### Safety Pharmacology

One safety pharmacology study (Study 130913.TFD) was conducted with PROJECT 17-1 or Project 17-5, the primary metabolite of PROJECT 17-2.

The objective of this study was to examine the in vitro effects of Project 17-5 (PROJECT 17-1) on the human ether-à-go-go-related gene (hERG) channel current (a surrogate for IKr, the rapidly activating delayed rectifier cardiac potassium current) at near-physiological temperature.

The stability of the test article formulations was confirmed during the method validation study. Test article concentrations were applied to the test system and dose solution analysis was conducted within the validated stability timeframe.

Samples for homogeneity determination were collected from the formulation reservoirs. The sample analysis indicated that all formulations were homogeneous at the beginning of testing. Samples of the test article formulation solutions collected from the outflow of the perfusion apparatus were analyzed for concentration verification. The results from the sample analysis indicated that the measured concentrations of PROJECT 17-1 at all test concentrations were within ± 15.0% of nominal concentrations (% relative error [RE] ± 15.0%), thereby meeting the acceptance criteria.

PROJECT 17-1 inhibited hERG current by (mean [SEM]) 1.2 (0.7)% at 10 µM (n = 4) and

3.4 (0.4)% at 100 μM (n = 3) versus 1.1 (0.6)% (n = 3) in control. hERG inhibition at 10 and 100 μM was not statistically significant (P < 0.05) when compared to vehicle control values. The IC50 for the inhibitory effect of PROJECT 17-1 on hERG potassium current was not calculated but was estimated to be greater than 100 μM.

Under identical conditions, the positive control (60 nM terfenadine) inhibited hERG potassium current by (mean [standard deviation]; n = 2) 87.5 (1.3)%. This result confirms the sensitivity of the test system to hERG inhibition.

## Toxicology

A nonclinical bridging study (Study 20015047) was conducted to evaluate comparability of PROJECT 17-2 and PROJECT 17-3 in monkeys. Additional studies were previously conducted to evaluate the hybridoma-derived ADC (PROJECT 17-3), the native antibody (PROJECT 17-4) and Project 17-5 (PROJECT 17-1), the free drug resulting from degradation of the ADC. A summary of the pivotal toxicology studies is presented in [End-of Text-Table 3.1].

### Brief Summary: Toxicology of PROJECT 17-3

A comprehensive safety assessment program included evaluation of the ADC, the unconjugated antibody and the free drug.

In an exploratory multi-dose study in rats (Study FKG00037), weekly administration (for 4 weeks) of PROJECT 17-4mcMMAF (a.k.a, PROJECT 17-3) at a dose of 3 mg/kg was well

tolerated. Doses of 10 and 30 mg/kg were associated with morbidity and mortality associated with renal failure secondary to glomerular nephropathy. The glomerular nephropathy was shown to result from immune-complex deposition. The formation of antibody complexes and its associated significant toxicity confounded data interpretation. Therefore the rat was considered not to be an appropriate species for further toxicity evaluation of PROJECT 17-3. An IND-enabling study was performed in cynomolgus monkeys and included multiple dose levels of the ADC (PROJECT 17-3) and single dose levels of the unconjugated antibody, free drug and vehicle control. All groups were dosed 1x weekly for 4 weeks. Data from the PROJECT 17-3 cohorts demonstrated a NOAEL of 6 mg/kg (the highest dose tested). Minor effects, considered not adverse, were observed in some laboratory measures. Native (unconjugated) antibody also demonstrated a NOAEL at the 6 mg/kg dose level. For the Project 17-5, a NOAEL was observed at 0.172 mg/kg. In summary, there were no adverse clinical observations, macroscopic or microscopic findings at the end of the dose phase and recovery in any animals attributed to the ADC, the unconjugated antibody or the free drug.

In 2 additional toxicology studies, toxicity evaluation of the free drug (Project 17-5), generated from intracellular degradation of PROJECT 17-3, was conducted in rats

(Study FKG00041) and monkeys (Study FKG00048). Four weekly intravenous doses of Project 17-5 administered to monkeys were not associated with any toxicologically significant findings. The NOAEL in monkeys was 0.5 mg/kg. This dose is approximately 3 times higher than the molar equivalent of the toxin in the ADC. Project 17-5 administered to rats once weekly for 4 weeks was associated with transient reductions in body weight gain at 1 mg/kg and the development of microscopic changes in the testes and epididymides at doses ≥ 0.3 mg/kg. These changes were completely reversed at the end of the recovery period. Pharmacokinetic/toxicokinetic studies of PROJECT 17-3 and free drug (Project 17-5) were performed from single and multiple dose studies in rats and cynomolgus monkeys. In the IND-enabling study in cynomolgus monkeys, the ADC toxicokinetics were linear with respect to PROJECT 17-3 dose. Systemic exposure increased Cmax and AUC proportionally with increase in dose. Peak serum concentrations were achieved at the end of dosing (1 hour) and declined biphasically with a T1/2λz of ~5 days. Circulating concentrations of the free drug (Project 17-5) were very low and represented ~1/106 that of the native ADC. Peak serum metabolite concentration was observed at 6 hours after dose of the ADC. The T1/2λz of the metabolite was ~70 hours which represented the metabolism of the ADC that occurs systemically. The toxicokinetic of PROJECT 17-3 were generally consistent across studies in cynomolgus monkeys. However, following repeated dosing in rats, some animals showed accelerated clearance and lower serum concentrations, considered to be a result of antibody development observed against the ADC. The shortened clearance was not seen in monkeys.

Tissue cross-reactivity of the hybridoma-derived antibody and ADC was determined in frozen human (Studies 8211392 and 8211391), monkey (Studies 8211390 and 8211388) and rat tissues. There was no specific binding noted in rat tissues. Both PROJECT 17-4 (unconjugated antibody) and PROJECT 17-3 (ADC) showed similar binding patterns in human and cynomolgus tissues. The antibody and ADC both stained kidney cortex and endometrial epithelium. Salivary gland stained positive in humans but not monkey. In monkeys, but not human tissue, epithelium and occasional blood vessels stained positive in breast, Fallopian tubules, colon, prostate, thymus and tonsil.

### Single-dose Toxicity

No single-dose toxicology studies were conducted with PROJECT 17-2.

Two single-dose toxicology studies were conducted with PROJECT 17-1 (primary metabolite) which are summarized in [[Table 10](#_bookmark54)].

### Table 10 Single-dose Studies with PROJECT 17-1

AST: aspartate aminotransferase; cys-mcM ne maleimidocaproyl-monomethylauristatin F; GLP:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study No.** | **Study Title** | **Species** | | **Summary** |
| R-TOX-44 | Exploratory non-GLP Single-Dose Range Finding Toxicity Study of SGD-1362 ( cys-mcMMAF) in Female Rats with a  14-day Recovery Phase | Rats | | Linear cys-mcMMAF single intravenous bolus injection at dose levels up to 25 mg/kg to female Sprague Dawley rats was well tolerated. Treatment related findings were limited to mild to moderate reductions in reticulocyte counts at dose levels  ≥ 17.5 mg/kg. The HNSTD and MTD were considered to be the highest dose tested of 25 mg/kg. The NOEL was considered to be 10 mg/kg due to the absence of any findings at this dose level. |
| 1019-008 | GLP single dose intravenous range- findings of SGD-1362 (cys-mcMMAF) in cynomolgus monkeys | Monkeys | | Linear cys-mcMMAF single intravenous bolus injection to cynomolgus monkeys (1 animal/sex/group) was well tolerated at doses up to 10 mg/kg. Findings were limited to minimal and transient increases in AST and/or total bilirubin at doses at or above 6 mg/kg and were considered not biologically relevant or adverse. The HNSTD and NOAEL were considered to be the highest dose of 10 mg/kg. The NOEL was 3 mg/kg. |
|  |  |
|  | | MAF: cystei |  | |

Good Laboratory Practice; HNSTD: highest nonseverely toxic dose; MTD: maximum tolerated dose; NOAEL: no-observed-adverse-effect-level; NOEL: no-observed-effect-level.

### Repeat-dose Toxicity- PROJECT 17-2

**4.3.3.1 A 4-Week Study Comparing PROJECT 17-3 and PROJECT 17-2 Administered by Intravenous Infusion in Cynomolgus Monkeys with a 6-Week Recovery Period (Study 20015047)**

The objectives of this study were to determine the potential toxicity and toxicokinetic characteristics of PROJECT 17-3 and PROJECT 17-2, when given at a comparable dose by intravenous infusion once weekly for 4 weeks to cynomolgus monkeys, and to evaluate the potential reversibility of any findings after a 6 week recovery period. The study design is shown in [[Table 11](#_bookmark57)].

The following parameters and end points were evaluated in this study: clinical signs (mortality/moribundity checks, cage side observations, detailed clinical observations and postdose observations), body weights, food consumption, physical examinations, clinical pathology parameters (hematology, clinical chemistry and urinalysis), bioanalysis and toxicokinetic parameters, antidrug antibody (ADA) analysis, gross necropsy findings, organ weights and histopathologic examinations.

### Table 11 Experimental Design for Monkey Study Comparing PROJECT 17-3 and PROJECT 17-2 (CRL Study 20015047)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Group No.** | **No. of Animals†** | | | | **Test Material** | **Dose Level**  **(mg/kg/week)** | **Dose Concentration (mg/mL)** | **Dose Volume (mL/kg/week)** |
| **Main Study** | | **Recovery** | |
| **Male** | **Female** | **Male** | **Female** |
| 1 | 2 | 2 | NA | NA | Control | 0 | 0 | 5 |
| 2 | 3 | 3 | 2 | 2 | PROJECT 17-3 | 6 | 1.2 | 5 |
| 3 | 3 | 3 | 2 | 2 | PROJECT 17-2 | 6 | 1.2 | 5 |

NA: not applicable.

†Main study and recovery animals were euthanized on days 29 and 71, respectively. Source: Study 20015047

The intravenous route of exposure was selected because this is the intended route of human exposure. The dose level of 6 mg/kg chosen for comparison of PROJECT 17-3 and PROJECT 17-2 was based on the maximum dose tested and NOAEL dose from exploratory and GLP multiple dose toxicity studies conducted with PROJECT 17-3. Individual ADC, TAb

(PROJECT 17-3 or PROJECT 17-2) and Project 17-5 serum concentration-time data obtained following 4 weekly doses were analyzed by noncompartmental methods using WinNonlin Pro version 5.2.1 (Pharsight Corp., Mountain View, CA). ADC, TAb and Project 17-5 concentrations that were below the assay’s lower limit of quantification were set to missing prior to toxicokinetic analyses. The sample size for each group was based on achieving 80% power for the primary comparison of AUC0-7d with the assumption of a true geometric mean ratio (GMR) of 1.1 and a coefficient of variation of approximately 20% based on studies conducted previously. The primary analysis for comparability was based on calculation of AUC0-7d and Cmax after the first dose for PROJECT 17-3 and PROJECT 17-2. The materials were to be considered comparable if the following criteria were met: 90% CIs of GMRs are within

0.70 to 1.43 for Cmax and AUC0-7d.

Administration of PROJECT 17-3 (Group 2) or PROJECT 17-2 (Group 3) by once-weekly intravenous infusion for 4 weeks was well tolerated in cynomolgus monkeys at levels of

6 mg/kg per week. All animals survived to the duration of the study. There were no clinical signs or changes in food consumption, detailed clinical observations, postdose observations, body weight, physical examination parameters that were attributed to PROJECT 17-3 or

PROJECT 17-2 administrations.

There were PROJECT 17-3 and PROJECT 17-2-related changes in hematology and clinical chemistry parameters. In general, the magnitude of these changes was similar for

PROJECT 17-3 and PROJECT 17-2-treated male and female animals. Changes in hematology parameters included decreased platelet counts and increased monocyte counts. Platelet counts were decreased approximately 40% from prestudy values for PROJECT 17-3- and PROJECT 17-2

–treated groups. The platelet changes were noted at all time points during the study and were generally not progressive over time. Since there were normal numbers of megakaryocytes in the bone marrow, increased platelet removal or decreased platelet production were not considered contributing factors and the cause of the decreased platelet counts was not determined. Mean monocyte counts were increased to approximately 5.7x-prestudy for PROJECT 17-3 and PROJECT 17-2 groups at all time points during the dosing phase with the differences being statistically significant for Group 3 females only on day 22. The increased monocyte counts were attributed to undefined acute-phase response, which is further supported by the clinical chemistry changes described below.

Changes in clinical chemistry parameters included increased ALT, AST, LDH, ALP, GGT, globulin and total protein and decreased albumin and A:G ratio. PROJECT 17-3 and

PROJECT 17-2-related increases in ALT, AST and LDH were of similar magnitude for both test articles and the collective increase in these 3 enzymes was attributed to soft tissue injury.

Increased ALP and GGT are usually associated with hepatobiliary injury. Increases in ALP and GGT were small (< 2-fold) and since there was no microscopic correlate in the liver, the cause for their increase is undetermined. In general mean globulin progressively increased to 1.5x prestudy and mean A:G ratio and albumin decreased to approximately 0.6x and 0.9x prestudy values for PROJECT 17-3 and PROJECT 17-2- treated groups. These changes are consistent with an acute-phase protein response. The above changes in hematology and clinical chemistry parameters returned to baseline levels by the end of recovery period suggesting full recovery.

Since these changes in hematology and clinical chemistry parameters did not result in any clinical signs and/or correlative changes in histopathology, none of these changes were considered adverse.

Toxicokinetic data indicated that the maximum serum AGS-16 concentrations for both

PROJECT 17-3 and PROJECT 17-2 were generally attained at the end of the intravenous infusion and showed a bi-exponential decline thereafter. Serum AGS-16 concentrations of the TAb were generally higher than the ADC concentrations. There were no sex related differences observed in the toxicokinetic characteristics for ADC, TAb and small molecule metabolite (Project 17-5) for both ADCs. Project 17-5 Cmax for both ADCs was attained between 6 to 12 hours post AGS-16 dose administration. The T½ z for Project 17-5 after administration of PROJECT 17-3 was calculated as 3.13 days and 3.89 days, after the first and last dose, respectively and for PROJECT 17-2 as 3.35 and 3.43 days after the first and last dose, respectively. The Cmax values for both ADC and TAb suggested a slight accumulation

(~1.35 – 2-fold). The 90% CIs of the GMRs for AUC07d and Cmax of ADC after the first dose

were within the prespecified comparability criteria (0.71.43) and therefore toxicokinetics of the 2 materials, PROJECT 17-3 and PROJECT 17-2, were considered to be comparable. ADA formation was observed in a single PROJECT 17-2-treated female during recovery phase.

There were no macroscopic findings at terminal or recovery euthanasia that were associated with PROJECT 17-3. Macroscopic findings at terminal euthanasia that were associated with PROJECT 17-2 administration were limited to multiple dark black pinpoint foci of the liver that were present in 1 male animal. The histological correlate for the finding was minimal hepatic sinusoid dilation.

PROJECT 17-3- and PROJECT 17-2-related organ weight changes at terminal sacrifice included increased spleen weight, spleen to body weight ratio and spleen to brain weight ratio for PROJECT 17-3 and PROJECT 17-2 males and/or females; increased liver to body weight ratio in PROJECT 17-2 males; and decreased uterus weight, uterus to body weight ratio and uterus to brain weight ratio for PROJECT 17-3 and PROJECT 17-2 females. There was no histological correlate for the spleen and uterus weight changes; however, the liver weight corresponded to sinusoid dilation seen histologically. Since there were only 2 recovery animals each in PROJECT 17-3 and PROJECT 17-2 groups and there were no control animals, organ weight changes in the recovery animals were not assessed.

Microscopic findings related to PROJECT 17-2 at the end of the dosing phase were present in the liver and seminal vesicle, and microscopic findings related to PROJECT 17-3 and

PROJECT 17-2 were present in the uterus. In the liver, minimal to moderate focal to multifocal dilation of the hepatic sinusoids was present in 2 of 3 PROJECT 17-2 dosed males. No female animals exhibited this finding. The small focal dilations were blood filled and were visible at necropsy in 1 animal. Liver sinusoid dilation is uncommon in young cynomolgus monkeys; however, the biological significance of the finding in the 2 monkeys in this study is unclear as there was no clinical pathology correlate and the change did not affect the clinical health of the animals. In the seminal vesicle, a mild increase in cellular apoptosis and mitotic figures was present in the glandular epithelium in 1 of 3 males treated with 6 mg/kg per week

PROJECT 17-2. This was the only male with a sexually mature seminal vesicle among all test animals. In the uterus, minimal to moderate increases in cellular apoptosis and/or mitotic figures were present in the endometrial glandular epithelium in 2 of 3 females treated with PROJECT 17-3 and in 2 of 3 females treated with PROJECT 17-2. The seminal vesicle and uterus changes were not present in any control animals. The increased cellular apoptosis and mitosis in dosed animals were considered likely due to the MMAF component of the ADC and expected pharmacologic effect based on its antimitotic activity. The degree of sexual maturity may also have affected the occurrence in individual animals. In recovery animals, there were no PROJECT 17-3 or PROJECT 17-2-related microscopic findings in liver, seminal vesicle or uterus.

Overall, there were no differences in toxicity and toxicokinetic characteristics of

PROJECT 17-3 and PROJECT 17-2 when given at a comparable dose by intravenous infusion once weekly for 4 weeks to cynomolgus monkeys. The hepatic sinusoidal dilatation noted in 2 of 6 monkeys at the end of dosing is an uncommon finding in cynomolgus monkeys.

However, this finding was not associated with functional impairment of the liver based on lack of correlation to clinical pathology changes, clinical signs or other microscopic changes and, therefore, is not anticipated to be clinically significant.

### 4.3.3.2 7-Week Intravenous Infusion Peripheral Nervous System (PNS) and Ocular Toxicology Study in Cynomolgus Monkeys with a 6-Week Recovery Phase (Study 8285949)

This study evaluated the potential for peripheral nervous system (PNS) and ocular toxicity of 2 MMAF containing ADC products. PROJECT 17-2 was included in this study to investigate if ocular toxicity could be detected in primates and to act as a negative control for the assessment of peripheral neuropathy. PROJECT 17-2 was given to primates (3/sex) once weekly for up to 7 weeks at a dose level of 6 mg/kg; 6 mg/kg was also the NOAEL determined from the nonclinical bridging study [discussed in Section 4.3](#_bookmark51).

Assessment of ocular toxicity was based on ophthalmic examinations (electroretinography and optical coherence tomography). Assessment of peripheral neuropathy was based on neurological examinations and electrophysiology measurements (nerve conduction velocity).

Three animals given 6 mg/kg per dose PROJECT 17-2 were sacrificed on days 32 (male),

40 (female) and 54 (male) of the dosing phase. The first animal was noted as ataxic and weak on day 19 of the dosing phase and continued to have observations, including hunched posture, ataxia, hypoactivity, low/no food consumption, thin body condition, pale gums and body weight loss. Consistent with ataxia, decreased muscle tone and flexor reflex were noted on day 25 of the dosing phase. As a result, the animal was not dosed on day 29 but due to persistent clinical observations and lack of recovery from these clinical symptoms, the animal was sacrificed on day 32 of the dosing phase. The next animal was noted as ataxic, weak, hypothermic and pale and with lean body condition on day 40 of the dosing phase, but became hunched and pale and was sacrificed that afternoon. Based on effects in these 2 animals, Group 4 was no longer dosed; the final dose for this group was at week 6 (day 36). The last animal was sacrificed after failing to recover from anesthesia following the electrophysiology procedure on day 54 of the dosing phase. A direct relationship of the early sacrifice of this animal to the drug could not be established, however, hunched posture, low food consumption and pale gingiva had previously been noted in this animal.

PROJECT 17-2-related clinical pathology findings in animals sacrificed at unscheduled intervals included decreased red cell mass (i.e., red blood cell count, hemoglobin and hematocrit) with a regenerative response. Other notable clinical pathology findings in these animals were generally consistent with inflammation and muscle injury and included decreased albumin and A:G ratio and increased globulin and AST activity. A definitive cause for the early sacrifice was not apparent based on clinical pathology data.

PROJECT 17-2-related microscopic findings in animals sacrificed at an unscheduled interval were mononuclear inflammation with histiocytic aggregates in the adipose tissue at the base of the heart; mononuclear and vascular/perivascular inflammation and proteinaceous casts in the kidney; mixed vascular/perivascular inflammation in the submucosa of the duodenum, jejunum, ileum and cecum; histiocytic aggregates in the submucosa of the colon; hemorrhages in the kidney and tunica muscularis of the duodenum, jejunum, cecum, colon and rectum; atrophy of centrilobular hepatocytes with congestion in the liver; mitosis/apoptosis of corneal epithelium of eyes; decreased lymphocytes in the thymus, spleen and mesenteric and mandibular lymph nodes; and hypercellularity of the marrow of the sternum.

Exposure to PROJECT 17-2 resulted in slowing of sural and peroneal nerve velocities at week 5 of the dosing phase, which was when ataxia was noted. Although the data are limited, no evidence of coasting (e.g., worsening or initial presence of neuropathy after completion of dosing) was noted and evidence of partial improvement in the conduction deficits was noted in animals given PROJECT 17-2 following 2 weeks of recovery. Among animals that survived until the scheduled sacrifice, PROJECT 17-2 administration had several clinical pathology effects generally consistent with inflammation and possible muscle injury. Notable hematology findings observed at multiple dosing phase time points were mostly limited to animals given 6 mg/kg per dose PROJECT 17-2 and included decreased red cell mass and reticulocyte count (for males; PROJECT 17-2 only), decreased platelet count and increased absolute monocyte and large unstained cell counts. Increased absolute neutrophil count and increased fibrinogen were also observed at a few dosing phase time points. Notable clinical chemistry findings observed at multiple dosing phase time points in animals given

6 mg/kg per dose PROJECT 17-2 included decreased albumin and A:G ratio, increased globulin and increased AST activity. All clinical pathology findings exhibited reversibility at the end of the recovery phase.

At the terminal sacrifice, PROJECT 17-2-related microscopic findings were present in the thymus, spleen and mesenteric and mandibular lymph nodes of the only surviving terminal sacrifice female. This animal had slightly decreased lymphocytes in the thymus and spleen and minimally decreased lymphocytes in the mesenteric and mandibular lymph nodes. None of the other PROJECT 17-2-related microscopic findings observed in animals from the unscheduled or terminal sacrifices were present at the recovery sacrifice, indicating complete recovery of those findings.

### Toxicity of PROJECT 17-1 (Project 17-5)

Repeat-dose toxicity studies of Project 17-5 were conducted in rats and monkeys. The studies and summary [results are provided in Table 12.](#_bookmark60)

### Table 12 Repeat-Dose Toxicity Studies with PROJECT 17-1 (Project 17-5)

|  |  |  |  |
| --- | --- | --- | --- |
| **Study No.** | **Study Title** | **Species** | **Study Summary** |
| 1019-1010 | GLP Repeat Dose (once daily for 5 days) Intravenous Toxicity Study of SDG-1362 (Project 17-5) in rats with a 2-week recovery period | Rats | The objective of this GLP repeat-dose study was to characterize the toxicities of linear Project 17-5 when administered intravenous once daily for 5 consecutive days in rats. Secondary objectives were to determine the reversibility of any toxicities and identify the HNSTD, NOAEL and/or NOEL. Fifteen CD® [Crl:CD®(SD)] rats/sex were administered either vehicle or linear Project 17-5 at dose levels of 1, 5 or 10 mg/kg per day. Animals were necropsied 3 days or 14 days post last dose. Study endpoints included morbidity and mortality, clinical observations, body weights, food consumption, clinical pathology (hematology, clinical chemistry, coagulation and urinalysis), ophthalmoscopic examinations, toxicokinetics, gross pathology and histopathology. Treatment-related findings were observed in clinical observations, ophthalmology, hematology, clinical chemistry and histopathology. No treatment- related findings were noted in body weights, food consumption, coagulation and urinalysis. Test article related changes included: increased incidence of corneal opacity, mild increase in neutrophils, platelet distribution width and minimal increases in liver enzymes (AST, ALT) without microscopic correlates in the liver. Microscopic findings in the lung consisted of minimal to mild increased alveolar histiocytosis in males and females at ≥ 1 mg/kg per day and minimal to mild increased subacute inflammation in males at ≥ 10 mg/kg per dose and females at ≥ 5 mg/kg per day and corresponded to increased lung weights. At recovery, minimal increased alveolar histiocytosis in the lung persisted in males and females at ≥ 5 mg/kg per day, but was resolved at the 1 mg/kg low dose level. There were no marked or consistent gender differences in the toxicokinetic parameters calculated for Project 17-5. Plasma Cmax was approximately dose proportional and exposure (AUC0–24h) was more than dose proportional across the dose range of 1 to 10 mg/kg per day of Project 17-5. Repeated intravenous administration of linear Project 17-5 (daily for  5 days) to male and female rats was tolerated at doses up to 10 mg/kg per day. Increased incidence in corneal opacity in males at ≥ 5 mg/kg per day was considered possibly related to treatment. Changes in lung weight and histopathology findings were likely Project 17-5 related, but could not be unequivocally considered adverse. The HNSTD and NOAEL were considered to be the highest dose of 10 mg/kg per day in both sexes. The NOEL was considered to be < 1 mg/kg per day due to increased alveolar histiocytosis in the lungs at all dose levels. |
| *Table continued on next page* | | | |

|  |  |  |  |
| --- | --- | --- | --- |
| **Study No.** | **Study Title** | **Species** | **Study Summary** |
| 1019-009 | GLP Repeat-Dose (once daily for 5 days) intravenous toxicity study of PROJECT 17-1  (Project 17-5) in cynomolgus monkeys with a 2-week recovery period | Monkeys | The objective of this GLP repeat-dose study was to characterize the toxicities of linear Project 17-5 when administered intravenous once daily for 5 consecutive days in monkeys. Secondary objectives were to determine the reversibility of any toxicities and identify the HNSTD, NOAEL and/or NOEL. Five cynomolgus monkeys/sex were administered either vehicle or linear Project 17-5 at dose levels of 0.5, 2 or 5 mg/kg per day daily for 5 consecutive days. Animals were necropsied 3 days or 14 days post last dose. Study endpoints included morbidity and mortality, clinical observations, body weights, food consumption, clinical pathology (hematology, clinical chemistry, coagulation and urinalysis), ophthalmoscopic examinations, electrocardiography evaluations, blood pressure, heart rate, respiratory rate, toxicokinetics, gross pathology, organ weights and histopathology. Treatment-related findings were limited to changes in hematology (increased lymphocytes, monocytes, large unstained cells) and serum chemistry (increased creatinine kinase). No treatment-related clinical signs of toxicity or effects on body weight, food consumption, coagulation, urinalysis, ophthalmology, electrocardiograms, blood pressure, heart rate, respiratory rate and gross and histopathology changes were observed. All changes had resolved by the end of study. There were no marked or consistent differences in the toxicokinetic parameters calculated for Project 17-5 in male and female monkeys on day 1 or day 5. AUC(0-24h) and Cmax were approximately dose proportional. Repeated (daily for 5 days) intravenous administration of linear Project 17-5 to male and female cynomolgus monkeys was well tolerated at doses up to 5 mg/kg per day. The highest dose level tested (5 mg/kg per day, daily for 5 days) was the HNSTD and NOAEL for this study. The NOEL was < 0.5 mg/kg per day due to increases in monocytes in both sexes and lymphocytes in females at all dose levels. |

ALT: alanine aminotransferase; AST: aspartate aminotransferase; Project 17-5: cysteine maleimidocaproyl-monomethylauristatin F; GLP: Good Laboratory Practice; HNSTD: highest nonseverely toxic dose; NOAEL: no-observed-adverse-effect-level; NOEL: no-observed-effect-level.

### Genotoxicity

No genotoxicity studies of PROJECT 17-2 have been conducted to date. The 3 genotoxicity studies summarized below were conducted with Project 17-5 and were GLP compliant.

### In Vitro Genotoxicity of PROJECT 17-1 (Project 17-5)

The studies listed in [[Table 13](#_bookmark63)] were conducted to evaluate the genotoxicity of PROJECT 17-1 (Project 17-5).

### Table 13 Genotoxicity Studies with PROJECT 17-1 (Project 17-5)

|  |  |  |  |
| --- | --- | --- | --- |
| **Study No.** | **Study Title** | **Species** | **Study Summary** |
| AE01BX.50 2ICH.BTL | Bacterial Reverse Mutation Assay | NA | PROJECT 17-1 was tested in the Bacterial Reverse Mutation Assay using *Salmonella typhimurium* tester strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* tester strain WP2 *uvr*A in the presence and absence of  Aroclor-induced rat liver S9. PROJECT 17-1 at dose levels up to 5000 µg per plate was concluded to be negative in the Bacterial Reverse Mutation Assay. |
| AE01BX.12 5M012ICH. BTL | In vivo Micronucleus Assay in Rats with PROJECT 17-1 | Rat | PROJECT 17-1, was evaluated for its clastogenic activity and/or disruption of the mitotic apparatus by detecting micronuclei in polychromatic erythrocyte cells in Sprague Dawley (Hsd:SD) rat bone marrow. Rats were administered vehicle control (PBS), positive control (cyclophosphamide monohydrate, 40 mg/kg) or PROJECT 17-1 as a single dose of 0, 10, 17.5 and 25 mg/kg. Femoral bone marrow was collected following scheduled euthanasia and bone marrow slides were prepared and stained with acridine orange. PROJECT 17-1 at doses up to and including a dose of 25 mg/kg was concluded to be negative in the rat bone marrow micronucleus assay. |
| AE01BX.70 4ICH.BTL | In vitro Mammalian Cell Gene Mutation Test(L5178Y/TK +/-  Mouse Lymphoma Assay) | NA | The objective of this study was to evaluate the genotoxic potential of PROJECT 17-1 in a GLP-compliant in vitro mammalian cell gene mutation test. PROJECT 17-1 was evaluated to determine its ability to induce forward mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells with and without Aroclor-induced rat liver S9. At concentrations ranging from 5.34 to 16.9 µg/mL (4- hour treatment with S9), 4 to 16.9 µg/mL (4-hour treatment without S9) and 0.475 to 3 µg/mL (24-hour treatment without S9), PROJECT 17-1 was negative in the L5178Y/TK+/- Mouse Lymphoma Mutagenesis Assay. |

GLP: Good Laboratory Practice; NA: Not applicable; PBS: phosphate buffered saline.

### Carcinogenicity

No studies have been conducted to date with PROJECT 17-2.

### Reproductive and Developmental Toxicity

No studies have been conducted to date with PROJECT 17-2.

### Local Tolerance

No studies have been conducted to date with PROJECT 17-2.

### Other Toxicity Studies

### Ocular Toxicity

Six non-GLP studies have been conducted to establish an animal model of ocular tolerability which included PROJECT 17-2 as a control. These studies are listed in [[Table 14](#_bookmark69)]. Additional details will be added to the IB should clinically meaningful information be obtained from these investigative studies.

### Table 14 Non-GLP Models of Ocular Tolerability

|  |  |
| --- | --- |
| **Study Title** | **Study/ Report No.** |
| A 4-Week Intravenous Administration – Ocular Tolerability Study Comparing Four Antibody Drug Conjugates in Dutch Belted Rabbits | COV 8330867 |
| Ocular Tolerability Study Comparing AGS34F and PROJECT 17-2 Antibody Drug Conjugates in Male Dutch Belted Rabbits During Weekly Intravenous Administration for Six Weeks | COV 8298493 |
| A Single Dose Study of PROJECT 17-2 by Intravenous Bolus Injection in Sprague- Dawley Rats | CRL 20064570 |
| A Single Dose Study of PROJECT 17-2 by Intravenous Bolus Injection in Sprague- Dawley Rats | CRL 20068088 |
| Non-GLP, 4-week Ocular Tolerability Study Comparing Four Antibody-Drug Conjugates in Dutch-Belted Rabbits | COV 8320275 |
| Non-GLP, single-dose, PROJECT 17-2 Intravenous Bolus in Sprague-Dawley Rat Assessing Corneal Mitotic Figures | CRL 20073394 |

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

This section cannot be completed in this update due to some of the toxicology reports not being available.

### List of References

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