

RE: PRINCIPLE - Addition of Inhaled Corticosteroid arm

McNaughton, Graham <Graham.McNaughton@mhra.gov.uk>

Mon 1/11/2021 16:40

To: Emma Ogburn <emma.ogburn@phc.ox.ac.uk>

Cc: Hannah Swayze <hannah.swayze@phc.ox.ac.uk>; Christopher Butler <christopher.butler@phc.ox.ac.uk>

Dear Emma,

The regulatory team has agreed to the 8 week extension to the use of PCCTU for labelling of budesonide.

However, they did express concerns that the use of PCCTU is in danger of becoming 'the norm.' Therefore, I reinforce that this really is a temporary measure and PCCTU should only be used for as long as is absolutely necessary. As soon as clinical services have been secured, labelling and QP release should switch to that site.

Kind regards,
Graham

Graham McNaughton PhD

Leading Senior Pharmaceutical Assessor

Clinical Trials Unit

Licensing Division

Medicines and Healthcare products Regulatory Agency

10 South Colonnade, Canary Wharf, London E14 4PU

Tel: +44 203 080 6148.

Email: graham.mcnaughton@mhra.gov.uk

The UK has left the EU, and the transition period ends on 31 December 2020. [Click here](#) to find out more.
If you have not done so, [please register now](#) for MHRA Submissions, so you are ready from 1 January 2021.

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More information can be found [here](#).

From: Emma Ogburn <emma.ogburn@phc.ox.ac.uk>

Sent: 08 January 2021 18:38

To: McNaughton, Graham <Graham.McNaughton@mhra.gov.uk>

Cc: Hannah Swayze <hannah.swayze@phc.ox.ac.uk>; Christopher Butler <christopher.butler@phc.ox.ac.uk>

Subject: RE: PRINCIPLE - Addition of Inhaled Corticosteroid arm

Great, thanks Graham.

Have a good weekend,

Emma

From: McNaughton, Graham <Graham.McNaughton@mhra.gov.uk>

Sent: 08 January 2021 17:20

To: Emma Ogburn <emma.ogburn@phc.ox.ac.uk>

Cc: Hannah Swayze <hannah.swayze@phc.ox.ac.uk>; Christopher Butler <christopher.butler@phc.ox.ac.uk>

Subject: RE: PRINCIPLE - Addition of Inhaled Corticosteroid arm

Thanks Emma,

I will take this to our regulatory group and get back to you ASAP.

Kind regards,
Graham

From: Emma Ogburn <emma.ogburn@phc.ox.ac.uk>
Sent: 08 January 2021 16:36
To: McNaughton, Graham <Graham.McNaughton@mhra.gov.uk>
Cc: Hannah Swayze <hannah.swayze@phc.ox.ac.uk>; Christopher Butler <christopher.butler@phc.ox.ac.uk>
Subject: RE: PRINCIPLE - Addition of Inhaled Corticosteroid arm

Hi Graham,

Thank you for this. I couldn't ascertain if Ringwood held a MIA for labelling so the clarification is really helpful!

I expect the PCCTU to need to label for a further 8 weeks – there are a few reasons as to why we haven't been able to secure clinical services to do this for us yet, namely:

Timelines – time taken to obtain a quote and clarify responsibilities and expectations, then a further delay with once agreed we would still have a further 6+ weeks to wait. Christmas, Brexit have also played a role in delays. We had also spent time with other clinical services such as Ringwood, in the hope that they could undertake this role at a quicker speed for us.

Funding and trial contractual agreements – the trial was initially given 6mths of funding which ended 30th Sep. Extension requests were submitted but only approved verbally just before Christmas. The University would have had to sign clinical service contracts in lieu of funds which carries a potential risk. We are still awaiting written confirmation of a costed extension.

Other trial arms closing –at the request of the TSC two were closed in fairly close succession, we now only have usual care and steroid arm open, this linked with increasing accruals means we have gone through the steroid at a faster rate than if we still had other drug arms open

The three new drug arms we hope to be open within weeks so our focus at present is to get these arms open – submission timelines:

Favipirivir – waiting for the Therapeutic Taskforce to confirm the supply route, they are looking to source with suppliers in the UK – trial submission package stalled until we know more. TTF wanted us to prioritise this drug.

Ivermectin – drug supply route confirmed, submission package nearly complete, will submit to Sponsor next week

Camostat – drug supply route confirmed, submission package in draft, if the documents are finalised and the Sponsor is happy to receive as one amendment (ivermectin and favi), we will

I hope this helps, happy to chat through anything,

BW
Emma

From: McNaughton, Graham <Graham.McNaughton@mhra.gov.uk>
Sent: 07 January 2021 19:59
To: Emma Ogburn <emma.ogburn@phc.ox.ac.uk>
Cc: Hannah Swayze <hannah.swayze@phc.ox.ac.uk>; Christopher Butler <christopher.butler@phc.ox.ac.uk>
Subject: RE: PRINCIPLE - Addition of Inhaled Corticosteroid arm

Dear Emma,

Happy New Year to you too!

I will have to take the proposal for extending the period during which PCCTU will label budesonide to our regulatory group for advice. I know they will ask some questions, so could you provide some additional information:

1. How much longer would you need PCCTU to label the budesonide?

2. What has caused the delay in securing clinical services?
3. What is the current status with securing clinical services?

Great to hear that the IMPs for the new arms will arrive ready to supply to patients. Do you have a timeline for the amendment submission?

Ringwood Pharmacy are **NOT** authorised to carry out clinical trial packaging, labelling and QP certification of IMPs. They are not carrying out this activity for any other clinical trials. They are involved in the supply chain but only have responsibility for storage and preparation of IMP (already labelled and QP certified) for shipping to patients. These are not considered to be manufacturing processes and do not need to be carried out under a MIA(IMP). Packaging, labelling and QP certification are manufacturing processes and require the site to hold a MIA(IMP). Ringwood Pharmacy do not hold a MIA(IMP).

Kind regards,
Graham

Graham McNaughton PhD

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From: Emma Ogburn <emma.ogburn@phc.ox.ac.uk>
Sent: 07 January 2021 13:56
To: McNaughton, Graham <Graham.McNaughton@mhra.gov.uk>
Cc: Hannah Swayze <hannah.swayze@phc.ox.ac.uk>; Christopher Butler <christopher.butler@phc.ox.ac.uk>
Subject: RE: PRINCIPLE - Addition of Inhaled Corticosteroid arm

Hi Graham,

Happy new year to you!

Currently in Principle, we only have two arms open – usual care and budesonide. I would like to ask for an extension for PCCTU to continue to label budesonide as we can procure the drug but we haven't yet been able to secure clinical services.

We are preparing a further amendment to include other drugs (favipirivir, ivermectin, camostat) which will come to the PCCTU packaged, labelled and QP released.

On another note, I understand that Ringwood Pharmacy have been given the greenlight to undertake such work? If you can, please can you confirm if this is correct?

Thanks for your help,
BW
Emma

Dr Emma Ogburn
CTU Director of Operations

Tel: 07710676303

E-mail: Emma.Ogburn@phc.ox.ac.uk

<http://www.phc.ox.ac.uk>



NUFFIELD DEPARTMENT OF
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From: McNaughton, Graham <Graham.McNaughton@mhra.gov.uk>

Sent: 12 November 2020 16:32

To: Christopher Butler <christopher.butler@phc.ox.ac.uk>

Cc: Hannah Swayze <hannah.swayze@phc.ox.ac.uk>; Emma Ogburn <emma.ogburn@phc.ox.ac.uk>

Subject: RE: PRINCIPLE - Addition of Inhaled Corticosteroid arm

Dear Chris,

The proposal for labelling to be performed at PCCTU for a short period of time (up to 8 weeks or until supplies labelled at Fisher Clinical Services become available, whichever is sooner) has been accepted. If there is a need for labelling to continue at PCCTU for longer than 8 weeks then you are asked to request additional approval from MHRA to cover such an extension.

My colleagues in the GCP inspectorate have also raised a question as to whether this labelling activity impacts on the insurance associated with the trial. This may be something you wish to review with the sponsor.

In terms of the amendment, I will approve the current submission on the basis that labelling will be carried out initially by PCCTU and then by Fisher. There is no need for you to change any of the documents now – I will include a copy of our email correspondence in our records so that it is clear what the supply chain is. However, when/if you submit a further amendment, please do confirm the supply chain arrangements for the ICS arm in the covering letter.

Kind regards,
Graham

Graham McNaughton PhD

Leading Senior Pharmaceutical Assessor

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From: Christopher Butler <christopher.butler@phc.ox.ac.uk>
Sent: 12 November 2020 11:22
To: McNaughton, Graham <Graham.McNaughton@mhra.gov.uk>
Cc: Hannah Swayze <hannah.swayze@phc.ox.ac.uk>; Emma Ogburn <emma.ogburn@phc.ox.ac.uk>
Subject: Re: PRINCIPLE - Addition of Inhaled Corticosteroid arm

Dear Graham,

This is good such news for the trial and indeed for my own personal morale!

Thank you so much for being so proactive on our behalf.

Best wishes

Chris

On 12 Nov 2020, at 11:17, McNaughton, Graham <Graham.McNaughton@mhra.gov.uk> wrote:

Dear Chris,

I have already made a request to colleagues to allow a similar flexibility to that used in the past (it's not a decision that I can make alone).

I understand the need for swift action on this so hope to have an answer for you by the end of the week, if not later today.

Kind regards,
Graham

Graham McNaughton PhD
Leading Senior Pharmaceutical Assessor
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From: Christopher Butler <christopher.butler@phc.ox.ac.uk>
Sent: 12 November 2020 10:06
To: McNaughton, Graham <Graham.McNaughton@mhra.gov.uk>
Cc: Hannah Swayze <hannah.swayze@phc.ox.ac.uk>; Emma Ogburn <emma.ogburn@phc.ox.ac.uk>
Subject: Re: PRINCIPLE - Addition of Inhaled Corticosteroid arm

Hi Graham,

Thank you Graham, that is clear.

The problem for us remains that we have a very narrow window during the current spike of this horrific pandemic to recruit into the Urgent Public Health Principle Trial in order to generate evidence that might help the many who will still suffer from the condition. Inhaled budesonide may be a really good intervention that helps people recover quicker, keeps them out of hospital, and protects their lungs: urgent trial answers are needed about the effectiveness of its use in community, where most patients are being treated and where early treatments could have major impact. Short term use of Inhaled Budesonide remains one of the safest medications there is.

Although an IMP in the context of this trial, it has been in widespread use for many many years, is already in wide use in primary care, and has virtually no interactions when used short term. Those already on an inhaled steroid will not be eligible to receive it. So while an IMP, as a licensed, well known and safe medication, it is not what I would call "experimental".

I hate to impose once again on your good offices, but could we therefore ask for an exemption that would allow me, personally, (qualified medical practitioner, Clinical Trials Unit Director) to start labelling an initial batch of the budesonide turboshalers myself, so we can start this arm of the trial while Fisher then labels the rest? It takes them a month to six weeks for Fisher to do this labelling, by which time we will have missed a key opportunity to recruit into the trial? We are all working on borrowed time and this 'second wave' came sooner and harsher than we anticipated.

As before, I will do the labelling myself in a properly controlled room where no other medication is being labelled. I will only label the medication we receive from the company. Each box will be closed with a package insert in it. I will not repackage. I will sign the log for each individual pack I label. It cannot get mixed up with the systems we have! A qualified nurse, also in attendance, managing the locked room, locked cabinets, temperature controls, log storage, etc. (I can do this for my own patients in my own practice in the Cynon Valley!) Each pack will be then also checked by a qualified pharmacist and signed off by them, before any items are issued to a trial participant.

Such an exemption would allow us to get going during this narrow window for recruitment, and carries virtually zero, if not zero risk; this process has been tried tested before and has worked very well with complete safety and rigour. Because of the distributed nature of primary care, we are at a disadvantage compared to pragmatic hospital trials that also are evaluating already licensed drugs, in that it seems hospital pharmacies can issue such medication more easily. It is in primary care where we can have the greatest reach and impact if we can proceed at pace, albeit safely!

Many thanks for considering,

Chris
Christopher C. Butler
BA MBChB DCH CCH MD FRCGP FFPH(Hon) FMedSci

Professor of Primary Care
Professorial Fellow, Trinity College
Clinical Director, Primary Care and Vaccines Collaborative Clinical Trials Unit
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01865 289670
christopher.butler@phc.ox.ac.uk

On 12 Nov 2020, at 08:23, McNaughton, Graham
<Graham.McNaughton@mhra.gov.uk> wrote:

Dear Chris,

I'm sorry to say that we cannot approve a supply chain that involves Ringwood Pharmacy carrying out clinical trial labelling. Clinical trial labelling is a manufacturing process and must be carried out at a site that holds a manufacturer's authorisation for investigational medicinal products, such as Fisher Clinical Services. After labelling, the IMP is required to be QP released for use in the trial. These are not activities that Ringwood Pharmacy is authorised to conduct.

Kind regards,
Graham

Graham McNaughton PhD

Leading Senior Pharmaceutical Assessor
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From: Christopher Butler <christopher.butler@phc.ox.ac.uk>
Sent: 11 November 2020 21:28
To: McNaughton, Graham <Graham.McNaughton@mhra.gov.uk>
Cc: Hannah Swayze <hannah.swayze@phc.ox.ac.uk>; Emma Ogburn <emma.ogburn@phc.ox.ac.uk>
Subject: Re: PRINCIPLE - Addition of Inhaled Corticosteroid arm

Dear Graham,

Many thanks.

Our proposal is for Ringwood Pharmacy to order the budesonide (pulmicort) turbobhalers direct from Astra Zeneca, label the units with an MHRA approved label, then to deliver the units to our Clinical Trials Unit for us to deliver directly to study participants according to the stated randomisation process. If so approved, Ringwood Pharmacy, would procure the devices QP released from AZ, label them, and then deliver them to us. Ringwood Pharmacy will provide a far more rapid and cost-efficient service. So you are correct that Ringwood would not be involved in manufacturing, merely labelling and transporting.

Happy to chat on the phone too tomorrow (Thursday) if that will be helpful.

My mobile number is 07944060594

With thanks and best wishes

Chris

Christopher C. Butler
BA MBChB DCH CCH MD FRCGP FFPH(Hon) FMedSci

Professor of Primary Care
Professorial Fellow, Trinity College
Clinical Director, Primary Care and Vaccines Collaborative Clinical Trials Unit
Clinical Director, NIHR Oxford Community Healthcare Medtech and Invitro diagnostics Co-operative
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Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Road,
Oxford OX2 6GG
01865 289670
christopher.butler@phc.ox.ac.uk

On 11 Nov 2020, at 18:06, McNaughton, Graham
<Graham.McNaughton@mhra.gov.uk> wrote:

Dear Chris,

I'm in the process of reviewing the latest substantial amendment for this trial and just wanted to confirm the supply chain for the Pulmicort Turbobhalers. Am I correct in thinking that clinical trial labelling and QP release will be performed by Fisher Clinical Services UK Limited and then the supplies sent to Ringwood Pharmacy for distribution to trial participants?

AstraZeneca UK Limited and Ringwood Pharmacy are both listed in the CTA application form as having manufacturing responsibilities but, from previous conversations we have had, I don't believe that to be the case (distribution is not considered to be a manufacturing process for IMPs). Please could you provide clarification? Happy to discuss by phone if that is easier.

Kind regards,
Graham

Graham McNaughton PhD

Leading Senior Pharmaceutical Assessor

Clinical Trials Unit

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