Inclusion of recovery animals in toxicity studies ?

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Outline

1. Incorporation of recovery animals – an “old” story
2. Toxicologic Pathology Forum opinion paper on control recovery
3. IQ 3R recovery working group
4. Few examples
5. Conclusions

Consideration on incorporation of recovery animals – an “old” story

Recommendations from a global cross-company data sharing initiative on the incorporation of recovery phase animals in safety assessment studies to support first-in-human clinical trials

Regulatory Toxicology and Pharmacology 70 (2014) 413–429

Fiona Sewell [a,*], Kathryn Chapman [a], Paul Baldrick [b], David Brewster [c], Alan Broadmeadow [d], Paul Brown [e], Leigh Ann Burns-Naas [f], Janet Clarke [g], Alex Constan [h], Jessica Couch [i], Oliver Czupalla [j], Andy Danks [k], Joseph DeGeorge [l], Lolke de Haan [m], Klaudia Hettinger [n], Marilyn Hill [o], Matthias Festag [p], Abby Jacobs [e], David Jacobson-Kram [e], Stephan Kopytek [q], Helga Lorenz [r], Sophia Gry Moesgaard [s], Emma Moore [t], Markku Pasanen [u], Rick Perry [v], Ian Ragan [w], Sally Robinson [x], Petra M. Schmitt [y], Brian Short [z], Beatriz Silva Lima [aa], Diane Smith [ab], Sue Sparrow [ac], Yvette van Bekkum [ad], David Jones [ae]

The expert working group had the following recommendations:

(1) Recovery phase animals are not included into any FIH nonclinical study design as default …

(4) Consideration should be given to including recovery animals in later (rather than earlier) studies …

(7) The number of groups to which recovery phase animals are added should be kept to a minimum. …

(8) For non-rodents, consideration should be given to not including recovery animals in the control group. …

What is the challenge ?

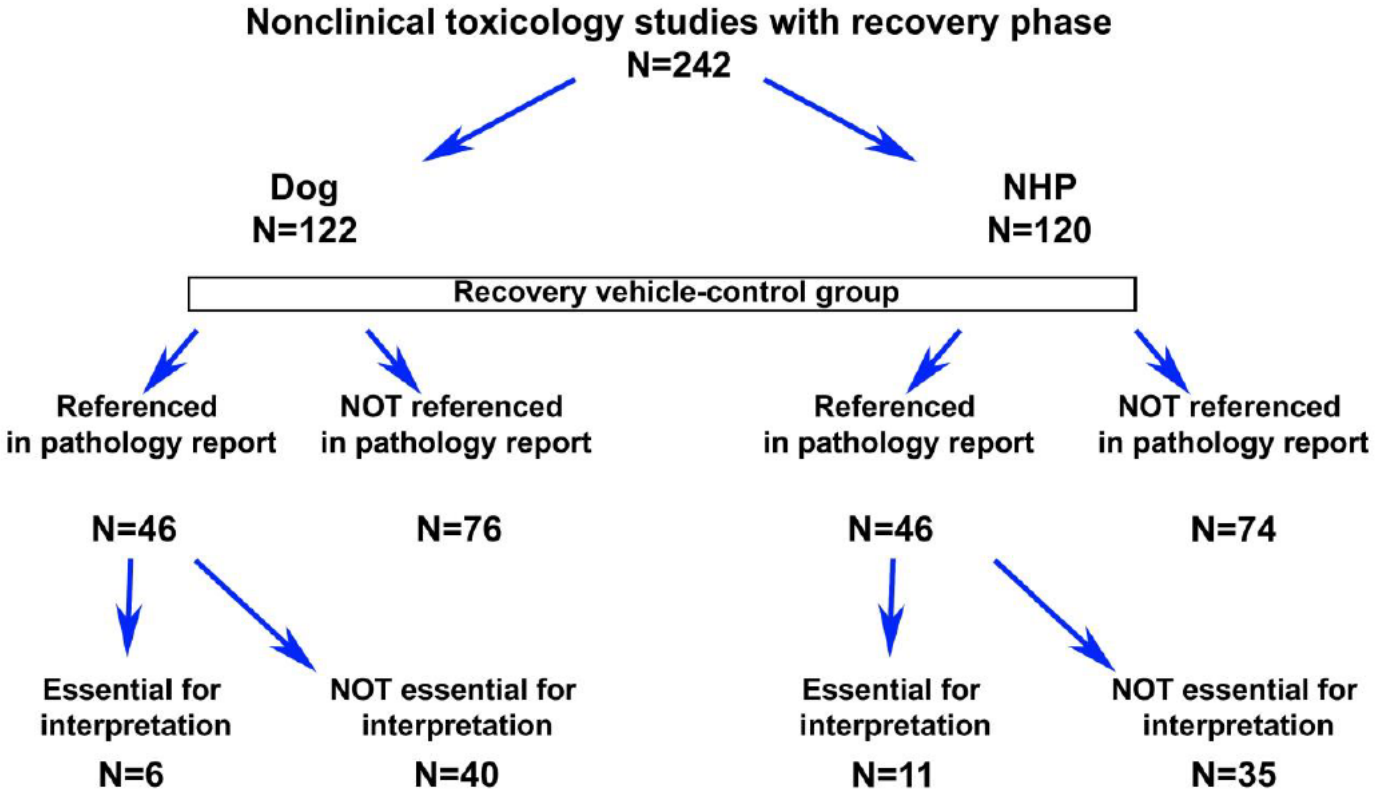
Diversity of approaches supports inclusion of recovery animals in preclinical studies supporting clinical trials despite operating under the same 3Rs principles and regulatory guidances [ICH S6, S9, M3(R2) and M3(R2) Q&A].

While the use of recovery animals may provide a valuable assessment of the reversibility of adverse toxicity (and/or delayed toxicity), there are instances where an informed position on reversibility may be confidently made while also minimizing animal use. However, such refinements to study design are not conducted uniformly.

Increasing demand for large animal species for toxicity assessments makes their availability particularly susceptible to shortages with potential to delay the development of novel therapeutics.

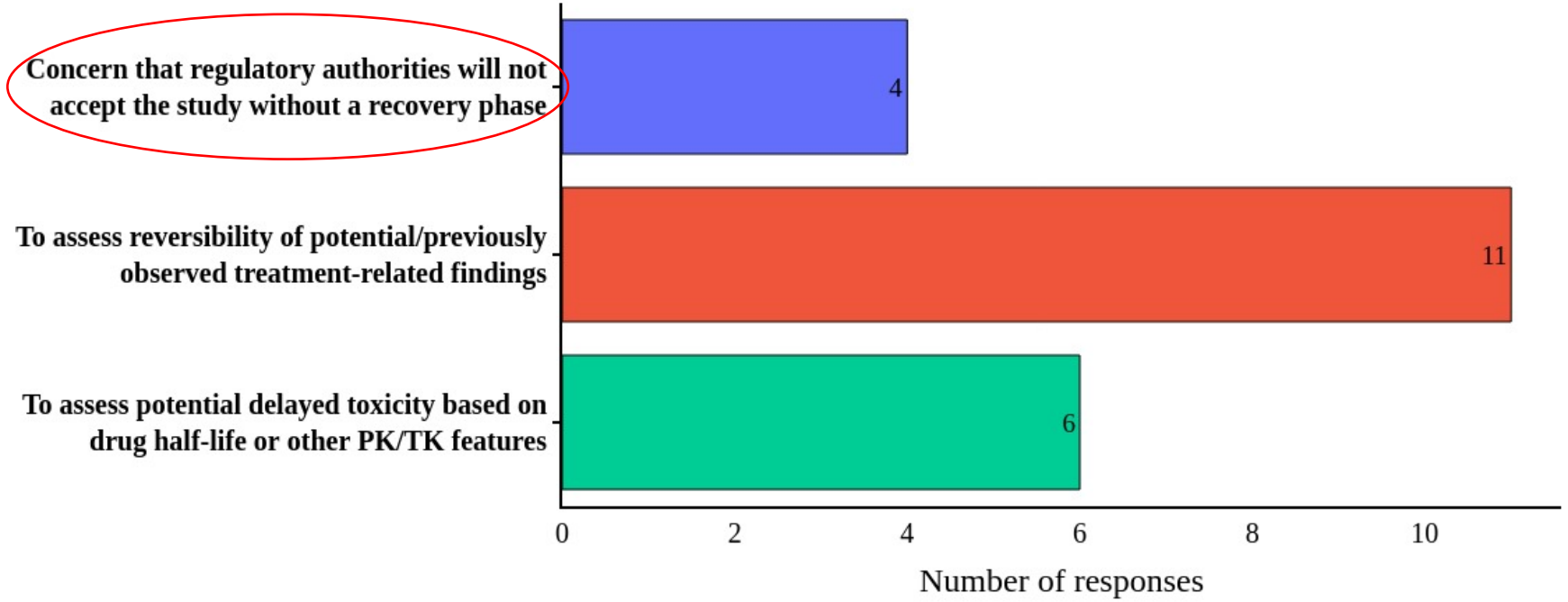
Increasing ethical consideration is also pushing to review preclinical package and study design of general toxicity studies to reduce number of animals used.

Toxicologic Pathology Forum: Opinion on Not Euthanizing Control Animals in the Recovery Phase of Non-Rodent Toxicology Studies (Toxicol Pathol. 2022 50(8): 950-956)



Recovery group had no impact on the study/program outcome except in a few cases where historical control data (HCD) were not robust enough (reproductive toxicity; new vehicle/formulation)

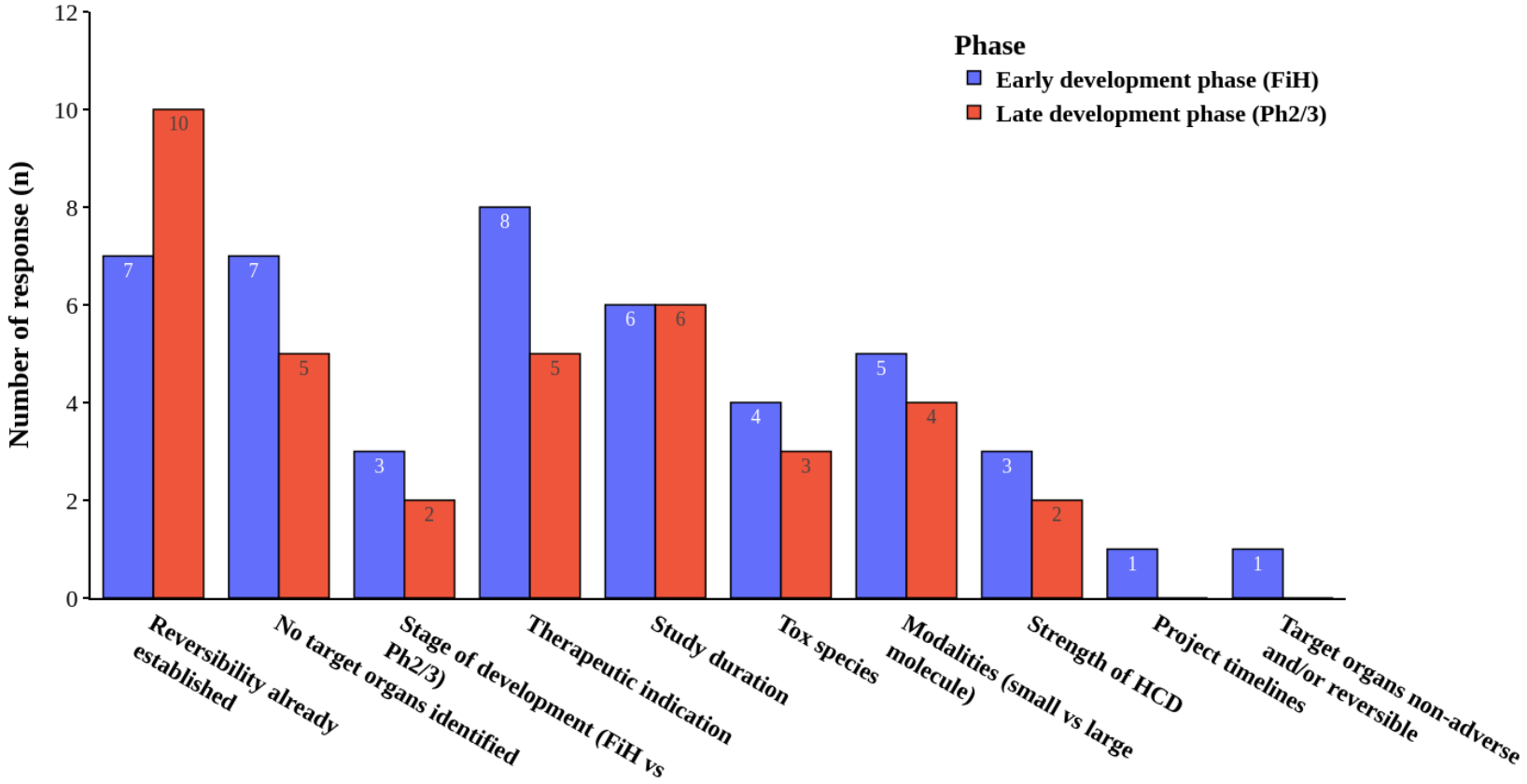
IQ 3Rs recovery working group - primary purpose of including recovery groups in a GLP study



Unpublished manuscript data 2023 (ready for submission)

This [MATERIAL] was developed with the support of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ, www.iqconsortium.org). IQ is a not-for-profit organization of pharmaceutical and biotechnology companies with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader research and development community

IQ 3Rs recovery WG - Major factors taken into consideration when making decision to include or not recovery group(s).



Unpublished manuscript data 2023 (ready for submission)

IQ 3Rs recovery working group - takeaway

Scientific evidence is the primary determinant behind inclusion of recovery groups in both early and late development studies.

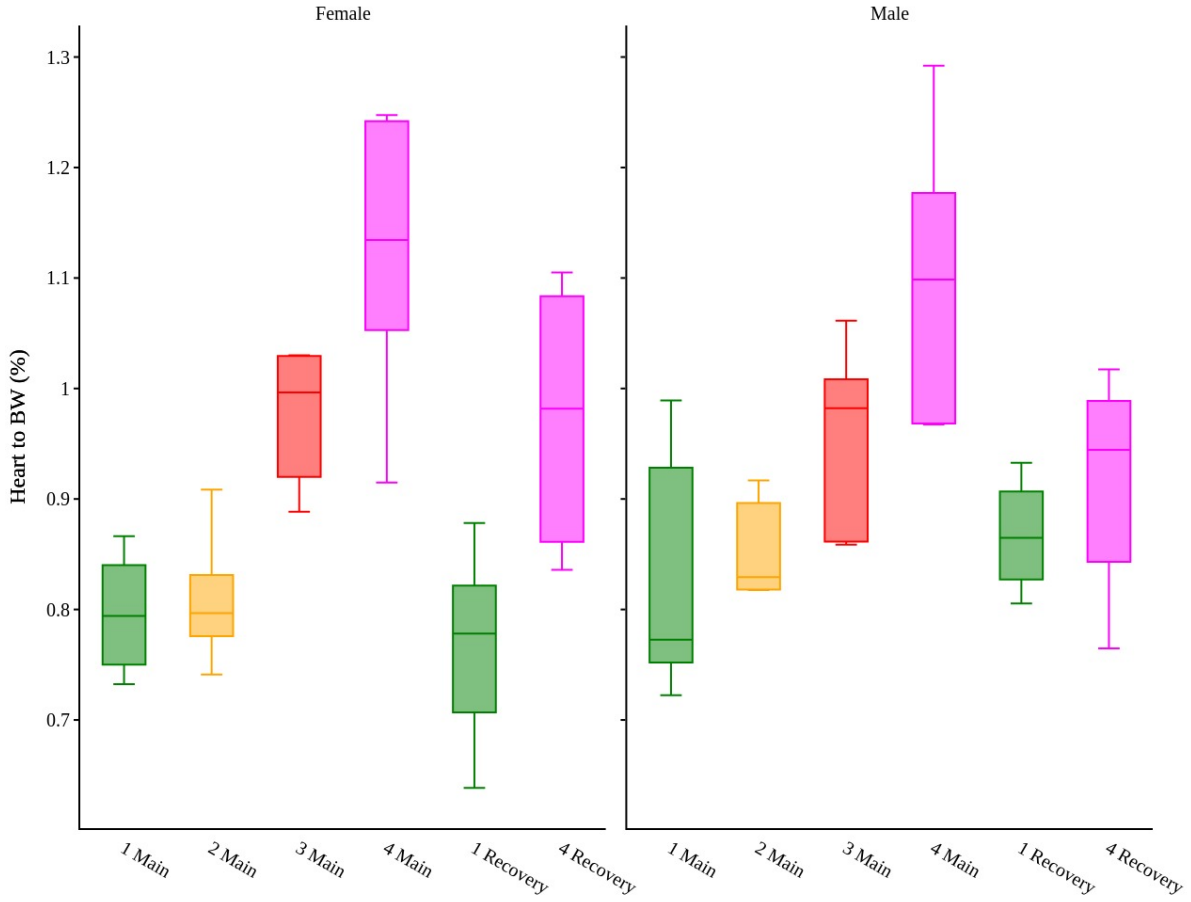
A review of case studies has shown multiple scenarios in which recovery animal groups can be minimized or excluded from toxicology studies, and successfully accepted by regulatory agencies:

- **Use of historical control data (HCD) to exclude recovery groups in large animal studies with standard vehicles regardless of indication or modality. Exclusion being more common with large molecules.**
- **Decision to include recovery groups in early studies vs chronic studies was driven partially by modality and partially by company strategy.**

Case studies demonstrated an alignment with recommendations of Sewell et al publication in 2014 to:

- **not include recovery phase animals into study design as default**
- **consider including recovery phase in later, rather than earlier, studies**
- **to minimize the number of groups to which recovery phase animals are added**
- **excluding recovery animals from control groups for non-rodents**

Organ weights, do we need a recovery control group ?



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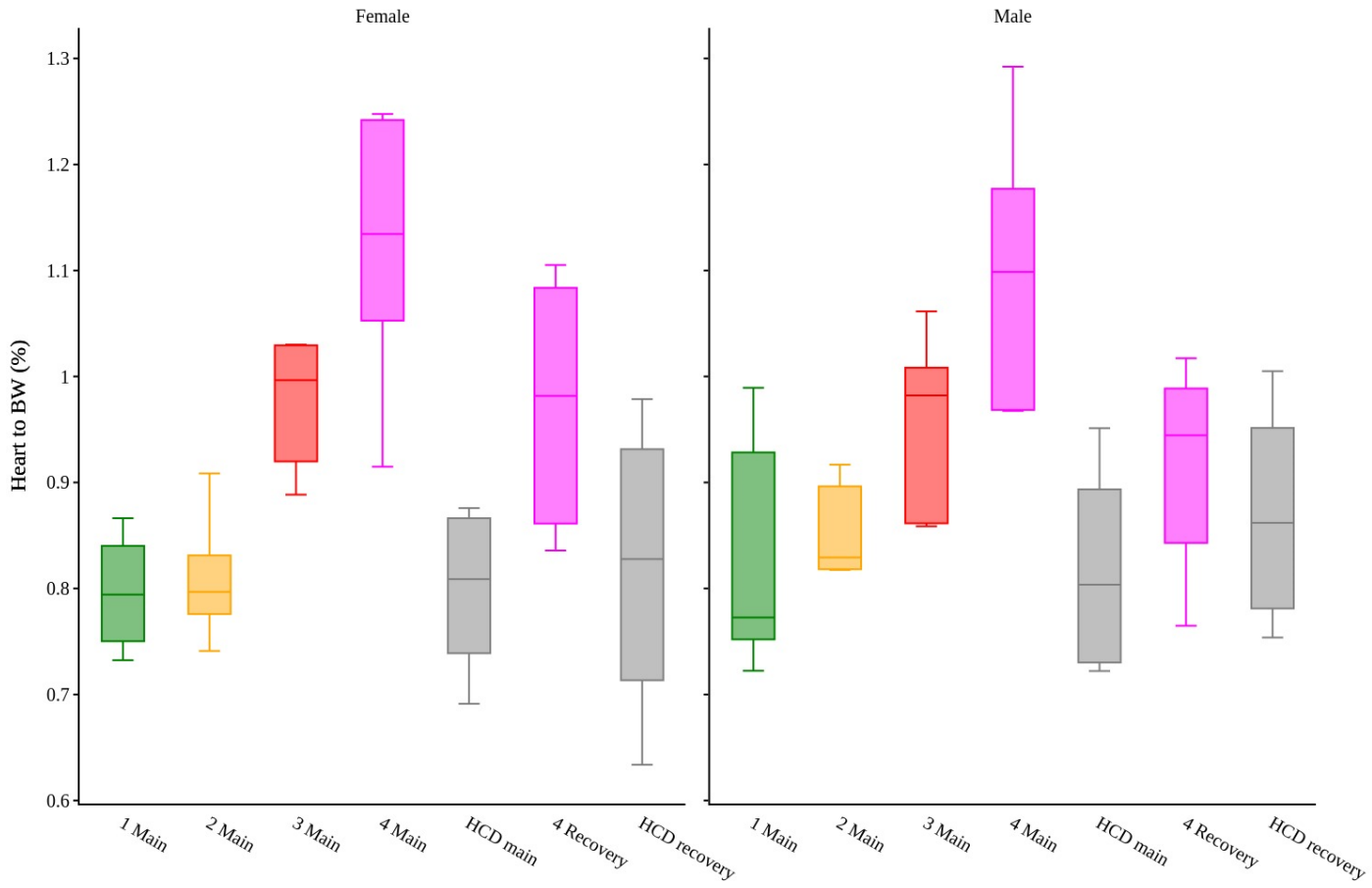
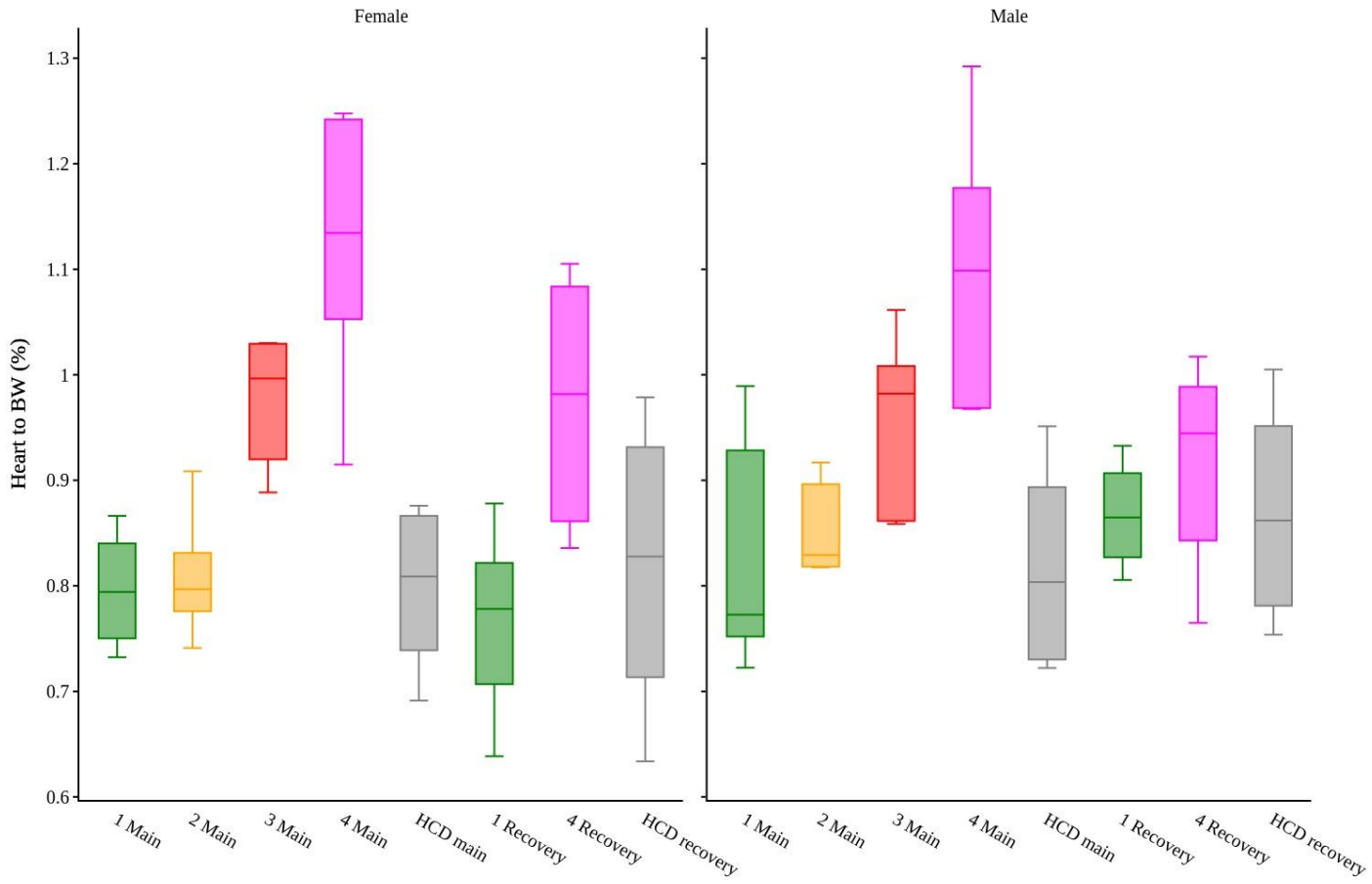


Organ weights, do we need a recovery control group ?



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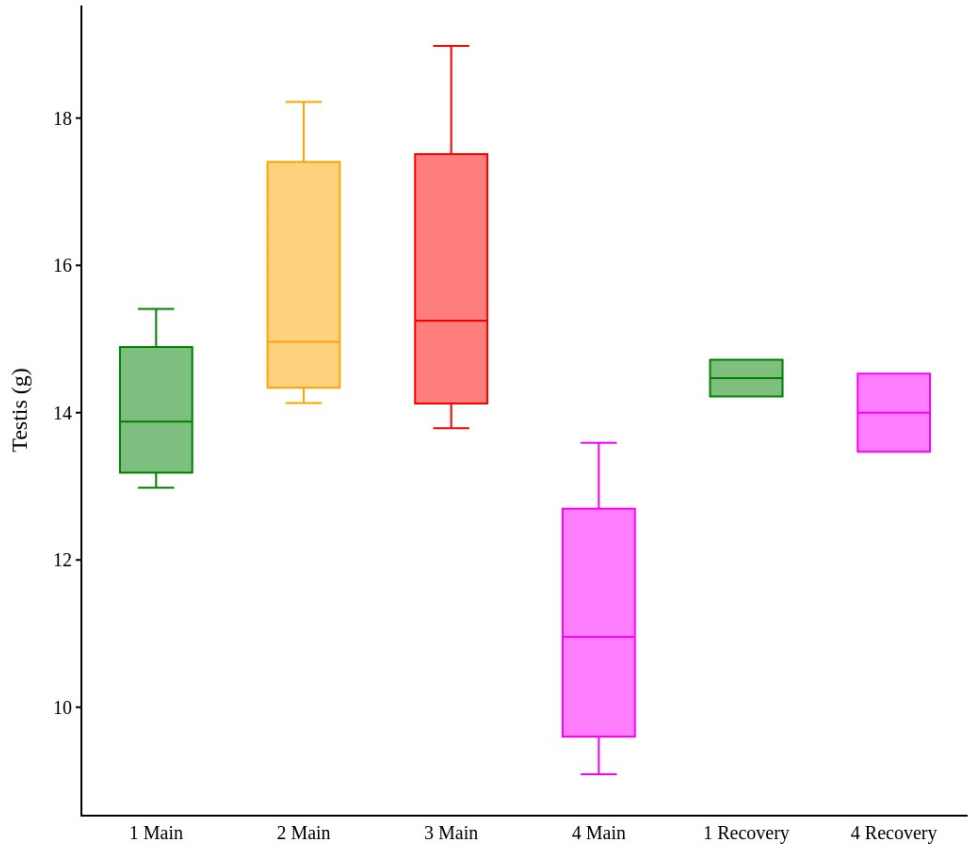
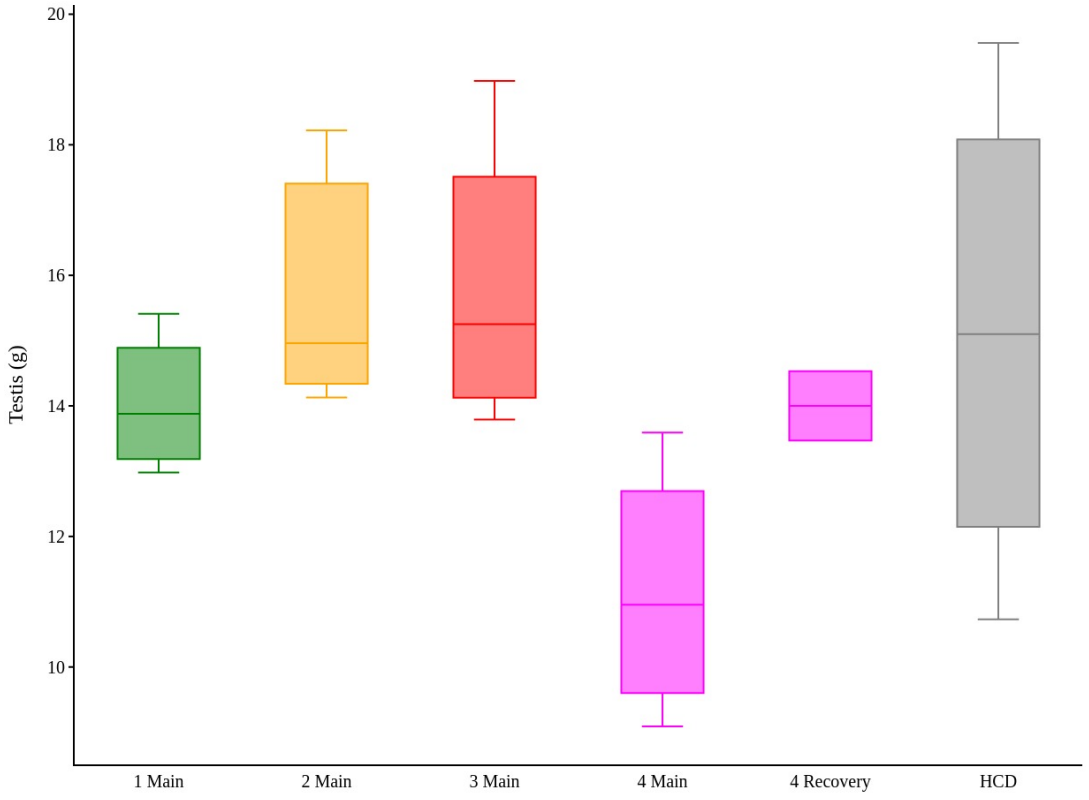
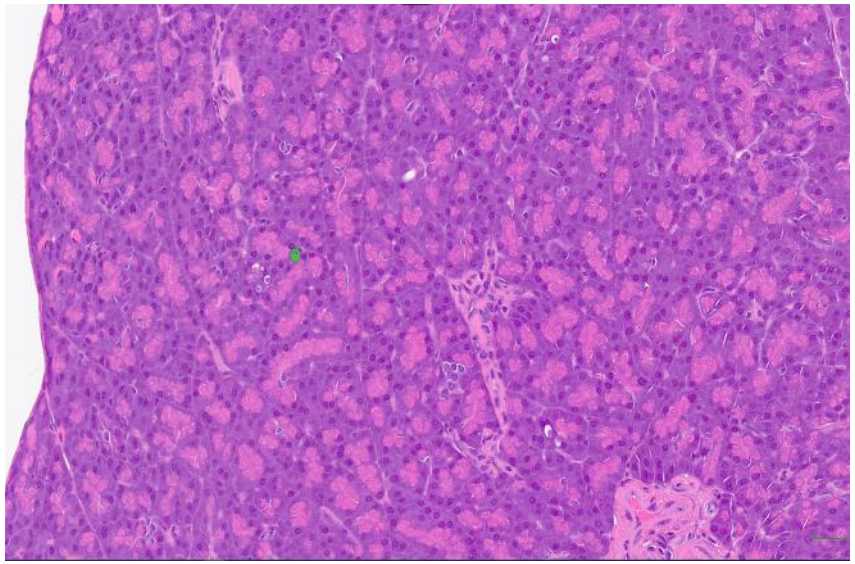
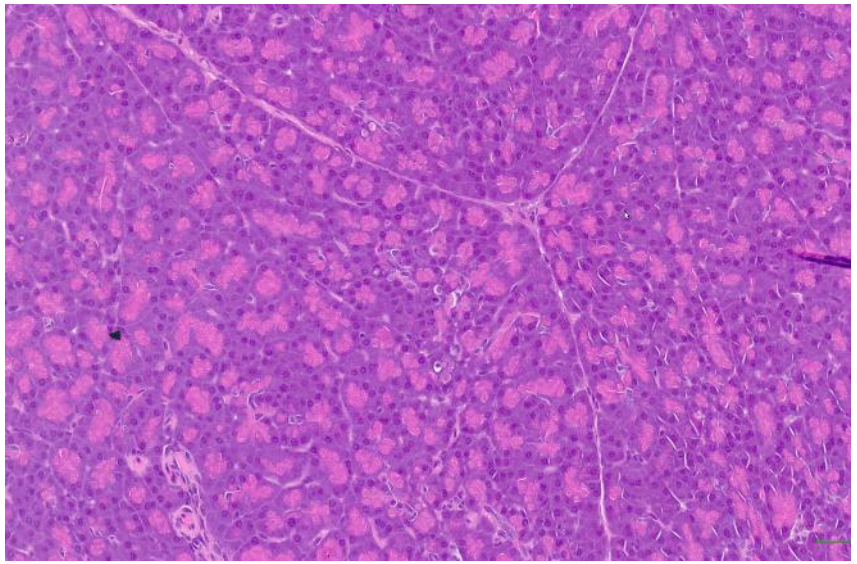




Microscopic finding. Do we need recovery ?





Finding	Control	Low	Mid	High	Control recovery	High recovery
Number of rats	20	20	20	20	12	12
Pancreas single cell necrosis						
Minimal	4	3	5	10	1	3

Microscopic finding. Do we need recovery ?

Finding	Control	Low	Mid	High	Control recovery	High recovery
Number of dogs	6	6	6	6	4	4
Myocardial degeneration						
Mild	0	0	0	1	0	0

Low incidence in a change with a small number of recovery animals is difficult to interpret.

Without a biomarker, it is often impossible to know if the recovery animals presented the same change observed in the dosing phase group, which is the object of the reversibility evaluation.

Historical control data, literature (and slides) can replace control recovery

HCD and literature are used to support non-compound-related effect, and could definitively replace or reduce use of control recovery group:

- **Literature supporting background related microscopic finding: Chamanza 2010 or Sato 2012 for cynomolgus monkey, Sato 2012 for dog and other publications pending system and/or study type**
- **HCD at CRO matching sex, age, origin/strain and/or route of administration and study duration/type can be obtained for body/organ weight, clinical pathology and microscopic findings.**

Yet, few "exotic" studies (i.e. non-standard route of administration, juvenile or chronic in old animals) will need recovery in control and test-article (TA) treated group due to lack of HCD and/or literature

Scenarios when recovery controls might be essential

In the case of a lack of robust HCD and slides (i.e. non-standard toxicity or long recovery period for example)

When specific TA-related or questionable changes are observed in non- protocol-specified tissues or extraneous tissues in a section meaning no or poor HCD and slides

If the vehicle is novel or not well characterized or procedure-induced changes confound the TA-induced changes

In instances where the initial toxicity profile includes reproductive toxicity

When the dosing regimen is intermittent (vaccine) or delayed toxicity is expected (AAV, target protein degrader)

But can we even fully avoid recovery groups ?

WoE approach on when to add recovery (or control recovery) group(s) in a toxicology study

Before a FIH enabling Study

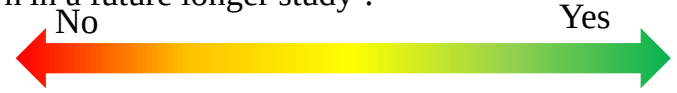
Is inclusion of recovery animals to fulfill internal guidelines or out of concern of regulatory rejection rather than based on scientific rationale?

Is intended indication oncology or another life-threatening or severe disease?

No delayed toxicity is expected for this drug due to prolonged half-life or other ADME properties

For large molecules, is the only safety concern related to pharmacology or immunogenicity?

If an adverse finding is anticipated, can reversibility be defended by a WoE approach or shown in a future longer study ?



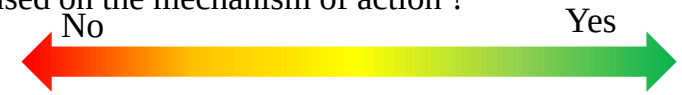
Sufficient HCD (or literature) to drop recovery animals from the control group?

After FIH enabling Study

Could demonstration of recovery from this study be applied to future molecules in this series/class?

If an unforeseen adverse finding was identified, can reversibility be defended by a WoE approaches ?

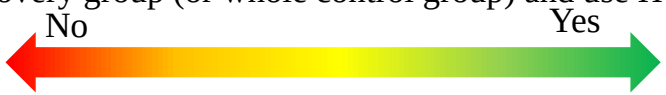
If no current adverse finding identified, are longer exposures expected to reveal novel findings based on the mechanism of action ?



If recovery must be demonstrated, can it be done with only one recovery group ?

If delayed toxicity was not observed, can recovery animals be excluded from future studies?

Was control group necessary for interpretation of drug-related findings ? Could we exclude control recovery group (or whole control group) and use HCD/literature?



Majority of **yes**, **exclusion** of recovery animals (or whole control group) from the study may be justified.

Otherwise, add **recovery** animals to the study. For biologics, control recovery animals could be returned to colony if no overt toxicity observed, HCD, standard vehicle and short recovery period.

Conclusion

There are multiple ways to reduce the use of recovery animals:

Expanding the use of HCD/literature in nonclinical toxicity studies

Not terminating control animals in the recovery phase of nonrodent nonclinical toxicology studies and reuse of these animals (even protein non-naïve monkeys)

Limiting recovery groups to one dose-level and omit control recovery groups by using pre-study, main phase data and HCD/literature to interpret the recovery data

Conducting first in human enabling studies with no recovery groups; with use of weight of evidence approach and historical control data to assess reversibility.

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