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Evaluation of VCH-759 monotherapy in hepatitis C infection☆

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***Background/Aims*: VCH-759 is a non-nucleoside inhibitor of HCV RNA-dependent polymerase with sub-micromolar IC_{50} values versus genotype 1a /1b replicons.**

***Methods*: The antiviral activity, pharmacokinetics and tolerability of VCH-759 administered as monotherapy for 10 days with a 14 day follow-up period were evaluated in 31 treatment-naïve genotype 1 participants. Three cohorts received: 400 mg thrice (t.i.d.), 800 mg twice (b.i.d.), 800 mg t.i.d or placebo.**

***Results*: VCH-759 was well tolerated with the most frequent adverse event being gastrointestinal upset in both the active and placebo groups attributable, in part, to the dosing vehicle. VCH-759 was rapidly absorbed and trough plasma levels were at or above the IC_{90} (non protein-adjusted) for all dosing regimens. The mean maximal decrease in HCV RNA $\log_{10}$ (IU/mL) was 1.97, 2.30 and 2.46 for 400 mg t.i.d., 800 mg b.i.d. and 800 mg t.i.d. doses. Viral polymerase genotypic sequencing revealed emergence of HCV variants in a majority of participants that coincided with on-treatment viral rebound.**

***Conclusions*: VCH-759 was well tolerated and achieved a $\geqslant 2$ $\log_{10}$ decline in HCV RNA with 800 mg b.i.d. and t.i.d doses. In a subset of participants, viral rebound was observed and associated with resistant variants. This data supports further evaluation of VCH-759 in combination with interferon–ribavirin treatment.**

***Keywords*: Non-nucleoside NS5b inhibitor; Proof-of-concept study; Antiviral activity; Safety and tolerability; Pharmacokinetics; Variant identification**

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Abbreviations: HCV, hepatitis C virus; RNA, ribonucleic acid; IC_{50}, 50% inhibitory concentration; t.i.d., three times daily; b.i.d., twice daily; IC_{90}, 90% inhibitory concentration; DNA, deoxyribonucleic acid; TI, therapeutic index; CC_{50}, 50% cytotoxic concentration; PK, pharmacokinetic; PIB, powder-in-bottle; RV, reconstitution vehicle; BMI, body mass index; ALT, alanine aminotransferase; PP, per-protocol; C_{max}, maximum concentration; T_{max}, time at maximum concentration; AUC, area-under-the-curve; $t_{1/2}$, half-life; LC/MS/MS, liquid chromatography/mass spectrometer/mass spectrometer; AE, adverse event; GI, gastro-intestinal; AST, aspartate aminotransferase; SD, standard deviation; SVR, sustained virological response; RVR, rapid virological response; STAT-C, specifically targeted antiviral therapy for Hepatitis C.

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1. Introduction

The hepatitis C virus (HCV) is a 9.6 kb positive strand ribonucleic acid (RNA) virus of the flaviviridae family, genus hepacivirus. The genome comprises a single open-reading frame coding for a ~3000 amino acid polypeptide which is further processed into individual structural (core, E1 and E2) and non-structural (NS2, NS3, NS4A, NS4B, NS5A and NS5B) proteins by host and viral NS2 (zinc-dependent) and NS3 (chymotrypsin-like) proteases [1]. The non-structural proteins function as enzymes or accessory factors involved in genomic replication. The viral replication strategy is similar to that of other positive strand viruses, with the initial synthesis of a replicative intermediate negative strand RNA by the NS5B RNA-dependent RNA polymerase. This negative strand RNA then serves as a template for genomic RNA production. The NS3 and the NS5B enzymes are key targets for anti-HCV therapy, as they are essential for HCV replication and infectivity [2–5]. The NS5B enzyme has the characteristic right-handed "fingers-palm-thumb" domain of polymerases [4]. The active site, which resides in the palm region, contains the conserved GDD motif of polymerases and is partially enclosed by the finger and thumb domains.

VCH-759 is a novel substituted thiophene-2-carboxylic acid derivative non-nucleoside inhibitor of HCV NS5B polymerase genotype 1a and 1b. This compound inhibits the NS5B (IC_{50} 1a = 0.41 μM and IC_{50} 1b = 0.38 μM) by binding to an allosteric site in the 'thumb' domain situated ~35 Å from the active site. X-ray crystallography studies suggest that inhibition of RNA synthesis initiation may result from enzyme conformational changes induced by occupancy of the compound binding site [6]. VCH-759 is active against HCV sub-genomic replicon in Huh-7 cells ($IC_{50} \approx 0.3$ μM for both 1a and 1b genotypes). The compound is also selective for the HCV NS5B polymerase relative to human DNA polymerases α, β and γ ($IC_{50} > 100$ μM). VCH-759 has a good *in vitro* therapeutic index (TI) (CC_{50}/IC_{50}) > 600 and non-clinical safety profile.

Given an estimated 170 million people worldwide infected by HCV and limitations of currently available interferon-based therapies, there is an important unmet need for novel, more effective, more convenient, and better tolerated anti-HCV treatments [7]. Hence, we evaluated the antiviral activity, safety, tolerability and HCV variant selection of VCH-759 administered as monotherapy for 10 days in HCV genotype 1a or 1b-infected treatment-naïve participants. Pharmacokinetic (PK) profile, plasma HCV RNA kinetics and correlation between VCH-759 plasma trough levels and HCV RNA reduction were also assessed.

2. Patients and methods

2.1. Study design

This was a randomized, double-blinded, placebo-controlled study conducted following research ethics review/institutional review board and approval at all participating sites. Consenting participants were assigned to VCH-759 doses (400 mg t.i.d., 800 mg b.i.d. and 800 mg t.i.d.) or corresponding placebo in a 3:1 ratio ($n = 12$ for 400 and 800 mg t.i.d. cohorts; $n = 8$ for 800 mg b.i.d cohort). Dosing occurred daily under direct supervision for 10 days at 7h:00, 13h:00 and 21h:00 for t.i.d. dosing, and at 7h:00 and 19h:00 for b.i.d. dosing. Before dosing, participants were required to consume a light meal. VCH-759 was supplied as an oral solution formulation in individual 120 mL clear glass bottles. The oral solution was reconstituted by combining the appropriate VCH-759 powder-in-bottle (PIB) dose in a 30% polyethylene glycol 400/15% Solutol® HS15 aqueous reconstitution vehicle (RV) (20 and 40 mL for the 400 and 800 mg doses, respectively).

2.2. Participants

Treatment-naïve, genotype 1-infected male or female participants between 18 and 60 years of age with a body mass index (BMI) ⩽33 kg/m^2 were recruited. Baseline plasma HCV RNA greater than 100,000 IU/mL, alanine aminotransaminase (ALT) values less than five times the upper limit of normal and a Metavir liver fibrosis stage between 0 and 3 were required.

2.3. Endpoint measures

The primary endpoint was defined as the absolute change in plasma HCV RNA levels between baseline to nadir measured with the COBAS Amplicor® HCV Monitor v.2 kit (Roche Diagnostics, Laval, QC). Blood samples for evaluation of the plasma HCV RNA viral load were collected at screening, before the first dose on Days 1–10 and at follow-up visits (Days 11, 17 and 24). Blood samples for NS5B polymerase sequencing were collected before the first dose on Day 1 and on Days 11, 17 and 24. Sequence analyses were performed at ViroChem Pharma.

The complete PK profile was obtained on Days 1 and 10 for the first daily dose. Approximately 6 mL of blood were collected at the following time points: for the t.i.d. cohorts, at 10 min before dosing (nominal time 0) and at 0.5, 1, 1.5, 2, 3, 4, 5 and 6 h after administration of study medication and for the b.i.d. cohort, 10 min before the morning dose (nominal time 0), at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8 and 10 h after administration of the study medication, and at 5 min before the evening dose (nominal time 12 h). For determination of pre-dose VCH-759 trough levels, blood was drawn within 10 min before the first dose on Days 2, 3, 4, 5, 6, 7, 8 and 9. On Day 11, blood sampling for VCH-759 plasma trough level quantification was collected at the same time as the Day 9 blood draw. A validated liquid chromatography/mass spectrometer/mass spectrometer bio-analytical method for the evaluation of VCH-759 plasma concentration was used [unpublished internal report; Anapharm, Quebec, Canada].

2.4. Statistical methods

The data were summarized using descriptive statistics. Change in plasma HCV RNA from baseline to subsequent time points was evaluated by a two-sample *t*-test. Comparisons between dosing groups and their respective placebo group were performed. Analyses of antiviral activity were based on per protocol (PP) participant population. A series of PK parameters (e.g., C_{max}, T_{max}, AUC, $t_{1/2}$) were determined from blood samples collected at pre-specified time points. Correlations between VCH-759 trough plasma levels and plasma HCV RNA from Day 2 through end of treatment were analyzed by Pearson's correlation coefficient.