

BUILDING AN INTEGRATED PRE-CLINICAL AND CLINICAL DATA PLATFORM TO ENABLE RAPID TRANSLATIONAL DATA REVIEW

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WHY IS THIS IMPORTANT?

- Translational evaluation of historical data can streamline, support and enhance program planning and provide critical insights from early discovery to post marketing of drugs
 - The information should flow both ways
 - Avoiding the “valleys of death”^{1,2}
- Data sharing initiatives happening in many industries
 - Prevention of data stagnation, being inaccessible in internal archives or databases
- Need for longitudinal review
 - Assessment of toxicity or adverse events doesn’t end
- FDA’s new outlook on animal experiments
 - Requirements shifting
 - Legacy and current animal data value increasing

1. Fernandez-Moure, JS Lost in Translation: The Gap in Scientific Advancements and Clinical Application, doi:10.3389/fbioe.2016.00043

2. Seyhan, AA Lost in translation: the valley of death across preclinical and clinical divide –identification of problems and overcoming obstacles, doi.org/10.1186/s41231-019-0050-7

THE CHALLENGE

TRANSLATIONAL SAFETY ASSESSMENT



SCALE OF DATA

The longer a development path or testing program – the more data produced



FORMAT OF DATA

Data comes in all different sizes and formats



INTERPRETATION OF DATA

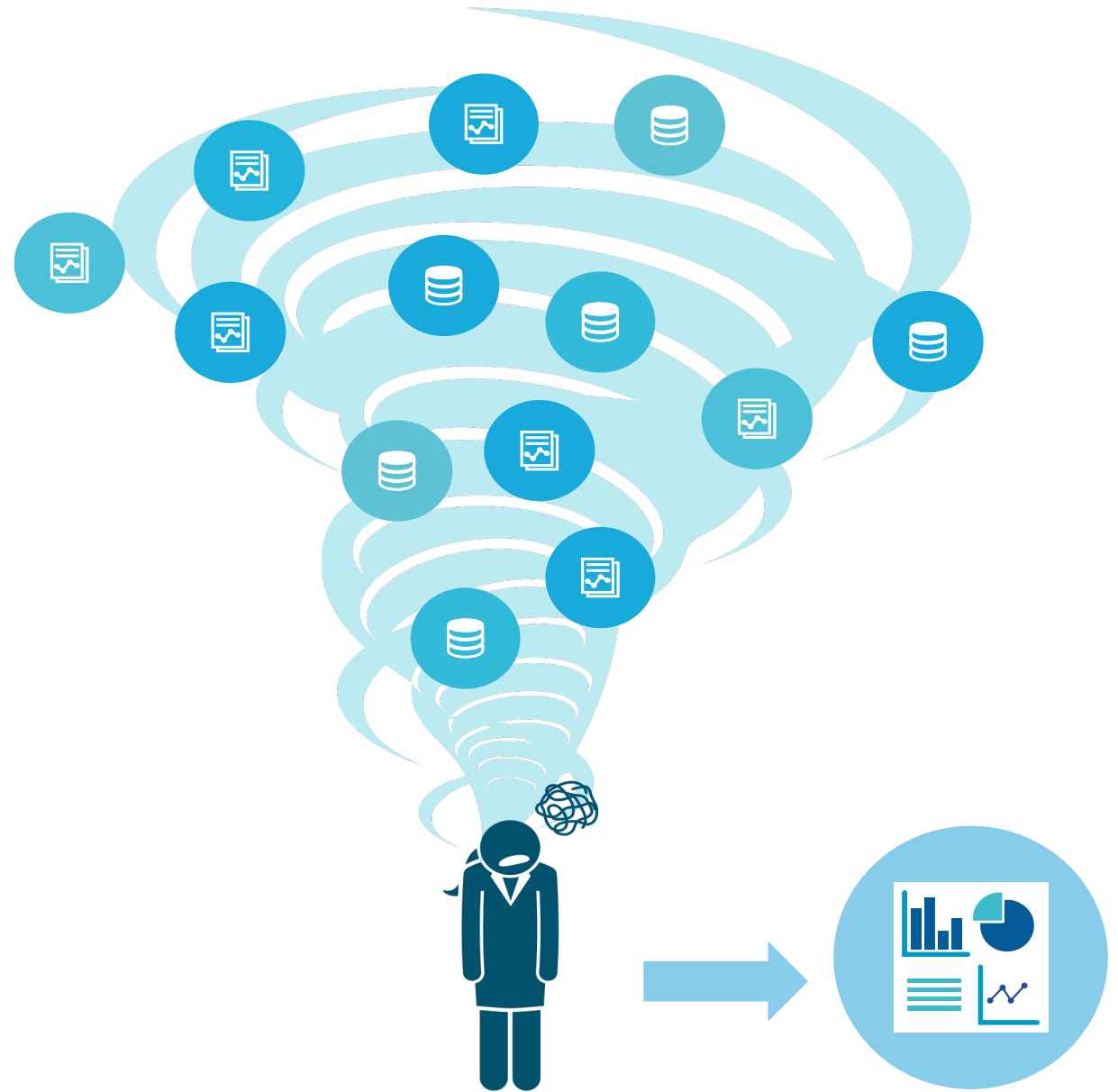
Joining information together is time intensive and requires expertise

THE RESULT?

DATA WHIRLPOOL

All of the data needs to be collected, organized and interpreted by the scientist to be presented coherently.

HOW CAN THIS BE IMPROVED?



A SYSTEM WITH MULTIPLE TOOLS AND DATABASES



Multiple Databases

Databases of different data types:

- Clinical
- Preclinical
- Public
- Private



Vocabulary Engine

Uses multiple ontologies to translate between terms
“...the first attempt to systematically map semantic concepts between preclinical and clinical data related to toxicity”*



Data Review

Tools to search databases and visualise information as tables, heatmaps and graphs



Text Mining

Use machine learning to harvest interpretation data from reports

* The eTRANSafe Project on Translational Safety Assessment through Integrative Knowledge Management: Achievements and Perspectives
<https://www.mdpi.com/1424-8247/14/3/237>

WHAT WOULD AN IDEAL BE?

DATA JOCKEY

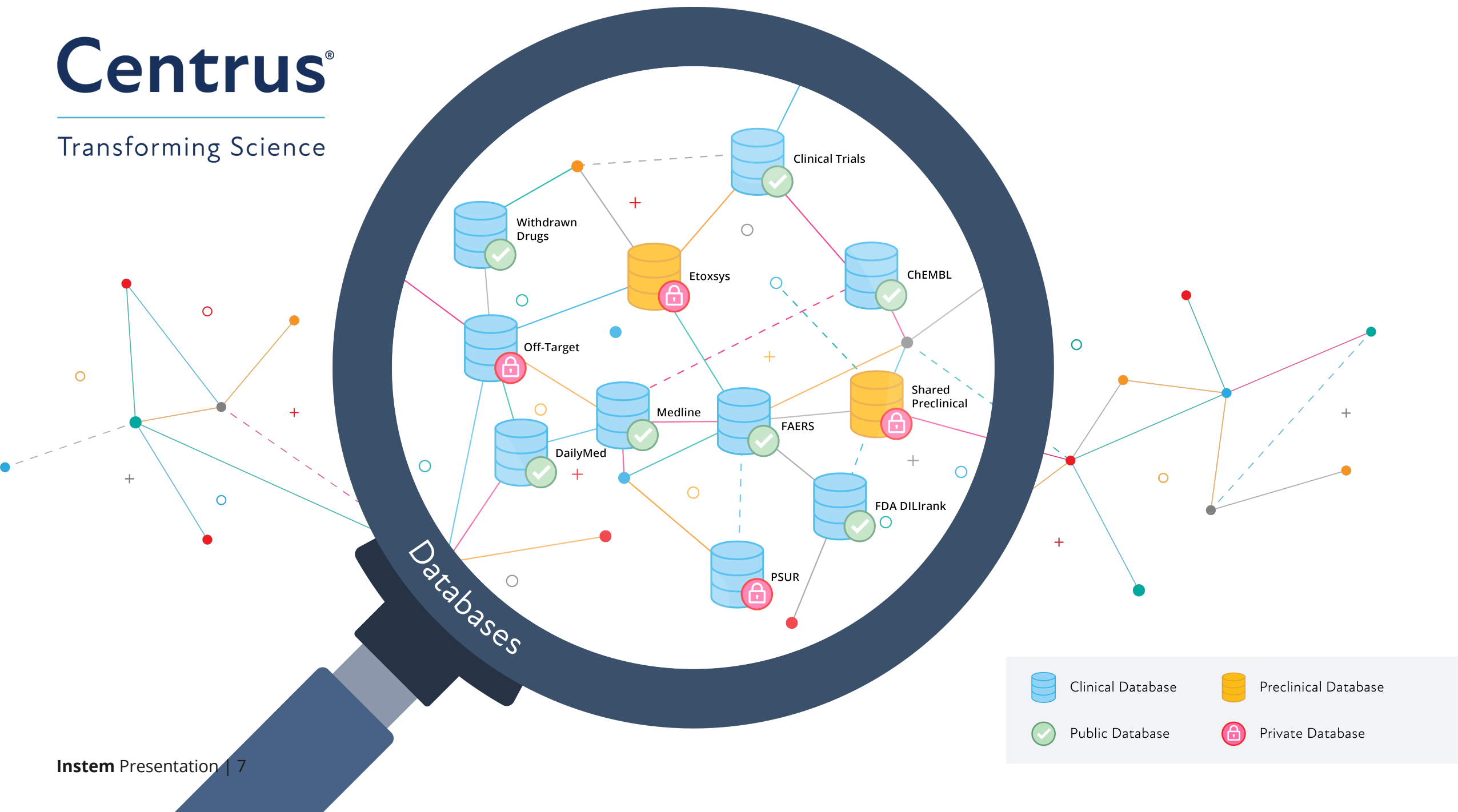
Coherent presentation and review of data allowing the scientist to focus on using that data to get to where they need to be in their assessments.

WHAT WOULD SUPPORT THIS?



Centrus[®]

Transforming Science



CLINICAL AND PRECLINICAL INTERPRETATION



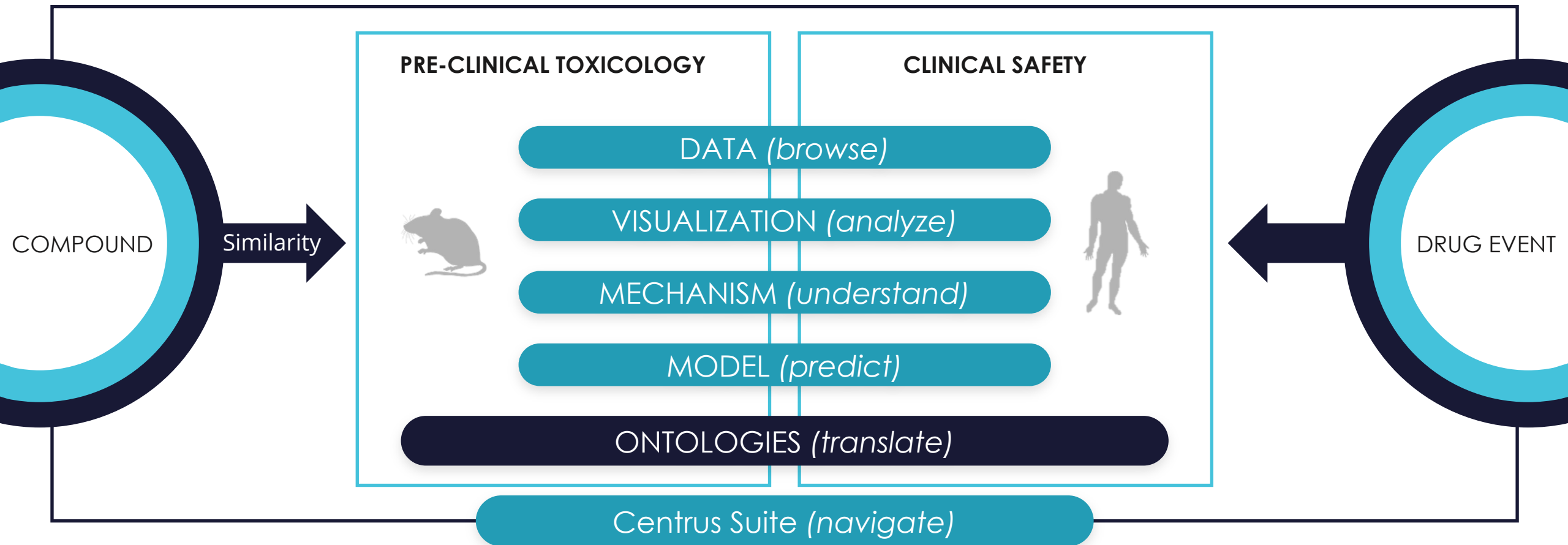
Hello!



Hold!



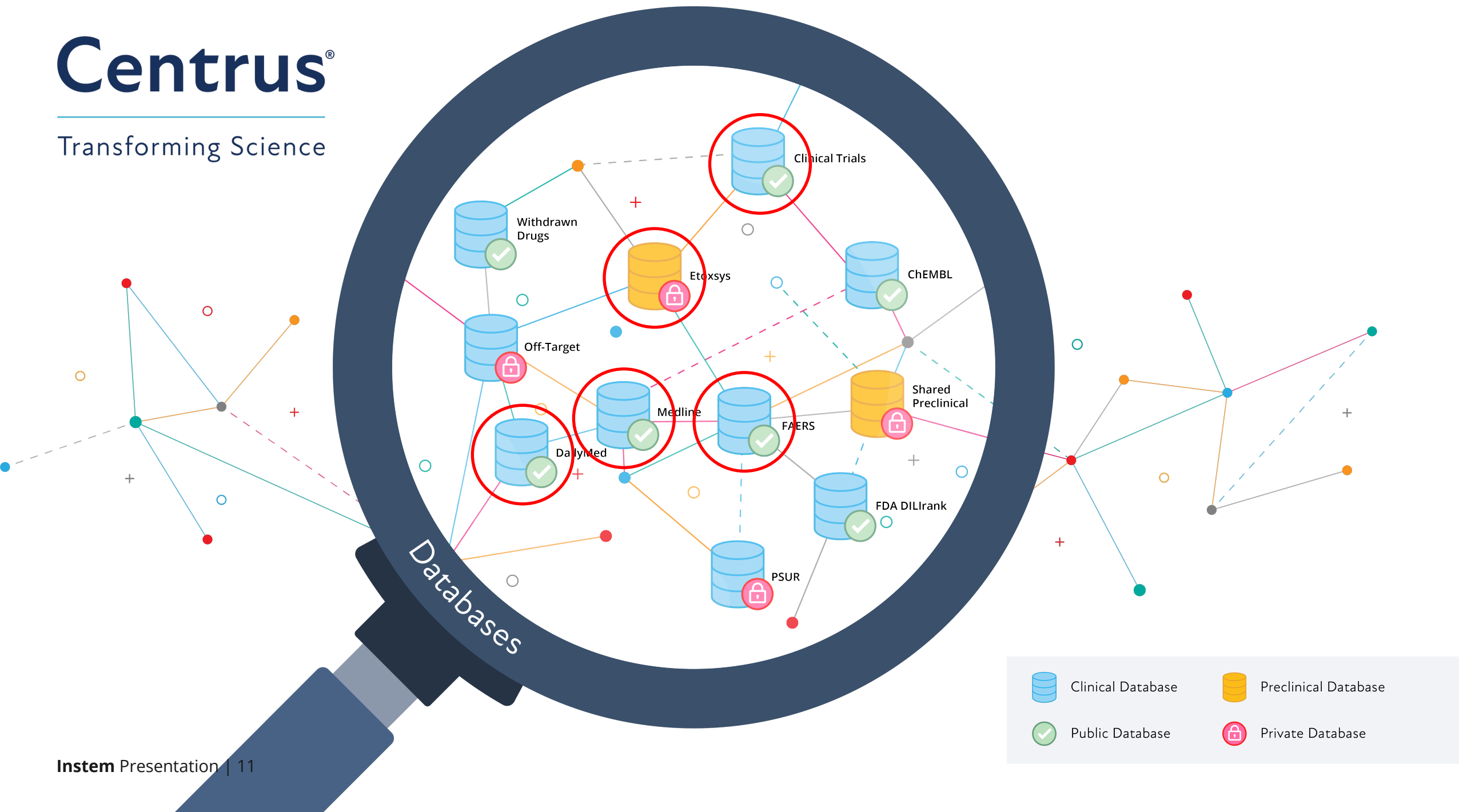
SUITE OVERVIEW



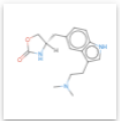
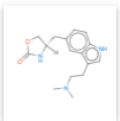
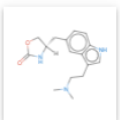
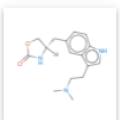
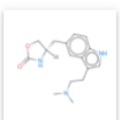
CASE STUDY

- Drug development does not occur from scratch every time
- Potential benefit in modifying existing compounds or using similar compounds or targets
- If developing something similar understanding the findings for this marketed product could help plan your programme, choose most-relevant species
- Example – selective 5-HT receptor agonist
- Review data for marketed drug - Zomig®

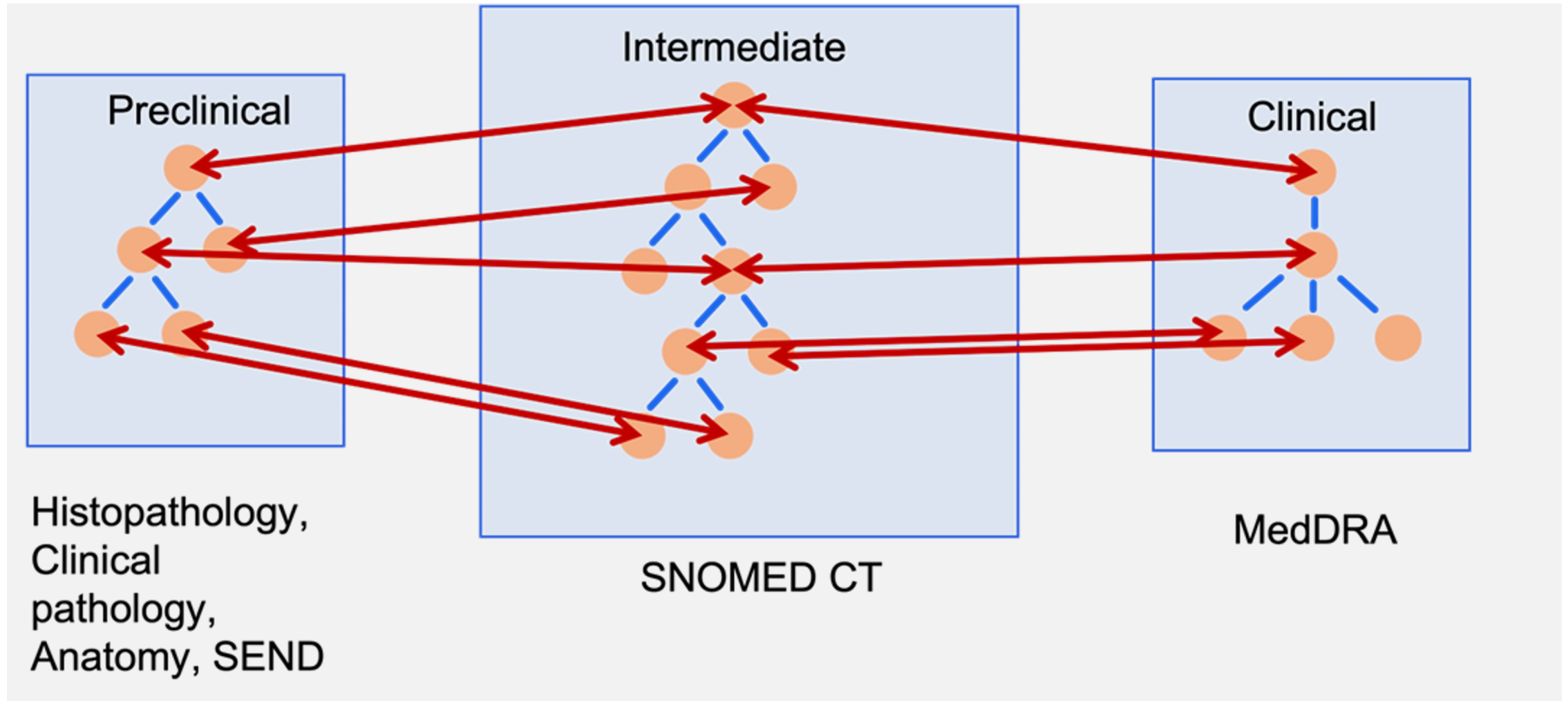




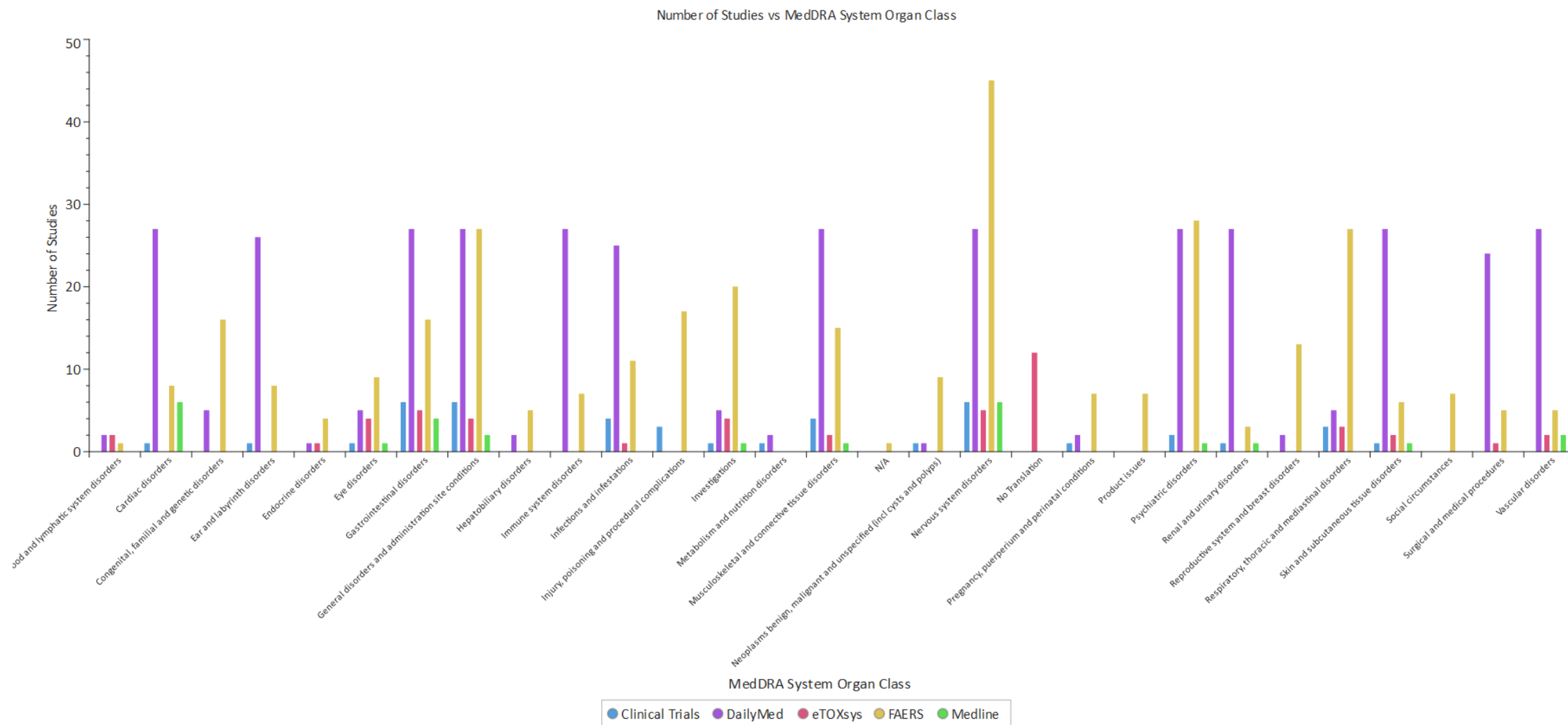
SEARCH RESULTS

Save query Excel Copy to clipboard Open in Sirona Send to Flame								
☐	Name	Structure	Compound ID	Organisation	Confidentiality	Source DB	Studies	
☐	zolmitriptan		135775	N/A	FULLY_SHAREABLE	Medline	Human: 20	
☐	zolmitriptan		135775	N/A	FULLY_SHAREABLE	Clinical Trials	Human: 8	
☐	ZOLMITRIPTAN		135775	N/A	FULLY_SHAREABLE	FAERS	Human: 327	
☐	ZOLMITRIPTAN		135775	N/A	FULLY_SHAREABLE	DailyMed	Human: 27	
☐	Zolmitriptan				FULLY_SHAREABLE	Etoxsys database	Rat: 11 Monkey: 2 Dog: 5 Mouse: 2	

UNIFYING ONTOLOGY



SYSTEM ORGAN CLASS GROUPINGS ACROSS DATABASES



SIRONA INVESTIGATIONS

Initial review – high level MedDRA SOC overlap between databases.

Measurement:
Compound:
Structure:
Database:
Number of Events:
zolmitriptan

MedDRA System Organ Class	CLINICAL	PRECLINICAL	CLINICAL
Blood and lymphatic system disorders	7	10	3
Cardiac disorders	144		174
Congenital, familial and genetic disorders	5		101
Ear and labyrinth disorders	31		186
Endocrine disorders	1	10	16
Eye disorders	16	272	107
Gastrointestinal disorders	477	3147	153
General disorders and administration site conditions	1613	136	442
Hepatobiliary disorders	2		80
Immune system disorders	81		50
Infections and infestations	54	4	139
Injury, poisoning and procedural complications	3		553
Investigations	12	45	157
Metabolism and nutrition disorders	5		
Musculoskeletal and connective tissue disorders	19	45	234
N/A			3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1		61
Nervous system disorders	675	269	2146
No Translation		23412	
Pregnancy, puerperium and perinatal conditions	1	2	43
Product issues			73
Psychiatric disorders	7	170	443
Renal and urinary disorders	7	84	65

EXCLUDE

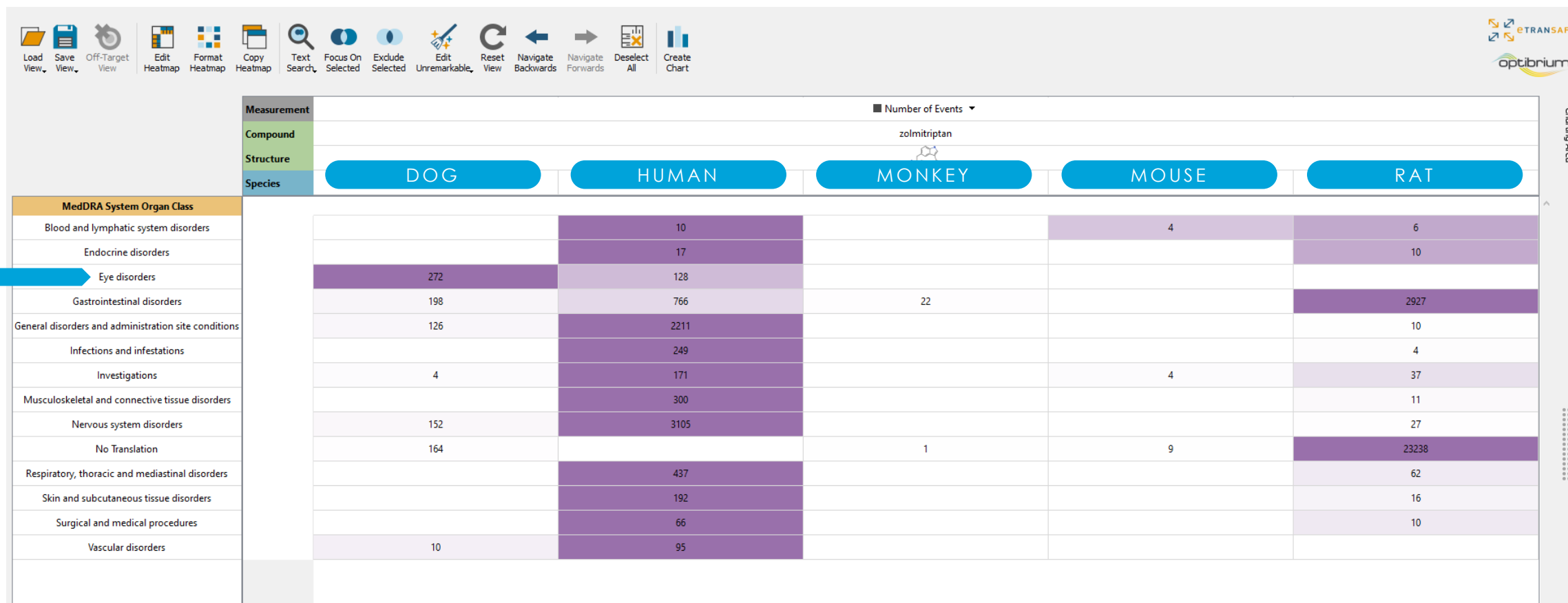
INCLUDE

EXCLUDE

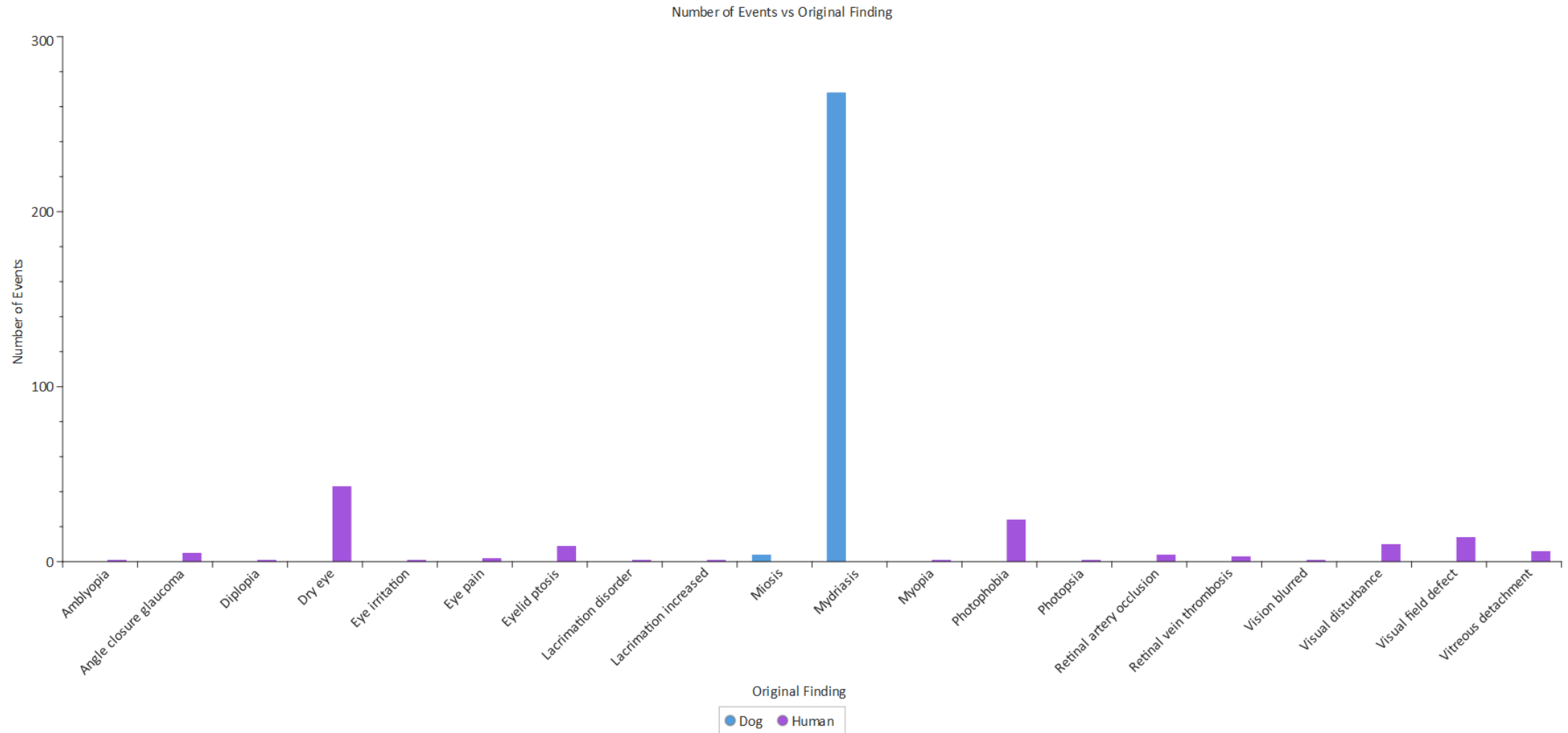
INCLUDE

SIRONA INVESTIGATIONS

Kept SOC where there were findings across all three databases, kept “No Translation” out of curiosity Used “Focus on Selected” and Added Species to the view

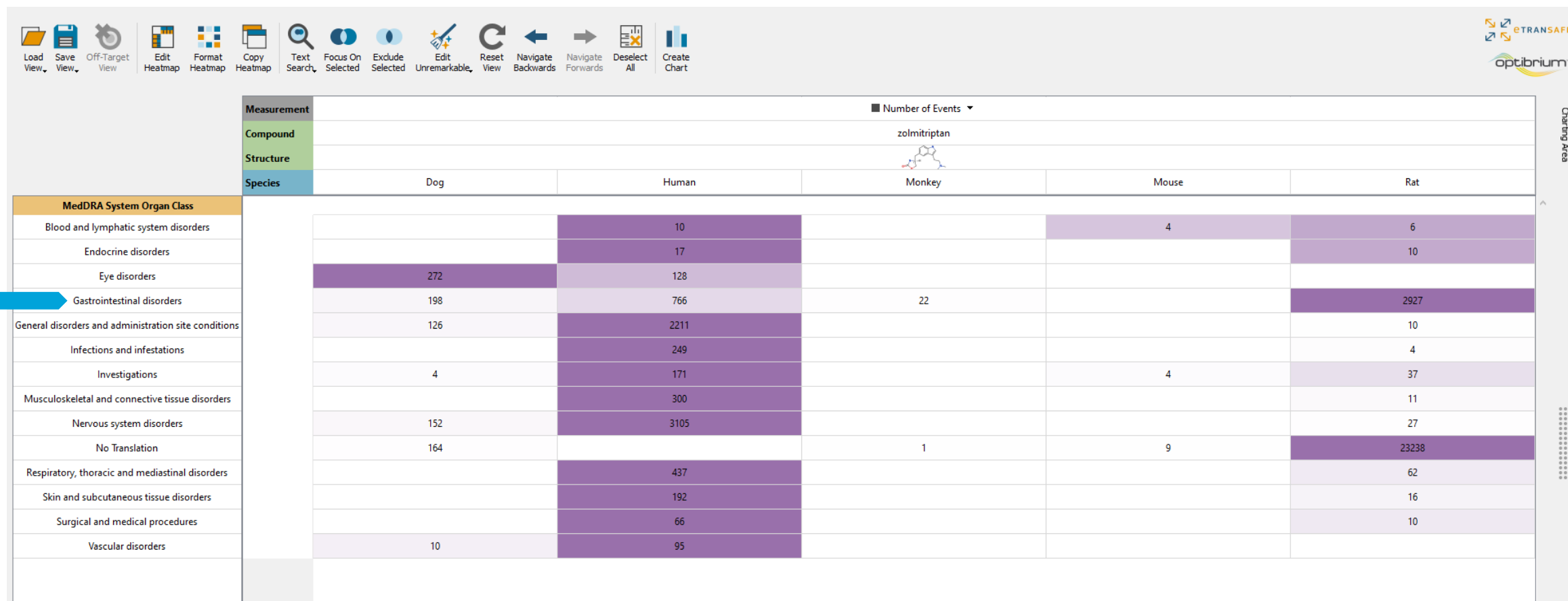


EYE DISORDER – HIGH OVERLAP?



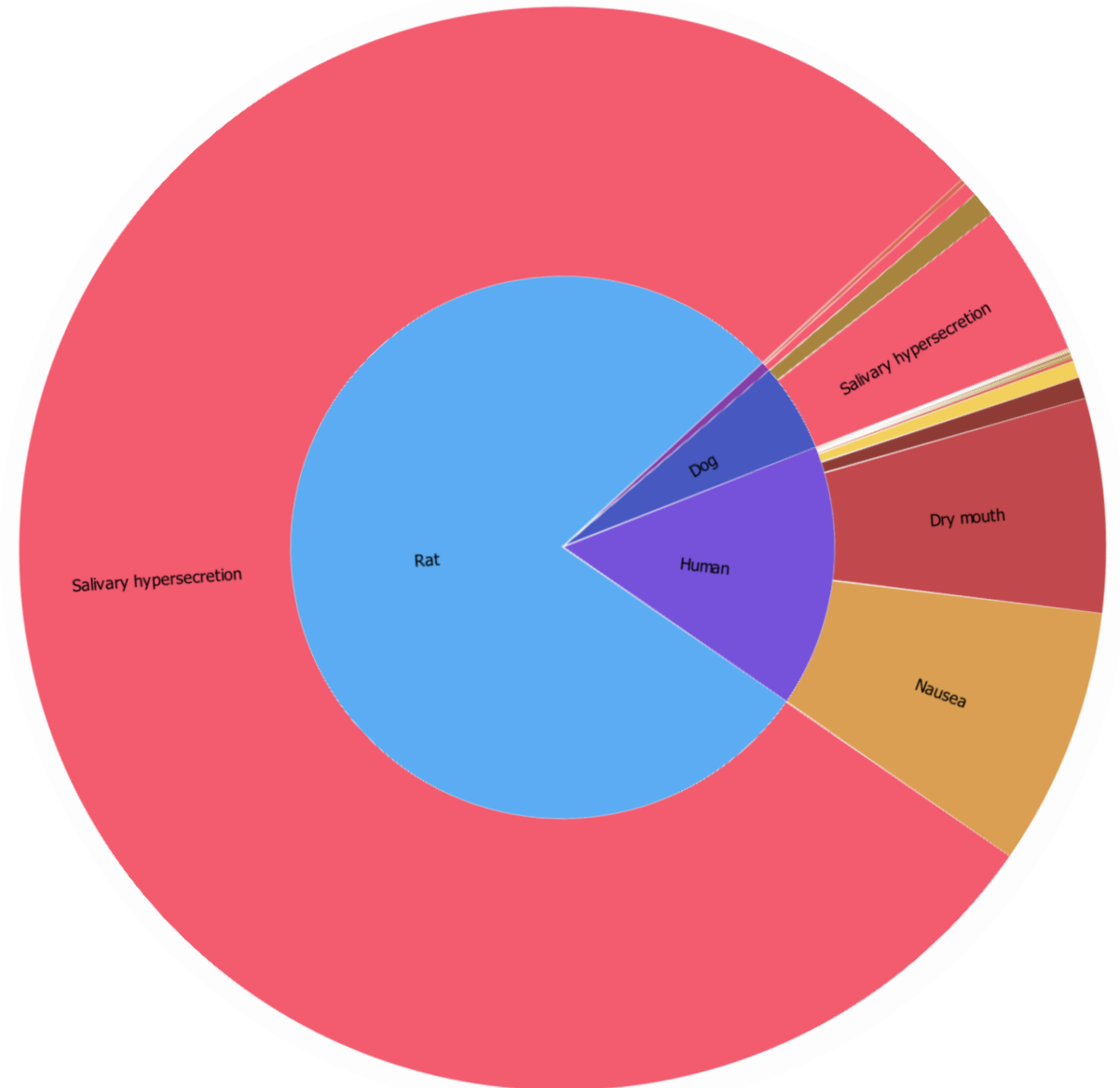
SIRONA INVESTIGATIONS

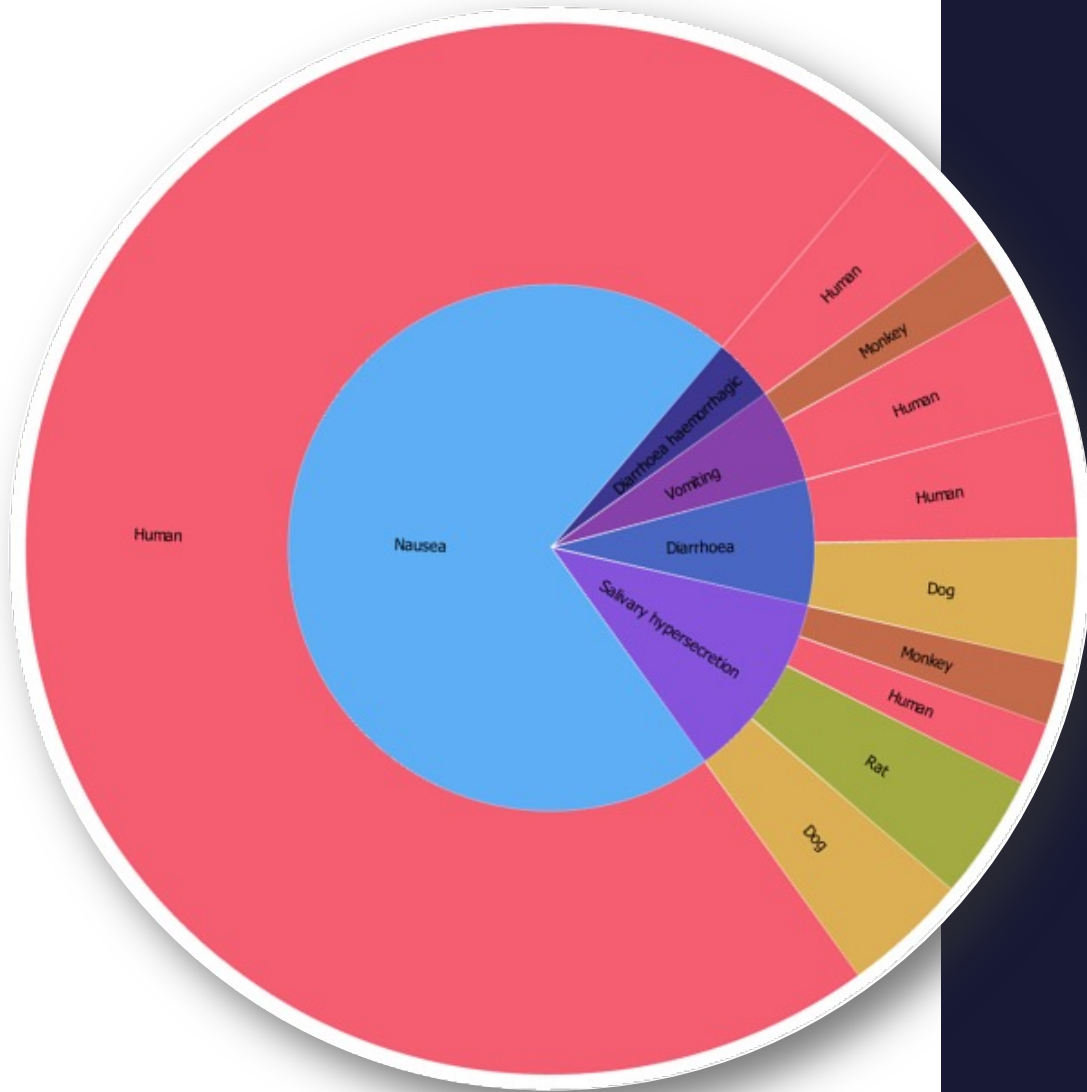
Next SOC of interest – Gastrointestinal disorders



SIRONA INVESTIGATIONS

- Gastrointestinal review – Salivary hypersecretion and nausea
- Scaling of outer ring corresponds to the Number of events
- Inner ring shows the different Species



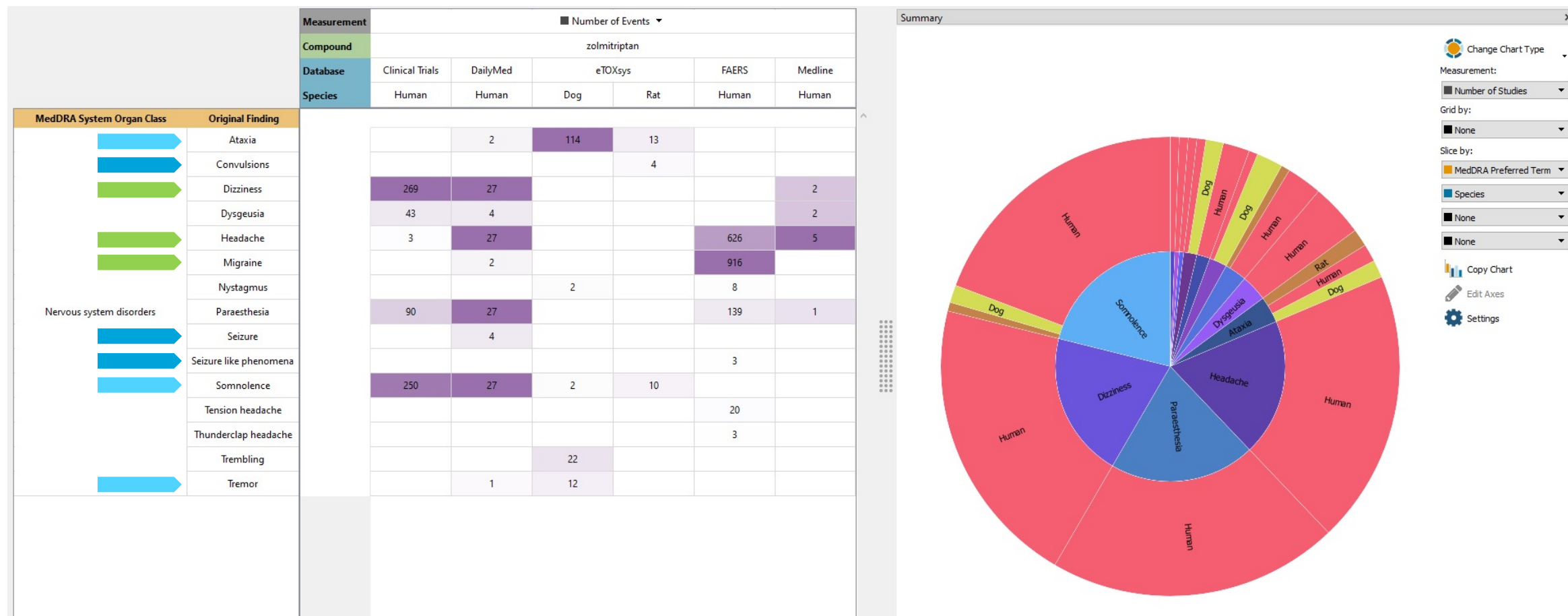


GASTROINTESTINAL FINDINGS

- Filters applied to account for the number of findings skewing presentation
- Sunburst plot shows findings in the center and number of studies per species on the outside ring
- Number of events for salivary hypersecretion in the rat (>1000) required using number of studies to be able to see the overlap
- Nausea = Salivary Hypersecretion ?

SIRONA INVESTIGATIONS

Nervous System Findings – Human unique terms AND species overlap identified



CASE STUDY CONCLUSIONS

Translatable findings:

- Somnolence and diarrhoea were seen across humans, rats and dogs
- Nausea/vomiting/hypersalivation were seen across humans, rats, monkeys and dogs
- Decreased activity/fatigue were seen across humans and dogs

GENERAL CONCLUSIONS

- Ontology and terminology allowed grouping of findings so that potential cross-species translation could be highlighted and reviewed
- Understanding the relative importance of findings such as these to the testing program could refine testing strategy
- A system which brings the data together and provides a framework for analysis can enhance the reviewer's capability and capacity
- Ensuring the system is modular and tools can be added for different types of analysis would provide additional benefits.

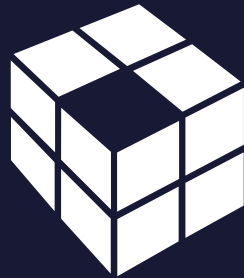


THANK YOU FOR THE INVITATION
AND YOUR ATTENTION.

ANY QUESTIONS?

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