sequani
NON CLINICAL

March 2018

ELLEGAARD EXHIBITOR HOSTED SESSION

ANTICANCER DRUG DEVELOPMENT COMPARISON OF TOXICITY IN MINIPIG AND MOUSE

ELLEGAARD
GÖTTINGEN MINIPIGS

sequani
NON CLINICAL
great people, great work, real results

Increasingly Cancer Touches

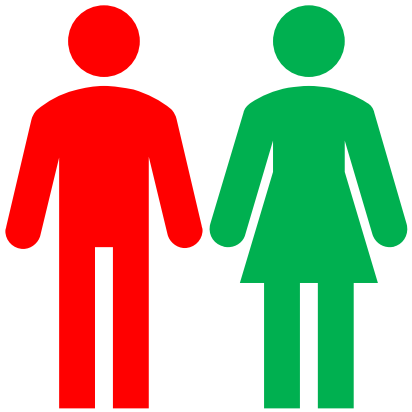
All of Our Lives

sequani
NON CLINICAL
great people, great work, real results

Increased Survival Driven by Animal Research

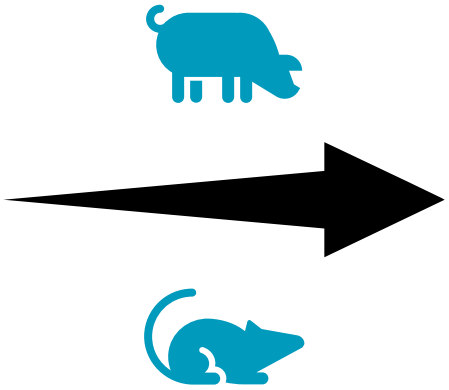
- Cancer Survival has Doubled in the Last 40 Years
- Animal Research Critical to this Progress
- Continued Animal Work Vital to Save More Lives

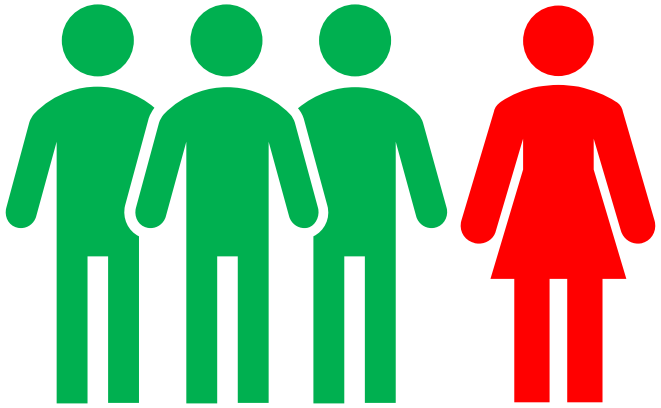
Forecast



Cancer will affect 1 in 2

Aspiration





Aspiration > 75% survival

Source – www.cancerresearchuk.org

sequani
NON CLINICAL
great people, great work, real results

Anticancer Drug Development

- ↑↑↑ of promising small molecule anticancer agents have been developed
- Few shown to be safe and efficacious in humans
- Considerable impact in Development and Human Cost
- Improved Pre-Clinical Assessment of candidates needed

sequani
NON CLINICAL
great people, great work, real results

Clinical ethics drives minimising pre-clinical toxicology

- Early stage clinical trials in cancer patients are often initiated with limited toxicology data
- A clinical trial at a dose < efficacious is undesirable
- A clinical trial producing unexpected severe toxicity is even worse

Most Commonly Used Model

Historically the Only Pre-Clinical Species

Similar to Human Genome

Variety of Genetic Models

Extensive Background Data

sequani NON CLINICAL
great people, great work, real results

Predictivity Non-Clinical to Clinical

Mouse

- Not always reliable – drugs work well at preclinical stage but ineffective in clinical trials – e.g. 9-aminocamtothecin
- Mouse bone marrow potentially less sensitive than human
- Fundamental challenge for clinical cancer drug development

sequani NON CLINICAL
great people, great work, real results

Other Species

NHP

- Likely similar bone marrow sensitivity to man
- Expensive
- Ethical concerns
- Disease status (immunosuppression)

Dog

- Possibly similar bone marrow sensitivity to man
- Prone to emesis
- Ethical concerns (charities)

Minipig

- Possibly similar bone marrow sensitivity to man
- Less prone to emesis
- High throughput – cost effective
- Reduced ethical concern

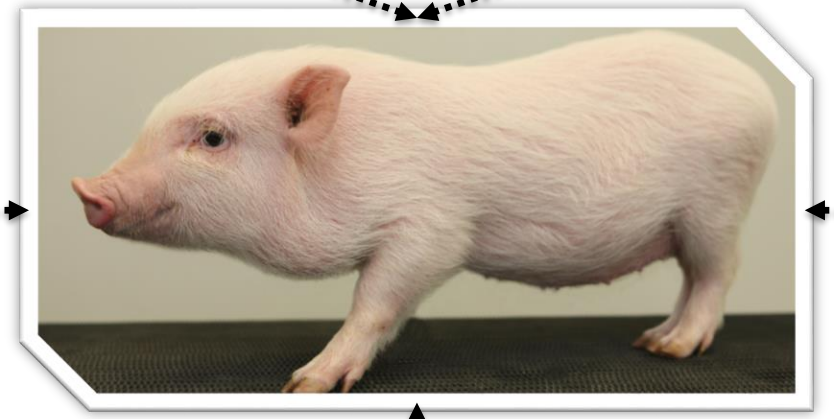
sequani NON CLINICAL
great people, great work, real results

Alternative species

Growing use – well accepted non-rodent species

Regulatory pressure to use two species

Similar to Human Genome



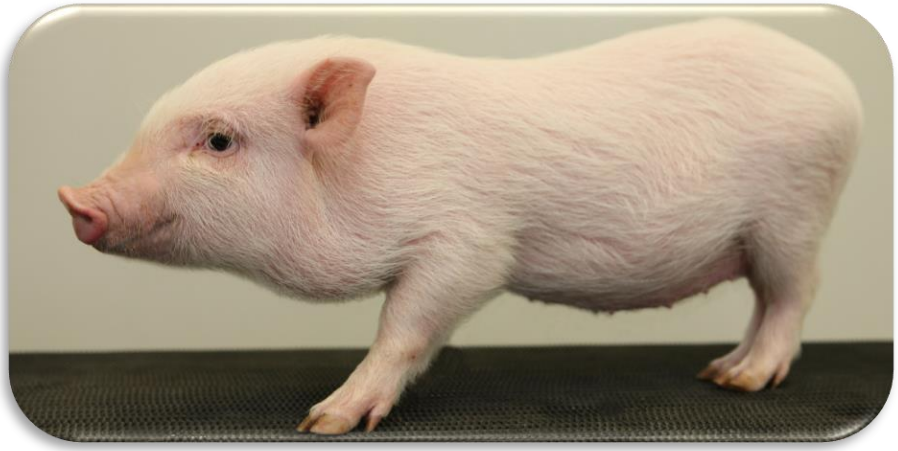
Increasing # Genetic Models

Extensive Background Data

sequani
NON CLINICAL
great people, great work, real results

STUDY DATA COMPARISON

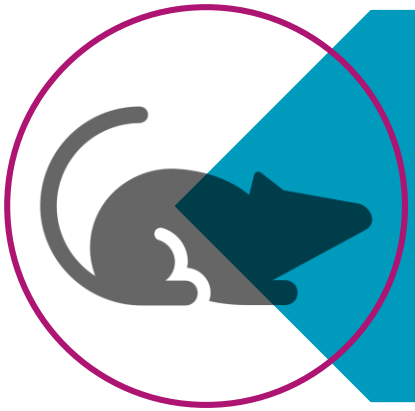
Mouse versus Minipig



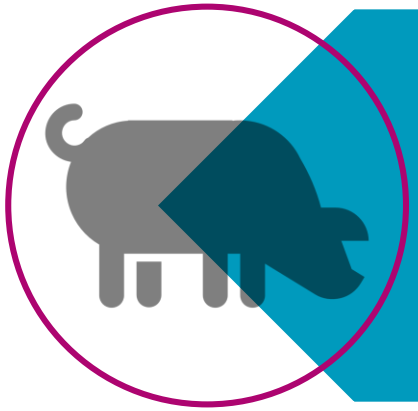
sequani NON CLINICAL
great people, great work, real results

Non-Clinical Studies conducted

Test Item : Novel Oral Anti-cancer drug (non-solid tumours)



Preliminary and 14 Day Study in the Mouse



- MTD and Range Finder in the Minipig
- 28 Day Minipig with a 28 Day Treatment-Free Period

Study Design

Group	Dose level (mg/kg bid)	Number of animals		Duration of dosing
		Males	Females	
Preliminary phase				
5	150	2	2	7 days
6	225	2	2	up to 7 days
7	100	2	2	7 days
8	125	2	2	7 days
Dose range finding phase				
1	75	12	12	14 days
2	125	12	12	12 days
3	75	3	3	14 days
4	125	3	3	13 days

Study Design - Phase 1

Group	Animal	Dose level (mg/kg bid) on Days						
		1 - 4	5 - 11	12 - 25	26 - 32	33	34 - 37	
1	Male 95	0	6	ND	9	ND	12	Necropsy (Day 34)
	Female 98	0	6	ND	9	ND	12	Necropsy (Day 37)

Study Design – Phase 2

Group	Animal Numbers		Dose (mg/kg bid)
	Males	Females	
2	97	99	6
3	101	100	9

Study Design

Group	Number of animals		Animal ID numbers		Dose level (mg/kg bid)	Dose concentration (mg/mL bid)
	Males	Females	Males	Females		
1	5	5	33 - 37	51 - 53, 57, 58	Control	0
2	3	3	38 - 40	46 - 48	3	0.6
3	5	5	41 - 45	49, 50, 54 - 56	6	1.2

sequani NON CLINICAL
great people, great work, real results

Dose Level Comparison

	Mouse	Minipig
Dose Level	mg/kg BID	
Low	75	3
High	125	6

Minipig dose levels more in line with human dose levels

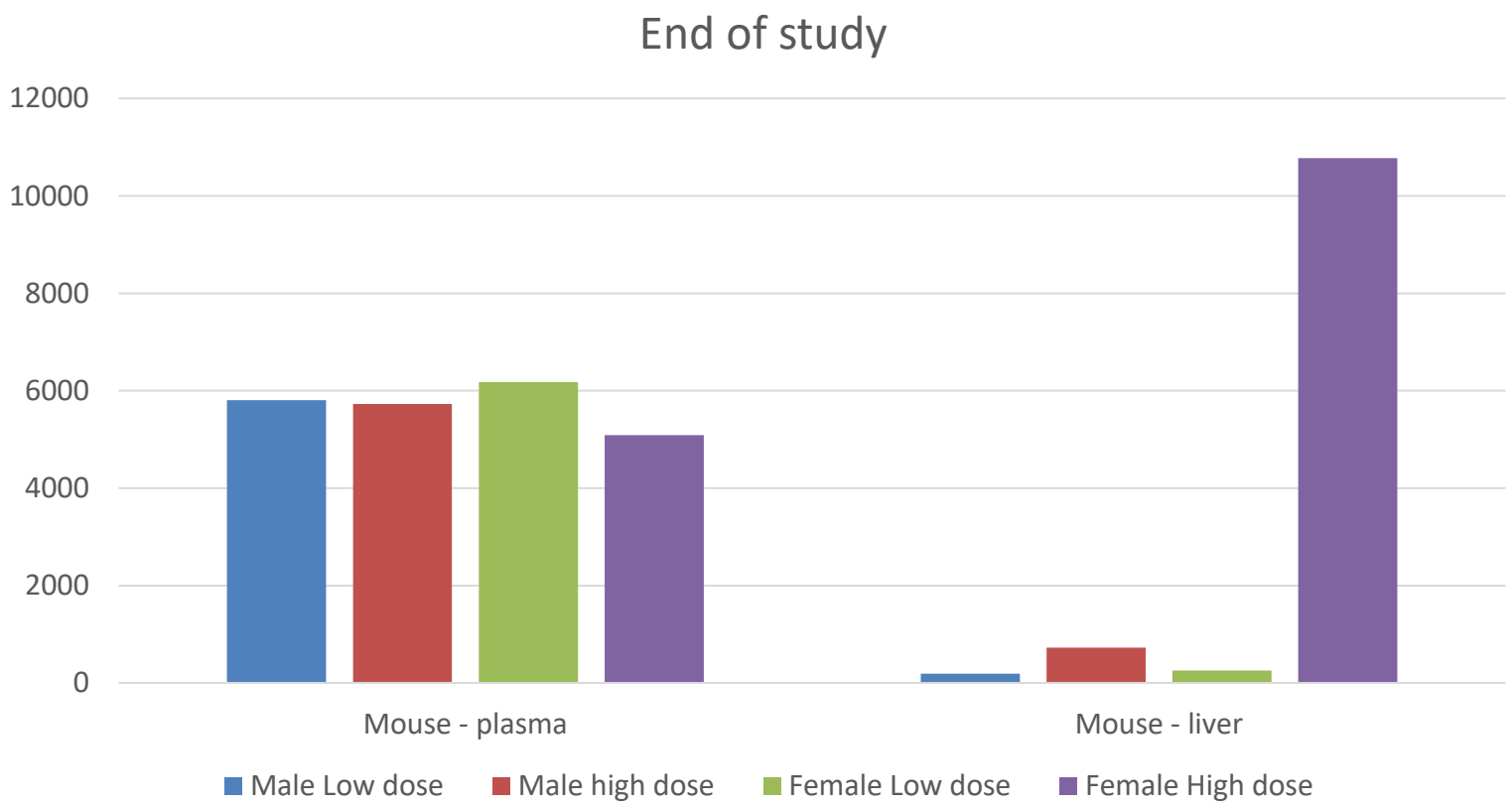
sequani NON CLINICAL
great people, great work, real results

Measured Study Endpoints

	Mouse	Minipig
Clinical Observations	post-dose and daily	post-dose and daily
Body weights	twice weekly, daily	weekly
Food consumption	twice weekly	
Ophthalmoscopy		acclimatisation and end of study
Electrocardiograms		acclimatisation and end of study
Haematology	end of study	acclimatisation and end of study **(additional 0.1 mL taken twice weekly)**
Blood Chemistry	end of study	acclimatisation and end of study
Urinalysis		at necropsy, by cystocentesis
Proof of Absorption/TK	end of study	Day 1 and Day 28
Organ weights		
Pathology		

Proof of Absorption - Mouse

Plasma and Liver concentrations

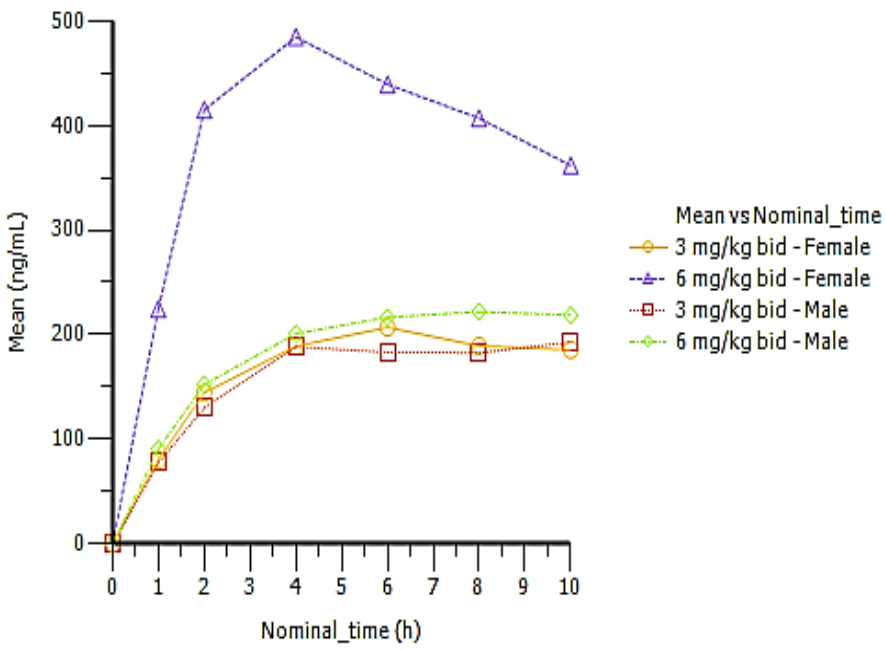


sequani NON CLINICAL
great people, great work, real results

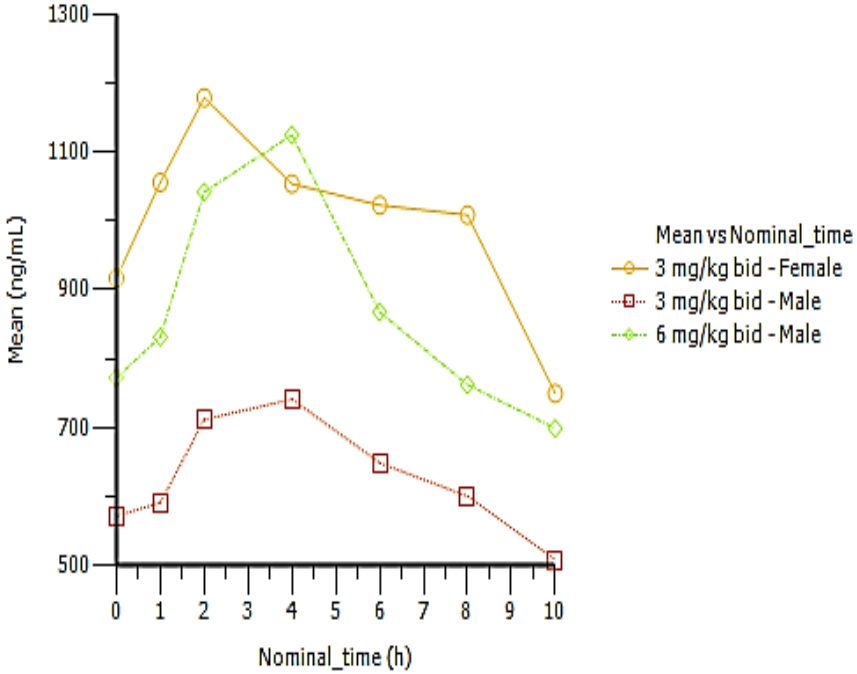
TK Data - Minipig

Mean Plasma Profiles

Day 1



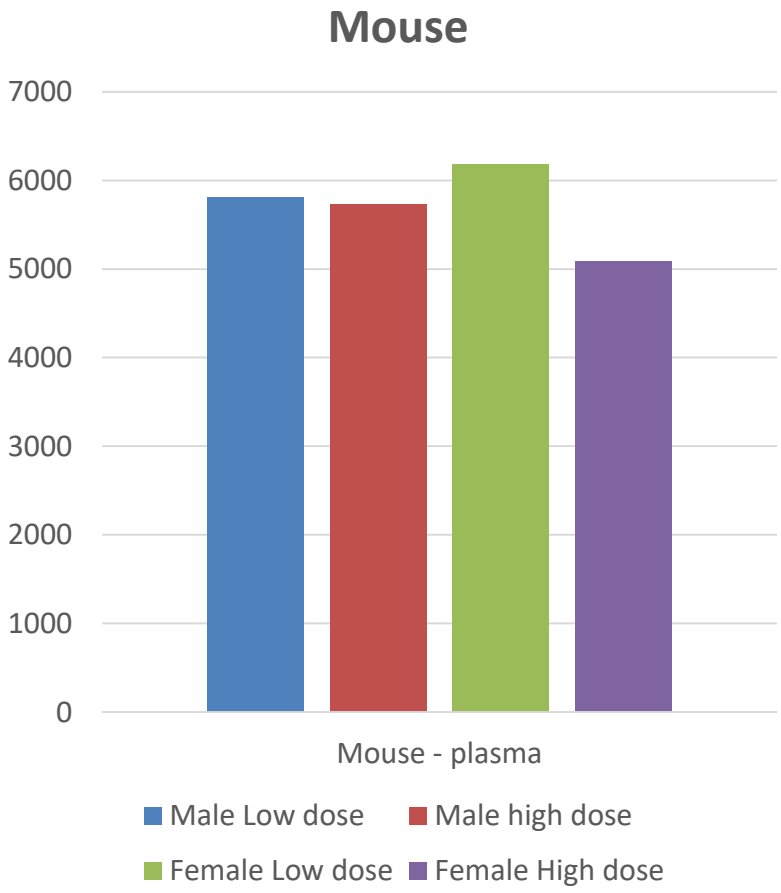
Day 28

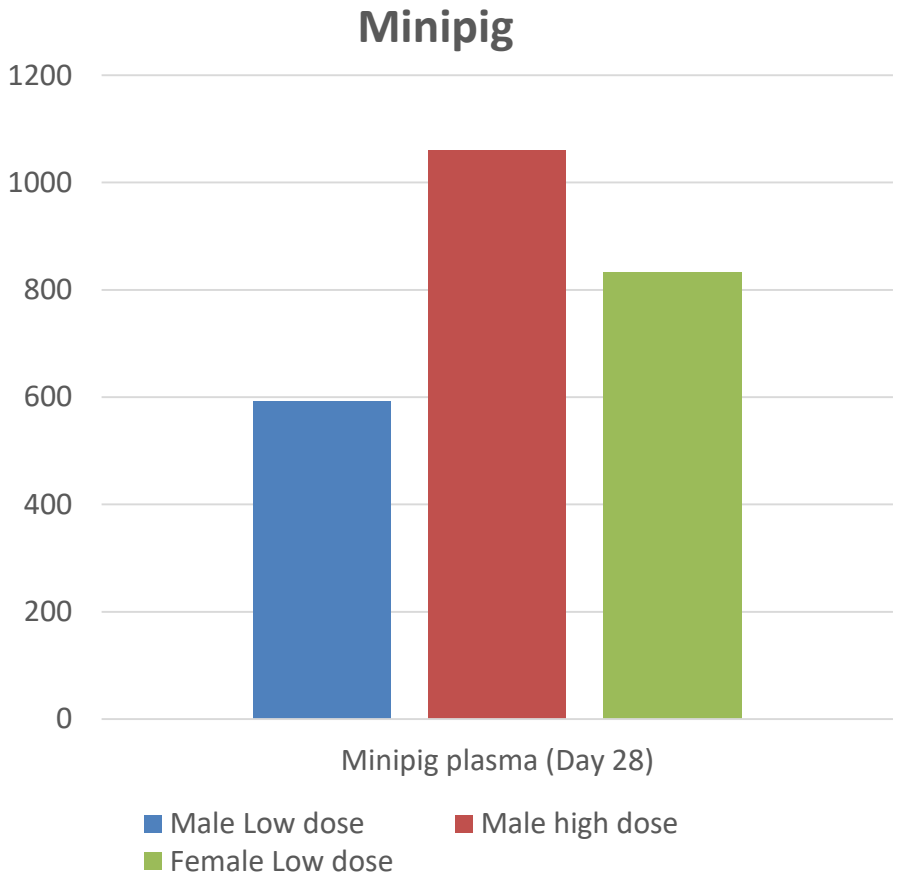


sequani NON CLINICAL
great people, great work, real results

Proof of Absorption comparison

Plasma concentrations – end of study (1 hour)





sequani NON CLINICAL
great people, great work, real results

Clinical Observations - Similarities to Human

Mouse

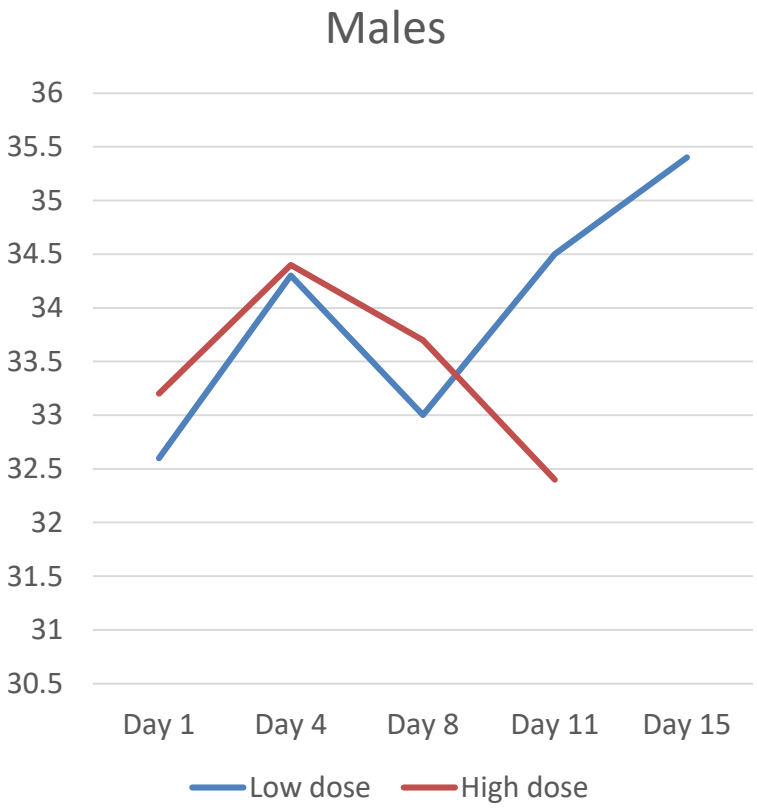
- Piloerection
- Pale Extremities
- Decreased Activity
- Hunched Posture

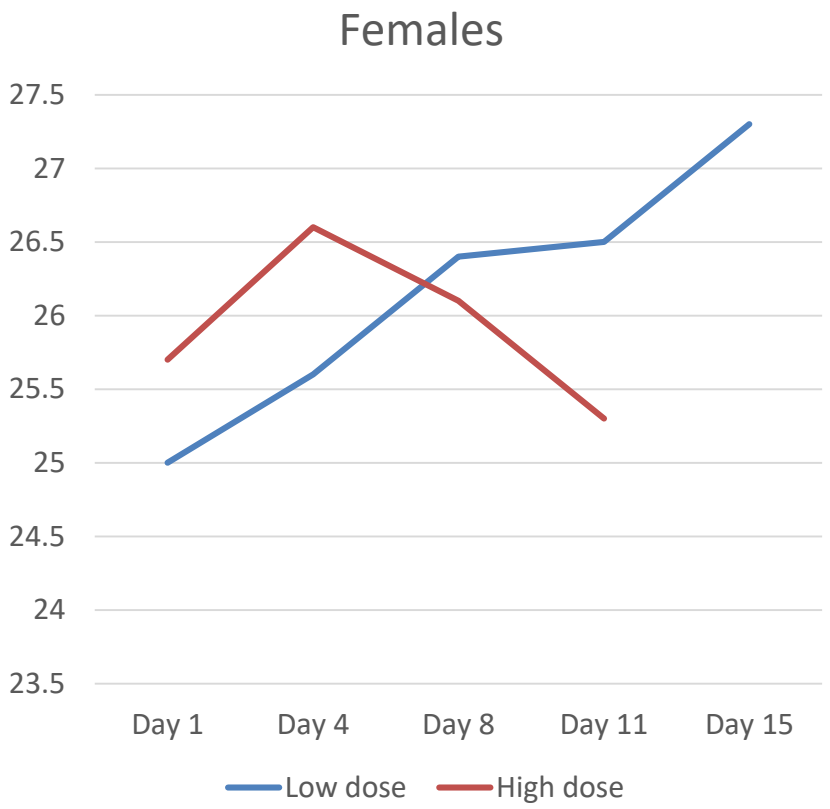
Minipig

- Tremors
- Vomiting
- Subdued Behaviour

In-Life Findings – Body weights

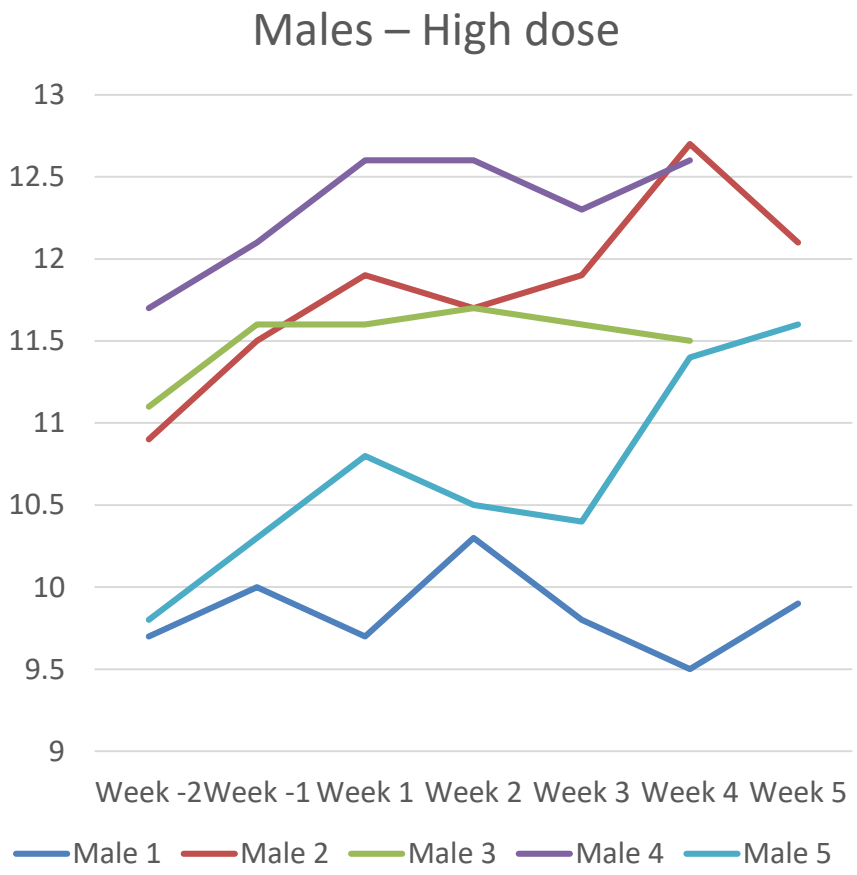
Mouse

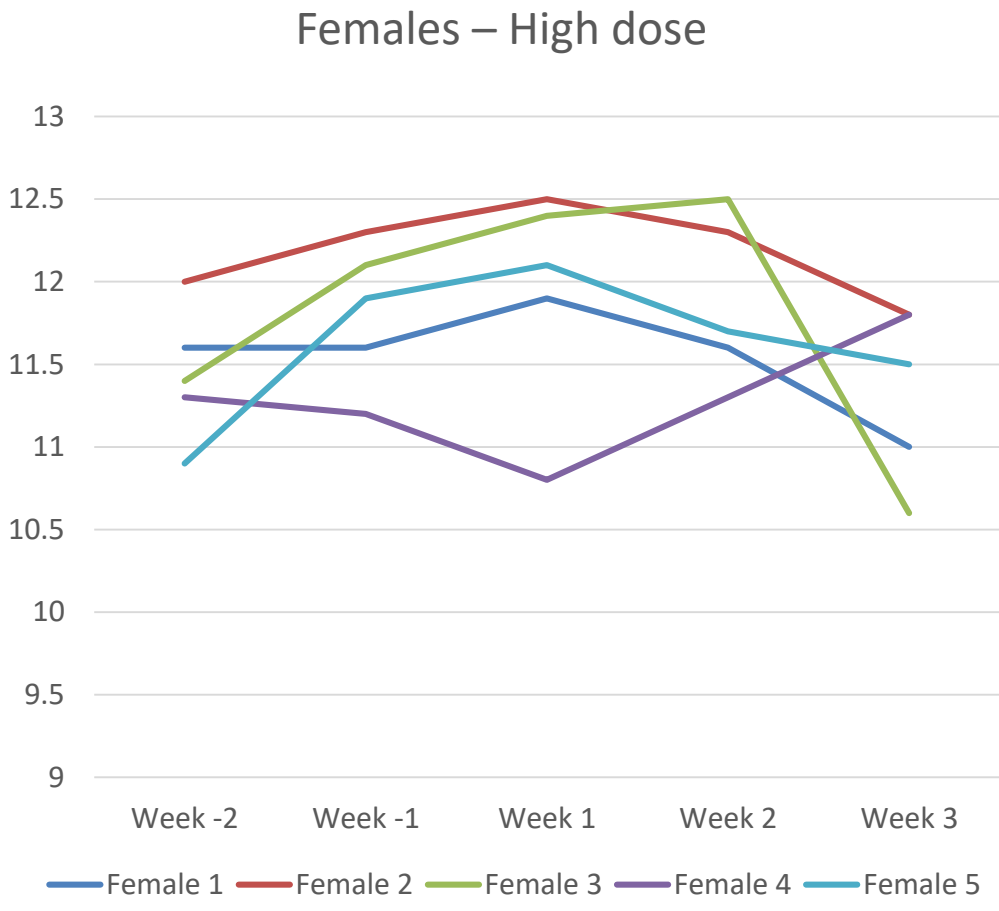




In-Life Findings – Body weights

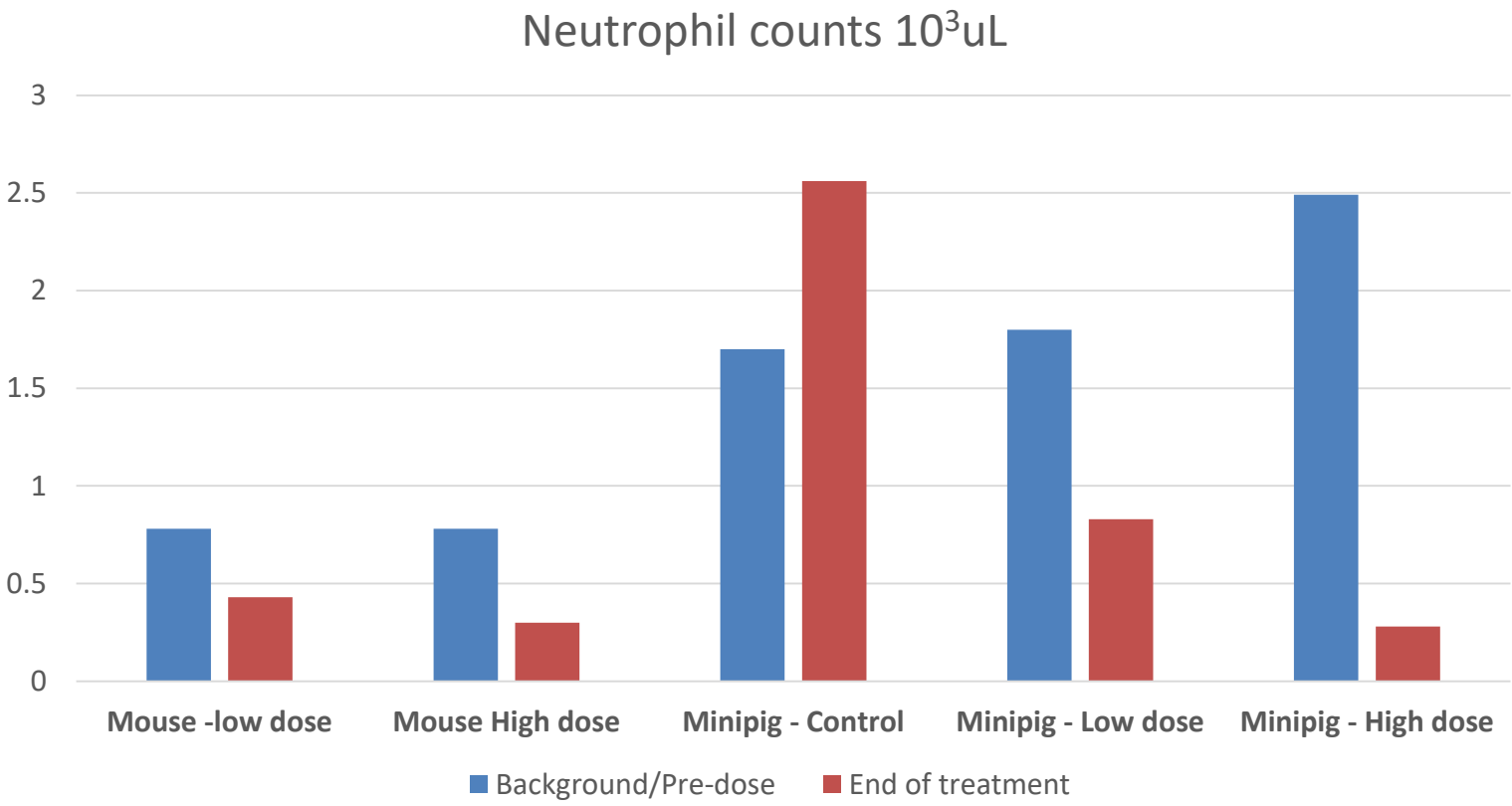
Minipig





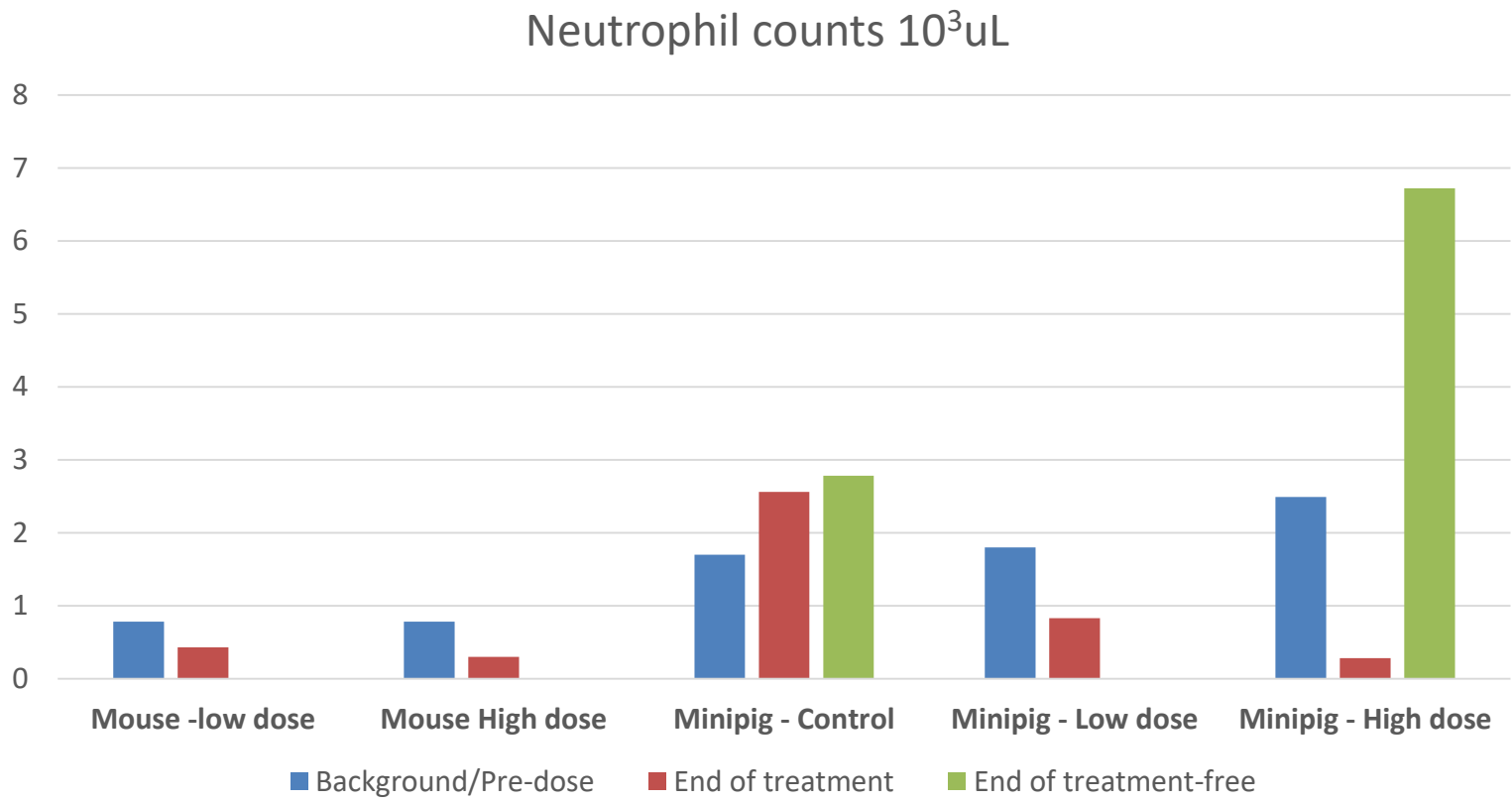
sequani NON CLINICAL
great people, great work, real results

Clinical Pathology Results - Males

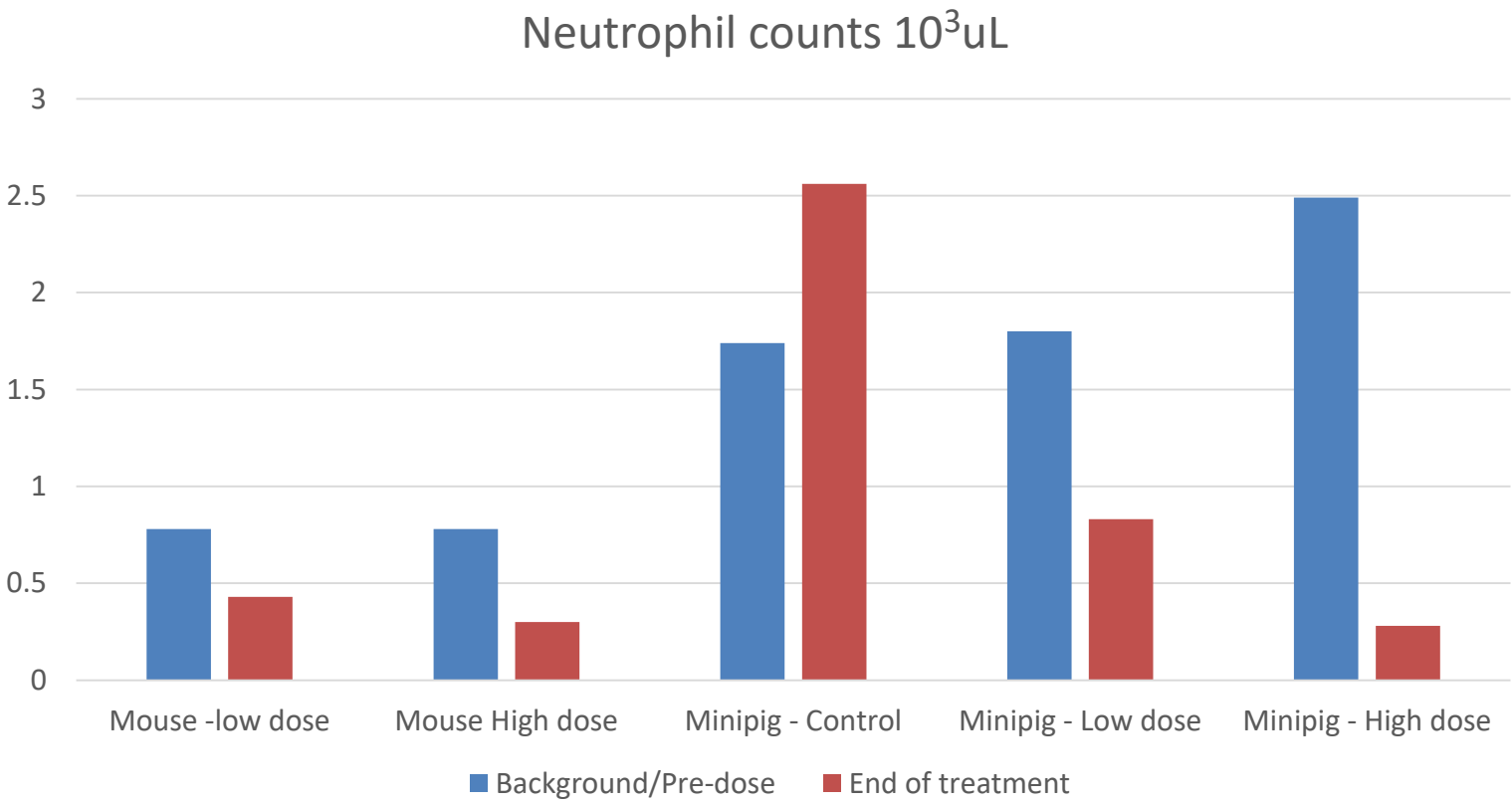


sequani NON CLINICAL
great people, great work, real results

Clinical Pathology Results - Males

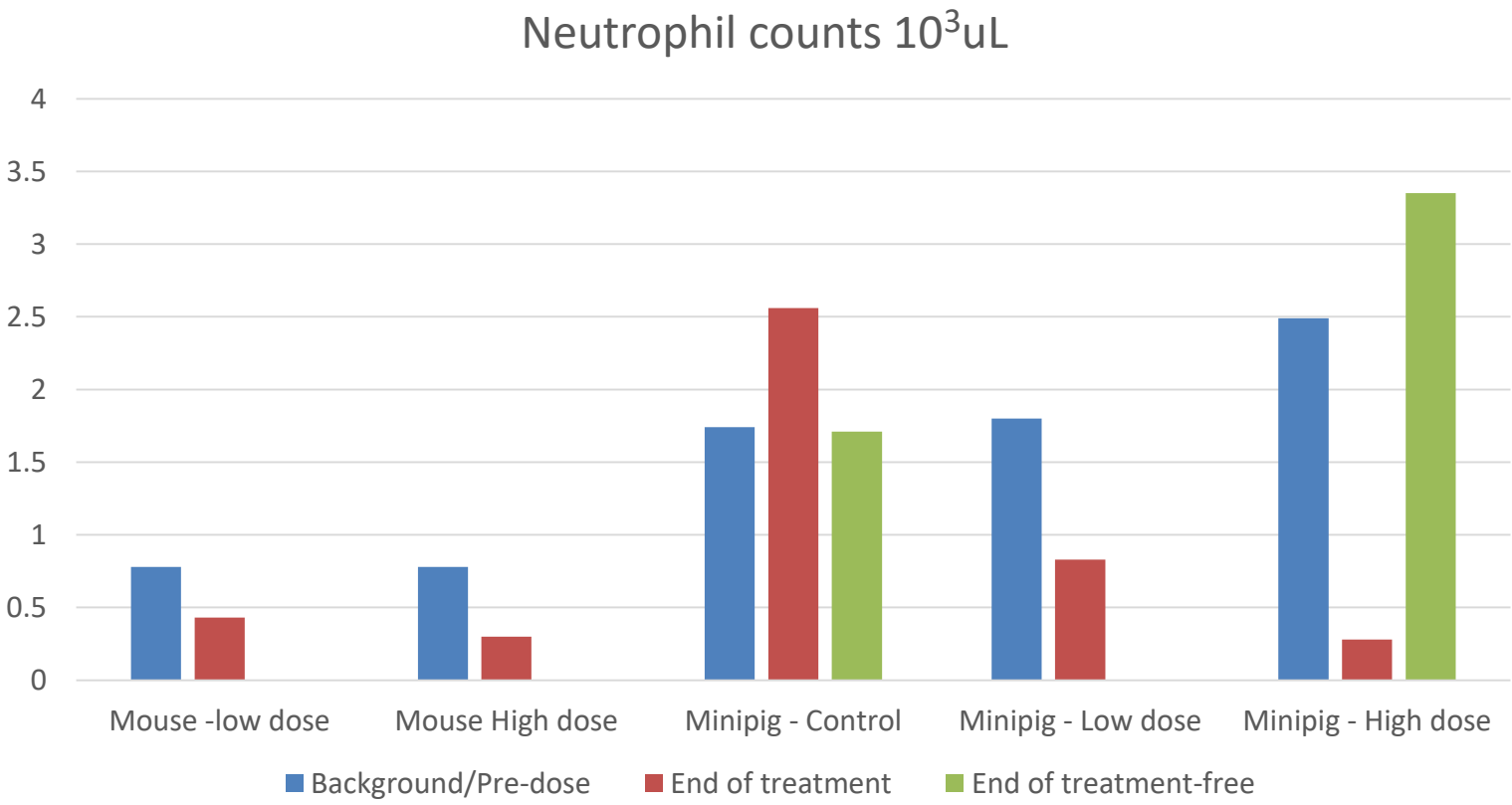


Clinical Pathology Results - Females



sequani NON CLINICAL
great people, great work, real results

Clinical Pathology Results - Females

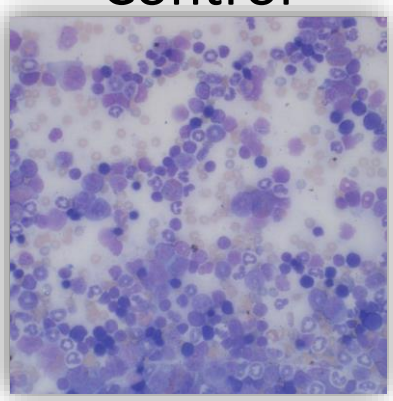


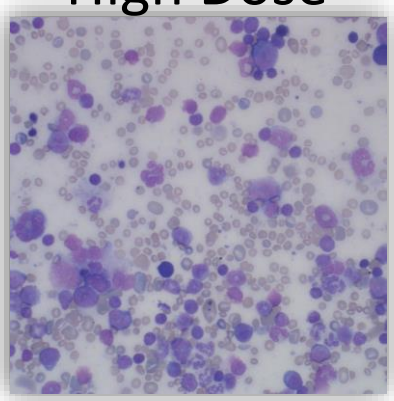
sequani
NON CLINICAL
great people, great work, real results

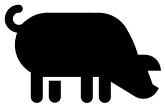
Bone Marrow Smear

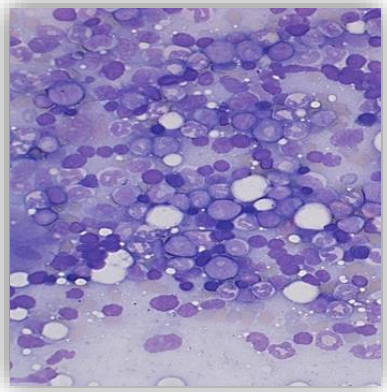
Control

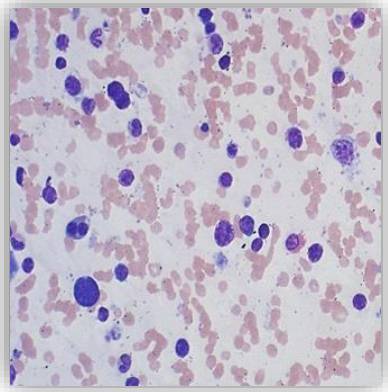
High Dose









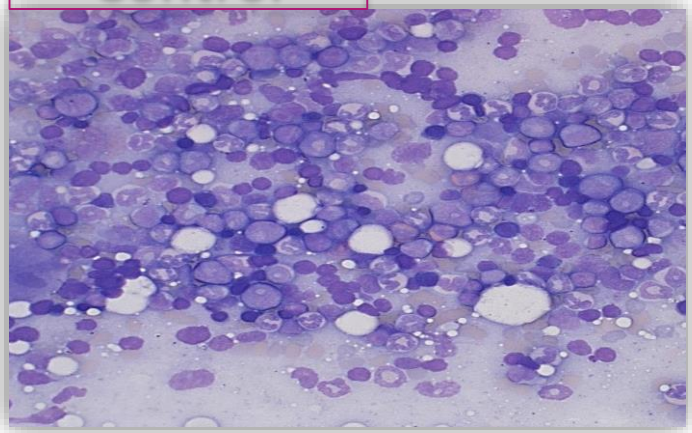


sequani NON CLINICAL
great people, great work, real results

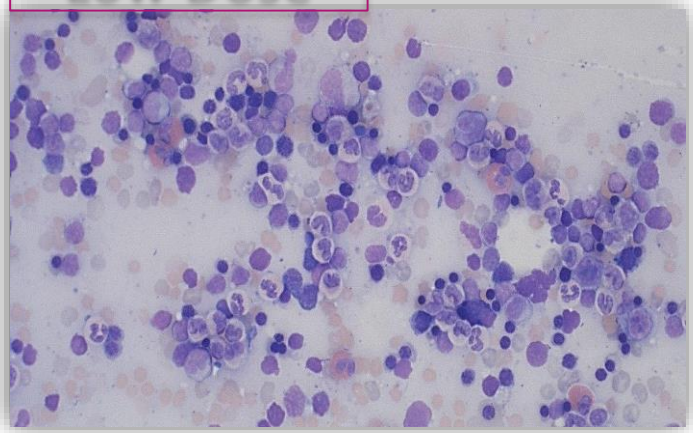
Bone Marrow Smear Depletion

Minipig

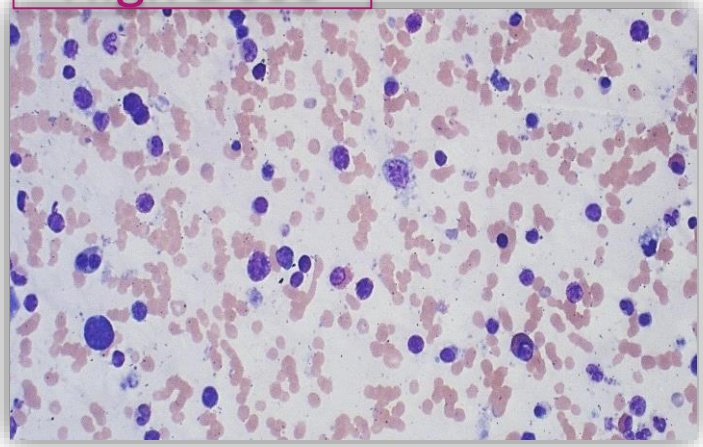
Control



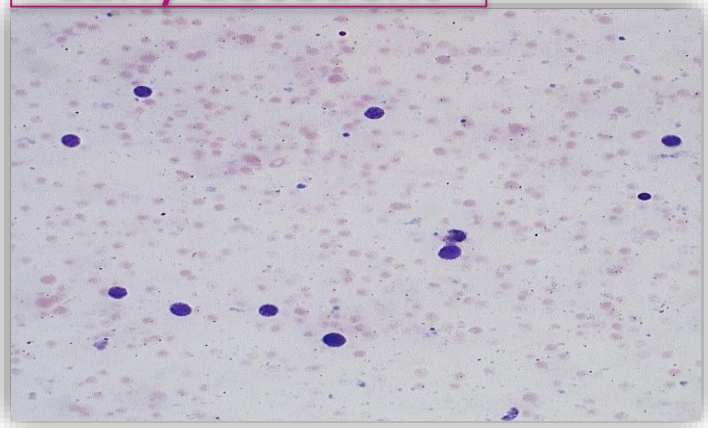
Low Dose



High Dose

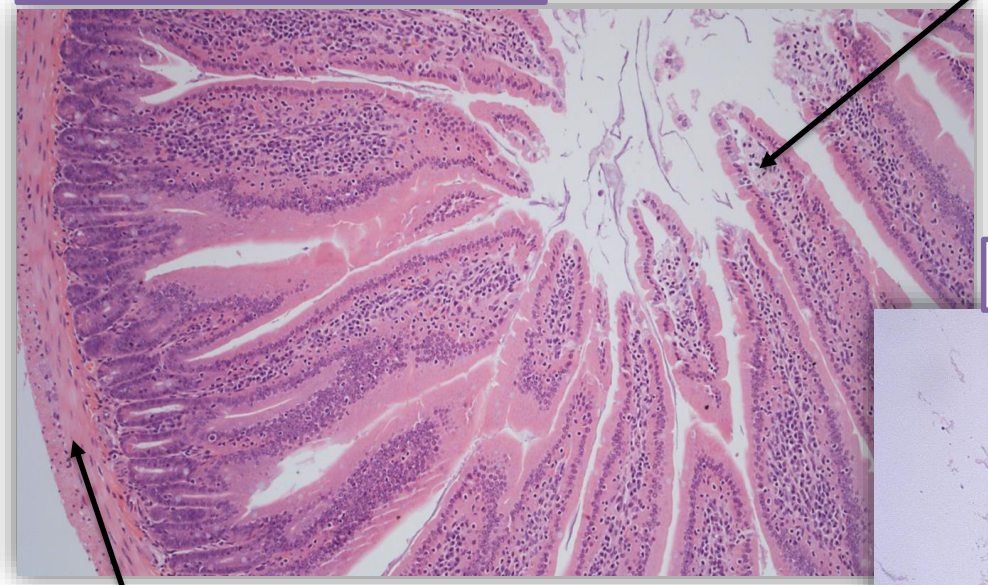


Early decedent



Mouse Pathology

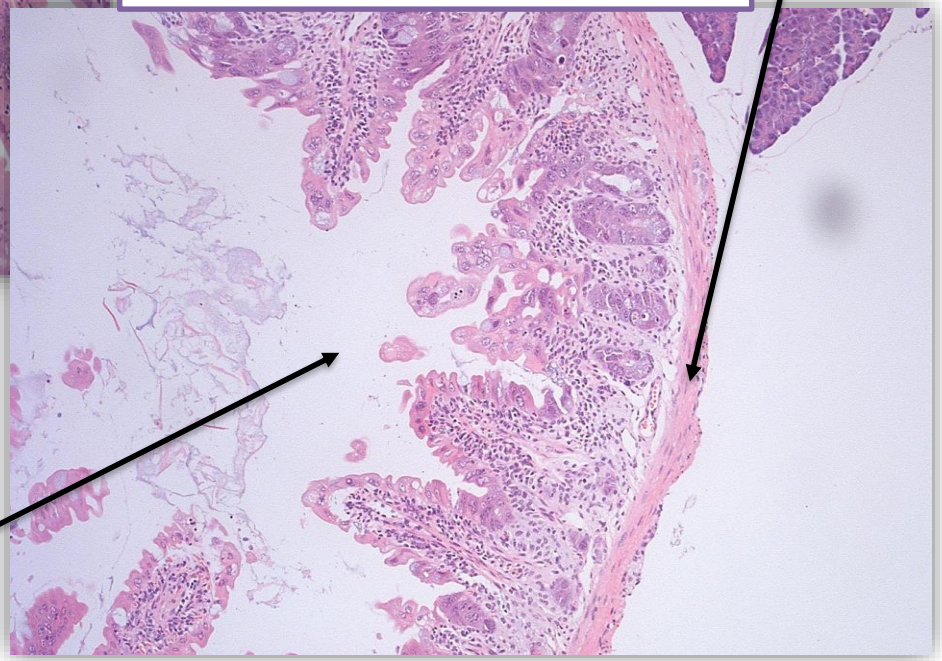
Control mouse- duodenum



Villi protruding into centre region

Crypt cells, nicely basophilic

Treated mouse - duodenum



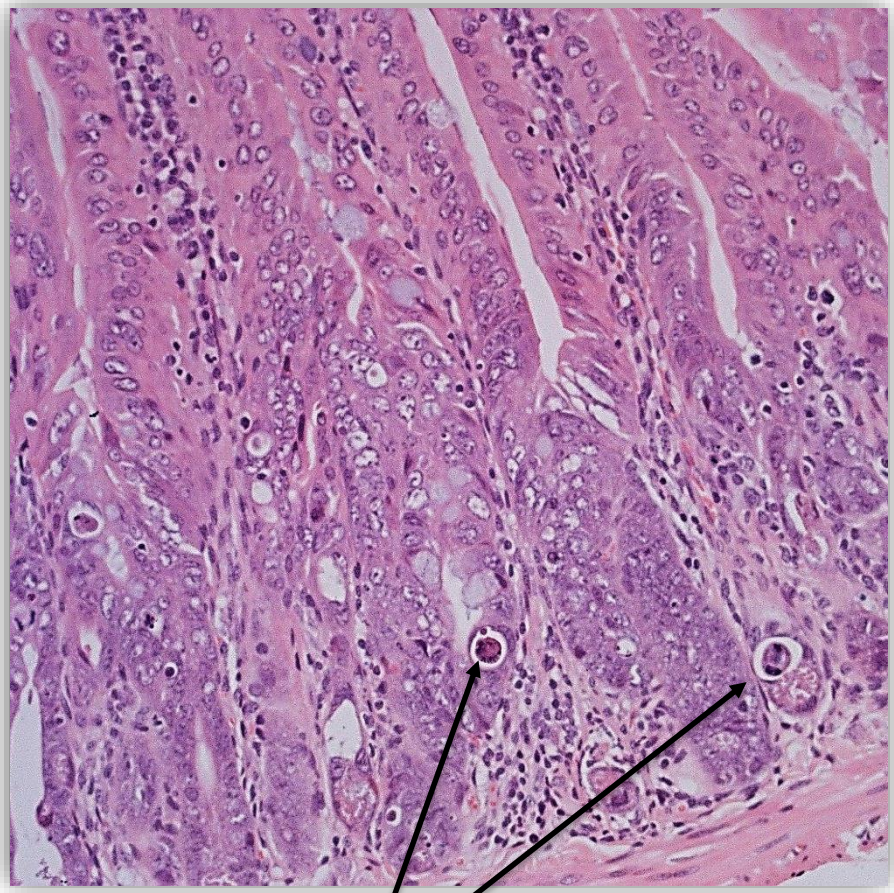
Very little basophilia

No/limited replenishment of cells

sequani NON CLINICAL
great people, great work, real results

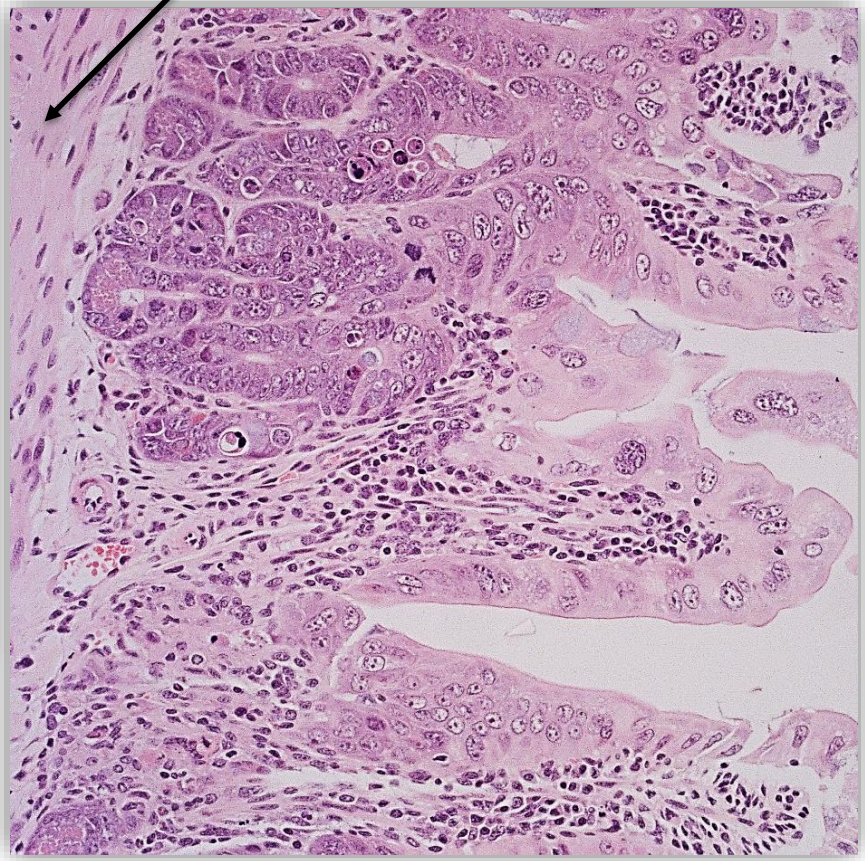
Pathology

Treated mouse – duodenum



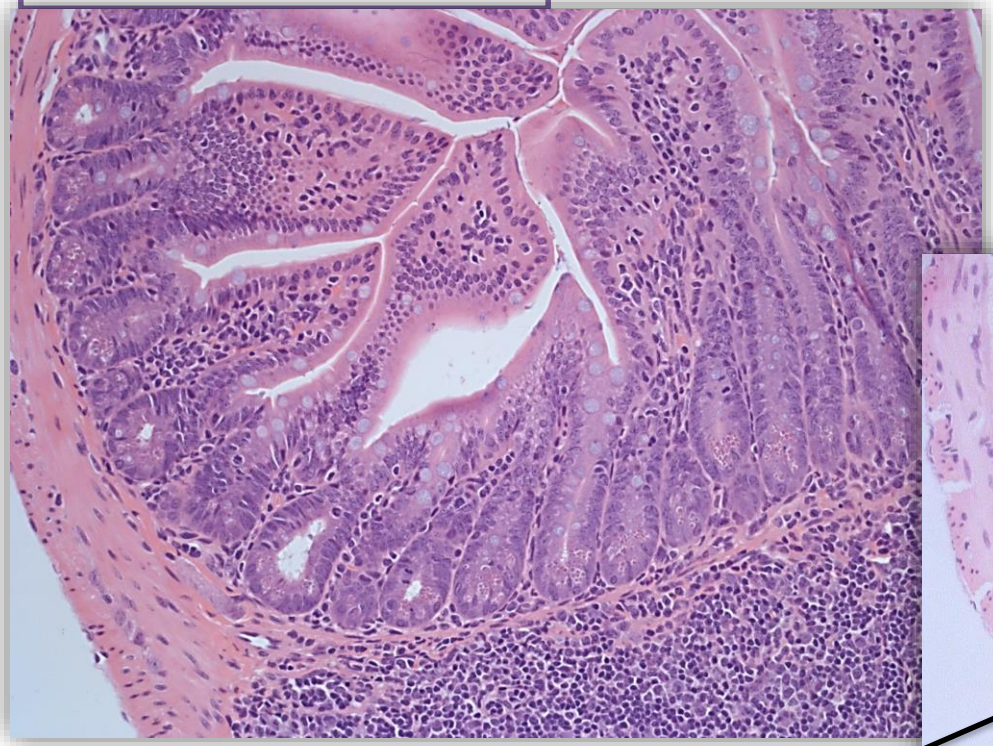
Apoptopic bodies

Crypt region knocked out

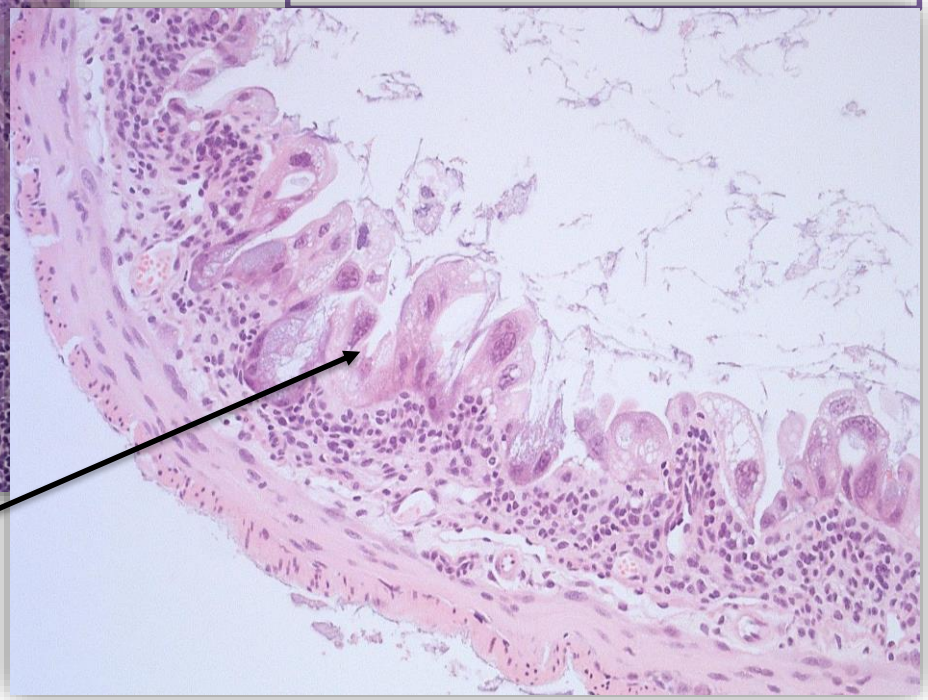


Mouse Pathology

Control mouse- ileum



Treated mouse – ileum



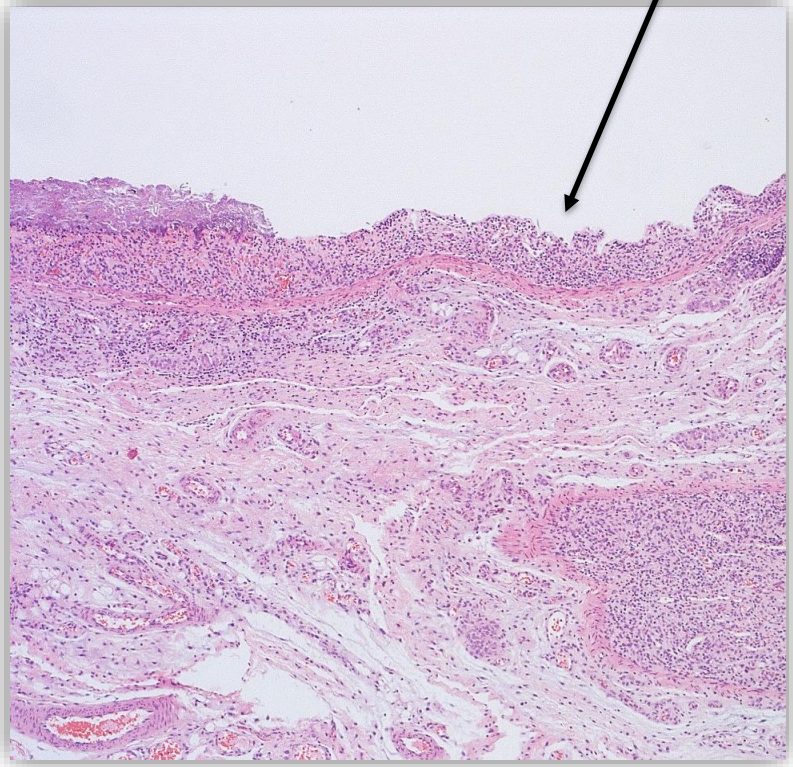
Abnormally shaped nuclei and abnormal cell turnover

Pathology - Minipig

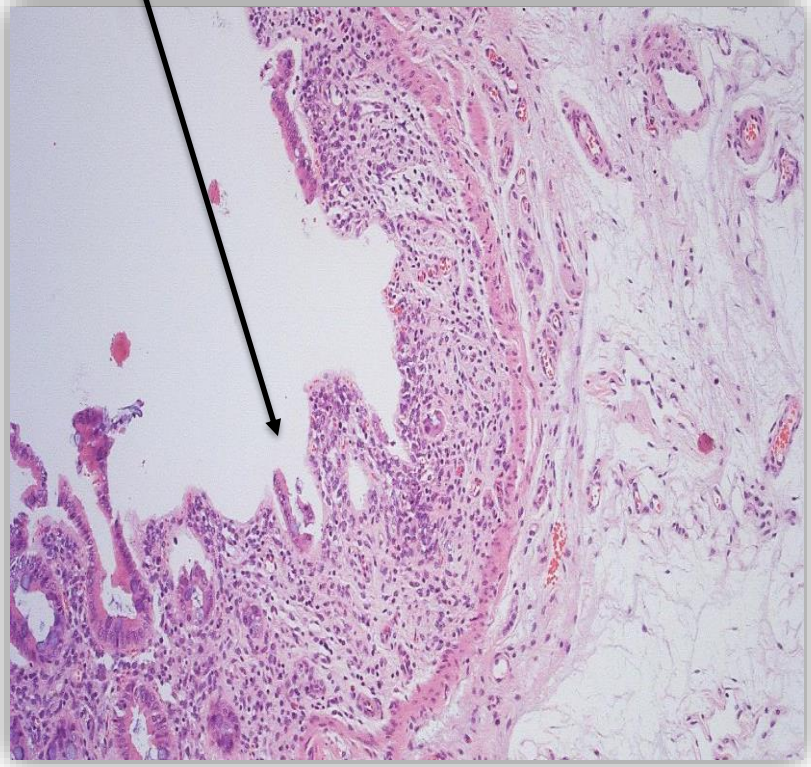
Minipig Pathology

Surface focal erosions

Caecum



Colon



sequani NON CLINICAL
great people, great work, real results

Longer duration repeat dose toxicity study

- Animals closely monitored (haematology) and taken off dose when necessary
- Clinical signs and pathology similar to man
- Haematology: reduction in total white cell count (neutropenia, lymphocytopenia)
  → changes fully reversible
- Main pathology: bone marrow and intestines
- There were <u>non-responders</u> on the study!

sequani NON CLINICAL
great people, great work, real results

Clinical use in humans

- Expected dose levels similar to those selected for minipigs, mice > 10x higher
- Main pathology in humans:
  Haematology and bone marrow
- Responders and non-responders (man and minipig)

sequani NON CLINICAL
great people, great work, real results

Pros and Cons

	Pros		Cons	
	Minipig	Mouse	Minipig	Mouse
Pre-clinical cost		√	√	
Additional Haematology monitoring	√			√
Similarity to humans :-				
Clinical signs	√			√
Haematology effects	√			√
Bone marrow effects	√			√

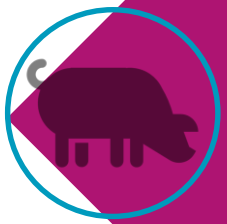
Overall Conclusions

most frequently used model for anticancer drugs.

frequent disappointments when moving into clinical trials.

high cost in both financial and human terms of clinical failures.

better preclinical model is called for.



offers a viable non-rodent species or alternative to commonly used rodent models.

monitor parameters throughout the study.

although the initial cost is higher

outweighed by improved prediction of clinical efficacy.

sequani
NON CLINICAL
great people, great work, real results

Acknowledgements

Client for allowing me to share the data

Ellegaard

Sequani Personnel

sequani
NON CLINICAL
great people, great work, real results

Thank you for your Attention

Easy Questions ????