[Note: A 90-day continuous subcutaneous infusion study of UT-15 (lot numbers LRX-97J01 and LRX-98A01) in rats (conducted at
Study No. 585D-103-434-97), using osmotic pumps, at 0 (vehicle control), 0 (saline control), 50, 150 and 450 ng/kg/min, revealed no significant toxicological findings except for implantation site lesions (swelling, edema and inflammation) and significantly increased absolute and relative spleen weights in all treated female groups (dose dependent) and in the high dose male group. Increased absolute and relative liver (high dose females) and heart (high dose males) weights were also observed.

A 28-day continuous subcutaneous infusion study in rats (conducted at
study number 1458), at targeted doses up to 450 ng/kg/min, compared the toxicological effects of a batch of UT-15 (lot number UT15MIX-99G001) that had a different impurity profile to the lot that was previously tested (lot number UT15RP-98I001) in the 26-week rat toxicity study. No significant differences in the toxicological profiles of these lots were noted.]



APPEARS THIS WAY
ON ORIGINAL

**Twenty-six Week Subcutaneous Continuous Infusion Toxicity Study in Dogs Followed by a 4-Week Recovery Period**

Testing Facility: [redacted]

Study Number: 2129-98 [redacted] Lab.'s No.)

Study Dates: Initiation of Treatment – November 2, 1998
Terminal Sacrifice – May 3 to June 4, 1999

GLP Compliance: The study was conducted in compliance with GLP regulations.

Animals: Beagle dogs ( [redacted] 4/sex/ group, housed individually in stainless steel cages and fed once daily with 400 g of [redacted] 25% Lab Dog Diet #8727C, were about 8 months old (males weighed 7.1 to 10.6 kg and females 7.0 to 10.5 kg) at the onset of treatment. An additional three dogs/sex/group were assigned to the vehicle control and high dose groups for the recovery phase of the study.

Dose Levels and Mode of Administration: The target dose levels and the concentrations of dosing solutions are given below.

| *Treatment Groups* | Target Dose Levels[1] | | *Concentration* |
|---|---|---|---|
| | mg/kg/min | mg/kg/day | mg/ml |
| 1. Saline control[2] | 0 | 0 | 0 |
| 2. Vehicle control[3] | 0 | 0 | 0 |
| 3. Low dose | 50 | 0.072 | 0.06 |
| 4. Mid dose | 100 | 0.144 | 0.12 |
| 5. High dose | 200 | 0.288 | 0.24 |

[1.] The test and control articles were administered at a constant rate of 0.05 ml/kg/hour to achieve target dose levels. [2.] Saline control animals received 0.9% sodium chloride for injection USP. [3.] Vehicle control animals received the vehicle containing sodium citrate, citric acid, sodium chloride and meta-cresol dissolved in water for injection USP (pH 6.8 – 7.4).

UT-15 (Lot No. UT15-98H01) solutions were prepared weekly by dilution of appropriate volumes of UT-15 stock solution (10 mg/ml) with the vehicle to achieve the desired concentrations. The dosing solutions were filtered through a [redacted] filter to assure sterility.

Analyses of test article concentrations at three different time points during the study showed that the concentrations of the dosing solutions were about [redacted] (values corrected for volatiles and other impurities) of the nominal values.

It is stated that "the dose levels were selected by the sponsor together with the study director based on available data."

The test and control articles were infused subcutaneously, 24 hours/day, at a rate of 0.05 ml/kg/hour. The infusion site on the dorsal side was surgically prepared, and the catheter was inserted under local anesthesia and secured in place. The catheter was connected to medical grade tubing that was passed through a jacket and tether system to the outside of the cage door. The infusion line was then connected to the reservoir containing the test article solution. The infusion rate was controlled using an infusion pump.

The infusion site was changed approximately every 7 days (to another dorsal site). A topical antiseptic (4% chlorhexidine gluconate) was applied to the surgical sites throughout the treatment period. During the treatment period, animals (both control and treated) exhibiting skin lesions (wound, dermatitis, ulceration, edema and/or erythema) were treated with topical applications of 10% iodine and/or 0.05 or 4% chlorhexidine gluconate.

Observations/Measurements: Animals were observed daily for clinical signs and mortality. A detailed clinical examination was performed one week prior to initiation of dosing and once weekly thereafter, with particular attention paid to surgical sites. Body weights were recorded for all animals one week prior to initiation of treatment, weekly during treatment and recovery periods and at study termination. Food consumption was recorded daily. Indirect ophthalmoscopy and slit lamp examinations were performed for all animals during the pretreatment period and also during weeks 13 and 26. Electrocardiograms (limb leads I, II and III; and augmented leads aVR, aVL and aVF) were recorded for all animals during the pretreatment period and also during treatment weeks 13 and 26. Hematology [RBC, WBC (total and differential), platelet and reticulocyte counts, hemoglobin, hematocrit, MCV, MCH, MCHC, prothrombin time, activated partial thromboplastin time, and blood cell morphology] and serum chemistry (urea nitrogen, creatinine, glucose, cholesterol, triglycerides, total protein, albumin, globulin, ALT, AST, alkaline phosphatase, bilirubin, calcium, sodium, potassium, phosphorus and chloride) evaluations, and urinalysis were performed on all animals pretest and during treatment weeks 13 and 26, and on all recovery animals at the end of the recovery period .

Blood samples were collected from all dogs pretest and on days 1, 7, 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, 168 and 182 for toxicokinetic evaluations. Blood samples were collected 3 hours post start of infusion on day 1, and at the same hour on each of the remaining occasions. (Only blood samples from the first three dogs/sex/group were analyzed; samples collected from the remaining animals were discarded.)

All main phase animals were euthanized after 26 weeks of treatment, and all recovery phase animals were kept for an additional 4 weeks (without dosing) before sacrifice.

Complete necropsies were performed on all animals. Adrenals, brain, epididymides, heart, kidneys, liver, lungs, ovaries, prostate, spleen, testes, thymus, thyroids (with para-

thyroids) and uterus were weighed. Representative sections of adrenals, aorta (thoracic), brain, cecum, cervix, colon, epididymides, esophagus, eyes, femoral bone, gallbladder, heart, last infusion site, kidneys, lacrimal glands, liver, lungs, lymph nodes (mesenteric and mandibular), mammary gland, optic nerves, ovaries, pancreas, pituitary, prostate, rectum, salivary gland (mandibular), sciatic nerve, skeletal muscle, skin and subcutis, small intestine (duodenum, ileum and jejunum), spinal cord (cervical), spleen, sternum and marrow, stomach, testes, thymus, thyroids with parathyroids, tongue, trachea, urinary bladder, uterus and vagina, and all abnormal tissues were fixed in neutral buffered 10% formalin (except epididymides, eyes, optic nerves and testes which were fixed in Zenker's fluid).

Three femoral bone marrow smears were prepared from each animal, but were not evaluated.

Tissues were processed and stained with hematoxylin and eosin/phloxine for microscopic examination. Histopathological examination was performed on all above listed tissues from all animals.

Data were analyzed for homogeneity of variance using Levene Median and for normality using Kolmorogov-Smirnov tests. Homogeneous data were analyzed using the analysis of variance and the significance of intergroup differences was tested using Dunnett's t test. Heterogeneous data were analyzed using Kruskal-Wallis test, and the significance was tested by Dunn's test.

Results: There were no deaths in this study.

The most frequently observed clinical signs in animals of all dose groups, including controls, included the presence of lumps (firm), swellings (soft) and/or swellings around the lumps at or around the infusion site. The incidence and severity of these clinical signs were higher in drug-treated groups (especially in the high dose group) than in saline or vehicle controls. Generally, the lumps/swellings appeared 1 to 3 days following the start of infusion or the change to a new infusion site and they gradually disappeared 2 to 6 days later.

Dose-dependent erythema around the infusion site was observed in females of all dose groups, including a few saline control animals. In males, erythema was frequently seen in mid and high dose animals.

Animals from all drug-treated groups exhibited pain (sensitivity to touch) when palpated at the infusion site, the incidence being higher in the high dose group than in other groups.

Other clinical signs, including decreased activity, prostration, loose feces and wounds at the infusion sites, were observed sporadically in a few animals of one or more dose groups.

No treatment-related clinical signs were seen at the end of the recovery period.

Dose-dependent decreases in mean body weights (2 to 10%), compared to body weights on Day 1, were noted during the first 1 to 4 weeks of treatment in all dose groups (both sexes). Reductions in body weights (1-3%) were also noted for saline and vehicle controls during this period. No further significant decreases in body weights were noted in any dose groups by about Day 29, and the animals started to gain weight thereafter. By the end of the treatment period (Day 183), the mean body weights of treated and control groups were 2-7% and 5-10% higher, respectively, than corresponding values on day 1.

At the end of the recovery period, the body weight gains were comparable in the high dose and vehicle control groups.

During the first week of treatment, the food consumption of the high dose group (both sexes) was significantly lower than control. The food consumption improved considerably during the second and third weeks of treatment, and by the fourth or fifth week, the food consumption of the high dose group was comparable to that of controls. There were no significant treatment-related effects on food consumption at other dose levels.

During the recovery period, food intake was comparable in treated and control groups.

There were no treatment-related ocular findings in the study.

The test-drug had no effects on electrocardiographic parameters including the morphology of the P, QRS and T complexes, PR and QT intervals, ST segment, mean electrical axis, and heart rate.

Reversible, non dose-related increases in mean white cell counts (9 – 113%; mainly due to an increase in neutrophils), compared to controls, were noted in the mid and high dose groups of both sexes during treatment weeks 13 and 26.

No significant treatment-related findings were seen in the clinical chemistry and urinalysis parameters.

Although not statistically significant, increases in the absolute (14 – 35%) and relative (31%) mean spleen weight, compared to vehicle control, were seen in both sexes of the high dose group. After the recovery period, the mean spleen weight was still higher in the high dose male group than in control.

Macroscopically, thickening of the infusion site and masses around the infusion site were seen in some of the control dogs and in the majority of the drug-treated dogs.

No treatment-related macroscopic findings were noted after 4 weeks of recovery.

DOCKET ALARM

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

**LAW FIRMS**
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

**FINANCIAL INSTITUTIONS**
Litigation and bankruptcy checks for companies and debtors.

**E-DISCOVERY AND LEGAL VENDORS**
Sync your system to PACER to automate legal marketing.