



Refractory Asthma
Stratification Programme

August 2020

Breathe Deep: Issue 8

Welcome to the eighth issue of the Refractory Asthma Stratification Programme (RASP-UK) newsletter!

Save the date for the 2020 General Assembly Meeting - Inside

Inside:

- Activities and highlights since the 2019 General Assembly
- Feedback from the MRC Precision Medicines Group
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Welcome to the sixth Refractory Asthma Stratification Programme - UK Newsletter

by **Gabrielle Gainsborough, Consortium Manager**

Welcome to the latest issue of our RASP-UK newsletter. All of our core studies have now completed their patient phase and our work strand teams are busy analysing this data. We are working hard to get our knowledge management platform established as well as working with our partners to analyse our bio-banked samples. Some of our plans have been impacted by the COVID-19 pandemic but we are aiming to deliver more results in 2020. **We hope to share the top-line data from the WS4 MEX and MAPLE studies with you via an on-line meeting on 27 August 2020.**



We hope you enjoy this newsletter. As always, we would be delighted to hear from you if you would like to share any relevant news with the consortium through this newsletter or if you have any suggestions or comments on the RASP-UK programme. You may even like to contribute a short article. So please get in touch with me, Gabrielle Gainsborough, at Niche Science & Technology Ltd.
gabrielle.gainsborough@niche.org.uk

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Work-strand 1

Biostratification manuscript

By **Tim Hardman**
Managing Director
Niche Science & Technology Ltd.



Data from our biostratification study became available as 2019 drew to a close. Although the data demonstrated that we had not met our primary endpoint for the Intention-to-Treat population, our pre-specified Per-Protocol analysis, which excluded potentially confounding data from participants who couldn't (for one reason or another) follow the protocol, was positive and consistent with our pre-study assumptions. In addition, it was clear from further analysis of patients who could follow the protocol that those who reduced treatment according to biomarker directed therapy showed no evidence of clinical deterioration, despite being on lower corticosteroid doses.

As we started to begin to draft a manuscript to describe our findings a debate arose over where we might publish our work. We suspected that our failure to achieve a clear statistically significant outcome for our primary endpoint would mean our first choice journal for publication, Lancet, would not be interested in the manuscript. However, the Executive Management Team were certain that the questions behind the biostratification study remained valid and the findings are very likely to impact on future treatment paradigms for patients suffering with severe asthma. The team felt that the work's importance was similarly reflected in the level of UK Medical Research Council support and that from pharmaceutical companies within our consortium.

We were aware that the GSK sponsored CAPTAIN (Clinical study of Asthma Patients receiving Triple therapy through A single INhaler) study evaluating combined fluticasone furoate, umeclidinium and vilanterol in patients whose asthma is inadequately controlled, was also close to reporting and that the findings of the two studies complemented each other and could be combined to provide even greater insight into the management of severe asthma. Essentially, the CAPTAIN study supported the use of a biomarker of corticosteroid response (blood eosinophil count) to identify benefit from high dose inhaled corticosteroids, whereas we had clearly demonstrated the challenges in trying to reduce corticosteroid dose using a wider panel of biomarkers.

After discussions with the CAPTAIN team it was decided that the best chance for publication in the Lancet would be to make a paired submission so that both findings would be reported together in the same issue. The submission was made in April this year.

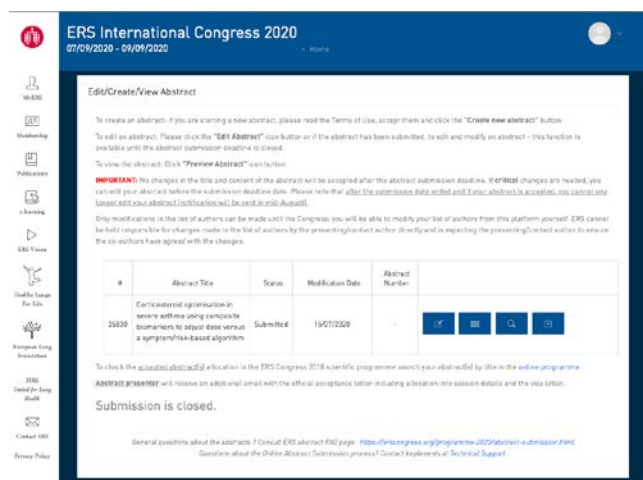


Work-strand 1 (cont.)

Biostratification manuscript

In our letter to the editor we noted how we believe that taken together the data from these two studies would create a paradigm shift in the clinical approach to asthma treatment that would inform future international treatment guidelines. The overriding message we wanted to give was that once established on high dose treatment, biomarker driven dose reduction is challenging in symptomatic patients and prior to progression to high dose inhaled and systemic corticosteroid treatment, predictive biomarkers of therapeutic response should be assessed and used to guide clinical decisions. We also noted that our observations are likely to prove useful in the specific patient population on maintenance systemic corticosteroids, assisting clinicians with decisions relating to the suitability of patients for biologics after additional rescue steroids.

It had originally been decided by the Leadership Team not to send an abstract to this years European Respiratory Society (ERS) meeting as we had been focusing on the manuscript. However, ERS introduced an extended deadline for RCT trials. After consideration it was decided that as we are in limbo waiting for Lancet's decision we would submit an abstract after all. The restrictions for the abstract were pretty tight (1810 characters). But we turned around, approved and submitted a succinct summary in just 3 days.



In the intervening time we received a rejection from the Lancet. However, our submission was kindly passed on to Lancet Respiratory Medicine (LRM). Fortunately, Emma Grainger recognized the importance of our two studies and was eager to offer the opportunity to transfer our submission to LRM if we could respond to the Lancet reviewer's comments appropriately. The comments were minor, even complementary in several places. CAPTAIN suffered the same fate and we now head towards LRM together.

Following on from the positive response from Dr Grainger we were asked to put forward our submissions for the ALERT sessions at the ERS virtual conference - as you might imagine this represents a very generous recognition of our work. To be able to qualify we needed to provide our corrected version of the manuscript with our responses to the reviewers to LRM within 5 days, which we did. This was a titanic task, generating a 19-page response letter. Over half of the comments from the reviewers were statistical in nature, we also had a couple of typos and changes to table headings. The actual 'changes' to the manuscript were minimal and we don't expect they will generate any controversy. Hopefully, we will hear shortly whether referees feel we have provided an adequate set of responses.

Update on work strand progress

Work-strand 1 INCA-SUN adherence intervention study

By Joanne Walsh, Research Nurse

The INCA Sun Study is a multicentre, prospective, randomized controlled study in uncontrolled asthma. We finished recruitment in February 2020, totalling 220 participants from 10 sites within Ireland and the United Kingdom. We have an overall attrition rate of 9.1%. A breakdown of the figures per site and our attrition rate can be seen below. The study timelines are still on schedule with the last patient, last visit planned for September 2020. Data cleaning is ongoing and will continue until October 2020 with database lock scheduled for November 2020.

Site	Recruited at site	Completed	Yet to complete	Withdrew from study
Beaumont Public	103	88	8	7
Beaumont Private	32	28	2	2
Cork	25	16	4	5
Connolly	20	17	3	0
Belfast	12	9	0	3
SVUH	8	8	0	0
Craigavon	6	3	2	1
Drogheda	5	2	2	1
Cavan	4	1	3	0
Guys & St. Thomas	3	0	2	1
Altnagelvin	2	0	2	0

As with many active research studies, the COVID-19 pandemic has had a significant impact on the INCA Sun Study. Our study population is adults with moderate to severe asthma, which means they are considered 'at risk' by governments in Ireland and the United Kingdom. Our participants are required to attend for visits monthly throughout the study. As we are a large multi-site trial, we had to act fast to issue guidance and put measures in place for the safety of our participants and our study teams. We issued guidance to all our sites mid-March with instructions for conducting visits as per government guidelines to ensure optimal safety. With the evolving nature of the pandemic, we revisited our guidance as further Public Health instructions were issued. The current measures we have in place are that all study visits are being conducted via phone. Study inhalers are collected via courier and returned to the research centre. Inhalers are dispensed in blocks of 3 months to participants to reduce frequency of contact. We have increased our communication and support with all sites. All visits are discussed case by case ensuring arrangements made suit local policy at all research sites and the participants.

For updates on the latest INCA technology news follow us on twitter: @INCA_team or visit our website: <http://www.incadevice.com/>



Update on work strand progress (cont.)

Work-strand 1: Biostratification Study

By Dr Avril Horn,
Work- Strand 1 Project Manager



It is 13 months since the last patient completed their final visit in the biostratification study. The results were presented in December, and were a testament to all of the work that had gone in to the study by patients and study staff.

Since December, the Niche team has worked with everyone on site to ensure that the study has been closed out appropriately. All of the biomarker samples have been accounted for, and plans are now underway to have these analysed with other consortium collaborators. All of the Niox VEROs have been transferred to those sites that have continued involvement in other studies in the RASP programme.

Thank you for your assistance when we were on site and for last minute requests for copies of documents. Hopefully you've all now seen a copy of the Clinical Study Report which was circulated on 30 Jun 20. We will be transferring the Trial Master File to QUB in the next couple of months, circumstances permitting.

Update on sample analysis

In parallel to the analyses of the clinical database we are busy with plans to analyse the 'omics' samples collected during the Biostratification study and the wider programme. We are working with our colleagues at Amgen to analyse the RNA samples from the WS1 Biostratification and the WS4 MEX studies. We've had some delays as a result of COVID but it is hoped that the data from the Biostratification study samples will be available in October 2020, with the MEX sample data following sometime in early 2021.

We have established a new collaboration with a group at the Karolinska Institute in Sweden. Sven-Erik Dahlen who was part of the UBIOPRED consortium will analyse the urine samples from both the WS1 Biostratification and WS4 MEX studies. Our aim is to quantify the eicosanoid metabolites as well as non-targeted urinary metabolomics in these urine samples. We expect to have preliminary results from the WS1 Biostratification study samples in Q3 2021 and for MEX in Q4 2021.

Finally we are working with other consortium partners to establish plans for the analysis of the remaining samples. We hope to update you later in the year as our plans evolve. Most of the ongoing work was pre-specified as part of our application to the MRC. We will have some samples left in storage and the RASP-UK EMT are happy to consider proposal for suggested analyses of these samples.

Update on work strand progress (cont.)

Work-strand 2: Bronchoscopy Study

By Peter Bradding, Work-Strand 2 Lead and Bev Hargadon,
Clinical Manager, NIHR Leicester Biomedical Research Centre

Recruitment was completed on 31 Oct 19. Bronchoscopies have been performed on 53 patients, with 52 providing biopsy samples for the primary outcome. We will also have data from a Leicester-Genentech study examining the effect of inhaled corticosteroids on the airway transcriptome in healthy volunteers, which will provide information about the confounding effect of corticosteroids on airway gene expression in asthma, and potentially allow a more accurate analysis of the abnormalities linked to severe asthma and relative corticosteroid resistance.

While our final numbers are below the original targets, we still have sufficient for analysis, in unique cohorts of patients. Activities to finalise the database have been delayed by the impact of the COVID-19 pandemic however the team hopes to have this completed in the next few weeks.



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Work Strand 3 The Study of Mechanisms of Action of Omalizumab in Severe Asthma

By Ratko Djukanovic,
SoMOSA Chief Investigator/Work Strand 3 Lead
and, SoMOSA Project Manager



SoMOSA is now fully delivered. The final study report was sent to Novartis on schedule!! Although the PGD2 metabolite in urine, the primary outcomes on the basis of which power calculation was done, was not predictive of clinical response to Omalizumab, we have identified many biomarkers that change differently in Omalizumab responders. Since omics biomarkers were predefined co-primary outcomes with the PGD2 metabolite, the study was a success!

The manuscript in which we want to sharing our findings with the scientific and clinical communities is underway. You will soon be receiving a request to list the colleagues who have been involved in SoMOSA so that they can be acknowledged. There will of course be much opportunity to discuss the manuscript.

Once again, I wish to thank you all for engaging so enthusiastically in the SoMOSA study, the first to explore in such depth the mechanisms whereby Omalizumab, or indeed any biological for asthma, works. Many thanks also to Novartis for trusting us to deliver and to add to the understanding of how this biologic works.

Update on work strand progress (cont.)

Work-strand 4 Progress Update

**Rekha Chaudhuri, WS4 Lead and
Jane McDowell, Clinical Research Fellow**

MEX - Inflammatory profile of Mepolizumab EXacerbations in participants with severe refractory eosinophilic asthma (the MEX study).

Data analysis is well under way for the MEX study. This study explores the inflammatory profile and mechanisms of exacerbations in mepolizumab-treated patients and how these can be differentiated clinically.

When analysis is complete, the team will aim to present the data to the Consortium using an online platform. We have submitted a late breaker abstract for the ERS 2020 and are aiming for a manuscript submission in a respiratory journal in summer 2020.

Dr Freda Yang (Glasgow), Dr Sarah Diver (Leicester), Ms Katie Borg (Oxford), Dr Jane McDowell (Belfast). RASP WS4 fellows also include Dr Stephen Smith (Glasgow) and Dr Rahul Shrimanker (Oxford).



MAPLE – a study of the additional effect of 14 days high dose oral corticosteroid compared to placebo in patients established on mepolizumab therapy. In this study participants were randomised after being treated with mepolizumab for at least three months to receive two weeks of prednisolone and placebo in a crossover fashion.

Data cleaning is now complete and analysis is under way. Preliminary results will be discussed with the investigators in the coming weeks. The team has a late breaker abstract accepted for the ERS 2020 and is aiming for a manuscript submission in respiratory journal in winter 2020.

BenRex – a study of exacerbation events while on benralizumab treatment. This study will also collect data on outcomes and predictors of response with benralizumab treatment and a comparison of different assessment tools of asthma control and quality of life.

The study aims to enroll 150 patients across 14 sites and there are seven patients in the study. A further nine sites were being prepared to start when the study was placed on a recruitment hold as a result of the COVID-19 pandemic. The seven patients enrolled by Glasgow have been managed by converting to self-injection pens and collection of some of the data by phone calls. The team is closely monitoring the situation in the UK and hope to make some decisions over the next few weeks about re-starting recruitment.

Update on work strand progress (cont.)

Work-strand 1: Biostratification Study manuscript addendum

While waiting for the LRM the review process we recognise that Journal review times have increased slightly during the COVID pandemic. It is possible that our work will be expedited.

In the meantime we are carrying some additional analyses on the clinical data from the biomarker study.

1. Given the difference in ITT and PP analyses, we are performing some additional analyses using causal inference to try and add further robustness to our PP conclusions (see Hernan et al, N Engl J Med 2017; 377:1391-1398).
2. We are also interested in the behavioural aspects of decisions to follow (or not) treatment advisories in both arms of the study....this work has started and has produced some interesting preliminary outcomes.....more to follow.
3. We are also working to examine the exacerbation data within the study which will present an interesting comparisons with the MEX and BENREX datasets (see below WS4) – as well as further analyses to explore outcomes in patients with dissociated symptoms and biomarker profiles analysis.

Upcoming RASP events

- On-line meeting to share the top-line MEX and MAPLE data – 27 August 2020 SAVE THE DATE!
- Virtual ERS – 7-9 September 2020. We hope to have several abstracts at this meeting
- MRC Precision Medicines Review – November 2020
- RASP-UK 2020 General Assembly Meeting – 1 December 2020 SAVE THE DATE!
We hope to be able to welcome you all again to our general assembly meeting. We'll be keeping a close eye on how restrictions for face to face events are evolving and we'll be in touch in the autumn with more details.

RASP Website: The RASP-UK website holds copies of all relevant study documents through the secure login portal at <http://www.rasp.org.uk/>

If you would like to add any documents to the website or if you have and questions or comments on the website, please contact Gabrielle at Niche Science & Technology Ltd (gabrielle.gainsborough@niche.org.uk)

RASP on Twitter: Please follow us on twitter https://twitter.com/Br3ath3_Deep