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Preclinical and Clinical Development of a Novel Ondansetron Extended-Release Injectable Suspension: Evaluation of Safety, Efficacy and Pharmacokinetics in Moderately and Highly Emetogenic Chemotherapy

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Abstract

Chemotherapy-Induced Nausea and Vomiting (CINV) has a great negative impact on cancer therapy and patient's quality of life. The objective of the current investigation is to establish the safety, efficacy and pharmacokinetics of novel Ondansetron Extended-Release Injectable Suspension (OERIS) through preclinical and clinical development. Maximum tolerated dose assessment, sub-acute toxicity study in rats, pharmacokinetic study in dogs were carried out on OERIS to support safety and pharmacokinetics. Further, in healthy volunteers (Phase-1), 3 doses (35, 70 and 100 mg) of OERIS were administered to evaluate the pharmacokinetics and safety profile. In an Investigator initiated trial with patients receiving Moderately Emetogenic Chemotherapy (MEC) and Highly Emetogenic Chemotherapy (HEC), OERIS (100 mg/ml, i.m.) was evaluated along with dexamethasone (8 mg, i.v.). The primary end point was complete response (no emesis or rescue medication) in acute and delayed phases of CINV. No toxicity was observed with OERIS and the No Observed Adverse Effect Level (NOAEL) was found to be 150 mg/kg, i.m. in rats, which is approximately 160 times of recommended ondansetron human dose (0.15 mg/kg, i.v.). OERIS provided prolonged release of drug for ≥ 5 days for prevention of acute and delayed phases of CINV in patients receiving MEC and HEC. Further, OERIS prolonged the therapeutic plasma concentrations of drug, that was well tolerated and found to be safe in healthy human volunteers. With the Investigator initiated trial, OERIS has shown 100% complete response in acute phase of MEC and HEC, whereas complete response in delayed phase was observed to be 83.33% and 66.67% in MEC and HEC patients respectively. To conclude, OERIS demonstrated good safety and efficacy along with favorable pharmacokinetics in patients receiving MEC/HEC, which could be a promising therapy with improved patient compliance and thereby the therapeutic outcome.

Keywords: Chemotherapy; CINV; extended release; HEC; MEC; MTD; NOAEL; ondansetron

Abbreviations: 5-HT: 5-Hydroxy tryptamine; AE: Adverse Event; AUC: Area Under Curve; CC: Complete Control; CR: Complete Response; CINV: Chemotherapy-induced Nausea and Vomiting; ER: Extended Release; ECOG: Eastern Cooperative Oncology Group; FDA: Food and Drug Administration; HEC: Highly emetogenic chemotherapy; IAEC: Institutional Animal Ethics Committee; IEC: Institutional Ethics Committee; IIT: Investigator Initiated Trial; IP: Investigational Product; LLOQ: Lower Limit of Quantification; MEC: Moderately emetogenic chemotherapy; MTD: Maximum Tolerated Dose; NK1: Neurokinin-1; NOAEL: No Observed Adverse Effect Level; OECD: Organization for Economic Co-operation and Development; OERIS: Ondansetron Extended Release Injectable Suspension; PK: Pharmacokinetics; QoL: Quality of Life; RLD: Reference Listed Drug; SD: Sprague-Dawley; TR: Total Response; ULN: Upper Limit of Normal; ULOQ: Upper Limit of Quantification

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is the most common and distressing side-effect of moderately and highly emetogenic chemotherapy regimens, which can affect up to 40% of cancer patients. Nausea and vomiting are the most feared as well as the most common adverse effects among the patients undergoing chemotherapy [1]. CINV can interference with activities of daily living, suggesting a profound negative effect on patient's quality of life [2,3]. Fear of chemotherapy-induced nausea

and vomiting is sufficient for many patients to postpone or even refuse potentially life-saving treatment. However, antiemetics can reduce the emesis, increases the treatment compliance and thereby the effectiveness of treatment, hence can improve the patient outcome. Despite the development of new antiemetic agents, CINV remains an issue for many patients [4]. Moreover, there is substantial financial burden associated with CINV due to the substantial costs of antiemetic medications [5]. Hence, cost effective medicines are also the need of the hour in addressing the CINV in cancer patients. Further, there are diverse unmet medical needs, viz., identifying and managing patients prone to CINV, optimizing the control of non-acute forms of CINV, and improving the patients' adherence to cancer treatment guidelines [6-8].

5-HT3 receptors are ubiquitous in the enteric, sympathetic, parasympathetic and sensory nervous systems and in the central nervous system (CNS). In humans, 5-HT3 receptors are mainly expressed in enterochromaffin cells of the gastrointestinal mucosa, which are innervated by vagal afferents, and the area postrema of the brain stem, which forms the chemoreceptor trigger zone (CTZ) [9,10]. Ondansetron was initially approved for medical use in 1991 as a competitive and selective antagonist of serotonin (5-hydroxytryptamine) 5-HT3 subtype receptors, which is intended for the prevention and treatment of nausea and vomiting associated with initial and repeat courses of emetogenic chemotherapy and the postoperative nausea and/or vomiting (Zofran FDA Label, 2021).

Ondansetron's precise mode of action in the control of nausea and vomiting is unknown. Chemotherapeutic agents and radiotherapy may cause release of 5-HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-HT3 receptors. Ondansetron blocks the initiation of this reflex. Further, activation of vagal afferents may also cause a release of 5-HT in the area postrema, located on the floor of the fourth ventricle, and this can also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is attributed to the selective antagonism of 5-HT3 receptors on neurons located in the peripheral as well as central nervous system [11,12]. It is 100 times more potent than metoclopramide at this site and shows limited binding to other receptors and has a wide therapeutic window. Ondansetron is an effective antiemetic in cancer patients, having both central and peripheral actions in patients undergoing radiotherapy, cytotoxic chemotherapy or general anesthesia [13].

Ondansetron is not highly protein bound (70-76%) over the pharmacologically effective plasma concentration range of 10 to 500 ng/ml. Circulating drug also distributes into erythrocytes and is extensively metabolized in humans with approximately 5% of radio-labeled dose recovered as the parent compound from the urine. In adult cancer patients, the mean ondansetron elimination half-life was 4 h, and there was no difference in the multi-dose pharmacokinetics over a 4-day period (Zofran FDA Label, 2021). FDA recommends the use of 5-HT3 receptor antagonists as a pharmacological intervention for acute and delayed phases of nausea and vomiting in patients receiving moderately or highly emetogenic chemotherapy. Although various newer classes of antiemetics and other 5-HT3 receptor antagonists are available, ondansetron is still in use widely for CINV [8,14]. Ondansetron is a well-established drug in the market for more than 3 decades and approved for the prevention of nausea and vomiting induced by chemotherapy, radiation and post-operative surgery by USFDA and EMA.

Ondansetron extended release (ER) injectable suspension (OERIS) is a novel formulation of ondansetron developed by Shilpa Medicare with an intention to prevent acute and delayed phases of CINV that provides a therapeutic effect for 5 days following a single i.m. dose. Further, when used in combination with other antiemetic drugs like NK1 receptor antagonists (e.g. aprepitant, fosaprepitant), ondansetron (oral or novel OERIS) also offered an effective and safe alternative therapy in patients undergoing initial and repeated courses of MEC or HEC (Weinstein et al, 2020). This long-acting agent is an important and promising new treatment, which is the need of the hour for patients with cancer, in part because adherence to antiemetic therapy remains low with conventional daily ondansetron therapy. As a single injection, the use of OERIS was found to be effective in preventing acute and delayed phases of CINV associated with cancer patients undergoing MEC or HEC.

Materials and Methods

Shilpa Medicare Limited has developed a novel ondansetron extended-release injectable suspension (OERIS). OERIS is a novel lipid-based drug delivery system which is intended to be administered by intramuscular injection creating a depot in the tissues, there by sustained release of the drug can be achieved with extended pharmacokinetic profile that exceeds 7 days.

Preclinical Studies

Animals and ethical statement

Male and female Wistar and SD rats, male Beagle dogs were used in the current investigation. All the procedures employed in the present investigation were approved by the respective institutional animal ethics committees with prior approvals before initiating any experimental proceedings. For maximum tolerated dose (MTD) study of OERIS by intramuscular route, a total of 56 Sprague-Dawley rats (28 male and 28 female) and for MTD study with intravenous route, a total of 46 Sprague-Dawley rats (23 male and 23 female) were used. Both the protocols were approved by Apollo Biosciences, Institutional Animal Ethics Committee (IAEC ABS-IAEC-008- 2020-21). Further, a total of 96 (48 male + 48 female) Wistar rats were used for 4-week repeat dose (one dose/week) toxicity study. The study has been approved by IAEC of Liveon Biolabs Private Limited (LBPL-IAEC-068- 10/2020). For pharmacokinetic study, 24 male Beagle dogs were used. The test

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site is certified by the committee for the purpose of control and supervision of experiments on animals (CPCSEA Certification No. 1312/PO/RcBiBt-S/RcBiBt-L/09/CPCSEA).

Toxicity studies

Maximum Tolerated Dose (MTD) study

Maximum Tolerated Dose study was conducted in Sprague Dawley (SD) rats as per OECD guidelines and Schedule Y. Ondansetron extended release injectable suspension was administered by intramuscular route weekly once [on Day-0 (After randomization) and Day-7] to 56 (28 male and 28 female) rats, which were divided into six groups viz., Group 1: Vehicle control, Group 2: Ondansetron 12 mg/kg, Group 3: Ondansetron, 108 mg/kg, Group 4: Ondansetron, 168 mg/kg, Group 5: Ondansetron, 216 mg/kg and Group 6: Ondansetron, 288 mg/kg. All the animals were observed for up to 14 days. In case of Maximum Tolerated Dose (MTD) study of ondansetron intravenous injection (Reference formulation or RLD) in Sprague Dawley rats, ondansetron was administered intravenously daily for 14 days to 46 rats (23 male and 23 female), which were divided into four groups viz., Group 1: Vehicle control, Group 2: Ondansetron, 12 mg/kg, i.v. Group 3: Ondansetron, 18 mg/kg, i.v. and Group 4: Ondansetron, 24 mg/kg, i.v. All the animals were observed for up to 14 days for any toxicity signs.

Repeated dose toxicity study

A 4-week repeated dose (one dose/week) toxicity study with two weeks recovery period was conducted according to OECD guidelines to assess the toxicological profile of the OERIS in Wistar rats by intramuscular route. A total of 96 rats (48 male + 48 female) were distributed into eight groups. Rats from G1, G1R groups were administered with placebo/vehicle at a dose volume of 1.5 ml/kg, whereas the G2, G3, and G4, G4R groups were administered with ready to use test formulation at the doses of 40 mg/kg, 100 mg/kg and 150 mg/kg with the dose volume of 0.4, 1.0 and 1.5 ml/kg respectively over a period of 4 consecutive weeks (i.e. five intramuscular injections on day 1st, 8th, 15th, 22nd and 29th) followed by 2-weeks of treatment free period for the recovery groups (G1R and G4R).

Additionally, two reference item (ondansetron injection, i.v.) groups (G5, 6 male + 6 female) and (G5R, 6 male + 6 female) were included and administered through slow bolus intravenous injection daily at a dose of 12 mg/kg with the dose volume of 6 ml/kg for 28 consecutive days, the G5R (recovery) group was followed for additional 2 weeks treatment free period. All the animals were observed for clinical signs, local tolerance at injection site, skin reactions, morbidity/mortality, body weight changes, detailed clinical examination, food consumption, clinical pathology (hematology, coagulation, clinical chemistry and urinalysis), gross pathology, organ weights/index at termination period for main and recovery groups. Histopathological examination was carried out on the preserved organs of placebo control (G1), the high dose (G4) and reference item dose (G5) group of rats.

Pharmacokinetic study in male Beagle dogs

This study was conducted to determine the pharmacokinetics of ondansetron following administration of various ondansetron formulations to male Beagle dogs by intravenous bolus and intramuscular administration. The typical study design is summarized in Table 1. A total of 6 groups were planned with G1 and G2 administered with 4 and 24 mg of RLD ondansetron, i.v., whereas G3 and G4 groups were administered with novel OERIS formulation by two injection sites through i.m. route (TF-2 and TF-3), where as G5 and G6 groups were treated with the same formulation (TF-2 and TF-3) at single injection site by i.m. route.

All the animals were fasted overnight, and feed was provided with 4 h post dose, water was provided ad libitum during the study period. Blood samples were collected from each dog (treated with OERIS, i.m.) at 0 (pre-dose), 0.5, 1, 2, 4, 8, 16, 24, 36, 48, 72, 96, 120, 144, 168 and 240 h post dose. For i.v. route of administration (RLD), blood samples were collected at 0 (pre-dose), 0.167, 0.33, 0.5, 0.75, 1, 2, 4, 8, 12 and 24 h post dose. At each time point, 0.25 ml of blood was withdrawn from jugular vein and transferred to labeled K2EDTA coated tubes as an anticoagulant (200 mM, 20 µL/ml of blood). Plasma samples were stored below -60 ºC until bioanalysis and samples were analyzed for ondansetron content using LC-MS/MS with a Lower Limit of Quantification (LLOQ) of 0.100 ng/ml and Upper Limit of Quantification (ULOQ) of 200 ng/mL.

Clinical studies

Phase 1 Clinical study

An open label, parallel group, dose-escalation, comparative pharmacokinetic, safety and tolerability study were conducted to establish the safety and tolerability of single ascending doses of test arm up to 100 mg dose of novel ondansetron extended-release formulation to determine the maximum tolerated dose (MTD) and the absolute bioavailability of single ascending doses of test arm as i.m. injection. Study also planned to determine single dose pharmacokinetics of test arm as i.m. injection, to assess the dose proportionality of ascending doses of test arm up to 100 mg and further to compare the pharmacokinetics of ondansetron administered as i.m. extended-release injectable suspension with intravenously administered ondansetron injection in 24 healthy subjects. The study had test and reference arms. The test arm was conducted in 3 cohorts, each consisting of 6 healthy adult human subjects. The reference arm was conducted in 1 cohort consisting of 6 healthy adult human subjects. The study was conducted at Cliantha Research Limited, Ahmedabad, Gujarat, India.

Ethical statement

The study commenced only after a written approval was obtained from the IBIOME-Institutional ethics committee. The study was conducted from November 2022 to April 2023 at

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Cliantha Research Limited, Ahmedabad, India.

Inclusion and exclusion criteria

Inclusion criteria

Inclusion criteria included the subjects aged between 18 to 45 years old, both inclusive, Gender: Male and/or non-pregnant, non-lactating female, BMI: 18.5 to 30.0 kg/m2, both inclusive, non-smokers and non-tobacco users, normal skin without obscuring tattoos, pigmentation or lesions, adequate venous access in upper extremities, serum hemoglobin within normal range. Female subjects of childbearing potential should agree to practice effective birth control for at least 30 days after study completion and willing to provide written informed consent to participate in the study.

Exclusion Criteria

Exclusion criteria included the subjects with history of allergic responses to ondansetron or other 5-HT3 receptor antagonists, had significant diseases or clinically significant abnormal findings during screening, any disease or condition like diabetes, psychosis or others, which might compromise the haemopoietic, gastrointestinal, renal, hepatic, cardiovascular, respiratory, central nervous system or any other body system, history or presence of bronchial asthma; Used any hormone replacement therapy within 3 months prior to the dose; Depot injection or implant of any drug within 3 months prior to the dose, used CYP enzyme inhibitors or inducers within 30 days prior to the dose; History or evidence of drug dependence or of alcoholism or of moderate alcohol use; History of difficulty with donating blood or difficulty in accessibility of veins; Positive hepatitis screen, positive test result for HIV antibody and/or syphilis; Volunteers who had received a known investigational drug within seven elimination half-lives of the administered drug prior to the housing; Volunteers who had donated blood or loss of blood 50 ml to 100 ml within 30 days or 101 ml to 200 ml within 60 days or >200 ml within 90 days prior to dosing, intolerance to venipuncture, institutionalized volunteers; Any food allergy, intolerance, restriction or special diet that, in the opinion of the principal investigator or sub-investigator; Used any prescribed medications within 14 days, used any OTC products, vitamin and herbal products, etc., within 7 days; Used grapefruit and grapefruit containing products within 7 days, creatinine clearance values < 90 ml/min, Dehydration (Grade 2 or higher); Volunteer having QT interval > 440 ms (for female) or QT interval > 420 ms (for male) during screening; History of phenylketonuria and received ondansetron within 4 days prior to the dose.

IP administration and blood sampling

In Cohort-1, 2 & 3 of test arm, subjects received single dose intramuscular injection of test product, 0.35 ml (35 mg), 0.7 ml (70 mg) & 1.0 ml (100 mg) respectively. In reference arm cohort, a single dose intravenous injection of reference product (ondansetron, i.v. injection) at strength of 2 mg/mL and a dose of 0.15 mg/kg was diluted in normal saline to make final volume of 75 mL saline solution and administered thrice every 8 hours interval through intravenous route via infusion pump approximately over 15 min (+2 min) in lying down position. For test arm (Cohort-1, 2 & 3), blood samples were collected at pre-dose (0.0 hours) and at 0.167, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 12.0, 16.0, 24.0, 30.0, 36.0, 42.0, 48.0, 54.0, 60.0, 66.0, 72.0, 78.0, 84.0, 90.0, 96.0, 102.0, 108.0, 114.0, 120.0, 126.0, 132.0, 138.0 144.0, 150.0, 156.0, 162.0, 168.0, 240.0, 336.0 and 504.0 hours post dose. The plasma samples were shipped to the Bioanalytical facility for further analysis.

For reference arm, blood samples were collected at pre-dose (0.0 hours prior to morning dosing) and at 0.167, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0 (before second dosing), 8.167, 8.25, 8.5, 8.75, 9.0, 9.5, 10.0, 12.0, 14.0, 16.0 (before third dosing), 16.167, 16.25, 16.5, 16.75, 17.0, 17.5, 18.0, 20.0, 22.0 and 24.0 hours post morning dosing after the start of infusion. The plasma samples were shipped to the Bioanalytical facility for further analysis. Plasma samples were assayed by a validated LCMS/MS method developed at Bioanalytical Lab, Shilpa Medicare Limited, which is specific for the determination of ondansetron.

Pharmacokinetic profiling and statistical analysis

Pharmacokinetic parameters were calculated using Phoenix® WinNonlin® professional software (Version 8.1.1) and statistical analysis was performed on the pharmacokinetic parameters using SAS® statistical software (Version 9.4; SAS Institute Inc., USA).

Investigator Initiated Trial (IIT)

This study was carried out in accordance with the earlier reported clinical studies conducted on anti-emetics for chemotherapy-induced nausea and vomiting [15-18]. Objective of this Investigator initiated trial was to evaluate the efficacy and safety of ondansetron extended-release injectable suspension (100 mg/ml) administered intramuscularly for prevention of acute and delayed CINV in cancer patients undergoing MEC or HEC.

Ethical statement

The study commenced only after the approval obtained from the Institutional Ethics Committee (IEC). The study was conducted from 07 June 2023 to 15 July 2023 at Indur Cancer Hospital, Nizamabad and St. Ann's General and Cancer Hospital, Warangal.

Inclusion and exclusion criteria

Inclusion criteria

Inclusion criteria of patients included male and/or non-pregnant female patients ≥ 18 years of age, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, men and/or women with histologically or cytologically confirmed malignancy, scheduled to receive a single-day MEC or HEC regimen, scheduled to receive MEC regimen for the treatment of a malignant tumor:

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cyclophosphamide IV (500 to 1500 mg/m2), IV doxorubicin (≥ 40 mg/m2) and IV epirubicin (≥ 60 mg/m2), scheduled to receive Highly Emetogenic Chemotherapy (HEC) regimen for the treatment of a malignant tumor, scheduled to receive a single dose of HEC (i.e. cisplatin ≥ 60 mg/m2, cyclophosphamide > 1500 mg/m2, carmustine [BCNU] > 250 mg/m2, dacarbazine [DTIC] or mechlorethamine), female patients of either non-childbearing potential and child-bearing potential with a negative urine dipstick pregnancy test within 24 hours prior to the first dose, hematologic and metabolic status: total neutrophils ≥ 1500/mm3, platelets ≥ 100000/mm3, without known liver metastases: bilirubin ≤ 1.5 × Upper Limit of Normal (ULN), liver enzymes: Aspartate aminotransferase (AST) and/or Alanine aminotransferase (ALT) ≤ 2.5 × ULN; - with known liver metastases: AST and/or ALT ≤ 5.0 × ULN, serum creatinine ≤ 1.5 mg/dl and creatinine clearance ≥ 60 ml/min.

Exclusion criteria

Exclusion criteria of patients included subjects with vomiting or more than mild nausea within 24 h before study drug administration, QTc interval > 500 ms or > 0 ms change from baseline, if female, pregnant or lactating, current use of illicit drugs or current evidence of alcohol abuse, symptomatic primary or metastatic CNS malignancy, active peptic ulcer disease, gastrointestinal obstruction, increased intracranial pressure, hypercalcemia, an active infection or any uncontrolled medical condition, known hypersensitivity or contraindication to 5-HT3 receptor antagonists or dexamethasone, participation in a clinical trial involving ondansetron administered in combination with palonosetron, any investigational drugs taken within 4 weeks prior to Day 1 of chemotherapy cycle 1, systemic corticosteroid therapy at any dose within 72 hours prior to Day 1 of chemotherapy cycle 1, scheduled to receive bone marrow transplantation and/or stem cell rescue therapy, any medication with known or potential antiemetic activity within 24 hours prior to Day 1 of chemotherapy cycle 1, history or predisposition to cardiac conduction abnormalities, except for incomplete right bundle branch block, history of risk factors for Torsades de Pointes, severe cardiovascular diseases, including myocardial infarction within 3 months prior to Day 1 of chemotherapy cycle 1, unstable angina pectoris, any illness or condition that, in the opinion of the investigator, may confound the results of the study or pose unwarranted risks in administering the investigational product and concurrent medical condition that would preclude administration of dexamethasone such as systemic fungal infection or uncontrolled diabetes.

Number of Patients

A total of 12 patients with confirmed malignant disease who were scheduled to receive moderately or highly emetogenic chemotherapy regimens [1:1] were included in the study. All patients were administered with dexamethasone (8 mg, i.v.) as premedication at least 30 min before the initiation of MEC/HEC as per the PI discretion.

i. **Group 1:** Patients (n=6) with confirmed malignant disease who are scheduled to receive single-day moderately emetogenic chemotherapy regimen were injected with OERIS 100 mg/ml, i.m. during the two cycles of MEC chemotherapy (one dose of study drug was injected at each cycle) and all the patients were hospitalized during chemotherapy at both the cycles.

ii. **Group 2:** Patients (n=6) with confirmed malignant disease who are scheduled to receive single day highly emetogenic chemotherapy regimen were injected with OERIS 100 mg/ ml, i.m. during the two cycles of HEC chemotherapy (one dose of study drug was injected at each cycle) and all the patients were hospitalized during the course of chemotherapy at both the cycles.

Patients were enrolled as per the inclusion and exclusion criteria during the screening period. If more than 5 emetic episodes occurred during the conduct of study, either a combination or alone of dexamethasone and fosaprepitant was used as per the PI discretion as rescue medication and supportive care. Premature termination of the study could be performed, if it is deemed justifiable to discontinue the study for medical or safety reasons, PI might terminate the trial for safety, administrative, or other reasons.

Study end points

a. **Primary end point**

Proportion of patients with complete response (CR) during the acute phase (0 to 24 h) and delayed-onset phase (24 to 120 h) following the administration of chemotherapy in Cycle 1 and Cycle 2. CR was measured in 24-h increments up to 120 h in both the Cycles.

b. **Secondary end points**

i. Proportion of patients, following the completion of chemotherapy Cycle 1 (0-120 h) and Cycle 2 (0- 120 h) with CR during the overall treatment.

ii. Proportion of patients, following the completion of chemotherapy Cycle 1 (0-120 h) and Cycle 2 (0- 120 h), with complete control (CC) and total response (TR) during the acute phase, delayed-onset phase, and during the overall treatment.

iii. Proportion of patients, following the completion of Cycle 1 and Cycle 2, with major control of emesis (≤ 2 emetic episodes), minor (3-5 emetic episodes) and failure (> 5 emetic episodes) during the acute phase, delayed-onset phase, and overall treatment in cycle 1 (0- 120 h) and cycle 2 (0-120 h).

iv. Severity of nausea measured daily and overall treatment in cycle 1 (0-120 h) and cycle 2 (0-120 h).

v. Subject's global satisfaction with antiemetic therapy during the acute phase and overall trial period, recorded in 24-hour increments in 2 cycles.

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vi. Quality of Life (QoL) assessment, the impact of nausea and vomiting on Day 5 at 2 chemo cycles.

Blood sample collection

Blood was collected for hematology and clinical chemistry at screening, end of cycle 1, before cycle 2 (day -1 before start of cycle 2) and end of cycle 2 (day 5 of cycle 2). Blood samples were collected by venepuncture using a disposable sterile syringe and a needle at each time of collection. Total blood loss for the study was 22 ml ± 2 ml.

Statistical Analysis

In this study, SAS Version 9.4 was used for statistical analysis. As it is an observational study, qualitative data are expressed as proportion of subjects.

Results

Preclinical studies

Toxicity studies

Maximum tolerated dose (MTD) & Repeated dose toxicity studies

In maximum tolerated dose study of OERIS, 100 mg/mL, i.m., the dose levels tested were 12 mg/kg, 108 mg/kg, 168 mg/kg, 216 mg/kg & 288 mg/kg in Sprague Dawley (SD) rats. From all the tested groups of animals, no morbidity or mortality or change in body weight were noticed during the 14-day observation period. During the terminal necropsy, OERIS did not show any signs of evident toxicity and also did not induce any gross pathological abnormalities in the target tissues/organs of the treated rats. In maximum tolerated dose study of reference ondansetron by intravenous injection, SD rats were treated with 12 mg/kg, 18 mg/kg and 24 mg/kg dose levels. Animals treated with 18 mg/kg and 24 mg/kg have shown evident toxicity signs like tremors and convulsions. A total of 7 & 9 animals showed mortality in the groups treated with higher dose, i.e. 18 and 24 mg/kg, i.v. respectively. However, 12 mg/kg dose did not adversely affect body weight gain during the 14-day observation period and also no mortality was observed. Further, during the terminal necropsy, animals did not show any signs of evident toxicity and gross pathological alterations in the tissues/organs of the treated rats at 12 mg/kg, i.v. dose level. For the 4-weeks repeated dose toxicity study of OERIS (100 mg/ml) in Wistar rats by intramuscular route, no clinical signs and morbidity/mortality, injection site reactions and no changes in body weight and feed consumption were observed across all treated groups. There were no test item-related alterations in hematology, coagulation, clinical chemistry, terminal fasting body weights, organ weights, urinalysis and pathological end points. Based on the above results the "No Observed Adverse Effect Level (NOAEL)" of OERIS was determined to be 150 mg/kg, i.m.

Pharmacokinetic study in male Beagle dogs

From this study, it was evident that pharmacokinetic exposures of proposed formulation of ondansetron has shown low pattern of release than the conventional ondansetron intravenous formulation, however the novel OERIS formulation maintained the therapeutic plasma concentrations till day 5. Pharmacokinetic exposure data in this study revealed that, at all sampling time points evaluated in the study, none of systemic concentrations of proposed novel OERIS formulation did exceed either 4 mg or 24 mg RLD i.v. dose Cmax (Figure 1 & 2). However, the concentrations of proposed OERIS formulation observed to be above the Cmin concentrations after single intravenous dose for a period of 240 h (10 days). Also, AUC & half-life of novel formulation were found to be increased achieving the sustained and prolonged release of drug (Table 2 & 3).

Table 1: Pharmacokinetic study design of novel ondansetron extended release i.m. formulation in male Beagle dogs.

Group	Dose formulation	Product	Dose (mg/dog)	Dose volume (mL/dog)	Drug Conc. (mg/mL)	Route of Administration	No. of Male Beagle Dogs
G1	RLD_1	Ondansetron injection, 2 mg/ml*	4	2	2	i.v.	4
G2	RLD_1	Ondansetron injection, 2 mg/ml*	24	12	2	i.v.	4
G3	TF_2	Ondansetron injectable suspension 100 mg/ml	100	1#	100	i.m.	4
G4	TF_3	Ondansetron injectable suspension 100 mg/ml	100	1#	100	i.m.	4
G5	TF_2	Ondansetron injectable suspension 100 mg/ml	100	1@	100	i.m.	4
G6	TF_3	Ondansetron injectable suspension 100 mg/ml	100	1@	100	i.m.	4
# 1 mL of dose formulation was administered at two i.m. injection site (0.5 ml/ site)							
@1 mL of dose formulation was administered at single i.m. injection at biceps femoris muscle							

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*Marketed product ondansetron injection, 2 mg/ml (Emeset) (Manufacturer: Cipla Ltd.)
TF-2 Test Formulation-2 (OERIS Batch #1); TF-3 Test Formulation-3 (OERIS Batch #2)

Table 2: Summary of plasma pharmacokinetic parameters of reference listed drug, ondansetron, i.v. in male Beagle dogs.

Treatment	Group	Route/ Dose (mg/dog)	C_0 (ng/mL)	AUC_{last} (ng.h/mL)	AUC_{inf} (ng.h/mL)	$T_{1/2}$ (h)	CL (mL/min)	V_{ss} (L)	MRT_{last} (h)
Ondansetron	G1	*i.v.*/4	110 ± 27.4	106 ± 23.7	107 ± 23.4	0.878 ± 0.139	644 ± 123	40.3 ± 8.65	1.12 ± 0.217
(RLD)	G2	*i.v.*/24	828 ± 280	715 ± 71.7	716 ± 71.5	1.28 ± 0.160	563 ± 56.1	36.3 ± 7.96	1.17 ± 0.122

Table 3: Summary of plasma pharmacokinetic parameters (mean ± SD) of ondansetron extended-release injectable suspension (OERIS), i.m. in male Beagle dogs.

Treatment	Group	Route/ Dose (mg/dog)	C_{max} (ng/mL)	T_{max} (h)	AUC_{last} (ng.h/mL)	AUC_{inf} (ng.h/mL)	$T_{1/2}$ (h)	MRT_{last} (h)
Ondansetron (OERIS)	G3	*i.m.*/100	52.8 ± 19.2	4	2360±479	2610±819	64.6±36.4	63.2±13.4
	G4	*i.m.*/100	68.4 ± 36.1	4	2970±555	4750±1510	203±158	79.4±23.8
	G5	*i.m.*/100	56.4±13.1	4	2410±409	2500±451	48.3±14.1	52.6±15.1
	G6	*i.m.*/100	62.9±19.5	4	2780±527	3200±796	87.7±31.5	69.3±6.94

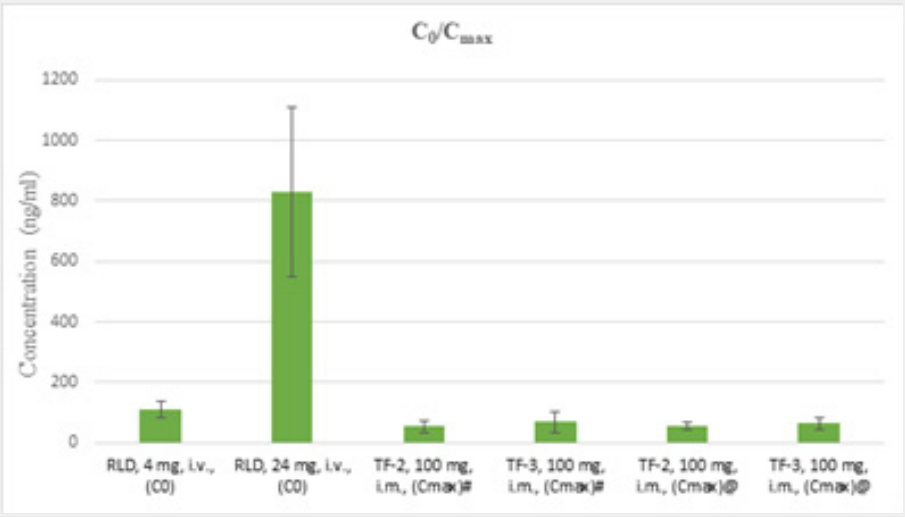

Figure 1: C0 or Cmax of ondansetron intravenous injection (RLD) and ondansetron extended-release intramuscular injection in male Beagle dogs, TF-2, TF-3, two different batches of OERIS, 100 mg/ml, #- two injection sites, @- single injection site.

Clinical studies

Phase 1 clinical study

Subject disposition

A total of 24 Asian male healthy volunteers in two arms i.e. 18 subjects in test arm and 6 subjects in reference arm with a mean (± SD) age of 34.1 (± 6.10) and 31.0 (± 7.82) years respectively were enrolled in the study. The study was conducted with 4 cohorts, i.e. 3 test cohorts and 1 reference cohort, each consisting of 6 healthy volunteers.

Safety

There were no serious adverse events (AE) reported in the study. A total of two (02) adverse events were reported by

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two (02) subjects during the entire study. One (01) AE (blood creatinine increased) which was considered possibly related; and one (01) AE (blood glucose decreased) which was unlikely related to the test product (Cohort-2). Both AEs were found to be mild in severity.

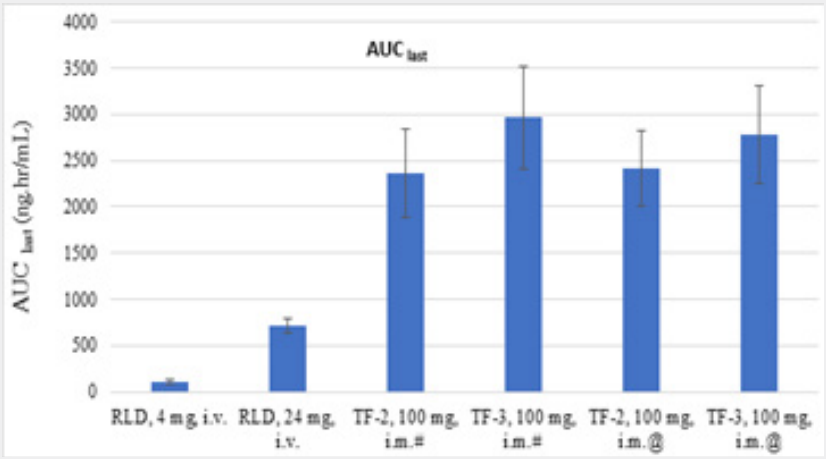

Figure 2: AUClast of ondansetron intravenous injection (RLD) and ondansetron extended-release intramuscular injection in male Beagle dogs, TF-2, TF-3, two different batches of OERIS, 100 mg/ml, #- two injection sites, @- single injection site.

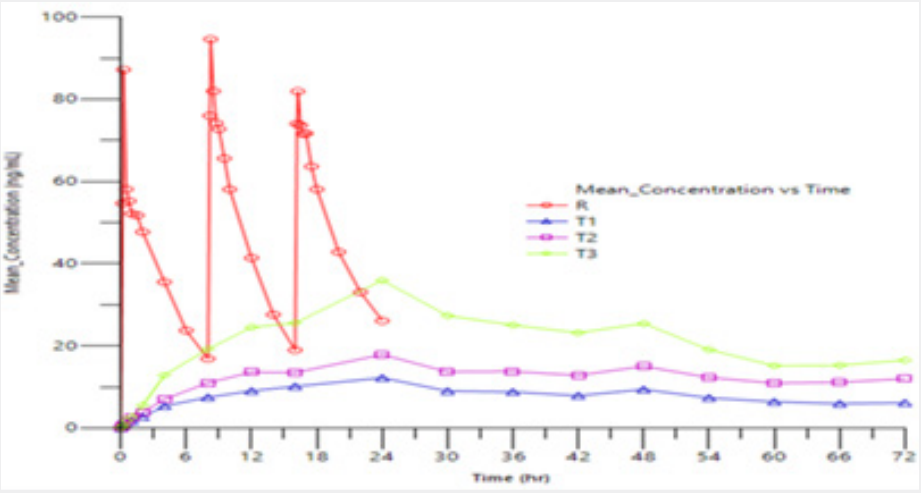

Figure 3: Plasma concentration Vs. Time profile of ondansetron (RLD-R or Test-T) during Phase-1 study in healthy subjects: Novel ondansetron extended-release formulation showed low pattern of release in all 3 test cohorts (T1-35 mg, T2-70 mg, T3-100 mg) when compared to Reference Listed Drug (R).

Summary of Pharmacokinetics

Ondansetron systemic concentrations were evident up to 504 hours (21 days) following a single i.m. injection and the pharmacokinetic data was provided in Table 4 and Figure 3 & 4.

Partial AUC

Cmax and partial AUCs estimated from Phase 1 pharmacokinetic study indicated a low pattern of drug release. Cmax was found to be 36.792 ng/mL for OERIS at 100 mg, i.m. whereas RLD, i.v. dose resulted in a Cmax of 102.488 at a dose of 0.15 mg/Kg. Further, AUC0-24 h (ng/mL) *(h) was found to be 522.004 and 1015.709 for OERIS, i.m. and RLD, i.v. respectively, which shows that, proposed extended-release formulation would be much safer than the conventional marketed i.v. formulation.

Absolute Bioavailability

Based on the PK parameters assessed, the absolute bioavailability was calculated using simulated AUC of reference products (ondansetron injection, i.v.). The F24 T/R ratios were observed as 13%, 23% and 32% for cohort 1, 2 & 3 respectively

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vs. reference for 0-168 hours. Further, the F24 T/R ratio was observed as 7%, 18% and 16% for cohort 1, 2 & 3 respectively Vs. reference during 0- 504 hours.

Comparison of Pharmacokinetics

From the PKprofiling, T/R ratio of Cmax was observed as 12.37%, 21.14% & 26.71% for cohort 1, 2 & 3 respectively and T/R ratio of AUCt was observed as 165.73%, 394.08% & 379.90% for cohort 1, 2 & 3 respectively. As there are no Investigational Product (IP) related dose limiting toxicity for the highest dose (100 mg) administered in the study of novel OERIS formulation, 100 mg dose was considered as the maximum tolerated dose in this study.

Investigator Initiated Trial (IIT)

Demographics

A total of 12 Asian patients (7 Female and 5 male) with the mean (± SD) age of 54.3 (± 12.69) years were enrolled in the study. The mean (± SD) height and weight were 152.8 (± 9.24) cm and 50.9 (± 8.32) kg respectively.

Adverse Events

There were no serious adverse events (SAE) or injection site reactions reported by the subjects in the entire study. There was a total of 28 adverse events (AE) reported by the subjects which were mild in severity and were detailed as in Table 8. Investigators concluded that all the reported AEs were not related to the investigational product.

Number of emetic episodes

There were no emetic episodes that occurred in the acute phase of both cycle-1 and cycle-2 of patients receiving either MEC or HEC. However, in the delayed onset phase, one subject reported minor control of emesis (3-5 emetic episodes) during cycle-1 and cycle-2 of MEC. In patients receiving HEC, one subject reported minor control (3-5 emetic episodes) during the delayed phase of cycle-1 and the same subject reported major control (≤ 2 emetic episodes) during the delayed phase of cycle-2. In the overall study of either MEC or HEC subjects, one subject (who received HEC) was a treatment failure (> 5 emetic episodes). Rescue medication was started at 95.12 h for this failed subject during cycle-2 (Table 5).

Table 4: Summary of Pharmacokinetic data (mean ± SD) for ondansetron in healthy subjects for Phase-1 study.

Ondansetron Phase-1 study				
Paramater	Test Product (OERIS)			Reference (0.15 mg/Kg) thrice in a day
	Cohort-1 (35 mg)	Cohort-2 (70 mg)	Cohort-3 (100 mg)	
Cmax (ng/ml)	12.334 ± 4.874	22.413 ± 12.300	36.792 ± 31.227	102.488 ± 50.166
AUCt (h*ng/ml)	1531.442 ± 364.821	4009.2 ± 2568.624	3638.552 ± 1185.018	1015.662 ± 539.675
AUCinf (h*ng/ml)	1819.028 ± 640.415	6016.517 ± 6608.049	3905.37 ± 1059.716	1216.769 ± 745.179
AUC24 (h*ng/ml)	198.011 ± 91.182	280.544 ± 173.996	522.004 ± 445.032	1015.662 ± 539.675
Tmax (h) [Median (Min-Max)]	24 (24-48)	36 (24-336)	24 (24-240)	0.25 (0.25-0.25)
T1/2 (h)	135.89 ± 82.182	402.28 ± 638.084	112.21 ± 96.684	4.531 ± 1.283

Table 5: Evaluation of emesis in Investigator initiated trial with patients receiving either MEC or HEC.

Group	Cycle	Type of Phase	No Emesis (%)	Minor control (%)	Major control (%)	Failure (%)
MEC	Cycle-1	Acute	6 (100.0)	0 (0.00)	0 (0.00)	0 (0.00)
		Delayed Onset	5 (83.33)	1 (16.67)	0 (0.00)	0 (0.00)
		Overall Treatment	5 (83.33)	1 (16.67)	0 (0.00)	0 (0.00)
	Cycle-2	Acute	6 (100.0)	0 (0.00)	0 (0.00)	0 (0.00)
		Delayed Onset	5 (83.33)	1 (16.67)	0 (0.00)	0 (0.00)
		Overall Treatment	5 (83.33)	1 (16.67)	0 (0.00)	0 (0.00)
HEC	Cycle-1	Acute	6 (100.0)	0 (0.00)	0 (0.00)	0 (0.00)
		Delayed Onset	5 (83.33)	1 (16.67)	0 (0.00)	0 (0.00)
		Overall Treatment	5 (83.33)	1 (16.67)	0 (0.00)	0 (0.00)
	Cycle-2	Acute	6 (100.0)	0 (0.00)	0 (0.00)	0 (0.00)
		Delayed Onset	4 (66.67)	0 (0.00)	1 (16.67)	1 (16.67)
		Overall Treatment	4 (66.67)	0 (0.00)	1 (16.67)	1 (16.67)

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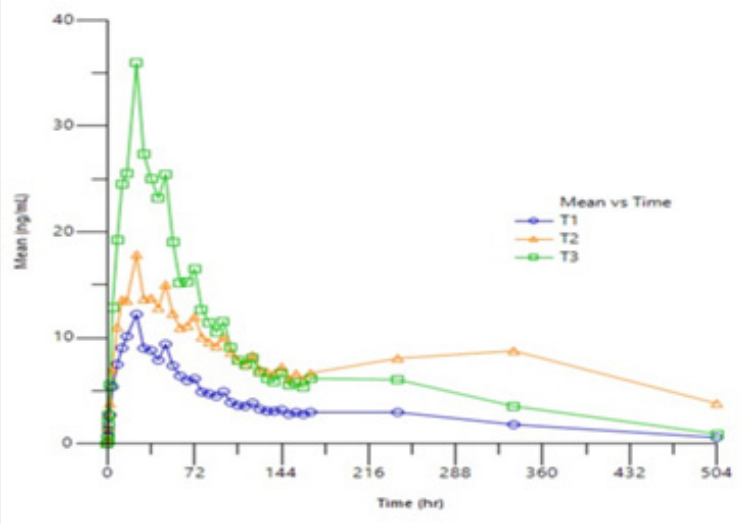

Figure 4: Plasma concentration Vs. Time profile of ondansetron extended-release formulation (OERIS) during Phase-1 study in healthy subjects: Demonstration of systemic drug concentrations of ondansetron up to 504 hours (21 days) following a single OERIS i.m. injection in all 3 test cohorts (T1-35 mg, T2-70 mg, T3-100 mg).

Severity of Nausea

No nausea was observed in acute phase of both cycle 1 and cycle 2, whereas in delayed onset phase, two subjects experienced mild nausea during both cycle 1 and cycle 2 in the entire study (Table 6).

Assessment of global satisfaction and quality of life

Global satisfaction and quality of life of each subject was assessed at end of cycle-1, cycle-2 along with safety follow up. At the end of cycle-1, nine subjects were found to be strongly satisfied, one subject was satisfied, one subject was slightly satisfied, and one subject was slightly dissatisfied. During safety follow up, it was found that seven subjects were strongly satisfied, two subjects were satisfied, and three subjects were slightly satisfied. At the end of the study, a total of eleven subjects were strongly satisfied, and one subject was slightly dissatisfied (Table 7).

Table 6: Assessment of severity of nausea in Investigator initiated trial with OERIS formulation.

Cycle	Order	Assessment Questions	NO (%)	NONE (%)	YES (%)	MILD (%)
Cycle-1	Acute phase (0 to 24 hours)	Did you feel nausea before your chemo-therapy?	12 (100.0)	0 (0.00)	0 (0.00)	0 (0.00)
		Did you have nausea after chemotherapy?	12 (100.0)	0 (0.00)	0 (0.00)	0 (0.00)
		Severity of the patient's Nausea	0 (0.00)	12 (100.0)	0 (0.00)	0 (0.00)
	Delayed onset Phase	Did you have nausea after chemotherapy?	10 (83.33)	0 (0.00)	2 (16.67)	0 (0.00)
		Severity of the patient's Nausea	0 (0.00)	10 (83.33)	0 (0.00)	2 (16.67)
	Overall Treatment	Did you have nausea after chemotherapy?	10 (83.33)	0 (0.00)	2 (16.67)	0 (0.00)
		Severity of the patient's Nausea	0 (0.00)	10 (83.33)	0 (0.00)	2 (16.67)
Cycle-2	Acute phase (0 to 24 hours)	Did you feel nausea before your chemo-therapy?	12 (100.0)	0 (0.00)	0 (0.00)	0 (0.00)
		Did you have nausea after chemotherapy?	12 (100.0)	0 (0.00)	0 (0.00)	0 (0.00)
		Severity of the patient's Nausea	0 (0.00)	12 (100.0)	0 (0.00)	0 (0.00)
	Delayed onset Phase	Did you have nausea after chemotherapy?	10 (83.33)	0 (0.00)	2 (16.67)	0 (0.00)
		Severity of the patient's Nausea	0 (0.00)	10 (83.33)	0 (0.00)	2 (16.67)
	Overall Treatment	Did you have nausea after chemotherapy?	10 (83.33)	0 (0.00)	2 (16.67)	0 (0.00)
		Severity of the patient's Nausea	0 (0.00)	10 (83.33)	0 (0.00)	2 (16.67)

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Table 7: Global satisfaction score during Investigator initiated trial with OERIS.

		Score						
Cycle	Quality of Life (QoL) Assessment	Strongly Dissatisfied (%)	Dissatisfied (%)	Slightly Dissatisfied (%)	Neither Satisfied nor Dissatisfied (%)	Slightly Satisfied (%)	Satisfied (%)	Strongly Satisfied (%)
End of Cycle-1	How much do you satisfy with the study Drug?	0 (0.00)	0 (0.00)	1 (8.33)	0 (0.00)	1 (8.33)	1 (8.33)	9 (75.00)
Safety follow up	How much do you satisfy with the study Drug?	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (25.00)	2 (16.67)	7 (58.33)
End of Cycle-2	How much do you satisfy with the study Drug?	0 (0.00)	0 (0.00)	1 (8.33)	0 (0.00)	0 (0.00)	0 (0.00)	11 (91.67)

Efficacy Results

OERIS, i.m. injected once for each chemocycle along with dexamethasone (8 mg, i.v.), demonstrated improved efficacy response in preventing acute, delayed and over all treatment phases of chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately or highly emetogenic chemotherapy. In the Investigator-initiated trial, all 6 subjects (100%) who received MEC and all 6 subjects (100%) who received HEC achieved 100% complete response (CR) during the acute phase (0 to 24 h). Among 6 subjects, 5 out of 6 subjects (83.33%) who received MEC achieved CR during the delayed-onset phase (>24 to 120 h). Among 6 subjects, 4 out of 6 subjects (66.67%) who received HEC, achieved CR during the delayed phase (>24 to 120 hours) and during the overall risk period (0 to 120 hours), in MEC, 5 out of 6 subjects (83.33%) achieved CR and in HEC, 4 out of 6 subjects (66.67%) achieved CR (Figure 5).

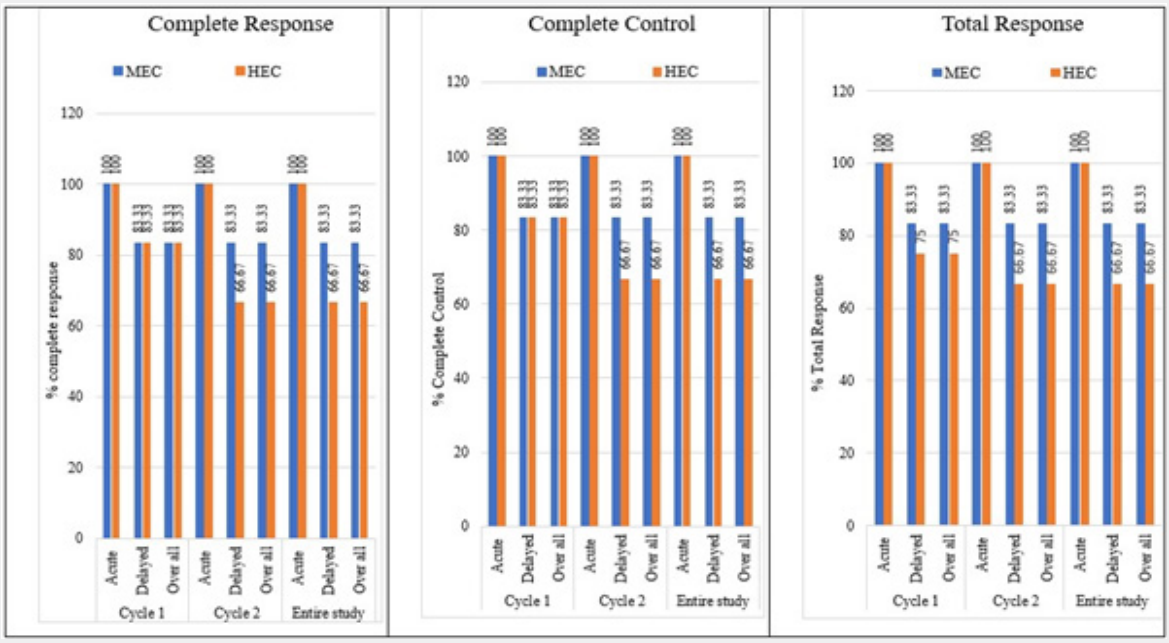

Figure 5: The proportion of patients in acute, delayed and overall treatment with complete response (CR), complete control (CC) and total response (TR) during Investigator initiated trial. During the acute phase of cycle-1 and 2 of either MEC or HEC, complete response and complete control for OERIS treatment were observed to be 100%, while moderate reduction in complete response and complete control was observed during delayed phase of MEC or HEC patients.

Discussion

Shilpa Medicare Limited has developed a novel formulation of ondansetron (OERIS) that provides sustained release of the drug over 5 days (120 h) with an aim of improving treatment adherence in cancer patients by preventing chemotherapy-induced nausea and vomiting, who are receiving moderately or highly emetogenic chemotherapy with a single i.m. injection. In the current investigation, safety, efficacy and pharmacokinetics of OERIS were established with suitable non-clinical and clinical

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investigational studies. Ondansetron is one of the medications most commonly used for the treatment of nausea and vomiting. It has an excellent utility as antiemetic drug for the prevention of chemotherapy-induced and radiation-induced nausea and vomiting, and also for the prevention of post-operative nausea and vomiting (PONV), and as an off-label use for the prevention and treatment of nausea and vomiting associated with pregnancy as evidenced with previous literature [8,19,20].

Table 8: Treatment emergent adverse events-Coded according to MedDRA, Version 25.1.

	Cycle 1 (%)	Cycle 2 (%)	Total (%)
Total Number of AEs	10(35.71)	18(64.29)	28(100.0)
Gastrointestinal disorders	10(35.71)	15(53.57)	25(89.29)
Anal fissure	1(3.57)	0 (0.00)	1(3.57)
Constipation	2(7.14)	0(0.00)	2(7.14)
Nausea	3(10.71)	2(7.14)	5(17.86)
Vomiting	4(14.29)	13(46.43)	17(60.71)
General disorders and administration site conditions	0(0.00)	1(3.57)	1(3.57)
Decreased appetite	0(0.00)	1(3.57)	1(3.57)
Nervous system disorders	0(0.00)	1(3.57)	1(3.57)
Headache	0(0.00)	1(3.57)	1(3.57)
Vascular disorders	0(0.00)	1(3.57)	1(3.57)
Tumour haemorrhage	0(0.00)	1(3.57)	1(3.57)

Historically, conventional oral and intravenous formulations of ondansetron or granisetron have not demonstrated efficacy against delayed phase of CINV. However, the results of our Investigator initiated trial demonstrated that, OERIS (100 mg/ml) provides sustained release of the drug and maintains therapeutic concentrations of ondansetron for more than 5 days, translating into clinically meaningful benefits for patients receiving MEC and HEC, where the risk period for CINV after receiving highly and moderately emetogenic chemotherapy usually lasts for 4-7 days. This can further avoid non-compliance associated with conventional ondansetron formulations, that requires daily administration either for CINV or other indications viz. PONV, pregnancy associated nausea and vomiting etc. Proposed novel OERIS test formulation in current investigation showed modified, i.e. slow and prolonged release of ondansetron that may offer several advantages over the conventional and immediate-release formulations as evidenced in EMA-Guideline on pharmacokinetic and clinical evaluation of modified release dosage forms [21].

Further, with OERIS formulation administration, limited fluctuations in drug plasma concentrations were observed, which might have resulted in more optimized and continuous effects and reduced incidence or intensity of adverse drug reactions. Less frequency of administration and thereby, the potential improvement of patient compliance could be potentially possible with novel OERIS formulation. Furthermore, the non-oral route of administration and no requirement of multiple doses during each chemo cycle makes OERIS a promising treatment option for cancer patients who are on repeated multicycle chemotherapy. Moreover, slow and progressive release of drug from the novel ondansetron depot formulation and prolongation of the half-life of ondansetron is expected to provide long-lasting prevention and control of CINV and PONV with a single i.m. administration. This also avoids sudden rush of the drug into the systemic circulation unlike the case of i.v. RLD and thereby limiting the side effects profile, viz. headache, constipation and QTc prolongation. Intramuscular route was employed in the current investigation as the effects are desired over a longer period of time and absorption can continue for weeks after injection. Bulky muscles have good vascularity, and therefore the injected drug quickly reaches the systemic circulation and thereafter into the specific site of action, bypassing the first-pass metabolism as well.

Furthermore, it also avoids the gastric factors governing drug absorption and moreover cancer patients who are on repeated chemotherapies could miss or face difficulties in consuming oral anti-emetic treatment for multiple times resulting in treatment non-compliance. Proposed extended-release ondansetron formulation can potentially avoid these non-compliance related issues associated with regular conventional anti-emetic medications and thereby improves the quality of life of the patients undergoing cancer treatment. And moreover, patients could successfully complete the scheduled chemotherapy cycles with the controlled emesis as planned by the oncologists, which

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can result in an effective cancer therapy and thereby a better disease prognosis.

MTD, repeated dose (14-days and 4-weeks studies in rats) toxicity studies and pharmacokinetic studies were conducted with the novel OERIS formulation. Based on the toxicity study data, the "No Observed Adverse Effect Level (NOAEL)" was determined to be 150 mg/kg, i.m. Using this data, the first-in-human dose was calculated as 100 mg, i.m. for conducting the Phase 1 clinical study in healthy volunteers. From the pharmacokinetic study conducted in Beagle dogs, the Cmax of OERIS, 100 mg dose was found to be lesser than the C0 of ondansetron (RLD) administered intravenously at dose level of 4 mg and 24 mg. The AUC of OERIS, 100 mg dose was near to the ondansetron injection administered intravenously at a dose of 24 mg. Hence, ondansetron extended-release formulation has shown slow release of drug when compared to reference ondansetron i.v. injection, which indicates the much more safety of the novel OERIS formulation [22].

In Phase 1 clinical trial with healthy adult volunteers, safety of OERIS has been established and was well tolerated (as there were no reported deaths and/or serious TEAEs) at 100 mg dose. From the pharmacokinetic study after a single injection of 100 mg of OERIS, the drug was slowly absorbed and eliminated with a median Tmax of 24 h and a mean T1/2 of 112.21 h. The mean Cmax was found to be 36.79 ng/ml and the mean AUC24, AUCt, and AUCinf values were 522, 3638, and 3905 h*ng/ml respectively. Further, OERIS at a dose of 100 mg showed partial AUCs at every 24 h in the range of 522 h*ng/ml (day 1), 637 h*ng/ml (day 2) and 423 h*ng/ml (day 3), which were near to the 24 h AUC range of both oral and intravenous conventional ondansetron formulations (32 mg). Based on the reported Cmax and partial AUCs with low pattern of release for ondansetron extended-release injection when compared with conventional ondansetron intravenous injection, it is evident that proposed novel ondansetron extended release i.m. formulation would be much safer than the conventional formulations with similar or even better efficacy for a longer duration of action [23].

In an Investigator initiated trial, OERIS administered once for each chemotherapy cycle along with dexamethasone (8 mg, i.v.), demonstrated improved efficacy response in preventing acute, delayed and over all treatment phases of chemotherapy-induced nausea and vomiting in patients receiving moderately or highly emetogenic chemotherapy. Reduction in the emesis, nausea and improved quality of life during the acute and delayed phases (0-120 h) was observed in adult patients and was well controlled up to next chemotherapy cycle (3-4 weeks) with a single i.m. injection, which indicates the potential utility of OERIS.

Further to this, an attempt was made to compare the results obtained from the Investigator initiated clinical trial of OERIS, i.m. with the efficacy responses obtained from published literature of granisetron extended-release subcutaneous injection (GERSI) and palonosetron i.v. injection (Gralla et al, 2014; Kovács et al, 2017; Aapro et al, 2006; Gabrail et al, 2015; Schnadig et al, 2016). In MEC subjects, during acute phase, CR achieved was found to be at 100%, 83% and 81% for OERIS (100 mg, i.m.), GERSI (250 mg) and palonosetron (0.25 mg) i.v. injection respectively. During the delayed phase, 83%, 69% and 74% of CR was achieved for OERIS, GERSI and palonosetron i.v. injection respectively. In HEC subjects, CR achieved during acute phase was at 100%, 70% and 59% with OERIS, GERSI and palonosetron i.v. injection respectively. In delayed phase 66.67%, 50% and 45.3% of CR was achieved with OERIS, GERSI and palonosetron i.v. injection respectively. Overall, the safety of the proposed OERIS (100 mg/ml) was well established at preclinical stage and also in healthy volunteers at escalating doses in Phase 1 clinical study. Investigator initiated clinical trial on OERIS (100 mg, i.m.) achieved sustained activity with better efficacy in preventing nausea and emesis in patients receiving moderately and highly emetogenic chemotherapy as evidenced by CR, CC, TR. Moreover, it was observed that, at the end of chemocycle-2, global satisfaction score was high with more than 90% of the study subjects being strongly satisfied with the study drug OERIS.

However, a major limitation of the current investigation is the smaller sample size employed in the Investigator initiated trial. In order to establish an adequate efficacy and safety of the developed novel ondansetron formulation, further large scale, well-controlled randomized clinical trial need to be conducted in cancer patients receiving multiple cycles of MEC and HEC. Current investigation of developed novel ondansetron extended-release injectable suspension formulation by i.m. route demonstrated potential safety and efficacy in reducing the nausea and vomiting episodes associated with the moderately and highly emetogenic chemotherapy in cancer patients. Moreover, this novel formulation avoids non-compliance that may be associated with daily anti-emetic treatment requirement and enables cancer patients to complete their chemotherapy cycles scheduled by the oncologist so as to improve patients' health related quality of life (HQOL) and thereby, the disease prognosis. Further clinical investigation of the developed novel ondansetron extended-release formulation for its efficacy is warranted in large scale clinical studies.

Further, by developing this novel ondansetron long-acting formulation, not only the cancer patients will benefit, but is also useful for post-operative nausea and vomiting and also the nausea and vomiting associated with pregnancy due to its safe and longer duration of action for more than 5 days. A Phase 3 randomized double-blind clinical trial being planned further with a larger population of CINV patients receiving MEC and HEC (1:1), where the arm-1 will be treated with OERIS, 100 mg, i.m. and arm–2 with reference drug (RLD) injected by i.m. route. The primary objective of this further study would be the efficacy assessment and the secondary objective will be the safety assessment.

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Conflict of Interest

All the authors of the present research investigation are the current employees of Shilpa Medicare Limited, Hyderabad.

References

1. Dranitsaris G, Molassiotis A, Clemons M, Roeland E, Schwartzberg L, et al. (2017) The development of a prediction tool to identify cancer patients at high risk for chemotherapy-induced nausea and vomiting. Ann Oncol 28(6): 1260-1267.
2. Cohen L, de Moor CA, Eisenberg P, Ming EE, Hu H (2007) Chemotherapy-induced nausea and vomiting: incidence and impact on patient quality of life at community oncology settings. Support Care Cancer 15(5): 497-503.
3. Haiderali A, Menditto L, Good M, Teitelbaum A, Wegner J (2011) Impact on daily functioning and indirect/direct costs associated with chemotherapy-induced nausea and vomiting (CINV) in a US population. Support Care Cancer 19(6): 843-851.
4. Gupta K, Walton R, Kataria SP (2021) Chemotherapy-Induced Nausea and Vomiting: Pathogenesis, Recommendations, and New Trends. Cancer Treat Res Commun 26: 100278.
5. Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, et al. (2011) American Society of Clinical Oncology. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 29(31): 4189-4198.
6. de Boer-Dennert M, de Wit R, Schmitz PI, Djontono J, v Beurden V, et al. (1997) Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. Br J Cancer 76(8): 1055-1061.
7. Lorusso D, Bria E, Costantini A, Di Maio M, Rosti G, et al. (2017) Patients' perception of chemotherapy side effects: Expectations, doctor-patient communication and impact on quality of life - An Italian survey. Eur J Cancer Care (Engl) 26(2).
8. Rao KV, Faso A (2012) Chemotherapy-induced nausea and vomiting: optimizing prevention and management. Am Health Drug Benefits 5(4): 232-240.
9. Markham A, Sorkin EM (1993) Ondansetron. An update of its therapeutic use in chemotherapy-induced and postoperative nausea and vomiting. Drugs 45(6): 931-952.
10. Ye JH, Ponnudurai R, Schaefer R (2001) Ondansetron: a selective 5-HT(3) receptor antagonist and its applications in CNS-related disorders. CNS Drug Rev 7(2): 199-213.
11. Wilde MI, Markham A (1996) Ondansetron. A review of its pharmacology and preliminary clinical findings in novel applications. Drugs 52(5): 773-794.
12. Hesketh PJ (2008) Chemotherapy-induced nausea and vomiting. N Engl J Med 358(23): 2482-2494.
13. Simpson KH, Hicks FM (1996) Clinical pharmacokinetics of ondansetron. A review. J Pharm Pharmacol 48(8): 774-781.
14. Vrabel M (2007) Is ondansetron more effective than granisetron for chemotherapy-induced nausea and vomiting? A review of comparative trials. Clin J Oncol Nurs 11(6): 809-813.
15. Gralla RJ, Bosnjak SM, Hontsa A, Balser C, Rizzi G, et al. (2014) A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. Ann Oncol 25(7): 1333-1339.
16. Aapro MS, Grunberg SM, Manikhas GM, Olivares G, Suarez T, et al. (2006) A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Ann Oncol 17(9): 1441-1449.
17. Gabrail N, Yanagihara R, Spaczyński M, Cooper W, O'Boyle E, et al. (2015) Pharmacokinetics, safety, and efficacy of APF530 (extended-release granisetron) in patients receiving moderately or highly emetogenic chemotherapy: results of two Phase II trials. Cancer Manag Res 7: 83-92.
18. Schnadig ID, Agajanian R, Dakhil C, Gabrail NY, Smith RE, et al. (2016) APF530 (granisetron injection extended-release) in a three-drug regimen for delayed CINV in highly emetogenic chemotherapy. Future Oncol 12(12): 1469-1481.
19. Hesketh PJ, Kris MG, Basch E, Bohlke K, Barbour SY, et al. (2017) Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 35(28): 3240-3261.
20. Gan TJ, Belani KG, Bergese S, Chung F, Diemunsch P, et al. (2020) Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting. Anesth Analg 131(2): 411-448.
21. Kovács G, Wachtel A, Basharova E, Spinelli T, Nicolas P, et al. (2017) Palonosetron compared with ondansetron in pediatric cancer patients: multicycle analysis of a randomized Phase III study. Future Oncol 13(19): 1685-1698.
22. (2022) National Library of Medicine, Dailymed; Prescribing information of Ondansetron injection; 4 mg/ 2 mL.
23. Weinstein C, Jordan K, Green S, Saleem K, Elizabeth B, et al. (2020) Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy regimens: a subgroup analysis from a randomized clinical trial of response in subjects by cancer type. BMC Cancer 20(1): 918.

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