

**[ICH E2F]**

**[MODEL DSUR – Non-Commercial Sponsor]**

**Vasculogenesis Growth Factor-2 (VGF-2)**

**Development Safety Update Report #2**

Period covered: April 17, 2010 – April 16, 2011

Sponsor:

Affiliation:

Address:

Date: May 13, 2011

Signed .....

[name, title]

Note: This Development Safety Update Report contains confidential information. This report includes unblinded adverse event data.

## EXECUTIVE SUMMARY

Vasculogenesis Growth Factor-2 (VGF-2) is a 37-kD polypeptide, a member of the XYZ superfamily of growth factors. VGF-2 exerts mitogenic effects on vascular endothelial cells (through interaction with the VGF-R receptor), and stabilizes endothelial cell-cell junctions. Through these mechanisms, VGF-2 is thought to accelerate the development of collateral blood vessels.

DrugCo, Inc. is developing VGF-2 for the angina pectoris indication in patients with stable coronary artery disease. We are evaluating the effects of VGF-2 in patients with peripheral artery disease (PAD). In an experimental rabbit PAD model (unilateral femoral artery ligation), we demonstrated that VGF-2 stimulates collateral development through an increase in arteriogenesis (demonstrated with positive bromodeoxyuridine labeling), enhances limb perfusion (fluorescent microspheres), and increases limb survival. We initiated a Phase II trial to evaluate the effects of VGF-2 in patients with PAD: “Safety and Activity of VGF-2 in Peripheral ArterY Disease, SAVY”). Our primary objective is to assess the safety, tolerability, and pharmacokinetics of VGF-2 in the PAD population. We also seek to gain some evidence of the biological activity of VGF-2, as indicated by improvement in the 6-minute walk test (6-MWT). Because the VGF-R receptor is thought to be up-regulated during ischemia, each subject will receive 3 infusions of VGF-2 (or placebo) during treadmill exercise (Days 1, 3, and 5, see protocol).

Based on non-clinical data and experience gained in subjects with coronary artery disease (completed Phase I/II studies; ongoing Phase III study), DrugCo, Inc. has reported that VGF-2’s main safety concerns are hypotension, proteinuria, hepatotoxicity, and anemia. As has been reported with a number of heparin-binding growth factors, the hypotensive effect is thought to be mediated by NO-dependent vasodilatation; the mechanisms responsible for proteinuria, hepatotoxicity, and anemia are unknown. Additional concerns regarding this polypeptide relate to its potential to cause exaggerated neovascularization (particularly retinal neovascularization) and stimulation of tumor development, although we are unaware of any cases of retinal neovascularization or tumor promotion in DrugCo’s coronary artery disease

development program. In our PAD study, all subjects undergo retinal photography at baseline and Week 24; to date, there has been no evidence of retinal neovascularization in any subject. One subject experienced an adverse event for a new tumor, although it is very likely that this was a pre-existing condition (described in detail in this report).

There has been concern regarding hepatotoxicity of VGF-2. In a rat toxicology study, where rats were repeatedly exposed to high doses of VGF-2 (600 mg/kg X 21 days), there was evidence of acute, non-cholestatic liver injury. On a per-weight basis, the planned exposure is 140-fold less than this in our ongoing study (subjects are receiving only a single dose of VGF-2, with 30 mg/kg the highest dose planned). One subject in the 1 mg/kg X3 cohort developed elevated transaminases 4 weeks after receiving VGF-2. Transaminases peaked at 7-times the upper limit of normal, with small increases in bilirubin and alkaline phosphatase. The history was confounded, however, because the subject had been receiving concomitant drug “X,” which is well-known to be hepatotoxic. Both drugs were discontinued, and liver function studies returned to normal after three months. Although transaminase elevations with drug “X” are fairly common, the subject had been receiving drug “X” for three years and transaminases had been consistently normal. In contrast, the temporal relationship between hepatic injury and VGF-2 administration is suggestive of a causal effect. We have revised the protocol to exclude subjects with a history of hepatic disease, and now include more intensive monitoring of transaminases and bilirubin. In the period of this DSUR, we also revised the Investigator’s Brochure and Informed Consent to include the potential for liver injury.

We are not aware of any other new or potentially important safety issues during this reporting period.

In light of the early stage of development of VGF-2 in PAD, the risks still seem acceptable when considered in light of the serious morbidity of PAD, and the potential of this therapy to foster the development of arterial collaterals and ameliorate symptoms. By excluding potential subjects with cancer, retinal neovascularization, and a history of hepatic disease, and by carefully monitoring subjects for signs of toxicity, we believe the risks are well-managed.

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## 1. Introduction

This is the second Development Safety Update Report (DSUR) for Vasculogenesis Growth Factor-2 (VGF-2), covering the period from April 17, 2010 to April 16, 2011. Our IND went into effect on April 17, 2009, and this is the Development International Birth Date.

VGF-2 is a biotechnology-derived product, an arteriogenic, heparin-binding 37-kD polypeptide growth factor belonging to the XYZ family of growth factors. The product has been shown to accelerate collateral development in dog and pig models of coronary artery disease, and DrugCo is developing the product for the treatment of angina pectoris in patients with coronary artery disease (see letter of cross-reference to DrugCo, Inc. IND provided with our original IND submission). The product is provided as a lyophilized powder (500 mg/vial) that is reconstituted in sterile water prior to intravenous infusion. The product and diluent used in this study are provided to our institution by DrugCo, and are identical to the product being evaluated in studies in coronary artery disease.

Our laboratory has developed evidence that VGF-2 accelerates development of collaterals in a rabbit hindlimb model of PAD, where we demonstrated enhanced limb collateral perfusion (using fluorescent microspheres), flow (laser doppler), vascular development (bromodeoxyuridine labeling), blood pressure, and limb survival (Writer FL, et. al., J Adv Med. 2008; 23:632). See the Investigator's Brochure (latest version [revision 2] submitted in IND amendment 0012) for further details.

The objective of the clinical study "SAVY" is to evaluate the safety, tolerability, and pharmacokinetics of VGF-2 in patients with PAD and intermittent claudication, and to obtain preliminary evidence of biological activity (increased exercise capacity).

The scope of this DSUR is our Phase II trial of VGF-2 in subjects with PAD. We have provided a copy of this report to the manufacturer and supplier of VGF-2, DrugCo, Inc.

## **2. Worldwide Marketing Authorization Status**

To our knowledge, VGF-2 is not authorised for sale in any country at this time.

## **3. Actions Taken in the Reporting Period for Safety Reasons**

### a. elevated transaminases

Subject 111 was noted to have elevated hepatic enzymes on his Day 28 visit (December 23, 2010; see details under 7.2.b, below). Our Data Monitoring Committee (DMC) considered this event at their January 15, 2011 meeting. In light of this adverse event, and DrugCo's demonstration of hepatic injury associated with repeated, high doses of VGF-2 in a pre-clinical study, we revised the protocol as follows:

Serology for hepatitis will now be included in the screening laboratory evaluation, and the following subjects will be excluded from study participation:

1. prior history of hepatitis;
2. transaminases above upper limit of normal for local laboratory: aspartate aminotransferase (AST), alanine aminotransferase (ALT), or gamma glutamyl transpeptidase (GGTP);
3. positive serology for hepatitis A, B, or C.

In the original protocol, subjects were to have hepatic function studies assessed at screening, and Weeks 2, 6, 12, 24, and 36 weeks. In light of the adverse event in subject 111, subjects will undergo more frequent and more comprehensive assessment of hepatic function.

Specifically, all subjects will undergo assessment of ALT, AST, GGTP, alkaline phosphatase, lactate dehydrogenase (LDH), and direct and indirect bilirubin at screening, and Weeks 1, 2, 4, 6, 12, 18, 24, and 36.

We have revised the section of the Consent Form under "risks of participation," pages 5-6:

(additions in underlined font, deletions in ~~strike-out font~~):

Page 5:

“Your participation in this study entails some risk of liver damage. In a study conducted by the drug’s manufacturer, doses of VGF-2 about 140-times higher than the highest dose you could receive as a participant in this study caused liver injury in a rat. One patient in this study who received VGF-2 developed a liver problem 3 weeks after his dose. It is not clear if the liver problem was directly related to VGF-2, another drug the patient was taking, or some other factor. ~~Although the VGF-2 dose you might receive is very low compared to the dose that caused liver problems in rats, there is a risk of liver problems with this drug.~~ We will check your blood for evidence of liver problems before you enter the study, and if your blood tests indicate that you have had a liver problem, you will not be enrolled in the study. If you are eligible for the study and decide to participate ~~in the study,~~ we will re-test your blood for evidence of liver damage 1, 2, 4, 6, 12, 18, 24, and 36 weeks after you receive the drug (or placebo).”

Page 6:

“The total amount of blood required for the study will be about 10 ounces (300 mL)~~7 ounces (210 mL).~~”

We have taken no other actions for safety reasons during the period of this DSUR, and have received no requests that place limitations on our study.

#### **4. Changes to Reference Safety Information**

The safety section of the Investigator’s Brochure (IB) is currently in revision, and will be submitted to the Agency by June 30, 2011.

#### **5. Inventory of Clinical Trials Ongoing and Completed during the Reporting Period**

This DSUR covers a single study: “Safety and Activity of VGF-2 in Peripheral Artery Disease, SAVY”). The primary objectives of this Phase II study are to assess the tolerability, safety, tolerability, and pharmacokinetics of VGF-2 in patients with PAD. In addition, the study will evaluate the effects of VGF-2 on exercise capacity, as assessed by the six-minute walk test (6-MWT). “SAVY” is being conducted at a single site (----- Hospital, ----- University, City, State). The study is being conducted under U.S. IND 00000.

“SAVY” is a double-blind, placebo-controlled, serial, dose escalation study. We plan to enroll 64 adult subjects (age  $\geq 18$  years) with symptomatic PAD over three years.

Within each group of 16 subjects, three-quarters of the subjects (12) will be randomized to VGF-2, and one-quarter (4) to placebo. Randomization is being carried out with a variable block size (4 or 8). Each subject receives 30-minute intravenous infusions of VGF-2 (or placebo) during treadmill exercise on Days 1, 3, and 5. Subjects will be monitored through 36 weeks. The study scheme is summarized below (with dosing on 3 separate days, the total dose is three-times the doses listed below):

- Group 1: VGF-2, 1 mg/kg, or placebo (n = 16; randomization 3:1)
- Group 2: VGF-2, 3 mg/kg, or placebo (n = 16; randomization 3:1)
- Group 3: VGF-2, 10 mg/kg, or placebo (n = 16; randomization 3:1)
- Group 4: VGF-2, 30 mg/kg, or placebo (n = 16; randomization 3:1)

Study status: The first visit for the first patient was September 21, 2009. As of April 16, 2011, 20 subjects have been enrolled (approximately 1 subject per month). Enrollment was initially much slower than anticipated, but increased during the past 12 months after the hiring of a nurse practitioner to assist in recruitment. The first dosing group has been completed (1 mg/kg), and 4 subjects have been enrolled in the second dosing group (3 mg/kg).

## **6. Estimated Cumulative Exposure**

### **6.1 Cumulative Subject Exposure in the Development Program**

The study remains blinded, and the numbers of subjects exposed are based on the randomization scheme:

Subject exposure through April 16, 2011:

1 mg/kg	n = 12
3 mg/kg	n = 2, 3, or 4
10 mg/kg	n = 0
30 mg/kg	n = 0
placebo	n = 4, 5, or 6

Given that the trial remains blinded, we cannot provide demographic data by treatment group. For the study as a whole, 70% of subjects are male, and 55% of subjects are age 65 and older. Eighty percent (80%) of subjects are Caucasian, 15% are of African ancestry, and 5% are Asian.

## **6.2 Patient Exposure from Marketing Experience**

Not applicable.

## **7. Data in Line Listings and Summary Tabulations**

### **7.1 Reference Information**

We used the Medical Dictionary for Regulatory Activities (MedDRA) version 13.1 for the coding of adverse events. The Investigator's Brochure in effect at the beginning of this reporting period (version 2) served as the reference document for determination of "expectedness" for all adverse events. Relevant safety data are presented using interval line listings and cumulative summary tabulations in Appendices 5 and 6, respectively. The 4 serious adverse events in this reporting period are presented here as narratives.

### **7.2 Line Listings of Serious Adverse Reactions (SARs) during the Reporting Period**

a. Subject 103 is a 67 year-old female who presented to the emergency room on March 16, 2009 (26 days after treatment with VGF-2, 3 mg/kg, or placebo) with acute ischemia of

the right lower extremity (critical limb ischemia). She was admitted to \_\_\_\_\_ Hospital in City, State, and underwent angioplasty with a \_\_\_\_\_ stent, but subsequently required an above-the-knee amputation for refractory ischemia. Ischemic complications are part of the natural history of PAD. As agreed to previously with the FDA, these events are not being reported in expedited fashion. Treatment assignment has not been unblinded for this subject.

b. Subject 111 is a 69 year-old male who was noted to have elevated transaminases at his Day 28 visit (December 23, 2010). His treatment assignment was unblinded, and it was determined that he had received a total dose of 255 mg VGF-2 (1 mg/kg X3) on November 24, 26, and 28, 2010. Of note, the subject had been taking drug X for dyslipidemia for 22 months, which is known to be hepatotoxic. Drug X was discontinued on December 23, 2010. Liver ultrasound was non-diagnostic; liver biopsy was considered, but the patient refused. Transaminases peaked at 7-times the upper limit of normal on January 12, 2011 and decreased thereafter. Bilirubin and alkaline phosphatase were slightly increased; prothrombin time was normal. Serology studies for viral etiologies were negative. The subject was seen in consultation by the Liver Service. Although they noted that drug X provided a plausible etiology for the transaminase elevations, they opined that it does not typically cause transaminase elevations of this magnitude, and that it usually causes toxicity early, whereas subject 111 had been using drug X for approximately two years without problems. In light of the magnitude of the transaminase elevations, the negative serology for infectious causes of hepatitis, and the temporal association between transaminase elevation and VGF-2 administration, the Liver Service thought that VGF-2 may have been causally related to the transaminase elevations in this subject. By Month 4 (March 24, 2011), all liver function tests had returned to normal. Given the potential hepatotoxicity of drug X, it was not re-started; but the patient was switched to drug "A" for management of his dyslipidemia. None of the other subjects in the study have experienced transaminase elevations.

c. Subject 105 is a 64 year-old male who experienced transient unilateral visual loss (O.S.) on October 31, 2010, 5 months after receiving VGF-2, 1 mg/kg IV X 3 (total dose = 231 mg). (Treatment allocation for this subject was unblinded.) The subject was evaluated by his ophthalmologist in City, State, and he was found to have central retinal artery occlusion. This was thought to be embolic in origin, as the patient has a history of paroxysmal atrial

fibrillation and non-compliance with warfarin. An echocardiogram showed a small left atrial thrombus, and anticoagulation was re-instituted. His visual loss had resolved as of the Week 26 visit, and his retinal examination was reported to be similar to baseline.

d. Subject 121 is a 62 year-old male who was recently diagnosed with metastatic prostate cancer. He received VGF-2, 1 mg/kg IV X 3 or matching placebo on November 17, 19, and 21, 2010, and sought evaluation for a number of complaints consistent with urinary obstruction in early April, 2011 (~4.5 months after receipt of test drug). His Prostatic Specific Antigen (PSA) was found to be 402 ng/mL (upper limit of normal = 4.0 ng/mL), and a technetium-99m MDP bone scan demonstrated numerous intense foci of increased activity throughout the shoulder girdle, spine, and pelvis, consistent with metastatic disease. A prostatic biopsy was obtained on April 13, 2011, and an expedited IND safety report was submitted for this serious adverse event. As of the cutoff date for this DSUR, the pathology was unknown, but the neoplasm was assumed to be malignant based on the positive bone scan and the markedly elevated PSA. In retrospect, the subject had been having symptoms of urinary retention for a number of months prior to enrollment. In July, 2010 (4 months prior to enrollment), he was found to have an irregular prostate by his internist, who recommended further evaluation; however, the patient refused a workup at that time because of issues with his health insurance coverage. In retrospect, this tumor was likely pre-existing, but a role for the test drug can not be ruled out. As of the cut-off date for the DSUR, the treatment code for this subject has not been unblinded.

### **7.3 Cumulative Summary Tabulations of Serious Adverse Events**

All of the SAEs reported in the study are summarized in Section 7.2, with the exception of an SAE for hypotension that occurred in subject 102 during infusion of the initial dose of VGF-2 on October 29, 2009. This was fully described in the previous DSUR. Because VGF-2 is known to cause hypotension (based on non-clinical studies) and because this effect is described in the Investigator's Brochure and Consent Form, no additional actions were taken on the basis of this SAE.

Appendix 6 presents a cumulative table of the number of serious adverse events (SAEs) that have been reported during the development program, organized by SOC. The table presents SAE counts under the following column headings: VGF-2, Placebo, and code unbroken.

## **8. Significant Findings from Clinical Trials during the Reporting Period**

### **8.1 Completed Clinical Trials**

Not applicable. SAVY is the only trial in this IND, and the only study covered by this DSUR, and it is ongoing.

### **8.2 Ongoing Clinical Trials**

A DMC monitors study safety data for each cohort once the Day 28 data are received. After analyses of unblinded safety data from the 1 mg/kg cohort, they recommended continuation of the study without alteration.

A concern that came to light during this reporting period is hepatotoxicity, based on the adverse event in subject 111. The event is described fully in Section 7.2.b., and in the Summary of Important Risks, Section 19.4.

### **8.3 Long-Term Follow-up**

Not applicable. At present, patients completing SAVY are not subject to long-term follow up.

### **8.4 Other Therapeutic Use of Investigational Drug**

Not applicable. No expanded access or compassionate use programmes exist for VGF-2.

### **8.5 New Safety Data Related to Combination Therapies**

Not applicable, as VGF-2 is a monotherapy.

## **9. Safety Findings from Non-interventional Studies**

VGF-2 is not marketed in any country, and no observational or epidemiological studies have been initiated.

## **10. Other Clinical Trial/Study Safety Information**

Not applicable.

## **11. Safety Findings from Marketing Experience**

VGF-2 is not approved for marketing in any country.

## **12. Non-clinical Data**

Data from EXP-05, a recently completed 6-month rabbit study, are presently undergoing analysis. Rabbits (n=24) were subjected to unilateral femoral artery ligation and randomized 1:1 to receive VGF-2, 10 mg/kg intravenously, X3, or saline vehicle, as in prior studies. Whereas our previous studies assessed the effect of VGF-2 on collateral function at 3 weeks, EXP-05 was extended to 6 months, to assess the long term effect of VGF-2. Moreover, we obtained microsphere limb perfusion data at serial time points (baseline; and weeks 1, 2, 4, 12, and 24) to determine whether limb collateral function is maintained (or regresses) after withdrawal of VGF-2. We obtained a number of common clinical laboratory tests from the rabbits, and these data are currently under analysis.

## **13. Literature**

VGF-2 was shown to reduce infarct size and improve left ventricular function in a canine model of acute coronary occlusion (Scientist XY, et. al., Southeastern J Exp Med. 2011; 142:98). There were no important safety issues described in the paper, although the focus of the study was biological activity, and not toxicology.

An abstract of our rabbit limb perfusion study (EXP-05, described briefly in Section 12) was accepted for a poster presentation at the 27<sup>th</sup> Annual Scientific Sessions of the \_\_\_\_\_ Society, and the abstract is attached to this DSUR.

## **14. Other DSURs**

DrugCo, Inc. submits a DSUR for VGF-2 for the stable angina/coronary artery disease patient population on an annual basis under US IND #00000.

## **15. Lack of efficacy**

Not applicable. Although PAD is a serious and life-threatening disease, subjects are permitted to receive approved therapies while participating in our study. Efficacy of VGF-2 has yet to be demonstrated in the PAD population, and lack of efficacy is not an issue.

## **16. Region-Specific Information**

### **16.1 Cumulative Summary Tabulation of Serious Adverse Reactions**

Not applicable. Not required by U.S. regulations.

### **16.2 List of Subjects Who Died during the Reporting Period**

None.

### **16.3 Subjects who Dropped Out in Association with any Adverse Event in the Reporting Period**

All subjects enrolled thus far have received their planned 3 doses of study medication on Days 1, 3, and 5. Subject 106 dropped out of the study after the Day 28 visit, because of difficulties in arranging transportation to our site. Although the subject did experience a number of non-serious adverse events (headache, myalgias, and nausea, reported 15 days after receiving the initial dose), these were not claimed to factor into the subject's decision to drop out of the study.

### **16.4 Significant Phase I Protocol Modifications**

All modifications to the Phase I protocol have been previously reported.

### **16.5 Significant Manufacturing Changes**

Not applicable. The product is manufactured by DrugCo., Inc.

### **16.6 Description of the General Investigation Plan for the Coming Year**

We plan to continue enrollment in SAVY. To date, we have enrolled 20 of 64 planned subjects. We hope to be able to increase enrollment to approximately 3 subjects per month, and our goal is to have the trial fully enrolled by mid-2012.

### **16.7 Log of Outstanding Business with Respect to the US IND**

None.

## **17. Late-Breaking Information**

Subsequent to the data lock point of this DSUR, we received the pathology report on subject 121 (prostatic cancer, see 7.2.d), indicating prostatic cancer with a Gleason score of 7. Though staging data were incomplete, we made a decision to unblind the treatment

assignment, and learned that the subject had received placebo. Although the subject had not received VGF-2, this case caused a great deal of consternation, and this was discussed extensively with the DMC, and with our colleagues in our oncology department. In retrospect, this subject had evidence of cancer prior to study entry. Given the theoretical potential of this angiogenic peptide to stimulate tumour development, we recognized that the development of even a single case of cancer in a VGF-2-treated subject in this relatively small study could importantly impact the study in a negative way. Moreover, because PAD is a disease of the elderly, and because the vast majority of PAD subjects have a significant history of tobacco use, the development of cancer should be *expected* in our study. In light of these considerations, we made a decision to require cancer screening for all subjects enrolled in SAVY, per American Cancer Society recommendations. We are currently working on a protocol revision to require negative cancer screening studies as a criterion for enrollment. Our goal is to reduce the probability of enrolling subjects with pre-existing cancer.

#### **18. Overall Safety Assessment**

The main changes to the overall safety assessment during this reporting period are greater concern regarding hepatotoxicity and the theoretical concern of a role for VGF-2 in tumor stimulation.

Since the initial DSUR, the most concerning safety finding was a subject who developed transaminase elevations (7-times the upper limit of normal), 4 weeks after receiving VGF-2, 1 mg/kg X3. There were only minor changes in alkaline phosphatase and bilirubin; the transaminase elevations resolved completely, without symptoms or complications. High doses of VGF-2 have been associated with acute hepatocellular toxicity in rats; therefore, VGF-2 was considered to be potentially hepatotoxic when the clinical study was initiated. Although the clinical case was confounded by concomitant use of the lipid-lowering drug “X” which is well-known to be hepatotoxic, the temporal relationship between VGF-2 administration and the development of hepatic injury suggested a causal role for VGF-2. The protocol has been revised to exclude subjects with a history of hepatic disease or positive serology for hepatitis, and transaminases and bilirubin will now be monitored more

intensively throughout the study. The Investigator's Brochure and Informed Consent have been revised to include a brief description of the clinical case of liver injury.

A subject who had received placebo developed metastatic prostate carcinoma while on study. This was likely a pre-existing condition, and served mostly to underscore the concern regarding VGF-2's potential role in tumor stimulation. As a result of this experience, we have decided to implement a protocol amendment requiring cancer screening studies as a prerequisite for study enrollment. (Patients may enter the study with documentation of negative cancer screening studies obtained within one year of study entry, or may obtain cancer screening studies at our Institution.) Hopefully, these measures will prevent at least some subjects with pre-existing tumors from enrolling in the study.

### **18.1 Evaluation of the Risks**

Overall, VGF-2 has been well-tolerated. The main safety concerns identified by the manufacturer, acute hypotension, proteinuria, and anemia, have yet to be observed in our study. Perhaps this is because these toxicities appear to be dose-related (primarily at doses  $\geq 10$  mg/kg X 5), and the highest dose administered in our study to date has been 3 mg/kg X3. Other concerns regarding this angiogenic peptide relate to its pro-angiogenic effects (here the theoretical concerns are retinal neovascularization and tumor stimulation) and hepatotoxicity.

- Retinal neovascularization: To date, we have obtained baseline and follow-up ocular photography on all subjects in SAVY, and there has been no evidence of retinal neovascularization in any subject.
- Tumor stimulation: There was a serious adverse event for metastatic prostate carcinoma; however, the subject had received placebo. As noted above, we are taking steps to reduce the chance of enrolling subjects with preexisting tumors (through implementation of cancer screening, see above). Stimulation of tumor development remains a theoretical concern, and it is included in the Informed Consent.

- **Hepatotoxicity:** The risk of hepatotoxicity has been highlighted above, and is described in detail in this report. We have revised the protocol to exclude subjects with a history of hepatic disease or positive hepatitis serology, and implemented more frequent monitoring of hepatic enzymes.

There were no deaths in this reporting period, and no dropouts related to adverse events.

Other serious adverse events were considered by the DMC to be unrelated to VGF-2. These included a subject who developed critical limb ischemia 26 days after receiving VGF-2 or placebo, where the event was considered to be consistent with the natural history of the underlying PAD. Another subject developed embolic central retinal artery occlusion, 5 months after receiving VGF-2. He had a background of paroxysmal atrial fibrillation, had been non-compliant with his prescribed warfarin therapy, and was found to have an embolic source (a left atrial thrombus). The DMC did not attribute the event to the VGF-2.

## **18.2 Benefit-risk Considerations**

At the present stage of development, the risk of VGF-2 seems acceptable in light of its potential benefit (amelioration of PAD). With this DSUR, there is stronger evidence of a risk of hepatic injury, and we have made appropriate changes in the protocol and informed consent, as noted in this report. By excluding subjects with a history of hepatic disease, and monitoring transaminases more frequently, we hope to detect hepatic transaminase elevations at an earlier stage, and diminish risk. These risks should be considered in light of the significant morbidity of PAD and VGF-2's potential to ameliorate claudication, improve function, and enhance limb salvage.

## **19. Summary of Important Risks**

**19.1 Proteinuria.** VGF-2 has been associated with mild proteinuria in DrugCo's Phase I/II studies in subjects with coronary artery disease. To date, neither new nor worsened proteinuria have been observed in our PAD subject population. Subjects are monitored with 24-hour urinary protein excretion at baseline, weeks 2 and 24.

**19.2 Hypotension.** Acute hypotension was observed in 9% of subjects in DrugCo's completed coronary artery disease studies. Decreases in blood pressure were self-limited and dose-related, and affected by the rate of VGF-2 infusion. We have observed only mild, transient hypotension in SAVY, likely because our VGF-2 dose and infusion rate are much less than in DrugCo's coronary artery disease study. (The infusion rate in our PAD study is only 20% of the rate being used in DrugCo's coronary artery disease studies.) One subject developed transient orthostatic dizziness, and it is possible that hypotension may become more of an issue when we reach higher dosing cohorts.

**19.3 Anemia.** Peptide growth factors related to VGF-2 have been noted to cause mild anemia, with direct bone marrow toxicity the putative mechanism. A few subjects in SAVY (2 subjects in the VGF-2 group and 1 in the placebo group) have experienced mild decreases in hemoglobin, with normal RBC morphology and decreased reticulocyte counts. Of note, these subjects undergo numerous phlebotomies for clinical laboratory tests, which make the changes difficult to interpret. We plan to continue monitoring for anemia, and will investigate any cases.

**19.4 Hepatic toxicity.** In a rat toxicology study, where rats were exposed to high doses of VGF-2, there was evidence of acute hepatocellular injury. On a per-weight basis, the highest planned exposure in our study (30 mg/kg X3) is 140-fold less than the no-effect dose in rats. One subject in the 1 mg/kg X3 cohort developed acute liver injury, 4 weeks after receiving VGF-2. Transaminases peaked at 7-times the upper limit of normal, with small increases in bilirubin and alkaline phosphatase. The history was confounded, however, because the subject had been receiving the concomitant lipid lowering drug "X," which is well-known to be hepatotoxic. Both drugs were discontinued, and transaminases returned to normal after 3 months. The temporal relationship between hepatic injury and VGF-2 administration is suggestive of a causal effect; therefore, we have revised the protocol to exclude subjects with a history of hepatic disease, and now include more intensive monitoring of transaminases and bilirubin. In the period of this DSUR, we also revised the Investigator's Brochure and Informed Consent to include the potential for liver injury.

## **20. Conclusions**

The risks remain fairly consistent with the experience described in our previous DSUR, and we conclude that the information obtained in this reporting period justifies continuation of the study, with the modifications noted in this DSUR.

## Appendices to the DSUR

- 1 Investigator’s Brochure (if required): Not applicable**
- 2 Cumulative Table of Important Regulatory Advice: Not applicable**
- 3 Status of Ongoing and Completed Clinical Trials:**

Study	Phase	Country	Study Title	Study design	Dosing regimen	Study population	FVFP*	Planned enrollment	Subject exposure**
SAVY	II	USA	Safety and Activity of VGF-2 in PAD	Randomized, double-blind, placebo-controlled, serial dose escalation	1, 3, 10, or 30 mg/kg X 3; or placebo X 3 (Days 1, 3, and 5), by IV infusion	Age >40, PAD with intermittent claudication, ankle-brachial index <0.8	9/21/09	64	12 subjects exposed to 1 mg/kg X 3; up to 4 subjects exposed to 3 mg/kg X 3

## 4 Cumulative Summary Tabulations of Demographic Data:

**Table 1 Estimated cumulative subject exposure to VGF-2 by age and gender:**

Age (yr)	Number of subjects		
	Male	Female	Total
40 – 50	1	0	1
51 – 60	4	1	5
61 – 70	7	2	9
71 – 80	2	3	5
>80	0	0	0
<b>Total</b>	<b>14</b>	<b>6</b>	<b>20</b>

**Table 2** Estimated cumulative subject exposure to VGF-2 by ethnic origin:

<b>Ethnic origin</b>	<b>Number of subjects</b>
Caucasian	18
Black	1
Oriental	1
Other	0
Total	20

**5 Line Listings of Serious Adverse Reactions (SARs):**

Study/ Subject #	Country Gender Age	Serious ADR(s)	Outcome	Time to Onset	Suspect Drug	Daily dose Route Formulation	Dates of Treatment	Comments
SAVY 102	US Male 58	hypotension	resolved	12 minutes	VGf-2	1 mg/kg X3 (intravenous)	10/29/09, 11/1/09, 11/3/09	58 year-old male, became hypotensive (88/52) during VGf-2 infusion while on treadmill. The subject had mild dizziness, without pre-syncope or syncope. He responded to decreasing the drug infusion rate, saline, and leaving the treadmill to assume the Trendelenburg position. He was treated on days 3 and 5 without hypotension. Dehydration on Day 1 may have contributed to the hypotension.
SAVY 103	US Female 67	critical ischemia, right lower extremity	sequelae	26 days	blinded	3 mg/kg X3 or placebo (intravenous)	3/16/11, 3/18/11, 3/20/11	67 year-old female presented with critical limb ischemia of the right lower extremity. She was admitted to _____ Hospital in City, State, underwent angioplasty with a _____ stent, but subsequently required an above-the-knee amputation for refractory ischemia.
SAVY 111	US Male 69	Elevated hepatic transaminases	resolved	28 days	VGf-2	1 mg/kg X3 (intravenous)	11/24/10, 11/26/10, 11/28/10	69 year-old male developed elevated transaminases at Day 28. He had been taking Drug X for 22 months. Drug X was discontinued. Liver ultrasound was non-diagnostic; liver biopsy refused. Transaminases peaked at 7-times the upper limit of normal at 8 weeks and declined thereafter. Serology studies for viral etiologies were negative.
SAVY 105	US Male 64	transient unilateral visual loss (O.S.); central retinal artery occlusion; atrial fibrillation (AF)	resolved	5 months	VGf-2	1 mg/kg X3 (intravenous)	6/23/10, 6/25/10, 6/27/10	64 year-old male with transient unilateral visual loss (O.S.) He was found to have central retinal artery occlusion, thought to be embolic in origin, associated with AF. The patient had known paroxysmal AF and non-compliance with warfarin. Echocardiogram showed a small left atrial thrombus. Anticoagulation was re-instituted, and visual loss resolved within 4 weeks. Final retinal examination unchanged from baseline.
SAVY 121	US Male 62	metastatic prostate cancer	ongoing	5 months	blinded	3 mg/kg X3 or placebo (intravenous)	11/17/10, 11/19/10, 11/21/10	Developed urinary obstruction ~4.5 months after test drug; PSA >400; bone scan C/W metastatic disease. Prostate biopsy pending. In retrospect, prostatism and an abnormal prostate examination predated enrollment.

**6 Cumulative Summary Tabulation of Serious Adverse Events (SAEs):**

<b><u>System Organ Class</u></b>			
Preferred term	VGF-2	placebo	Code unbroken
<b><u>Cardiac disorders</u></b>	<b>1</b>	<b>0</b>	<b>0</b>
Atrial fibrillation	1	0	0
<b><u>Vascular disorders</u></b>	<b>1</b>	<b>0</b>	<b>1</b>
Right lower extremity ischemia, requiring PTA, stent, amputation	0	0	1
Hypotension	1	0	0
<b><u>Investigations</u></b>	<b>1</b>	<b>0</b>	<b>0</b>
Elevated alanine transaminase	1	0	0
<b><u>Neoplasms, benign, malignant, and unspecified</u></b>	<b>0</b>	<b>0</b>	<b>1</b>
Prostate cancer	0	0	1
<b><u>Eye Disorders</u></b>	<b>1</b>	<b>0</b>	<b>0</b>
Decreased visual acuity, central retinal artery occlusion, left eye	1	0	0

**7 Scientific Abstracts**

See attached.

**Regional Appendices (as required by regional regulatory authority):**

**1 Cumulative summary tabulation of serious adverse reactions**

Not applicable.

**2 List of subjects who died during the reporting period;**

None.

**3 List of subjects who dropped out of studies during the reporting period;**

No subjects dropped out in relation to an adverse event.

**4 Significant Phase I protocol modifications;**

Not applicable.

**5 Significant manufacturing changes**

Not applicable.