SMART-C

Simplified Monitoring – A Randomised Trial in hepatitis C

VHCRP1701

A phase IIIb, open-label, multicentre, international randomised controlled trial of simplified treatment monitoring for 8 weeks glecaprevir (300mg)/pibrentasvir (120mg) in chronic HCV treatment naïve patients without cirrhosis

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Pharmacy Manual

Study Specific Supplement

Version 1.0 dated 9 Aug 2017

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1. Communication, Contacts and Summary of Procedures

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

2. Study Identifiers

1. Protocol number: 1701 (used in participant ID number from baseline onwards)
2. Screening Number: 333 (used in screening ID at screening visit only)

At sites where regulations restrict the collection of full date of birth and/or initials, the following conventions will be used:

- Date of birth will be entered as 01/01/YYYY
- Initials will be entered as AA-AA, BB-BB, CC-CC etc.

3. Protocol Synopsis

Rationale	Current standard on-treatment monitoring in clinical trials involves clinic-based visits every 4 weeks. In the DAA era where treatments are highly tolerable, effective and short duration, this intensive monitoring strategy may no longer be required. A simplified on-treatment monitoring strategy is hypothesised to be non-inferior to the standard clinical trial on treatment monitoring strategy. If successful, a simplified on-treatment monitoring strategy is likely to be highly attractive to patients, clinicians and health care payers. It has the potential to improve the rapid

	scale up of treatment providing population level benefits in the reduction of global hepatitis C disease burden.
Study Design	Phase IIIb, randomised, controlled, multicentre, international trial. Eligible patients will be randomised into one of two on-treatment monitoring strategies; standard clinical trial monitoring (4-weekly on-treatment visits) vs simplified monitoring (no on-treatment visits). Randomisation will be 1:2 (standard vs simplified) and all participants will receive treatment with glecaprevir (300mg)/pibrentasvir (120mg) for 8 weeks.
Primary Objective	To compare the proportion of participants with undetectable HCV RNA (HCV RNA <LLOQ) at 12 weeks post-treatment (SVR12) following 8 weeks treatment with glecaprevir (300mg)/pibrentasvir (120mg) in HCV treatment naïve non-cirrhosis chronic HCV patients who have received a standard versus simplified schedule of safety and virological monitoring
Hypotheses	In treatment naïve non-cirrhosis patients with chronic HCV (genotypes 1-6) the sustained virological response rate 12 weeks following treatment with glecaprevir (300mg)/pibrentasvir (120mg) among those receiving a simplified monitoring schedule will be non-inferior to that in those receiving a standard monitoring schedule based on the intention-to-treat (ITT) population.

4. Study Products

The study product used in SMART-C is glecaprevir/pibrentasvir. All study drugs will be provided by AbbVie Pty Ltd.

Glecaprevir/pibrentasvir is a fixed-dose combination of glecaprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and pibrentasvir, an HCV NS5A inhibitor, and is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection.

4.1 Study product information

Product information for glecaprevir/pibrentasvir will be supplied to participating sites as an Investigator's Brochure.

4.2 Packaging

Glecaprevir and pibrentasvir are presented as a co-formulated, film-coated, immediate release tablet. The tablet strength is 100 mg glecaprevir and 40 mg pibrentasvir. The tablets are pink-colored, oblong biconvex shaped and debossed with "2nd" on one side. The tablets do not contain gluten. The tablets contain lactose.

Glecaprevir/pibrentasvir 100mg/40mg tablets are packaged in bottles of 30 tablets. Three bottles are required for 4 weeks of treatment (this includes two extra days of treatment). Participants in the Standard Arm will require 3 bottles at baseline and 3 bottles at week 4. Participants in the Simplified Arm will require 6 bottles at baseline.

4.3 Labelling

Study products will be labelled with a label booklet or a single panel label affixed to the outside of the bottle. The booklet label contains the label for each country. The label for each country may vary slightly and will be translated into the local language as per country specific requirements. The drug label contains the following:

- Subject ID
- Investigator's name
- Lot number
- Expiry date
- Dosing instructions
- Storage instructions

No re-labelling of the study drug is expected. In case re-labelling is needed, the sponsor will provide detailed guidance and documentation.

The pharmacist will complete the following fields on the label: "**Subject ID"** and **"Investigator's name"**.

Sponsor: University of New South Wales UNSW Sydney NSW 2052 Australia Tel: +61 2 9385 0900
Protocol: VHCRP1701 - SMART-C
Investigator: _____
Glecaprevir/Pibrentasvir 100 mg/40 mg Film-coated Tablet
30 Tablets
FOR ORAL USE ONLY
Lot Number: **XX-XXXXXX**
Expiry Date: **DD MM YYYY**
Subject ID: **1701-_____-__**
Bottle #: _____
Take as directed by your Investigator.
Store below 25°C. Keep out of the reach of children.
For Clinical Trial Use Only.

Figure 1: Study drug label for Australia/New Zealand

NOTE: The bottle number will be pre-filled with a number by AbbVie. This number has no specific meaning for SMART-C. Bottles can be dispensed in any order.

5. Storage

Glecaprevir/pibrentasvir should be stored between 15°C (59°F) and 25°C (77°F).

Temperature excursions outside the storage range are to be reported to *The Kirby Institute, UNSW Sydney* within **24 hours** using the *Investigational Product Storage Temperature Deviation Notification Form* (Attachment D). The drug product must be quarantined until Kirby Institute instruction.

For each temperature excursion, The Kirby Institute will advise whether the drug is still usable or must be destroyed.

Care should be taken to ensure that the study drug is stored in dry conditions.

Study participants should be counselled by the study staff to store glecaprevir/pibrentasvir bottles at room temperature, not in the refrigerator.

6. Handling

6.1 Study Drug received at the site

It is planned that a maximum of 10 participants will be enrolled at each site. Only one study drug shipment is planned for each site. This initial shipment will contain all drug supply for 8 weeks for the planned number of enrolled participants at each site. On receipt of the study drug, ensure that the information on the packing slip matches the study product received. Please complete Section 3 of the Study Product Order and Receipt Form (Attachment C) and email to smartc@kirby.unsw.edu.au or fax a copy to +61 2 9385 9214.

Study drug re-supply is not planned. However, study drug stock for each site will be closely monitored by the Project Coordinator and a re-supply will be organised if needed.

6.2 Dispensing procedures

Only authorized site personnel according to the SMART-C Site Signature and Study Responsibilities Log can dispense the study drug.

At baseline (week 0), participants will be randomised into the standard monitoring or simplified monitoring group. Site personnel are responsible for the randomisation and to provide these details to the site pharmacy or the site personnel responsible for dispensing the study drug. The quantity of study product to dispense varies depending on the study arm as follows:

- **Standard monitoring** arm participants will be dispensed with 4 weeks treatment supply (3 bottles) at Baseline and 4 weeks treatment supply (3 bottles) at Week 4 visit.
- **Simplified monitoring** arm participants will be dispensed with 8 weeks treatment supply (6 bottles) at Baseline.

  NOTE: each bottle contains two extra tablets

6.3 Accountability Requirements

The Master Investigational Product (IP) Accountability Log (see Attachment A) is to be used to record receipt of study drug deliveries, study drug dispensing, balance of study drug on hand and study drug returns to site at SVR12.

Dispensing:

Record the date dispensed, participant ID, randomisation group, number of bottles dispensed, dispensed by and balance remaining for each dispensing.

Returns:

All participants will be required to return the study drug to the site at the SVR12 visit. Returned study drug must not be dispensed again. Study drug may not be relabeled or reassigned for use by other participants. A tablet count for each return must be performed.

Enter date returned, number of bottle returned, number of tablets returned and returned for each participant.

For participants in the Standard Arm, please complete the study drug return details against the week 4 dispensing. The baseline dispensing should have no returns against it. You should enter the comment “recorded at week 4” into the baseline returns column.

SMART-C

Master Investigational Product (IP) Accountability Log

Kirby Institute

Sponsor: Kirby Institute	**Protocol Number:** VHCRP1701	**Investigational Product:** Glecaprevir/pibrentasvir
Site Name:	**Site number:**	**Principal Investigator:**

Lot/Batch No.:		**Expiration Date:** (dd/mm/yy)	
Shipment 1	Date received (dd/mm/yy):	Received by (initials/date):	Number of bottles received:
Shipment 2	Date received (dd/mm/yy):	Received by (initials/date):	Number of bottles received:

IP Dispensation						**IP Return**				**Comments**
Date dispensed (dd/mm/yy)	**Participant ID number**	**Rand. group**	**Number of bottles dispensed**[1]	**Dispensed by** (initials/date)	**Stock available after dispensation** (number of bottles)	**Date returned** (dd/mm/yy)	**Number of bottles returned**	**Number of tablets returned**	**Returned to** (initials/date)	
		☐ Standard ☐ Simplified								
		☐ Standard ☐ Simplified								
		☐ Standard ☐ Simplified								
		☐ Standard ☐ Simplified								
		☐ Standard ☐ Simplified								
		☐ Standard ☐ Simplified								
		☐ Standard ☐ Simplified								

[1]Participants in the standard arm will be dispensed with four-week supply (three bottles) at Baseline and Week 4 visits. Participants in the simplified arm will be dispensed with eight-week supply (6 bottles) at Baseline visit.

SMART-C

Kirby Institute

Pharmacy: Master Participant Randomisation Log

Study Title:	**SMART-C**	**Site Name:**	
Protocol Number:	**VHCRP1701**	**Site Number:**	
Sponsor:	**The Kirby Institute**	**Principal Investigator:**	

Participant ID	Medical Record Number	Participant Name	Date of Birth *(dd-mm-yyyy)*	Randomisation arm
1701-				☐ Standard ☐ Simplified
1701-				☐ Standard ☐ Simplified
1701-				☐ Standard ☐ Simplified
1701-				☐ Standard ☐ Simplified
1701-				☐ Standard ☐ Simplified
1701-				☐ Standard ☐ Simplified
1701-				☐ Standard ☐ Simplified

INFORMATION IS STRICTLY CONFIDENTIAL

Attachment C: SMART-C Product Order and Receipt Order Form

SMART-C

UNSW SYDNEY

Kirby Institute

Study Product Order and Receipt Form

Site number:	**Date of order:** Day Month 2 0 Year
Site name:	
Principal Investigator:	

TO BE COMPLETED BY THE KIRBY INSTITUTE

SECTION 1: ORDER DETAILS			
Product name: Glecaprevir/Pibrentasvir		Quantity required: *(number of bottles)*	
Shipping details:			
Receiver's name		Receiver's phone number	
Receiver's delivery address		Receiver's fax number	
		Receiver's email	
Order requested by:			
Name:	Signature:	Date:	

TO BE COMPLETED BY THE STUDY DRUG DISTRIBUTOR

SECTION 2: DISPATCH DETAILS			
Batch No.:	Expiry date: *(dd/mmm/yyyy)*	Quantity sent: *(number of bottles)*	
Order prepared by:			
Name:	Signature:	Date of shipment:	

TO BE COMPLETED BY THE STUDY PRODUCT RECEIVER

SECTION 3: RECEIPT DETAILS			
Quantity received: *(number of bottles)*	Was the shipment received in good condition*: Yes ☐ No ☐ **(sealed boxes, complete documentation, shipment details, study product details & shipment conditions)*		
Comments: *(if applicable)*			
Order received by:			
Name:	Signature:	Date:	

Send completed form to the SMART-C Project Coordinator by fax (+61 2 9385 9214) or email to smartc@kirby.unsw.edu.au

RETAIN ORIGINAL IN THE PHARMACY FILE

Attachment D: SMART-C Investigational Product Storage Temperature Deviation Form

SMART-C

Protocol Title: A phase IIIb, open-label, multicentre, international randomised controlled trial of simplified treatment monitoring for 8 weeks glecaprevir (300mg)/pibrentasvir (120mg) in chronic HCV treatment naïve patients without cirrhosis

Protocol No: VHCRP1701

INVESTIGATIONAL PRODUCT STORAGE TEMPERATURE DEVIATION FORM

Please **EMAIL** this notification to smartc@kirby.unsw.edu.au **OR FAX** to +61 2 93859214

Site:_____ **Site Number:**_____ **Investigator**_____

Product affected by temperature deviation	Glecaprevir (100mg)/Pibrentasvir (40mg) tablets
Date of start of temperature deviation	____/ _____/ _____ *(dd/mon/yyyy)*
Temperature Excursion *[Temperature excursion defined as storage temperature outside 15°C (59°F) - 25°C (77°F)]*	
Duration of Temperature Excursion	
Quantity Affected *(i.e. number of bottles)*	
Description of Event *(Including action taken/quarantine details)*	

PLEASE ATTACH AN UP-TO-DATE STORAGE TEMPERATURE LOG

Name of person reporting deviation **Signature** **Date**

KIRBY INSTITUTE TO COMPLETE		
Outcome	☐ Acceptable temperature excursion - *Investigational product considered to be safe to use.* ☐ Unacceptable temperature excursion - *Investigational product to be destroyed as per Kirby Institute instructions.*	
Name	**Signature**	**Date**

SMART-C Investigational Product Storage Temperature Deviation Form V2.0_9Aug2017