RESULTS & DISCUSSION
A. Acute Studies in mice and rats
Acute Maximum Tolerated Dose (MTD) and LD₅₀ of WCK 771 and WCK 793 was determined by administration for 6 weeks old Swiss mice (5 males, 5 females) per group at doses between 425 to 575 mg/kg (between 350 and 450 mg/kg for WCK 771) and 150 to 300 mg/kg in Swiss mice (5 males, 5 females) at doses between 400 to 600 mg/kg (between 350 and 400 mg/kg for WCK 793). The LD₅₀ was calculated by Probit analysis.

B. Lethality study in Beagle dog
Lethality study was performed by the administration of WCK 771 in Beagle dogs (male and female) at single dose of 125 mg/kg of body weight with corresponding sodium (Na) salt at dosages of 125 and 250 mg/kg.

C. Phototoxicity study in Swiss mice
For phototoxicity assessment, the irradiated Swiss mice (6 males/group) were exposed to UVA light for 1 hour before and after dosing for 4 hours and for similar duration on 4 consecutive days. The mean light intensity in the UVA chamber was adjusted to 0.1-0.2 mW/cm² to get a spectrophotometric distribution of the light wavelength between 320 and 400 nm. The mean light intensity of the ambient light was 40 lux. A maximum total irradiation dose was approximately 18 J/m²/day (2). The mice of WCK 771 were divided into different groups, i.e., 100, 200, and 300 mg/kg, Levo was administered at a dose of 200 mg/kg with 350 mg/kg and Sile was administered as a single dose of 25 mg/kg. The mean light intensity of each group was 30 lux.

D. Genotoxicity study in Swiss mice - Micronucleus and chromosomal aberration
Micronucleus (MN) and chromosomal aberration (CA) assays of WCK 771 were carried out in Swiss mice (6 males/group) at doses 60 mg/kg body weight for 4 days and 400 mg/kg for a 7-day repeat-dose study. Cyclophosphamide (CP) was used as positive control at a single dose of 120 mg/kg in different groups of mice. All treated and control mice were sacrificed 24, 48, and 72 hours after the last dose. Chromosomes (40) analyzed from bone marrow cells from femoral bone were processed and stained in 10% Giemsa stain. The frequency of micronucleated polychromatic erythrocytes (MNPCE) and CA was assessed.

E. Chromototoxicity study in Beagle dog pups (3-month old)
The potential of WCK 771 to induce chromatotoxicity was studied in Beagle dog pups (3 months old). The pups were divided into different groups with five pups per group. Each consisting of 1 male and 1 female were administered intravenously with WCK 771 at dose levels of 0.15, 0.20 mg/kg body weight respectively.

F. Long-term studies in Wistar rats and Beagle dogs
Six-week-old Wistar rats (6 males & 6 females) per group and 8-month-old Beagle dogs (3 males & 3 females) per group were administered intravenously with WCK 771 at doses of 0.75, 1.5, 2.25, and 3.0 mg/kg, respectively for 28 consecutive days. Animals were observed for mortality, clinical signs, body weight and food intake, Histopathological examinations, urinalysis, hematology, clinical chemistry, organ weights, gross, and histopathology were conducted at termination.

G. Comparative venous toxicity study of WCK 771 and WCK 793
Groups of 5-week-old Wistar rats (6 males & 6 females) were administered intravenously with WCK 771 and WCK 793 at doses of 0.250, 0.500, and 0.750 mg/kg respectively for 24 consecutive days. Blood samples from each rat was monitored for venous blood and pH. Phototoxicity Severity Rating
- The No Observed Effect Level (NOEL) of WCK 771 was 200 mg/kg which was comparable to Levo and it is 54 times above the phototoxic dose.

H. Normal: iV. Increase: CG = Clinical Sign; CP = Clinical Pathology; GP = General Pathology; H = Histopathology
- From day 23: 'D' from day 16 of dosing.
- Lesions in liver may be due to l.i. dosing. Few rats with severe vesicular bladders were subjected to histopathological scoring.
- Clinical signs like lethargy and convulsions were not observed.
- Wistar rats and Beagle dogs tolerated 28-day repeated i.v. administration of WCK 771 upto a dose of 400 and 800 mg/kg respectively. WCK 771 did not show significant organ-specific toxicity upto a daily dose of 300 mg/kg (i.e., 20 mg/kg in human dose) in rats and 50 mg/kg (7.5 mg/kg in human dose) in dogs.

G. Comparative venous toxicity study of WCK 771 and WCK 793
- WCK 771 did not exhibit phototoxicity in Beagle dog pups.

F. 28-day Subacute Study in Wistar rats and Beagle dogs
Parameters
- Rat Dosage (mg/kg) Levo: NOEL, LODL: 200 / 300 mg/kg Levo: NOEL, LODL: 200 / 300 mg/kg Sile: Sile, CRa: Sile, 25 mg/kg
- Dose Groups (mg/kg) WCK 771 (70 mg/kg) 25 50 100 150 200 250 300 350 400 450 500
- Time Period (Min / CA) WCK 771 (170) 180 250 300 350 400 450 500 550 600 650 700

H. Phototoxicity
- No phototoxicity was observed.

I. CONCLUSIONS
In several toxicity studies, WCK 771 exhibited superior safety profile by i.v. route. WCK 771 phelbitis potential is lower than corresponding sodium salt as well as improving its suitability for repeated parenteral administration.

In repeat dose tox studies in dogs and rats, histopathological changes in organs were insignificant.

REFERENCES