

Population time-activity modeling and simulation supporting the reduced dosimetry collection for radioligand therapy (RLT) clinical trials

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Background

- NeoRay is a Ph I/IIa open-label, multi-center study to evaluate the safety, tolerability, whole-body distribution, radiation dosimetry and anti-tumor activity of [¹⁷⁷Lu]Lu-NeoB administered in patients with advanced solid tumors (for whom no standard therapy is available, tolerated or appropriate) which are known to overexpress GRPR (gastrin-releasing peptide receptors). This study consists of a dose escalation (Ph I), and an expansion part (Ph IIa).
- Dosimetry is an essential measurement in radioligand therapy (RLT) enabling dosage selection to deliver safe and efficacious treatments to patients with a favorable benefit-risk.
- Dosimetry collection process is burdensome to patients both in terms of imaging time in a SPECT/CT (Single Photon Emission Computed Tomography/Computed Tomography) scanner and number of visits to the clinical site.
- Additionally, it results in a significant logistical burden for hospitals, especially if serial imaging over several days is required.

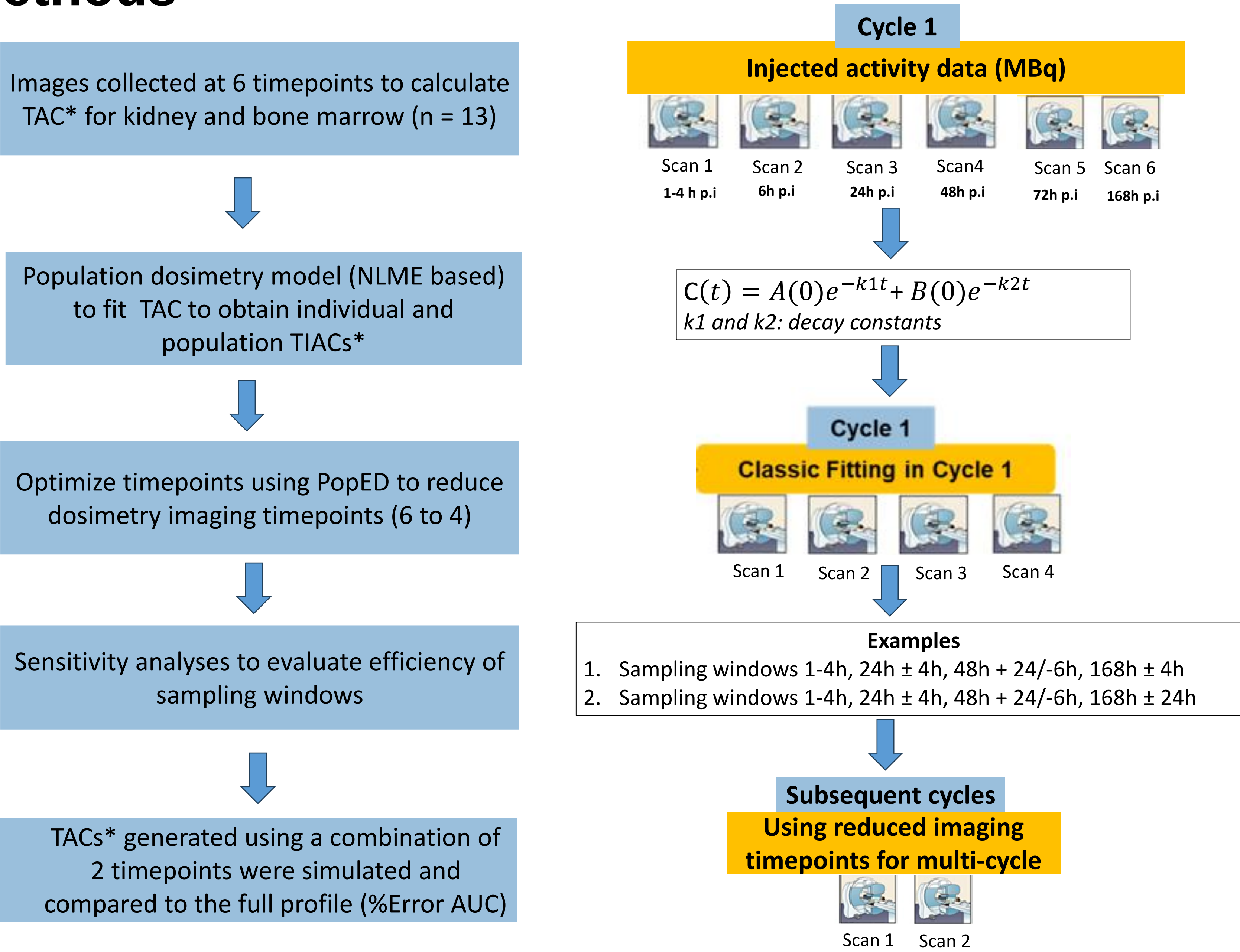
Cycle and day	Time (hr)	Note
C1D1	1 h ± 3 h	Between 60 min and 180 min (1-3 h) after the end of infusion, together with a SPECT/CT from vertex of skull to mid-thigh
	6 h	After the end of infusion
C1D2	24 h ± 1 h	After the end of infusion, together with a SPECT/CT from vertex of skull to mid-thigh
C1D3	48 h ± 1 h	After the end of infusion
C1D4	72 h ± 1 h	After the end of infusion
C1D8	168 h ± 24 h	After the end of infusion

Table 1: NeoRay Ph I dosimetry Whole-body (WB) planar images timepoints

Objective

- Demonstrate the application of design optimization and NLME modeling to reduce the kidney and bone marrow (BM) dosimetry imaging timepoints for [¹⁷⁷Lu]Lu-NeoB (AAA603) clinical trials using NeoRay Phase I dose escalation dosimetry data.
- To reduce 6 to 4 timepoints on cycle 1 Ph I/II studies when there is no prior knowledge about the biodistribution of the compound in the specific human disease population.
- To reduce timepoints from 4 to 2
 - in the subsequent cycles in the above-mentioned Ph I/II studies or
 - starting from the first cycle and subsequent cycles when we already have the prior knowledge of the compound biodistribution in the specific human disease population

Methods



Results

- The final kidney and BM models were bi-exponential decay including random effects on all parameters without any covariate effects. All parameters for the final models were estimated with reasonable precision with maximum RSE of 56.6% for kidney and 67.2% at most for BM.
- The design optimization of the original 6 timepoints design led to the selection of two optimal designs (1-4, 24, 48 and 168 h) and (1-4, 24, 72 and 168 h) based on the precision of the parameter estimates for kidney and BM.
- The tested sampling windows in the sensitivity analysis did not show non-negligible changes in efficiency and RSEs of parameters between the simulations for both organs.
- The combination of imaging acquisition for reduced 2 timepoint dosimetry for kidney and BM at 1-4 h and 72 h provided a lower error, followed by the combination of 1-4 h and 48 h.

Figure 1: Visual predictive check (VPC) for kidney (left) and bone marrow (right) percent injected dose

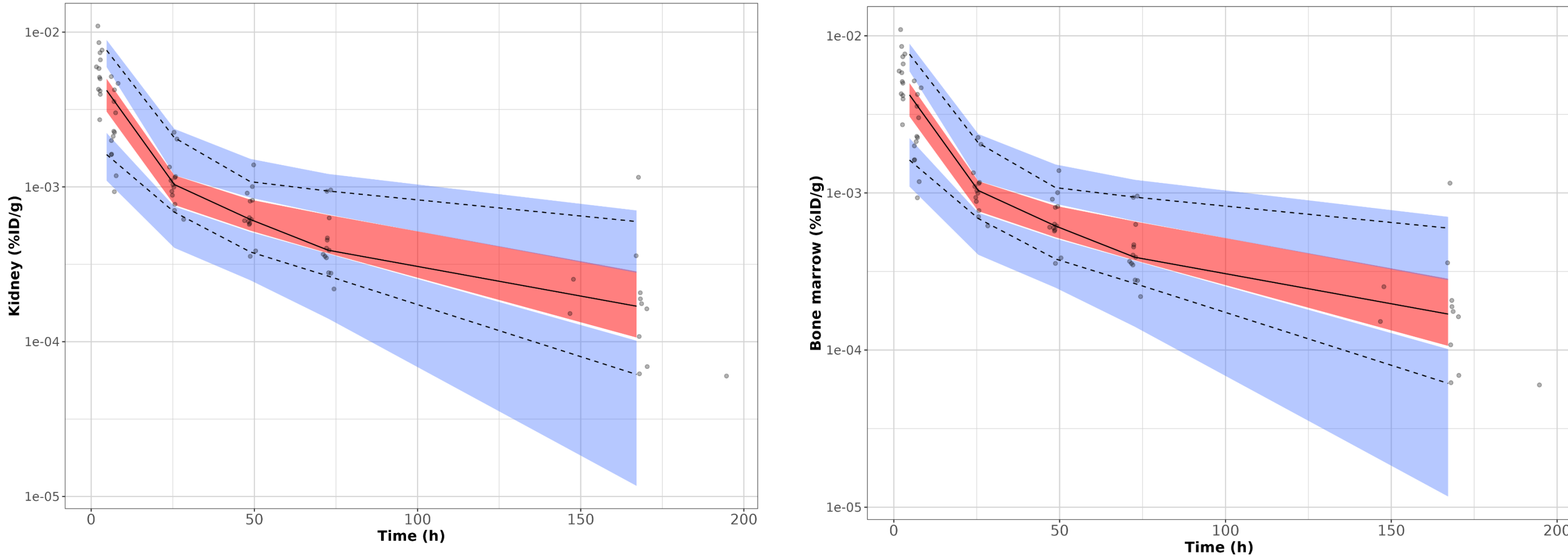


Figure 2: TAC simulated using reduced 2 timepoints overlaid with observed 6 timepoints

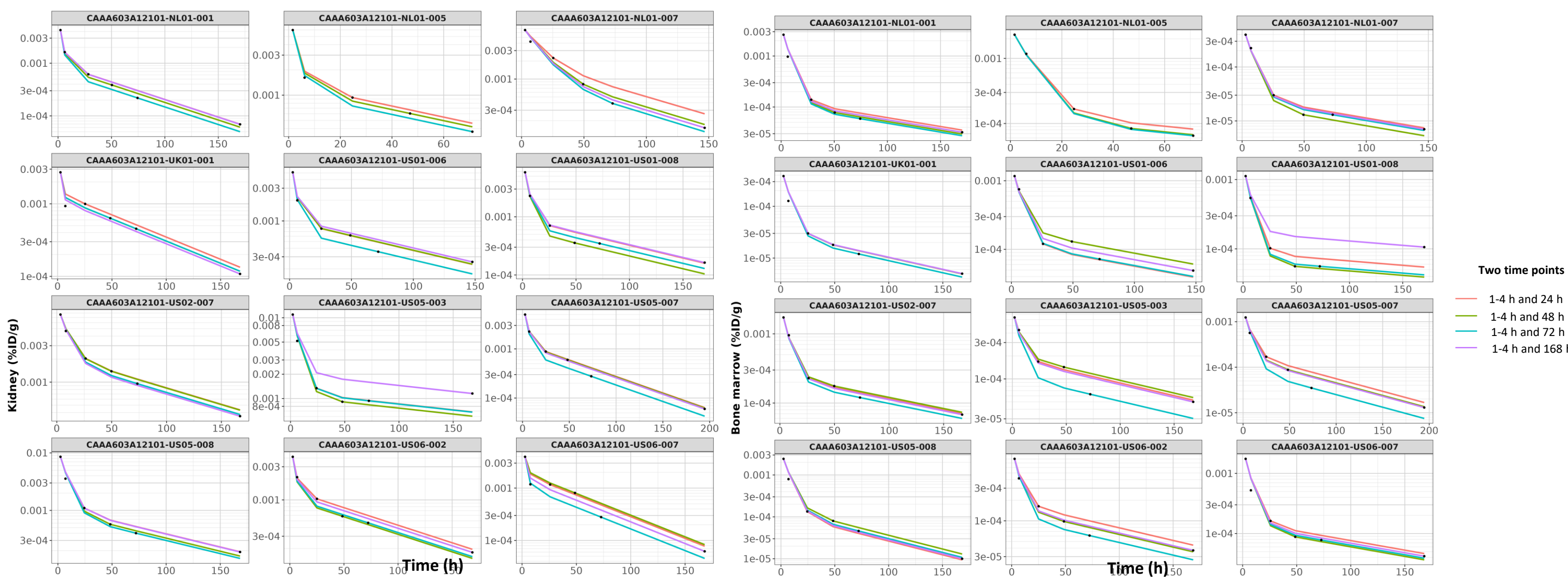
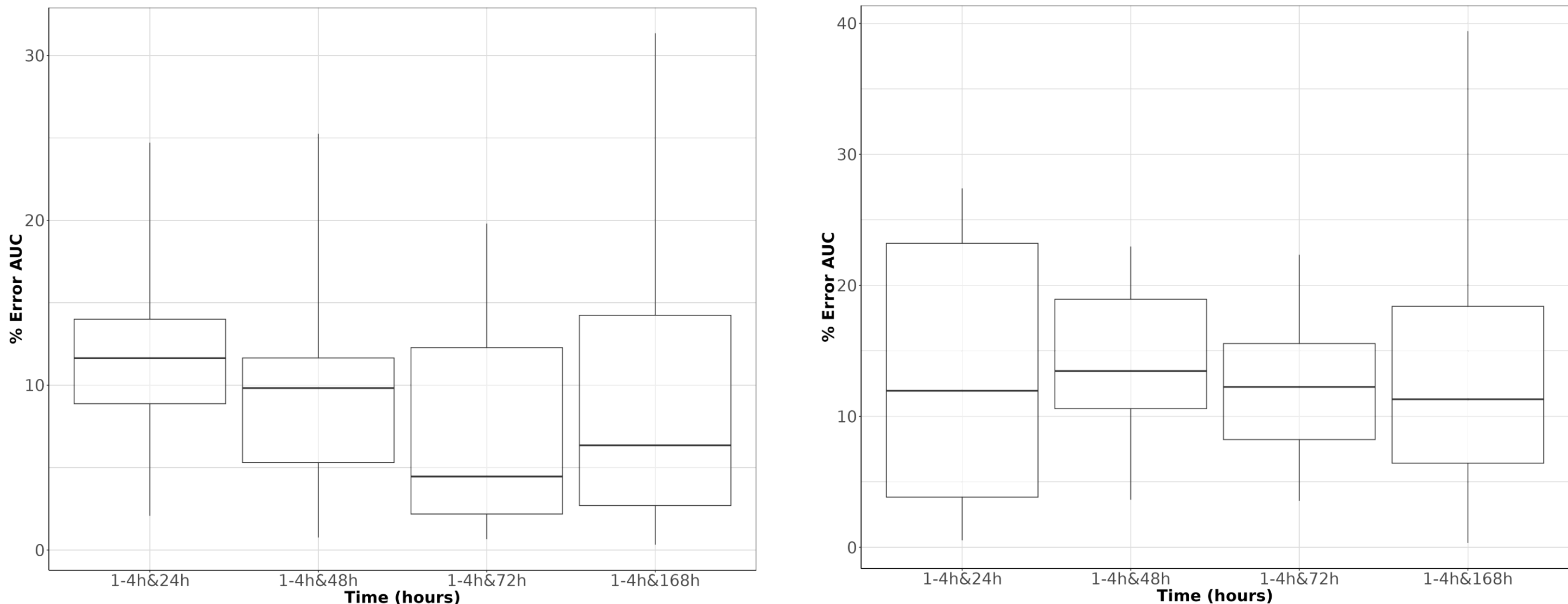


Figure 3: %Error AUC between observed and predicted TAC for kidney and BM



Conclusions

- Number of imaging timepoints were reduced from 6 timepoints to 4 timepoints (1-4 h, 24 ± 6 h, 48 + 24/- 6 h and 168 ± 24 h) on cycle 1 and similar TACs were obtained from 1-4 h and 48 h or 1-4 h and 72 h scans for kidney and BM.
- %Error AUC results support imaging timepoints for dosimetry at later cycles for kidney and BM can be reduced to either 1-4 h and 48 h or 1-4 h and 72 h timepoints.
- Proposed methodology was accepted by the Federal Office for Radiation Protection (BfS) and is being implemented in Novartis across NeoB programs.

Acknowledgements

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*TAC: Time activity curve, TIAC: Time integrated activity coefficient = AUC of TAC

