Supplementary Material 2

Participants Inclusion and Exclusion Criteria

Participants

D.1.1 Inclusion Criteria

1. Males and females 18-75 years of age who were willing and able to provide written informed consent and comply with all trial 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 IBD, clinical and colonoscopic evidence (in line with the patient's standard of care; within 18 months) 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 20 mg/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 trial treatment. For the purposes of this trial, a female subject of childbearing potential was defined as a woman who had not had a hysterectomy, bilateral oophorectomy, or medically-documented ovarian failure. Women $\leq$ 50 years of age with amenorrhea of any duration would be considered to be of childbearing potential,
8. All sexually active women of childbearing potential must have agreed to use two forms of highly effective method of contraception from the Screening Visit throughout the trial period and for 99 days following the last dose of trial drug. If using hormonal agents the same method must have been used for at least 1 month before trial dosing and subjects must use a barrier method as the other form of contraception. Lactating women must have agreed to discontinue breast feeding before trial investigational medicinal product (IMP) administration,
9. Men, if not vasectomised, must have agreed to use barrier contraception (condom plus spermicide) during

heterosexual intercourse from screening through to trial completion and for 99 days from the last dose of trial IMP,

10. Patients weight ≥ 40 kg.

D.1.2 Exclusion Criteria

1. Presence of documented secondary sclerosing cholangitis on prior clinical investigations,
2. Presence of alternative causes of liver disease, that were 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 were excluded if the Investigator considered autoimmune hepatitis as the predominant liver injury,
3. Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) >10 x ULN or bilirubin >3 x ULN or International normalized ratio (INR) >1.3 in the absence of anti-coagulants,
4. Serum creatinine > $130 \mu mol/L$ or platelet count < $50 \times 10^9/L$,
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 >10 mg/day, biologics (i.e. monoclonal antibodies) and or hospitalisation for colitis within 90 days. Prior use of biologics was 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 trial drug half-life is greater than 12 days,
18. Any other condition which in the opinion of the Investigator renders the subject a poor risk for inclusion into the trial,
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 human immunodeficiency virus (HIV) positive status.

D.1.3 Withdrawal Criteria

Participants had the right to withdraw from the trial at any time for any reason. For patients that discontinued trial treatment or declined further participation, final assessments were performed. Results of the evaluations and observations, together with a description of the reasons for trial withdrawal were recorded on the Withdrawal Form. All patients continued to be followed-up (if they agreed), and all information and tissue samples were collected until the point of retraction and analysed. Patients removed from trial treatment due to adverse events (clinical or laboratory) were treated and followed up according to local medical practice. All pertinent information concerning the outcome of such treatment was recorded on the Withdrawal Form.

The following were justifiable reasons for the Investigator to withdraw a patient from the trial:

- Unacceptable toxicity,
- Unforeseen events: any event which in the judgement of the Investigator made further treatment inadvisable,
- Serious Adverse Event (SAE) requiring discontinuation of treatment,
- Withdrawal of consent,

- Serious violation of the trial protocol (including persistent patient attendance failure and persistent non-compliance),
- Withdrawal by the Investigator for clinical reasons not related to the trial treatment.

D.1.4 Setting

Data were collected in the clinical sites and entered onto a trial-specific database.

D.1.5 Screening and recruitment process

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.

Patients were invited to participate in the BUTEO trial from seven 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-Sept-2015 and 19-Jun-2018.

D.1.6 Concomitant Medication

All medication that each patient was taking at the time, or within 3 months of enrolment were recorded on case report forms (CRFs). New medications or changes to current medications during the trial were also recorded. The pharmaceutical/trade name, dose, route of administration, indication, start/stop date of each new medication within the trial was also recorded. Any drug that was licensed within the United Kingdom and Europe, that was deemed necessary for the patient's health-care, was permitted at the discretion of the Chief Investigator (CI).

Prohibited medications included:

- Biological drugs (i.e. monoclonal antibodies) other than the IMP,
- Initiation during the trial period of any therapy that has the potential to change serum ALP, e.g. high dose steroids, methotrexate, fenofibrate, UDCA or related agents,
- In those patients receiving UDCA in compliance with the inclusion criteria, changes in UDCA dosage are

  not permitted during the trial period,
- Live vaccinations in the six weeks prior to Baseline Visit 2 (this is an inclusion criteria) through to six weeks after the last BTT1023 infusion.