U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	021135
Supplement #	S-024
Drug Name:	Venofer (Iron Sucrose Injection USP)
Indication(s):	Pediatric Chronic Kidney Disease
Applicant:	Luitpold Pharmaceuticals, Inc.
Submitted date:	September 30, 2011
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Review Priority:	Standard
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Keywords: Binomial proportion, CMH test, p-value, confidence interval, mITT

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1 EXECUTIVE SUMMARY

The primary objective of study 1VEN03017 was to compare the safety profile of 3 Venofer iron maintenance regimens over a 12-week period in erythropoietin (EPO) treated pediatric chronic kidney disease (CKD) subjects. The main efficacy endpoint was a composite referred to as clinical success, for the 12 week post-baseline period, of hemoglobin between 10.5 g/dL and 14.0 g/dL, inclusive, transferrin saturation (TSAT) between 20% and 50%, inclusive, and stable erythropoietin dosing [±25 % of baseline dose] or a decrease more than 25% in erythropoietin dose). The study was sized corresponding to a dose-response objective.

There were some discrepancies in the clinical study report, which provided doubt that clinical success rates were as high as reported. The Agency pointed out these discrepancies to the Sponsor in the March 29, 2012 teleconference, and requested the Sponsor to explain the discrepancy in writing. Further details are provided in Section 3.1.

The Sponsor investigated and responded to the Agency on April 6, 2012, and provided the revised clinical success rates of 26.1%, 22.2%, and 30.0% in 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg arms, respectively. This reviewer has verified those clinical success rates.

Key results

- There were no statistically significant pair-wise differences in clinical success rates over the 12-week post-baseline period observed between the Venofer 0.5 mg/kg (26.1%), Venofer 1.0 mg/kg (22.2%), and Venofer 2.0 mg/kg (30.0%) dose groups. A dose-response relationship was not demonstrated.

- All patients except one subject from the Venofer 2.0 mg/kg arm had stable EPO dosing during the 12-week post-baseline period.

2 INTRODUCTION

2.1 Overview

Study 1VEN03017 was a randomized, controlled open-label trial in pediatric chronic kidney disease (CKD) subjects on stable erythropoietin (EPO) therapy. At the time of randomization, subjects were stratified according to method of dialysis (hemodialysis dependent [HDD] or non-HDD) and weight (<50 kg and ≥50 kg) into 3 dosing arms: 0.5 mg/kg, 1.0 mg/kg, or 2.0 mg/kg of Venofer®, with a maximum single dose of 100mg. *The HDD-CKD subjects received study medication once every other week for 6 doses. Non-HDD subjects received study medication once every 4 weeks for 3 doses.* Non-HDD CKD subjects received study medication once every 4 weeks for 3 doses. Study drug was administered to HDD-CKD subjects on Days 0, 14, 28, 42, 56, and 70. Study drug was administered to non-HDD-CKD subjects on Days 0, 28, and 56. The primary objective was to compare the safety of the 3 dosing regimens over a 12 week period. Efficacy was assessed via a composite termed clinical success (achieving, for the 12-week post-baseline period, hemoglobin between 10.5 g/dL and 14.0 g/dL, inclusive, transferrin saturation (TSAT) between 20% and 50%, inclusive, and stable EPO dosing [±25% of baseline dose] or a decrease more than 25% in EPO dose). The study was conducted between 24 October 2005 and 23 January 2009. A total of 141 subjects were treated and evaluated for safety. Twenty-eight sites in the United States of America and Russia recruited the patients. The data were obtained to further support prior Phase 3 studies. All subjects (n = 131) who received at least 1 dose of study drug, had a stable EPO dose for at least 8 weeks before randomization, and had at least 1 post-baseline hemoglobin and ferritin assessment were included in the mITT Population. Key information is presented in Table 2.1.1 below.

Table 2.1.1: List of all studies included in analysis

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
1VEN03017	Phase 4	12 weeks	12 weeks	47	Pediatric CKD

2.2 Data Sources

EDR Location \\CDSESUB4\NONECTD\NDA021135\4927089\labeling and two compact disks were the source of study report and datasets. The SAS datasets *dlabdata.xpt*, *doconmeds.xpt*, *ard_eff.xpt* and *eval.xpt*, and *ard_clin.xpt* were used in this review.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The Sponsor's datasets dlabdata.xpt, doconmeds.xpt submitted through the September 7, 2011 compact disks were not easily manageable for safety and efficacy analyses. The Sponsor was asked to resubmit the efficacy data. The dataset ard_eff.xpt submitted in the November 1, 2011 compact disk contained information that was inconsistent with what was in dlabdata.xpt, and doconmeds.xpt. The derived dataset ard_clin.xpt, which was later submitted on April 12, 2012, was good.

The Sponsor, in its original submission, had reported that most subjects achieved clinical success during the 12-week study period with no statistically significant pair-wise differences in clinical success rates observed between the Venofer 0.5 mg/kg (89% clinical success), Venofer 1.0 mg/kg (84.4% clinical success), and Venofer 2.0 mg/kg (87.5% clinical success) dose groups.

However, there were some discrepancies in the clinical study report, which provided doubt that clinical success rates were as high as reported.

On March 16, 2012, an information request was sent by the Division of Hematology Products (DHP) for clarification of the determination of the main efficacy endpoint of "clinical success" for study 1VEN03017. In particular, DHP made two requests:

1. *Please clarify what appear to be discrepancies between Tables 11.4a and 11.4c on pages 48 and 49 of your clinical study report. For example, from Table 11.4a only five subjects on the 0.5 mg/kg Venofer arm are regarded as "failures" for clinical success; however, in Table 11.4c, 16 subjects on the 0.5 mg/kg Venofer arm have excursions of TSAT below 20% anytime post-baseline. At a patient-level, Subject 703005 is listed as a "success" for clinical success, but apparently had excursions for hemoglobin (16 g/dL) at week 12 and an excursion for TSAT (88%) at week 8.*

2. *Please also provide the location (dataset) and variables that list the values for hemoglobin, TSAT, and EPO dosing at the 4 week, 8 week and 12 week visits.*

On March 21, 2012 (received March 22, 2012), Luitpold submitted their response to the information request. On March 26, 2012, DHP requested a teleconference with Luitpold and provided two points for discussion (*shown in italics under discussion section*) in follow-up to Luitpold's response.

The Agency pointed out these discrepancies to the Sponsor in the March 29, 2012 teleconference, and requested the Sponsor to explain the discrepancy in writing.

Luitpold acknowledged the discrepancies in the data pointed out by the FDA. They stated that after receiving the FDA's inquiries, it was determined that the data management company was not determining "clinical success" by the definition provided in the protocol. Consequently, the numbers given for the clinical success rates are not correct. Since the submission, Luitpold has changed data management to a new company (i.e., (b) (4)).

The Sponsor investigated and responded to the Agency on April 6, 2012, and provided the revised clinical success rates of 26.1%, 22.2%, and 30.0% in 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg arms, respectively. The Sponsor also submitted the revised labeling package insert on April 6, 2012.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 1VEN03017 was a randomized, controlled, open-label trial of pediatric chronic kidney disease (CKD) subjects on stable erythropoietin (EPO) therapy. At the time of randomization, subjects were stratified according to method of dialysis (HDD or non-HDD) and weight (<50 kg and ≥50 kg) into 3 dosing arms: 0.5 mg/kg, 1.0 mg/kg, or 2.0 mg/kg of Venofer®, with a maximum single dose of 100 mg. Hemodialysis dependent-CKD subjects received study medication once every other week for 6 doses. Non-HDD CKD subjects received study medication once every 4 weeks for 3 doses. Study drug was administered to HDD-CKD subjects on Days 0, 14, 28, 42, 56, and 70. Study drug was administered to non-HDD-CKD subjects on Days 0, 28, and 56. Study schedule of evaluations are provided in Table 3.2.1 below. Male and female pediatric subjects with CKD aged 2 to 21 years, inclusive, who fulfilled the inclusion criteria, did not meet any of the exclusion criteria, who completed the consent, were included in the study. Twenty-eight sites in the United States of America and Russia recruited the patients.

Table 3.2.1: Schedule of evaluations

	Screening Phase (-3 up to -42 D*)		Treatment Phase							
Procedure	Screen 1	Optional 2	Visit 1 D* 0	Visit 2 D* 14	Visit 3 D* 28	Visit 4 D* 42	Visit 5 D* 56	Visit 6 D* 70	EOS 7 D* 84	Follow-up
Informed consent	X									
Physical exam.	X		X						X	
Vital signs	X		X	X	X	X	X	X	X	
Hematologic parameters	X	X			X		X		X	
Iron Indices	X	X			X		X		X	
Administration of Study Drug			X	X	X	X	X	X	X	
Concomitant med.	X	X	X	X	X	X	X	X	X	X
AE Assessment			X	X	X	X	X	X	X	X

* Days

Randomization occurred after the subject had successfully met all of the inclusion criteria. A fax randomization system was used. The subject randomization form was returned with a treatment group within 1 business day.

A sample size of approximately 120 subjects (15-20 subjects for each combination of dose group and age group [≤12 years and >12 years]) were randomized to receive study drug. This sample size of 120 subjects was based upon a Fisher's exact test for differences among proportions within each age group, at 90% power and a two-sided alpha level of 0.05, with the assumption of a 15% clinical success rate in the 0.5 mg/kg Venofer group, a 40% clinical success rate in the 1.0 mg/kg group, and an 80% clinical success rate in the 2.0 mg/kg group. The clinical success rates were estimated from previous studies of Venofer®. For an adverse event incidence rate of 20%, a sample size of 120 subjects provided an appropriately narrow 95% confidence interval of approximately 13% to 27% (20%±7%).

Clinical success rate was the main efficacy endpoint. Clinical success for a subject was defined as achieving, for the 12-week post-baseline period, the following criteria:

- Hemoglobin between 10.5 g/dL and 14.0 g/dL, inclusive,
- TSAT between 20% and 50%, inclusive, and
- Stable EPO dosing [±25% of baseline dose] or a decrease more than 25% in EPO dose.

3.2.2 Statistical Methodologies

Method of dialysis (hemodialysis [HDD] or non-HDD), and weight (<50 kg or ≥50 kg) were the two stratification factors at randomization. The Cochran-Mantel-Haenszel was used to compare clinical success between the treatment arms: Venofer 0.5 mg/kg, Venofer 1.0 mg/kg, and Venofer 2.0 mg/kg. The modified intent-to-treat (mITT) population was analyzed. The mITT population was defined as all randomized subjects who (i) received at least 1 dose of study drug, (ii) had a stable EPO dose for at least 8 weeks before randomization, and (iii) had at least 1 post-baseline hemoglobin and ferritin assessment. There were three treatment arms. Table 3.2.2 below provides the distribution of subjects by strata and treatments.

Table 3.2.2: Numbers of subjects by weight, dialysis method, and treatment arm- mITT dataset

Stratum	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg	Total (%)
Weight < 50 kg; HDD	16	19	16	51 (40%)
Weight < 50 kg; non-HDD	12	13	13	38 (29%)
Weight ≥ 50 kg; HDD	13	10	8	31 (24%)
Weight ≥ 50 kg; non-HDD	5	3	3	11 (8%)
Total	46	45	40	131

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The youngest patient was 2 years of age and the oldest was 20 years old. The mean age of a patient was 13.5 years. The mean baseline hemoglobin was 12.15 g/dL. The mean baseline TSAT was 32.7. The mean baseline ferritin was 299.3 (n = 79). The mean baseline EPO dose was 5585 units. Eighty-two (58%) patients were male and 59 (42%) patients were female. Mean weight of a patient was 42.2 kg. Median weight was 42 kg. For ethnicity, 81 (57%) patients were Caucasian and non-Hispanic, 30 (21%) patients were black, 27 (19%) patients were Hispanic, 2 (1.4%) patients were Asian, and 1 (0.7%) patient belonged to another ethnicity. Baseline weight (<50 kg vs. ≥50 kg), and dialysis method (hemodialysis dependent [HDD] vs. non-HDD), were stratification factors at randomization. The following Table 3.2.3 shows the distribution of subjects by weight, dialysis method, and by treatment (0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg).

Table 3.2.3: Numbers of subjects by weight, dialysis method, and treatment arm

Stratum	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg	Total (%)
Weight < 50 kg; HDD	16	20	19	55 (39%)
Weight < 50 kg; non-HDD	12	13	13	38 (27%)
Weight ≥ 50 kg; HDD	14	10	11	35 (25%)
Weight ≥ 50 kg; non-HDD	5	4	4	13 (9%)
Total	47	47	47	141*

* One-hundred and forty-one patients were treated and evaluated for safety.

As stated earlier, it was planned to have 120 subjects in the study. A total of 145 patients were screened and randomized. The numbers of subjects randomized to 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg were 49, 47, and 49, respectively. One-hundred and twenty subjects completed the study. A total of 25 patients, 8 from 0.5 mg/kg arm, 6 from 1.0 mg/kg arm, and 11 from 2.0 mg/kg arm, discontinued from the study. As per the dataset eval.xpt, the intent-to-treat set included 136 subjects. However, as per the dataset ard_eff.xpt, there were 131 mITT subjects.

3.2.4 Results and Conclusions

3.2.4.1 Sponsor's results of April 30, 2012

As mentioned in Section 3.1, there were some discrepancies in the clinical study report, which provided doubt that clinical success rates were as high as reported. The Agency pointed out these discrepancies to the Sponsor in the March 29, 2012 teleconference. On April 6, 2012 and subsequently on April 30, 2012, the Sponsor provided the revised clinical success rates to be 26.1%, 22.2%, and 30.0% in 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg arms, respectively.

3.2.4.2 Reviewer's results

3.2.4.2.1 Primary composite endpoint

In the mITT population a total of 89 (68%) subjects weighed less than 50 kg whereas the remaining 42 (32%) subjects were 50 kg or over 50 kg. Eighty-two (62.6%) subjects were hemodialysis dependent (HDD) and the remaining 49 (37.4%) subjects were non-HDD.

The clinical success rate was the main efficacy endpoint. The CMH test for comparing the equality of clinical success rates among the three arms indicated no differences among treatments (p-value = 0.702) for the mITT dataset.

The mITT dataset included 131 subjects who received at least 1 dose of study drug. The clinical success rates in the 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg arms were 12/46 (26.1%), 10/45 (22.2%), and 12/40 (30%), respectively. Table 3.2.4 below includes: (i) Pair-wise treatment comparisons in clinical success rates were made using the Cochran-Mantel-Haenszel (CMH) test- stratified by weight and method of dialysis, and (ii) Ninety-five per cent confidence intervals on the differences in clinical success rates between the treatments. Table 3.2.4 also contains the p-values (shown in parenthesis after the CMH test p-value) for the Breslow-Day test for homogeneity of odd ratios.

Table 3.2.4: Overall clinical success: pair-wise treatment comparisons- the mITT dataset

Treatment comparison	CMH test p-value (Breslow-Day test p-value)	Difference in proportions	95% Confidence interval On Difference
0.5 mg/kg − 1.0 mg/kg	0.6504 (0.56)	0.0386	(–0.1370, 0.2143)
0.5 mg/kg − 2.0 mg/kg	0.5704 (0.18)	–0.0391	(–0.2296, 0.1513)
1.0 mg/kg − 2.0 mg/kg	0.407 (0.018)	–0.0778	(–0.2647, 0.1091)

There were no statistically significant pair-wise treatment differences in overall clinical success rates observed between the Venofer 0.5 mg/kg (26.1%), Venofer 1.0 mg/kg (22.2%), and Venofer 2.0 mg/kg (30%) dose groups in the proportion of subjects who achieved overall clinical success during the 12-week study period. A dose-response relationship, the primary objective was not demonstrated.

3.2.4.2.2 Components of the composite efficacy endpoint

12-week post-baseline hemoglobin

The proportions of subjects with post-baseline hemoglobin between 10.5 g/dL and 14.0 g/dL in the 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg arms were 27/46 (58.7%), 21/45 (46.7%), and 18/40 (45.0%), respectively. Table 3.2.5 below includes: (i) Pair-wise treatment comparisons in rates of post-baseline of hemoglobin between 10.5 g/dL and 14.0 g/dL were made using the CMH test- stratified by weight and method of dialysis, and (ii) Ninety-five per cent confidence intervals on the differences in post-baseline rates of post-baseline of hemoglobin 10.5 g/dL and 14.0 g/dL between the treatments. Table 3.2.5 also contains the p-values (shown in parenthesis after the CMH test p-value) for the Breslow-Day test for homogeneity of odd ratios.

Table 3.2.5: Hemoglobin flag: pair-wise treatment comparisons

Treatment comparison	CMH test p-value (Breslow-Day test p-value)	Difference in proportions	95% Confidence interval On Difference
0.5 mg/kg − 1.0 mg/kg	0.2487 (0.2943)	0.1203	(−0.0834, 0.3240)
0.5 mg/kg − 2.0 mg/kg	0.2824 (0.9257)	0.1370	(−0.0728, 0.3468)
1.0 mg/kg − 2.0 mg/kg	0.9116 (0.1160)	0.0167	(−0.1955, 0.2288)

There were no statistically significant pair-wise treatment differences in rates of post baseline hemoglobin between 10.5 g/dL and 14.0 g/dL between the Venofer 0.5 mg/kg (58.7%), Venofer 1.0 mg/kg (46.7%), and Venofer 2.0 mg/kg (45%) dose groups.

Post-baseline transferrin saturation

The proportions of subjects with post-baseline transferrin saturation (TSAT) between 20% and 50% in the 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg arms were 15/46 (32.6%), 18/45 (40%), and 20/40 (50%), respectively. Table 3.2.6 below includes: (i) Pair-wise treatment comparisons in post-baseline rates of TSAT between 20% and 50% were made using the CMH test- stratified by weight and method of dialysis, and (ii) Ninety-five per cent confidence intervals on the differences in post-baseline rates of TSAT between 20% and 50% between the treatments. Table 3.2.6 also contains the p-values (shown in parenthesis after the CMH test p-value) for the Breslow-Day test for homogeneity of odd ratios.

Table 3.2.6: Transferrin saturation: pair-wise treatment comparisons

Treatment comparison	CMH test p-value (Breslow-Day test p-value)	Difference in proportions	95% Confidence interval on Difference
0.5 mg/kg − 1.0 mg/kg	0.2487 (0.2943)	−0.0739	(−0.2710, 0.1232)
0.5 mg/kg − 2.0 mg/kg	0.2824 (0.9257)	−0.1739	(−0.3797, 0.0319)
1.0 mg/kg − 2.0 mg/kg	0.9116 (0.1160)	−0.1000	(−0.3109, 0.1109)

There were no statistically significant pair-wise treatment differences in post baseline rates of TSAT between 20% and 50% between the Venofer 0.5 mg/kg (32.6%), Venofer 1.0 mg/kg (40%), and Venofer 2.0 mg/kg (50%) dose groups.

Erythropoietin (EPO) stability

EPO was stable for all subjects except one from the 2.0 mg/kg arm. It was not possible to perform CMH test.

3.3 Evaluation of Safety

No specific safety analyses are done in this review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Clinical success rate by gender

There were 78 (59.4%) male subjects in the study. The clinical success rates among male subjects in the 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg arms were 7/25 (28%), 7/25 (28%), and 6/28 (21.4%), respectively. Table 4.1.1 below includes 95% confidence intervals on the differences in clinical success rates between the treatments among males. There were no pair-wise differences observed between the Venofer 0.5 mg/kg, Venofer 1.0 mg/kg, and Venofer 2.0 mg/kg dose groups in the proportion of male subjects who achieved clinical success.

Table 4.1.1: Overall clinical success: pair-wise treatment comparisons in males

Treatment comparison	Difference in proportions	95% Confidence interval
0.5 mg/kg − 1.0 mg/kg	0.0000	(−0.2489, 0.2489)
0.5 mg/kg − 2.0 mg/kg	0.0657	(−0.1668, 0.2983)
1.0 mg/kg − 2.0 mg/kg	0.0657	(−0.1668, 0.2983)

There were 53 (40.5%) female subjects in the study. The clinical success rates among female subjects in the 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg arms were 5/21 (23.8%), 3/20 (15%), and 6/12 (50%), respectively. Table 4.1.2 below includes 95% confidence intervals on the differences in clinical success rates between the treatments among females. There were no pair-wise differences observed between the Venofer 0.5 mg/kg, Venofer 1.0 mg/kg, and Venofer 2.0 mg/kg dose groups in the proportion of female subjects who achieved clinical success.

Table 4.1.2: Overall clinical success: pair-wise treatment comparisons in females

Treatment comparison	Difference in proportions	95% Confidence interval
0.5 mg/kg − 1.0 mg/kg	0.0881	(−0.1521, 0.3282)
0.5 mg/kg − 2.0 mg/kg	−0.2619	(−0.5984, 0.0746)
1.0 mg/kg − 2.0 mg/kg	−0.3500	(−0.6733,−0.0267)

4.1.2 Clinical success rate by age-group

There were 44 (33.6%) subjects ≤ 12 years of age in the study. The clinical success rates among these subjects in the 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg arms were 2/12 (16.7%), 2/17 (11.8%), and 3/15 (20%), respectively. Table 4.1.3 below includes 95% confidence intervals on the differences in clinical success rates between the treatments among females. There were no pair-wise differences observed between the Venofer 0.5 mg/kg, Venofer 1.0 mg/kg, and Venofer 2.0 mg/kg dose groups in the proportion of subjects (≤ 12 years of age) who achieved clinical success.

Table 4.1.3: Overall clinical success: pair-wise treatment comparisons in subjects ≤12 years of age

Treatment comparison	Difference in proportions	95% Confidence interval
0.5 mg/kg − 1.0 mg/kg	0.0490	(−0.2116, 0.3096)
0.5 mg/kg − 2.0 mg/kg	−0.0333	(−0.3256, 0.2590)
1.0 mg/kg − 2.0 mg/kg	−0.0824	(−0.3362, 01715)

There were 87 (66.4%) subjects over 12 years of age in the study. The clinical success rates among these subjects in the 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg arms were 10/34 (29.4%), 8/28 (28.6%), and 9/25 (36%), respectively. Table 4.1.4 below includes 95% confidence intervals on the differences in clinical success rates between the treatments among females. There were no pair-wise differences observed between the Venofer 0.5 mg/kg, Venofer 1.0 mg/kg, and Venofer 2.0 mg/kg dose groups in the proportion of subjects (≤ 12 years of age) who achieved clinical success.

Table 4.1.4: Overall clinical success: pair-wise treatment comparisons in subjects >12 years of age

Treatment comparison	Difference in proportions	95% Confidence interval
0.5 mg/kg − 1.0 mg/kg	0.0084	(−0.2184, 0.2353)
0.5 mg/kg − 2.0 mg/kg	−0.0659	(−0.3085, 0.1767)
1.0 mg/kg − 2.0 mg/kg	−0.0743	(−0.3261, 0.1775)

4.1.3 Clinical success rate by race

There were 77 (58.8%) Caucasian and non-Hispanic subjects in the study. The clinical success rates in these subjects in the 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg arms were 9/28 (32.1%), 5/23 (21.7%), and 8/26 (30.8%), respectively. Table 4.1.5 below includes 95% confidence intervals on the differences in clinical success rates between the treatments among the Caucasian and non-Hispanic subjects. There were no pair-wise differences observed between the Venofer 0.5 mg/kg, Venofer 1.0 mg/kg, and Venofer 2.0 mg/kg dose groups in the proportion of Caucasian and non-Hispanic subjects who achieved clinical success.

Table 4.1.5: Overall clinical success: pair-wise treatment comparisons in Caucasian and non-Hispanic subjects

Treatment comparison	Difference in proportions	95% Confidence interval
0.5 mg/kg − 1.0 mg/kg	0.1040	(−0.1375, 0.3456)
0.5 mg/kg − 2.0 mg/kg	0.0137	(−0.2340, 0.2616)
1.0 mg/kg − 2.0 mg/kg	−0.0903	(−0.3350, 0.1544)

Subgroup analyses for other ethnic groups are not performed in this review due to the low numbers in each group.

4.2 Other Special/Subgroup Populations

4.2.1 Clinical success rate by dialysis method

Dialysis method (HDD vs. non-HDD) and weight (<50 kg vs. ≥50 kg) were stratification factors at randomization. Clinical success rates by strata are summarized in Table 4.2.1 below.

Table 4.2.1: Clinical success by strata

Stratum	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg
Weight < 50 kg; HDD	4/16 (25%)	6/19 (31.6%)	1/16 (6.3%)
Weight < 50 kg; non-HDD	3/12 (25%)	1/13 (7.7%)	5/13 (38.5%)
Weight ≥ 50 kg; HDD	4/13 (30.8%)	3/10 (30%)	4/8 (50%)
Weight ≥ 50 kg; non-HDD	1/5 (20%)	0/3 (0%)	2/3 (66.7%)
Total	12/46 (26.1%)	10/45 (22.2%)	12/40 (30%)

There were 82 (62.6%) hemodialysis dependent (HDD) subjects in the study. The clinical success rates in these subjects in the 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg arms were 8/29 (27.6%), 9/29 (31%), and 5/24 (20.8%), respectively. A summary of results on clinical success in HDD subjects is provided in Table 4.2.2 below.

Table 4.2.2: Overall clinical success: pair-wise treatment comparisons for hemodialysis dependent (HDD) subjects

Treatment comparison	Difference in proportions	95% Confidence interval
0.5 mg/kg − 1.0 mg/kg	−0.0345	(−0.2686, 0.1996)
0.5 mg/kg − 2.0 mg/kg	0.0675	(−0.1624, 0.2974)
1.0 mg/kg − 2.0 mg/kg	0.1020	(−0.1320, 0.3360)

There were 51 (36%) non-hemodialysis dependent (non-HDD) subjects in the study. The clinical success rates in these subjects in the 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg arms were 4/17 (23.5%), 1/16 (6.75%), and 7/16 (43.75%), respectively. A summary of results on clinical success in non-HDD subjects is provided in Table 4.2.2 below.

Table 4.2.3: Overall clinical success: pair-wise treatment comparisons for non-hemodialysis dependent (non-HDD) subjects

Treatment comparison	Difference in proportions	95% Confidence interval
0.5 mg/kg − 1.0 mg/kg	0.1728	(−0.0611, 0.4067)
0.5 mg/kg − 2.0 mg/kg	−0.2022	(−0.5180, 0.1136)
1.0 mg/kg − 2.0 mg/kg	−0.3750	(−0.6455, −0.1045)

4.2.2 Clinical success rate by weight

Study 1VEN03017 included 89 (67.9%) subjects whose weight was less than 50 kg. The clinical success rates in these subjects in the 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg arms were 7/28 (25%), 7/32 (21.9%), and 6/29 (20.7%), respectively. Table 4.2.4 below includes 95% confidence intervals on the differences in clinical success rates between the treatments among the subjects who weighed less than 50 kg. There were no pair-wise differences observed between the Venofer 0.5 mg/kg, Venofer 1.0 mg/kg, and Venofer 2.0 mg/kg dose groups in the proportion of subjects who achieved clinical success.

Table 4.2.4: Overall clinical success: pair-wise treatment comparisons for subjects with weight less than 50 kg

Treatment comparison	Difference in proportions	95% Confidence interval
0.5 mg/kg − 1.0 mg/kg	0.0312	(−0.1838, 0.2463)
0.5 mg/kg − 2.0 mg/kg	0.0431	(−0.1747, 0.2610)
1.0 mg/kg − 2.0 mg/kg	0.0118	(−0.1937, 0.2174)

Study 1VEN03017 included 42 (32.1%) subjects whose weight was 50 kg or greater. The clinical success rates in these subjects in the 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg arms were 5/18 (27.8%), 3/13 (23.1%), and 6/11 (54.5%), respectively. Table 4.2.5 below includes 95% confidence intervals on the differences in clinical success rates between the treatments among the subjects who weighed less than 50 kg. There were no pair-wise differences observed between the Venofer 0.5 mg/kg, Venofer 1.0 mg/kg, and Venofer 2.0 mg/kg dose groups in the proportion of subjects who achieved clinical success.

Table 4.2.5: Overall clinical success: pair-wise treatment comparisons for subjects whose weight was 50 kg or over 50 kg

Treatment comparison	Difference in proportions	95% Confidence interval
0.5 mg/kg − 1.0 mg/kg	0.0470	(−0.2616, 0.3557)
0.5 mg/kg − 2.0 mg/kg	−0.2677	(−0.6274, 0.0920)
1.0 mg/kg − 2.0 mg/kg	−0.3146	(−0.6876, 0.0582)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The sample size of 120 was based on a Fisher's exact test for differences among proportions within each age group [≤12 years and >12 years] at 90% power and an alpha level 0f 0.05, with the assumption of a 15% clinical success rate in the 0.5 mg/kg Venofer group and a 40% clinical success rate in the 1.0 mg/kg group, and an 80% clinical success rate in the 2.0 mg/kg group. A test for a comparison of proportions between the 0.5 mg/kg arm and the 1.0 mg/kg requires 65 subjects in each arm. The Sponsor recruited just 47 subjects in each treatment arm.

As seen from Table 3.2.3, the stratum "Weight ≥50 kg; non-HDD" has small numbers of subjects in all treatment groups. The sample proportions may not be assumed to be approximately normally distributed. The hyper geometric distribution could be used to derive the CMH test to compare the clinical success. But the number of strata is just four. The sum of the "weighted differences" may not be assumed to follow normal distribution. Therefore, the CMH test statistic having a chi-square distribution with 1 degree of freedom is questionable.

5.2 Collective Evidence

Not applicable.

5.3 Conclusions and Recommendations

- There were no statistically significant pair-wise differences in the main efficacy endpoint of clinical success rates over the 12-week post-baseline period observed between the Venofer 0.5 mg/kg (26.1%), Venofer 1.0 mg/kg (22.2%), and Venofer 2.0 mg/kg (30.0%) dose groups. A dose-response relationship was not demonstrated.

- Should the labeling changes based on this study be made, it should be clearly stated that a dose-response relationship was not demonstrated.

5.4 Labeling Recommendations

Labeling package should include clinical success rates for all three arms.
It also should include the statement "A dose-response relationship was not demonstrated".

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/s/

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