Infection<br>subjects affected / exposed<br>occurrences (all)  | 7 / 186 (3.76%)<br>8    | 0 / 9 (0.00%)<br>0 |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 28 / 186 (15.05%)<br>31 | 0 / 9 (0.00%)<br>0 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 22 March 2018    | <p>Amendment 1, Protocol version 3.0:</p> <p>Change of allowed periods and time points for study procedures during treatment phase: Study procedures on 'Day 1 of each treatment cycle before administration of FTD/TPI in the respective cycle/start of the observation cycle or within previous 3 days (maximum 72 hours) unless otherwise indicated below' (previously 2 days).</p> <p>Addition of a note: In case of any delay of the treatment start in the following treatment cycle, restaging has to be performed after 8 weeks or within previous 7 days (equivalent to duration of two treatment cycles with FTD/TPI without any treatment delay).</p> <p>Adjustment of text according to schedule of assessments (Section 2): Questionnaires EORTC-QLQ C30 and EQ-5D-5L including EQ VAS as paper version on Day 1 of the respective cycle or within previous 2 days.</p> <p>Update of information according to new SmPC for Lonsurf®: Update of one sentence on hepatic impairment: FTD/TPI is not recommended for use in patients with baseline moderate or severe hepatic impairment (National Cancer Institute [NCI] Criteria Group C and D defined by total bilirubin &gt; 1.5 x ULN), as a higher incidence of Grade 3 or 4 hyperbilirubinaemia is observed in patients with baseline moderate hepatic impairment, although this is based on very limited data.</p> <p>Update of information on interactions: Deletion of one sentence: Inductive effect of tipiracil on human CYP isoforms cannot be excluded.</p> |
| 30 July 2018     | <p>Amendment 2, Protocol version 4.0:</p> <p>Updated information: Extension of the limitation of the early benefit assessment for Lonsurf® to 1 April 2020 (previously two years from 02 Feb 2017).</p> <p>The 1st of October 2018 as an optional data extract date for interim analysis – depending on whether this date or the time point of 50 evaluable patients permanently termination study treatment is earlier – was deleted.</p> <p>The following sentence was deleted: An interim report in the format of an integrated clinical study report will be prepared within three months after data extract date of the interim statistical analysis.</p>   |
| 07 December 2018 | <p>Amendment 3, Protocol version 5.0:</p> <p>Change of study duration: Extension of the estimated accrual period from 1 year to 15 months. Extension of estimated study duration from 24 to 27 months. Change of Planned end of study from QII 2019 to QIV 2019.</p> <p>Change of sample size calculation: Addition of a table for sample sizes for alternative values of type I error if recruitment of 24 patients in Group B could not be achieved.</p>   |
| 29 April 2019    | <p>Amendment 4, Protocol version 6.0:</p> <p>Change of duration of questioning quality of life: Extension of the time period for questioning of quality of life for patients treated with FTD/TPI for more than one year: questioning for the duration of treatment, at the end-of-treatment visit and at Month 1 of follow up.</p>  |



|                 |   |
|-----------------|---|
| 31 January 2020 | <p>Amendment 5, Protocol version 7.0:<br/>Extension of the study duration until the end of 2020.</p> <p>Additional analysis, study report and annual safety report (required because of extension of study duration).</p> |
|-----------------|---|

Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported