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BUTEO: a clinical trial of BTT1023 in patients with primary sclerosing cholangitis (PSC)

Submission date
11/03/2015

Recruitment status
No longer recruiting

Registration date
11/03/2015

Overall study status
Completed

Last Edited
25/04/2023

Condition category
Digestive System

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Current plain English summary as of 12/02/2019:
Background and study aims
Primary sclerosing cholangitis (PSC) is an uncommon autoimmune chronic liver disease in which the bile ducts of the liver reduce in size over time as a result of inflammation and scarring (fibrosis). It often occurs in patients that have an inflammatory disease of the colon, for example, ulcerative colitis. Bile ducts are tubes which take bile (a liquid produced by the liver) to the intestines. Bile is like as detergent breaking up fat from the food we eat into small droplets that can then be absorbed into the body. It also allows us to absorb vitamins A, D, E and K from our diet. In people suffering from PSC, bile that is normally carried by these ducts builds up within the liver. This blockage to bile flow results in damage to liver cells, leading to inflammation and scarring. Over time, this scarring can affect the whole liver. The liver does have regenerative abilities and can usually re-grow without scarring when damaged. However, in PSC, this healing process does not work properly. A combination of scar tissue and irregular re-growth of the liver can lead eventually to cirrhosis. There are, at present, no treatments for patients with PSC and most patients with symptomatic disease eventually need a liver transplant. This study tests whether the antibody, BTT1023, which targets a protein involved in inflammation and scarring, is safe as well as effective in the treatment of PSC. BTT1023 targets a protein called VAP-1 and this enzyme has been studied in many autoimmune diseases including PSC, where studies show it to be important. PSC is diagnosed by MRI scans usually but blood tests can be used to follow the disease, including in particular elevations in one particular marker of bile duct inflammation, alkaline phosphatase (ALP). The aim of this study is to see whether the study drug can be given safely to patients diagnosed with PSC and whether it reduces inflammation and scarring.

Who can participate?
Adults aged 18-75 diagnosed with PSC

What does the study involve?
Participants undergo an initial screening process to see whether they can take part in the study, involving two visits over a period of 8 weeks. They are then given 7 infusions of the BTT1023 drug over a period of 11 weeks. Participants are followed up though 2 visits over a 6 week period. Blood tests and scans are used to see whether the drug is working.

What are the possible benefits and risks of participating?
The study is intended to see whether this new drug can reduce the level of inflammation and scarring in the liver. If so, this could potentially slow down liver damage. Possible risks of this study include side effects from the drug, the drug not being effective, and the drug dose being too low. If the TB blood test (tested for as part of screening) indicates TB exposure, then a follow-up chest x-ray is recommended, which involves a very small dose of x-rays equivalent to a few days of background radiation in the UK. The risk from this dose is negligible. BTT1023 has previously been used in studies involving patients with rheumatoid arthritis and with psoriasis. To date no major safety concern has been seen and participants are monitored carefully throughout the study.

Where is the study run from?
1. Queen Elizabeth Hospital (UK)
2. John Radcliffe Hospital (UK)
3. Queens Medical Centre (UK)
4. Royal Victoria Infirmary (UK)
5. Addenbrooke's Hospital, Cambridge (UK)
6. Royal Free Hospital, London (UK)

When is the study starting and how long is it expected to run for?
February 2015 to October 2018

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Anna Rowe

Previous plain English summary:
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February 2015 to February 2018

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Anna Rowe

Contact information

Type(s)
Scientific

Contact name
Ms Anna Rowe

Contact details
I-ACT Team,
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Birmingham
United Kingdom
B15 2TH

Additional identifiers

EudraCT/CTIS number
2014-002393-37

IRAS number

ClinicalTrials.gov number
NCT02239211

Secondary identifying numbers
Version 5; 18051

Study information

Scientific Title
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 (VAP1), in the treatment of patients with primary sclerosing cholangitis (PSC)

Acronym
BUTEO

Study objectives
The aim of this trial is to assess whether the antibody, BTT1023, which targets a protein involved in inflammation and scarring, is safe as well as effective in the treatment of primary sclerosing cholangitis (PSC).

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee East Midlands - Derby, 06/01/2015, ref: 14/EM/1272

Study design
Non-randomised; Interventional; Design type: Not specified, Treatment

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Primary sclerosing cholangitis

Interventions
Current interventions as of 12/02/2019:
BTT1023 will be given to patients using intravenous infusion. With informed consent, patients who have been diagnosed with PSC and whose ALP is elevated, will be eligible to be screened to take part in the study. The trial will be conducted at 6 hospital sites in England and lasts approximately 25 weeks from the first day of screening through to the last follow up visit. The screening phase involves 2 visits over an 8 week period. The treatment phase of the trial lasts for 11 weeks and includes 7 infusions of the BTT1023 study drug. Blood tests and scans will be used to see if the drug is working.

Previous interventions:
BTT1023 will be given to patients using intravenous infusion. With informed consent, patients who have been diagnosed with PSC and whose ALP is elevated, will be eligible to be screened to take part in the study. The trial will be conducted at 3 hospital sites in England and lasts approximately 25 weeks from the first day of screening through to the last follow up visit. The screening phase involves 2 visits over an 8 week period. The treatment phase of the trial lasts for 11 weeks and includes 7 infusions of the BTT1023 study drug. Blood tests and scans will be used to see if the drug is working.

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
BTT1023

Primary outcome measure
Current primary outcome measures as of 22/03/2017:
Reduction in serum alkaline phosphatase (ALP) by 25% or more from baseline to Day 99

Previous primary outcome measures:
Alkaline phosphatase; Timepoint(s): Week 12

Secondary outcome measures
Current secondary outcome measures as of 22/03/2017:
1. Safety and tolerability: treatment compliance (including patient withdrawal) and Serious Adverse Event (SAE) and Adverse Event (AE) frequency
2. Any change (improvement or worsening) from baseline to Day 99 in:
2.1. Quality of life questionnaires: EQ-5D, Fatigue Severity Scale, Pruritus Visual Analogue Score (VAS), Inflammatory Bowel Disease (IBD) Diaries (if applicable)

2.2. Tests of liver fibrosis: enhanced liver fibrosis (ELF) and Fibroscan
2.3. Individual markers of liver biochemistry and function (aspartate transaminase [AST], alanine transaminase [ALT], ALP, gamma glutamyl transferase [GGT], bilirubin, albumin, International Normalised Ratio [INR]) and composite risk scores (Mayo PSC Risk score and model for end-stage liver disease [MELD] score)
2.4. Liver disease assessed using LiverMultiscan® MRI imaging
3. Changes in sVAP-1/SSAO as a biomarker of liver disease activity across the study period

Previous secondary outcome measures:
Safety; Timepoint(s): Throughout, week 1 to week 12

Overall study start date
01/02/2015

Completion date
23/10/2019

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 12/02/2019:
1. Males and females 18 - 75 years of age who are willing and able to provide informed, written consent and comply with all study requirements
2. Clinical diagnosis of PSC as evident by chronic cholestasis of more than six months duration with either a consistent MRI showing sclerosing cholangitis or a liver biopsy consistent with PSC in the absence of a documented alternative aetiology for sclerosing cholangitis
3. In those with concomitant Inflammatory Bowel Disease, clinical and colonoscopic evidence within the last year of stable disease, without findings of high grade dysplasia
4. In those on treatment with ursodeoxycholic acid (UDCA), therapy must be stable for at least 3 months and at a dose not greater than 20mg/kg/day. In those not on treatment with UDCA at the time of screening, a minimum of 8 weeks since the last dose of UDCA should be recorded
5. Serum ALP greater than 1.5 x upper limit of normal (ULN)
6. Stable serum ALP levels (levels must not change by more than 25% from Screening Visit 1 and Screening Visit 2)
7. Female subjects of childbearing potential must have a negative pregnancy test prior to starting study treatment. For the purposes of this study, a female subject of childbearing potential is a woman who has not had a hysterectomy, bilateral oophorectomy, or medically-documented ovarian failure. Women ≤ 50 years of age with amenorrhea of any duration will be considered to be of childbearing potential
8. All sexually active women of childbearing potential must agree to use two forms of highly effective method of contraception from the Screening Visit throughout the study period and for 99 days following the last dose of study drug. If using hormonal agents the same method must have been used for at least 1 month before study dosing and subjects must use a barrier method as the other form of contraception. Lactating women must agree to discontinue breast feeding before study investigational medicinal product administration
9. Men, if not vasectomised, must agree to use barrier contraception (condom plus spermicide) during heterosexual intercourse from screening through to study completion and for 99 days from the last dose of study investigational medicinal product
10. Patients must weigh ≥ 40kg

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1. Males and females 18 - 75 years of age who are willing and able to provide informed, written consent and comply with all study requirements
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3. In those with concomitant Inflammatory Bowel Disease, clinical and colonoscopic evidence within the last year of stable disease, without findings of high grade dysplasia
4. In those on treatment with ursodeoxycholic acid (UDCA), therapy must be stable for at least 8 weeks and at a dose not greater than 20mg/kg/day. In those not on treatment with UDCA at the time of screening, a minimum of 8 weeks since the last dose of UDCA should be recorded
5. Serum ALP greater than 1.5 x upper limit of normal (ULN)
6. Stable serum ALP levels (levels must not change by more than 25% from Screening Visit 1 and Screening Visit 2)
7. Female subjects of childbearing potential must have a negative pregnancy test prior to starting study treatment. For the purposes of this study, a female subject of childbearing potential is a woman who has not had a hysterectomy, bilateral oophorectomy, or medically-documented ovarian failure. Women ≤ 50 years of age with amenorrhea of any duration will be considered to be of childbearing potential
8. All sexually active women of childbearing potential must agree to use two forms of highly effective method of contraception from the Screening Visit throughout the study period and for 99 days following the last dose of study drug. If using hormonal agents the same method must have been used for at least 1 month before study dosing and subjects must use a barrier method as the other form of contraception. Lactating women must agree to discontinue breast feeding before study investigational medicinal product administration
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Original inclusion criteria:
1. Males and females 18-75 years of age who are willing and able to provide informed, written consent and comply with all study requirements
2. Clinical diagnosis of PSC as evident by chronic cholestasis of more than six months duration with either a consistent MRI showing sclerosing cholangitis or a liver biopsy consistent with PSC in the absence of a documented alternative aetiology for sclerosing cholangitis
3. In those with concomitant inflammatory bowel disease, clinical and colonoscopic evidence within the last year of stable disease, without dysplasia
4. In those on treatment with Ursodeoxycholic acid (UDCA), therapy must be stable for at least 3 months, and at a dose not greater than 20mg/kg/day
5. Serum ALP greater than 2xULN
6. Female subjects of childbearing potential must have a negative serum pregnancy test prior to starting study treatment. For the purposes of this study, a female subject of childbearing potential is a woman who has not had a hysterectomy, bilateral oophorectomy, or medically-documented ovarian failure. Women = 50 years of age with
amenorrhea of any duration will be considered to be of childbearing potential
7. All sexually active women of childbearing potential must agree to use a highly effective method of contraception from the Screening Visit throughout the study period and for 105 days following the last dose of study drug. If using hormonal agents the same method must have been used for at least 1 month before study dosing and subjects must use a barrier method as the other form of contraception. Lactating women must agree to discontinue nursing before study investigational medicinal product administration
8. Men, if not vasectomized, must agree to use barrier contraception (condom plus spermicide)

during heterosexual intercourse from screening through to study completion and for 105 days from the last dose of study investigational medicinal product

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
75 Years

Sex
Both

Target number of participants
Planned Sample Size: 59; UK Sample Size: 59

Total final enrolment
23

Key exclusion criteria
Current participant exclusion criteria as of 12/02/2019:
1. Presence of documented secondary sclerosing cholangitis on prior clinical investigations.
2. Presence of alternative causes of liver disease, that are considered by the Investigator to be the predominant active liver injury at the time of screening, including viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis. Patients with possible overlap syndrome with autoimmune hepatitis are excluded if the Investigator considers autoimmune hepatitis as the predominant liver injury.
3. AST and ALT >10 x ULN or bilirubin >3 x ULN or INR >1.3 in the absence of anti-coagulants
4. Serum creatinine >130µmol/L or platelet count <50 x 109/L
5. Any evidence of hepatic decompensation past or present, including ascites, episodes of hepatic encephalopathy or variceal bleeding
6. Recent cholangitis within last 90 days or ongoing need for prophylactic antibiotics
7. Pregnancy or breast feeding
8. Harmful alcohol consumption as evaluated by the Investigator
9. Flare in colitis activity within last 90 days requiring intensification of therapy beyond baseline maintenance treatment; use of oral prednisolone >10mg/day, biologics (i.e. monoclonal antibodies) and or hospitalisation for colitis within 90 days. Prior use of biologics is not a contraindication to screening
10. Diagnosed cholangiocarcinoma or high clinical suspicion of cholangiocarcinoma either clinically or by imaging
11. Concurrent malignancies or invasive cancers diagnosed within past 3 years except for adequately treated basal cell and squamous cell carcinoma of the skin and in situ carcinoma of the uterine cervix
12. Presence of a percutaneous drain or bile duct stent
13. Major surgical procedure within 30 days of screening
14. Prior organ transplantation

15. Known hypersensitivity to the investigational product or any of its formulation excipients
16. Unavailable for follow-up assessment or concern for subject's compliance
17. Participation in an investigational trial of a drug or device within 60 days of screening or 5 half-lives of the last dose of investigational drug, where the study drug half-life is greater than 12 days
18. Any other condition that in the opinion of the Investigator renders the subject a poor risk for inclusion into the study
19. Positive screening test for tuberculosis (TB) (including T-SPOT.TB TB test), unless respiratory review confirms false positive test results
20. Receipt of live vaccination within 6 weeks prior to screening visit 2
21. Known HIV positive status

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20. Receipt of live vaccination within 6 weeks prior to baseline visit
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3. AST and ALT > 10 x ULN or Bilirubin >3xULN or INR>1.3 in the absence of anti-coagulants.
4. Serum creatinine >130µmol/L or Platelet count <50x109/L.
5. Any evidence of hepatic decompensation past or present, including ascites, episodes of hepatic encephalopathy, variceal bleeding.
6. Recent cholangitis within last 90 days or ongoing need for prophylactic antibiotics.
7. Pregnancy or breast feeding.
8. Harmful alcohol consumption as evaluated by the investigator.
9. Flare in colitis activity within last 90 days requiring intensification of therapy beyond baseline maintenance treatment; use of oral prednisolone >10mg/day, biologics and or hospitalisation for colitis within 90 days.
10. Diagnosed cholangiocarcinoma or high clinical suspicion over dominant stricture.
11. Active malignancy (within 3 years of diagnosis), other than non-melanomatous skin cancer.
12. Presence of a percutaneous drain or bile duct stent.
13. Major surgical procedure within 30 days of screening or prior organ transplantation;
14. Known hypersensitivity to the investigational product or any of its formulation excipients; inability to receive simple anti-inflammatory
agents' peri-infusion.
15. Unavailable for follow-up assessment or concern for subject's compliance.
16. Participation in an investigational trial of a drug or device within 60 days of screening or 5 half-lives of the last dose of investigational drug, where the study drug half-life is greater than 12 days.
17. Any other condition that in the opinion of the investigator renders the subject a poor risk for inclusion into the study.
18. Positive screening test for tuberculosis (including T-SPOT.TB TB test), unless respiratory review confirms false positive test results
19. Receipt of live vaccination within 6 weeks prior to baseline visit

Date of first enrolment
02/04/2015

Date of final enrolment
19/06/2018

Locations

Countries of recruitment
England

United Kingdom

Study participating centre

Queen Elizabeth Hospital
Birmingham
United Kingdom
B15 2TH

Study participating centre
John Radcliffe Hospital
Oxford
United Kingdom
OX3 9DU

Study participating centre
Queens Medical Centre
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Royal Victoria Infirmary
Newcastle
United Kingdom
NE1 4LP

Study participating centre
Addenbrooke's Hospital
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Royal Free Hospital
London
United Kingdom
NW3 2QG

Sponsor information

Organisation
University of Birmingham

Sponsor details
Edgbaston
Birmingham
England
United Kingdom
B15 2TT

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The trialists plan on submitting the results of the trial to a high impact peer reviewed journal within 1 year of the overall trial end date. The local investigators will be notified when the results are published. If a patient wishes to be contacted with the results, the Investigators will be able to relay the information in an easily comprehensible form.

Intention to publish date
01/02/2020

Individual participant data (IPD) sharing plan
The current data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	03/07/2017		Yes	No
Basic results	EudraCt results	01/02/2020	03/08/2021	No	No
Results article		01/03/2022	25/04/2023	Yes	No
HRA research summary			28/06/2023	No	No