Clinical trial results:
A multicenter, randomized, double blind placebo controlled trial of Micronized purified Flavonoid-Fraction (MPFF) in the management of radiation proctitis

Summary

EudraCT number	2019-001916-44
Trial protocol	AT
Global end of trial date	13 October 2023

Results information

Result version number	v1 (current)
This version publication date	12 September 2024
First version publication date	12 September 2024

Trial information

Trial identification

Sponsor protocol code	MiFlaPRO_2019

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04335617
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medizinische Universität Innsbruck
Sponsor organisation address	Innrain 52, Innsbruck, Austria, 6020
Public contact	University Hospital for Visceral, Transplant and Thoracic Surgery, Medizinische Universität Innsbruck, 0043 51250422600, marijana.ninkovic@tirol-kliniken.at
Scientific contact	University Hospital for Visceral, Transplant and Thoracic Surgery, Medizinische Universität Innsbruck, 0043 51250422600, marijana.ninkovic@tirol-kliniken.at

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	27 June 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 October 2023
Global end of trial reached?	Yes
Global end of trial date	13 October 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The goal of the study is to compare the number of necessary interventions required to stop radiation proctitis inducing rectal bleeding in patients receiving Daflon® in comparison to patients in the control group receiving Placebo within 12 months of medical treatment.

Protection of trial subjects:

The MiFlaPRO study was conducted in strict accordance with the ethical principles originating from the Declaration of Helsinki, relevant regulatory requirements, and Good Clinical Practices (GCP). The study protocol was designed to ensure the protection of participant rights, safety, and well-being throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 February 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	0
From 65 to 84 years	36
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

49 patients were screened for inclusion, of which n=38 were randomized. N=9 patients did not meet inclusion/exclusion criteria, and n=2 patients did not participate in the trial.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Daflon

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Daflon
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

six tablets daily for the first four days, four tablets daily for the next three days, followed by two tablets daily for the remaining treatment period.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

six tablets daily for the first four days, four tablets daily for the next three days, followed by two tablets daily for the remaining treatment period.

Number of subjects in period 1	Daflon	Placebo
Started	21	17
Completed	13	14
Not completed	8	3
Adverse event, serious fatal	2	-
Consent withdrawn by subject	4	1

Physician decision	-	1
Adverse event, non-fatal	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Daflon
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Daflon	Placebo	Total
Number of subjects	21	17	38
Age categorical Units: Subjects			
From 65-84 years	20	16	36
85 years and over	1	1	2
Age continuous Units: years			
median	75.7	78.1	
inter-quartile range (Q1-Q3)	72.5 to 79.3	74.8 to 80.6	-
Gender categorical Units: Subjects			
Female	3	0	3
Male	18	17	35

Subject analysis sets	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The efficacy analysis in the MiFlaPRO study was conducted using the ITT population, which included all randomized patients who received at least one dose of the investigational product, Daflon®, or placebo

Reporting group values	Intention-to-treat		
Number of subjects	38		
Age categorical Units: Subjects			
From 65-84 years	36		
85 years and over	2		
Age continuous Units: years			
median			
inter-quartile range (Q1-Q3)			
Gender categorical Units: Subjects			
Female	3		
Male	35		

End points

End points reporting groups

Reporting group title	Daflon
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The efficacy analysis in the MiFlaPRO study was conducted using the ITT population, which included all randomized patients who received at least one dose of the investigational product, Daflon®, or placebo

Primary: Number of necessary interventions per patient required to manage macroscopic rectal bleeding

End point title	Number of necessary interventions per patient required to manage macroscopic rectal bleeding

End point description:

The primary efficacy endpoint was the number of necessary interventions per patient required to manage macroscopic rectal bleeding due to radiation proctitis over the 12-month treatment period.

End point type	Primary

End point timeframe:

12-month period

End point values	Daflon	Placebo	Intention-to-treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	21	17	38	
Units: Patients	5	4	9	

Statistical analyses

Statistical analysis title	Number of necessary interventions to stop bleeding

Statistical analysis description:

The primary efficacy endpoint was defined as the number of necessary treatment interventions per patient required to stop radiation proctitis induced rectal bleeding within 12 months after the randomization date. The number of these necessary interventions was compared between Daflon® and Placebo.

Comparison groups	Daflon v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.05
Method	two-sided Mann-Whitney U-Test

Notes:

[1] - The statistical analysis showed no significant difference between the two groups regarding the number of interventions required (p=0.97). This indicates that there was no advantage of Daflon over placebo in reducing the need for surgical or interventional treatments for radiation proctitis.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12.02.2020-13.10.2023 (12 month per patient)	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups	
Reporting group title	Daflon
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Daflon	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 21 (23.81%)	3 / 17 (17.65%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Skull fracture			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Central venous catheter removal			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (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	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Hematochezia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Functional gastrointestinal disorder			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax spontaneous			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			

subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Daflon	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 21 (57.14%)	14 / 17 (82.35%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Parathyroid tumour benign			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Investigations			
Faecal calprotectin increased			
subjects affected / exposed	0 / 21 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Haemoglobin decreased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			

Immunisation reaction			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Anaemia			
subjects affected / exposed	3 / 21 (14.29%)	3 / 17 (17.65%)	
occurrences (all)	5	3	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 21 (9.52%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Hematochezia			
subjects affected / exposed	1 / 21 (4.76%)	4 / 17 (23.53%)	
occurrences (all)	1	5	
Mucous stools			
subjects affected / exposed	2 / 21 (9.52%)	4 / 17 (23.53%)	
occurrences (all)	2	4	
Anal incontinence			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Anal pruritus			
subjects affected / exposed	3 / 21 (14.29%)	4 / 17 (23.53%)	
occurrences (all)	3	4	
Dyschezia			

subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Proctalgia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Ascites			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Rectal ulcer			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Skin lesion			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Rheumatic disorder			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 21 (4.76%)	1 / 17 (5.88%)	
occurrences (all)	1	1	

Urinary tract infection			
subjects affected / exposed	1 / 21 (4.76%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Pneumonia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Staphylococcal skin infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Helicobacter gastritis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Iron deficiency			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2020	Monocentric to mulitcentric (addition of 7 sites)
05 June 2020	Addition of 4 sites (including update of CIP)
01 February 2022	Study extension (incl. update of CIP) and principal investigators changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported