Toxicology Testing

Service List

Mammalian Toxicology

BioReliance® by SAFC

Table of Contents

Transgenic Carcinogenicity Studies

The use of animal models to determine the carcinogenic potential of pharmaceuticals is a required part of evaluating the overall safety of many new drug products. Advances in our understanding of the mechanisms of carcinogenesis combined with the ability to create transgenic animals have given toxicologists new tools with which to test materials for potential carcinogenic activity.

In 1997, the International Conference on Harmonisation (ICH) S1B Guideline "Testing for Carcinogenicity of Pharmaceuticals" approved the worldwide use of transgenic models to test for carcinogenicity. Much of the early work that led to acceptance by the FDA was performed by BioReliance under a National Toxicology Program (NTP) contract. BioReliance also participated in the International Life Sciences Institute (ILSI) validation that was the impetus for FDA acceptance. BioReliance has offered these studies commercially for over a decade.

28-Day Toxicity Study General Parameters

- Ten male and 10 female wild type (non-transgenic littermates) per group
- Following an optional 5 Day preliminary range-finding test, groups of animals (10 male and 10 female each) are treated daily by the designated route to one of at least three dose levels of test article for 28 consecutive days; a control group is treated with vehicle only at the same dose volume and time schedule
- Animals are observed twice daily for moribundity and mortality and once daily for clinical signs of toxicity; body weights and food consumption are measured weekly
- Animals are sacrificed on Day 29; blood is collected for selected hematology and chemistry studies and a complete necropsy is performed with selected tissues processed for histopathology on high dose and control mice
- Read down of target tissues in mid and low dose groups if necessary
- Optional TK cohort
- Routes of Administration include oral gavage, subcutaneous, intravenous injection and dosed feed

Protocol	Assay Description
2G3R	**28-Day Toxicity Study in CByB6F1 Mice for Tg.rasH2 Carcinogenicity Study**
2G3P	*28-Toxicity Study in C57Bl/6 Mice for p53+/- Carcinogenicity Study – available upon request*

26-Week Carcinogenicity Study General Parameters

- 25 male and 25 female mice per dose, at least three test article dose levels plus vehicle and positive control (10 mice/sex for positive control)
- Vehicle control articles administered daily for 26 weeks by the prescribed dose route (positive control administered only in week 1 of study)
- Animals are observed daily for moribundity, mortality; weekly for clinical signs of toxicity, body weights and food consumption (if required); weekly palpations
- After 26 weeks all animals are sacrificed (positive controls sacrificed at 13-16 weeks); complete necropsy performed with a full range of tissues processed for histopathology in all dose groups and vehicle control.
- Optional TK cohort
- Routes of Administration include oral gavage, subcutaneous, intravenous injection and dosed feed

Protocol	Assay Description
7G8R	**26-Week Carcinogenicity Study with Tg.rasH2 Transgenic Mice**
7G8P	*26-Week Carcinogenicity Study with p53+/- Transgenic Mice – available upon request*

Repeated-Dose Studies

28-Day Toxicity Study in Rodents and Rabbits (General Parameters)

- Forty male and 40 female animals per sex
- Following a range-finding test, groups of animals (10 male and 10 female) are treated daily with one of three dose levels of test article for 28 consecutive days; a control group is treated with vehicle only at the same dose volume and time schedule
- Animals are observed twice daily for moribundity and mortality and once daily for clinical signs of toxicity; body weights and food consumption are measured weekly
- Functional Observational Battery (FOB) will be conducted in the fourth exposure week if required
- Animals are sacrificed on day 29; blood is collected for selected hematology, coagulation and chemistry studies; urinalysis and ophthalmology will also be performed and a complete necropsy is performed with selected tissues processed for histopathology on high dose and control mice
- Read down of target tissues in mid and low dose groups if necessary
- Routes of Administration include oral gavage, subcutaneous, intravenous injection and dosed feed

Protocol	Assay Description
2G31	**28-Day Repeated-Dose Oral Toxicity Study in Rats**
2F31	**28-Day Repeated-Dose Dosed Feed Toxicity Study in Rats**

13-Week Subchronic Toxicity Study in Rodents (General Parameters)

- Forty male and 40 female animals main study; 20 males and 20 females in Recovery group if required
- Following a range-finding test, groups of animals (10 or 15 male and 10 or 15 female) are treated daily with one of three dose levels of test article for 90 consecutive days; a control group is treated with vehicle only at the same dose volume and time schedule
- Animals are observed twice daily for moribundity and mortality and once daily for clinical signs of toxicity; body weights and food consumption are measured weekly
- Functional Observational Battery (FOB) will be conducted in the last exposure week if required
- Animals are sacrificed after 13 weeks and 2 weeks later if a recovery group;; blood is collected for selected hematology, coagulation and chemistry studies; urinalysis and ophthalmology will also be performed and a complete necropsy is performed with selected tissues processed for histopathology on high dose and control mice
- Read down of target tissues in mid and low dose groups if necessary
- Routes of Administration include oral gavage, subcutaneous, intravenous injection and dosed feed

Protocol	Assay Description
7G31/7G32	**13-Week Subchronic Oral Toxicity Study in Rats /Mice**
7F31/7F32	**13-Week Subchronic Dosed Feed Toxicity Study in Rats /Mice**

Please note: other study designs available on request.
GeneTox endpoints, including Micronucleus, Comet and *Pig-a* Assays can be added to any Repeated-Dose Study

Custom Vaccine Toxicology Studies

Protocol	Assay Description
Study Specific	**Vaccine Toxicity Study in Rats, Mice or Rabbits** • Groups of animals, are treated with 2-3 dosages of the vaccine, based on the proposed clinical dosages, frequency and route of administration; control groups are treated with the adjuvant and/or vehicle alone on the same schedule • Animals are observed daily for mortality and moribundity and for clinical signs of toxicity at a frequency defined by the protocol; body weights are measured weekly • Animals are sacrificed at a protocol-defined time after the last dose administration and after a recovery period • Blood is collected for selected hematology and chemistry studies and a complete necropsy is performed with selected tissues processed for histopathology • Blood is collected for determination of antibody response to the vaccine at a frequency defined by the protocol • Optional body temperature monitoring if required

Contract Pathology Services

Protocol	Assay Description
PA-100	**Necropsy and Histopathology Services** • Perform and supervise necropsies
PA-200	**Pathology Slide Reading** • Primary evaluation of pathology slides • Pathology report preparation
PA-300	**Peer Review Pathology Slide Reading** • Peer review of pathology slides/target • Verification/reconciliation of evaluation • Report preparation
PA-400	**Non-GLP Clinical Pathology Services** • Complete Hematology • Clinical Chemistry with custom profiles

Analytical Chemistry Services

Protocol	Assay Description

GTCHEM	**Analytical Method Validation**
	• Transfer Validation (Sponsor Method)
	• Full Validation (BioReliance Method)
	• Methodology
	  ○ HPLC or GC
	  ○ UV/Vis
	  ○ LC/MS/MS

DSA	**Dosing Solution Analysis**
	• Formulation Verification
	• Methodology
	  ○ HPLC or GC
	  ○ UV/Vis
	  ○ LC/MS/MS

STABIL	**Stability Analysis** • Stability determination • Homogeneity determination • Purity determination
SR/SS	**Other Standard Services** • Sample Retention • Storage Services

Toxicokinetics/Pharmacokinetics (TK/PK)

Protocol	Assay Description
BIOA	**BioAnalysis** Analysis of plasma samples from in vivo studies on LC/MS/MS
TKA	**TK Analysis Report** Comprehensive Toxicokinetics analysis report including PK/TK calculations with tables

Specialty Studies

Protocol	Assay Description
FOB	**Functional Observation Battery** • Available as an assessment in one of these two options: 1. Neurotoxicity screen ▪ added to any general toxicity study ▪ for CNS Therapeutics 2. Phenotyping of transgenic and knockout animals • Using Modified Irwin Testing Battery
Please Inquire	**Integrated Genetic Toxicology Endpoints to Repeated-Dose Studies** • Micronucleus Assay • Comet Assay • Chromosome Aberration Assay • *Pig-a* Gene Mutation Assay

Studies for Nucleic Acid Based Therapeutics

Protocol	Assay Description
9N91-6	**Single or Repeated-Dose DNA Plasmid or Virus Vector Pharmacokinetics Studies in Rodents or Rabbits** • Male and/or female rats, mice, or rabbits dosed via oral gavage, intravenous, intramuscular or other appropriate route • Groups of animals in multiples of 5or 10 per timepoint per sex per dose • Animals are treated once or repeatedly, a control group is treated with vehicle only at the same dose volume and time schedule • Animals are observed twice daily for moribundity and mortality, and once daily for clinical signs of toxicity: body weights and food consumption are measured weekly • Animals are sacrificed at scheduled interim and terminal timepoints for analysis of plasmid DNA distribution in selected tissues • PCR analysis of test articles is optimized prior to study conduct • Can be combined with toxicology endpoints

Information and Ordering

For additional information or to place studies, please contact:

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