Clinical trial results:
A single arm, two-stage, multi-centre, phase II clinical trial investigating the safety and activity of the use of BTT1023, a human monoclonal antibody targeting vascular adhesion protein (VAP-1), in the treatment of patients with primary sclerosing cholangitis (PSC)

Summary

EudraCT number	2014-002393-37
Trial protocol	GB
Global end of trial date	18 January 2019

Results information

Result version number	v1 (current)
This version publication date	01 February 2020
First version publication date	01 February 2020

Trial information

Trial identification

Sponsor protocol code	RG_13-027

Additional study identifiers

ISRCTN number	ISRCTN11233255
ClinicalTrials.gov id (NCT number)	NCT02239211
WHO universal trial number (UTN)	-
Other trial identifiers	CRCTU CAS number: HE2022, Sponsors RG Number: RG_13-027, Sponsors SAF number: ERN_13-1461

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Vincent Drive, Edgbaston, Birmingham, United Kingdom, B15 2TT
Public contact	BUTEO Trial Coordinator, University of Birmingham, +44 0121 371 8117, BUTEO@trials.bham.ac.uk
Scientific contact	BUTEO Trial Coordinator, University of Birmingham, +44 0121 371 8117, BUTEO@trials.bham.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	08 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 January 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

1) To determine the activity of the anti-VAP-1 antibody BTT1023 in patients with PSC as measured by a decrease in ALP levels (primary endpoint) with secondary endpoints to include various measures of liver injury and fibrosis.
2) To evaluate the safety, effective dose and tolerability of BTT1023 in patients with PSC.

Protection of trial subjects:

The trial was comprised of two components, an initial run-in period to confirm the therapeutic dose, which followed into a Phase II Simon's two-stage design.

Given the unpredictable nature of PSC and natural variation of ALP levels, a two-stage screening process over 4–7 weeks was incorporated into the trial, whereby the ALP levels must not vary by more than 25% between screening visit 1 and 2 in order to continue trial enrolment.

Participants were all patients with a clinical diagnosis of PSC; this was established using recognised eligibility criteria.

In order to comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, an accurate record of all Adverse Events reported by Investigators were maintained throughout the trial.

Background therapy:

Not applicable

Evidence for comparator:

BTT1023 is a fully-human monoclonal IgG4 immunoglobulin with antigen-binding specificity for human VAP-1.
BTT1023 blocks the leucocyte adhesion receptor VAP-1 which helps position inflammatory cells and activ ated myofibroblasts in areas of ongoing fibrogenesis in the liver. Inhibition of VAP-1 with BTT1023 is expected to impact fibrotic liver disease by reducing inflammatory cell and activated fibroblast accumulation.

Data from previous studies of RA and psoriasis patients supports the use of a therapeutic dose of 8 mg/kg which was well tolerated.
BTT1023 was administered as repeated intravenous infusions at weekly to biweekly intervals up to a maximum of 7 consecutive doses at 8 mg/kg body weight over 11 weeks.

Actual start date of recruitment	02 February 2015
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: 23

Worldwide total number of subjects	23
EEA total number of subjects	23

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)	21
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were invited to participate in the BUTEO trial from six NHS hospitals. Potential participants were identified directly by the trial Clinician and/or Research Nurse by using a variety of methods i.e. hospital clinics, outpatient lists and patient referrals from other NHS hospitals.

Recruitment ran between 08-Sep-2015 and 19-Jun-2018.

Pre-assignment

Screening details:

Screening including any non-standard of care assessments commenced following informed consent and prior to patient registration in order to confirm eligibility. Given the unpredictable nature of PSC and natural variation of ALP levels, a two-stage screening process over 4–7 weeks was incorporated into the trial.

Pre-assignment period milestones

Number of subjects started	35[1]
Number of subjects completed	23

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Change in ALP level between screening visits: 3
Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Patient availability: 1
Reason: Number of subjects	Elevated ALK Phosphate: 1
Reason: Number of subjects	ALT levels high: 1
Reason: Number of subjects	Cholangitis (point 6 of exclusion criteria): 1
Reason: Number of subjects	Elevated Bilirubin: 1
Reason: Number of subjects	Parotid lump warranting oncology referral: 1
Reason: Number of subjects	Positive T-Spot test: 1
Reason: Number of subjects	On transplant list: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Pre-assignment patients were screened for eligibility, those who did not meet the eligibility criteria were not enrolled into the trial.

Period 1

Period 1 title	Registration
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	BTT1023
Arm description: -	
Arm type	Experimental

Investigational medicinal product name	BTT1023
Investigational medicinal product code	BTT1023
Other name	Timolumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BTT1023
was administered as repeated intravenous infusions at weekly to biweekly intervals up to a maximum of 7 consecutive 8 mg/kg doses, therefore the total dose received was 56 mg/kg by all patients in the trial.

Number of subjects in period 1	BTT1023
Started	23
Completed	22
Not completed	1
patient ineligible post registration	1

Period 2

Period 2 title	Treated Patients
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	BTT1023

Arm description: -

Arm type	Experimental
Investigational medicinal product name	BTT1023
Investigational medicinal product code	BTT1023
Other name	Timolumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BTT1023 was administered as repeated intravenous infusions at weekly to biweekly intervals up to a maximum of 7 consecutive 8 mg/kg doses, therefore the total dose received was 56 mg/kg by all patients in the trial.

Number of subjects in period 2	BTT1023
Started	22
Completed	22

Period 3

Period 3 title	Efficacy
Is this the baseline period?	Yes[2]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	BTT1023

Arm description: -

Arm type	Experimental
Investigational medicinal product name	BTT1023
Investigational medicinal product code	BTT1023
Other name	Timolumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BTT1023 was administered as repeated intravenous infusions at weekly to biweekly intervals up to a maximum of 7 consecutive 8 mg/kg doses, therefore the total dose received was 56 mg/kg by all patients in the trial.

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Analysis will be carried out on a modified intention-to-treat basis in which only patients who have received at least one infusion at the confirmed dose of BTT1023 will be analysed.

Number of subjects in period 3[3]	BTT1023
Started	22
Completed	19
Not completed	3
Consent withdrawn by subject	2
Missing one treatment visit	1

Notes:

[3] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Analysis will be carried out on a modified intention-to-treat basis in which only patients who have received at least one infusion at the confirmed dose of BTT1023 will be analysed.

Baseline characteristics

Reporting groups	
Reporting group title	Efficacy

Reporting group description: -

Reporting group values	Efficacy	Total	
Number of subjects	22	22	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	20	20	
From 65-84 years	2	2	
85 years and over	0	0	
Adults	0	0	
Adult	0	0	
Age continuous Units: years			
median	48		
inter-quartile range (Q1-Q3)	38 to 51.7	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	18	18	
Ethnicity Units: Subjects			
Caucasian	20	20	
South Asian	2	2	
Alcohol Consumption Units: Subjects			
0 units	7	7	
1-7 units	12	12	
7-14 units	2	2	
15-21	1	1	
>22 units	0	0	
Alcohol History Units: Subjects			
Have consumed alcohol	4	4	
Never consumed alcohol	1	1	
Not applicable	15	15	
Missing	2	2	
Cardiovascular Event			

Units: Subjects			
No	14	14	
Yes	8	8	
Myocardial Infarction Units: Subjects			
No	7	7	
Yes	0	0	
Not Applicable	14	14	
Missing	1	1	
Cerebrovascular Accident Units: Subjects			
No	7	7	
Yes	0	0	
Not Applicable	14	14	
Missing	1	1	
Peripheral Vascular Disease Units: Subjects			
No	7	7	
Yes	0	0	
Not Applicable	14	14	
Missing	1	1	
Hypertension Units: Subjects			
No	5	5	
Yes	2	2	
Not Applicable	14	14	
Missing	1	1	
Hyperlipidaemia Units: Subjects			
No	7	7	
Yes	0	0	
Not Applicable	14	14	
Missing	1	1	
Other Medical Condition Units: Subjects			
No	0	0	
Yes	8	8	
Missing	0	0	
Not applicable	14	14	
Current Symptoms of Primary Sclerosing Cholangistis			
Current symptoms of Primary Sclerosing Cholangistis experienced by patients at time of screening			
Units: Subjects			
No	5	5	
Yes	17	17	
Not applicable	0	0	
Current PSC Symptom: Tiredness Units: Subjects			
No	4	4	
Yes	13	13	
Not applicable	5	5	

Current PSC Symptom: Jaundice Units: Subjects			
No	17	17	
Yes	0	0	
Not applicable	5	5	
Current PSC Symptom: Fever Units: Subjects			
No	17	17	
Yes	0	0	
Not applicable	5	5	
Current PSC Symptom: Abdominal Pain Units: Subjects			
No	13	13	
Yes	4	4	
Not applicable	5	5	
Current PSC Symptom: Bowel Movement Units: Subjects			
No	12	12	
Yes	4	4	
Not Applicable	5	5	
Missing	1	1	
Current PSC Symptom: Skin Irritation Units: Subjects			
No	3	3	
Yes	14	14	
Not applicable	5	5	
Current PSC Symptom: Nausea Units: Subjects			
No	16	16	
Yes	1	1	
Not applicable	5	5	
Current PSC Symptom: Vomiting Units: Subjects			
No	16	16	
Yes	1	1	
Not applicable	5	5	
Smoking History: Current Smoker			
Patient smoking status and history at date of screening.			
Units: Subjects			
No	22	22	
Yes	0	0	
Smoking History: Previous Smoker			
Patient smoking status and history at date of screening.			
Units: Subjects			
No	17	17	
Yes	5	5	
History of Inflammatory Bowel Disease Units: Subjects			
No	8	8	
Yes	14	14	

Previous/Known Drug Allergies Units: Subjects			
No	17	17	
Yes	5	5	
Diagnosis of Disease Units: Subjects			
Established	12	12	
New	8	8	
Not Applicable	2	2	
Response to Previous UDCA Units: Subjects			
UDCA naive	3	3	
UDCA non-responder	7	7	
UDCA responder	8	8	
Not Applicable	4	4	
Basis for Diagnosis Units: Subjects			
Blood work	3	3	
Histology	6	6	
Imaging	12	12	
Not Applicable	1	1	
History of Autoimmune Disease Units: Subjects			
No	17	17	
Yes	5	5	
History of Prior Surgery Units: Subjects			
No	10	10	
Yes	12	12	
Medication Taken			
History of medication taken within the three months prior to trial registration.			
Units: Subjects			
No	2	2	
Yes	19	19	
Not Applicable	1	1	
Allergy History: Allergic Rhinitis Units: Subjects			
No	22	22	
Yes	0	0	
Allergy History: Allergic Asthma Units: Subjects			
No	19	19	
Yes	3	3	
Allergy History: Allergic Eczema Units: Subjects			
No	20	20	
Yes	2	2	
Allergy History: Food Allergies Units: Subjects			
No	20	20	
Yes	2	2	

Allergy History: Other Allergies Units: Subjects			
No	19	19	
Yes	3	3	
Absolute ALP Percentage Change Units: Subjects			
median	5.65		
inter-quartile range (Q1-Q3)	4.06 to 16.2	-	
Period of Alcohol Abstinence Units: Years			
median	8.5		
inter-quartile range (Q1-Q3)	6.25 to 11.5	-	
Previous Smoking Duration Units: Years			
median	7.5		
inter-quartile range (Q1-Q3)	2.75 to 14	-	
Previous Smoking Amount Units: Cigarettes per day			
median	10		
inter-quartile range (Q1-Q3)	7.5 to 10	-	
Age of Inflammatory Bowel Disease onset Units: Years			
median	23		
inter-quartile range (Q1-Q3)	19.25 to 35.25	-	
Onset Age of Primary Sclerosing Cholangitis Units: Years			
median	37		
inter-quartile range (Q1-Q3)	25 to 41.75	-	

End points

End points reporting groups

Reporting group title	BTT1023
Reporting group description: -	
Reporting group title	BTT1023
Reporting group description: -	
Reporting group title	BTT1023
Reporting group description: -	

Primary: Response at visit 10

End point title	Response at visit 10[1]

End point description:

Primary Outcome: To determine the activity of the anti-VAP-1 antibody BTT1023 in patients with PSC as measured by a decrease in ALP levels (primary endpoint).

Primary Outcome Measure: Response at Day 99: a reduction in serum alkaline phosphatase (ALP) by 25% or more from baseline to Day 99.

Percentage change in ALP was calculated as: (ALP(visit 10) - ALP(visit 3, pre-infusion))/ALP(visit 3, pre-infusion).
The target reduction in ALP was 25%.

Statistical analysis description:
This trial was designed with a Simon's two-stage using the following parameters: alpha = 0.10 (type I error), beta = 0.2 (1-beta=power), P0 = 0.15, P1 = 0.30.
P0 and P1 correspond to the required reduction in patients experiencing raised levels of ALP from 85%to 70%, i.e. 1-0.85=0.15 and 1-0.70=0.30.
The Simon’s two-stage minimax design requires 3 responses out of 18 evaluable patients at the interim analysis to continue, and 9 of 37 at the final analysis.

End point type	Primary

End point timeframe:

Percentage change in ALP measured between visit 3 pre-infusion (the first treatment visit) and visit 10 (the first follow-up visit, day 99).

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: This is a single arm trial with a Simon's two-stage design therefore interpretation is made with respect to desirable characteristics.

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Response				
Reduction of 25% or greater	2			
No reduction of 25% or greater	19			
Data missing	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Compliance

End point title	Treatment Compliance

End point description:

If a patient had been fully compliant with the protocol, they would have attended 11 visits: screening visits 1 & 2; treatment visits 3-9; and follow-up visits 10 & 11.
Here we present counts of patients who complied with trial visits per protocol

End point type	Secondary

End point timeframe:

Treatment compliance during the trial period.

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Persons				
Attended all trial visits	19			
Did not attend all trial visits	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Compliance

End point title	Treatment Compliance

End point description:

If a patient had been fully compliant with the protocol, they would have attended 11 visits: screening visits 1 & 2; treatment visits 3-9; and follow-up visits 10 & 11.
Here we present descriptive summary information regarding the number of visits attended.

End point type	Secondary

End point timeframe:

Treatment compliance within trial period.

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Visits				
arithmetic mean (full range (min-max))	10.64 (5 to 11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Compliance

End point title	Treatment Compliance

End point description:

End point type	Secondary

End point timeframe:

Withdrawals from trial treatment during trial period.

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Withdrawals				
Withdrew consent to treatment	2			
Did not withdraw consent to treatment	20			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Compliance

End point title	Treatment Compliance

End point description:

End point type	Secondary

End point timeframe:

The length of time on trial treatments calculated as the time (in days) between the first treatment with BTT1023 and the last treatment with BTT1023.

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Days				
arithmetic mean (full range (min-max))	73.14 (1 to 80)			

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D Health Questionnaire: EQ-5D 5L

End point title	EQ-5D Health Questionnaire: EQ-5D 5L

End point description:

The EQ-5D-5L (EuroQol 5-Dimensional 5 Levels) descriptive system comprises of five dimensions (mobility; self-care; usual activities; pain or discomfort; and anxiety/depression). Each dimension has five response levels: no problems; slight problems; moderate problems; severe problems; unable to/extreme problems. Responses are coded as single-digit numbers (1-5) expressing the severity level selected in each dimension with lower numbers equating to better functionality (and vice versa). The digits for the five dimensions can be combined in a 5-digit code that describes the respondent's health state.
Each health state is then transformed to an index score using England specific estimates attained from Devlin et al. (2018).
The maximum index score is 1.00, while the minimum index score is -0.285. For EQ-5D 5L index scores, higher scores equate to better functionality.
Percentage change in EQ-5D 5L index score is calculated as: (EQ-5D 5L(visit 10) - EQ-5D 5L(visit 3))/EQ-5D 5L(visit 3)

End point type	Secondary

End point timeframe:

Percentage change in EQ-5D 5L index score measured between visit 3 pre-infusion (the first treatment visit) and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	21[2]			
Units: Percentage Change(test unit: index score				
arithmetic mean (full range (min-max))	-5.52 (-59.24 to 20.63)			

Notes:

[2] - One patient had information pertinent to this outcome missing.

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D Health Questionnaire: EQ-VAS

End point title	EQ-5D Health Questionnaire: EQ-VAS

End point description:

The EQ-VAS (EuroQol Visual Analogue Scale) records the respondent's overall current health today on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' (corresponding to a score of 100) and 'The worst health you can imagine' (corresponding to a score of 0).
The EQ-VAS provides a quantitative measure of the patient's perception of their overall health.

Percentage change in EQ-VAS was calculated as: (EQ-VAS(visit 10) - EQ-VAS(visit 3))/EQ-VAS(visit 3).

End point type	Secondary

End point timeframe:

Percentage change in EQ-VAS measured between visit 3 (the first treatment visit) and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	21[3]			
Units: Percentage Change (Test Units: EQ-VAS)				
arithmetic mean (full range (min-max))	-3.76 (-40.98 to 23.08)			

Notes:

[3] - One patient had data pertinent to this outcome missing.

Statistical analyses

No statistical analyses for this end point

Secondary: Fatigue Severity Scale (FSS)

End point title	Fatigue Severity Scale (FSS)

End point description:

The Fatigue Severity Scale (FSS) is a method of evaluating the impact of fatigue on a patient through methods of a short questionnaire that requires patients to rate their level of fatigue. The FSS questionnaire contains nine statements, graded from 1 to 7 based on how accurately the statement reflects the patient condition during the past week and the extent to which they agree or disagree that the statement applies to them. A low value (e.g.1) indicates strong disagreement with the statement, whereas a high value (e.g. 7) indicates a strong agreement.
Percentage change in FSS score is calculated as: (FSS(visit 10) - FSS(visit 3))/FSS(visit 3).

End point type	Secondary

End point timeframe:

Percentage change in Fatigue Severity Scale (FSS) score measured between visit 3 (the first treatment visit) and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	21[4]			
Units: Percentage Change (Test Units: FSS)				
arithmetic mean (full range (min-max))	-2.28 (-41.67 to 33.33)			

Notes:

[4] - One patient had data pertinent to this outcome missing.

Statistical analyses

No statistical analyses for this end point

Secondary: Pruritus Visual Analogue Scale (VAS)

End point title	Pruritus Visual Analogue Scale (VAS)

End point description:

The purpose of the visual analogue scale (VAS) was to measure the amount of pruritus (itching) that patients experience while participating in the BUTEO trial. The following reference was given "Mark with a pen on the line below how much you were bothered by itchiness over the past 24 hours. The far left indicates 'no itching' and far right indicates 'intolerable/severe itching'."

Percentage change in pruritus VAS was calculated as (pruritus VAS(visit 10) - pruritus VAS(visit 3))/pruritus VAS(visit 3).

End point type	Secondary

End point timeframe:

Percentage change in Pruritus Visual Analogue Scale (VAS) measured between visit 3 (the first treatment visit) and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	20[5]			
Units: Percentage Change(Test Unit:Pruritus VAS				
arithmetic mean (full range (min-max))	115.97 (-98.15 to 2550.00)			

Notes:

[5] - Two patients had data pertinent to this outcome missing.

Statistical analyses

No statistical analyses for this end point

Secondary: Inflammatory Bowel Disease (IBD) Diary: Number of Stools

End point title	Inflammatory Bowel Disease (IBD) Diary: Number of Stools

End point description:

The Inflammatory Bowel Disease (IBD) diary was completed by 14 people. All participants who completed the diary had IBD and the 8 patients who did not complete the diary did not have IBD.
As the diary was completed on 7 consecutive days before visit, for the descriptive analyses provided here, the median average is first calculated for each time point, to give the median number of stools per day, and then the difference in averages calculated. The median was used due to the highly skewed nature of this outcome.
The percentage change in number of stools could not be calculated for one patient as at the reference period, screening visit 2, they had a median average of 0 stools per day. This patient has been excluded from the analysis otherwise the mean and upper bound of the range cannot formally be quantified.

The percentage change in median number of stools per day is calculated as: (Stools per day(visit 10) - Stools per day(visit 2))/Stools per day(visit 2).

End point type	Secondary

End point timeframe:

Percentage change in the median number of stools per day measured between screening visit 2 and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	12[6]			
Units: Percentage Change in No of Stools a day				
arithmetic mean (full range (min-max))	25.79 (-33.33 to 200)			

Notes:

[6] - One patient had outcome data missing. Percentage change could not be calculated for one patient.

Statistical analyses

No statistical analyses for this end point

Secondary: Inflammatory Bowel Disease (IBD) Diary: Frequency of Blood in Stool

End point title	Inflammatory Bowel Disease (IBD) Diary: Frequency of Blood in Stool

End point description:

The Inflammatory Bowel Disease (IBD) diary was completed by 14 people. All participants who completed the diary had IBD and the 8 patients who did not complete the diary did not have IBD.
As the diary was completed on 7 consecutive days before visit, for the descriptive analyses provided here, the median average is first calculated for each time point, to give the median frequency of blood in stools per day, and then the difference in averages calculated. The median is used due to the skewed nature of the outcome.
Due to the high presence of there being on average 0 instances of blood in the stools per day at both time points, the difference between the two time points is instead used (as '0/0' cannot be evaluated).
The difference in the median frequency of blood in stools per day is calculated as: Blood in Stools per day(visit 10) - Blood in Stools per day(visit 2)

End point type	Secondary

End point timeframe:

Difference in the median frequency of blood in stools per day measured between screening visit 2 and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	13[7]			
Units: Difference in Freq Blood in Stools a day				
arithmetic mean (full range (min-max))	0 (0 to 0)			

Notes:

[7] - One patient had data pertinent to this outcome missing.

Statistical analyses

No statistical analyses for this end point

Secondary: Inflammatory Bowel Disease (IBD) Diary: Abdominal Pain/Cramp

End point title	Inflammatory Bowel Disease (IBD) Diary: Abdominal Pain/Cramp

End point description:

The Inflammatory Bowel Disease (IBD) diary was completed by 14 people. All participants who completed the diary had IBD and the 8 patients who did not complete the diary did not have IBD.
Patients were asked to rate their abdominal pain/cramp score on a scale of 0 to 3 where: 0 = none; 1 = mild; 2 = moderate; and 3 = severe.
As the diary was completed on 7 consecutive days before visit, for the descriptive analyses provided here, the median average is first calculated for each time point to give the median abdominal pain per day, and then the difference in averages calculated. Furthermore, by using the median, the summary

measure should always fall on an integer, giving a more meaningful value given the categorical of the data.
Many individuals reported their abdominal pain to be 'good' (graded 0) at either/both visit(s). Therefore, the percentage change cannot often be calculated. To give a more meaningful sample size, the difference has instead been used.

End point type	Secondary

End point timeframe:

Difference in the median abdominal pain/cramp between screening visit 2 and visit 10 (the first follow-up visit, day 99).
Calculated as: median abdominal pain/cramp score per day(visit 10) - median abdominal pain/cramp score per day(screening visit 2)

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	13[8]			
Units: Median Abdominal Pain/Cramp Score				
arithmetic mean (full range (min-max))	0.08 (-1 to 1)			

Notes:

[8] - One patient had data pertinent to this outcome missing.

Statistical analyses

No statistical analyses for this end point

Secondary: Inflammatory Bowel Disease (IBD) Diary: General Wellbeing

End point title	Inflammatory Bowel Disease (IBD) Diary: General Wellbeing

End point description:

The Inflammatory Bowel Disease (IBD) diary was completed by 14 people. All participants who completed the diary had IBD and the 8 patients who did not complete the diary did not have IBD.
Patients were asked to rate their general wellbeing score on a scale of 0 to 3 where: 0 = good; 1 = average; 2 = poor; and 3 = very poor.
As the diary was completed on 7 consecutive days before visit, for the descriptive analyses provided here, the median average is first calculated for each time point to give the median general wellbeing score, and then the difference in averages calculated. Furthermore, by using the median, the summary measure should always fall on an integer, giving a more meaningful value given the categorical of the data.
Many individuals reported their general wellbeing to be 'good' (graded 0) at either/both visit(s). Therefore, the percentage change cannot often be calculated. To give a more meaningful sample size and values, the difference has instead been used.

End point type	Secondary

End point timeframe:

Difference in the median general wellbeing between screening visit 2 and visit 10 (the first follow-up visit, day 99).
Calculated as: median general wellbeing score per day(visit 10) - median general wellbeing per day(screening visit 2)

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	13[9]			
Units: Difference in General Wellbeing score				
arithmetic mean (full range (min-max))	0 (-1 to 1)			

Notes:

[9] - One patient had data pertinent to this outcome missing.

Statistical analyses

No statistical analyses for this end point

Secondary: Enhanced Liver Fibrosis (ELF)

End point title	Enhanced Liver Fibrosis (ELF)

End point description:

Percentage change in Enhanced Liver Fibrosis (ELF) score is calculated as: (ELF(visit 10) - ELF(screening visit 2))/ELF(screening visit 2).

End point type	Secondary

End point timeframe:

Percentage change in the enhanced liver fibrosis score measured between screening visit 2 and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	0[10]			
Units: Percentage Change(Test Units:ELF result)				
arithmetic mean (full range (min-max))	(to)			

Notes:

[10] - Data pertinent to this outcome was unavailable at the time of preparation of this report.

Statistical analyses

No statistical analyses for this end point

Secondary: Fibroscan: kPa

End point title	Fibroscan: kPa

End point description:

Percentage change in Fibroscan kPa score is calculated as: (kPa (visit 10) - kPa (screening visit 2))/kPa (screening visit 2).

End point type	Secondary

End point timeframe:

Percentage change in the Fibroscan kPa result measured between screening visit 2 and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Percentage Change (Test Units: kPa)				
arithmetic mean (full range (min-max))	13.58 (-54.75 to 122.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fibroscan: IQR

End point title	Fibroscan: IQR

End point description:

Percentage change in Fibroscan IQR score is calculated as: (IQR (visit 10) - IQR (screening visit 2))/IQR (screening visit 2).

End point type	Secondary

End point timeframe:

Percentage change in the Fibroscan IQR result measured between screening visit 2 and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Percentage Change (Test Units: IQR)				
arithmetic mean (full range (min-max))	65.72 (-53.33 to 400)			

Statistical analyses

No statistical analyses for this end point

Secondary: Liver Function Tests: AST

End point title	Liver Function Tests: AST

End point description:

Percentage change in Aspartate Transaminase (AST, IU/L) score is calculated as: (AST(visit 10) - AST(screening visit 2))/AST(screening visit 2).

End point type	Secondary

End point timeframe:

Percentage change in Aspartate Transaminase (AST, IU/L) measured between screening visit 2 and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	20[11]			
Units: Percentage Change (Test Units: IU/L)				
arithmetic mean (full range (min-max))	-2.52 (-36.56 to 56.67)			

Notes:

[11] - Data pertinent to this outcome was missing for two patients.

Statistical analyses

No statistical analyses for this end point

Secondary: Liver Function Tests: ALT

End point title	Liver Function Tests: ALT

End point description:

Percentage change in Alanine Transaminase (ALT, IU/L) score is calculated as: (ALT(visit 10) - ALT(screening visit 2))/ALT(screening visit 2).

End point type	Secondary

End point timeframe:

Percentage change in Alanine Transaminase (ALT, IU/L) measured between screening visit 2 and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	21[12]			
Units: Percentage Change (Test Units: IU/L)				
arithmetic mean (full range (min-max))	1.14 (-45.07 to 88.64)			

Notes:

[12] - One patient had data pertinent to this outcome missing.

Statistical analyses

No statistical analyses for this end point

Secondary: Liver Function Tests: ALP

End point title	Liver Function Tests: ALP

End point description:

Percentage change in Alkaline Phosphatase (ALP, IU/L) score is calculated as: (ALP(visit 10) - ALP(screening visit 2))/ALP(screening visit 2).

End point type	Secondary

End point timeframe:

Percentage change in Alkaline Phosphatase (ALP, IU/L) measured between screening visit 2 and visit 10

(the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Percentage Change (Test Units: IU/L)				
arithmetic mean (full range (min-max))	-3.57 (-34.26 to 49.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: Liver Function Tests: GGT

End point title	Liver Function Tests: GGT

End point description:

Percentage change in Gamma Glutamyl Transferase (GGT, IU/L) score is calculated as: (AST(visit 10) - AST(screening visit 2))/AST(screening visit 2).

End point type	Secondary

End point timeframe:

Percentage change in Gamma Glutamyl Transferase (GGT, IU/L) measured between screening visit 2 and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	20[13]			
Units: Percentage Change (Test Units: IU/L)				
arithmetic mean (full range (min-max))	-8.73 (-37.48 to 24.64)			

Notes:

[13] - Two patients had data pertinent to this outcome missing.

Statistical analyses

No statistical analyses for this end point

Secondary: Liver Function Tests: Albumin

End point title	Liver Function Tests: Albumin

End point description:

Percentage change in Albumin (g/L) score is calculated as: (Albumin (visit 10) - Albumin (screening visit 2))/Albumin (screening visit 2).

End point type	Secondary

End point timeframe:

Percentage change in Albumin (g/L) measured between screening visit 2 and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Percentage Change (Test Units: g/L)				
arithmetic mean (full range (min-max))	-2.45 (-12.77 to 10.26)			

Statistical analyses

No statistical analyses for this end point

Secondary: Liver Function Tests: Direct Bilirubin

End point title	Liver Function Tests: Direct Bilirubin

End point description:

Percentage change in Direct Bilirubin (umol/l) score is calculated as: (Direct Bilirubin(visit 10) - Direct Bilirubin(screening visit 2))/Direct Bilirubin(screening visit 2).

End point type	Secondary

End point timeframe:

Percentage change in Direct Bilirubin (umol/l) measured between screening visit 2 and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	18[14]			
Units: Percentage Change (Test Units: umol/l)				
arithmetic mean (full range (min-max))	5.92 (-66.67 to 300.00)			

Notes:

[14] - Data pertinent to this outcome was missing for four patients.

Statistical analyses

No statistical analyses for this end point

Secondary: Liver Function Tests: Indirect Bilirubin

End point title	Liver Function Tests: Indirect Bilirubin

End point description:

Percentage change in Indirect Bilirubin (umol/l) score is calculated as: (Indirect Bilirubin(visit 10) - Indirect Bilirubin(screening visit 2))/Indirect Bilirubin(screening visit 2).

End point type	Secondary

End point timeframe:

Percentage change in Indirect Bilirubin (umol/l) measured between screening visit 2 and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	15[15]			
Units: Percentage Change (Test Units: umol/l)				
arithmetic mean (full range (min-max))	-10.66 (-62.5 to 66.67)			

Notes:

[15] - Data pertinent to this outcome was missing for 7 patients.

Statistical analyses

No statistical analyses for this end point

Secondary: Liver Function Tests: International Normalised Ratio

End point title	Liver Function Tests: International Normalised Ratio

End point description:

Percentage change in International Normalised Ratio (INR) score is calculated as: (INR(visit 10) - INR(screening visit 2))/INR(screening visit 2).

End point type	Secondary

End point timeframe:

Percentage change in International Normalised Ratio (INR) measured between screening visit 2 and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Percentage Change (Test Units: Ratio)				
arithmetic mean (full range (min-max))	-0.32 (-11.11 to 11.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Model for End Stage Liver Disease (MELD)

End point title	Model for End Stage Liver Disease (MELD)

End point description:

The Model for End Stage Liver Disease (MELD) is a summary demographic of component parts:

creatinine (umol/L), bilirubin (umol/L), and international normalised ratio (INR).

Percentage change in MELD score is calculated as: (MELD (visit 10) - MELD (screening visit 2))/MELD (screening visit 2).

End point type	Secondary

End point timeframe:

Percentage change in Model for End Stage Liver Disease (MELD) score measured between screening visit 2 and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	20[16]			
Units: Percentage Change (Test Unit:MELD Score)				
arithmetic mean (full range (min-max))	-1.58 (-30 to 83.33)			

Notes:

[16] - Data pertinent to this outcome was missing for two patients.

Statistical analyses

No statistical analyses for this end point

Secondary: Mayo PSC Risk Score

End point title	Mayo PSC Risk Score

End point description:

Percentage change in Mayo PSC Risk Score) score is calculated as: (Mayo PSC Risk Score(visit 10) - Mayo PSC Risk Score(screening visit 2))/Mayo PSC Risk Score(screening visit 2).

End point type	Secondary

End point timeframe:

Percentage change in Mayo PSC Risk Score measured between screening visit 2 and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	20[17]			
Units: Percentage Change (Test Unit:Risk Score)				
arithmetic mean (full range (min-max))	0.38 (-91.38 to 390.16)			

Notes:

[17] - Data pertinent to this outcome was missing for two patients.

Statistical analyses

No statistical analyses for this end point

Secondary: PK Data

End point title	PK Data

End point description:

For all PK data measurements, the percentage change in blood serum is calculated as: (PK (visit 10) - PK (visit 3))/PK (visit 3).

End point type	Secondary

End point timeframe:

Percentage change in PK data in blood serum measured between visit 3 (the first treatment visit) and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	0[18]			
Units: Percentage Change				
arithmetic mean (full range (min-max))	(to)			

Notes:

[18] - Data pertinent to this outcome was unavailable at the time of preparation of this report.

Statistical analyses

No statistical analyses for this end point

Secondary: LiverMultiscan MRI Imaging

End point title	LiverMultiscan MRI Imaging

End point description:

Percentage change in LiverMultiscan MRI Imaging scoree is calculated as: (LiverMultiscan (visit 11) - LiverMultiscan (screening visit 2))/LiverMultiscan (screening visit 2).

End point type	Secondary

End point timeframe:

Percentage change in LiverMultiscan MRI Imaging score measured between screening visit 2 and visit 11 (the second follow-up visit).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	0[19]			
Units: Percentage Change				
arithmetic mean (full range (min-max))	(to)			

Notes:

[19] - Data pertinent to this outcome was unavailable at the time of preparation of this report.

Statistical analyses

No statistical analyses for this end point

Secondary: s-VAP1/SSAO Biomarker

End point title	s-VAP1/SSAO Biomarker

End point description:

Percentage change in s-VAP1/SSAO Biomarker is calculated as: (s-VAP1/SSAO(visit 10) - s-VAP1/SSAO(visit 3))/s-VAP1/SSAO(screening visit 3).

End point type	Secondary

End point timeframe:

Percentage change in s-VAP1/SSAO Biomarker measured between visit 3 (the first treatment visit) and visit 10 (the first follow-up visit, day 99).

End point values	BTT1023			
Subject group type	Reporting group			
Number of subjects analysed	0[20]			
Units: Percentage Change				
arithmetic mean (full range (min-max))	(to)			

Notes:

[20] - Data pertinent to this outcome was unavailable at the time of preparation of this report.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe: Date of consent, (Visit 1: screening) and continued until the final follow-up visit (Visit 11: day 120), or alternatively up to 45 days post last drug infusion if the patient withdrew from the trial prior to completion of all 7 drug infusions.

Adverse event reporting additional description:

Adverse Events (AEs) were reported on an AE form and returned to the Trials Office. AE's were reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4. SAE forms were faxed to the Trials Office; seriousness and causality were determined independently by a by a Clinical Coordinator.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	BTT1023- All patients

Reporting group description:

All patients registered on the trial.

Serious adverse events	BTT1023- All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 23 (17.39%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Infusion related reaction			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			

subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	BTT1023- All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 23 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	8 / 23 (34.78%)		
occurrences (all)	14		
Surgical and medical procedures			
Other: Insertion of artificial urinary sphincter			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Localized edema			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Aching chest, right side of			

body				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Bilateral rash to arms where cannula dressings were placed				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	2			
Other: Cold, cough and tickly throat				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Emotional				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Hay fever				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Infusion reaction				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Intermittent bursitis left shoulder				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Intermittent pharyngeal fascitis				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Left side groin pain during infusion				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Night sweats				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Pain in left shoulder / back /hip				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Right shoulder pain				

subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Sluggish/Aching			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Flu like symptoms			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	3		
Infusion related reaction			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	10 / 23 (43.48%)		
occurrences (all)	20		
Chills			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Other: Intermittent phlegm sitting in throat			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Mild inspiratory wheeze on right middle lobe chest			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Asthma			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	4 / 23 (17.39%)		
occurrences (all)	6		
Sore throat			

subjects affected / exposed	4 / 23 (17.39%)		
occurrences (all)	4		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Investigations			
Blood corticotrophin decreased			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Aspartate transaminase decreased			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Bilirubin increased			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Calcium decreased			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: CRP increased			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Estimated Glomerular Filtration Rate decreased			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Ferritin increased			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Haemoglobin decreased			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	2		
Other: Hypercholestraemia			

subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Hypoalbuminemia				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Indirect bilirubin increased				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Non significant raised QTC left ventricular hypertrophy				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Phosphates decreased				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Platelets increased				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	4			
Other: Reduced Ferritin levels				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Sodium decreased				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: C-reactive protein increased				
subjects affected / exposed	2 / 23 (8.70%)			
occurrences (all)	2			
Other: Urea increased				
subjects affected / exposed	2 / 23 (8.70%)			
occurrences (all)	3			
Other: APTT decreased				
subjects affected / exposed	3 / 23 (13.04%)			
occurrences (all)	4			
Other: Direct bilirubin increased				
subjects affected / exposed	3 / 23 (13.04%)			
occurrences (all)	5			

Activated partial thromboplastin time prolonged				
subjects affected / exposed	5 / 23 (21.74%)			
occurrences (all)	9			
White blood cell decreased				
subjects affected / exposed	6 / 23 (26.09%)			
occurrences (all)	25			
Other: Urea decreased				
subjects affected / exposed	7 / 23 (30.43%)			
occurrences (all)	21			
Platelet count decreased				
subjects affected / exposed	8 / 23 (34.78%)			
occurrences (all)	18			
Other: Creatinine decreased				
subjects affected / exposed	11 / 23 (47.83%)			
occurrences (all)	29			
Blood bilirubin increased				
subjects affected / exposed	14 / 23 (60.87%)			
occurrences (all)	59			
Lymphocyte count decreased				
subjects affected / exposed	16 / 23 (69.57%)			
occurrences (all)	92			
Alanine aminotransferase increased				
subjects affected / exposed	21 / 23 (91.30%)			
occurrences (all)	59			
Aspartate aminotransferase increased				
subjects affected / exposed	21 / 23 (91.30%)			
occurrences (all)	71			
Alkaline phosphatase increased				
subjects affected / exposed	22 / 23 (95.65%)			
occurrences (all)	49			
GGT increased				
subjects affected / exposed	22 / 23 (95.65%)			
occurrences (all)	50			
Other: Monocytes increased				

subjects affected / exposed	4 / 23 (17.39%)			
occurrences (all)	10			
Other: Monocytes decreased				
subjects affected / exposed	13 / 23 (56.52%)			
occurrences (all)	43			
Other: Mean cell volume increased				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences (all)	1			
Other: Basophils decreased				
subjects affected / exposed	2 / 23 (8.70%)			
occurrences (all)	6			
Other: Mean cell haemoglobin increased				
subjects affected / exposed	2 / 23 (8.70%)			
occurrences (all)	2			
Other: Red blood cell increased				
subjects affected / exposed	2 / 23 (8.70%)			
occurrences (all)	4			
Other: White blood cell increased				
subjects affected / exposed	2 / 23 (8.70%)			
occurrences (all)	7			
Other: Total protein decreased				
subjects affected / exposed	2 / 23 (8.70%)			
occurrences (all)	8			
Other: Neutrophils decreased				
subjects affected / exposed	2 / 23 (8.70%)			
occurrences (all)	6			
Other: Mean cell volume decreased				
subjects affected / exposed	3 / 23 (13.04%)			
occurrences (all)	4			
Other: Eosinophils decreased				
subjects affected / exposed	4 / 23 (17.39%)			
occurrences (all)	25			
Other: INR decreased				
subjects affected / exposed	4 / 23 (17.39%)			
occurrences (all)	5			

Other: Red blood cell count decreased			
subjects affected / exposed	4 / 23 (17.39%)		
occurrences (all)	12		
Other: Mean cell haemoglobin decreased			
subjects affected / exposed	5 / 23 (21.74%)		
occurrences (all)	6		
Other: Red blood cell distribution width increased			
subjects affected / exposed	5 / 23 (21.74%)		
occurrences (all)	14		
Other: Eosinophils increased			
subjects affected / exposed	6 / 23 (26.09%)		
occurrences (all)	26		
Other: Total protein increased			
subjects affected / exposed	10 / 23 (43.48%)		
occurrences (all)	19		
Other: Neutrophils increased			
subjects affected / exposed	12 / 23 (52.17%)		
occurrences (all)	30		
Other: Red blood cells decreased			
subjects affected / exposed	14 / 23 (60.87%)		
occurrences (all)	27		
Other: Haematocrit decreased			
subjects affected / exposed	17 / 23 (73.91%)		
occurrences (all)	44		
Injury, poisoning and procedural complications			
Wrist fracture			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Cardiac disorders			
Other: Borderline prolonged OT interval			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Borderline QTc on ECG			

subjects affected / exposed occurrences (all) Other: Hypotension subjects affected / exposed occurrences (all) Other: Low grade hypertension subjects affected / exposed occurrences (all) Other: Sinus rhythm- abnormal ECG subjects affected / exposed occurrences (all) Sinus bradycardia subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1 1 / 23 (4.35%) 1 1 / 23 (4.35%) 4 1 / 23 (4.35%) 1 2 / 23 (8.70%) 2		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Other: Diplopia in all directions subjects affected / exposed occurrences (all) Presyncope subjects affected / exposed occurrences (all)	 1 / 23 (4.35%) 1 1 / 23 (4.35%) 1 1 / 23 (4.35%) 1 2 / 23 (8.70%) 2		
Blood and lymphatic system disorders Leukocytosis subjects affected / exposed occurrences (all) Anemia subjects affected / exposed occurrences (all)	 2 / 23 (8.70%) 6 17 / 23 (73.91%) 44		
Eye disorders			

Other: allergic retinitis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Gastrointestinal disorders			
Anal pain			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Gastrointestinal pain			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: 4 columns of varices seen. The columns of varix seem to become bigger at 35cm. Grade 3			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Barrett's Oesophagus			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Increased stool frequency due to pouchitis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Intermittent tenesmus			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Loss of appetite			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Mouth ulcer			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Oesophageal Candidiasis			

subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Portal hypertensive gastropathy			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Spider naevi			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Ulcerative colitis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	4 / 23 (17.39%)		
occurrences (all)	4		
Abdominal pain			
subjects affected / exposed	5 / 23 (21.74%)		
occurrences (all)	7		
Colitis			
subjects affected / exposed	5 / 23 (21.74%)		
occurrences (all)	5		
Other: Loose bloody stools x2			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Hepatobiliary disorders			
Other: Cholangitis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Chronic liver failure requiring pre-emptive liver transplantation			

subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Mild hepatomegaly			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Right upper quadrant pain			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Hepatomegaly			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Other: Chronic Venous eczema on both lower limbs			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Creatinine decreased			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Dry mouth			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Itchy chest			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Itchy scalp			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Mild foliculitis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Psoriasis on legs and hands			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Rash on forehead			

subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Redness around umbilicus			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Removal of Viral wart on left ankle			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Right side of head above ear, insect bite with swelling and discharge			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Sensitive skin over varicose vein on calves			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Sunburn			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Vitiligo eczema			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	10 / 23 (43.48%)		
occurrences (all)	14		
Other: Poriasis			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Endocrine disorders			

Hyperthyroidism subjects affected / exposed occurrences (all) Hypothyroidism subjects affected / exposed occurrences (all) Other: Type I diabetes subjects affected / exposed occurrences (all)	 1 / 23 (4.35%) 2 1 / 23 (4.35%) 1 1 / 23 (4.35%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Chest wall pain subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all) Other: Osteoarthritic nodes in fingers on of the right hand subjects affected / exposed occurrences (all) Other: Osteoathritis subjects affected / exposed occurrences (all) Other: Polyarthralgia subjects affected / exposed occurrences (all) Other: Swelling of both hands subjects affected / exposed occurrences (all) Other: Vertebral haemangioma subjects affected / exposed occurrences (all) Other: Worsening right knee pain	 1 / 23 (4.35%) 1 1 / 23 (4.35%) 1 1 / 23 (4.35%) 2 1 / 23 (4.35%) 1 1 / 23 (4.35%) 1 1 / 23 (4.35%) 1 1 / 23 (4.35%) 1 1 / 23 (4.35%) 1		

subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	5 / 23 (21.74%)		
occurrences (all)	8		
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	3		
Gallbladder infection			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Viral infection			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Wound infection			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Upper respiratory infection			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hypercalcemia			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	4		
Hypernatremia			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Other: Vitamin D Deficiency			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Hyperglycemia			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Hypokalemia			

subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	8		
Hyponatremia			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	4		
Hypocalcemia			
subjects affected / exposed	4 / 23 (17.39%)		
occurrences (all)	12		
Hypoalbuminemia			
subjects affected / exposed	5 / 23 (21.74%)		
occurrences (all)	37		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 March 2015	This amendment contained: - Changes to Section 7.6.1 – wording updated to prevent additional samples being taken - Grammatical errors and line spacing errors corrected
27 November 2015	This amendment contained: - Updates to contact details throughout the protocol - Trial inclusion and exclusion criteria updated and clarified - Screening period reduced to 6-8 weeks - Schedule of Events updated: 1) Enhanced Liver Fibrosis (ELF) test included as a research sample; 2) Central alkaline phosphatase (ALP) tests included for Visits 3-11; 3) Tests for Anti-Drug Antibodies (ADA) and Pharmacodynamics (PD) and Quality of Life (QoL) assessment not performed at Screening Visits 1 & 2 and 4) Clarification of MRI Scans - Inclusion of Screening Number and addition of Section 7.11- Contraception and Pregnancy
16 March 2016	This amendment contained: - Clarification of inclusion criteria; ALP value reduced from >2 x ULN to >1.5 x ULN - Pre-medications updated to include hydrocortisone at Visits 3-5 - Section 8.1.2 "Hypersensitivity, Infusion Reactions and Infusion Related Reactions" added - Additional telephone number for Trial Office added throughout the protocol
27 March 2018	Clarification of inclusion criteria; minimum patient's weight criteria added and validity of colonoscopy results altered from within 1 year to within the patient's standard of care. Timing of interim analysis clarified - Information added regarding Acorda, Biotie's parent company and correction of grammatical errors.
31 July 2018	This amendment concerns the change of Chief Investigator and Trial Coordinator. Change in Data Protection Regulations, updated text regarding GDPR.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This report fulfills the criteria and structure for EudraCT. A full analysis and study publication are being processed to better express the results for dissemination.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28674140