Clinical trial results:
A Phase I/IIa study of TG6002 (VV TK-RR-FCU1) administered by intravenous (IV) infusions in combination with oral flucytosine (5-FC) in patients with advanced gastro-intestinal (GI) tumors

Summary

EudraCT number	2018-000039-28
Trial protocol	FR BE ES
Global end of trial date	23 February 2023

Results information

Result version number	v1 (current)
This version publication date	03 January 2024
First version publication date	03 January 2024

Trial information

Trial identification

Sponsor protocol code	TG6002.02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03724071
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	TRANSGENE S.A.
Sponsor organisation address	400 boulevard Gonthier d'Andernach - Parc d'innovation – CS80166, Illkirch-Graffenstaden, France, 67405
Public contact	Medical Affairs, TRANSGENE S.A., 33 388279155, clinical.trials@transgene.fr
Scientific contact	Medical Affairs, TRANSGENE S.A., 33 388279155, clinical.trials@transgene.fr

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 August 2022
Global end of trial reached?	Yes
Global end of trial date	23 February 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the phase I part is to determine the optimal scheme of administration and the recommended Phase II dose (RP2D) for TG6002 administered as multiple intravenous (IV) infusions in combination with flucytosine (5-FC) in patients with advanced GI tumors.

Secondary objectives include the assessessment of the safety and tolerability of multiple TG6002 infusions at escalating doses and determination of the Maximum Tolerated Dose (MTD), if any, of two schemes of administration of TG6002 combined with oral 5-FC.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	01 October 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Regulatory reason
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Spain: 28
Worldwide total number of subjects	51
EEA total number of subjects	51

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)	27
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First participant signed informed consent form on 10 October 2018. Last participant last visit occurred on 30 May 2022, before long term follow-up.

Pre-assignment

Screening details:

Of 65 screened participants, 51 were included in the trial (35 patients in Arm A and 16 patients in Arm B) and 14 patients were excluded (13 because they were ineligible and 1 declined to participate).

Period 1

Period 1 title	Overall study (overall period, phase I)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Cohorts of 3-6 patients administered with TG6002 IV infusion at dose levels ranging from 1 x 10E6 to 3 x 10E9 pfu every week for 3 weeks in combination with oral 5-FC at the dose of 200 mg/kg/day for 16 days

Arm type	Experimental
Investigational medicinal product name	TG6002
Investigational medicinal product code	TG6002
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were administered at dose levels of TG6002 ranging from 1 x 10E6 to 3 x 10E9 pfu by IV infusion every week for 3 weeks (D1 / D8 / D15)

Investigational medicinal product name	5-FC
Investigational medicinal product code	
Other name	Ancotil
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were given the total dose of 200 mg/kg/day of oral 5-FC (split in 4 daily intakes) from Day 5 to 7, Day 12 to 14 and Day 19 to 28.

Arm title	Arm B

Arm description:

Cohorts of 6 patients administered with TG6002 IV infusion at dose levels ranging from 1 x 10E9 to 3 x 10E9 pfu on Day 1, 3 and 5 in combination with oral 5-FC at the dose of 200 mg/kg/day for 10 days

Arm type	Experimental
Investigational medicinal product name	TG6002
Investigational medicinal product code	TG6002
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were administered at dose levels of TG6002 ranging from 1 x 10E9 to 3 x 10E9 pfu by IV

infusion on D1, D3 and D5

Investigational medicinal product name	5-FC
Investigational medicinal product code	
Other name	Ancotil
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were given the total dose of 200 mg/kg/day of oral 5-FC (split in 4 daily intakes) from Day 9 to 18 .

Number of subjects in period 1	Arm A	Arm B
Started	35	16
Completed	33	12
Not completed	2	4
Consent withdrawn by subject	1	1
Clinical situation (ECOG 4 in a context of PD)	-	1
Adverse event, non-fatal	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Cohorts of 3-6 patients administered with TG6002 IV infusion at dose levels ranging from 1 x 10E6 to 3 x 10E9 pfu every week for 3 weeks in combination with oral 5-FC at the dose of 200 mg/kg/day for 16 days	
Reporting group title	Arm B
Reporting group description:	
Cohorts of 6 patients administered with TG6002 IV infusion at dose levels ranging from 1 x 10E9 to 3 x 10E9 pfu on Day 1, 3 and 5 in combination with oral 5-FC at the dose of 200 mg/kg/day for 10 days	

Reporting group values	Arm A	Arm B	Total
Number of subjects	35	16	51
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	19	8	27
From 65-84 years	16	8	24
85 years and over	0	0	0
Age continuous Units: years			
median	64	64	
full range (min-max)	46 to 76	32 to 78	-
Gender categorical Units: Subjects			
Female	11	11	22
Male	24	5	29
ECOG performance status Units: Subjects			
Score 0	19	6	25
Score 1	16	10	26
Score 2	0	0	0
Score 3	0	0	0
Score 4	0	0	0
Tumor stage at initial diagnosis Units: Subjects			
Stage IA	2	0	2
Stage IB	1	0	1
Stage IIA	1	2	3
Stage IIB	5	1	6
Stage IIIA	0	2	2

Stage IIIB	4	0	4
Stage IIIC	0	1	1
Stage IV	22	10	32
Primary location of disease Units: Subjects			
Colon	14	6	20
Esophagus	1	1	2
Pancreas	8	6	14
Rectum	4	1	5
Stomach	2	0	2
Other GI location	6	2	8

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Cohorts of 3-6 patients administered with TG6002 IV infusion at dose levels ranging from 1 x 10E6 to 3 x 10E9 pfu every week for 3 weeks in combination with oral 5-FC at the dose of 200 mg/kg/day for 16 days

Reporting group title	Arm B

Reporting group description:

Cohorts of 6 patients administered with TG6002 IV infusion at dose levels ranging from 1 x 10E9 to 3 x 10E9 pfu on Day 1, 3 and 5 in combination with oral 5-FC at the dose of 200 mg/kg/day for 10 days

Primary: Safety and tolerability of TG6002 and 5-FC

End point title	Safety and tolerability of TG6002 and 5-FC[1]

End point description:

Patients were assessed for dose limiting toxicities (DLT) as well as for safety and tolerability of the treatment. A DLT was defined as any of the following treatment-related AEs occurring during the DLT period [Day 1 to Day 28]: any grade 4 toxicity (except isolated Grade 4 lymphopenia lasting ≤ 7 days), grade 3 hypotension or allergic reaction/hypersensitivity, grade 3 skin lesions: ulcerative dermatitis or skin changes with pain interfering with function, at least 10 disseminated pustular lesions, laboratory grade 3 non-hematologic toxicity persisting for >7 days except an increase in AST and/or ALT (>5x ULN), which may last >7 days if total bilirubin is normal or grade 1, drug-induced liver injury fulfilling the criteria of the Hy's law, grade 3 hematologic toxicity persisting for > 7 days, myocardial infarction or myocarditis, disseminated intravascular coagulation.

End point type	Primary

End point timeframe:

Patients were assessed for dose limiting toxicity (DLTs) occurring within 28 days of administration of the first TG6002 infusion.

Notes:

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

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	16		
Units: Events				
Dose Limiting Toxicities (DLTs)	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (and serious adverse events) were recorded from the first study treatment administration up to 28 days after the last administration of study treatment. SAE related to study treatment were recorded with no time limitation.

Adverse event reporting additional description:

Adverse event information was collected by regular investigator assessment and regular laboratory testing.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Arm A

Reporting group description:

Cohorts of 3-6 patients administered with TG6002 IV infusion at dose levels ranging from 1 x 10E6 to 3 x 10E9 pfu every week for 3 weeks in combination with oral 5-FC at the dose of 200 mg/kg/day for 16 days

Reporting group title	Arm B

Reporting group description:

Cohorts of 6 patients administered with TG6002 IV infusion at dose levels ranging from 1 x 10E9 to 3 x 10E9 pfu on Day 1, 3 and 5 in combination with oral 5-FC at the dose of 200 mg/kg/day for 10 days

Reporting group title	Safety population

Reporting group description:

Participants who received at least one dose of either study drug

Serious adverse events	Arm A	Arm B	Safety population
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 35 (51.43%)	6 / 16 (37.50%)	24 / 51 (47.06%)
number of deaths (all causes)	32	12	44
number of deaths resulting from adverse events	2	0	2
Investigations			
Fibrin D dimer increased	Additional description: Fibrin D dimer increased		
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased	Additional description: Blood bilirubin increased		
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased	Additional description: Hepatic enzyme increased		

subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain	Additional description: Cancer pain		
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain	Additional description: Tumour pain		
subjects affected / exposed	0 / 35 (0.00%)	2 / 16 (12.50%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension	Additional description: Hypertension		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Spinal cord compression	Additional description: Spinal cord compression		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder	Additional description: Cognitive disorder		
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression	Additional description: Disease progression		
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		

subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction	Additional description: Large intestinal obstruction		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage	Additional description: Small intestinal haemorrhage		
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage	Additional description: Upper gastrointestinal haemorrhage		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic function abnormal	Additional description: Hepatic function abnormal		
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute	Additional description: Hepatitis acute		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia	Additional description: Hyperbilirubinaemia		
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury	Additional description: Drug-induced liver injury		

subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism	Additional description: Pulmonary embolism		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax	Additional description: Pneumothorax		
subjects affected / exposed	2 / 35 (5.71%)	0 / 16 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary tract obstruction	Additional description: Urinary tract obstruction		
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Liver abscess	Additional description: Liver abscess		
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection	Additional description: Device related infection		
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis	Additional description: Device related sepsis		
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Septic shock	Additional description: Septic shock		
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Staphylococcal infection	Additional description: Staphylococcal infection		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia	Additional description: Hypercalcaemia		
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm A	Arm B	Safety population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 35 (97.14%)	16 / 16 (100.00%)	50 / 51 (98.04%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain	Additional description: Tumour pain		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Vascular disorders			
Hypertension	Additional description: Hypertension		
subjects affected / exposed	8 / 35 (22.86%)	7 / 16 (43.75%)	15 / 51 (29.41%)
occurrences (all)	20	10	30
Hypotension	Additional description: Hypotension		
subjects affected / exposed	5 / 35 (14.29%)	5 / 16 (31.25%)	10 / 51 (19.61%)
occurrences (all)	8	7	15
General disorders and administration site conditions			

Chills	Additional description: Chills		
subjects affected / exposed	14 / 35 (40.00%)	8 / 16 (50.00%)	22 / 51 (43.14%)
occurrences (all)	32	19	51
Face oedema	Additional description: Face oedema		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Fatigue	Additional description: Fatigue		
subjects affected / exposed	19 / 35 (54.29%)	7 / 16 (43.75%)	26 / 51 (50.98%)
occurrences (all)	24	9	33
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	2 / 35 (5.71%)	0 / 16 (0.00%)	2 / 51 (3.92%)
occurrences (all)	2	0	2
Chest pain	Additional description: Chest pain		
subjects affected / exposed	2 / 35 (5.71%)	0 / 16 (0.00%)	2 / 51 (3.92%)
occurrences (all)	2	0	2
Asthenia	Additional description: Asthenia		
subjects affected / exposed	0 / 35 (0.00%)	4 / 16 (25.00%)	4 / 51 (7.84%)
occurrences (all)	0	4	4
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	2 / 35 (5.71%)	0 / 16 (0.00%)	2 / 51 (3.92%)
occurrences (all)	2	0	2
Performance status decreased	Additional description: Performance status decreased		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	24 / 35 (68.57%)	16 / 16 (100.00%)	40 / 51 (78.43%)
occurrences (all)	56	30	86
Reproductive system and breast disorders			
Pelvic discomfort	Additional description: Pelvic discomfort		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Tonsillar ulcer	Additional description: Tonsillar ulcer		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Pleuritic pain	Additional description: Pleuritic pain		

subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Oropharyngeal discomfort	Additional description: Oropharyngeal discomfort		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Hypoxia	Additional description: Hypoxia		
subjects affected / exposed	1 / 35 (2.86%)	1 / 16 (6.25%)	2 / 51 (3.92%)
occurrences (all)	1	1	2
Haemoptysis	Additional description: Haemoptysis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	6 / 35 (17.14%)	0 / 16 (0.00%)	6 / 51 (11.76%)
occurrences (all)	6	0	6
Dysphonia	Additional description: Dysphonia		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Cough	Additional description: Cough		
subjects affected / exposed	5 / 35 (14.29%)	2 / 16 (12.50%)	7 / 51 (13.73%)
occurrences (all)	5	2	7
Psychiatric disorders			
Insomnia	Additional description: Insomnia		
subjects affected / exposed	1 / 35 (2.86%)	1 / 16 (6.25%)	2 / 51 (3.92%)
occurrences (all)	1	2	3
Anxiety	Additional description: Anxiety		
subjects affected / exposed	2 / 35 (5.71%)	0 / 16 (0.00%)	2 / 51 (3.92%)
occurrences (all)	2	0	2
Investigations			
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
subjects affected / exposed	1 / 35 (2.86%)	3 / 16 (18.75%)	4 / 51 (7.84%)
occurrences (all)	1	3	4
Amylase increased	Additional description: Amylase increased		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		

subjects affected / exposed	3 / 35 (8.57%)	4 / 16 (25.00%)	7 / 51 (13.73%)
occurrences (all)	3	4	7
Blood bilirubin increased	Additional description: Blood bilirubin increased		
subjects affected / exposed	4 / 35 (11.43%)	0 / 16 (0.00%)	4 / 51 (7.84%)
occurrences (all)	4	0	4
Lipase increased	Additional description: Lipase increased		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Weight decreased	Additional description: Weight decreased		
subjects affected / exposed	5 / 35 (14.29%)	0 / 16 (0.00%)	5 / 51 (9.80%)
occurrences (all)	6	0	6
Injury, poisoning and procedural complications			
Procedural pain	Additional description: Procedural pain		
subjects affected / exposed	1 / 35 (2.86%)	1 / 16 (6.25%)	2 / 51 (3.92%)
occurrences (all)	2	1	3
Cardiac disorders			
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed	4 / 35 (11.43%)	3 / 16 (18.75%)	7 / 51 (13.73%)
occurrences (all)	8	5	13
Sinus tachycardia	Additional description: Sinus tachycardia		
subjects affected / exposed	1 / 35 (2.86%)	1 / 16 (6.25%)	2 / 51 (3.92%)
occurrences (all)	1	1	2
Palpitations	Additional description: Palpitations		
subjects affected / exposed	0 / 35 (0.00%)	2 / 16 (12.50%)	2 / 51 (3.92%)
occurrences (all)	0	2	2
Nervous system disorders			
Headache	Additional description: Headache		
subjects affected / exposed	3 / 35 (8.57%)	3 / 16 (18.75%)	6 / 51 (11.76%)
occurrences (all)	5	5	10
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed	1 / 35 (2.86%)	3 / 16 (18.75%)	4 / 51 (7.84%)
occurrences (all)	1	3	4
Dizziness	Additional description: Dizziness		
subjects affected / exposed	1 / 35 (2.86%)	1 / 16 (6.25%)	2 / 51 (3.92%)
occurrences (all)	1	1	2
Blood and lymphatic system disorders			

Lymphopenia	Additional description: Lymphopenia		
subjects affected / exposed	1 / 35 (2.86%)	7 / 16 (43.75%)	8 / 51 (15.69%)
occurrences (all)	1	8	9
Leukocytosis	Additional description: Leukocytosis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Coagulopathy	Additional description: Coagulopathy		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Anaemia	Additional description: Anaemia		
subjects affected / exposed	7 / 35 (20.00%)	5 / 16 (31.25%)	12 / 51 (23.53%)
occurrences (all)	7	6	13
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	0 / 35 (0.00%)	3 / 16 (18.75%)	3 / 51 (5.88%)
occurrences (all)	0	3	3
Gastrointestinal disorders			
Aphthous ulcer	Additional description: Aphthous ulcer		
subjects affected / exposed	0 / 35 (0.00%)	2 / 16 (12.50%)	2 / 51 (3.92%)
occurrences (all)	0	2	2
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	7 / 35 (20.00%)	5 / 16 (31.25%)	12 / 51 (23.53%)
occurrences (all)	9	6	15
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed	1 / 35 (2.86%)	1 / 16 (6.25%)	2 / 51 (3.92%)
occurrences (all)	1	1	2
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed	4 / 35 (11.43%)	1 / 16 (6.25%)	5 / 51 (9.80%)
occurrences (all)	5	1	6
Vomiting	Additional description: Vomiting		
subjects affected / exposed	11 / 35 (31.43%)	3 / 16 (18.75%)	14 / 51 (27.45%)
occurrences (all)	13	5	18
Nausea	Additional description: Nausea		
subjects affected / exposed	15 / 35 (42.86%)	5 / 16 (31.25%)	20 / 51 (39.22%)
occurrences (all)	18	6	24
Large intestinal obstruction	Additional description: Large intestinal obstruction		

subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Gingival discomfort	Additional description: Gingival discomfort		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
subjects affected / exposed	2 / 35 (5.71%)	2 / 16 (12.50%)	4 / 51 (7.84%)
occurrences (all)	2	2	4
Flatulence	Additional description: Flatulence		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Constipation	Additional description: Constipation		
subjects affected / exposed	5 / 35 (14.29%)	1 / 16 (6.25%)	6 / 51 (11.76%)
occurrences (all)	5	1	6
Ascites	Additional description: Ascites		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	12 / 35 (34.29%)	5 / 16 (31.25%)	17 / 51 (33.33%)
occurrences (all)	16	11	27
Hepatobiliary disorders			
Hepatitis	Additional description: Hepatitis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Hyperbilirubinaemia	Additional description: Hyperbilirubinaemia		
subjects affected / exposed	1 / 35 (2.86%)	1 / 16 (6.25%)	2 / 51 (3.92%)
occurrences (all)	1	1	2
Hypertransaminasaemia	Additional description: Hypertransaminasaemia		
subjects affected / exposed	3 / 35 (8.57%)	2 / 16 (12.50%)	5 / 51 (9.80%)
occurrences (all)	3	2	5
Skin and subcutaneous tissue disorders			
Rash maculo-papular	Additional description: Rash maculo-papular		

subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Rash erythematous	Additional description: Rash erythematous		
subjects affected / exposed	2 / 35 (5.71%)	0 / 16 (0.00%)	2 / 51 (3.92%)
occurrences (all)	2	0	2
Pruritus	Additional description: Pruritus		
subjects affected / exposed	2 / 35 (5.71%)	2 / 16 (12.50%)	4 / 51 (7.84%)
occurrences (all)	2	2	4
Hyperhidrosis	Additional description: Hyperhidrosis		
subjects affected / exposed	1 / 35 (2.86%)	2 / 16 (12.50%)	3 / 51 (5.88%)
occurrences (all)	2	3	5
Decubitus ulcer	Additional description: Decubitus ulcer		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Skin lesion	Additional description: Skin lesion		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Sacral pain	Additional description: Sacral pain		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Back pain	Additional description: Back pain		
subjects affected / exposed	4 / 35 (11.43%)	0 / 16 (0.00%)	4 / 51 (7.84%)
occurrences (all)	4	0	4
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	4 / 35 (11.43%)	1 / 16 (6.25%)	5 / 51 (9.80%)
occurrences (all)	4	1	5
Infections and infestations			
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Genital herpes	Additional description: Genital herpes		

subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Gingivitis	Additional description: Gingivitis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Oral candidiasis	Additional description: Oral candidiasis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Rash pustular	Additional description: Rash pustular		
subjects affected / exposed	1 / 35 (2.86%)	3 / 16 (18.75%)	4 / 51 (7.84%)
occurrences (all)	1	3	4
Rhinitis	Additional description: Rhinitis		
subjects affected / exposed	2 / 35 (5.71%)	0 / 16 (0.00%)	2 / 51 (3.92%)
occurrences (all)	2	0	2
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Hypophosphataemia	Additional description: Hypophosphataemia		
subjects affected / exposed	0 / 35 (0.00%)	2 / 16 (12.50%)	2 / 51 (3.92%)
occurrences (all)	0	2	2
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed	1 / 35 (2.86%)	1 / 16 (6.25%)	2 / 51 (3.92%)
occurrences (all)	1	1	2
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	2 / 35 (5.71%)	1 / 16 (6.25%)	3 / 51 (5.88%)
occurrences (all)	2	1	3
Hypocalcaemia	Additional description: Hypocalcaemia		
subjects affected / exposed	1 / 35 (2.86%)	1 / 16 (6.25%)	2 / 51 (3.92%)
occurrences (all)	1	1	2
Hypoalbuminaemia	Additional description: Hypoalbuminaemia		
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	1 / 51 (1.96%)
occurrences (all)	0	1	1

Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	9 / 35 (25.71%)	5 / 16 (31.25%)	14 / 51 (27.45%)
occurrences (all)	9	6	15

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2018	Protocol V3.0 dated 15-Jun-2018 : addition of an eligibility criteria (patients must have been previously exposed to fluoropyrimidine-based chemotherapy) and revision of a DLT criterion (in order to delete the exclusion of Grade 3 Flu-like symptoms).
25 July 2019	Protocol V5.0 dated 25-Jul-2019: add a 5th cohort (with a TG6002 dose of 1x109 pfu), add a biopsy on Day 5, update eligibility criteria (biopsies of tumor metastatic lesions are to be performed in all patients from 3 x10E8 pfu cohort, and non-active inflammatory bowel disease is no longer considered as an exclusion criterion), add the collection of archival serum and plasma samples on Day 5, to add the severe Drug-induced liver injury as a DLT and to prolong the screening period from 14 to 28 days.
12 November 2020	Protocol V9.0 dated 12-Nov-2020: add the arm B with a new administration scheme (TG6002 infusion on Day 1, Day 3, and Day 5 and 5-FC intakes during 10 consecutive days from Day 9 to Day 18 in arm B) and 4 cohorts (from 1x10E9 to 1x10E10) and adapt the sampling and exams timepoints accordingly. Changes were implemented to the initial arm A: remove the 24h timepoint for PK analysis and add the 1h hour timepoint, for humoral immune response (anti-VV) and neutralizing antibodies add a timepoint on Day 7 and on Day 14, for PBMC remove the Day 28 timepoint and add the Day 43 timepoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 February 2023	The trial was prematurely terminated per Sponsor decision on 23 February 2023 after the completion of the phase I portion and before the commencement of the phase II, for reasons other than safety.	-

Notes:

Limitations and caveats

None reported