Protocol:

A multicentre, OBSERVational, case control study to determine the efficacy and safety of Lumacaftor/Ivacaftor in patients with severe lung disease and Cystic Fibrosis

The OBSERVE CF Study

# Introduction

Treatment with Lumacaftor/Ivacaftor (LUM/IVA) for 24 weeks has been shown to improve FEV1 and reduce exacerbation frequency in subjects with CF who are homozygous for the F508del mutation of CFTR and have an FEV1 40-90% of predicted normal values 1. In this study cohort continuation of LUM/IVA treatment for 96 weeks further demonstrated that LUM/IVA reduced the annual rate of decline in FEV12.

In these clinical trials dyspnoea and chest tightness were commonly reported side effects and the symptoms in most cases were described as mild and transient1. It is not known if people with CF who have more severe lung disease (i.e. FEV1 <40% predicted) and who were ineligible for the clinical trials referred to above, experience either similar benefits or adverse symptoms when treated with LUM/IVA.

Access to LUM/IVA for people with CF (and who are homozygous for the F508del mutation) with severe lung disease (i.e. FEV1 <40% predicted) is now available in Australia via a compassionate program (CAP), though the efficacy and safety of the treatment in this group of patients remains unclear. Recent reports have raised concerns that LUM/IVA treatment in CF patients with severe lung disease leads to, at least transiently, a fall in lung function and a higher incidence of chest tightness. Clearly, in this group of patients any fall in lung function may be clinically serious. Further, up to 30% of patients receiving LUM/IVA discontinue treatment because of the persistence of respiratory adverse events associated with the treatment 3,4.

This study aims to add to emerging data on the safety and efficacy of LUM/IVA in people with CF who have severe lung disease.

# Aim

To determine the safety and efficacy of LUM/IVA in subjects >12 years of age with CF, homozygous for F508del mutation of CFTR and an FEV1<40% of predicted normal, by comparing those patients treated with LUM/IVA with a cohort of age and sex matched CF controls with another set of mutations that lead to severe CFTR dysfunction (belonging to Class I, II or III), with an FEV1<40%5.

# Outcomes

**Primary outcome**:

Number of exacerbations of CF lung disease requiring the use of intravenous antibiotics during a 12 month observation period. This will include all exacerbations treated with IV antibiotics, including hospitalisation and hospital in the home treatment.

**Secondary outcomes**:

* Mean rate of change in FEV1 percent predicted
* Mean rate of change in BMI and/or Z score
* Time to first exacerbation relative to treatment initiation
* Number of hospitalisation with a pulmonary exacerbation
* Number of IV antibiotic episodes delivered by hospital in the home service
* In addition we will compare the number of pulmonary exacerbations each group (intervention and control) have had, compared to the number of exacerbations they have had in the prior 12 months.
* Hospitalisations with any CF-related problems
* Death
* Lung transplantation
* Chest tightness or dyspnoea
* Discontinuation of treatment i.e. LUM/IVA
* Treatment emergent adverse events

Data Source

Patient data will be provided by 12 CF centres throughout Australia who have patients receiving LUM/IVA via CAP. At each site a pair i.e. LUM/IVA and a case matched control, of patients will constitute a data pair. Clinical data collected at sites in medical records as part of routine outpatient clinic attendances and in-patient hospitalisations over a 12 month period will constitute the source material. The number of data pairs per site will be determined by the number of patients receiving LUM/IVA via CAP at each specified site.

In reference to participants, the following criteria will apply:

**Inclusion criteria:**

* Cystic Fibrosis; defined by the presence of two mutations known to cause dysfunction in CFTR, aged greater than or equal to 12 years.
* LUM/IVA intervention arm, with be homozygous for Phe508del and have commenced treatment with LUM/IVA on the compassionate access programme. Participants will need to have commenced treatment prior to March 2017 to potentially have at least 12 months of data available.
* Control arm will be age and sex matched by the sites. Subjects will only be eligible if they have never received LUM/IVA or Ivacaftor alone or Tezecaftor/Ivacaftor. Subjects must have mutations in CFTR that will result in Class I or Class II dysfunction.
* Sufficient data to assess the frequency of exacerbations requiring the use of IV antibiotics over a period of at least 12 months treatment with LUM/IVA.

Sample size

Wainwright et al 1, found that 251 of 371 participants who received a placebo treatment exacerbated, compared to 152 of 369 participants who received LUM/IVA during the treatment period during a phase III placebo-controlled clinical study.

These data suggest that to assess for superiority with a binary outcome of exacerbation versus no exacerbation, 144 patients (i.e. 72 LUM/IVA recipients and 72 case-matched controls) will be required to provide a 90% chance of detecting, with significance at the 5% level, an increase in the primary outcome measure from 33% in the matched control group to 59% in the LUM/IVA group (no exacerbation).

Control cases: These will be people with a CFTR mutation that precipitates severe disease and who have not received LUM/IVA. Each control will be matched for sex, FEV1 (+/- 5%) and age (+/- 5 years for those aged >18 years or +/- 1 year those aged 12 to <18 years) to each LUM/IVA recipient. The period of review for controls will be that period from one annual review to the subsequent annual review assessment 12 months distant. If the latter annual review visit is missed, a clinical assessment nearest to their birthdate (the date on which annual reviews are routinely scheduled) will be utilised.

Data Capture

Retrospective clinical data will be sourced from patient medical records and entered into an excel data file at each participating site. Data will include:

* Date consent provided
* Site of origin
* ACFDR identifier
* CFTR genotype
* Date of birth
* Gender
* Date LUM/IVA start
* Date LUM/IVA discontinuation
* Report of chest tightness or dyspnoea (date, FEV1, duration, treatment)
* Treatment emergent adverse events
* Exacerbations during the 12 month observation period (requiring intravenous antibiotics, duration, FEV1 at start of exacerbation and end)
* Dates of hospitalisation for CF (requiring IV antibiotics)
* FEV1 % predicted (at baseline, 3, 6, and 12 months)
* Height (at baseline, 3, 6, and 12 months)
* Weight (at baseline, 3, 6, and 12 months)
* Lung transplantation date if applicable
* Baseline CF treatments: DNAse, hypertonic saline, Tobramycin, colistin, azithromycin
* CF-associated comorbidities: CF-related diabetes, liver cirrhosis, osteoporosis, symptomatic sinusitis, current ABPA

Participant Privacy

To preserve patient privacy study participants will be identified in the study data file by their Australian Cystic Fibrosis Data Registry (ACFDR) code. This ACFDR collates data derived from participating clinical sites and publishes an annual report to provide researchers with an overview of the health and demographics of the CF population in Australia. Participating clinical sites contribute data to the ACFDR and only the clinical site that enters clinical data into the register is able to identify a specific person by reference to a specific ACFDR code. It is not the intention of the investigators of this study (i.e. The OBSERVE CF study)to seek to identify any individual patient described by the data captured for the purposes of this study.

References

1. Wainwright CE, Elborn JS, Ramsey BW. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. N Engl J Med 2015;**373**(18):1783-4
2. Konstan MW, McKone EF, Moss RB, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. Lancet Respir Med 2017;**5**(2):107-18.
3. Popowicz N, Wood J, Tai A, et al. Immediate effects of lumacaftor/ivacaftor administration on lung function in patients with severe cystic fibrosis lung disease. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society 2017;**16**(3):392-94.
4. Hubert D, Chiron R, Camara B, et al. Real-life initiation of lumacaftor/ivacaftor combination in adults with cystic fibrosis homozygous for the Phe508del CFTR mutation and severe lung disease. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society 2017;**16**(3):388-91
5. Hull J. Cystic fibrosis transmembrane conductance regulator dysfunction and its treatment. J R Soc Med 2012;**105 Suppl 2**:S2-8.



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A multicentre, OBSERVational, case control study to determine the efficacy and safety of Lumacaftor/Ivacaftor in patients with severe lung disease and Cystic Fibrosis

The OBSERVE CF Study

This information form describes an observational clinical study that requests information from your medical record or, if you are the carer of a child aged 12 to less than 18 years, your child’s medical record. If you are the carer of a child who has CF and whose medical record is the subject of this request for consent please read either “your child”, “your child’s”, “their” or “they” as is appropriate where “you” or “your” is written below.

**INFORMATION FOR PARTICIPANTS**

This study aims to collect data to determine the safety and efficacy of Orkambi in people with CF who have severe lung disease. Anyone with CF with an FEV1 of less than 40% was not included in the world-wide clinical trials used to test the safety and efficacy of Orkambi. As a result we do not have much information on the impact of Orkambi in people with CF who have severe lung disease. That is, an FEV1 less than 40% predicted.

We would like to ask *your* permission to access data from your medical record that has been entered as part of your routine CF care over a 12 month period because you have an FEV1 of less than 40%. The information we are seeking will be that which describes your lung function (FEV1), the medications you used, what CF-related conditions you had (e.g. CF-related diabetes, sinusitis), the details of exacerbations you were hospitalised for and treatment of these episodes during the 12 month period. We will also retrieve from your medical record your height, weight, age and gender.

We are going to compare two groups of people with CF: those who have used Orkambi for 12 months via a compassionate access program and those who also have an FEV1 of less than 40% but who are not homozygous for deltaF508 and therefore not suitable to use Orkambi. You are being approached because you belong to one of these two groups of people.

**Who is doing this research?**

The study is being organised at the John Hunter Hospital/Hunter Medical Research Institute in Newcastle, NSW by Prof. Peter Wark (Respiratory Medicine John Hunter Hospital).

**Do you have to agree to be volunteer your medical information for this study?**

No. Participation in this study is entirely voluntary. You do not have to take part in it. If you do take part, you can withdraw at any time without having to give a reason. You can also ask that any data collected concerning you be withdrawn from the study. Note however, that if you choose to withdraw your consent and the researchers have included your data in a presentation made before the date of your request to withdraw your data will not be able to be retracted.

**What would you be asked to do if you agree to participate and are there any risks?**

You will not have to do anything and there are no risks. We are only collecting information that has been recorded during your routine CF treatment and outpatient clinic visits.

**How will your privacy be protected?**

Your Australian Cystic Fibrosis Data Registry (ACFDR) code will be used to label medical data that will be entered into an electronic data capture tool specific for this study. Only your doctor or clinic nurse who already know you and are aware of your clinical records will be able to link you with any data entered into the study data capture tool under this code. To anyone else who analyses or sees a presentation or publication of this data you will be unidentifiable and completely anonymous.

Further, any personal information that is accessed will be used and stored in accordance with Commonwealth Privacy Laws and any Privacy Act that applies in the state/territory in which you reside.

This information statement is for you to keep.

Thank you for considering this invitation.

Prof. Peter Wark

Senior Staff Specialist

Investigator

**Complaints about this research**

This research has been approved by the Hunter New England Human Research Ethics Committee of Hunter New England Local Health District, Reference [insert reference number when known].

Should you have concerns about your rights as a participant in this research, or you have a complaint about the manner in which the research is conducted, it may be given to the researcher, or, if an independent person is preferred, to Dr Nicole Gerrand, Manager, Research Ethics and Governance Unit, Hunter New England Human Research Ethics Committee, Hunter New England Local Health District, Locked Bag 1, New Lambton NSW 2305, telephone (02) 49214950, email Hnehrec@hnehealth.nsw.gov.au

**Consent Form**

|  |  |
| --- | --- |
| Short Title | The OBSERVE CF study. |
| Protocol Title | A multicentre, OBSERVational, case control study to determine the efficacy and safety of Lumacaftor/Ivacaftor in patients with severe lung disease and Cystic Fibrosis |
| HREC Reference |  |
| Coordinating Investigator | Professor Peter Wark |
| Location  |  |

**Declaration by Participant or Parent/Guardian**

* I have read the Participant Information Sheet or someone has read it to me in a language that I understand.
* I understand the purposes of the study and why the clinical data is being sought by the researchers.
* I give permission for my doctor to provide my clinical information to the investigators for the purposes of this study. I understand that such information will remain confidential.
* I have had an opportunity to ask questions and I am satisfied with the answers I have received.
* I freely agree to my participating in this research study as described and understand that I am free to withdraw at any time during the research study without affecting my future health care but also understand that my information may be unable to be withdrawn if it has been used in the presentation of study data in medical journals or at meetings before I notify the study doctor of my request to withdraw.
* I understand that I will be given a signed copy of this consent form to keep.

***Please print unless a signature is requested***

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| --- | --- | --- | --- |
|  |  |  |  |
|  | Name of Participant and/or Parent/Guardian  |  |  |
|  |  |  |  |
|  | Signature of Participant or Parent/Guardian |  | Date |  |  |
|  |

**Declaration by Study Doctor**

I have given a verbal explanation of the research study, its purposes, data sought and how privacy will be maintained and I believe that the participant or parent/guardian and child has understood that explanation.

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|  |
|  | Name of Study Doctor |  |  |
|  |  |
|  | Signature |  |  Date |  |  |
|  |