1. SYNOPSIS

Sponsor: Oncolytics Biotech Inc.	
Name of Finished Product: REOLYSIN®	
Name of Active Ingredient: Wild-Type Reovirus Type 3 (Dearing Strain)	
Study Title: A Dose Targeted Phase I/II Study to Evaluate the Feasibility, Safety, and Biological Effects of Intravenous Administration of a Wild-Type Reovirus (REOLYSIN®) in Combination with Paclitaxel and Carboplatin to Patients with Advanced Malignancies (REO 011)	
Investigator(s): Dr. Kevin Harrington; Dr. Geoff Hall	
Study Center(s): This study was conducted at two investigational sites in the United Kingdom (UK): Royal Marsden Hospital, Sutton; and St. James Hospital, Leeds	
Publication (reference): Karapanagiotou E, *et al.* Phase I/II trial of oncolytic reovirus (REOLYSIN®) in combination with carboplatin/paclitaxel in patients with advanced solid cancers. Poster presented at the International Society for Biological Therapy of Cancer; 2008; San Diego. Karapanagiotou E, *et al.* Phase I/II trial of oncolytic reovirus (Reolysin) in combination with carboplatin/paclitaxel in patients (pts) with advanced solid cancers. [abstract]. J Clin Oncol 2009; 28:15s (suppl; abstr 3080). Karapanagiotou E, *et al.* A phase I/II study of oncolytic reovirus plus carboplatin/paclitaxel in patients with advanced solid cancers with emphasis on squamous cell carcinoma of the head and neck (SCCHN) [abstract]. J Clin Oncol 2010; 27 suppl; abstr e14519.	
Study Period: **Initiation Date (first patient enrolled):** 23 May 2007 **Completion Date (last patient completed):** 24 March 2010	**Study Phase:** 1/2
Study Objectives: **Phase 1:** *Primary* • To determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and safety profile of REOLYSIN when administered in combination with paclitaxel and carboplatin. In the case of no dose-limiting toxicity occurring, the trial was to be stopped when dose escalation of REOLYSIN reaches $3x10^{10}$ daily x 5. • To recommend dose and schedule for future investigation.	

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Study Objectives (cont.):

Secondary

- To evaluate the humoral and cellular immune response to reovirus when given with paclitaxel and carboplatin.
- To evaluate pharmacokinetics (PK) of paclitaxel and carboplatin when combined with REOLYSIN.
- To measure tumor responses and duration of response, and describe any evidence of antitumor activity.
- To assess any extent of 'shedding' of virus from patients.

Phase 2:

Primary

- To measure tumor responses and duration of response, and describe any evidence of antitumor activity (complete response [CR], partial response [PR], CR + PR, CR + PR + stable disease [SD]).

Secondary

- To determine the safety and tolerability of REOLYSIN when administered in combination with paclitaxel and carboplatin to patients with advanced or metastatic head/neck cancer.

Methodology: This was an open-label, dose-targeted, combination therapy, two-center Phase 1/2 study in patients with advanced solid tumors, including head and neck cancer. REOLYSIN was given intravenously (IV) over 60 min on Days 1-5 of each 21-day cycle. In the Phase 1 portion of the study, the starting dose of REOLYSIN was $3x10^9$ tissue culture infective $dose_{50}$ ($TCID_{50}$), with planned escalations to $1x10^{10}$ $TCID_{50}$ and $3x10^{10}$ $TCID_{50}$. Paclitaxel was given as a fixed dose of 175 mg/m^2 IV as a 3-hour infusion on Day 1 followed by carboplatin dosed to a targeted area under the plasma concentration versus time curve (AUC) of 5 mg/mL x min (according to the Calvert formula) over 30 min on Day 1. Three patients were to be entered initially at each of the three planned REOLYSIN dose levels. If no unexpected Grade 3/4 toxicity occurred in two or more patients, escalation of REOLYSIN was to be made to the next dose level. Escalation could only occur when two patients had been treated with two cycles of therapy on the previous dose level.

All patients treated in each cohort underwent repeated safety evaluations (Days 8 and 15 and on Day 1 of the next cycle) before enrollment in the next dose cohort could start. For a patient to be considered evaluable for dose-escalation decisions, the patient must have received at least one cycle or have been withdrawn from the study as a result of a drug-related toxicity. If a patient withdrew from the study without meeting these criteria, the patient was to be replaced in that cohort. Decisions to escalate to the next level, or, when appropriate, to an intermediate level, were made jointly by the investigator and sponsor's medical monitor based on review of all the available data. If one out of three patients in a dose group experienced a DLT during the first cycle, three more patients were to be added to that dose group. If two or more patients in a dose group experienced a DLT during the first cycle, the previous lower dose was to be the recommended dose for study in the second phase of the trial. Intra-patient dose escalations were not permitted.

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During the Phase 2 study, patients with head and neck cancer were to be treated at the REOLYSIN dose recommended from the Phase 1 study. Once the dosing schedule for the Phase 1 portion of the protocol had been completed by either defining the MTD or by completing the cohorts as planned, patients in the top cohort completed all safety evaluations (Days 8, 15, and 1 of the next cycle) prior to initiation of the Phase 2 study. This is to ensure that there were no safety issues before continuing to the Phase 2 portion of the protocol. Evaluation of tumor status was conducted at baseline and at the ends of Cycle 3, 6, and 8. Patients whose tumors were accessible to biopsy were asked to undergo tumor biopsy (baseline and post-therapy) to evaluate the biological effects of combination viral and radiotherapy. Safety was assessed throughout the study.
Number of Patients (planned and analyzed): The total number of patients to be evaluated in the Phase 1 portion was dependent on the number of dose levels tested before the MTD was established. Up to 20 evaluable patients were planned; 13 patients were enrolled and analyzed, including three patients each at the $3x10^9$ $TCID_{50}$ (Cohort 1) and $1x10^{10}$ $TCID_{50}$ (Cohort 2) dose levels and seven patients at the $3x10^{10}$ $TCID_{50}$, dose level (Cohort 3). For the Phase 2 portion, 14 evaluable patients with head/neck cancer were planned; 18 patients were enrolled and dosed.
Diagnosis and Main Criteria for Inclusion: Adult (≥ 18 years) patients diagnosed with advanced or metastatic solid tumors refractory to standard therapy or for which no curative standard therapy existed, and for whom paclitaxel plus carboplatin was appropriate chemotherapy, were eligible for enrollment. In addition, patients had either measurable or evaluable disease. Other key eligibility criteria included no continuing acute toxic effects of any prior chemotherapy or surgical procedures; no receipt of chemotherapy, radiotherapy, immunotherapy, or hormonotherapy within 28 days prior to receiving study drug; an Eastern Cooperative Oncology Group (ECOG) Performance Score of ≤ 2, and a life-expectancy of at least 3 months. For the Phase 2 study, the advance solid tumors were limited to head/neck cancer; otherwise, all other inclusion criteria from the Phase 1 study applied. Patients with brain metastasis(es); clinically significant cardiac disease; dementia or altered mental status; or any other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with study participation or study drug; and pregnant or breastfeeding women were excluded from participation.
Test Product, Dose and Mode of Administration, Lot Number: REOLYSIN is an opaque, milky-white liquid containing up to $3x10^{11}$ $TCID_{50}$; the starting dose was $3x10^9$ $TCID_{50}$, with planned escalation to $1x10^{10}$ $TCID_{50}$ and $3x10^{10}$ $TCID_{50}$; IV; lot no. 2007#5154P, 2007#5158H, 2007#5161N, 2007#5167A, 2007#5168A, 122-06003, 122-07010, 122-07011, 122-07012, and 122-07013. In combination with: Paclitaxel 175 mg/m^2 IV plus carboplatin AUC 5 mg/mL x min (according to the Calvert formula) (commercial product was obtained by the study site)

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Duration of Treatment: Patients could continue to receive therapy under this protocol until they experienced either progressive disease (PD) or unacceptable drug-related toxicity that did not respond to either supportive care or dose reduction.

Reference Therapy, Dose and Mode of Administration, Lot Number: Not applicable

CRITERIA FOR EVALUATION

Efficacy: Efficacy was a secondary assessment in the Phase 1 study. In the Phase 2 study, the primary endpoint was any evidence of antitumor activity in patients with head/neck cancer (CR, PR, CR + PR, or CR + PR +SD).

Evaluation of tumor status was conducted at baseline and at the ends of Cycle 3, 6, and 8. For measurable disease, computer tomography (CT) scan, magnetic resonance imaging (MRI), or clinical examination was used, as outlined in the Response and Evaluation Criteria in Solid Tumors (RECIST). A complete (CR) or partial response (PR) was to be confirmed at least 4 weeks after the first assessment that documents response and every two cycles thereafter until disease progression, study termination, initiation of subsequent anticancer therapy, death, loss to follow-up, or withdrawal of consent. Tumor markers could also be used to assess response; prostate-specific antigen (PSA) and cancer antigen CA-125 could be used as endpoints of response in patients with prostatic and ovarian carcinoma.

Pharmacokinetics: During the Phase 1 dose escalation phase only, blood samples were taken for PK assessments of paclitaxel and carboplatin (observed concentration at the end of the infusion [C_{inf}], the area under the concentration versus time curve from time 0 to the sampling time at the last quantifiable concentration [AUC_{0-t}], AUC estimated from time 0 to infinity [$AUC_{0-\infty}$], the apparent terminal half-life [$t_{½}$], total systemic clearance [CL], mean residence time [MRT], and apparent volume of distribution [V_{ss}]) during the first cycle of treatment at the following time points: 0 min (pre-paclitaxel), 15 min, 30 min, 1h, 2h, 3h (pre-carboplatin), 3h 15min, 3.5h (pre-REOLYSIN), 4.5h, 6h, 8h, and 24h and 48h (pre-REOLYSIN Day 2 and Day 3).

Pharmacokinetic studies were not included in the expanded or Phase 2 portion of this study.

Other Evaluations:

Viral shedding: For the Phase 1 study only, patients had blood samples collected for the detection of REOLYSIN virus during the first two cycles. Reverse transcriptase-polymerase chain reaction (RT-PCR) was used to determine the presence of viral ribonucleaic acid (RNA) at baseline and 4 hours after the last dose of REOLYSIN on Day 5 and Day 15 during the first two cycles. Urine, stool, and sputum samples were analyzed for virus detection by RT-PCR pre-treatment on Day 1, 4 hours after the last dose on Day 5, and on Day 15 during Cycles 1 and 2. If the viral shedding results were negative at the Day 15 sample, the Day 1 sample for Cycle 2 could be omitted.

Presence of neutralizing antibodies: For the Phase 1 study only, neutralizing antibodies to reovirus were taken at baseline, on Day 8, and weekly thereafter for the first two cycles.

Tumor biopsy: Patients whose tumors were accessible to biopsy were asked to undergo tumor biopsy (baseline and post-therapy) to evaluate viral replication within the tumor and the biological effects of viral therapy in the Ras signaling pathway. The timing of the second biopsy was varied

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to optimize the biological data generated by this assessment.

Safety: The safety of REOLYSIN in combination with paclitaxel and carbopatin was assessed by evaluating the type, frequency, and severity of adverse events (AEs) and changes in clinical laboratory tests (hematology, chemistry, and urinalysis), immunogenicity, physical examination findings, vital signs, and electrocardiograms (ECGs). AEs and laboratory abnormalities were graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Statistical Methods: The Phase 1 study was descriptive in nature and not designed to provide inferential results regarding safety or antitumor activity.

For the analysis of efficacy in the Phase 2 study, any patient in the Phase 1 portion who met the inclusion/exclusion criteria for Phase 2 and was treated at the same dose (i.e. the dose used in Phase 2 study) were included in the Phase 2 efficacy analysis. The Phase 2 study used the Gehan design to allow for early rejection of an ineffective treatment.

Descriptive statistics were used to summarize baseline patient characteristics, treatment administration, safety variables, and signs of antitumor activity.

All patients who received at least one dose of REOLYSIN were included in the safety analysis. Incidence of Serious and non-serious AEs, including those that were dose limiting, were tabulated by dose, organ system, preferred term, severity, and relationship to the treatment agents (as judged by the treating physicians).

RESULTS AND CONCLUSIONS

Patient Disposition and Demographics: Thirty-one patients with advanced solid tumors were enrolled and dosed in this study: three patients each in the first two cohorts, $3x10^9$ $TCID_{50}$ and $1x10^{10}$ $TCID_{50}$, and 25 patients in Cohort 3 ($3x10^{10}$ $TCID_{50}$). Cohort 3 included seven patients who received REOLSYIN $3x10^{10}$ $TCID_{50}$ in the Phase 1 study and 18 additional patients who received the same maximum Phase 1 dose in the Phase 2 study. Twenty-four of the 31 patients had head and neck cancer.

All 31 patients who received at least one dose of REOLYSIN during the Phase 1 and 2 studies were included in the Safety population. Eight patients had evaluable paclitaxel and carboplatin plasma concentration data in the Phase 1 study and were included in the pharmacokinetic analyses, including all six patients in Cohorts 1 and 2, and two patients in Cohort 3.

Most (24/31; 77.4%) patients were male. Twenty-five (80.6%) patients were White; five (16.1%) were Asian, and one (3.2%) was in the Other category. Study participants ranged in age from 27 to 78 years. Mean age by dose group ranged from 47.5 years in the $3x10^9$ $TCID_{50}$ group to 59.0 years in the $3x10^{10}$ $TCID_{50}$ group. Overall, weight ranged from 44.5 to 93.0 kg and body mass index (BMI) ranged from 16.9-32.2 kg/m^2. Variability in some demographic characteristics was found among dose groups at baseline (e.g., mean age and weight); however, these differences were considered unlikely to affect interpretation of PK or safety results.

Almost all patients underwent prior surgery (29 patients; 93.5%) and received prior chemotherapy (28 patients; 90.3%). Eleven patients (35%) had received more than one prior chemotherapy. All but one of the19 head and neck cancer patients evaluable for response were considered to be platinum refractory.

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Efficacy Results: Antitumor activity of REOLYSIN plus paclitaxel and carboplatin was observed in this study of patients with advanced or metastatic solid tumors. Overall, among 26 patients who received at least two cycles of therapy and were evaluable for assessment of tumor response, 18 had a tumor response or stable disease for a total disease control rate of 69%. Among 24 patients with head and neck cancer, 19 were evaluable for response and eight (42%) had tumor shrinkage consistent with a complete response (n=1) or partial response (n=5) or dramatic clinical responses (n=2), and six patients (32%) had stable disease for a total disease control rate of 74%. Seven of these patients received the maximum eight cycles of treatment allowed by the protocol. Median duration of SD/PR was 7 months (range: 3-16 months). Among four patients with melanoma, one had a partial response and one had stable disease and both patients received eight cycles of treatment and were still in response at the end of treatment. One patient with endometrial cancer had a clinical response but stable disease by RECIST criteria throughout the eight cycles of treatment. Furthermore, one patient with synovial sarcoma had stable disease. Mean and median overall survival in the 24 patients with head and neck cancer were 8.5 and 7.1 months, respectively.
Pharmacokinetic Results: A complete summary of the PK results is provided in the Pharmacokinetic Report. In brief, PK parameters of paclitaxel and carboplatin, including CL, V_{ss}, and $t_{½}$, were not appreciably different when administered in combination with increasing doses of REOLYSIN. Furthermore, PK parameters of paclitaxel and carboplatin administered in combination with REOLYSIN were not appreciably different to corresponding parameters derived from previously conducted studies using similar paclitaxel and carboplatin dosing regimens in patients with cancer.
Other Results: Viral shedding was observed infrequently (four patients). The results suggest that there is rapid clearance of the virus from the circulation, which is unaffected by the administration of paclitaxel and carboplatin. When REOLYSIN was administered to patients as a monotherapy, the maximum amount of NARA produced compared to patients treated with REOLYSIN in combination with paclitaxel/carboplatin was 5-fold greater. In addition, when the agent was combined with the chemotherapy, the maximum elevation of NARA was not reached until much later in the treatment cycles. Only one tumor biopsy was obtained and available for analysis of viral replication (Patient 01-0305). REOLYSIN $3x10^{10}$ $TCID_{50}$ showed no cytopathic effect (CPE) and therefore there was no evidence of actively replicating virus in the sample, and analysis for reovirus RNA by RT-PCR was negative.
Safety Results: All 31 (100%) patients experienced at least one treatment-emergent AE. The most frequently reported AEs or observed toxicities overall were leukopenia (80.6%); neutropenia (74.2%); thrombocytopenia (70.1%); alopecia (64.5%); pyrexia (61.3%); fatigue (38.7%); decreased hemoglobin, decreased hematocrit, and nausea (35.5% each); and lymphopenia (29.0%). Adverse events were assessed as study drug (paclitaxel, carboplatin, and/or REOLYSIN)-related in 30 (96.8%) patients. The most frequently reported study drug-related AEs overall were alopecia

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(61.3%); pyrexia (58.1%); anemia (41.9%); and fatigue, RBC count decreased, and nausea (35.5% each). Adverse events assessed as related to REOLYSIN were reported in 26 (89.3%) patients. The most frequently reported REOLYSIN-related AEs were pyrexia (54.8%), chills (25.8), fatigue (19.4%), and nausea and increased creatine kinase-monobasic (CK-MB) (16.1% each). The REOLYSIN-related AEs were generally mild in severity and manageable without study drug dose reduction or discontinuation. Most of the events were assessed by the investigator as mild in severity. The most common Grade ≥3 AEs or toxicities were neutropenia (48.4%), lymphopenia (45.1%), leukopenia (41.9%), pyrexia (16.1%), and decreased hemoglobin/anemia (9.7%), followed by chills, myalgia and urinary tract infection (6.5% each).

Four deaths occurred within 30 days after the last dose of study drug, all due to disease progression. Seventeen (54.8%) patients experienced at least one treatment-emergent serious adverse event (SAE). The only SAE attributed to REOLYSIN was pyrexia; SAEs attributed to concomitant chemotherapy included pyrexia, anemia, sepsis, febrile neutropenia, hypotension, and diarrhea. Four (12.9%) patients were withdrawn from the study due to an AE. None of the events that led to discontinuation of study drug were related to REOLYSIN.

REOLSYIN administration appeared to have minimal effects on vital signs as the differences in mean systolic and diastolic blood pressure at 15, 30, and 60 minutes after the REOLYSIN infusion was completed were small.

Conclusions:

- Escalating doses of REOLYSIN up to $3x10^{10}$ $TCID_{50}$ administered IV on Days 1-5 of each cycle were well tolerated when administered in combination with the standard dose of IV paclitaxel 175 mg/m^2 and carboplatin AUC 5 on Day 1, with predictable toxicity observed. The MTD was not reached.
- Overall, among 26 patients who received at least two cycles of therapy and were evaluable for assessment of tumor response, 18 had a tumor response or stable disease for a total disease control rate of 69%.
- Among 24 patients with head and neck cancer, 19 were evaluable for response and eight (42%) had tumor shrinkage consistent with a complete response (n=1) or partial response (n=5) or dramatic clinical responses (n=2), and six patients (32%) had stable disease for a total disease control rate of 74% Median duration of stable disease or better was 6 months (range 3-10 months). The response rate of 42% appears notably higher than the historical response rate of 3% to 10% reported in the literature for such patients.
- Mean and median overall survival in the 24 patients with head and neck cancer were 8.5 and 7.1 months, respectively, which compare favorably with an expected survival of 4.5 months in published studies in the second-line platinum-refractory recurrent/metastatic setting.

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Conclusions (Cont.):

- The most frequently reported AEs or observed toxicities overall were leukopenia (80.6%); neutropenia (74.2%); thrombocytopenia (70.1%); alopecia (64.5%); pyrexia (61.3%); fatigue (38.7%), decreased hemoglobin, decreased hematocrit, and nausea (35.5% each); and lymphopenia (29.0%). Most of the events of alopecia, neutropenia, leukopenia, lymphopenia, and anemia were attributed to the concomitant chemotherapy.
- The most frequently reported REOLYSIN-related AEs were pyrexia (54.8%), chills (25.8), fatigue (19.4%), and nausea and increased CK-MB (16.1% each). The REOLYSIN-related AEs were generally mild in severity and manageable without study drug dose reduction or discontinuation.
- The most common Grade 3-4 AEs or toxicities were neutropenia (48.4%), lymphopenia (45.1%), leukopenia (41.9%), pyrexia (16.1%), and decreased hemoglobin/anemia (9.7%), followed by chills, myalgia, and urinary tract infection (6.5% each). The incidence of Grade ≥ 3 neutropenia (48.4%) seems favorable with the incidence of such toxicity for the same doses and schedule of paclitaxel (52%) and carboplatin (16%) monotherapy according to Taxol® and carboplatin prescribing information.
- REOLYSIN in increasing doses had no apparent effect on the pharmacokinetics of co-administered paclitaxel and carboplatin.
- Viral shedding was observed infrequently (four patients). The results suggest that there is rapid clearance of the virus from the circulation, which is unaffected by the administration of paclitaxel and carboplatin.
- When REOLYSIN is administered to patients as a monotherapy, the maximum amount of NARA produced compared to patients treated with REOLYSIN in combination with paclitaxel/carboplatin is 5-fold greater. In addition, when the agent is combined with the chemotherapy the maximum elevation of NARA is not reached until much later in the treatment cycles.
- Based on results of this study, a recommended dose of REOLYSIN for Phase 3 studies is defined at $3x10^{10}$ $TCID_{50}$ when combined with standard doses of paclitaxel and carboplatin.

Date of Report: 09 November 2010