Pharmacy Manual

Trial Title:	PRedicting Outcomes For Crohn's dIsease using a moLecular biomarkEr (PROFILE) trial
EudraCT Number:	N/A (non-CTIMP study)
ISRCTN:	11808228
REC Reference:	17/EE/0382
IRAS ID:	220851
Design of Trial:	Randomised, multi-centre, biomarker-stratified, open-label trial in patients newly diagnosed with Crohn's disease
Date Commenced:	December 2017

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Co-ordinating Centre:	Cambridge Clinical Trials Unit, Box 401, Coton House, Addenbrooke's Hospital, Cambridge, CB2 0QQ. Tel: 01223 254 666

ABBREVIATIONS

PTM	Pharmacy trial manual
TC	Trial coordinator
SmPC	Summary of Product Characteristics

TRIAL OUTLINE

Purpose: To demonstrate that a whole blood prognostic biomarker can be used at diagnosis to facilitate the delivery of appropriately personalised therapy in Crohn's disease, and that this improves clinical outcomes.

Primary objective: To demonstrate that a whole blood prognostic biomarker can improve outcomes by facilitating the delivery of personalised therapy from diagnosis in Crohn's disease.

Secondary objectives: To demonstrate that a whole blood prognostic biomarker can improve quality of life and health resource allocation by enabling appropriately personalised therapy to be initiated at diagnosis in Crohn's disease.

Recruitment: 400 participants.

Trial treatment: Corticosteroids. Infliximab and one of the following immunomodulatory medications; Azathioprine OR 6-Mercaptopurine and Allopurinol OR Methotrexate and Folic acid. Adalimumab.

Contact information

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Tel: 01223 254 666 (direct).

Trial pharmacist may be contacted (normal on-site working hours Tues-Fri):lynne.Whitehead@addenbrookes.nhs.uk
Tel: 01223 216 057 (direct); 01223 217 045 (pharmacy trials office).

Change control history

Date	Version	Change Description	Reason for change
11/01/18	V2.0	Section 1, 2.1, 2.2, 4.3, 5, 8, & 10.3	For clarity
09/01/18	V3.0	Section 2.1, 2.2 ,5.1, 5.2, 8, and 12.	Use of Prednisolone broadend to corticosteroids as per protocol V4.0 Update email address in appendix
09/07/20	V4.0	Section 2.1, 4, 6, 8	Removed instances of reducing in front of steroids, updated distributor name, clarified use of Adalimumab, updated screening window, in line with protocol 4.2
16/11/20	V4.1	Appendices	Updated order form to include another email address.

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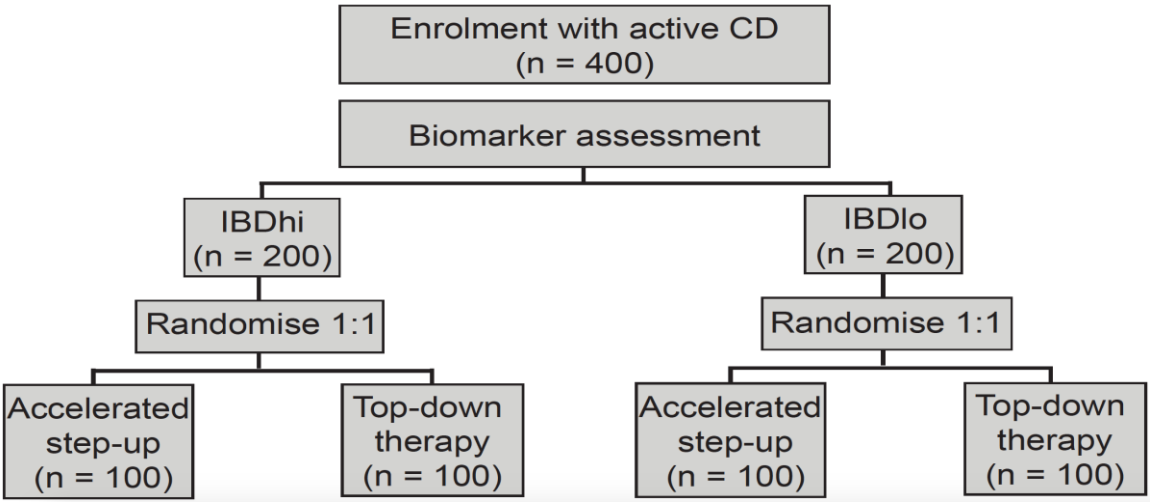
1 TRIAL SYNOPSIS



2 PHARMACY MANUAL SUMMARY

2.1 Description of study treatment regimen for each arm

"Top-Down" therapy

• 8 week course of corticosteroids started at screening. The rate of weaning should be accelerated once Infliximab is commenced.

• Anti-TNFα Infliximab started 2 weeks (±7 days) after randomisation and one of the following immunomodulatory medications: Azathioprine OR 6-Mercaptopurine and Allopurinol OR Methotrexate. Combination therapy should be used unless otherwise clinically indicated. In such instances, monotherapy with anti-TNF agent can be given following approval from the Chief Investigator.

• Disease flares: 8 week course of corticosteroids

"Accelerated Step-Up" therapy

• 8 week course of corticosteroids started at screening.

• Flare 1: 12 week course of corticosteroids and one of the following options: Azathioprine OR 6-Mercaptopurine and Allopurinol OR Methotrexate.

• Flare 2: Add in Infliximab. Combination therapy should be used unless otherwise clinically indicated. In such instances, monotherapy with anti-TNF agent can be given following approval from the Chief Investigator.

• Flare 3+: 8 week course of corticosteroids.

Oral vitamin D and calcium replacement to be prescribed as per local hospital guidelines, whilst participants on all regimen of corticosteroids.

2.2 Pharmacy resources

PROFILE is an open-label, outpatient study, requiring secondary care patient-specific dispensing of Infliximab, corticosteroids and supportive care as applicable*, over approximately 48 weeks per patient. Maintenance prescription and monitoring for immunomodulator medication such as Azathioprine will follow local practice and guidelines, including shared care guidelines. Out of hours dispensing is not required for this trial.

* Supportive care i.e. Vitamin D & Calcium is not limited to secondary care

3 PHARMACY ACTIVATION

The following must be completed/be in place prior to site activation:

- REC approval.
- HRA Approval.
- Research & Development (R&D) and other local approvals as applicable.
- Signed Participating Site Agreement.
- Site initiation visit.

A Pharmacy Site File will not be provided by Sponsor.

4 INFLIXIMAB

4.1 Key points

Infliximab (Remsima) 100mg vials will be supplied free-of-charge to participating sites as standard commercial stock (single vial in a carton 8.8 cm high x 5 cm wide x 5 cm deep) via OTC Direct Ltd, using a trial-specific PIP code.

See protocol for dosing information and supportive treatments. The study permits a maximum of 9 infliximab dispensings per patient: all treatment reverts to locally managed and funded pathways after the completion of the week 48 study visit.

Trial specific prescriptions and labelling are not a Sponsor requirement: sites may use to ensure appropriate use of trial stock if preferred.

Dose rounding as per local practice is permitted.

Preparation and administration of the Infliximab should follow each site's policies and procedures. Vial sharing (e.g. for sites utilising CIVAS services) is permitted if required, providing the number of vials used for PROFILE patients can be accurately reconciled and does not exceed the quantity that would be required if preparing doses individually.

No formal trial accountability is required but sites must have a procedure that demonstrates that infliximab usage for PROFILE participants reconciles accurately with orders received. Inventory/accountability logs are available upon request for use by sites opting for ring-fencing and trial-specific dispensing.

4.2 Ordering information

4.2.1 Initial shipment

When a new site is opened to recruitment, the TC will notify OTC Direct Ltd to authorise release of free of charge Infliximab to the named site; **the site will need to submit the initial order themselves.**

Remsima should be ordered by email using the order form in Appendix 1, localised with site details and contacts, and copying in the TC. Orders received before 12 noon on a working day, will be dispatched the next working day.

If a site requires orders to be made via the Trust centralised procurement system, the TC should be contacted to discuss. The ordering PIP code for PROFILE Remsima is **6838312**.

4.2.2 Subsequent orders

After the initial shipment of Infliximab, it is the site pharmacy's responsibility to maintain adequate stocks of Remsima, using ordering procedure as above. Sites should use recruited patient records to ensure that significant excess stock does not remain at site after all patients have recruited treatment. Sites should aim to be ordering stock no more frequently than monthly if local storage permits and should discuss with the TC if this is not possible.

4.3 Shipment & receipt at sites

Infliximab will be shipped by OTC Direct Ltd at 2-8°C using standard wholesaler approved supply chain, alongside non-trial hospital supplies as appropriate, with delivery documentation (copy of order form) referencing the PROFILE study and named site trial pharmacy staff. There is no trial-specific temperature monitoring process during transit. The Infliximab must be checked, acknowledged and moved to appropriately temperature controlled conditions immediately upon receipt by the site. The shipping documentation supplied must be checked and stored in the pharmacy.

Following receipt checks, Infliximab judged suitable for use should be added to the local inventory as appropriate and placed into appropriately controlled and monitored storage, to which only appropriately trained and authorised pharmacy staff have access (for example, to prevent PROFILE Remsima being used as part of non-trial hospital supplies).

In the event of damage to PROFILE Remsima at receipt, the product must be segregated and quarantined. The TC should then be contacted for further advice.

5 ALL OTHER STUDY MEDICATIONS (EXCEPT ADALIMUMAB)

5.1 Prescription charges and pre-payment certificate

- Oral medications should be prescribed and dispensed as per usual local protocols, including GP shared care arrangements, where relevant (e.g. for

thiopurine prescription and blood test monitoring).* Arrangements for safety monitoring blood tests must be clearly defined as per standard local protocols.

In order to manage prescription costs if required, a 12-month prescription Pre-Payment Certificate application form should be completed at the screening visit, for patients who would otherwise be liable for prescription charges, and submitted to the local finance office for authorisation (cost for 2019/20 is £105.90). Only if patient is subsequently randomised, then this form should be submitted immediately after the randomisation visit and can be backdated, to ensure reimbursement of medications dispensed at the screening visit if required (providing appropriate receipts can be presented).

For the initial 8 week course of corticosteroids (with bone protection medication as per local practice), local trials pharmacists may be willing to dispense this and directly invoice your local finance department for the prescription costs. Failing this, participants should be reimbursed for this initial medication cost from the travel expenses budget per participant, pending prescription Pre-Payment Certificate being organised.

*Sites utilising third party pharmacy services for Outpatients may be used.

5.2 Additional oral medication information

For corticosteroids, Azathioprine, 6-Mercaptopurine and Allopurinol, Methotrexate and Folic acid - see protocol for dosing information and other supportive treatments.

- Trial specific prescriptions and labelling are not a Sponsor requirement but may be used if local practice requires.
- Dose rounding/alternate day dosing as per formulation strengths available to best achieve protocol dose is permitted as local practice allows.
- Any UK-licensed preparation supplied from participating site may be used, ordered via standard procurement route, no trial-specific requirements.
- No formal trial accountability required: to follow local practice.
- All local safety procedures to be followed including adherence to local GP shared care guidelines.

6 ADALIMUMAB

If participants are either severely intolerant of Infliximab, experience persistent, mild intolerance despite a slower infusion rate and pre-treatment as per local practice, or develop anti-Infliximab antibodies, then they can be switched onto Adalimumab only after discussion with the Chief Investigator.

Once approved by CI, standard hospital process should be followed for dispensing and supply of drug.

Reimbursement for the cost of Adalimumab should be invoiced directly to Cambridge Hospitals NHS Foundation trust via the TC.

7 STORAGE & MONITORING REQUIREMENTS

All medications should be stored as per SmPC as per locally approved temperature monitoring procedures.

It is the responsibility of the site pharmacy to ensure there is a quarantine procedure in place following local policies and procedures.

Temperature excursions during storage should follow local policies and procedures with regard to continuing suitability of medicines for use.

It is the responsibility of the site pharmacy that to ensure it can respond to any Competent Authority or manufacturer-led recall for study medications used in PROFILE, to patient-level if required.

8 SCREENING/RANDOMISATION

There will be 2 weeks (+10 days) between screening and the baseline/randomisation visit. All patients at screening will be prescribed corticosteroids. For patients in the "Top-Down" arm the first Infliximab treatment visit will be 2 weeks (+/-7 days) after the baseline/randomisation visit. Randomisation and baseline assessments may be performed on the same day.

As each participant enters screening, the study team will manually assign a sequential study ID number (three numbers), which will also identify the site using four proceeding alphanumerics (e.g. xxxx-xxx).

If the participant is eligible and proceeds to randomisation, this will be performed by the local Investigator or delegated research staff via the Sealed Envelope web based system provided by the CCTU (instructions in the randomisation system user manual). Automatic notification of randomisations will be sent to the local site pharmacy, a person(s) from the local site pharmacy must be delegated the role to receive these emails and supply the system admin (TC) the appropriate details so an account can be set up. The web based randomisation notification should be filed in the Pharmacy site file to enable checking of treatment arm allocated.

The web based system does not control aspects of Infliximab distribution or expiry date management for this trial.

9 MONITORING

There will be no routine pharmacy monitoring unless triggered by Sponsor. The TC will maintain records of PROFILE Remsima orders against numbers of patients recruited at site and treatment allocation assigned.

The pharmacy may be requested to send scanned copies of inventory and/or Drug Accountability Logs (or other documentation demonstrating appropriate usage of Remsima if study accountability records not maintained) by email to the study monitor. There must be no personally identifiable information on any documentation sent to CCTU.

10 DRUG DESTRUCTION/DISPOSAL

Local drug destruction/disposal policy should be followed.

10.1 Returns

Returns to pharmacy are not required for accountability purposes.

10.2 Expired IMP

It is the responsibility of the site pharmacy to ensure that all medications used are within their expiry dates.

Sponsor permission for destruction of expired, unused PROFILE Remsima should be obtained prior to destruction, and stock should then be destroyed according to local policy and this recorded by means of a destruction/disposal certificate as appropriate.

10.3 Damaged or unsuitable due to temperature deviation

Medications which have become unusable due to a temperature deviation either during transit or storage at site should be destroyed according to local policy and recorded using a destruction/disposal certificate as appropriate.

11 REPORTS/CORRESPONDENCE

Please file any general correspondence regarding the PROFILE trial in the Investigator Site File.

12 Appendices

12.1 Order form

Trial name	***PROFILE***

Date of Request	/ /	Requestor	*[Delegated responsible for ordering]*
Site name	***[Site]***	Phone Number	
Site code		Email Address	

Investigator Name	*[PI NAME]*
Shipping Attention	*[Pharmacy Lead name]*
Shipping Address	*[Pharmacy Address 1]*
	[Pharmacy Address 2]
	[Pharmacy Address 3]
	[Pharmacy Address 4]
	[Pharmacy Address 5]
Shipping Phone Number	*[Pharmacy Phone Number]*
Shipping Fax Number	*[Pharmacy Fax Number]*

Medication	**Strength/ description**	**Quantity (number of vials)**
Infliximab (Remsima)	**One vial contains 100 mg of infliximab. After reconstitution each mL contains 10 mg of infliximab.**	

When completed, please email this form (stating "PROFILE Shipment Request<site name>" in message header to:

add-tr.profile@nhs.net
Sylwia.Karpinska@alliance-healthcare.co.uk
Amy_Dandridge@otc-direct-ltd.com
pfoulger@predictimmune.com
jlakin@predictimmune.com