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Annual Report to the Environmental Protection Agency and Ministry of Primary Industries (NZ)

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1 List of Abbreviations

AE	Adverse Event
CNS	Clinical Network Services
CV	Curriculum Vitae
DIR	Dealing Involving Release
EPA	Environmental Protection Agency
GM	Genetically Modified
GMO	Genetically Modified Organism
ICF	Informed Consent Form
MPI	Ministry of Primary Industries
NZ	New Zealand
OGTR	Office of the Gene Technology Regulator (Australia)
SAE	Serious Adverse Event
SIV	Site Initiation Visit

2 Introduction

In accordance with Control 7 of the "EPA-MPI compliance expectations for APP202601 controls". *The New Zealand sponsor must submit a report that shows compliance with the above controls, to the EPA and MPI, six months after the commencement of the Phase 3 clinical trial, then on or before 30 June every year thereafter until the conclusion of the Phase 3 clinical trial*.

This is the first report to the Environmental Protection Agency (EPA) and Ministry of Primary Industries (MPI) regarding the Genetically Modified Organism (GMO) "Pexa-Vec", approved for use in a clinical trial on the 27th October 2015. This report outlines a summary of the evidence/information demonstrating compliance provided to the EPA and MPI, for the period of approximately six months after the commencement of clinical trial (first patient dosed) on the 20th January 2016, in the control (Standard of care arm, Sorafenib), however, the first patient dosed with Pexa-Vec was on 29th March 2016.

3 Compliance Measures

The EPA approved the study on the 27th October 2015 until the conclusion of the Phase 3 trial. SillaJen is the Applicant and Clinical Network Services (CNS) Pty Ltd is the NZ Agent/Consultant. The first Site Initiation Visit (SIV) was conducted in New Zealand (NZ) on the 14th and 15th of December 2015 at the Auckland clinical trials unit.

The EPA was notified by CNS of the planned commencement of the study in Auckland on the 23rd December 2015, one month prior to the first patient being dosed (in the control cohort), in accordance with Control 2 of the EPA-MPI compliance expectations for APP202601 controls. An additional notification was sent on the 19th May 2016 to notify the EPA of an additional site in Christchurch. Although the patients at the Christchurch site will not receive Pexa-Vec (receiving the standard of care only, Sorafenib), they are part of the study group.

The CV and medical registrations of medical practitioners injecting Pexa-Vec intratumourally were provided to the EPA in accordance with Controls 2 and 3 which show the investigator's involved in the study are appropriately qualified.

All appropriate personnel have been trained in the handling of this GMO product in accordance with Controls 1, 2 and 3 (records can be provided to the EPA on request). In addition, according to Control 1 (Note 1), the date(s) de-identified trial participants were intratumorally administered with Pexa-Vec, including the name of the practitioner who administered Pexa-Vec and where the administration occurred (trial site), has been recorded in a master

checklist. The signed master checklist can be provided to the EPA and MPI on request. This is listed on each IT injection preparation and administration sheet and the master checklist will be the site delegation log which lists who is registered to perform the study and their roles/responsibilities.

The following documentation has been provided to the EPA on the 19th August 2015 during the submission/approval period:

- The completed application form to obtain approval to release new organisms (with references)
- The Phase 3 clinical trial protocol
- Additional confidential information (the structure of Pexa-Vec and the genetic elements of the expression cassette of Pexa-Vec).
- The Investigator's Brochure for the Phase 3 clinical trial
- CVs for the Principal Investigator (Professor Gane) and the interventional radiologists (Drs Holden and Merriless) at the Auckland clinical trial site
- Pexa-Vec usage guidelines
- The attachments for the "Dealings including intentional release"(DIR) license submitted in Australia
- The Genetically Modified (GM) checklist for Pexa-Vec
- Protocol for Pexa-Vec Transmission Investigations and Concerned Staff (dated 23rd December)
- The Master Informed Consent Form (ICF)
- The Instructions for Participants
- Site initiation checklist
- Pexa-Vec JX594-HEP024 monitoring visit checklist
- Pexa-Vec JX594-HEP024 process flow
- Pexa-Vec JX594-HEP024 license signature sheet
- Medical waste disposal procedures in place at the clinical trial site
- SillaJen risk matrix
- Pexa-Vec JX594-HEP024 Biohazard container accountability log

In accordance with Control 4, patients were provided with a biohazard container before treatment for the disposal of any dressings used to dress the pustules. Individuals were instructed to return these containers to the trial site for medical waste disposal, instructions which are documented in the ICF (ADHB ICF Version 1. 4 dated 22nd December 2015 based on NZ Main ICF V1.4 dated 15th December 2015).

Control 7 states, please provide a signed statement from the person(s) responsible for Control 4a-b that declares all trial participants were provided with a biohazard container before Pexa-Vec administration, and were instructed to return the biohazard container. A copy of the Biohazard accountability log will be sent to CNS to forward to the EPA/MPI on request.

In accordance with Control 5, there have been no occurrences of Pexa-Vec-induced adverse effects resulting from confirmed events of Pexa-Vec transmission from Pexa-Vec treated individuals to untreated individuals or animals, notifiable to the EPA/MPI. Standard safety blood samples as per the protocol are sent to a central lab in Singapore.

A contingency plan identifying appropriately qualified people that are available to investigate reports of adverse effects suspected to be related to Pexa-Vec transmission has been developed.

- Contingency plans v1.0_12Feb2016

This document covers both EPA/MPI and Australian Office of the Gene Technology Regulator (OGTR) Dealing Involving Release (DIR) 140 licence conditions. This document is available on request.

4 Adverse Events

There have been one (1) report of Serious Adverse Events (SAEs) in a patient dosed with Pexa-Vec in New Zealand (cut-off date 6th June 2016). Two (2) SAEs has been reported in the US in a patient dosed with Pexa-Vec. All of the SAEs were non-transmission SAEs. Notably, there have been no reports of AEs/SAEs resulting from confirmed events of transmission to date and there is no requirement under the EPA controls to report AE/SAEs that do not result in transmission. Serious adverse event listings are available on request.

No transmissions to other persons or animals have been reported to date. Patients who developed pustules were given biohazard containers and trained on pustule management, In accordance with EPA-MPI controls. The development of pustules following Pexa-Vec administration is deemed expected. No other concerns have been noted.

In accordance with Control 6, adequate stocks (at least 2 doses) of Vaccinia Immunoglobulin (VIG) and cidofovir, within their expiry dates, are stored at the Auckland clinical trial site and will be for the duration of the trial. Practically speaking, this equates to 12 vials of VIG where 8.4 vials are needed for a 70 kg person. So, 12 vials would cover one dose for a large or average person and 2 doses for small (up to 50 kg) patients. Additional stock is held in Singapore to send as needed (26 hours total delivery time).

Two vials of cidofovir are kept at the Auckland clinical trial site. One vial equates to one dose for a patient up to 75 kg, so two vials of cidofovir should equate to two doses. Again, there are additional stocks in Singapore that can be shipped if needed.

Currently, there are 12 Vials of Vaccinia immunoglobulin – lot#11207673 Expiry: Feb 2022 and two injections of cidofovir – lot# 150130 Expiry: Dec 2016 at the Auckland clinical trial site.