### Safety Pharmacology

A total of 4 safety pharmacology studies were performed in accordance with Good Laboratory Practice (GLP) and guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). A solid dispersion formulation (SDF) of PROJECT 1 was used for in vivo studies to improve drug absorption from the GI tract. The dose levels and plasma concentration levels have been expressed as the active moiety (PROJECT 1).

### Effects on Central Nervous System in Rats

PROJECT 1 was administered once orally at dose levels of 100, 300, and 800 mg/kg to male and female rats (Study Project 1-PT-0003). PROJECT 1 had no effect on the general physical condition or behavior in male and female rats.

### Effects on In Vitro Human Ether-à-go-go Related Gene Current

The effects of PROJECT 1 on the hERG current were studied in hERG transfected HEK293 cells using the whole-cell patch-clamp technique (Study Project 1-PT-0001). The compensated suppression rate of PROJECT 1 at concentrations of 3 × 10−7, 3 × 10−6, and 3 × 10−5 mol/L were 8.1%, 9.6%, and 2.5%, respectively. No statistically significant difference was observed at these 3 test concentrations when compared to the rate in the control group.

### Effects on In Vitro Action Potential Duration

The effects of PROJECT 1 on action potentials in isolated guinea-pig papillary muscles were studied using the glass-electrode technique under a surface-superfusing condition (Study Project 1-PT-0002). The test solutions of PROJECT 1 prepared at concentrations of 3 × 10−7,

3 × 10−6, and 3 × 10−5 mol/L were applied for 30 min onto isolated papillary muscles in each experimental group. In the PROJECT 1 groups, no effects on action potential duration, resting membrane potential, action potential amplitude, or dV/dt max were observed at any concentration.

### Effects on Respiratory and Cardiovascular System in Monkeys

PROJECT 1 was administered orally at dose levels of 10, 100, and 800 mg/kg

(Study Project 1-PT-0004). There were no test article-related changes in blood pressure (systolic, diastolic, and mean), heart rate, any electrocardiogram parameter [PR interval, QRS duration, QT interval, and QTc (corrected with Fridericia’s formula)], respiratory rate, any blood gas parameter (arterial blood pH, arterial oxygen and carbon dioxide tension, and hemoglobin oxygen saturation), any electrolyte (ionized calcium, sodium, potassium, and chloride), or intra-abdominal body temperature at any dose level. As for clinical signs, vomiting (white foam) was observed in 2 animals on the day of dosing (approximately 2 or

8.25 h after dosing) at 800 mg/kg.

### Toxicology

A total of 20 toxicology studies were conducted in rats, monkeys, mice and rabbits as part of the PROJECT 1 development program. All pivotal studies were performed in accordance with GLP and ICH. A SDF of PROJECT 1 was used for in vivo pivotal studies to improve drug absorption from the GI tract. The maximum dose levels of PROJECT 1 SDF in each study were set based on the maximum feasible concentration (80 mg/mL) of PROJECT 1 SDF. The dose levels and plasma concentration levels have been expressed as the active moiety (PROJECT 1). An overview of toxicology studies of PROJECT 1 can be found in [End-of-Text Tables 3.1, 3.2 and 3.3].

### Single-Dose Toxicity

Tabulated results of single-dose toxicity studies can be found in [End-of-Text Table 3.4].

### Single-Dose Oral Toxicity in Rats

Rats were given a single oral administration of PROJECT 1 at 800 and 1600 mg/kg (Study Project 1-TX-0001). No deaths occurred in any animal of the main groups. Salivation was observed in 2 out of 5 males in the 1600 mg/kg group from 5 to 30 min after dosing. No abnormal findings were noted in the 800 mg/kg or the 1600 mg/kg female groups throughout the observation period.

### Single-Dose Oral Toxicity in Monkeys

PROJECT 1 was given as a single oral administration to cynomolgus monkeys at a dose of

800 or 1200 mg/kg (Study Project 1-TX-0002). No deaths occurred in either group. In the male treated with 800 mg/kg, total bilirubin, AST, and ALT levels increased on day 1 of dosing. In the male dosed with 1200 mg/kg, grayish-white watery feces (excretion of unabsorbed test article), an increase in total bilirubin level, and a decrease in chloride level were observed on day 1 of dosing. In the female dosed with 1200 mg/kg, vomitus with the test article was found 233 min after dosing.

### Repeat-Dose Toxicity

Tabulated results of repeat-dose toxicity studies can be found in [End-of-Text Tables 3.5 and 3.6].

### 4-Week Repeated Dose Oral Toxicity in Rats

PROJECT 1 was administered orally once daily for 4 weeks at dose levels of 30, 100, 300, and 800 mg/kg to male and female rats (Study Project 1-TX-0005). Decreased food consumption was noted in females in the 800 mg/kg group on days 1 to 7 of dosing. In urinalysis, low total sodium excretion was noted in females in the 800 mg/kg group. In blood chemistry, low total protein, globulin, alpha1-globulin ratio, and triglycerides, and high albumin and albumin/globulin ratios in males in the 800 mg/kg group were noted. Low chloride was noted in females in the 300 and 800 mg/kg groups; however, this change was considered to be toxicologically insignificant because no clear dose dependency was noted, and no toxicological changes were noted in any other electrolyte or in histopathology of the urinary system. Regarding organ weights, high absolute and relative thyroid (total), and high relative brain and lung weights in males in the 800 mg/kg group were noted. High or a tendency toward high absolute and relative liver weights was noted in females in the 100, 300, and

800 mg/kg groups, however, this change was considered to be toxicologically insignificant because no toxicological changes were noted in blood chemistry or in histopathology of the liver. From these results it was concluded that the NOAEL of PROJECT 1 when administered orally to rats for 4 weeks was 300 mg/kg/day for males and females. Changes noted during the dosing period recovered during the 4-week recovery period.

### 4-Week Repeated Dose Oral Toxicity in Rats at an Extra-high dose

PROJECT 1 was administered orally once daily for 4 weeks at a dose level of 1600 mg/kg to male and female rats (Study Project 1-TX-0020). During the dosing period, 2 females died and 1 female was sacrificed due to moribundity in the 1600 mg/kg group between days 17 and 21 of dosing. In the females in the 1600 mg/kg group that died and that which was sacrificed due to moribundity, salivation was observed between day 13 of dosing and the day of gross pathology, and a decrease in spontaneous activity, reddening skin, bradypnea, lacrimation, decrease in stool volume, soft stool, and soiled (urine) perineal region were observed between 2 days before the day of gross pathology and the day of gross pathology. Prone position and hypothermia were also observed in 2 of these 3 animals on the day of gross pathology. Suppression of body weight gain was noted from the early stage of the dosing period. In hematology, high values in the erythroid parameters, basophil count and ratio, monocyte, neutrophil, and large unstained cell counts, and low value in eosinophil ratio were noted in the animal that was sacrificed due to moribundity.

In pathological examinations, black foci in mucosa of glandular stomach in gross pathology, low absolute and relative spleen weights and high or tendencies toward high absolute and/or relative liver weights in organ weights, and a decrease in zymogen granules in the acinar cells in the pancreas, necrosis of the lymphocytes in the cortex of the thymus, erosion in the glandular stomach, atrophy of the white pulp in the spleen, and atrophy of the Peyer’s patches in histopathology were noted. General conditions worsened rapidly, no severe changes were noted in pathological examinations, and the cause of death/moribundity was unclear. During the dosing period, in males and females that survived, salivation, low total sodium excretion in urinalysis, high platelet count and low eosinophil ratio in hematology, low triglycerides and high alpha2-globulin ratio in blood chemistry were noted. In addition, in males that survived, low total protein, globulin, alpha1-globulin and beta-globulin ratios in blood chemistry, black foci in mucosa of glandular stomach and erosion in the glandular stomach in pathological examinations were noted. In females that survived, a decrease in spontaneous activity, reddening skin, lacrimation, decrease in stool volume, abnormal respiratory tones in clinical signs, low body weight, body weight gain, and food consumption, low specific gravity in urinalysis, high reticulocyte ratio and low eosinophil and erythrocyte count, and hemoglobin concentration in hematology, low sodium and high total cholesterol and blood urea nitrogen in blood chemistry, and atrophy of the thymus in histopathology were noted. No abnormalities were observed in ophthalmology or organ weights in any group. Changes noted during or at the end of the dosing period recovered during the 4-week recovery period. From the results, overt toxicity including death and moribundity was noted, when PROJECT 1 was repeatedly administered at a dose level of

1600 mg/kg/day.

### 13-Week Repeated Dose Oral Toxicity in Rats

PROJECT 1 was administered orally once daily for 13 weeks at dose levels of 30, 100, 300, and 800 mg/kg to male and female rats (Study Project 1-TX-0015). At 300 mg/kg, erosion in the glandular stomach was noted in 1 male at the end of the dosing period. At 800 mg/kg, reddening of the skin, a transient decrease in stool volume, decreased body weight, and decreased food consumption was observed in 1 female on day 62 of dosing. Reddening of the skin was also noted in another female on day 73 of dosing. In addition, the following test article-related changes were noted during or at the end of the dosing period: low total sodium excretion in females in urinalysis; low erythrocyte count and high mean corpuscular volume in males in hematology; low glucose and beta-globulin ratio in males and females, low total protein, globulin, and sodium in males, and high blood urea nitrogen and alpha1-globulin ratio in females in blood chemistry; high relative kidney weight in males and high relative liver weight in females, and erosion in the glandular stomach in 1 female, in which black foci in the mucosa of the glandular stomach had been observed grossly. From these results it was concluded that the NOAEL of PROJECT 1 when administered orally to rats for 13 weeks was 100 mg/kg/day for males and 300 mg/kg/day for females. Changes noted during or at the end of the dosing period were not noted during or at the end of the 4-week recovery period.

### 4-Week Repeated Dose Oral Toxicity in Monkeys

PROJECT 1 was administered orally once daily for 4 weeks at dose levels of 10, 30, 100, and 800 mg/kg to male and female cynomolgus monkeys (Study Project 1-TX-0006). In the

800 mg/kg group, vomiting was observed in males and females on 1 to 5 days mainly during weeks 1 and 2 of dosing. Salivation was observed in males and females immediately after dosing. Decreased body weight was noted in males and females. Low erythrocyte count, hematocrit value, and hemoglobin concentration were noted in 1 male and 1 female on

day 27 of dosing. High triglycerides were noted in males and females on days 14 and/or 27 of dosing, and high glucose was noted in 1 male on days 14 and 27 of dosing. High relative liver weight in males and low absolute and relative adrenal weights in1 female were noted. From these results it was concluded that the NOAEL of PROJECT 1 when administered orally to monkeys for 4 weeks was 100 mg/kg/day for males and females. The changes noted during the dosing period recovered during the 4-week recovery period.

### 13-Week Repeated Dose Oral Toxicity in Monkeys

PROJECT 1 was administered orally once daily for 13 weeks at dose levels of 10, 30, 100, and 800 mg/kg to male and female cynomolgus monkeys (Study Project 1-TX-0016). In the

100 mg/kg group, vomiting was observed in 1 female approximately 1 or 4 h after dosing for 4 days, and salivation was observed once in 1 female immediately after dosing. Low erythrocyte count in males at weeks 7 and 13 of dosing, and high eosinophil count and ratio in 1 female at week 13 of dosing were noted. High globulin and low A/G were noted in

1 female at week 13 of dosing. In the 800 mg/kg group, vomiting was observed in all males and females mainly approximately 1 or 4 h after dosing for 1 to 35 days sporadically during the dosing period. Salivation was observed in all males and females immediately after dosing for 3 to 79 days from week 2 of dosing. Abnormal stool color (grayish white) was

observed in all males and females for 1 to 34 days from week 8 of dosing. Decreased body weight was noted in males and females during the dosing period. Low erythrocyte count and hemoglobin concentration in males and females, and low hematocrit value and high eosinophil count and ratio in females were noted at weeks 7 and/or 13 of dosing. Low albumin and high triglycerides in males, high globulin in 1 male, and low A/G in males and females were noted at weeks 7 and/or 13 of dosing. Low absolute and relative thymus weight in females and high relative liver weight in males and females were noted at the end of the dosing period. During the recovery period, vomiting was observed in 1 male in the

800 mg/kg group, and abnormal stool color (grayish-white) was observed in 1 male and 1 female on day 1 of recovery, but no abnormalities were observed thereafter. High

eosinophil count and/or ratio were noted in 1 male and 3 females in the 800 mg/kg group at week 4 of recovery, and no clear recovery was shown. Other changes noted during the dosing period disappeared. From these results, it was concluded that the NOAEL of PROJECT 1 when administered orally to cynomolgus monkeys for 13 weeks was 30 mg/kg/day for males and females. The changes noted during the dosing period recovered during the 4-week recovery period except high eosinophil count and ratio in hematology.

### Genotoxicity

Tabulated results of genotoxicity studies can be found in [End-of-Text Tables 3.7 and 3.8].

### In Vitro Reverse Mutation

The mutagenicity of PROJECT 1 was examined in the presence and absence of S9 Mix using *Salmonella typhimurium* TA100, TA98, TA1535, and TA1537, as well as *Escherichia coli* WP2 uvrA (Study Project 1-TX-0007). PROJECT 1 inhibited the growth of TA100, TA1535 and TA1537 at 5000 mcg/plate, but not of TA98 and WP2 uvrA without metabolic activation, and the growth inhibition was not shown in all strains with metabolic activation. At doses of 156 to 5000 mcg/plate, PROJECT 1 did not increase the mean number of revertant colonies by 2-fold more than in the vehicle control group for any bacterial strain tested, regardless of the presence or absence of metabolic activation. These results indicate that PROJECT 1 has no mutagenic potential.

### In Vitro Chromosome Aberration

PROJECT 1 was evaluated for the potential to induce chromosomal aberrations under 3 treatment conditions, i.e., 6-h treatment in the presence of S9 Mix plus 6- and 24-h

treatments in the absence of S9 Mix, using a Chinese hamster lung fibroblast cell line (Study Project 1-TX-0008). In the 6- and 24-h treatment groups without metabolic activation, chromosomal aberrations were analyzed over a concentration range of 300 to 500 mcg/mL and 50 to 150 mcg/mL, respectively. In the 6-h treatment group with metabolic activation, chromosomal aberrations were analyzed over a concentration range of 200 to 400 mcg/mL. PROJECT 1 did not increase significantly the number of chromosomally aberrant cells when compared to the vehicle control. The results indicate that PROJECT 1 has no potential to induce chromosomal aberrations.

### Micronucleus in Mice

PROJECT 1 was administered orally once daily for 2 days (at an approximately 24-h interval) to male and female mice at dose levels of 300, 600, and 1200 mg/kg/day

(Study Project 1-TX-0009). In the 1200 mg/kg group, 1 male was found dead before dosing on day 2. In this group, incomplete eyelid opening and a (slight) decrease in spontaneous activity were observed in 2 males on days 1 to 3, including in the animal that died, and incomplete eyelid opening was observed in 2 females on day 2. No decrease in body weight was noted in any test article group. No significant increase in the incidence of micronucleated polychromatic erythrocytes (%) was noted in any test article group when compared with the negative control group. A significant decrease in the ratio of polychromatic erythrocytes (%) was noted in males in the 1200 mg/kg group when compared with the negative control group. It was concluded that, under the conditions of this study, PROJECT 1 solid dispersion did not induce micronuclei arising from chromosomal aberrations in male or female mice when tested in vivo.

### Carcinogenicity

No studies have been generated with PROJECT 1 so far.

### Reproductive and Developmental Toxicity

Tabulated results of reproductive and developmental studies can be found in [End-of-Text Tables 3.10, 3.11 and 3.12].

### Effects on Fertility and Early Embryonic Development in Rats

PROJECT 1 was administered orally to male and female rats at dose levels of 100, 300 and 800 mg/kg/day once daily for 2 weeks before mating and throughout the mating period and up to the day of implantation for females and for 4 weeks before mating, throughout the mating period and up to the day before necropsy for males (Study Project 1-TX-0017). A decrease in food consumption was observed in the females of the 300 and 800 mg/kg groups and males of the 800 mg/kg group. In the females of the 800 mg/kg group, low body weight and suppressed body weight gain were noted during the gestation period. No toxicological effects from the administration of the test article were noted in the general condition, estrous cycle or gross pathological findings in any dosage group. No test article-related effects were

noted in the days until copulation, copulation index, fertility index, numbers of corpora lutea, implantations or live embryos, or pre- and post implantation loss indices in any dosage group. The NOAEL of PROJECT 1 is estimated to be 300 mg/kg/day for general toxicity in males and 100 mg/kg/day for general toxicity in females, and 800 mg/kg/day for fertility of males and females and early embryonic development.

### Effects on Embryo-Fetal Development in Rats

PROJECT 1 was administered orally to pregnant rats at dose levels of 100, 300 and

800 mg/kg/day from day 7 to 17 of gestation (Study Project 1-TX-0013). In the 300 mg/kg or above groups, a temporal decrease in body weight associated with decreased food consumption was noted on the day after the start of administration. In the 800 mg/kg group,

body weight showed low values on days 12, 14, 15 and 16 of gestation and food consumption showed low values from day 8 to day 12 of gestation in comparison with those in the control group. In the indices of embryo-fetal development, no test article related effects were noted, including number of corpora lutea, number of implantations, index of embryo-fetal deaths, number of live fetuses, sex ratio of live fetuses, fetal body weight, placental weight or progress of ossification. No abnormalities were observed in the placenta of live fetuses and there were no external, visceral or skeletal abnormalities/variations attributable to the administration of the test article. The NOAEL of PROJECT 1 is estimated to be 100 mg/kg/day for toxicity in dams and 800 mg/kg/day for embryo-fetal development.

### Effects on Embryo-Fetal Development in Rabbits

PROJECT 1 was administered orally to pregnant rabbits at dose levels of 10, 30 or 100 mg/kg/day for 13 days from day 6 to 18 of gestation (Study Project 1-TX-0014).

Suppression of body weight gain and transient decrease in food consumption during the administration period were observed at 100 mg/kg/day as well as 1 abortion. Abortion occurred in 1 dam that exhibited decreases in body weight, food consumption and fecal output. Effects on embryo-fetal development as seen in the fetal mortality and morphology such as external abnormalities, visceral abnormalities or variations, or skeletal abnormalities or variations including placental abnormalities were not noted in any treated group. No suppression of fetal growth as expressed by fetal body weight and placental weight including the progress of ossification was observed in any treated group. The NOAEL of PROJECT 1 was judged to be 30 mg/kg/day for general toxicological effect in dams and 100 mg/kg/day for embryo-fetal development.

### Local Tolerance

No studies have been performed with PROJECT 1.

### Other Toxicity Studies

Tabulated results of a combination toxicity study can be found in [End-of-Text Table 3.16].

### A 13-Week Repeated-dose Oral Combination Toxicity with Tamsulosin Hydrochloride in Rats

PROJECT 1 and tamsulosin hydrochloride were orally administered at dose levels of 0/0, 300/0, 0/30, 100/30, and 300/30 mg/kg/day (as PROJECT 1/tamsulosin) once daily for 13 weeks to male and female rats (Study Project 1-TX-0023). Incomplete eyelid opening was observed in all animals in the tamsulosin alone and 100/30 and 300/30 mg/kg groups during the dosing period, and this finding was considered related to a pharmacological action of tamsulosin.

However, this finding did not worsen with combination treatment. High blood urea nitrogen was noted in females in the PROJECT 1 alone and 300/30 mg/kg as PROJECT 1/tamsulosin groups and this change did not worsen with combination treatment. High relative liver weight in females in the PROJECT 1 alone group and in both sexes in the 300/30 mg/kg as PROJECT 1/tamsulosin group, and high absolute and relative spleen weights in males in the tamsulosin alone group were noted. These changes did not worsen with combination treatment. In conclusion, no synergistic or new toxicity was seen with combination treatment of PROJECT 1 and tamsulosin.

## 4.4 Integrated Nonclinical Overview and Conclusion: Potential Clinical Relevance

PROJECT 1 is a potent and selective antagonist of EP1 receptor in rats. The antagonistic activity of PROJECT 1 at rat and human EP1 receptors is similar. Since no species difference for EP receptors are reported (Breyer & Breyer, 2000), it is assumed that the selectivity of PROJECT 1 for rat EP1 over other EP receptors is similar for human EP receptors. In further nonclinical studies, PROJECT 1 inhibited the decrease in bladder compliance induced by PGE2. It also increased bladder capacity in the acetic acid-induced urinary frequency model in rats.

Regarding the effect on urethral/voiding function, PROJECT 1 inhibited urethral pressure increase and residual urine increase induced by the EP1/3 agonist sulprostone. In addition, PGE2 induced decrease in urethral pressure in the presence of PROJECT 1. These results suggest that PROJECT 1 may improve storage symptoms by inhibiting PGE2-dependent detrusor contractions and may also have an effect on voiding symptoms.

A major metabolite H1 showed EP1 antagonistic activity, but with a lower potency than PROJECT 1. H1 had selectivity for the EP1 receptor over other EP receptors or various receptors.

In the safety pharmacology studies, PROJECT 1 revealed no effects on the central nervous system, hERG current or action potentials, the cardiovascular system or the respiratory system.

After a single oral administration of PROJECT 1 to rats and monkeys, PROJECT 1 showed linear pharmacokinetics in a dose range between 1 and 10 mg/kg. The absolute bioavailability was

~50% in rats and ~10% in monkeys. The t1/2 was 1.6 to 2.6 h in rats and 4.6 to 5.2 h in monkeys. In vitro studies using P-gp-expressing cells revealed that PROJECT 1 is a weak inhibitor for P-gp with IC50 value of 91.8 mcmol/L, and that PROJECT 1 is a substrate for P-gp.

After a single oral administration of 3 mg/kg 14C-PROJECT 1 to rats, radioactivity was rapidly distributed to the tissues and no long-time tissue retention was observed. In vitro plasma protein binding of PROJECT 1 was very high, being > 98% in all species examined.

When 14C-PROJECT 1 was orally administered to rats at a dose of 3 mg/kg, the unchanged drug was detected as a major peak in plasma. In bile and urine, unchanged PROJECT 1 was hardly detected, whereas several metabolite peaks were detected. In vitro metabolite profiling studies using cryopreserved hepatocytes and liver microsomes showed no presence of human-specific metabolites.

In vitro studies using human liver microsomes and recombinant enzymes suggested that CYP2B6, CYP2C8, CYP3A4/5, UGT1A1, UGT1A3, and UGT1A8 would be involved in the metabolism of PROJECT 1. PROJECT 1 showed moderate inhibition activity for CYP2C8 and CYP2C19 with Ki values of 2.3 mcmol/L and 5.2 mcmol/L, respectively. PROJECT 1 also showed weak induction activity for CYP2C8 and 3A4; treatment of human hepatocytes with 30 mcmol/L PROJECT 1 caused increases in CYP2C8 and CYP3A4 mRNA levels (2.30- and 6.20-fold increase, respectively).

After a single oral administration of 3 mg/kg 14C-PROJECT 1 to rats, the administered radioactivity was mainly excreted in the feces via bile.

The nonclinical toxicity package consisting of single and repeated-dose studies in rats and monkeys, a repeated-dose combination toxicology study with tamsulosin in rats, reproductive studies in rats and rabbits, and in vitro and in vivo genotoxicity studies, does not preclude further development of PROJECT 1. The main targets for PROJECT 1 are the GI tract, liver, hematopoietic system and electrolyte homeostasis. The findings on the GI tract are related to erosion in the glandular stomach in rats, vomiting and salivation in monkeys. In the

single-dose study in monkeys increased liver function parameters (AST, ALT and bilirubin) were observed. However, in the repeated-dose toxicity studies only increased liver weight was observed in both rats and monkeys, without effects on blood chemistry or histopathological changes in the liver. The hematopoietic findings in rats and monkeys, i.e., low erythrocyte count, hematocrit value, and hemoglobin concentration, were not accompanied by histopathological changes in bone marrow, spleen or thymus. High eosinophil count and ratio were noted during dosing and recovery period in monkeys, however, no abnormal changes were noted in leukocyte count and other differential leukocytes; therefore, toxicological significance of these changes was unclear. The effects on the electrolyte homeostasis comprised low plasma sodium and chloride, and low sodium excretion in rats. Although no changes in other electrolytes or histopathology in any related organs were observed and no similar findings were seen in monkeys, it is known that

EP1 receptor inhibition could reduce the renal capacity of sodium excretion

[Breyer & Breyer, 2000]. The exposures at which these findings were observed exceed the exposure at the highest dose of the multiple ascending dose study in humans [[Table 2](#_bookmark70)]. The 13-week repeated dose combination toxicology study showed no synergistic or renewed toxicity when PROJECT 1 is combined with tamsulosin. This dataset supports the conduct of clinical studies for up to 13 weeks treatment.

### Table 2 Exposure Ratios of PROJECT 1 Between Animals and Humans

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Species/ Study Duration** | **Dose** | **Sex (M/F)** | **AUC24**  **(ng·h/mL)** | **Exposure Ratios† Based on 400 mg Human Dose**  **(Selected Dose for LUTS/BPH POC Study)** |
| **Rat, 4 weeks, po (Project 1-TX-0005)** | 300 mg/kg  (NOAEL) | M | 23932.40 | 3.6 |
| F | 146995.00 | 22.4 |
| 800 mg/kg (LOAEL) | M | 53493.14 | 8.2 |
| F | 544980.42 | 83.1 |
| **Rat, 13 weeks, po (Project 1-TX-0015)** | 100 mg/kg  (NOAEL) | M | 13225.20 | 2.0 |
| 300 mg/kg (NOAEL) | F | 251496.72 | 38.3 |
| 300 mg/kg  (LOAEL) | M | 87507.51 | 13.3 |
| 800 mg/kg  (LOAEL) | F | 841828.16 | 128.3 |
| **Monkey, 4 weeks, po (Project 1-TX-0006)** | 100 mg/kg (NOAEL) | M | 88411.74 | 13.5 |
| F | 29846.34 | 4.5 |
| 800 mg/kg (LOAEL) | M | 1220533.10 | 186.0 |
| F | 1460977.48 | 222.7 |
| **Monkey, 13 weeks, po (Project 1-TX-0016)** | 30 mg/kg (NOAEL) | M | 15825.62 | 2.4 |
| F | 12914.96 | 2.0 |
| 100 mg/kg (LOAEL) | M | 96283.09 | 14.7 |
| F | 29371.45 | 4.5 |
| **Human, healthy subjects, multiple, po (Project 1-CL-0005)** | 400 mg (qd) | YM | 6561 | NA |

† Exposure ratios were calculated by dividing the AUC24 in animals by the AUCtau in humans (average value of healthy subjects) at doses of 400 mg (qd).

YM: young male; NA: not applicable; LOAEL: lowest observed adverse effect level; NOAEL: no observed adverse effect level; LUTS: lower urinary tract symptoms; BPH: benign prostatic hyperplasia; POC: proof of concept

### List of References

Breyer MD, Breyer RM. Prostaglandin E receptors and the kidney. Am J Physiol Renal Physiol.

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