SUMMARY OF TOXICOLOGY DATA
GS-omega/kappa-Hxtx-Hv1a

Chemical Code # 6089, Document Processing Number (DPN) 53181
SB 950 # NA
2/19/15

DATA GAP STATUS

Chronic toxicity, rat: Study not submitted nor required.¹
Chronic toxicity, dog: Study not submitted nor required.¹
Oncogenicity, rat: Study not submitted nor required.¹
Oncogenicity, mouse: Study not submitted nor required.¹
Reproduction, rat: Study not submitted nor required.¹
Developmental toxicity, rat: Study not submitted nor required.¹
Developmental toxicity, rabbit: Study not submitted nor required.¹
Gene mutation: Study not submitted nor required.¹
Chromosome effects: Study not submitted nor required.¹
DNA damage: Study not submitted nor required.¹
Neurotoxicity: Study not required, no adverse effect indicated

Toxicology one-liners are attached.

All record numbers for the above study types through 53181-0012 (Document No. 28335) were examined. This includes all relevant studies indexed by DPR as of 2/19/15.

In the 1-liners below:
  indicates an acceptable study.
Bold face indicates a possible adverse effect.
### indicates a study on file but not yet reviewed.

File name: T150219
Revised by T. Moore, 2/19/15
¹ Toxicology data for GS-omega/kappa-Hxtx-Hv1a have been submitted and reviewed as a biochemical. These studies are not required at this time. The active ingredient is a peptide which is readily susceptible to proteolytic degradation. The rodent subchronic toxicity, developmental toxicity and mutagenicity studies stipulated under Tier 1 are not required.
NOTE: The following symbols may be used in the Table of Contents which follows:
- * = data adequately address FIFRA requirement
- † = study(ies) flagged as “possible adverse effect”
- N/A = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

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METABOLISM AND PHARMACOKINETICS
Study not submitted nor required.

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat
53181-0005; 265748; “Acute Oral Toxicity Up and Down Procedure in Rats”; (J. Durando; Product Safety Labs, Dayton, NJ; Study No. 32855; 12/6/11); Three female Sprague Dawley rats were dosed orally with 5000 mg/kg of VST-006325 (batch no. 1234600; purity: 33%) (vehicle: distilled water). No deaths resulted from the treatment. No treatment-related clinical signs were evident. No treatment-related lesions were noted in the necropsy examination. LD50 (F) > 5000 mg/kg; Toxicity Category IV; Study acceptable. (Moore, 8/21/12)

Acute dermal toxicity
53181-0005; 265749; “Acute Dermal Toxicity Study in Rats”; (J. Durando, Product Safety Labs, Dayton, NJ; Study No. 33040; 12/6/11); The skin of five Sprague-Dawley rats/sex was exposed to 5000 mg/kg of VST-006325 (batch no. 1234600; purity: 33%) for 24 hours under an occlusive wrap. The test material was moistened with distilled water. No deaths resulted from the treatment. No treatment-related clinical signs were evident. No treatment-related lesions were noted in the necropsy examination. LD50 (M/F) > 5000 mg/kg; Toxicity Category IV; Study acceptable. (Moore, 8/21/12)

Acute inhalation toxicity, rat
53181-0005; 265750; “Acute Inhalation Toxicity Study in Rats”; (C. Lowe; Product Safety Labs, Dayton, NJ; Study No. 33305; 1/24/12); Five Sprague-Dawley derived rats/sex were exposed nose-only to 2.05 mg/l (gravimetric) of VST-006325 (batch no. 1234603; purity: 32%) for 4 hours. The mean MMAD (GSD) was 3.65 (2.47) um. No deaths resulted from the exposure. One animal demonstrated an irregular respiration. All of the animals lost weight through day 1. Weight loss persisted for 3 animals through day 3 and/or day 7. No treatment-related lesions were evident in the necropsy examination. LC50 (M/F) > 2.06 mg/l; Toxicity Category IV; Study acceptable. (Moore, 8/21/12)

Primary eye irritation, rabbit
53181-0005; 265751; “Primary Eye Irritation Study in Rabbits”; (J. Durando; Product Safety Labs, Dayton, NJ; Study No. 33041; 1/7/12); The eyes of 3 female New Zealand albino rabbits were treated by ocular instillation with 0.1 ml (0.09 g)/eye of VST-006325 (batch no. 1234600; purity: 33%). No corneal opacity nor iritis were evident during the 72-hour observation period. No conjunctival redness, chemosis nor discharge were noted at 24 hours post-dose and thereafter. Toxicity Category IV; Study acceptable. (Moore, 8/22/12)

Primary dermal irritation
53181-0005; 265752; “Primary Skin Irritation Study in Rabbits”; (J. Durando; Product Safety Labs, Dayton, NJ; Study No. 33042; 12/6/11); The skin of 3 male New Zealand albino rabbits was exposed to 0.5 g/site, one site/animal, of VST-006325 (batch no. 1234600; purity: 33%) for 4 hours under a semi-occlusive wrap. Erythema, grade 2 (3/3), was noted at 1 hour post-
exposure, diminishing to grades 2 (2/3) and 1 (1/3) at 24 hours, grades 2 (1/3) and 1 (2/3) at 48 hours, grade 1 (2/3) at 72 hours and clearing by 7 days. Edema, grade 1 (3/3) was evident at 1 and 24 hours post-exposure, diminishing to grade 1 (2/3) at 48 and 72 hours and clearing by 7 days. Toxicity Category III; Study acceptable. (Moore, 8/22/12)

Dermal sensitization
53181-0005; 265753; “Dermal Sensitization Study in Guinea Pigs (Buehler Method)”; (J. Durando; Product Safety Labs, Dayton, NJ; Study No. 33045; 2/7/12); The skin of 20 male Hartley albino guinea pigs was treated with 0.4 g/site, one site/animal, of a 75% preparation of VST-006325 (batch no. 1234600; purity: 33%) in mineral oil, using an occlusive 25 mm Hill Top Chamber, for 6 hours, once per week for 3 weeks in the induction phase. Twenty seven days after the 1st induction treatment, these animals were challenged with a dose of 0.4 g/site of the 75% preparation in mineral oil for 6 hours. A naive control group of 10 male guinea pigs was treated in the same manner. In the challenge, at 24 and 48 hours post-application, none of the induced group demonstrated a positive response. None of the ten naive control animals had a positive score at either 24 or 48 hours post-application as well. The test material is a not dermal sensitizer as determined in the Buehler assay. The positive control was functional. Study acceptable. (Moore, 8/22/12)

SUBCHRONIC STUDIES  (units of mg/kg/day unless specified)

Oral toxicity, rat:
Study not submitted nor required.

Oral toxicity, non-rodent:
Study not submitted nor required.

Dermal toxicity, 21/28-day or 90-day:
Study not submitted nor required.

CHRONIC STUDIES

Chronic, rat
Study not submitted nor required.

Chronic, dog
Study not submitted nor required.

Oncogenicity, rat
Study not submitted nor required.

Oncogenicity, mouse
Study not submitted nor required.

GENOTOXICITY

Gene mutation
Study not submitted nor required.

Chromosome damage
Study not submitted nor required.
DNA damage or miscellaneous effects
Study not submitted nor required.

**REPRODUCTIVE TOXICITY, RAT**
Study not submitted nor required.

**DEVELOPMENTAL TOXICITY**
- **Rat**
  Study not submitted nor required.
- **Rabbit**
  Study not submitted nor required.

**NEUROTOXICITY**
- **Acute neurotoxicity, rat**
  Study not submitted nor required.
- **90-day neurotoxicity, rat**
  Study not submitted nor required.
- **Developmental neurotoxicity, rat**
  Study not submitted nor required.
- **Delayed neurotoxicity, hen**
  Study not submitted nor required.

**Mechanistic Study**
53181-0012; 282335; “ATX II and GS-omega/kappa-Hxtx-Hv1a Effects on the Mammalian Voltage-Gated Na⁺ Channels”; (L. Bao; Vesteron Corporation, Kalamazoo, MI; no study number provided; 10/2/14); In the assay, the NG108-15 neuron cell line was utilized as the *in vitro* membranous matrix for the voltage gated Na⁺ channel. This cell line is a hybridization of mouse N18TG2 neuroblastoma cells and rat C6-BU-1 glioma cells with Sendai virus. ATX II, a mammalian toxin which is derived from the sea anemone was selected as a positive control in the assay. This toxin specifically slows tetrodotoxin (TTX)-sensitive Na⁺ channel inactivation in mammals in the same manner as delta-HXTX-Hv1a, which has been identified as the mammalian toxin in the spider venom, does. Both toxins have been shown to bind to neurotoxin receptor site 3, one of at least 7 neurotoxic receptor sites which have been identified on voltage-gated Na⁺ channels. At least 5 types of voltage-gated TTX sensitive Na⁺ channels are expressed on the membranes of the NG108-15 neuron cell line, NaV1.1, NaV1.2, NaV1.3, NaV1.6 and NaV1.7. In the assay, the polarization of the Na⁺ channels was demonstrably inactivated by TTX, specifically identifying the channels of interest. ATX II delayed the inactivation of the stimulus on the Na⁺ channel in a dose-related manner at concentrations in the nanomolar range. In contrast, GS-omega/kappa-Hxtx-Hv1a had virtually no effect on either the activation or inactivation of the stimulus at a concentration up to 100 µmolar. These study results specifically demonstrated that GS-omega/kappa-Hxtx-Hv1a does not affect the target site in which the funnel web spider venom manifests its mammalian toxicity. **No adverse effect indicated. Summary report.** (Moore, 2/18/15)

**IMMUNOTOXICITY**
Study not submitted nor required.
ENDOCRINE DISRUPTOR STUDIES
Study not submitted nor required.

SUPPLEMENTAL STUDIES
Studies not submitted.