



## Clinical trial results:

### 5-Fluorouracil (5-FU), folinic acid and irinotecan (FOLFIRI) versus 5-FU and folinic acid as second-line chemotherapy in patients with biliary tract cancer (IRIBIL): a randomized open-label phase 2 study

#### Summary

EudraCT number	2015-004028-69
Trial protocol	DE
Global end of trial date	31 October 2024

#### Results information

Result version number	v1 (current)
This version publication date	07 November 2025
First version publication date	07 November 2025

#### Trial information

##### Trial identification

Sponsor protocol code	IRIBIL
-----------------------	--------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: DRKS00012595

Notes:

#### Sponsors

Sponsor organisation name	Goethe University Frankfurt
Sponsor organisation address	Theodor-Stern-Kai 7, 60590 / Frankfurt, Germany,
Public contact	Studienambulanz Medizinische Klinik 1, Universitätsklinikum der Goethe-Universität Frankfurt, +49 (0)696301-87769, Finkelmeier@med.uni-frankfurt.de
Scientific contact	Studienambulanz Medizinische Klinik 1,, Universitätsklinikum der Goethe-Universität Frankfurt, +49 (0)696301-87769, Finkelmeier@med.uni-frankfurt.de

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 September 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2024
Global end of trial reached?	Yes
Global end of trial date	31 October 2024
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

- Determination of the progression free survival (PFS) in FOLFIRI arm > 2 months

Protection of trial subjects:

Second-line systemic chemotherapy is performed regularly in patients progressing under first-line therapy. After failure of Gemcitabin and Cisplatin antineoplastic therapies are commonly switched to 5-FU based second-line therapies. 5-FU and folinic acid have been shown to be a safe and effective chemotherapeutic backbone in patients with cholangiocarcinoma but also in other cancers of the gastrointestinal tract such as gastric and colorectal cancer. Irinotecan is widely and regularly used in patients with gastric and colorectal cancer but also in patients with cholangiocarcinoma and has a favourable safety profile. Typical side effects of irinotecan, 5-FU and folinic acid are hematotoxicity, diarrhea and hand-food-skin reaction (for details see „Fachinformation irinotecan, 5-FU and folinic acid“) which are manageable with supportive therapies and dose reductions. However, there has been no evidence from prospective randomized trials that the addition of irinotecan to 5-FU and folinic acid improves the outcome of patients suffering from cholangiocarcinoma. Due to its favourable toxicity profile and its evident potency proven in several trials in patients with gastric and colorectal cancer the addition of irinotecan to 5-FU and folinic acid is expected to improve the overall survival of patients with cholangiocarcinoma with only modest increase of toxicity.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 August 2017
Long term follow-up planned	Yes
Long term follow-up rationale	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: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

Notes:

### Subjects enrolled per age group

In utero	0
----------	---

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

## Subject disposition

### Recruitment

Recruitment details:

First patient in: August 2017

Last patient in: February 2024

Therapy duration: 12 months

Follow-up duration: every 6 weeks after EOT until death

56 patients (2:1 randomisation) were planned. In Amendment V3.0, the sample size was changed to 23 patients treated with FOLFIRI. Arm B was closed

### Pre-assignment

Screening details:

The screening period is the time preceding enrollment and includes the 28-day period for performing screening assessments.

32 patients were screened, 5 patients were screening failures due to laboratory reasons or patients unwillingness to participate in the trial.

### Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Arm A

Arm description:

FOLFIRI Arm (5-Fluorouracil, Folinic Acid, Irinocetan)

Arm type	Experimental
Investigational medicinal product name	IRINOTECAN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Irinotecan is manufactured by Fresenius Kabi Deutschland GmbH, Else-Kröner-Straße 1, 61352 Bad Homburg vor der Höhe and other pharmaceutical companies. It is produced in a dosage of 20 mg/mL in vials of 2 mL, 5 mL, 15, and 25 mL. It will be administered in a dosage of 180 mg/m<sup>2</sup> over 1,5h after intravenous infusion of supportive medication including a 5-HT<sub>3</sub> receptor antagonist and 8mg dexamethasone. Irinotecan vials contain 20 mg/mL irinotecan and sorbitol, lactic acid, sodium hydroxide, hydrochlorid acid. Irinotecan must be diluted in a 250 mL bag containing 5 % glucose or 0.9 % sodium chloride.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

5-FU is a generic drug which is manufactured by Medac, Gesellschaft für klinische Spezialpräparate mbH, Theaterstr. 6, 22880 Wedel, Germany and other companies. It is produced in vials with a dosage of 50 mg/ml. It will administered together with oncofolic 400 mg/m<sup>2</sup> body surface in a dosage of 2000 mg/m<sup>2</sup> body surface over 48h in a self portable elastomeric infusion system (e.g. Baxter infusor) in an outpatient setting after intravenous infusion of supportive drugs including such as granisetron or ondasetron and dexamethasone 8mg. Infusion via a port system is mandatory. Patients in arm A

(FOLFIRI) receive an intravenous infusion of 180 mg/m<sup>2</sup> irinotecan over 1,5h before 5-FU/oncofolic administration.

5-FU can be ordered in bottles of 5 to 200 mL. 5-FU bottles contain 5-FU 50mg/m<sup>2</sup> and sodium hydroxide and water for injection. It is a colorless or pale yellow solution. 5-FU may only be dissolved in 0.9 % sodium chloride or in 5 % glucose

Investigational medicinal product name	Folinic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Folinic acid is manufactured by Medac, Gesellschaft für klinische Spezialpräparate mbH, Theaterstr. 6, 22880 Wedel, Germany. It will be administered in both treatment arms in dosage of 400mg/m<sup>2</sup> body surface in combination with 5-FU 2000 mg/m<sup>2</sup> body surface over 48h in a self portable elastomeric infusion system (e.g. Baxter infusor). Folinic acid can be ordered in vials of 2-18 mL containing 54.65 mg/ml Folinic acid disodium salt, corresponding to 50 mg/ml Folinic acid.

<b>Arm title</b>	Arm B
------------------	-------

Arm description:

5-Fluorouracil (5-FU), Folinic Acid

Arm type	Active comparator
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

5-FU is a generic drug which is manufactured by Medac, Gesellschaft für klinische Spezialpräparate mbH, Theaterstr. 6, 22880 Wedel, Germany and other companies. It is produced in vials with a dosage of 50 mg/ml. It will be administered together with oncofolic 400 mg/m<sup>2</sup> body surface in a dosage of 2000 mg/m<sup>2</sup> body surface over 48h in a self portable elastomeric infusion system (e.g. Baxter infusor) in an outpatient setting after intravenous infusion of supportive drugs including such as granisetron or ondasetron and dexamethasone 8mg. Infusion via a port system is mandatory. Patients in arm A (FOLFIRI) receive an intravenous infusion of 180 mg/m<sup>2</sup> irinotecan over 1,5h before 5-FU/oncofolic administration.

5-FU can be ordered in bottles of 5 to 200 mL. 5-FU bottles contain 5-FU 50mg/m<sup>2</sup> and sodium hydroxide and water for injection. It is a colorless or pale yellow solution. 5-FU may only be dissolved in 0.9 % sodium chloride or in 5 % glucose.

Investigational medicinal product name	Folinic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Infusion

Dosage and administration details:

Folinic acid is manufactured by Medac, Gesellschaft für klinische Spezialpräparate mbH, Theaterstr. 6, 22880 Wedel, Germany. It will be administered in both treatment arms in dosage of 400mg/m<sup>2</sup> body surface in combination with 5-FU 2000 mg/m<sup>2</sup> body surface over 48h in a self portable elastomeric infusion system (e.g. Baxter infusor). Folinic acid can be ordered in vials of 2-18 mL containing 54.65 mg/ml Folinic acid disodium salt, corresponding to 50 mg/ml Folinic acid. It is a colorless or pale yellow solution. Folinic acid should be stored at 2-8°C until mixture with 5-FU. After mixture with 5-FU or dilution in 0.9% sodium chloride it is stable for 72 h at 20-25°C.

<b>Number of subjects in period 1</b>	Arm A	Arm B
Started	23	4
Completed	23	4

## Baseline characteristics

### Reporting groups

Reporting group title	overall trial
-----------------------	---------------

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	27	27	
Age categorical			
Age >=18 years			
Units: Subjects			
Adults (18-64 years)	9	9	
From 65-84 years	18	18	
85 years and over	0	0	
Gender categorical			
In this phase II trial male and female patients are enrolled. It is assumed that more men will be enrolled.			
Units: Subjects			
Female	8	8	
Male	19	19	

## End points

### End points reporting groups

Reporting group title	Arm A
Reporting group description: FOLFIRI Arm (5-Fluorouracil, Folinic Acid, Irinocetan)	
Reporting group title	Arm B
Reporting group description: 5-Fluorouracil (5-FU), Folinic Acid	

### Primary: Determination of the progression free survival (PFS)

End point title	Determination of the progression free survival (PFS)
End point description: Note that because of low recruiting, the primary aim was changed in the last protocol version where Arm B (control) was stopped. While the original primary aim was the comparison between the two treatment arms with the logrank test ( $p=0.304$ ), the updated primary aim was to prove that median PFS was at least 2 months in Arm A (FOLFIRI) with a one-sided test and significance level of $\alpha=10\%$ . Table 10 already shows that the two-sided confidence interval of median PFS in Arm A (FOLFIRI) was 2.2 to 14.5 months and, therefore, completely above the reference value of 2 months. The one-sided test gives a p-value of $p<0.0001$ and the primary aim could be successfully proved.	
End point type	Primary
End point timeframe: from start to tumor progression	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	4		
Units: decimal numbers (months)				
median (confidence interval 90%)	5.1 (2.2 to 14.5)	5.6 (1.4 to 14.5)		

### Statistical analyses

Statistical analysis title	Activity analysis
Statistical analysis description: Standard descriptive methods will be used to present all relevant data. Continuous data will be summarized with the following items: frequency, median, range and mean and standard deviation. Quantitative data during study course (during treatment and/or follow up) are summarized as mean or medium, minimum and maximum value observed in each patient during the observation time course and illustrated by individual curves. Categorical data will be presented in with frequencies and percentages of	
Comparison groups	Arm A v Arm B



Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
Parameter estimate	Median difference (final values)
Point estimate	2
Confidence interval	
level	90 %
sides	1-sided
lower limit	0.1

Notes:

[1] - ITT analysis

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

treatment period

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

### Dictionary used

Dictionary name	CTCAE
-----------------	-------

Dictionary version	4
--------------------	---

### Reporting groups

Reporting group title	all patients
-----------------------	--------------

Reporting group description: -

Serious adverse events	all patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 27 (37.04%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
thromboembolic event			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
hematoma			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
stroke			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
stenosis upper GI-tract			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
acute kidney injury			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Biliary tract infection (cholangitis)			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
infections and infestations-bloodstream infection			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
infections and infestations cholangitis			

subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
hyperglycemia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
hyponatremia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	all patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 27 (88.89%)		
Vascular disorders			
hematoma			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
thromboembolic event			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	4		
Nervous system disorders			
nervous system disorders - other			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
blood and lymphatic system disorders- other			

subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
fever			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
general disorders and administration site conditions-other			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
pain			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	4		
ascites			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
diarrhea			
subjects affected / exposed	11 / 27 (40.74%)		
occurrences (all)	9		
mucositis oral			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
nausea			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	3		
vomiting			

subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  respiratory, thoracic and mediastinal disorders - other subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2  2 / 27 (7.41%) 2		
Hepatobiliary disorders hepatobiliary disorder- other subjects affected / exposed occurrences (all)	5 / 27 (18.52%) 4		
Psychiatric disorders insomnia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Musculoskeletal and connective tissue disorders back pain subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Infections and infestations infections and infestations- other subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 4		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2020	Clarificatin of end of study
01 March 2021	Number of FOLFIRI treated patients was reduced to 23 patients and arm B (5-FU/folinic acid) was closed.
24 November 2021	Protocol and informed consent form were adapted due to change of PI from Prof. Oliver Waidmann to Prof. Fabian Finkelmeier.

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported