Study Protocol

Title:

Orkambi in Patients with Cystic Fibrosis and Severe Liver Disease

Clinical Trial Protocol Version 2.0

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Table of contents

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2. Background

Cystic fibrosis is a genetic disease with multisystem involvement and is associated with high rates of premature death. Cystic fibrosis affects approximately 3000 people in Australia (1). Cystic fibrosis is caused by gene mutations that result in deficient or dysfunctional cystic fibrosis transmembrane conductance regulator (CFTR) protein, an anion channel that is normally present in the epithelial membrane. Phe508del is the most common CFTR mutation with approximately 45% of patients with cystic fibrosis being homozygous for this allele (2). The Phe508del CFTR mutation causes a processing defect that severely reduces protein levels at the epithelial membrane (3).

Orkambi is a combination of lumacaftor (a CFTR corrector) and ivacaftor (a CFTR potentiator) that is approved for patients two years and above with homozygous Phe508del in Australia. Orkambi provides a modest absolute improvement in FEV1 (range from 2.6 to 4.0%; $p<0.001$) and was also found to reduce the rate of pulmonary exacerbations (4, 5). In a study involving paediatric patients between age 6 to 11 years old, Orkambi was shown to also improve sweat chloride levels, body mass index, Cystic Fibrosis Questionnaire-Revised respiratory domain scores and lung clearance index (6).

There are some known side effects with the administration of Orkambi including cough, nasal congestion, infective pulmonary exacerbation and headache (4, 6, 7). While the randomised controlled clinical trials of Orkambi did not suggest Orkambi was associated with significant liver impairment, some patients on Orkambi have developed elevation of transaminase levels including alanine transferase (ALT) and aspartate transferase (AST) levels. Patients with pre-existing cirrhosis and/or portal hypertension were excluded from the trials although some case reports have suggested worsening liver function and one patient developed hepatic encephalopathy within 5 days of commencing Orkambi. Only a minority of patients have required cessation of Orkambi due to impaired liver functions (8) and in many interruption of the drug only has been required. Limited studies have shown an increased medication exposure ($AUC_{0\text{-}12hr}$ by approximately 50% and maximum drug concentration [C_{max}] by approximately 30%) in subjects with moderately impaired hepatic function (Child-Pugh class B), although no studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C) (8). Hence, taking into account the expected higher

exposure of medication in patients with liver impairment, the FDA have recommended administering lower doses of Orkambi to patients (8).

In the initial study (Protocol version 1.3; 27 January 2020), half dose Orkambi was administered in four patients with cystic fibrosis and severe liver disease over a period of four days. The results from the study revealed that the exposure to Lumacaftor-Ivacaftor was low in all four patients. Based on the Prescribing Information (8), the expected AUC0-12 for patients on Lumacaftor 200mg/ Ivacaftor 250mg twice a day was Lumacaftor 198 mg.h/L (65) and Ivacaftor 250mg = 3.66 mg.h/L (2.25). In our patient cohort on half dose Orkambi, the mean AUC0-12 for Lumacaftor was 24.08 mg.h/L (5.26) and Ivacaftor was 0.63 mg.h/L (0.32). Hence, our patients only achieved 12% of expected Lumacaftor and 17% of target Ivacaftor levels.

Throughout the study period of four days, our patients had stable liver function tests and none of the patients described significant medication side effects. It is hypothesized that the low drug levels on half dose Orkambi are due to decreased drug absorption secondary to the patient's severe liver disease, and that steady state was not yet achieved. However, by projection, it is unlikely that acceptable drug levels will be obtained, even with further dosing over a period of weeks.

Based on these findings, a revision to the protocol has been made. In this modified protocol, patients will be commenced on half dose Orkambi with pharmacokinetic studies performed at the end of two weeks, at study drug steady state, with liver function monitoring throughout. The study will then continue with full dose Orkambi. Faecal samples will also be obtained to gain an understanding regarding drug absorption on both medication doses, in this patient population. As patients between 2 to 5 years old are now eligible for Orkambi, these patients will also be included in this study.

3. Objectives

Primary Objective
To describe the pharmacokinetics of Orkambi in paediatric patients with cystic fibrosis and severe liver disease

Secondary Objective
To assess the safety of Orkambi in patients with severe liver disease

4. Study design

4.1. Methods

- This is a prospective study that will be conducted at the Queensland Children's Hospital
- All eligible patients meeting the inclusion and exclusion criteria below will be recruited to this study
- The following baseline measurements and interventions will be performed

4.2. Patient population

Inclusion criteria

- Children between 2 years and 18 years of age homozygous for *Phe508del-CFTR*
- Severe liver disease

Definition of severe cystic fibrosis related liver disease

- Liver cirrhosis (identified on liver biopsy/ liver ultrasound/ elastography) without portal hypertension
- Liver cirrhosis and portal hypertension (evidence of hypersplenism/ diagnosed on liver USS/ endoscopy findings i.e. varices)

Exclusion criteria

- Patients with previous organ transplant
- Haematological disorders
- Abnormal renal function, GFR < 20mL/min
- Prolonged QTc
- Cataracts
- Receiving drugs considered strong inhibitors/inducers of CYP3A enzymes
  - Strong CYP3A inhibitors – e.g. itraconazole, ketoconazole, posaconazole, voriconazole, telithromycin, clarithromycin
  - Strong CYP3A inducer – e.g. rifampin, St. John's wort, phenobarbital, carbamazepine, phenytoin

5. Study Procedures

5.1. Baseline

Baseline Measurements

To be performed within a month prior to the commencement of Orkambi:

- Identity – age, study number, date of birth, gender
- Lung function
- Bloods – Full blood count (FBE), CHEM20 (including liver function tests - ALT, AST, GGT, ALP, albumin, bilirubin), coagulation tests, ammonia levels, pharmacokinetic levels (control)
- Faecal sample (control)
- Imaging – abdominal ultrasound and elastography
- Growth measurements – weight, length, BMI
- Medications list including CYP3A inducers/inhibitors
- Previous sputum microbiology – over the last 12 months
- Ophthalmology examination (eye tests) to exclude cataracts
- Patients who were participants in the initial protocol will not require a repeat abdominal ultrasound, liver elastography or eye review prior to the commencement of this study. Previous results will be used as baseline for this study

5.2. Intervention

Patients will receive two weeks of half dose Orkambi followed by two weeks of full dose Orkambi, with safety monitoring (Tables 1 and 2).

5.2.1. Dosing

Half dose Orkambi

- 2 – 5 years (less than 14kg) = One packet of granules (Lumacaftor 100mg/ Ivacaftor 125mg) mixed with 1 teaspoon (5 mL) of soft food or liquid, once a day
- 2 – 5 years (greater than 14kg) = One packet of granules (Lumacaftor 150mg/ Ivacaftor 188mg) mixed with 1 teaspoon (5 mL) of soft food or liquid, once a day
- 6 – 11 years = Lumacaftor 100mg/ Ivacaftor 125mg twice a day
- 12 years and older = Lumacaftor 200mg/ Ivacaftor 125mg twice a day

Full dose Orkambi

- 2 – 5 years (less than 14kg) = One packet of granules (Lumacaftor 100mg/ Ivacaftor 125mg) mixed with 1 teaspoon (5 mL) of soft food or liquid, twice a day
- 2 – 5 years (greater than 14kg) = One packet of granules (Lumacaftor 150mg/ Ivacaftor 188mg) mixed with 1 teaspoon (5 mL) of soft food or liquid, twice a day
- 6 – 11 years = Lumacaftor 200mg/ Ivacaftor 250mg twice a day
- 12 years and older = Lumacaftor 400mg/ Ivacaftor 250mg twice a day

5.2.2. Pharmacokinetics methodology

Blood samples

- Pharmacokinetic study of Orkambi involving ivacaftor (major metabolites being hydroxymethyl-ivacaftor and ivacaftor-carboxylate) and lumacaftor
- Record time of dose administration
- Record time of blood collection
- 2.5mL of blood collected at below time points and placed on ice
- Allow blood to stand and clot between 15 - 30 minutes
- Remove clot by centrifuging at 1000 – 2000 x g for 10 minutes in refrigerated centrifuge
- Transfer serum into clean polypropylene tube using a Pasteur pipette with patient label and time (e.g. 2 hour [h] level)
- Maintain samples at 2-8C while handling
- Store samples at -80C
- Courier samples for drug assay to the University of Melbourne laboratory
- Pharmacokinetics analysis by the University of Queensland Centre for Clinical Research (UQCCR) team members

Faecal samples

- Faecal samples will be collected by the patient at the allotted time points at home using the provided apparatus
- Patients will record the number of bowel movements on the collection day
- The first faecal sample of the day will be collected, either in part or in whole
- Faecal samples are frozen immediately post collection by the patient
- Faecal samples are then transported to the clinic with a cool pack, at the time of the next research visit
- Faecal samples will be frozen to -80C and stored until time of courier
- Faecal samples will be couriered to the University of Melbourne laboratory for drug assay
- Pharmacokinetics analysis by the University of Queensland Centre for Clinical Research (UQCCR) team members

Pharmacokinetics parameter calculation methodology

- One, two- and three-compartment models will be developed with the non-parametric adaptive grid algorithm within the Pmetrics® package for R
- Differential equations will model elimination from the central compartment and intercompartmental distribution will be modelled as first-order processes
- Estimates of assay error will also be included in the modelling process
- Demographic and clinical characteristics considered physiologically plausible for affecting antibiotic PK (age, weight, CL_{CR}) will be tested for inclusion as covariates
- A covariate will be supported for inclusion if it attains a statistically significant improvement in the log likelihood ($P<0.05$) and/or improves the goodness-of-fit plots
- The goodness-of-fit will be evaluated by visual inspection of the observed-predicted plot, the coefficient of determination of the linear regression of the observed-predicted values and the log-likelihood values from each run
- Predictive performance evaluation will be premised on mean prediction error (bias) and mean bias-adjusted squared prediction error (imprecision) of the population and individual prediction models in the plasma compartment

5.2.3. Investigations

Half dose Orkambi (Day 1 – 14)

- Predose – Ensure all baseline investigations are performed
- Week 1 (between day 6 and 8) – full blood count, CHEM20, coagulation tests, ammonia levels, pharmacokinetic levels and faecal sample levels will be obtained
- Week 2 (day 13 to 14) – A pharmacokinetic profile will be obtained at 0, 2, 4, 6, 8 and 24 hours. In addition, the full blood count, CHEM20, coagulation tests, ammonia levels and faecal samples will be obtained. The participant will also have the lung function, vital signs, physical examination and growth parameters recorded

Full dose Orkambi (Day 15- 28)

- Investigations from day 13 will be used as the baseline investigations prior to commencing full dose Orkambi
- Week 3 (between day 20 and 22) – full blood count, CHEM20, coagulation tests, ammonia levels, pharmacokinetic levels and faecal sample levels will be obtained
- Week 4 (day 27 to 28) – A pharmacokinetic profile will be obtained at 0, 2, 4, 6, 8 and 24 hours. In addition, the full blood count, CHEM20, coagulation tests, ammonia levels and faecal samples will be obtained. The participant will also have the lung function, vital signs, physical examination and growth parameters recorded
- After day 28, Orkambi will no longer be made available to the patients from the trial

Protocol on half dose (Week 1 – 2)								
	Pre Dose Baseline	**Week 1** Day 6 - 8	**Week 2** Day 13 – 14					
			0h	2h	4h	6h	8h	24h
Bloods								
Full blood count	X	X	X					
CHEM20*	X	X	X					
Coagulation	X	X	X					
Ammonia	X	X	X					
Pharmacokinetics	X	X	X	X	X	X	X	X
Faecal sample	X	X	X					X
Lung function	X		X					
Imaging								
Abdominal US**	X							
Elastography**	X							
Vital signs	X		X					
Physical exam	X		X					
Growth measures	X		X					
Medication list	X							
Microbiology	X							
Ophthalmology**	X							

Table 1 – Participant timeline on half dose Orkambi

*CHEM 20 including liver function tests (ALT, AST, GGT, ALP, albumin, bilirubin)

**These tests are required in new patients who were not participants of the initial protocol

Protocol on full dose (Week 3 – 4)								
	Week 3 Day 20 - 22	**Week 4** Day 27 - 28						**Week 8**
		0h	2h	4h	6h	8h	24h	
Bloods								
Full blood count	X	X						X
CHEM20*	X	X						X
Coagulation	X	X						X
Ammonia	X	X						X
Pharmacokinetics	X	X	X	X	X	X	X	
Faecal sample	X	X					X	
Lung function		X						X
Vital signs		X						
Physical exam		X						
Growth measures		X						
Elastography								X

Table 2 – Participant timeline on full dose Orkambi
*CHEM 20 including liver function tests (ALT, AST, GGT, ALP, albumin, bilirubin)

6. Safety

6.1 Safety monitoring

- At week 8, a repeat full blood count, CHEM20, coagulation tests, ammonia levels, lung function tests and liver elastography will be obtained.
- A repeat eye review will also be performed within 3 to 4 months after the last dose of Orkambi
- During the study, should the liver function tests be elevated 3 times above the upper limit of normal or the ammonia levels double, the blood tests will be repeated within 3 days.
- Patients with persistent elevation of transaminases > 5 times upper limit of normal with previously normal function; or in severe cases, > 5 times upper limit of normal with bilirubin elevation (> 2 times upper limit of normal), worsening deranged coagulation (INR), or persistently elevated ammonia levels, may require cessation of the study drug.
- Should the patient require blood tests for clinical purposes, an opportunistic collection of a pharmacokinetic sample will be obtained at the same time, where possible.
- Should the patient present to the hospital for any routine visits or clinical purposes, an opportunistic collection of a faecal sample will also be obtained, where possible.

7. Outcomes

1. Determination of the pharmacokinetics of Orkambi, exposure (AUC 0-12h) and steady state (AUCss), in patients with severe liver disease on both half dose and full dose Orkambi
2. Assess the acute effects of Orkambi in this patient population on liver function changes.
3. Assess the absorption of Orkambi with faecal assay levels as a surrogate marker

8. Risks

The safety profile of ORKAMBI is from the pooled data of 1108 patients with cystic fibrosis 12 years and older who are homozygous for the *Phe508del* mutation. Overall, Orkambi has been well tolerated.

Very common side effects of Orkambi occurring in greater than 10% of CF participants include:

- Difficulty breathing (13% or 13 in 100)
- Inflammation of the nasal passages and pharynx (13% or 13 in 100)
- Nausea (13% or 13 in 100)
- Diarrhoea (12% or 12 in 100)

Common side effects of Orkambi in 5-10% of CF participants include:

- Upper respiratory tract infections (10%), fatigue (9%), abnormal respirations (9%), increased blood creatine phosphokinase (7%), rash (7%), flatulence (7%), runny nose (6%), influenza (5%)

8.1. Other side effects

Liver derangement has been reported in patients with CF receiving Orkambi. There have been three reported cases of severe liver related adverse reactions with Orkambi. However, the liver functions returned to normal with the discontinuation or interruption of Orkambi. In six patients with pre-existing cirrhosis and/or portal hypertension who received Orkambi, there was worsening liver function and hepatic encephalopathy was observed in one patient. These events occurred within 5 days of commencing Orkambi and resolved post discontinuation. No further pharmacokinetic studies have been performed in this patient population. In the clinical trials, some increase in liver transaminases were noted in patients, both on trial drug and placebo, although the patients on trial drug had a higher percentage of transaminitis. The liver functions returned to baseline post cessation of the trial drug.

8.2. Blood collection

- In order to facilitate blood collection, patients will be seen in the research building on day 1, day 2 and day 4.
- Blood tests will be taken either via accessing the patient's portacath, intravenous cannula insertion to aid frequent sampling, or venepuncture should intravenous cannula insertion be unsuccessful.
- To minimise discomfort, analgesia cream (i.e. EMLA) will be used prior to needling the portacath, intravenous cannula insertion or venepuncture.
- Patients may develop bruising, dizziness, redness at the site during portacath access, venepuncture, or intravenous cannula insertion.
- To obtain blood samples over the period of 8 weeks, a total of approximately three intravenous cannula insertions and/or six venepunctures may be required.

9. Consent

- The protocol for this project will be reviewed by the human research ethics committee (HREC) at the Queensland Children's Hospital
- Patients enrolled will be allocated a unique study number which will be used for data collection
- An enrolment log will be compiled including the patient's name, date of birth, hospital identification number and unique study number
- The enrolment log and study data will be kept separately and confidentially on Queensland Health password protected computers
- Written consent will be obtained from the parents of the participants and scanned into iEMR of the Queensland Children's Hospital
- Information sheets will be provided along with the opportunity to ask questions to ensure the parents and participants understanding of the trial prior to obtaining consent
- The patient's usual treatment will not be altered regardless of their participation in the trial
- The patient or their parents/guardians may withdraw from the trial at any stage

10. Data management

10.1. Data collection methods

- All data will be collected by the research team
- Data will then be entered into a secure database at the Queensland Children's Hospital, maintaining confidentiality in accordance with local legislation on privacy and use of health data
- All data records including consent documentation and electronic records will be kept for 15 years after the completion of the study as per Queensland Health policy
- The pharmacokinetic data will be analysed using standard approaches by the research pharmacokinetic team
- The safety bloods and imaging will be analysed by the research team using standard methodology

10.2. Sample management

- Study data and samples will be handled and analysed by the research team and the Queensland Children's Hospital pathology laboratory
- All samples will be labelled with the unique study number
- Samples will be stored and disposed within two years of completion of the trial

11. References

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