Statins in Metastatic Castration-Resistant Prostate Cancer

A multi-centre, open label trial of simvastatin in addition to docetaxel chemotherapy for metastatic castration-resistant prostate cancer

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CONFIDENTIAL
Statins in Metastatic Castration-Resistant Prostate Cancer

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Abbreviations and Terminology

Abbreviations and commonly used terms

ADT - androgen deprivation therapy
AE - adverse event
ALP - alkaline phosphatase
ALT - alanine aminotransferase
AST - aspartate aminotransferase
CRPC - castration-resistant prostate cancer
CRF - case report form
CTCAE - National Cancer Institute’s Common Terminology Criteria for Adverse Events
ELISA - enzyme-linked immunosorbent assay
GGT - gamma-glutamyl transpeptidase
HDL - high density lipoprotein
HREC - Human Research Ethics Committee
IHC - immunohistochemistry
INR - international normalised ratio
LDL - low-density lipoprotein
LFT - liver function test
PCWG3 - Prostate Cancer Working Group 3
PSA - Prostate Specific Antigen
SAE - serious adverse event
SUSAR - suspected unexpected serious adverse reaction
TMC - Trial Management Committee
ULN - upper limit of normal range
# Synopsis and Schema

## Protocol Synopsis

| Background | To date, biomarker studies in CRPC have mainly focused on changes in the cancer and their effects on therapeutic resistance and prognosis. However, the host environment (i.e. the patient) and its interactions with cancer is increasingly important, especially in light of the increasing association of prostate cancer and obesity. Our exploratory study was the first to profile the plasma lipidome of men with metastatic CRPC, and to identify plasma lipidomic profiles that are associated with survival in CRPC (Lin et al, unpublished).

Unsupervised analysis of baseline lipidomic profiles classified patients of a Phase 1 discovery cohort into two groups with significant survival differences (HR 2.31, 95% CI 1.44-3.68, p=0.0005), independent of chemotherapy response. The baseline levels of 46 lipids were individually prognostic, and predominantly sphingolipids. A prognostic three-lipid signature was derived, consisting of ceramide, sphingomyelin and phosphatidylcholine. This signature was associated with shorter overall survival in the Phase 2 cohort (HR 4.8, 95% CI 2.06-11.1, p=0.0003), and was an independent prognostic factor when modelled with clinicopathological factors or metabolic characteristics (Lin et al, unpublished).

Therefore, a key question is whether therapeutic modulation of a patient’s lipid profile will improve prognosis. However, the first step is to see if lipid modulation therapy can change the circulating lipidomic profile.

Statin therapy significantly reduces the plasma levels of ceramides, sphingomyelin and cholesterol in individuals with cardiovascular disease or metabolic syndrome, suggesting that such therapy could change the high risk lipid profile of CRPC patients. |

| General aim | To assess whether treatment with simvastatin during docetaxel chemotherapy for metastatic CRPC can reverse a poor prognostic circulating lipid signature. |

| Primary objective (endpoint) | To determine whether treatment with simvastatin during docetaxel chemotherapy can modulate circulating lipid profile by reducing levels of sphingolipid subclasses from baseline, thereby reverse a poor prognostic lipid signature. |

<p>| Secondary objectives (endpoints) | To determine whether treatment with simvastatin during docetaxel chemotherapy affects incidence of adverse events (CTCAE v4.03) |</p>
<table>
<thead>
<tr>
<th>Tertiary and correlative objectives</th>
<th>Exploratory biomarker studies</th>
</tr>
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</table>
| **Design**                         | This trial is a multi-centre, open label study of simvastatin in addition to docetaxel chemotherapy in patients with metastatic CRPC.  
60 patients will be treated with simvastatin 40mg daily for 12 weeks at the same time as they start docetaxel, which matches the cohorts from our plasma lipidomic study (Lin et al, unpublished). Patients will have plasma samples taken at baseline before they start simvastatin and after 12 weeks on simvastatin. LC-MS/MS will be used to profile the plasma lipidome at these two time points. |
| **Population**                     | Adult men with metastatic CRPC commencing docetaxel chemotherapy for disease progression, not already receiving a lipid lowering agent(s) e.g. statin, ezetimibe, fibrate. |
| **Study treatment**                | Simvastatin 40mg tablet orally daily for 12 weeks, commencing on day 1 of the first cycle of docetaxel chemotherapy. |
| **Assessments**                    |  
- Blood for plasma lipidomic study and serum metabolic profile is taken at baseline (pre-treatment) and after 12 weeks of simvastatin (on Day 85)  
- Clinic visits and routine blood tests including LFT are required at baseline, during treatment (every 3 weeks) and after 12 weeks of simvastatin (on Day 85)  
- Safety assessments will be performed during treatment and again at 21-30 days after the last dose of treatment. |
| **Statistical considerations**     | This is a single arm, pilot study. Assuming 25% of patients have the poor prognostic lipid signature at baseline (Lin et al, unpublished), a total sample size of 60 participants provides over 90% power with a 1-sided type 1 error of 10% (with an allowance of 10% for inevaluable participants and missing data), to detect conversion to the good prognostic signature in 50% of patients.  
A patient’s lipid signature will be analysed and classified as either good prognostic or poor prognostic as per our three-lipid signature model derived by logistic regression (Lin et al, unpublished). Rates of conversion from a poor prognostic signature to good prognostic will be analysed. |
Study Schema

**ENDPOINTS:**

- **Lipidomic profile**
- **Adverse events**

**Days**

- **Days -28 to -1**
- **Days 1**
- **Days 22**
- **Days 43**
- **Days 64**
- **Days 85**
- **Days 106**
- **Days 127**

**C1**

**C2**

**C3**

**C4**

**Docetaxel every 3 weeks**

**Simvastatin 40mg orally daily**

**Met CRPC**

Starting docetaxel

Not on lipid lowering agent

n=60
1 BACKGROUND

1.1 The need for new treatment strategies for prostate cancer
Despite a range of new therapeutics for metastatic castration-resistant prostate cancer (CRPC) (1), primary and secondary resistance to cytotoxic and anti-androgen therapies remains a key clinical hurdle. There is still an urgent need for new biomarkers and treatment strategies to improve patient outcome.

1.2 Lipid metabolism and prostate cancer
To date, biomarker studies in CRPC have mainly focused on changes in the cancer and their effects on therapeutic resistance and prognosis. However, the host environment (i.e. the patient) and its interactions with cancer is increasingly important, especially in light of the increasing association of prostate cancer and obesity.

The importance of lipid metabolism in prostate cancer is reflected by epidemiological evidence. For example, higher prostate cancer stage, grade and mortality are observed in obese men (2, 3). Furthermore, time to CRPC is seen to be reduced to 16 months in men who are positive for metabolic syndrome before the commencement of ADT, compared to 36 months in patients without metabolic syndrome (4). Collectively, these observations point to dysregulated lipid metabolism having a major influence on disease progression and the development of metastatic CRPC.

Mechanistically, these metabolic derangements may increase the risk for aggressive disease at a molecular level. Prostate cancer cells display increased lipogenesis and lipolysis, as well as altered metabolism of cholesterol and phospholipids (5). Lipids contribute to cancer growth as energy substrates, cell membrane constituents, and signalling molecules in the regulation of cell cycle, apoptosis, angiogenesis and inflammation (6, 7). However, the role of circulating lipids on the biology of prostate cancer cells is unclear.

Over 500 distinct lipid species from six main lipid classes have been identified in human plasma (8). These circulating lipids may influence the behaviour of cancer and immune cells, or may comprise of lipids released by cancer cells. Previous studies of circulating lipids in prostate cancer have mainly focused on a few lipid species (e.g. cholesterol, triacylglycerol), or the fatty acid profile of a lipid class (e.g. omega-3 fatty acid in phospholipids) in localised prostate cancer (9, 10). There are no studies of circulating lipids in metastatic CRPC.

1.3 Prognostic lipidomic signature from an exploratory study
Our group performed an exploratory study using lipidomic profiling of ~300 lipid species on plasma samples acquired from men with CRPC commencing first line docetaxel chemotherapy, to identify circulating lipids that are associated with overall survival and chemoresponse.

Unsupervised analysis of baseline lipidomic profiles classified patients of a Phase 1 discovery cohort into two groups with significant survival differences (HR 2.31, 95% CI 1.44-3.68, p=0.0005), independent of chemotherapy response. The baseline levels of 46 lipids were individually prognostic, and predominantly sphingolipids (Fig 1). A prognostic three-lipid signature was derived, consisting of ceramide, sphingomyelin and phosphatidylcholine. This signature was associated with shorter overall survival in the Phase 2 cohort (HR 4.8, 95% CI 2.06-11.1, p=0.0003), and was an independent prognostic factor when modelled with clinicopathological factors or metabolic characteristics (Fig 2).

Our exploratory study is therefore the first to profile the plasma lipidome of men with metastatic CRPC, and to identify plasma lipidomic profiles that are associated with survival in CRPC.
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**Fig 1:** Heatmap of baseline plasma levels of 46 lipids significantly associated with overall survival of the Phase 1 cohort. Lipidomic Profile 2 patients have worse prognosis, compared with Lipidomic Profile 1 patients. The proportion of these lipids out of the total detected in plasma for each lipid class/subclass is shown in brackets.

**Phase 2 cohort**

<table>
<thead>
<tr>
<th>Lipid signature</th>
<th>Median overall survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No signature</td>
<td>21.4 months (13.7-29.0)</td>
</tr>
<tr>
<td>3-lipid signature</td>
<td>11.3 months (8.3-14.3)</td>
</tr>
</tbody>
</table>

log-rank test p = 0.00007  
Hazard ratio = 4.78 (95% CI 2.06-11.1, p = 0.0003)

**Fig 2:** Overall survival curves of the Phase 2 validation cohort classified by the three-lipid signature.
1.4 Summary and rationale
A novel plasma lipid signature has been identified and validated to be associated with worse overall survival in metastatic CRPC. Therefore, a key question is whether therapeutic modulation of a patient’s lipid profile will improve his prognosis. Of particular interest is the observation that the majority of lipid species associated with prognosis belongs to the sphingolipid class.

Statin therapy has been known to significantly reduce the plasma levels of ceramides, sphingomyelin and cholesterol in individuals with cardiovascular disease or metabolic syndrome (11-14), suggesting that such therapy could change the high risk lipid profile of CRPC patients to improve their prognosis. Furthermore, lipophilic statins such as simvastatin have been found to be more effective than hydrophilic statins such as pravastatin in reducing the metastatic process in an in vitro model (15).

2 AIM AND OBJECTIVES

2.1 Aim
The aim is to assess whether treatment with simvastatin during docetaxel chemotherapy for metastatic CRPC can reverse a poor prognostic circulating lipid signature.

2.2 Hypothesis
The hypothesis is that simvastatin treatment will modulate the circulating lipid profile and reduce the levels of sphingolipid subclasses from baseline, thereby reversing the poor prognostic circulating lipid signature.

2.3 Objectives (endpoint)

2.3.1 Primary
- To determine whether treatment with simvastatin during docetaxel chemotherapy can modulate circulating lipid profile by reducing levels of sphingolipid subclasses from baseline, thereby reversing a poor prognostic lipid signature.

2.3.2 Secondary
- To determine whether treatment with simvastatin during docetaxel chemotherapy affects incidence of adverse events (CTCAE v4.03)

2.3.2 Tertiary
- Exploratory biomarker studies

3 DESIGN
This trial is a multi-centre, open label study of simvastatin in addition to docetaxel chemotherapy in patients with metastatic CRPC.

60 patients will be treated with simvastatin 40mg daily for 12 weeks at the same time as they start docetaxel, which matches the cohorts from our plasma lipidomic study (Lin et al, unpublished). Patients will have plasma samples taken at baseline before they start simvastatin and after 12 weeks on simvastatin. Liquid chromatography and electrospray ionisation-tandem mass spectrometry (LC-MS/MS) will be used to profile the plasma lipidome of the patients at these two time points.
4 SUBJECT POPULATION

Patients must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial. There will be no exceptions made to these eligibility requirements at the time of registration.

4.1 Target population

Adult men with metastatic CRPC commencing docetaxel chemotherapy for disease progression, not already receiving a lipid lowering agent(s) e.g. statin, ezetimibe, fibrate.

4.2 Inclusion criteria

1. Males with castration-resistant metastatic prostate cancer (as per PCWG3) AND commencing docetaxel chemotherapy for disease progression
2. Age ≥ 18 yrs
3. WHO ECOG performance status 0-2
4. Histological confirmation of prostate cancer
5. Adequate hepatic function with serum total bilirubin ≤ 1.5 x upper limit of normal range and ALT and AST ≤ 2.5x upper limit of normal range (or < 5.0 times ULN with documented liver metastases), serum albumin > 25 g/L, and ALP ≤ 5x upper limit of normal range
6. Adequate renal function (with calculated creatinine clearance >50 ml/min based on the Cockcroft-Gault method, 24 hour urine or GFR scan) and serum creatinine ≤ 1.5 x upper limit of normal range;
7. Willing and able to comply with all study requirements, including treatment and biospecimen collection
8. Signed written informed consent

4.3 Exclusion criteria

1. Patients already receiving a lipid lowering agent(s), or have received one in the last 4 weeks
2. Known hypersensitivity to statins or its excipients
3. Prior myopathy with a lipid lowering agent
4. Active hepatic disease, including chronic active hepatitis B or hepatitis C. Testing for these is not mandatory unless clinically indicated.
5. Serious medical or psychiatric conditions that might limit the ability of the patient to comply with the protocol.

4.4 Screening

Written informed consent must be signed and dated by the subject AND signed and dated by the Investigator, prior to any study-specific screening investigations being performed.

4.5 Registration

Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this study. There will be no exceptions made to these eligibility requirements at the time of registration. All enquiries about eligibility should be addressed by contacting Chris O’Brien Lifehouse prior to registration.

Subjects must be registered through Chris O’Brien Lifehouse before starting study treatment. Requests for registration will only be accepted from authorised investigators at the site once ethics approval is received. Treatment should start within 14 days after initial baseline blood collection.
5 TREATMENT PLAN

5.1 Administration of study treatment
Patients will be asked to take simvastatin 40mg tablet orally daily for 12 weeks, commencing on day 1 of the first cycle of docetaxel chemotherapy. All patients should return any remaining tablets to the Investigator at the end of their participation in the study.

5.2 Dose modifications
The dose for simvastatin is based on the recommended treatment dose for hyperlipidaemia. Dose modifications are not permitted in this study. Patients who need to come off the study should discontinue.

5.3 Concomitant medications/treatments

5.3.1 Recommended
No other medications or treatments are specifically recommended in this study.

5.3.2 Permitted
In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted with the following exceptions:

5.3.3 Prohibited
Concomitant treatment with potent CYP3A4 inhibitors (see Appendix 1), systemic sodium fusidate, gemfibrozil, ciclosporin or danazol is contraindicated.

The investigator should instruct the patient to notify the study site about any new medications he takes after the start of the study drug.

5.4 Treatment discontinuation
Study treatment will be permanently discontinued for any of the following reasons:
- Unacceptable toxicity as determined by the patient or site investigator
- Delay of treatment for >4 days due to non treatment-related adverse events.
- The investigator determines that continuation of treatment is not in the patient’s best interest.
- Occurrence of an exclusion criterion affecting patient safety, e.g. psychiatric illness.
- Required use of a concomitant treatment that is not permitted, as defined in section 5.3.3.
- Failure to comply with the protocol, e.g. repeatedly failing to attend scheduled assessments. If a patient has failed to attend scheduled assessments in the study, the Investigator must determine the reasons and document the circumstances as completely and accurately as possible in the medical records and CRF.
- The patient declines further study treatment, or withdraws their consent to participate in the study.

The reasons for discontinuing treatment will be documented in the subject’s medical record. Follow up of subjects who stop study treatment should continue according to this protocol (see section 6.2).
6 ASSESSMENT PLAN

6.1 Schedule of assessments

<table>
<thead>
<tr>
<th>Consent</th>
<th>Screening and eligibility assessment</th>
<th>Routine Review</th>
<th>Haematology</th>
<th>Biochemistry</th>
<th>Metabolic profile – fasting</th>
<th>Blood sample collection for lipidomic profiling – fasting</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Within 28 days prior to treatment</td>
<td>Within 14 days prior to treatment</td>
<td>Day 1 (prior to Cycle 1)</td>
<td>Day 22 (prior to Cycle 2)</td>
<td>Day 43 (prior to Cycle 3)</td>
<td>Day 64 (prior to Cycle 4)</td>
<td>Day 85</td>
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<tr>
<td>Consent</td>
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<tr>
<td>Routine Review</td>
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<td>Haematology</td>
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<tr>
<td>Metabolic profile – fasting</td>
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<tr>
<td>Blood sample collection for lipidomic profiling – fasting</td>
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<tr>
<td>Adverse Events</td>
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</table>

a) As per Investigator’s routine practice
b) Haematology includes full blood count with automated 5 cell differential and haemoglobin. These tests should be performed within 4 days of the specified time point
c) Biochemistry includes urea/creatinine clearance (calculated by Cockcroft-Gault formula), ALP, ALT, AST, GGT, albumin, bilirubin. These tests should be performed within 4 days of the specified time point
d) Metabolic profile includes (4 hours fasting) total triglyceride, total cholesterol, HDL, LDL, glucose, insulin
e) A kit will be provided for blood sample collection for lipidomic profiling
f) If chemotherapy dose delay or cessation occurs for any reason on the study, treatment with simvastatin should continue until completion at 12 weeks.

These are study specific assessments. Any of these assessments can be performed as clinically indicated.
6.2 Assessment phase definitions and special circumstances

6.2.1 Baseline
All baseline pre-treatment evaluation procedures must be performed within 14 days prior to treatment commencement.

6.2.2 On treatment
All patients on study must be evaluated according to the schedule outlined in section 6.1. Assessments during treatment may be performed within 4 days of the specified time point, unless otherwise specified. If chemotherapy dose delay or cessation occurs for any reason on the study, treatment with simvastatin should continue until completion at 12 weeks.

6.2.3 End of treatment
Routine assessments will be performed and final blood samples will be collected at the end of 12 weeks of treatment on Day 85.

6.2.4 Follow up after treatment: 21-30 day safety assessment after last dose
A safety assessment will be performed to include any adverse events occurring 21-30 days after the last dose of study treatment.

7 OUTCOMES, ENDPOINTS AND OTHER MEASURES

7.1 Primary outcome

7.1.1 Change in circulating lipid profile
The primary outcome of interest is the change in circulating lipid profile with the concomitant use of simvastatin in men commencing docetaxel chemotherapy for metastatic CRPC. The primary endpoint is a reduction in levels of sphingolipid subclasses from baseline, thereby reversing a poor prognostic lipid signature.

7.2 Secondary outcomes

7.2.1 Adverse events (worst grade according to NCI CTCAE v4.03)
The proportion of patients experiencing treatment-related toxicities, as defined by the Common Toxicity Criteria v4.0 of the National Cancer Institute (NCI CTC v4.03). See section 8.1 for the definition of an adverse event (AE), and reporting of Serious Adverse Events (SAEs). The NCI CTCAE v4.03 will be used to classify and grade the intensity of adverse events after each treatment cycle.

7.3 Tertiary outcomes

7.3.1 Exploratory biomarker studies
Biospecimens may be used for biological studies that include identification or validation of biomarkers. As the discovery of biomarkers is rapidly evolving, the definitive list of biomarkers remains to be determined.

Techniques used may include but are not restricted to immunohistochemistry, mass spectrometry and ELISA.
8 SAFETY REPORTING

8.1 Definitions

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below).

Adverse events include the following:
- All suspected adverse drug or device reactions
- All reactions from drug or device – overdose, abuse, withdrawal, sensitivity, toxicity or failure of expected pharmacological action (if appropriate)
- Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses
- Injury or accidents
- Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test)
- Any untoward event that occurs after the protocol-specified reporting period, which the Investigator believes may be related to the drug or device.

AEs must be reported as AEs even if they do not meet SAE criteria.

A SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that at any dose:
- results in death,
- is life-threatening (i.e. the subject is at risk of death at the time of the event),
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- other important medical events which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol.

NOTES:
- The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Important medical events which may not be immediately life-threatening or result in death or hospitalization but which may jeopardize the patient or may require intervention to prevent one of the listed outcomes in the definition above should also be considered serious.

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is related to the drug or device and is unexpected (i.e. not listed in the investigator brochure; or is not listed at the specific or severity that has been observed; or is not consistent with the risk information described in the Subject Information Sheet and Informed Consent Form or elsewhere in the protocol. (FDA, Safety Reporting Requirements for INDs and BA/BE Studies, draft guidance, September 2010).

An event is causally related if there is a reasonable possibility that the drug [intervention] caused the AE, i.e. there is evidence to suggest a causal relationship between the drug and the event (FDA, Safety Reporting Requirements for INDs and BA/BE Studies, draft guidance, September 2010).
For the purposes of this study, the following adverse events are not reported as SAEs:
- elective hospitalisation
- surgery for treatment of disease
- elective hospitalisation to simplify treatment or study procedures.

### 8.2 Reporting of serious adverse events (including SUSARs)

The investigator is responsible for reporting all Serious Adverse Events (including SUSARs) occurring during the study to the Chris O'Brien Lifehouse within 1 working day of the investigator becoming aware of the event using the SAE form. SAEs must be reported from when the patient has signed informed consent and up to 30 days from the end of study intervention. Any SAEs experienced after this 30 day period should only be reported if the investigator suspects a causal relationship to the investigational product.

SAE reports should be reported to the Chris O'Brien Lifehouse as per the procedure documented in the Study Manual.

The Chris O'Brien Lifehouse will provide SUSAR reports and SAE line listings to Investigators for submission to Human Research Ethics Committees (HRECs) as required. The Chris O'Brien Lifehouse will be responsible for providing reports to the Lead HREC.

If the SAE is not previously documented in the Investigator’s Brochure and is thought to be related to investigational product, the Chris O'Brien Lifehouse may urgently require further information from the investigator for Health Authority reporting.

The investigator must notify the local HREC as required.

The Chris O'Brien Lifehouse will submit ‘reportable safety events’ to the TGA in Australia. Events which are fatal or life-threatening will be reported within 7 calendar days with a follow-up report within an additional 8 calendar days or as specified in local regulations.

Events which are not fatal or life-threatening will be reported to the appropriate regulatory authorities by the sponsor within 15 calendar days or as specified in local regulations.

The following information will be recorded for each Serious Adverse Event:
- Event description including classification according to NCI CTCAE
- Primary and secondary diagnoses of event (If death/hospitalisation)
- Severity / Worst Grade
- Attribution to study intervention
- Expectedness
- Action taken with study intervention
- Impact of SAE (e.g. hospitalisation details)
- Outcome of SAE including end date if recovered

### 9 SPECIMEN COLLECTION

Chris O'Brien Lifehouse is the sponsor of the study and will coordinate and manage samples. Chris O'Brien Lifehouse will have ownership of the tissue and are custodians of the data collected.

#### 9.1 Blood collection

This blood collection is required for all study patients. Serum and plasma for biomarkers will be collected and initially processed at each site. The frozen samples will be sent to Chris O'Brien Lifehouse for analysis at the Baker Institute with A/Prof Peter Meikle.
10 TREATMENT INFORMATION - SIMVASTATIN

10.1 Description of investigational product
Simvastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a rate-limiting enzyme in cholesterol synthesis. It is a white crystalline powder, formulated as a tablet.

IUPAC/Chemical name:
\[1S \ [1\alpha,3\alpha,7\beta,8\beta(2S^*,4S^*), \ 8\alpha\beta][1,2,3,7,8,8a\text{-hexahydro-3,7\text{-dimethyl-8}-}[2\text{-}(\text{tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl})\text{ethyl]-1-naphthalenyl}-2,2\text{-dimethylbutanoate}]

Simvastatin 40mg will be supplied as tablets.

10.2 Expected possible simvastatin-related adverse events
The following information about expected possible simvastatin-related adverse events is obtained from the simvastatin product information (Zocor®, Merck Sharpe Dohme).

All patients must be continuously observed for treatment-related adverse events, especially myalgia, rhabdomyolysis, and renal and hepatic impairment. Standard monitoring for chemotherapy should also be continued throughout treatment.

10.2.1 Myopathy and rhabdomyolysis
Simvastatin occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase above 10x the upper limit of normal. Mild myopathy has been observed in approximately 10% of patients treated at simvastatin 40mg. Severe myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred.

In a clinical trial database in which 41,413 patients were treated with simvastatin with 24,747 (approximately 60%) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.08% at 40 mg/day.

Predisposing factors for myopathy include advanced age (>65 years), female gender, uncontrolled hypothyroidism and renal impairment.

10.2.2 Hepatic dysfunction
In clinical studies, persistent increases (to more than 3 X ULN) in serum transaminases have occurred in 1% of adult patients who received simvastatin. When the drug was interrupted or discontinued in these patients, transaminases usually fell slowly to pretreatment concentration. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. Some of these patients had abnormal liver function tests prior to therapy with simvastatin and/or consumed substantial quantities of alcohol.

10.2.3 Additional rare, known adverse events
The following additional, rare adverse events were reported either in uncontrolled clinical trials or in marketed use: pruritus, hair loss/alopecia, head ache/dizziness, muscle cramps, feeling weak/myalgia, depression, pancreatitis, paraesthesia, peripheral neuropathy, insomnia, stomach upset, nausea, vomiting, constipation, diarrhoea, gynaecomastia, anaemia, erectile dysfunction, and interstitial lung disease.
10.3 Supply of investigational product
Chris O'Brien Lifehouse will supply the study drug to conduct the study.

10.4 Drug accountability
All patients should return any remaining tablets to the Investigator at the end of their participation in the study. Tablets will be counted to monitor compliance.

11 STATISTICAL CONSIDERATIONS

11.1 Sample Size
This is a single arm, pilot study. Assuming 25% of patients have the poor prognostic lipid signature at baseline (Lin et al, unpublished), a total sample size of 60 participants provides over 90% power with a 1-sided type 1 error of 10% (with an allowance of 10% for inevaluable participants and missing data), to detect conversion to the good prognostic signature in 50% of patients.

11.2 Statistical analysis
A patient’s lipid signature will be analysed and classified as either good prognostic or poor prognostic as per our three-lipid signature model derived by logistic regression (Lin et al, unpublished). Rates of conversion from a poor prognostic signature to good prognostic will be analysed.

12 ADMINISTRATIVE ASPECTS

12.1 Ethics and regulatory compliance
This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans (© Commonwealth of Australia 2007), the NHMRC Australian Code for the Responsible Conduct of Research (© Australian Government 2007), and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008. To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the patient has provided written informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a subject. In this circumstance, Chris O’Brien Lifehouse, the principal investigator and HREC must be advised immediately.

12.2 Confidentiality
The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the Chris O’Brien Lifehouse and will only be available to people directly involved with the study and who have signed a Confidentiality Agreement.

12.3 Protocol amendments
Changes and amendments to the protocol can only be made by the Trial Management Committee. Approval of amendments by the Institutional HREC is required prior to their implementation. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the data collected, if required, will be incorporated in the amendment.

The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial subject(s).
12.4 Data handling and record keeping
All trial data required for the monitoring and analysis of the study will be recorded on the (e)CRFs provided. All required data entry fields must be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated.

Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as the results of diagnostic tests such as X-rays and laboratory tests. The investigator's copy of the case report forms serves as part of the investigator's record of a subject's study-related data.

The following information should be entered into the subject's medical record:

- Subject's name, contact information and protocol identification.
- The date that the subject entered the study, and subject number.
- A statement that informed consent was obtained (including the date).
- Relevant medical history
- Dates of all subject visits and results of key trial parameters.
- Occurrence and status of any adverse events.
- The date the subject exited the study, and a notation as to whether the subject completed the study or reason for discontinuation.

All study-related documentation at ANZ sites will be maintained for 15 years following completion of the study.

12.5 Clinical study report
A Clinical Study Report, which summarises and interprets all the pertinent study data collected, will be issued which may form the basis of a manuscript intended for publication.

12.6 Publication policy
The Trial Management Committee will appoint a Writing Committee to draft manuscript(s) based on the trial data. Manuscript(s) will be submitted to peer-reviewed journal(s). All publications must receive prior written approval from the TMC prior to submission.
13 REFERENCES

### 14 LIST OF APPENDICES

#### 14.1 Appendix 1: Common potent CYP3A4 inhibitors

<table>
<thead>
<tr>
<th>Drug metabolizing enzyme or transporter</th>
<th>Strong inhibitors</th>
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<tbody>
<tr>
<td>CYP3A</td>
<td>Boceprevir, clarithromycin, erythromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole</td>
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