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Summary of the Clinical Experience with S-095 Injection (Manganese Dipyridoxyl Diphosphate, Mn-DPDP)

David D. Shaw

Introduction

S-095 Injection, containing manganese dipyridoxyl diphosphate, is a paramagnetic contrast medium being developed for use in magnetic resonance (MR) imaging. It is anticipated that this agent will be particularly useful in imaging disease (e.g., cancer) of the liver and pancreas. The drug consists of manganese (II) bound to the ligand, dipyridoxyl diphosphate, forming a paramagnetic complex. The chemistry and preclinical biology of S-095 Injection have been published [1-4]. The physiochemical properties of S-095 Injection (145 mM) used in the studies to be presented are provided in Table 1. Based on the demonstrated biological safety and MR imaging efficacy of S-095 Injection, the compound was evaluated in a Phase I clinical trial in the United States and subsequently advanced into Phase II trials in the U.S. and Europe.

This paper will focus on the clinical results obtained with S-095 Injection in Phase I and II clinical trials worldwide. For all studies cited in this report, S-095 Injection was formulated by an *in situ* process and sterilized by filtration. The concentration of the formulation used was 145 mM and the osmolality was between 1000 and 1400 mOsm/kg. Prior to the initiation of each clinical study, the protocol was reviewed and approved by each center's Institutional Review Board. Phase I was conducted under the direction of Nycomed Salutar, Inc. and Sterling Winthrop Pharmaceuticals Research Division; and Phase II under the direction of Byk Gulden in Germany, and Sterling Winthrop Pharmaceuticals Research Division in the United States. The individual results of several of these clinical trials have been published separately [5-11]. The protocols for the U.S. and German Phase II trials were not prospectively designed so that data could be merged and analyzed, therefore results are separate in all tables. For information regarding protocol design, parameter measurements, etc., the reader is referred to the relevant publications cited above. The incidences of adverse events cited in this report are based on the total number reported,

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Table 1:
Selected physicochemical properties of S-095 Injection.

Concentration	145 mM
Osmolality	1000-1400 mOsm/kg water
pH	5.5-6.5
Viscosity (at 37°C)	2.031 cps
Relaxivity at 10 mHz, 37°C	
*r*1	2.4 $mM^{-1}s^{-1}$
*r*2	4.0 $mM^{-1}s^{-1}$
Thermodynamic stability constant (log K)	15.1

and no judgement regarding causality to S-095 Injection has been made.

Materials and Methods

Phase I

A single center (see acknowledgements) Phase I clinical trial in normal healthy male volunteers was conducted to evaluate the safety, tolerance, and contrast enhancing ability of S-095 Injection. All subjects were monitored for changes in vital signs, electrocardiogram, clinical chemistry, hematology, and urine chemistry for three days after the intravenous administration of S-095 Injection. In 12 subjects, MR scans of the liver were obtained at varying time points after administration. S-095 injection, containing 145 mM MnDPDP, was administered at ascending dosages of 0 (saline), 3, 10, 15, 20 and 25 µmol/kg. Administration rates varied from 139 µmol/min (infusion) to 2175 µmol/min (bolus).

Phase II: United States

A multicentered open-label Phase II clinical trial was conducted in the United States at four centers (see acknowledgements). The primary study objective was to evaluate the efficacy of S-095 Injection at dosages of 3, 5, 8, and 10 µmol/kg administered either as an intravenous infusion (145 µmol/min) or bolus injection (2175 µmol/min) in enhancing liver parenchyma in patients being referred for evaluation of focal liver pathology. A secondary objective was to assess the safety of S-095 Injection in this patient population. Conventional T1- and T2-weighted spin echo MR images were obtained prior to the administration of S-095 Injection, and T1-weighted images were obtained again from 5 to 60 minutes after administration. In addition, a full battery of clinical

chemistry, hematology, and urine chemistry evaluations was performed before and 24-36 hours after drug administration. Vital signs and the electrocardiogram were taken before, and at 1 and 5 minutes after, the completion of S-095 Injection administration. Patients were observed for unusual symptomatology immediately after administration, during the MR procedure, and at follow-up 24-36 hours later.

Phase II: Europe (Germany)

A multicentered open-label Phase II trial was conducted in Germany at seven centers (see acknowledgements). The objectives of these trials were similar to those for the U.S. trials. S-095 Injection (145 mM), however, was diluted with normal saline to a concentration of 10 or 50 mM, and was administered as an intravenous infusion (14-250 μmol/min). Selected clinical chemistries were performed before and 24 hours after drug administration. Vital signs were measured before administration and at the end of MR imaging. Conventional spin echo images were obtained before and up to one hour after S-095 Injection administration. Patients were also questioned regarding adverse events after administration and again at 24 hour follow-up.

Results

Phase I

Fifty-four (54) subjects were enrolled in the Phase I study; 40 received S-095 Injection and 14 received saline. Salient demographic information for these subjects is shown in Table 2. No differences were detected between the saline and S-095 Injection groups in age or weight. In general, no significant effect on clinical chemistry, hematology, urine chemistry or the electrocardiogram were noted after the administration of S-095 Injection. Transient, dosage and administration rate dependent increases in systolic pressure and pulse rate were recorded one to three minutes after administration. Baseline values were reapproximated within 5 to 10 minutes.

Of the 14 subjects who received saline, one (7%) reported an adverse event. Of the 40 subjects receiving S-095 Injection, 38 (95%) reported at least one adverse event. Table 3 summarizes the number of subjects with any adverse event by dosage. The most common adverse event reported in the S-095 Injection group was flushing. Flushing sensations, including warmth or heat, were transient and spontaneously

Table 2:
Phase I subject demographics. Mean values for age and weight are followed by the range.

	Saline	S-095 Injection
Subjects	14	40
Age (years)	36 (28-42)	33 (20)
Weight (kg)	78 (62-95)	74 (55-94)

Table 3:
Summary of adverse events (AE) reported in Phase I.

Dosage (μmol/kg)	Number Subjects	Number (percentage) of Subjects with: Any AE	Flushing	Nausea
0	14	1 (7%)	0	0
3	6	5 (83%)	4 (67%)	0
10	19	18 (95%)	16 (84%)	1 (5%)
15	7	7 (100%)	7 (100%)	1 (14%)
20	4	4 (100%)	4 (100%)	3 (75%)
25	4	4 (100%)	4 (100%)	2 (50%)

resolved within several minutes.

T1-weighted spin echo images (at 1.5T) revealed significant hepatic parenchymal enhancement for at least one hour after injection. The increase in signal-to-noise between 10 and 30 minutes after injection was approximately 35%, 90% and 95% for the 3, 10 and 15 μmol/kg groups, respectively. Thus, a dosage of 10 mmol/kg resulted in an almost doubling of hepatic parenchymal intensity. No discernable differences in image enhancement were noted in subjects receiving S-095 Injection by bolus administration as compared to infusion.

Phase II: United States

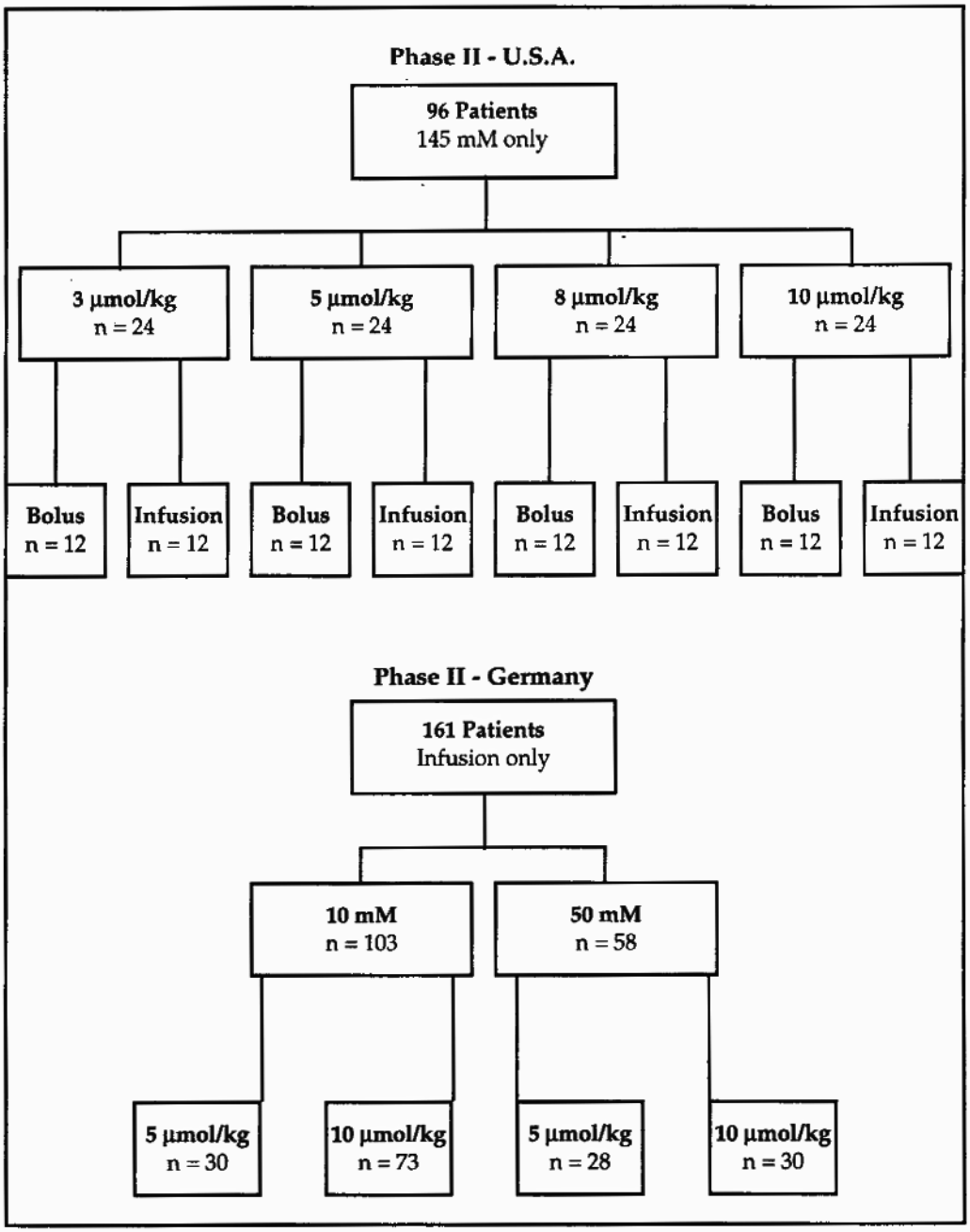
Ninety-six (96) consenting adult patients were entered into the trials conducted in the United States. Demographics for these patients are presented in Table 4. No particular differences were evident between the populations among the four centers. The distribution of patients by dosage and administration technique is schematically presented in Figure 1. Compared to baseline measurements, no clinically significant changes were detected in clinical chemistry, hematology, urine chemistry or the electrocardiogram at 24-36 hours after S-095 Injection administration. A minor, asymptomatic fall in serum iron was noted in several patients at 2 hours, with return to baseline levels at 24 hours. Transient increases in systolic blood pressure and pulse rate were recorded at 5 minutes after administration, returning to baseline within several minutes.

Of the 96 patients administered S-095 Injection, 38% reported no adverse events. Of those reporting at least one adverse event, flushing (55%) and nausea (9%) were the most com-

	United States	Germany
Number of Centers	4	7
Patients	96	161
Sex (M/F)	57/39	92/69
Age (years)	57 (18-86)	57 (26-83)
Weight (kg)	71 (41-109)	69 (47-110)

Table 4:
Phase II patient population demographics. Mean values and ranges for age and weight.

Figure 1 (bottom):
Distribution of Patients in Phase II by Concentration, Dosage, and Administration Rate.



	Percentage of Patients with Adverse Events	
	United States	**Germany**
Any Adverse Event	62%	30%
Type		
Flushing	55%	25%
Nausea	9%	2%
Headache	5%	4%
Vomiting	2%	0%
Dosage (μmol/kg)		
3	25%	
5	63%	31%
8	83%	
10	79%	30%

Table 5:
Summary of most prevalent adverse events reported in Phase II.

	Percentage of Patients with Flushing	
	U.S.	**Germany**
Dosage (μmol/kg)		
3	17%	
5	54%	24%
8	79%	
10	71%	25%
Administration Rate		
Bolus	60%	
Infusion	50%	25%
Concentration (mM)		
10		15 %
50		43%
145	55%	

Table 6:
Summary of flushing sensations reported in Phase II.

mon (Table 5). Table 6 summarizes the percentage of patients experiencing flushing by dosage, administration rate, and concentration. No difference in overall adverse events, or flushing in particular, was detected in association with the rate of administration. All adverse events were transient in nature and spontaneously resolved.

Spin echo images of the liver obtained at 15 to 30 minutes after administration of S-095 Injection showed a generally dose related increase in signal intensity. At dosages of 3, 5, 8, and 10 μmol/kg, the increases in signal intensity were 34, 51, 63, and 66%, respectively. Compared to the unenhanced images, images obtained after S-095 Injection were considered more informative in 48% of the cases, resulted in an

altered diagnosis in 18%, and detected more lesions in 10%.

Phase II: Europe (Germany)

One hundred sixty-one (161) consenting adult patients were entered in the trials conducted at seven centers in Germany. No significant differences among the centers were evident for patient age, sex, or weight (Table 4). Patients were predominantly referred for MR to evaluate primary liver cancer or metastatic disease. The distribution of patients by concentration and dosage is given in Figure 1. Compared to baseline measurements, no clinically significant changes were detected in clinical chemistry, hematology, urine chemistry, or the electrocardiogram values at 24 hours after S-095 Injection administration. No clinically significant changes in vitals signs were recorded.

Of the 161 patients administered S-095 Injection, 70% reported no adverse events. Of those reporting at least one adverse event, flushing (25%) and headache (4%) were the most common (Table 5). Table 6 summarizes the percentage of patients experiencing flushing by dosage, administration rate, and concentration. No difference in overall adverse events, including flushing in particular, was detected in association with dosage (24% of patients at 5 μmol/kg compared to 25% at 10 μmol/kg). However, the incidence of flushing was significantly less in those patients receiving S-095 Injection at a concentration of 10 mM compared to 50 mM. All adverse events were transient in nature and spontaneously resolved.

Overall, when compared to unenhanced images, images obtained after S-095 Injection were considered more informative in 53% of the cases, and resulted in an altered diagnosis in 4% of the cases.

Discussion

Biological and imaging studies in several species of animals demonstrated the selective distribution of the manganese dipyridoxyl dephosphate to the liver and pancreas [3,4]. Manganous ion (Mn^{2+}), containing five unpaired electrons, is sufficiently paramagnetic for use in magnetic resonance imaging [13]. In addition, considerable information is available on the toxicity, metabolism, and excretion of manganese [14-16].

The results from the Phase I study indicated that, at the dosages investigated, S-095 Injection was safe and provided enhancement of the liver. The overall incidence of adverse

events was higher than is normally reported for either gadolinium-based MR agents [17, 18] or iodine-based CT or x-ray agents [19]. The most common adverse event was a transient sensation of flushing during or shortly after administration. The incidence of flushing was both dosage and administration rate dependent. However, none of the volunteers in this study complained of any associated symptomology. The flushing sensations were transient and spontaneously resolved shortly after the administration was completed. Although dosage and administration rate dependent increases in systolic pressure and pulse rate were detected, these were also transient and elicited no symptomology. Measurement of MR signal intensity changes in the liver parenchyma suggested that dosages above 8 to 10 μmol/kg were not associated with further increase in signal intensity. The results of the Phase I study were sufficiently positive for the advancement of S-095 Injection into Phase II trials in patients with focal liver disease.

In the Phase II trials conducted in the United States and in Europe, the safety profile of S-095 Injection was consistent with that reported in Phase I. Again, the most prominent adverse event was a transient flushing sensation during drug administration. However, a difference in the incidence of patients with no reported reactions, and in the incidence of flushing in those that reported some adverse event was evident between the U.S. and European trials. Approximately twice as many patients in the U.S. trials reported some adverse event compared to the European trials. The difference was slightly more pronounced when the incidence of flushing was evaluated. Several explanations are possible.

First, patients in the U.S. are more likely to report reactions. Historically, this has been noted in similar trials using nonionic and ionic iodine-based agents [20]. Second, the concentration of drug administered, 10 or 50 mM in Europe and 145 mM in U.S., is an important factor in flushing sensations. Third, the administration rate, in μmol/min, is a determinant in the flushing sensation. Although the incidence of adverse events, especially flushing, was independent of dosage, but highly dependent on concentration and administration rate in the European trials, the data generated were not prospectively designed to be compared to that obtained in the U.S. trials.

Vital signs were only collected in the U.S. trials immediately after the administration of S-095 Injection, and the results corroborated those obtained in the Phase I trial. Namely, transient elevations in systolic blood pressure and pulse rate were associated, in a dosage and administration rate dependent fashion, with the administration of S-095

Injection. Although these changes were usually transient, resolved within several minutes, and were not associated with other symptomology, patients with compromised cardiovascular reflexes will need to be more precisely evaluated in future trials.

MR imaging efficacy was unequivocally demonstrated in the patient population evaluated in both the U.S. and European trials. Significant hepatic parenchymal enhancement was observed for up to one hour after the administration of S-095 Injection. Using conventional spin echo imaging the optimum dosage for liver enhancement was 8-10 μmol/kg. The results of imaging efficacy were consistent between the U.S. and European trials, with 48% and 53%, respectively, indicating that post S-095 Injection images were more informative than either T1- or T2-weighted images obtained before drug administration. In a select subgroup of patients evaluated at one center in Germany, pancreatic enhancement was similar to that seen with the liver [21].

Thus far, S-095 Injection has proven to be a safe and efficacious drug for MR enhancement of the liver and pancreas. Phase III studies will need to address more subtle issues of administration rate and concentration on the incidence of adverse events such as flushing.

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