Clinical trial results:
Randomised double-blind controlled phase II trial of Tocovid SupraBio in combination with pentoxifylline (PTX) in patients suffering long-term adverse effects of radiotherapy for pelvic cancer

Summary

EudraCT number	2012-004211-31
Trial protocol	GB
Global end of trial date	19 December 2019

Results information

Result version number	v1 (current)
This version publication date	12 December 2020
First version publication date	12 December 2020

Trial information

Trial identification

Sponsor protocol code	CCR3894

Additional study identifiers

ISRCTN number	ISRCTN17415294
ClinicalTrials.gov id (NCT number)	NCT02230800
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Royal Marsden NHS Foundation Trust
Sponsor organisation address	203 Fulham Road, London, United Kingdom, SW3 6JJ
Public contact	Senior Research Coordinator, The Institute of Cancer Research, 0044 2086613460, lone.gothard@icr.ac.uk
Scientific contact	Senior Research Coordinator, The Institute of Cancer Research, 0044 2086613460, lone.gothard@icr.ac.uk

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	07 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2019
Global end of trial reached?	Yes
Global end of trial date	19 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test the benefits of oral Tocovid SupraBio (tocotrienols) with pentoxifylline (PTX) in patients suffering chronic gastrointestinal adverse effects following curative pelvic radiotherapy for cancer.

Protection of trial subjects:

There are no reported side--effects of tocotrienol at the doses prescribed for the study, and no pain or distress due to trial participation was expected/experienced

Background therapy:

Not applicable

Evidence for comparator:

Treatment group
Tocovid SupraBio 200mg po bd plus pentoxifylline (PTX) 400mg po bd for 12 months

Control group
Matching placebos po bd for 12 months

The primary endpoint was change at 12 months in the bowel disease subset of the Modified IBDQ Quality of Life questionnaire. As this is a subjective patient self-assessment, we chose placebo tablets as comparators to the active drugs.

Actual start date of recruitment	25 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 62
Worldwide total number of subjects	62
EEA total number of subjects	62

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	26
From 65 to 84 years	36
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening data was not collected for patients approached but not entered into the trial.

Period 1

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

Blinding implementation details:

Treatment allocation was in a 2:1 ratio of Tocovid SupraBio+PTX:Matched placebo and was based on computer generated random permuted blocks (of block sizes 6 and 9). Randomisation was stratified by the severity of their symptoms (IBDQ-B≥60 vs. IBDQ-B<60) and average daily fat intake (≥90g fat/day vs. <90g fat/day). All IMPs including placebos were packaged, labelled and dispatched to investigator site as open label supplies. Pharmacy were unblinded in the study as was one internal monitor.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment group

Arm description:

Tocovid SupraBio* 200mg po bd plus pentoxifylline (PTX) 400mg po bd for 12 months.

*Combination of tocotrienols: d-gamma-tocotrienol + d-alpha-tocotrienol + d-delta-tocotrienol

Arm type	Experimental
Investigational medicinal product name	Pentoxifylline
Investigational medicinal product code	C04AD03
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

800 mg per day

Investigational medicinal product name	Tocovid SupraBio
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

400 mg per day

Arm title	Control group

Arm description:

Placebo tablets

Arm type	Placebo
Investigational medicinal product name	Placebo (matched to Pentoxifylline)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details: 800 mg per day	
Investigational medicinal product name	Placebo (matched to Tocovid SupraBio)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use
Dosage and administration details: 400 mg per day	

Number of subjects in period 1	Treatment group	Control group
Started	40	22
Completed	28	17
Not completed	12	5
Consent withdrawn by subject	3	1
Physician decision	-	1
Cancer recurrence	1	-
Adverse event, non-fatal	4	2
Patient did not comment treatment	-	1
Reason unknown	1	-
Did not commence treatment	2	-
To receive treatment for unrelated condition	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Treatment group
Reporting group description:	
Tocovid SupraBio* 200mg po bd plus pentoxifylline (PTX) 400mg po bd for 12 months. *Combination of tocotrienols: d-gamma-tocotrienol + d-alpha-tocotrienol + d-delta-tocotrienol	
Reporting group title	Control group
Reporting group description:	
Placebo tablets	

Reporting group values	Treatment group	Control group	Total
Number of subjects	40	22	62
Age categorical Units: Subjects			
Adults (18-64 years)	14	12	26
From 65-84 years	26	10	36
Age continuous Units: years			
median	67.5	63.6	
inter-quartile range (Q1-Q3)	60.1 to 71.1	54.9 to 68.4	-
Gender categorical Units: Subjects			
Female	17	9	26
Male	23	13	36
Daily fat intake Units: Subjects			
<90g/day	34	19	53
>=90g/day	6	3	9
IBDQ-B score Units: Subjects			
<60	21	12	33
>=60	19	10	29

Subject analysis sets	
Subject analysis set title	Treatment group evaluable
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants allocated Tocovid SuprbBio + PTX who are evaluable for the primary endpoint i.e. who completed the QOL questionnaires at baseline and 12 months	
Subject analysis set title	Control group evaluable
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients allocated to placebo who are considered evaluable for the primary endpoint i.e. who completed QOL at baseline and 12 months	

Reporting group values	Treatment group evaluable	Control group evaluable	
Number of subjects	31	20	
Age categorical Units: Subjects			
Adults (18-64 years)	11	11	
From 65-84 years	20	9	
Age continuous Units: years			
median	67.7	62.9	
inter-quartile range (Q1-Q3)	58.7 to 73.0	54.8 to 68.3	
Gender categorical Units: Subjects			
Female	14	9	
Male	17	11	
Daily fat intake Units: Subjects			
<90g/day	27	17	
>=90g/day	4	3	
IBDQ-B score Units: Subjects			
<60	18	11	
>=60	13	9	

End points

End points reporting groups

Reporting group title	Treatment group
Reporting group description:	
Tocovid SupraBio* 200mg po bd plus pentoxifylline (PTX) 400mg po bd for 12 months. *Combination of tocotrienols: d-gamma-tocotrienol + d-alpha-tocotrienol + d-delta-tocotrienol	

Reporting group title	Control group
Reporting group description:	
Placebo tablets	

Subject analysis set title	Treatment group evaluable
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants allocated Tocovid SuprbBio + PTX who are evaluable for the primary endpoint i.e. who completed the QOL questionnaires at baseline and 12 months	

Subject analysis set title	Control group evaluable
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients allocated to placebo who are considered evaluable for the primary endpoint i.e. who completed QOL at baseline and 12 months	

Primary: Change at 12 months in the bowel disease subset of the Modified IBDQ Quality of Life questionnaire.

End point title	Change at 12 months in the bowel disease subset of the Modified IBDQ Quality of Life questionnaire.
End point description:	

End point type	Primary
End point timeframe:	
Change at 12 months from baseline	

End point values	Treatment group evaluable	Control group evaluable		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	20		
Units: Patient self-assessment score				
arithmetic mean (confidence interval 95%)	6 (2.3 to 9.6)	8.1 (0.79 to 15.4)		

Statistical analyses

Statistical analysis title	Change at 12 months in bowel subset of IBDQ
Comparison groups	Treatment group evaluable v Control group evaluable

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.553
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	9.3
Variability estimate	Standard error of the mean
Dispersion value	3.6

Secondary: Change at 12 months in rectal IBDQ bleeding score between the two groups in those patients presenting with grade 2, 3 or 4 bleeding

End point title	Change at 12 months in rectal IBDQ bleeding score between the two groups in those patients presenting with grade 2, 3 or 4 bleeding

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Treatment group evaluable	Control group evaluable		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5[1]	3[2]		
Units: Patients				
Improvement	3	2		
No improvement	2	1		

Notes:

[1] - Only includes patients with grade 2, 3 or 4 bleeding at baseline

[2] - Only includes patients with grade 2, 3 or 4 bleeding at baseline

Statistical analyses

Statistical analysis title	Change at 12 months in rectal bleeding
Comparison groups	Treatment group evaluable v Control group evaluable

Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.999
Method	Fisher exact

Secondary: Change at 12 months in IBDQ faecal incontinence score between the two groups in those patients presenting with grade 1 or greater incontinence

End point title	Change at 12 months in IBDQ faecal incontinence score between the two groups in those patients presenting with grade 1 or greater incontinence

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Treatment group evaluable	Control group evaluable		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21[3]	10[4]		
Units: Patients				
Improvement	13	6		
No improvement	8	4		

Notes:

[3] - Only includes patients with grade 1 and above faecal incontinence at baseline

[4] - Only includes patients with grade 1 and above faecal incontinence at baseline

Statistical analyses

Statistical analysis title	Change at 12 months in faecal incontinence
Comparison groups	Treatment group evaluable v Control group evaluable
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.999
Method	Fisher exact

Secondary: Number of patients with late radiation-induced grade 3/4 adverse events

End point title	Number of patients with late radiation-induced grade 3/4 adverse events

End point description:

End point type	Secondary

End point timeframe:

Up to 24 months after randomisation

End point values	Treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36[5]	20[6]		
Units: Patients	7	2		

Notes:

[5] - Includes all patients with grading of late radiation-induced toxicity by CTCAE after rand

[6] - Includes all patients with grading of late radiation-induced toxicity by CTCAE after rand

Statistical analyses

No statistical analyses for this end point

Secondary: Physician assessment of rectal dysfunction using modified CTCAE version 4 grading

End point title	Physician assessment of rectal dysfunction using modified CTCAE version 4 grading

End point description:

End point type	Secondary

End point timeframe:

Upto 24 months after randomisation

End point values	Treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36[7]	20[8]		
Units: Patients	30	17		

Notes:

[7] - Includes all patients with grading of late radiation-induced toxicity by CTCAE after rand

[8] - Includes all patients with grading of late radiation-induced toxicity by CTCAE after rand

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From time of consent and up to 30 days following the last dose of the study medication

Adverse event reporting additional description:

Adverse events of any grade are reported by treatment group regardless of assesment of relatedness to treatment. If the same preferred term is reported for a patient twice with the same start date or with over-lapping start and end dates these are counted as a single event. Events are reported for patients who received at least 1 dose of treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Treatment group

Reporting group description:

Treatment group

Reporting group title	Placebo group

Reporting group description:

Placebo group

Serious adverse events	Treatment group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 38 (10.53%)	2 / 21 (9.52%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Second primary malignancy			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (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			
Fall			

subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vomiting			
subjects affected / exposed	1 / 38 (2.63%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction reduction			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (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	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Treatment group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 38 (92.11%)	20 / 21 (95.24%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Metastases to bladder			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Neoplasm malignant			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Prostate cancer recurrent			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Flushing			
subjects affected / exposed	2 / 38 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Hot flush			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			

Bunion operation			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 38 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	1 / 38 (2.63%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Hernia pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	15 / 38 (39.47%)	8 / 21 (38.10%)	
occurrences (all)	19	10	
Mucosal inflammation			
subjects affected / exposed	1 / 38 (2.63%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Polyp			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			

Vaginal haemorrhage			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 38 (2.63%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Nasal polyps			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Sinus disorder			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 38 (7.89%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Depression			
subjects affected / exposed	4 / 38 (10.53%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Investigations			
Blood cholesterol increased			
subjects affected / exposed	1 / 38 (2.63%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Blood creatine increased			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Cystoscopy			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

White blood cell count decreased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	0 / 38 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	3	
Hip fracture			
subjects affected / exposed	2 / 38 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Post procedural infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Atrial fibrillation			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	6 / 38 (15.79%)	3 / 21 (14.29%)	
occurrences (all)	6	3	
Lethargy			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

Migraine			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Neuralgia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Transient ischaemic attack			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Vestibular disorder			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	5 / 38 (13.16%)	1 / 21 (4.76%)	
occurrences (all)	5	3	
Abdominal pain			
subjects affected / exposed	3 / 38 (7.89%)	2 / 21 (9.52%)	
occurrences (all)	4	3	
Anal incontinence			
subjects affected / exposed	4 / 38 (10.53%)	5 / 21 (23.81%)	
occurrences (all)	4	9	
Anal pruritus			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Breath odour			

subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	3 / 38 (7.89%)	3 / 21 (14.29%)	
occurrences (all)	5	3	
Defaecation urgency			
subjects affected / exposed	3 / 38 (7.89%)	1 / 21 (4.76%)	
occurrences (all)	3	1	
Dental caries			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	12 / 38 (31.58%)	4 / 21 (19.05%)	
occurrences (all)	14	4	
Diverticulum			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Dry mouth			
subjects affected / exposed	0 / 38 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	7 / 38 (18.42%)	4 / 21 (19.05%)	
occurrences (all)	7	4	
Dysphagia			
subjects affected / exposed	4 / 38 (10.53%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Flatulence			
subjects affected / exposed	4 / 38 (10.53%)	6 / 21 (28.57%)	
occurrences (all)	9	9	
Frequent bowel movements			
subjects affected / exposed	6 / 38 (15.79%)	1 / 21 (4.76%)	
occurrences (all)	6	1	
Intestinal obstruction			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Large intestinal obstruction			

subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	9 / 38 (23.68%)	2 / 21 (9.52%)	
occurrences (all)	10	3	
Proctalgia			
subjects affected / exposed	5 / 38 (13.16%)	5 / 21 (23.81%)	
occurrences (all)	5	5	
Rectal haemorrhage			
subjects affected / exposed	7 / 38 (18.42%)	3 / 21 (14.29%)	
occurrences (all)	8	4	
Rectal polyp			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Rectal prolapse			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Rectal tenesmus			
subjects affected / exposed	6 / 38 (15.79%)	3 / 21 (14.29%)	
occurrences (all)	8	4	
Small intestinal bacterial overgrowth			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	2 / 38 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	5 / 38 (13.16%)	4 / 21 (19.05%)	
occurrences (all)	7	7	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Onychoclasis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

Pruritus			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Psoriasis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 38 (2.63%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Bladder pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Haematuria			
subjects affected / exposed	2 / 38 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Incontinence			
subjects affected / exposed	1 / 38 (2.63%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Nephrolithiasis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Urinary retention			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Urine odour abnormal			
subjects affected / exposed	1 / 38 (2.63%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	3 / 38 (7.89%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Back pain			
subjects affected / exposed	1 / 38 (2.63%)	3 / 21 (14.29%)	
occurrences (all)	1	3	
Bone lesion			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Costochondritis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Ear infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Enterobiasis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Gingivitis			

subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Lung infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Otitis media			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Sepsis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Skin infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Small intestinal bacterial overgrowth			
subjects affected / exposed	2 / 38 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	3	2	
Tooth infection			
subjects affected / exposed	1 / 38 (2.63%)	4 / 21 (19.05%)	
occurrences (all)	1	5	
Upper respiratory tract infection			
subjects affected / exposed	1 / 38 (2.63%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Urinary tract infection			
subjects affected / exposed	2 / 38 (5.26%)	2 / 21 (9.52%)	
occurrences (all)	5	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2015	Amended IMPD for Tocovid SupraBio
04 September 2015	New information related to Pentoxifylline
29 January 2016	Change to withdrawal criterion
23 May 2016	Change to IMPD for Pentoxifylline
01 November 2016	New information related to Pentoxifylline
25 April 2017	Change of Chief Investigator
22 February 2018	Change to SIMPD for Pentoxifylline (additional manufacturer)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported