## SUMMARY

**Title of Study:** A Dose-Ranging Efficacy, Safety, and Pharmacokinetic Study of Single Intravenous Doses of RS-25259 for Prevention of Nausea and Vomiting in Chemotherapy-Naive Cancer Patients Receiving Highly Emetogenic Chemotherapy

**Study No. and RS No.:** 25259S2330 and RS-25259-197

**Investigators and Study Centers:** Multiple

**Publications:** None

**Study Period:** April 1994—April 1995

**Clinical Phase:** II

**Objectives:** The objectives of this study were to (1) determine the dose-response relationship among single IV doses of RS-25259 over the dose range 1–90 µg/kg; the primary endpoint was the proportion of patients with a complete antiemetic response (no vomiting or retching) for 24 hours after highly emetogenic chemotherapy in chemotherapy-naive cancer patients; the efficacy of each dose was compared with the efficacy of the lowest dose; (2) assess the safety of single IV doses of RS-25259 administered over the range of doses tested in this patient population; and (3) assess the pharmacokinetics of single IV doses of RS-25259 over the range of doses tested in this patient population.

**Methodology:** This was a randomized, double-blind, multicenter, dose-ranging efficacy, safety, and pharmacokinetic study of IV RS-25259-197. Patients were randomized to receive one of five doses of study drug and were observed as inpatients and/or outpatients. Safety and efficacy evaluations were recorded periodically during the first 24 hours and then daily for the next 6 days following administration of study medication. Additionally, each patient was contacted 14 days postdosing to obtain further safety information. Blood samples for pharmacokinetic analysis were taken from patients at selected investigational sites before dosing and at various times up to 168 hours after dosing with study drug; the plasma portion was assayed for RS-25259 and RS-17825 (the N-oxide metabolite) concentrations, from which pharmacokinetic parameters were computed.

**Number of Subjects:** One hundred sixty-one patients (129 males, 32 females), 23–79 years of age were enrolled in this study. All patients are included in the safety evaluations. However, 13 patients were excluded from all efficacy analysis. Reasons for exclusion included various protocol violations (8 patients). Subsequently to establishing evaluability, 5 additional patients, all of whom received cyclophosphamide, were also excluded. Thus, efficacy analyses focused on only patients who received cisplatin-based chemotherapy. The distribution of evaluable patients by dose group is as follows: 0.3–1 µg/kg, 29 patients; 3 µg/kg, 24 patients; 10 µg/kg, 25 patients; 30 µg/kg, 24 patients; and 90 µg/kg, 48 patients.

**Diagnosis and Criteria for Inclusion:** Patients were men and women who had histologically proven cancer, were chemotherapy naive, and were scheduled to receive their first dose of emetogenic chemotherapy, either cisplatin (≥ 70 mg/m$^2$) or cyclophosphamide (> 1100 mg/m$^2$).

**Test Product, Dose and Mode of Administration, Formulation No., Batch/Lot No.:** RS-25259 was supplied in 5-mL glass vials at a concentration of 500 µg/mL. Patients were randomly assigned to one of five RS-25259 treatments. Prior to Amendments III and IV of the protocol, the treatments were 0.3, 1, 3,

10, or 30 µg/kg; following those amendments, they were 1, 3, 10, 30, or 90 µg/kg. Normal saline was used to dilute RS-25259 to a total injection volume of 25 mL. Study drug was administered 30 minutes before start of chemotherapy and given as a single bolus IV dose over 30 seconds. The formulation number RS-25259 was No. F25259-006 (Lot Nos. 25259-197-12479 and -1021881).

**Reference Therapy, Dose and Mode of Administration, Formulation No., Batch/Lot No.:** None

**Duration of Treatment:** Patients received a single IV dose of RS-25259-197 over 30 seconds and were subsequently followed for a total of 14 days.

**Criteria for Evaluation:** *Clinical Data*—The primary efficacy variable was the proportion of patients with a complete antiemetic response (no vomiting or retching, no rescue medication) for 24 hours after the start of chemotherapy. The efficacy of each dose was compared with the efficacy of the lowest dose. Secondary efficacy variables included the time to the first emetic episode, time to administration of rescue therapy, area under the nausea-intensity-by-time (NIT) curve based on categorical scale, time to treatment failure (either emesis or need for rescue medication, whichever occurred first), proportion of patients with complete control of emesis (no vomiting and only mild nausea or no nausea), and global rating of satisfaction with the control of nausea and vomiting based on a visual analog scale. These variables were supplemented by physical examination and vital signs data, laboratory findings, and adverse event data. *Pharmacokinetic Data*—Plasma concentrations and computed pharmacokinetic parameters for RS-25259 and RS-17825 were assessed.

**Statistical Methods:** Demographic and safety data were summarized; plasma concentrations and computed pharmacokinetic parameters were listed and statistically summarized by dose group; individual and mean plasma concentrations were plotted versus time; and computed parameters were analyzed for a dose relationship (e.g., dose proportionality, dose linearity).

**Summary and Conclusions:** RS-25259, administered as a single bolus intravenous injection of 3, 10, 30 or 90 µg/kg 30 minutes prior to high-dose cisplatin chemotherapy, was effective in suppressing chemotherapy-induced emesis for 24 hours. All four doses were approximately equally effective as compared with the combined results from a cohort of 0.3 and 1 µg/kg. The following table summarizes key efficacy parameters.

| Parameters | RS-25259 Dose (µg/kg) | | | | |
|---|---|---|---|---|---|
| | 0.3–1 | 3 | 10 | 30 | 90 |
| % Complete Control (24 hours) | 24 | 46 | 40 | 50* | 46 |
| % Complete Response (24 hours) | 24 | 39 | 40 | 48 | 46 |
| Median Time (hours) to Failure (first emetic episode or rescue $R_x$) | 5.6 | 22.7* | 19.0 | > 24* | 21.8* |

*statistically significant differences ($p < 0.05$) vs. lowest dose group

Safety evaluations and comparisons made between treatment groups all suggest that RS-25259 is a relatively safe therapeutic agent. No dose response–related adverse events were observed. One hundred twenty-nine of the 161 patients in the safety analyses (80.1%) experienced at least one adverse event during the study. A majority of events were rated as mild or moderate (469/559, 83.9%) and were considered probably not related to test medication (481/559, 86.0%). Incidence, frequency, severity, and relationships of adverse events appeared to be essentially equally distributed among the RS-25259 treatment groups. The most frequent adverse event reported was headache, followed by constipation, pain, asthenia, anorexia, and diarrhea. Serious adverse events that occurred were all judged by the treating physicians to be probably not related to chemotherapy. No dose-related toxicity was observed in electrocardiograms or laboratory parameters evaluations.

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