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Background Data in the Sinclair Nanopig™

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ABSTRACT

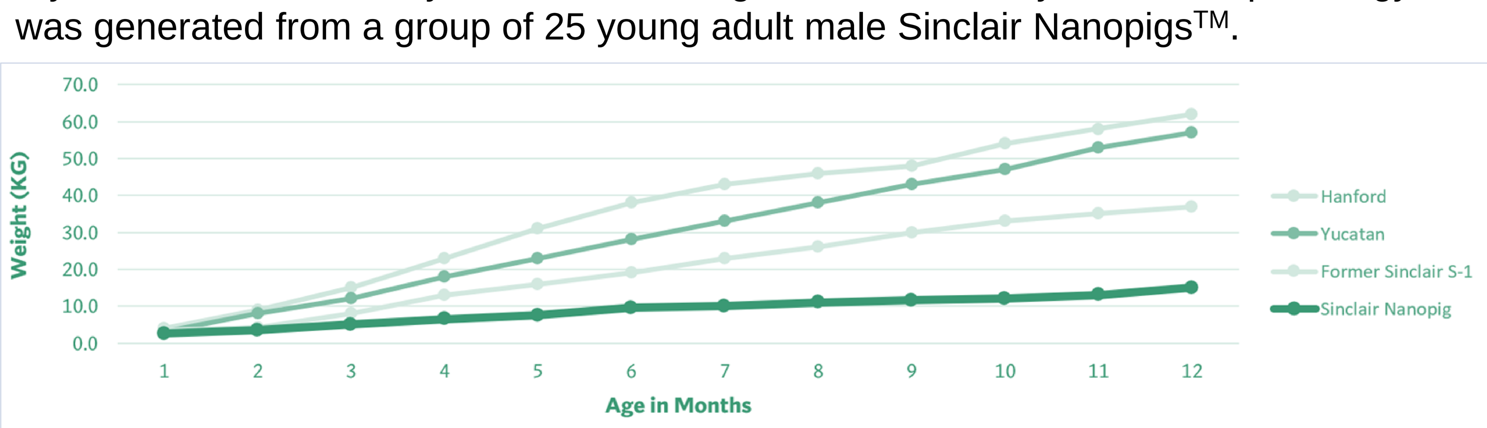
This poster presents body weight, hematology, serum chemistry, ECG, ophthalmology, and gross/microscopic pathology reference data for the Sinclair Nanopig™ at ages that correlate to using the Sinclair Nanopig™ in safety assessment. This data is critical for toxicologists and pharmacologists as a reference for normal variation among animal models used in nonclinical drug development. While there is considerable data for other breeds of miniature swine widely available to the research community, much of the data obtained from the Sinclair Nanopig™ is proprietary to the organizations utilizing the model. The Sinclair Nanopig™ is comparable to well-established breeds such as Yucatans and Gottingen minipigs® in terms of physiology and metabolism but is more similar in body weight to a beagle dog when maintained on a high-fiber, low-fat diet. This provides an advantage in using the Sinclair Nanopig™ in that less test article is needed for IND-enabling studies compared to the beagle dog or the Gottingen minipig®. The goal of this poster is to expand upon the standard reference data for the Sinclair Nanopig™ available to the entire research community.

INTRODUCTION

Miniature swine is a viable option as a non-rodent test system for studies to evaluate the safety and efficacy of new (bio)pharmaceuticals. It has long been understood that pigs have many anatomical, physiological, and functional similarities to humans, and miniature swine are easy to manage in a laboratory setting. There are several lineages of miniature swine that are purpose-bred for biomedical research. The Hormel Institute developed the Sinclair Miniature Swine in 1949. This lineage is also known as the "Minnesota Minipig" or "Hormel Minipig" and is one of the background lineages used to develop the Gottingen minipigs®. The Sinclair Nanopig™ was created from the Sinclair miniature swine (Sinclair S-1) through a concerted effort that involved selective breeding for smaller size and controlled feeding of a high fiber, low-fat minipig diet. This resulted in a miniature swine model comparable in body weight to a beagle dog, which mitigates previous challenges associated with utilizing swine models for standard pre-clinical studies, namely the amount of test articles needed for IND-enabling studies. The downsizing of the Sinclair S-1 did not involve any genetic manipulations to the lineage. Thus, the background data established in the Sinclair S-1 miniature swine remains highly relevant for the downsized Sinclair Nanopig™. However, as the request for the Sinclair Nanopig™ in nonclinical drug development continues to increase, it remains ever-important to continue to generate a robust database of background data in the Sinclair Nanopig™ itself.

METHODS

Venous blood samples were obtained from both male and female Sinclair Nanopigs™ from the following age groups: 2-3, 4-5, 6-7, 8-9, 10-11, and >12 months. Standard panels for hematology and serum chemistry, consistent with those performed for toxicology studies, were generated using GLP-validated equipment. ECG and ophthalmology examinations were conducted for male and female Sinclair Nanopigs at 3, 4-5, 6-7, and over 9 months of age. A board-certified veterinary ophthalmologist performed the ophthalmology examinations using a portable slit-lamp biomicroscope and a binocular indirect ophthalmoscope for the posterior segment. ECG leads I, II, III, aVR, aVF, and aVL were collected, and the following variables were derived: heart rate, PR-interval, QT-interval, QRS-interval, ST-interval, P-wave, and T-wave durations. The rhythm was also carefully reviewed for irregularities and arrhythmia. The pathology data was generated from a group of 25 young adult male Sinclair Nanopigs™.



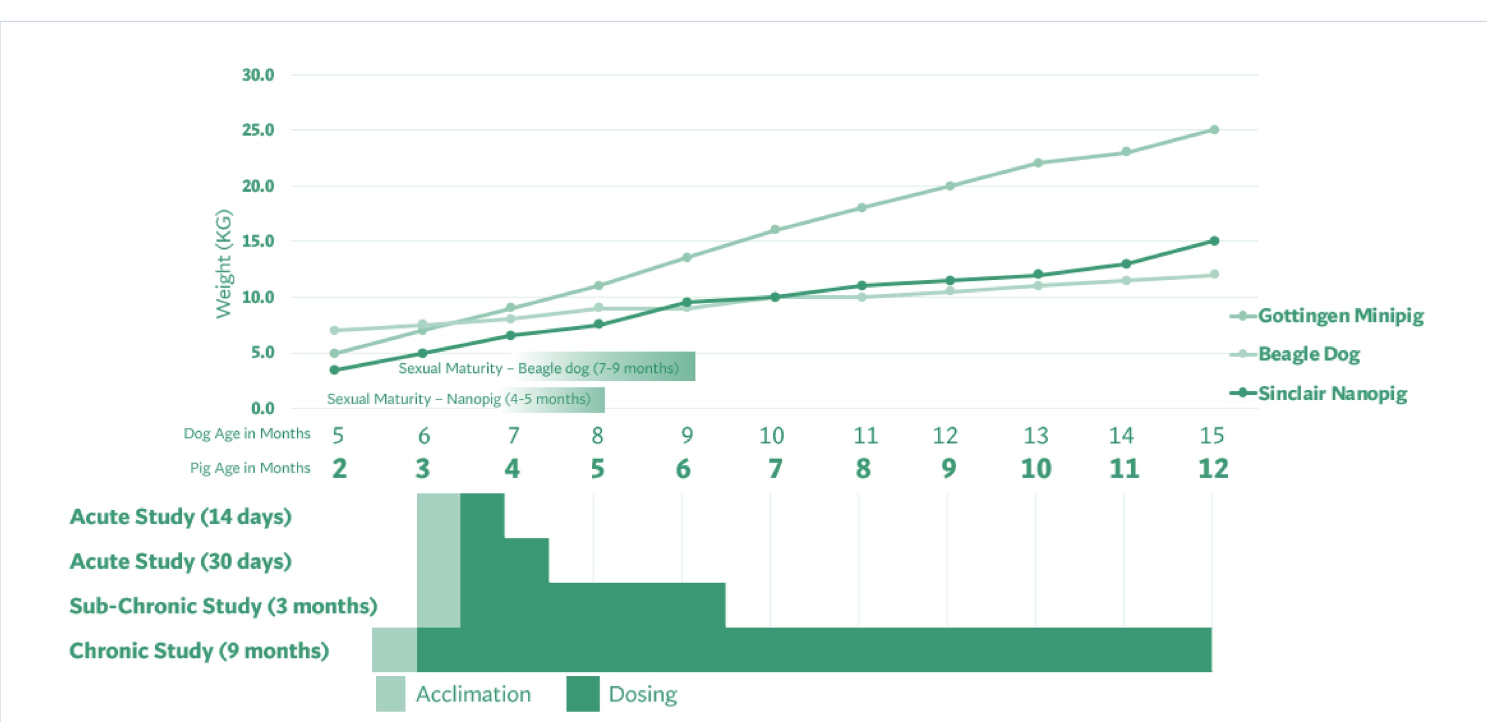


Table 1. Hematology Data

Hematology Parameters	Male 2-3 Months (n=54)				Female 2-3 Months (n=46)				Male 4-5 Months (n=42)				Female 4-5 Months (n=40)			
	Mean	SD	95% Reference Range		Mean	SD	95% Reference Range		Mean	SD	95% Reference Range		Mean	SD	95% Reference Range	
WBC (10³/µL)	14.5	2.9	9.0	19.8	14.2	2.4	10.2	18.3	13.7	2.7	9.5	19.9	13.77	2.5	9.3	18.8
RBC (10⁶/µL)	7.7	0.8	6.2	9.1	7.9	0.7	6.5	9.2	7.7	0.9	6.7	9.8	7.57	0.5	6.8	8.5
Hgb (g/dL)	14.3	1.3	11.8	16.6	14.5	1.0	12.5	16.0	14.7	1.9	11.4	17.9	14.54	0.9	12.9	16.2
HCT (%)	43.3	3.8	36.2	50.7	43.3	3.2	37.1	48.9	43.2	4.4	35.1	50.3	41.25	3.2	35.8	47.7
MCV (fL)	56.4	3.4	49.9	62.1	55.5	1.9	52.3	59.3	56.7	3.1	51.5	62.3	55.01	3.7	49.0	61.2
MCH (pg)	18.5	1.0	16.4	20.1	18.5	0.8	16.8	19.9	19.3	1.4	16.8	22.1	19.20	1.0	17.6	20.8
MCHC (g/dL)	32.9	0.8	31.4	34.4	33.3	0.8	31.8	34.6	33.8	1.7	30.7	36.8	34.94	1.2	32.4	36.5
PLT (10³/µL)	564.4	128.3	351.4	826.5	562.6	113.4	335.4	771.5	470.6	101.9	324.3	634.2	441.12	80.3	259.7	588.7
NEU (10³/µL)	3.4	1.5	0.5	6.2	2.8	1.3	0.1	5.3	3.7	1.5	1.6	6.4	3.19	1.0	1.4	5.1
NEU (%)	24.2	9.8	3.9	42.7	21.3	6.8	10.9	36.0	28.6	10.4	11.9	47.8	22.68	6.0	11.2	36.3
LYM (10³/µL)	9.4	2.5	4.1	13.9	10.1	2.0	7.0	13.0	8.8	1.7	5.7	11.3	9.85	2.3	5.8	14.4
LYM (%)	65.7	10.8	39.8	80.2	72.3	5.1	61.9	80.1	64.8	9.5	46.6	79.4	71.65	4.8	64.8	79.8
MONO (10³/µL)	0.63	0.18	0.37	1.13	0.85	0.38	0.25	1.70	0.49	0.15	0.28	0.75	0.53	0.17	0.31	0.88
MONO (%)	4.69	1.53	2.42	7.70	5.45	1.99	2.80	10.09	3.68	1.19	1.69	6.30	3.90	0.98	2.59	5.75
EOS (10³/µL)	0.19	0.13	0.03	0.45	0.15	0.07	0.04	0.30	0.14	0.07	0.05	0.29	0.18	0.07	0.09	0.30
EOS(%)	1.40	0.92	0.27	3.44	1.07	0.58	0.41	2.49	0.95	0.41	0.39	1.91	1.26	0.45	0.59	2.31
BAS (10³/µL)	0.06	0.05	0.01	0.15	0.04	0.01	0.02	0.07	0.05	0.04	0.01	0.12	0.03	0.01	0.01	0.06
BAS (%)	0.38	0.27	0.10	1.00	0.28	0.08	0.20	0.40	0.35	0.22	0.10	0.70	0.22	0.07	0.10	0.31
LUC (10³/µL)	0.16	0.09	0.03	0.34	0.13	0.09	0.03	0.37	0.11	0.08	0.00	0.29	0.13	0.03	0.09	0.17
LUC(%)	1.05	0.57	0.30	2.30	0.98	0.75	0.20	2.82	0.74	0.46	0.00	1.66	1.09	0.38	0.70	1.80
RET (10⁹/L)	84.1	43.8	19.0	177.0	95.2	45.5	28.6	177.2	77.4	25.1	38.1	128.2	65.63	27.2	25.2	124.1
RET (%)	1.1	0.6	0.3	2.5	1.2	0.6	0.4	2.7	1.0	0.3	0.5	1.7	0.86	0.3	0.3	1.6

Table 2. Serum Chemistry Data

Serum Chemistry Parameters	Male 2-3 Months (n=54)				Female 2-3 Months (n=46)				Male 4-5 Months (n=42)				Female 4-5 Months (n=40)			
	Mean	SD	95% Reference Range		Mean	SD	95% Reference Range		Mean	SD	95% Reference Range		Mean	SD	95% Reference Range	
BUN (mg/dL)	15.2	5.3	6.1	22.9	18.2	3.2	13.0	25.0	13.9	3.9	8.0	22.0	14.8	2.7	9.9	19.0
CRE (mg/dL)	0.9	0.2	0.5	1.3	0.9	0.2	0.5	1.3	1.1	0.2	0.8	1.5	1.1	0.1	0.9	1.3
GLU (mg/dL)	97.8	16.5	71.4	137.6	88.3	10.2	70.5	108.8	84.5	12.5	65.9	108.5	76.9	15.6	56.0	102.2
Na (mEq/L)	144.3	2.7	139.0	149.1	143.6	4.3	136.1	151.0	143.4	3.1	138.9	150.0	144.0	1.9	141.0	147.1
K (mEq/L)	5.9	0.7	4.6	7.1	6.4	0.7	5.0	7.8	5.8	0.8	4.3	7.1	6.0	0.8	4.8	7.3
Cl (mEq/L)	102.3	1.8	99.0	106.0	102.9	2.7	98.0	107.9	101.1	2.3	96.0	104.0	103.5	2.3	100.0	107.0
ALP (U/L)	96.4	22.6	63.1	135.8	85.3	19.5	55.1	121.6	68.3	18.9	39.0	106.2	66.9	16.5	32.9	98.2
ALT (U/L)	39.4	6.4	28.9	55.2	41.7	8.9	25.1	59.0	37.8	7.8	25.6	50.4	42.8	5.6	34.9	53.2
AST (U/L)	32.1	7.7	21.0	47.0	30.9	8.7	19.0	51.8	27.7	7.5	18.0	43.2	28.1	5.7	17.6	38.0
TBIL (mg/dL)	0.15	0.06	0.10	0.29	0.13	0.05	0.10	0.20	0.13	0.05	0.10	0.20	0.10	0.00	0.10	0.10
DBIL (mg/dL)	0.03	0.02	0.00	0.05	0.03	0.01	0.01	0.04	0.03	0.01	0.02	0.05	0.03	0.04	0.00	0.10
CK (U/L)	370.0	193.7	113.0	718.0	390.8	213.6	165.0	828.8	454.7	274.8	175.3	1246.1	283.8	116.0	156.0	541.3
GGT (U/L)	44.3	9.0	27.2	58.9	46.1	11.5	26.4	70.8	44.5	9.5	29.0	63.1	48.3	10.5	29.9	66.3
TP (g/dL)	6.2	0.6	5.1	7.1	6.1	0.4	5.4	6.8	6.6	0.4	5.9	7.3	6.2	0.2	5.8	6.7
ALB (g/dL)	4.1	0.4	3.1	4.8	3.9	0.3	3.5	4.4	4.2	0.3	3.8	4.7	4.0	0.2	3.5	4.3
GLOB (g/dL)	2.2	0.4	1.5	3.0	2.2	0.3	1.7	2.8	2.6	0.4	1.8	3.2	2.3	0.3	1.8	2.8
A\G ratio	1.8	0.4	1.2	2.7	1.8	0.4	1.1	2.4	1.7	0.4	1.0	2.4	1.8	0.3	1.2	2.2
AMY (U/L)	1044.3	250.5	678.1	1534.5	930.3	228.1	591.0	1462.3	1015.3	266.8	586.8	1511.7	972.9	195.4	643.6	1349.3
Ca (mg/dL)	11.3	0.6	10.5	12.5	11.4	0.5	10.3	12.3	11.1	0.5	10.4	12.3	10.8	0.5	10.1	11.7
PHOS (mg/dL)	8.1	0.8	6.3	9.3	8.1	0.6	7.0	9.3	8.1	0.9	6.8	9.7	7.5	0.5	6.5	8.3
CHOL (mg/dL)	94.9	24.8	51.1	129.7	105.5	29.8	62.3	160.9	103.2	19.8	67.0	138.2	92.4	12.9	68.5	113.2
TRIG (mg/dL)	43.8	15.0	23.7	79.4	42.5	15.8	22.1	81.8	34.1	11.7	18.0	59.2	33.2	9.3	18.9	54.1
LDH (U/L)	513.5	126.7	287.7	753.0	526.6	63.8	427.0	666.0	397.4	68.2	263.0	489.3	497.2	66.2	371.9	636.6

Table 3. Ophthalmology Findings

Observation	n	Left	Right
Discharge	148	80 (54%)	79 (53%)
Discharge 2	148	22 (15%)	24 (16%)
Congestion	148	6 (4%)	6 (4%)
Corneal Opacity	148	1 (1%)	0

Table 4. ECG Parameters

Parameter	Male				Female			
	Mean	SD	Range		Mean	SD	Range	
			Min	Max			Min	Max
HR (bpm)	94.0	20.9	60.9	153.9	100.9	16.9	72.1	157.3
RR (msec)	672.8	144.8	389.9	998.0	614.6	95.1	381.7	833.9
PR (msec)	99.6	12.0	87.1	133.2	97.8	14.4	79.3	155.1
QRS (msec)	57.6	8.6	38.8	72.0	56.3	11.4	31.7	72.7
QT (msec	268.6	33.5	212.7	344.4	255.3	18.4	194.7	295.1
QTc [Fridericia Correction] (msec)	308.0	31.8	254.2	379.3	301.6	23.9	242.7	349.3

Table 5. Pathology Findings

Gross Pathology (n=25):	No gross findings were identified at necropsy.	
Microscopic Findings (n=25):	**Incidence:**	**Comparison:**
Mononuclear cell infiltrates	High incidence in larynx (25/25) and kidney (21/25), often accompanied by renal tubular degeneration. Low incidence (≤4/25) noted in lung (peribronchialoar), brain (perivascular), liver, salivary glands, skin, and adrenal glands.	Common per INHAND: Nonproliferative and Proliferative Lesions of the Minipig. (Skydsgaard, 2021)
Mineralization in the pituitary gland	High incidence (17/25) of minimal multifocal	Common per INHAND. (Skydsgaard, 2021)
Testes background changes Sexual maturity also assessed: 21 mature (bilateral), 1 mature/immature (unilateral), 1 peripubertal.	Low incidence (3/23; 13%) of hypospermatogenesis or degeneration/atrophy consistent with unilateral atrophy/degeneration of testis (prostate and contralateral testis mature/peripubertal).	Common per INHAND. (Skydsgaard, 2021) (Up to 50% incidence in Göttingen Minipigs.)
Retained cartilage cores	High incidence (18/24) of was observed in the sternum/rib but not long bones.	Not mentioned in INHAND

RESULTS

Body weight data demonstrated that when the Sinclair Nanopig™ is maintained on a low-fat, high-fiber diet, their body weights are close to that of a beagle dog. Hematology and serum chemistry data from each age group was analyzed to obtain the mean, standard deviation, and 95% reference range. All data (clinical and anatomic pathology) were then compared to that of the original Sinclair S-1. The majority of the hematology, serum chemistry, and ECG data of the Sinclair Nanopig™ overlaps with that of the original Sinclair S-1 lineage. No difference in the ophthalmology findings between age groups or between males and females was consistent with findings from other lineages. The comparison of the pathology data demonstrates findings comparable to those of Gottingen minipigs®.

CONCLUSION

This data demonstrates consistency in the background data within the Sinclair S-1 lineage after downsizing the animal to the Nanopig™. Comparison with data from other miniature pig lineages demonstrates that the Sinclair Nanopig™ is a viable option when considering a miniature swine model for safety assessment studies and is comparable with other commonly used lineages. The weight of the Sinclair Nanopig™ is closer to a beagle dog, especially when adjusted for age to match when sexual maturity begins, and the age at which dosing most often occurs.

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