DARLO-C Study

Scale-up of treatment for hepatitis C infection among people who inject drugs: A phase IV, open-label, single arm, multicentre trial of grazoprevir/elbasvir for genotype 1 or 4 in people with chronic hepatitis C virus infection and recent injecting drug use

---

Manual of Operations

Study Specific Supplement

Table of Contents

Addendum

1. Site specific shipping and courier Instructions

1. Communication and Contacts and Summary of Procedures

Project Team Contact details:

Position	Name	Phone	Email
Project Coordinator	Carleen Fernandez	+61 2 9385 8375	cfernandez@kirby.unsw.edu.au
Project Coordinator (back-up)	Jodi Van Dyk	+61 2 9385 9968	jvandyk@kirby.unsw.edu.au
Principal Investigator	A/Prof Jason Grebely	+61 2 9385 0957	Jgrebely@kirby.unsw.edu.au
Principal Investigator	Prof Greg Dore	+61 2 9385 0900	Gdore@kirby.unsw.edu.au
Data Manager	Ecaterina Filep	+61 2 9385 0883	efilep@kirby.unsw.edu.au
Laboratory Coordinator	Danica Martinez	+61 2 9385 0983	dmartinez@kirby.unsw.edu.au
Study Email			darlo-c@kirby.unsw.edu.au

For all protocol, study or site management related questions, please contact the Project Coordinator.

For laboratory specific questions please contact the Laboratory Coordinator

2. Study Identifiers

1. Protocol number: 1510 (used in participant ID number from baseline onwards)
2. Screening Number: 444 (used in screening ID at screening visit only)

3. Study visits windows

The following visits windows are authorised during the study:

Study Visit week	Window
W4	+/- 7 days
W8	+/- 7 days
W12 (ETR)	+/- 14 days
W24 (SVR 12)	+/- 14 days
W36 (FU1)	+/- 14 days
W48 (FU2)	+/- 14 days
W60 (FU3)	+/- 14 days
W84 (FU4)	+/- 14 days
W108 (FU5)	+/- 14 days
W132 (FU6)	+/- 14 days
W156 (FU7)	+/- 14 days

Contact your study coordinator for advice on how to proceed for visits outside these windows.

4. Specimen collection and documentation

The following samples are collected for research at the time points specified below.

All participants must have resistance (RAS) testing performed at screening. Each screening kits contains a lab kit bag inside the main bag to be used for RAS testing. The RAS testing kitbag is sent to ICPMR. The main bag is sent to your local sample processing laboratory. See below for further details.

Visit Name	EDTA Plasma 10ml	EDTA Plasma 20ml	EDTA Whole Blood 4ml	Visit Abbreviation	Kit Type (see below for details)
Screening (444-XXX)		√*	√	SCR	1
Baseline		√	√	BSL	2
Week 4	√			WK4	3
Week 8	√			WK8	
Week 12 (ETR)	√			ETR	
Week 24 (SVR12)	√			SV12	
Week 36 (FU1)	√			FU1	
Week 48 (FU2)	√			FU2	
Week 60 (FU3)	√			FU3	
Week 84 (FU4)	√			FU4	
Week 108 (FU5)	√			FU5	
Week 132 (FU6)	√			FU6	
Week 156 (FU7)	√			FU7	

*10ml EDTA sent to ICPMR for RAS testing

Lab kits will be provided to the Site Coordinator and will contain all the materials required for specimen collection and sample storage at the local processing laboratory. There are three types of kits that will be provided as described below.

Kit type 1	Kit Type 2	Kit Type 3
SCR	**BSL**	**WK4/WK8/ETR/SVR12/FU1/FU 2/FU3/ FU4/FU5/FU6/FU7**
1 x specimen bag* containing: **Samples sent to local processing lab**: 1 x Laboratory Request Form *EDTA Collection* 1 x EDTA plasma (10ml) 4 x 1.8 mL cryovials (purple top) 4 x EDTA Plasma cryovial labels *Whole Blood Collection* 1 x EDTA whole blood (4ml) [a] 2 x 1.8 mL cryovials (red top) 2 x EDTA Whole Blood cryovial labels	1 x specimen bag 1 x Laboratory Request Form *EDTA Collection* 2 x EDTA plasma (10ml) 8 x 1.8 mL cryovials (purple top) 8 x EDTA Plasma cryovial labels *Whole Blood Collection* 1 x EDTA whole blood (4ml) 2 x 1.8 mL cryovials (red top) 2 x EDTA Whole Blood cryovial labels	1 x specimen bag 1 x Laboratory Request Form *EDTA Collection* 1 x EDTA plasma (10ml) 4 x 1.8 mL cryovials (purple top) 4 x EDTA Plasma cryovial labels
Samples to be sent to ICPMR: 1 x specimen bag** containing: 1 x ICPMR RAS testing Laboratory Request Form *EDTA Collection* 1 x EDTA plasma (10ml) 4 x 1.8 mL cryovials (purple top) 4 x EDTA Plasma cryovial labels		

** this specimen bag will arrive at sites packed inside the first specimen bag (*)

Screening kits are labelled with a screening ID number starting with 444. These kits must only be used for screening visits. If a patient is eligible and is enrolled in the study they will be assigned a subject ID by the Site Coordinator at the Baseline visit.

Each kit (except the screening kit) is labelled for a specific patient and a specific visit.

4.1 Resistance testing at screening ONLY

As part of its screening criteria DARLO-C will be testing research samples for resistance associated substitutions (RAS) at screening ONLY. RAS testing will be performed at The Westmead Institute (WI) located at Westmead Hospital after being received and processed by specimen reception at The Institute for Clinical Pathology and Medical Research (ICPMR) also at Westmead Hospital.

Sites will receive lab kits for each patient visit including screening. The screening kit will contain another specimen bag within the main specimen bag. This second bag will contain 1 x ICPMR RAS testing request form, 1 x EDTA, 4 x purple top cryovials and 4 x cryovial labels. This second specimen bag will be labelled

with a bright **YELLOW** label with the ICPMR details and is to be sent to ICPMR for RAS testing. The main specimen bag will be labelled with a bright **PINK** label with the AMR details and is to be sent to AMR for processing of research samples.

4.2 Cepheid GeneXpert HCV RNA point of care testing (sub-study sites only)

Point of care testing for HCV RNA detection will be performed at each visit at selected sub-study sites using the GeneXpert HCV RNA Viral Load assay for samples collected by finger-stick capillary whole-blood. Point of care testing will be undertaken in addition to the standard of care tests (local laboratory).

Sub-study sites will be trained by Cepheid on how to use the GeneXpert HCV RNA point of care testing machine. In addition please refer to the GeneXpert HCV RNA Point of Care testing manual and flow chart for further instruction on the finger-stick method and Cepheid cartridge and machine operation.

5. Study Drugs

Eligible patients will be prescribed via PBS S100 or S85 12 weeks of open-label elbasvir/grazoprevir (50mg/100mg daily) in an oral once-daily fixed dose combination. Dose modifications are prohibited.

The study drug is packaged in 2 x two weekly blister packs and will be dispensed monthly to study participants.

Participants should be counselled to return the study drug blister packs monthly. Study drug will be reconciled using a pill count on all returned blister packs. Participants will also be required to complete an adherence questionnaire.

Study participants should be counselled to store elbasvir/grazoprevir blister packs at room temperature not in the refrigerator.

Elbasvir/grazoprevir is to be administered once daily with or without food at the same time each day.

Each subject must be given the following instructions:

- maintain approximately the same daily dosing interval between study drug doses;
- swallow the study medication tablet whole;
- only remove the tablet immediately prior to dosing.

For a missed dose of study medication that is within 16hrs of the usual time of dosing, subjects should be instructed to take the missed dose of study medication as soon as possible during the same day. However, no more than the daily dose of elbasvir/grazoprevir should be taken on any calendar day.

Subjects should be cautioned never to double the next dose with a missed dose of study drug under any circumstances.

6. Data Collection

The following electronic data capture systems will be used for DARLO-C:

- OpenClinica for collection of clinical data
- ODK via tablet computer for collection of questionnaire data

7. Reporting Adverse Events and Serious Adverse Events

Adverse events will not be collected and reported as part of the DARLO-C study.

Only Serious Adverse Events encountered during treatment and for **4 weeks** after drug discontinuation must be reported on the Serious Adverse Event Form (found in the **Investigator Site File**) and on the SAE page of the case report form (CRF) in OpenClinica.

8. Monitoring and Quality Assurance

The DARLO-C study will be monitored. Sites can expect a minimum of three monitoring visits during the study. At a minimum, sites will have a site initiation visit, a monitoring visit during study conduct and a close out visit.

The study coordinator will contact the site 4 weeks prior to the proposed date to request a monitoring visit.

Two weeks prior to the confirmed visit date the study coordinator will provide the site with a list of patients which will be monitored. The site must ensure the medical record for the patients listed are available on the visit day.

9. Participant reimbursement

Participants will be reimbursed for their time and reasonable travel expenses for ALL study visits on the DARLO-C study. Each participant will be reimbursed $30 for each visit which equates to $390 over the course of the study. Payment will be in cash or vouchers depending on the clinic you attend.

9.1 Obtaining a participant reimbursement advance

- On receipt of the signed clinical trial agreement (CTRA) which contains the participant reimbursement payment details in Schedule 2, the Institution should submit a tax invoice for AUD1000 for participant reimbursement or notify the DARLO-C Project Coordinator that they would prefer the Kirby Institute to provide vouchers.
- If the Institution chooses to submit a tax invoice, they are responsible for drawing cash, cheque or vouchers to be stored at the clinic site.
- If the Institution chooses for the study to provide the vouchers, receipt of the vouchers must be acknowledged (by email, fax or phone contact) as per instructions from the DARLO-C Project Coordinator.
- After the Project Coordinator has received the acknowledgement from the institution, the vouchers will be activated. The vouchers are required to be activated prior to being given out to participants.
- The money/vouchers remain the responsibility of the DARLO-C site PI or designee, who will be responsible for their tracking and acquittal.

9.2 Storing and maintaining the money/vouchers

- The money/vouchers must be kept in a safe and secure manner at the site.
- Only DARLO-C study staff should have access to the money/vouchers.
- To minimise risk, when participant payments are made, the DARLO-C staff member should only take the required amount of money/vouchers and place it in an envelope.

9.3 When should participant reimbursement be made?

Each participant will be reimbursed $30 for ALL study visits which equates to $390 over the course of the study. Payment will be in case or vouchers depending on the clinic you attend.

9.4 Accounting for money/vouchers

- When the participant receives the money/voucher, for acquittal purposes, it is essential that they sign the participant reimbursement tracking log found found in the **Investigator Site File**.
- Sites may use their own clinic/hospital receipt. If so, receipts should be kept in the ISF to allow for the acquittal of the money/vouchers as required by the CRG.
- A tracking log of participant reimbursements (attachment 4) recording all monies/vouchers paid is to be maintained and should be stored in Section 10 of the ISF.

9.5 Acquittal process

- As requested by the clinical project coordinator, the institution must submit a copy of the tracking log for the acquittal of the money/vouchers. The original tracking log is kept at the institution.
- Upon request by the clinical project coordinator, any unspent money/vouchers will be returned to the CRG as per the clinical trial agreement (CTRA) which contains the participant reimbursement payment details in Schedule 2.

9.6 Re-ordering of Money/Vouchers

If more money/vouchers are required, the institution must submit a copy of the tracking log to CRG for acquittal as described in Section 10.5 with either the participant reimbursement voucher request form (found in the **Investigator Site File**) for vouchers or a tax invoice for additional money as described in Section 10.1.

9.7 Monitoring of reimbursement

The storage, allocation and tracking of money/vouchers (including the signed tracking log) will be checked at the monitoring visits.