The Altascientist

SCIENTIFIC JOURNAL

ISSUE NO. 47

SIZE MATTERS:

The Sinclair Nanopig® as a Translational Non-Rodent Model in Preclinical Research

Drug developers and scientists are constantly looking for animal models that are cost effective, aligned with research goals, and allow for lower test article (TA) usage without sacrificing scientific integrity and regulatory approval.

In this issue, we take a closer look at what makes the Sinclair Nanopig® a scientifically appropriate and cost-effective non-rodent species for your preclinical programs. We also review a case study in which the animal model was changed from a canine to the Sinclair Nanopig® for its reduced emesis.

WHY ARE MINIATURE SWINE IMPORTANT IN PRECLINICAL DRUG DEVELOPMENT?

In the continuum of preclinical drug development, the selection of appropriate animal models is crucial for providing the safety data that is required for a novel therapeutic to progress into clinical trials. Among non-rodent animal models, minipigs, including the smaller Sinclair Nanopig®, have emerged as a valuable species due to their unique physiological and anatomical similarities to humans.

THE MINIATURE SWINE MODEL ADVANTAGE:

1 Translational Relevance to Human Physiology

Miniature swine offer key anatomical and physiological similarities to humans that enhance the translational value of studies.

Key Human-Relevant Traits:

- Skin structure
- Gastrointestinal (GI) tract
- Cardiovascular system
- Liver metabolism

These systems in minipigs are more closely aligned with human biology than traditional non-rodent models (e.g., dogs or non-human primates). This similarity enhances the predictive power of pharmacokinetic (PK), pharmacodynamic (PD), and toxicological studies, especially when studying dermal, oral, or cardiovascular drug delivery.

2 Practicality

Miniature swine are a practical, cost-efficient model for preclinical toxicity testing.

- Their manageable size, particularly in laboratory-bred miniature and nano-sized breeds, allows for precise dosing, sampling, and longitudinal monitoring.
- Safety studies in the Sinclair Nanopig® typically start at the age of three to five months, while canines typically start at six months. At these ages, the Sinclair Nanopig® weighs less than standard beagles, which means less TA is needed for the first few months of dosing.
- Some programs require dosing to start after the animals have reached sexual maturity. The Sinclair Nanopig® reaches sexual maturity at a younger age (and body weight) than other minipigs, which means there are fewer TA requirements compared to other minipig models for these programs.

3 Suitability for Specialized Routes and Disease Models

Miniature swine are especially valuable in the following areas:

- **Dermal studies:** Their skin thickness and composition closely resemble human skin, making them ideal for testing transdermal formulations and topical products.
- **Oral delivery studies:** Their GI physiology supports accurate modeling of human oral drug absorption and metabolism.
- **Surgical modeling:** Their size and anatomy make them suitable for implantable device testing and surgical procedure simulations.
- **Juvenile toxicity studies:** Because of similarities in organ development, minipigs are increasingly used in pediatric drug development.

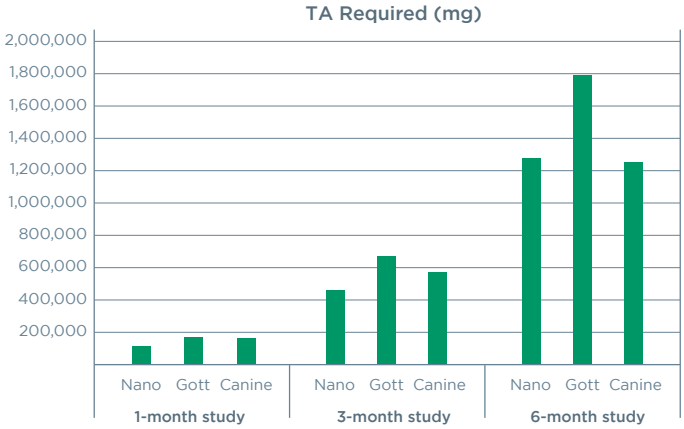
4 Regulatory Acceptance and Industry Trends

Based on the ICH M3 (R2), regulatory agencies such as the FDA and EMA accept miniature swine, like the Sinclair Nanopig®, for pivotal toxicology, safety pharmacology, and reproductive toxicology studies for small molecules, justified by data translatability to humans. As pharmaceutical pipelines grow more complex (e.g., biologics, gene therapy, and advanced delivery systems), additional non-rodent options are advantageous.

TEST ARTICLE USAGE: SINCLAIR NANOPIG® VS. CANINE MODEL

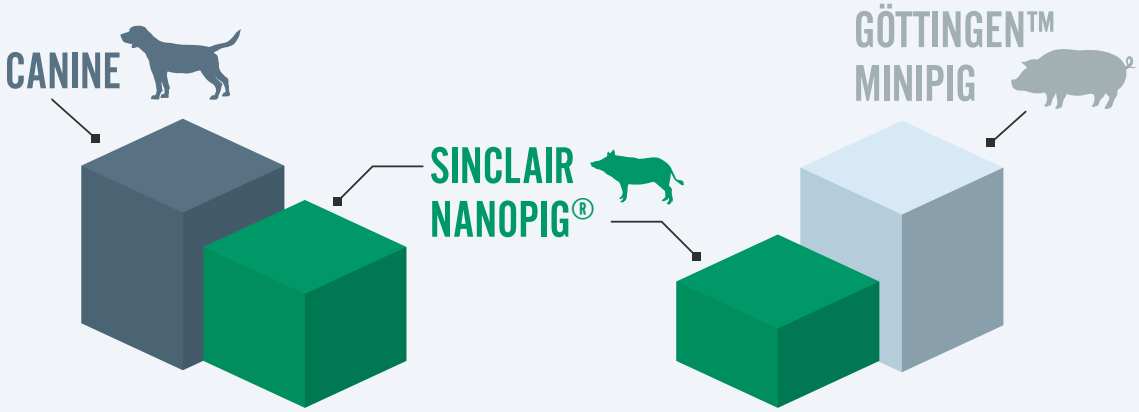
When comparing test article (TA) requirements, the Sinclair Nanopig® model shows reduced usage compared to the canine model in studies lasting under six months and utilizing juvenile animals. The chart below presents data from 1-, 3-, and 6-month studies in groups of six animals, using two different starting ages for the Sinclair Nanopig®. For the 1- and 3-month durations, the Sinclair Nanopig® required less TA overall. In the 6-month study, TA usage for the Sinclair Nanopig® model was comparable with that of canine models.

Starting age: Sinclair Nanopig® at 3 months, canine at 6 months



		Total TA Required (mg)	Difference vs. Sinclair Nanopig®
1-month study	Sinclair Nanopig®	112,896	
	Göttingen™	176,400	156%
	Canine	164,640	146%
3-month study	Sinclair Nanopig®	458,640	
	Göttingen™	670,320	146%
	Canine	564,480	123%
6-month study	Sinclair Nanopig®	1,270,080	
	Göttingen™	1,787,520	141%
	Canine	1,246,560	98%

Test Article Usage by Species



*4-week study, assuming animal body weights: ~ 5 kg (Sinclair Nanopig®), ~ 7.5 kg (Göttingen™ minipig), and 7 kg (beagle dog).

HISTORY AND REGULATORY ACCEPTANCE OF THE SINCLAIR NANOPIG®

The Sinclair Nanopig® is the result of over 12 years of selective breeding and diet control efforts. It was introduced in 2022 by Altasciences and Sinclair Bio Resources as the next-generation non-rodent model for drug safety assessment. Scientists reported reference values for the Sinclair Nanopig®, which included a limited growth rate and low body weight, resulting in lower TA usage for nonclinical studies.

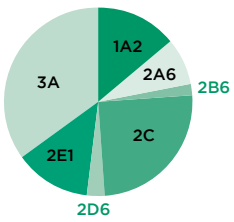
Regulatory acceptance of the Sinclair Nanopig® is supported by findings indicating similar clinical pathology data, organ weights, and background microscopic findings compared to other minipig breeds (Chen et al., 2023, pg. 13). Genome-based comparison of drug targets with quantitative tissue protein expression analysis allows rational prediction of pharmacology, cross-reactivity, and potential toxicity of human drugs in animal models, improving clinical translation and drug attrition for miniature swine in general (Vamathevan et al., 2013; Heckel et al., 2015).

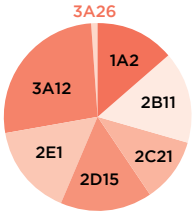
A recently published white paper from Altasciences provides genomic, proteomic, and functional characterization data—covering metabolism and immune systems—of the Sinclair Nanopig®. This data support the use of the Sinclair Nanopig® as a non-rodent species for drug safety assessment. Additionally, this data expands translational knowledge of the Sinclair Nanopig® helping to refine the selection and replace traditional non-rodent models in drug development.

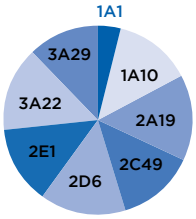
The white paper is the first report of a newly revealed chromosome-level-based version of the Sinclair Nanopig® genome. It also presents a comparative proteomic analysis of tissues with pharmaceutical relevance, along with critical information about metabolism and the immune system for translational research.

Functional genomics and proteomics play a crucial role in supporting the use of Sinclair Nanopig® for novel therapeutic development. They provide deeper insights into the intricate molecular mechanisms governing biopathology and physiology, essential for ensuring the safety and efficacy of drugs and biologics.

For example, cytochrome P450 enzymes (CYPs), mainly found within the mitochondria and endoplasmic reticulum of liver cells, are responsible for 70 to 80% of drug metabolism in humans. In the Sinclair Nanopig®, a total of 47 of the 57 CYP450 genes were identified and tested from the liver, kidney, and small intestine. The results demonstrated translatability between the Nanopig and humans. For two of the primary CYPs (CYP2C and CYP3A4), the Sinclair Nanopig® was found to be more similar in activity to humans than canines.







	Human	%		Beagle	%		Sinclair Nanopig®	%	
CYP1	1A2	14	**14**	1A2	14	**14**	1A1 1A2	3 10	**13**
CYP2	2A6 2B6 2C 2D6 2E1	8 2 25 3 13	**51**	 2B11 2C21 2D15 2E1	 16 11 16 16	**58**	2A19 2C49 2D6 2E1	11 10 11 10	**42**
CYP3	3A	35	**35**	3A12 3A26	27 1	**28**	3A22 3A29	11 9	**19**

Court MH. Canine cytochrome P-450 pharmacogenetics. 2013 CYP4/20/27 25

Altasciences' proprietary, searchable multi-omics database supports the use of the Sinclair Nanopig® in pharmacology, biomarker discovery, and drug safety assessment. Usage data shows the model is expanding into new areas of preclinical research, including gene therapy. As translational knowledge grows, industry adoption and regulatory acceptance continue to increase, reducing the reliance on traditional non-rodent models in drug development.

ALTASCIENCES CASE STUDY: REDUCED EMESIS IN THE SINCLAIR NANOPIG®

Study Overview

Altasciences was contracted to conduct safety studies in beagle dogs as part of an IND-enabling package for a small molecule. Due to excessive emesis/vomitus in the dogs, the Sinclair Nanopig® was chosen as a viable model to complete the studies.

Study Details

- **Drug Development Phase:** Preclinical (dose range finding studies, IND-enabling)
- **Class of Drug:** Small molecule
- **Animal Model:** Initially Beagle dog, completed with the Sinclair Nanopig®
- **Number of Animals:** 16
- **Dose Route:** Oral gavage
- **Dose Regimen:** Daily, for up to 10 days

Study Purpose

To establish the maximum tolerated dose (MTD) to guide in dose selection for subsequent IND-enabling studies.

Methods

This dose-range finding study involved daily dosing for up to 10 days. Animals were dosed once daily by oral gavage, with detailed clinical observations occurring approximately one hour post-dose. The study included body weights, food consumption, and clinical pathology, with necropsy and gross pathology. Blood draws occurred following the first and last dose for exposure assessment.

The Challenge

A dose-responsive increase in emesis/vomitus was observed with the mid- and high-dose groups having emesis/vomitus every day, often within 30 minutes of dose administration. Given the oral dose route, this frequency of emesis/vomitus resulted in limited exposure, particularly for the mid- and high-dose groups. Such frequent emesis/vomitus would compromise the ability to evaluate the systemic exposure and associated toxicity of the TA with repeated dosing.

The Solution and Results

We approached the client to determine other non-rodent species scientifically justified based on the metabolism of their TA, and together, determined the miniature swine as a viable option. Since miniature swine have a lower propensity for emesis and vomiting than beagle dogs, the dose-range finding study was repeated using the Sinclair Nanopig®. The latter was chosen from among other miniature swine species to deliver lower emesis/vomitus compromised the use of TA. The results from the repeated study included a much lower incidence of emesis/vomitus and an increase in systemic exposure, allowing the program to continue into IND-enabling GLP safety studies.

HOW ALTASCIENCES CAN HELP

Our preclinical facility in Columbia, MO, houses one of the largest miniature swine populations in the U.S., helping reduce both the time and cost of establishing test groups. The facility offers:

- 80 custom-designed animal rooms
- Experience with small molecules and biologics
- IND- and NDA-enabling toxicology and safety pharmacology services
- Lead times as short as six to eight weeks after contract signing

We have extensive experience in therapeutic areas where miniature swine are highly relevant, including dermal, gene therapy, metabolic diseases, inflammation, oncology, CNS disorders, ocular diseases, and HIV. Our skilled veterinary surgeons and experienced pharmacologists and toxicologists bring extensive knowledge across a range of modalities, molecules, and disease indications, to support *in vivo* studies that advance the development of your novel drug candidates.

Dosing routes available for miniature swine at Altasciences:

- aural
- intra-articular
- intramuscular
- IV infusion
- subcutaneous–injection or surgical implant
- dermal (topical)
- intra-bladder (females only)
- IV bolus
- oral (gavage and capsule)
- targeted GI sections for infusions/repeat bolus dosing

When you choose Altasciences, you will gain access to multiple research lineages of miniature swine, including the **Hanford™**, **Göttingen™**, **Sinclair Nanopig®**, and **Yucatan™**.

The Sinclair Nanopig® is the smallest of the produced breeds and can decrease your TA usage by as much as 50%.

ALTASCIENCES' RESOURCES

Scientific Poster Presentations

Highlights From the 17th Minipig Research Forum

Sub-retinal Injection of Sodium Iodate in Nanopigs®

The Sinclair Nanopig®—The Other Non-Rodent

Downsized Sinclair Nanopig® vs Göttingen Minipig—Similarities and Differences of Toxicological Reference

Range Data in Preclinical Safety Studies

Sinclair Nanopig®: From Multi-Omics Characterization to Toxicology Validation

Comparison of Cardiovascular and Respiratory Parameters in Three Strains of Research Pigs

White Paper

Whole Genome Sequencing, Proteomics, and Function Characterization of the Sinclair Nanopig® for (Bio)Pharmaceuticals Safety Assessment

Webinar

Sinclair Nanopig®—Next Generation Non-Rodent Model for (Bio)Pharmaceuticals Safety Assessment

Webpage

Miniature Swine in Nonclinical Studies

Scientific Article

The Altascientist Issue 32—Non-Rodent Species in Nonclinical Studies

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 30 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.

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