

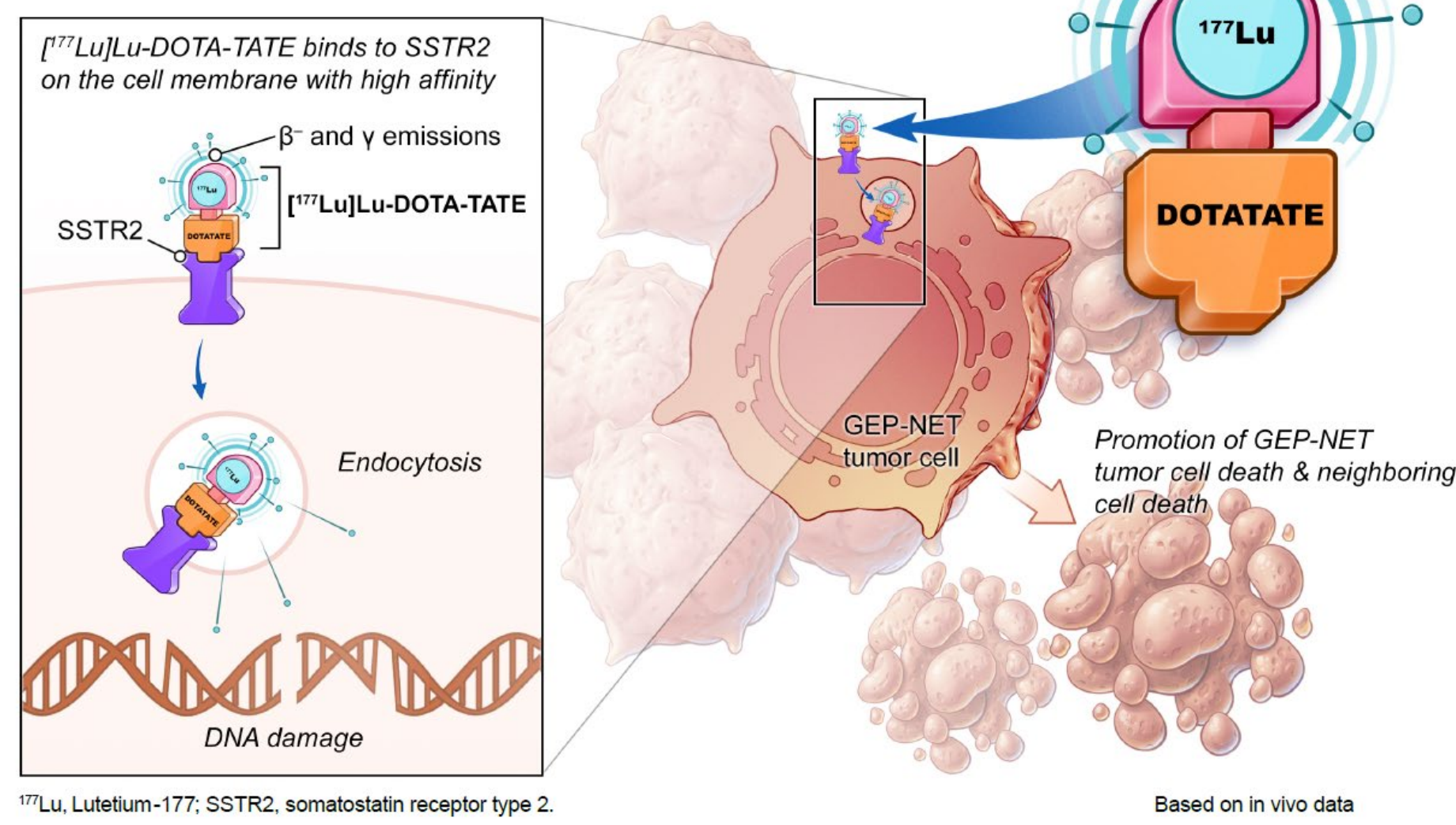
Lutathera dose determination and justification in adolescents via popPK and dosimetry modeling and simulation

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Background

Figure 1: Mechanism of action of [¹⁷⁷Lu]Lu-DOTA-TATE
[¹⁷⁷Lu]Lu-DOTA-TATE
SSTR-targeted peptide receptor radionuclide therapy



- [¹⁷⁷Lu]Lu-DOTA-TATE (Lutathera®) is an approved drug used for the treatment of somatostatin receptor-positive (SSTR-positive) advanced gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults¹.
- Unmet need of treatment options in adolescent patients (12 to <18 years) with advanced GEP-NET, which is a rare disease².
- Late diagnosis of NETs in children is not uncommon due to indolent nature of disease and can be at the stage when tumor is already metastatic and unresectable (as for adults)³.
- Full efficacy extrapolation from adults to the adolescent population is appropriate.
- Lutathera was approved for pediatric patients 12 years and older on 23-Apr-2024 by the US-FDA. The approval was based on NETTER-P study which is a Phase II, multicenter, open-label study to evaluate safety and dosimetry of [¹⁷⁷Lu]Lu-DOTA-TATE in adolescent patients with SSTR-positive GEP-NET tumors, and pheochromocytoma and paragangliomas (PPGL) (NCT04711135)⁴.

Objective

- Dose justification of full adult dose of 7.4 GBq over 4 cycles of [¹⁷⁷Lu]Lu-DOTA-TATE in the adolescent population (12 to <18 yr) for NETTER-P study with GEP-NET or PPGL.
- Confirming comparable exposure, and exposure-dosimetry relationship for kidney and bone marrow and applicability of flat dosing between adults and adolescents.

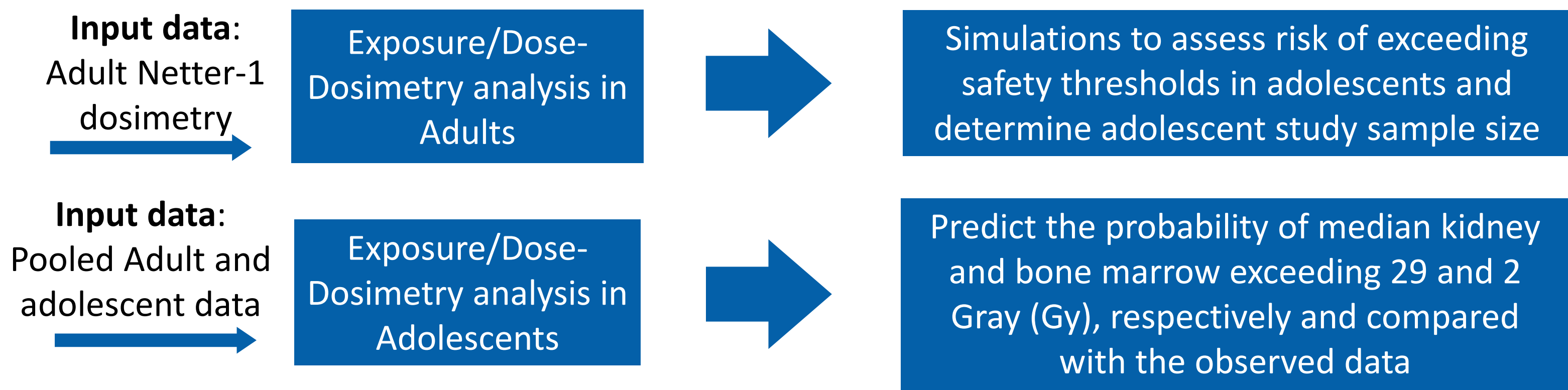
Method

- Data:** Adults have two cohorts, NETTER-1 (N = 20) and ERASMUS (N = 27) and adolescents, NETTER-P has N = 11.
- popPK model:** Developed using a two-compartment, zero order absorption with first-order elimination, and parameterized in terms of clearance and volume.
- Dosimetry model:** Exposure was not available for all subjects, therefore dose was used as a surrogate for dosimetry analysis.

$$\text{Kidney Dosimetry} = A \times \left[\frac{\text{Dose (GBq)}}{7.4} \right]^B \times \left[\frac{\text{CrCl}}{99} \right]^C$$
$$\text{Bone marrow} = D \times \left[\frac{\text{Dose (GBq)}}{7.4} \right]^E \times \left[\frac{\text{CrCl}}{99} \right]^F$$

CrCl - Creatinine clearance
A - Kidney dosimetry baseline
B - Dose effect on kidney
C - CrCl effect on kidney
D - Bone marrow dosimetry baseline
E - Dose effect on bone marrow
F - CrCl effect on bone marrow

Figure 2: Workflow for dosimetry modeling and simulation



Results

- A two-compartment model with linear elimination without any covariates adequately described the Lutathera PK in adults and adolescents.
- Adult dosimetry model was applied to an adolescent population (based on literature data⁵) without risk factors resulted in a 7.4 GBq dose administered on 4 cycles having a median kidney and bone marrow dosimetry values ≤29 Gy and ≤2 Gy respectively (Figure 3).
- Similar exposure between adolescents (NETTER-P) and adults (NETTER-1) was confirmed (Table 1).
- Neither exposure nor kidney and bone marrow dosimetry were clinically relevantly impacted by patient's age and body weight, indicating the appropriateness of flat dosing in adolescent population and similar dosing to adult population (Figure 4).
- Probability of median predicted and observed dosimetry exceeding respective thresholds in kidney and bone marrow for adults vs. adolescents remained similar.

Figure 3: Median dosimetry estimates (from 500 simulations of 240 subjects) for 4 cycle treatment as a function of creatinine clearance and dose

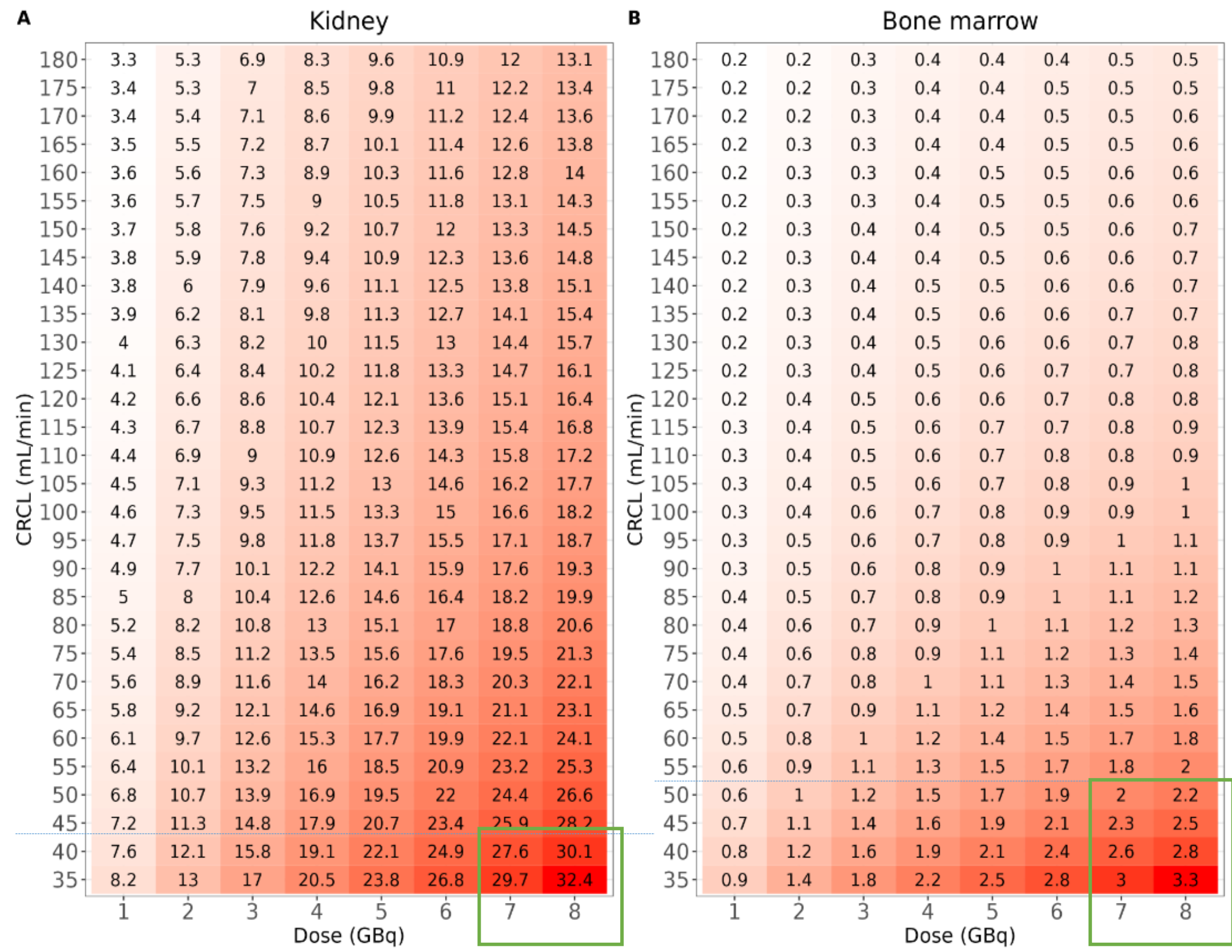
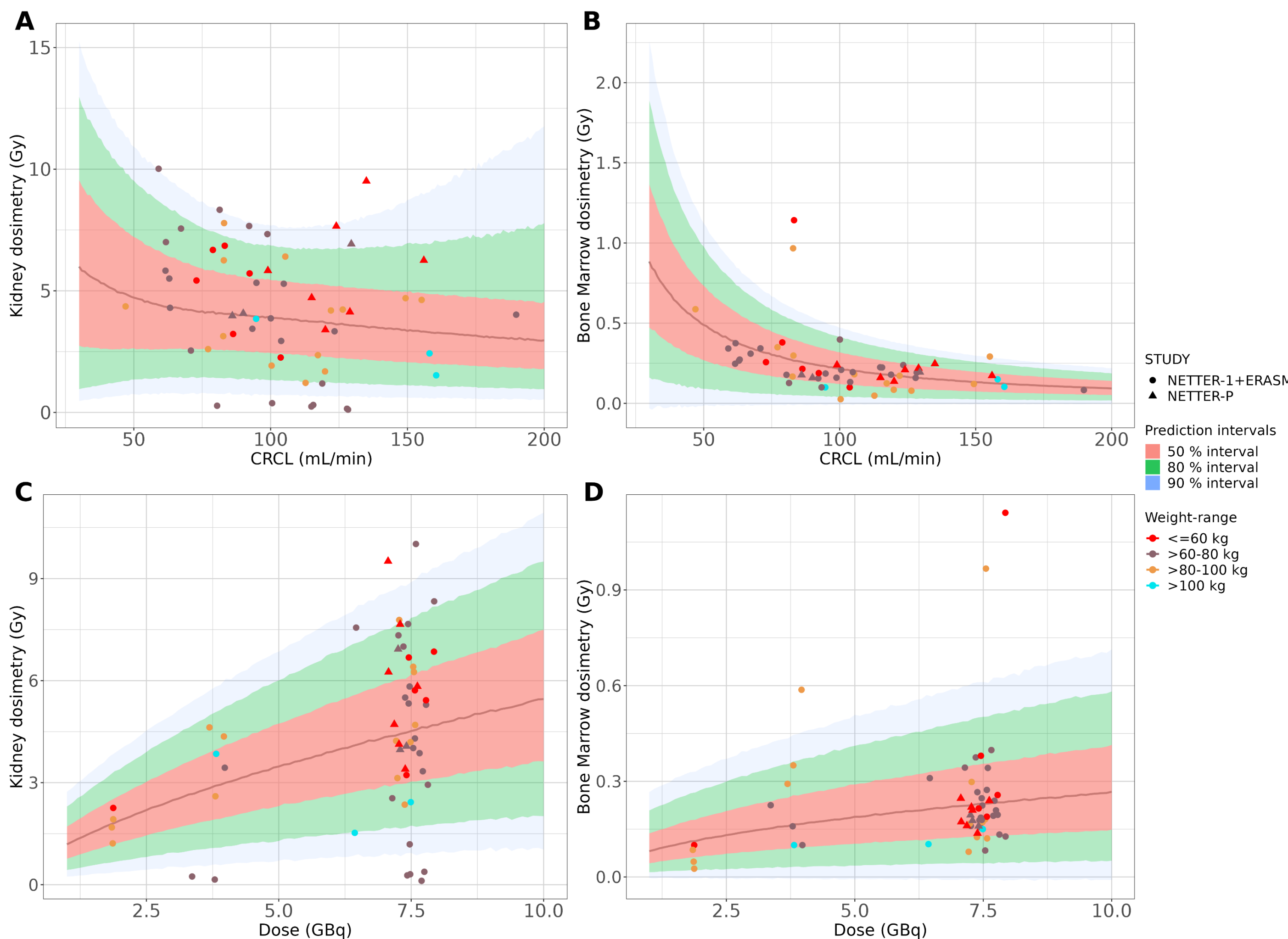


Table 1: Pharmacokinetic metrics predicted adult vs. predicted adolescent and observed adult vs. observed adolescent

Scenario	Population	N	AUClast (ng.h/mL) ^a
Observed	Adult GEP-NET	20	30.08 (50.38)
	Adolescent GEP-NET and PPGL	11	41.00 (24.15)
	Pooled Adult GEP-NET and adolescent GEP-NET and PPGL	31	33.57 (45.07)
Predicted	Adult GEP-NET	20	31.01 (40.95)
	Adolescent GEP-NET and PPGL	11	32.34 (10.43)
	Pooled Adult GEP-NET and adolescent GEP-NET and PPGL	31	31.48 (32.81)

^aGeometric mean (geometric CV%)

Figure 4: No impact of body weight on kidney and bone marrow dosimetry



Conclusions

- Comparable kidney and bone marrow dosimetry and exposure-response relationship between adults and adolescents were confirmed, with similar probabilities of median kidney and bone marrow dosimetry remaining at ≤29 Gy and ≤2 Gy EBRT thresholds, respectively.
- Based on modeling and simulation results presented, 7.4 GBq dose of [¹⁷⁷Lu]Lu-DOTA-TATE administered on 4 cycles for adults was confirmed to be appropriate in the adolescent population.

References

- Approved drugs - FDA approves lutetium Lu177 Dotatate for treatment of GEP-NETS.
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