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Feasibility of a pediatric microdose study of [^{14}C]midazolam to study the ontogeny of CYP3A-mediated drug metabolism

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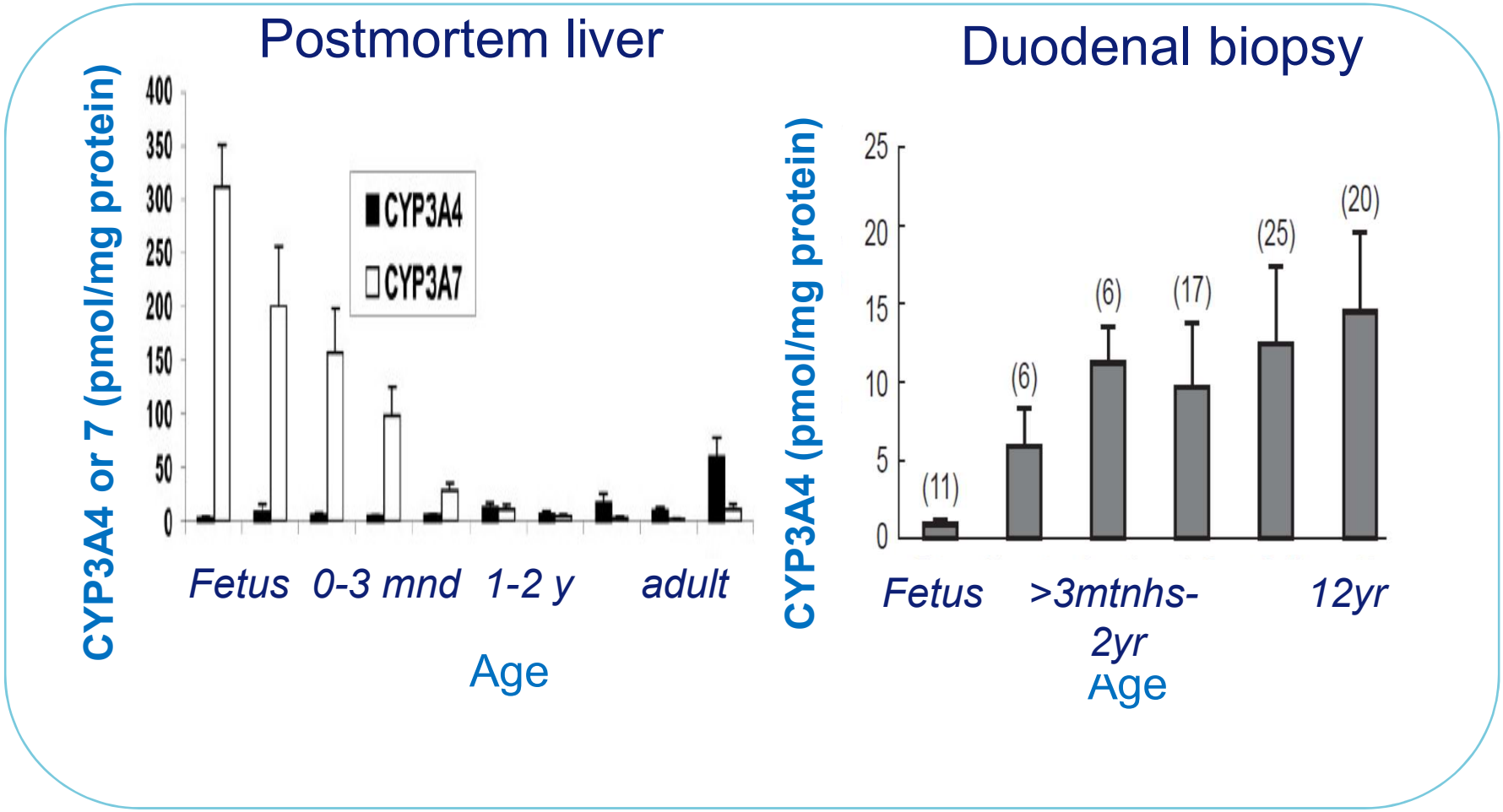
18-03-2017

TNO innovation for life

ZonMw

What is known – CYP3A ontogeny in vitro



1. Stevens et al. JPET, 2003
2. Johnson et al. Br J Clin Pharmacol, 2001

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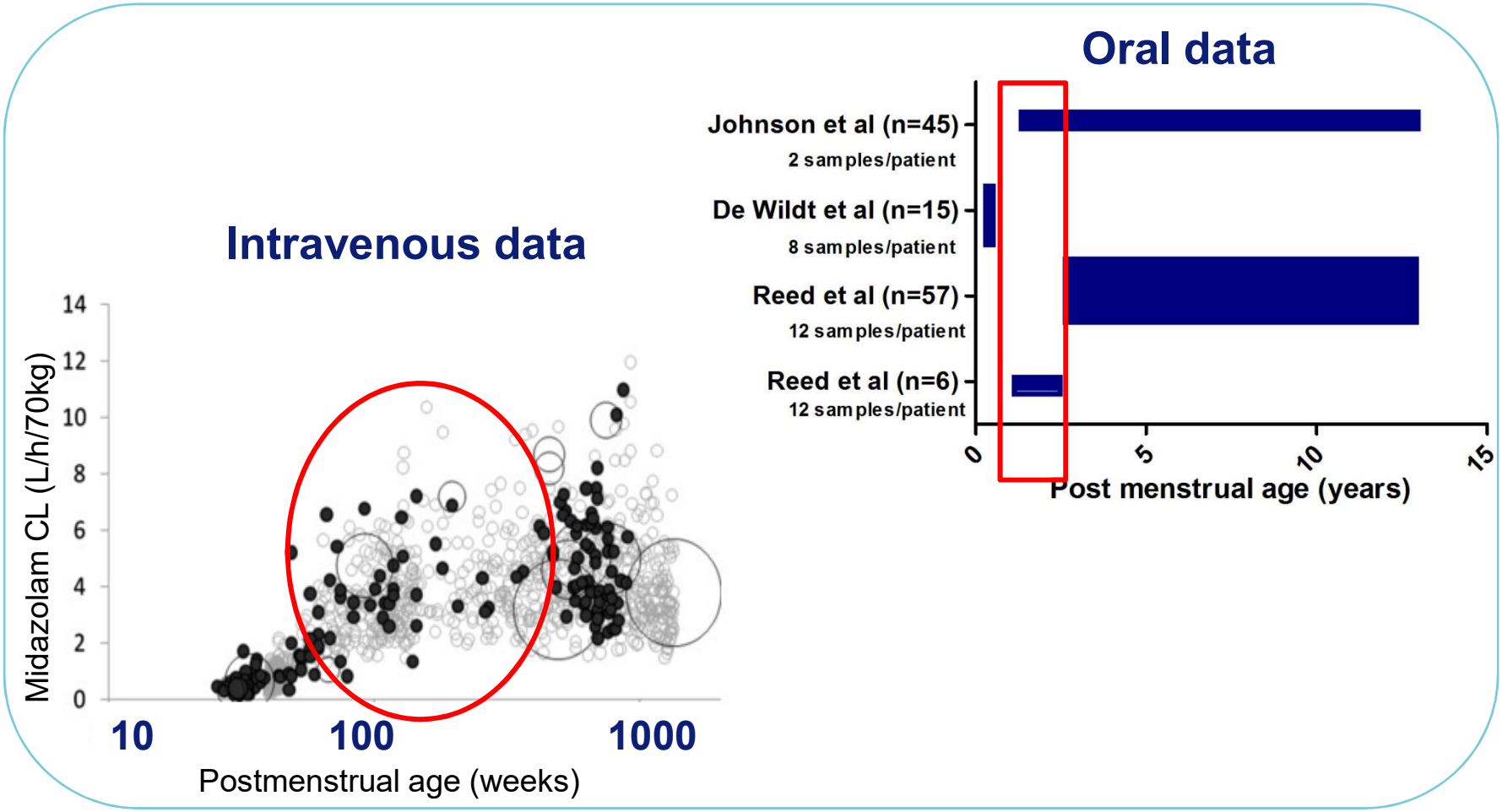
Knowledge gap CYP3A in vivo: midazolam CL as probe



1: Salem et al. Clin Pharmacokinet , 2014
2: Johnson et al. Br J Anaest, 2002
3: Reed et al. J Clin Pharmacol, 2001
4: De Wildt et al. Br J Clin Pharmacol, 2002

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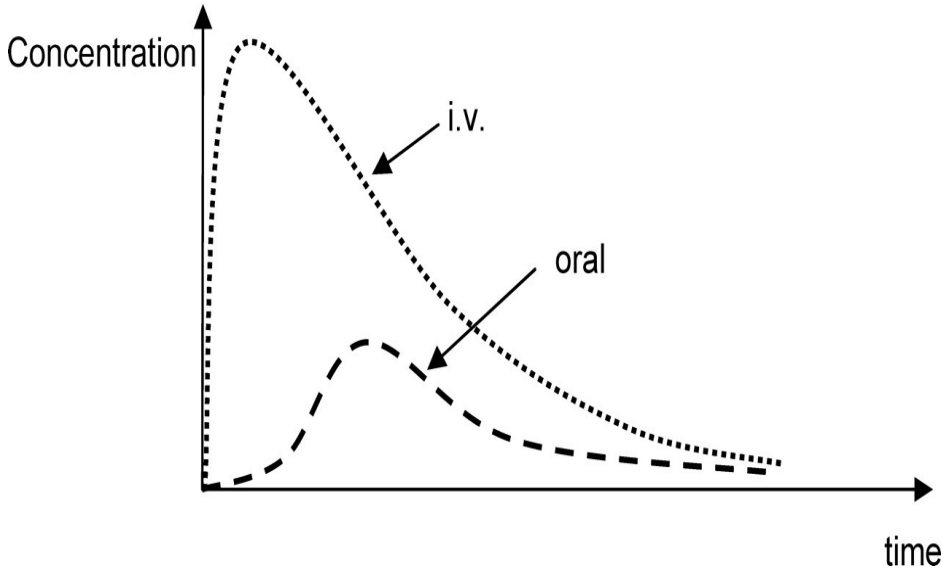
Fill this gap with microdosing

$$F = AUC_{oral} / AUC_{iv}$$



^{14}C-midazolam

FDA, 2006
EMA ,2008

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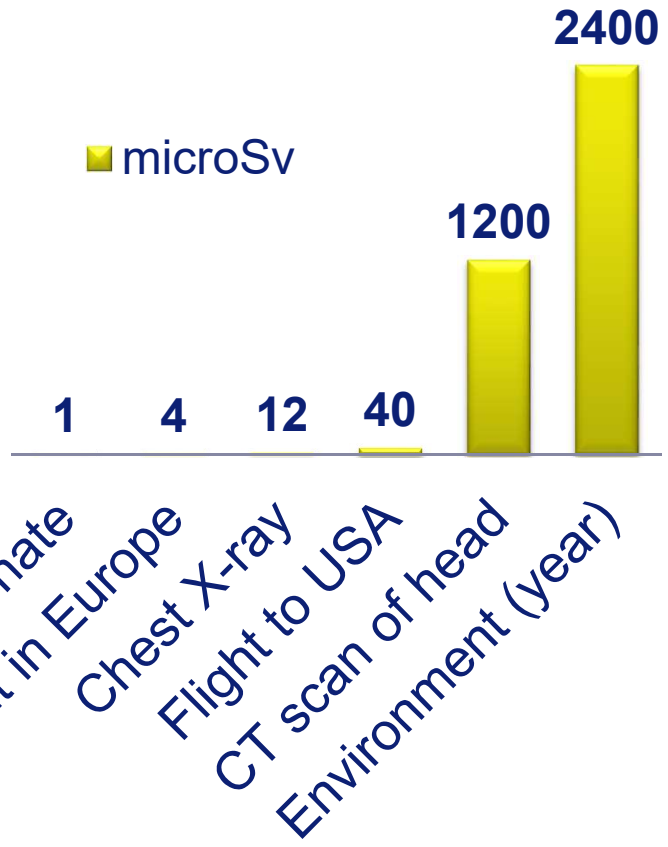
Radioactivity in kids?



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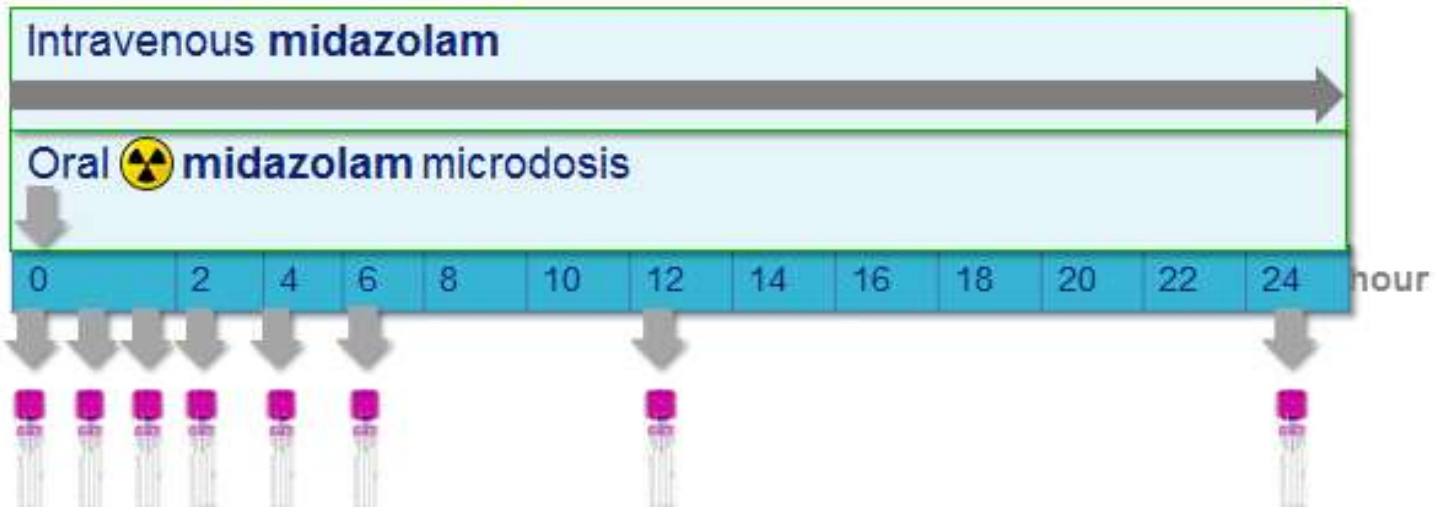
Study aim and design

Aim: To study the impact of age on intestinal and hepatic CYP3A activity using the oral and IV clearance of midazolam

Design: PK microtracer study, 0-6 yrs of age, n=60



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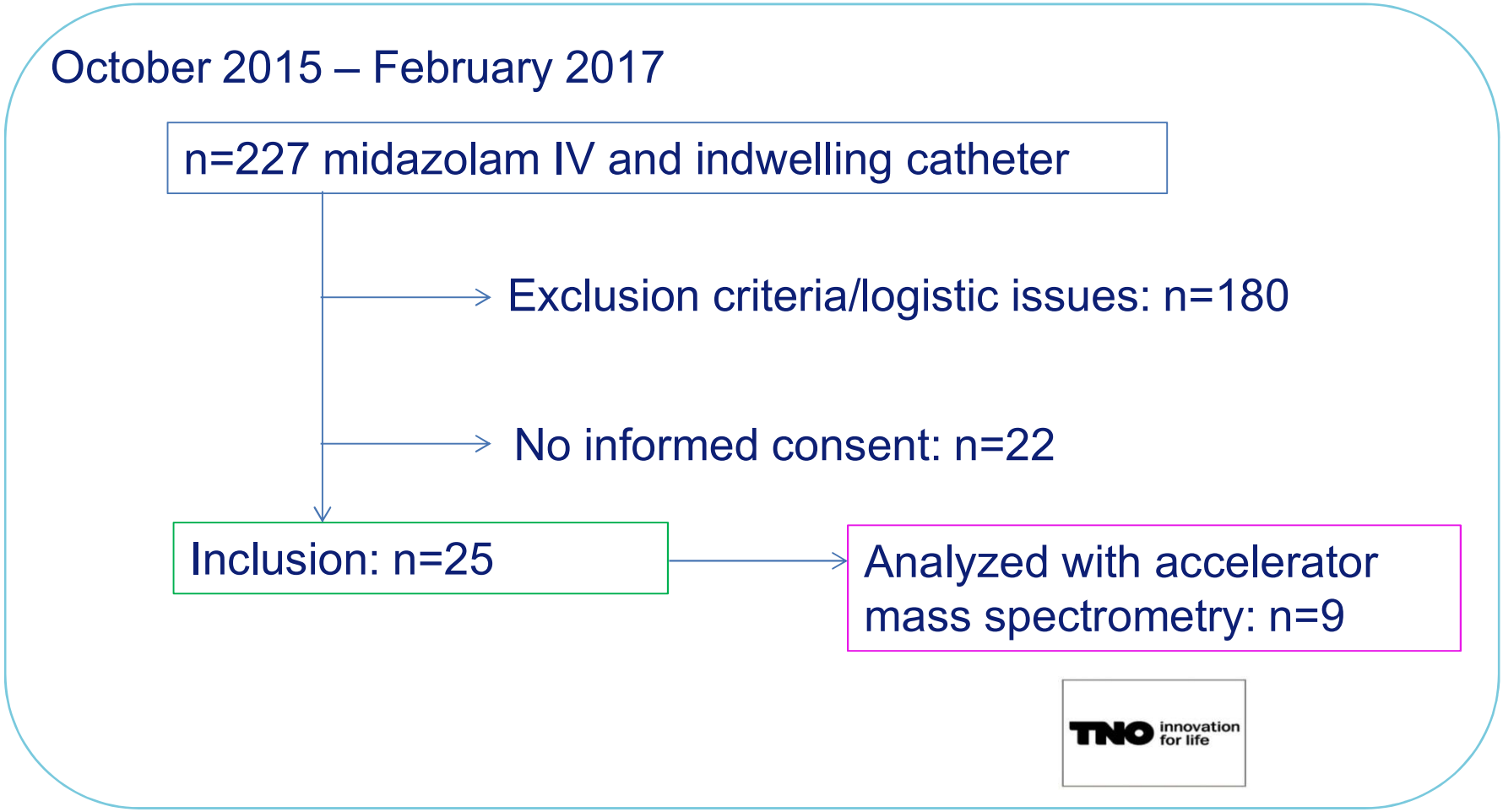
Preliminary results



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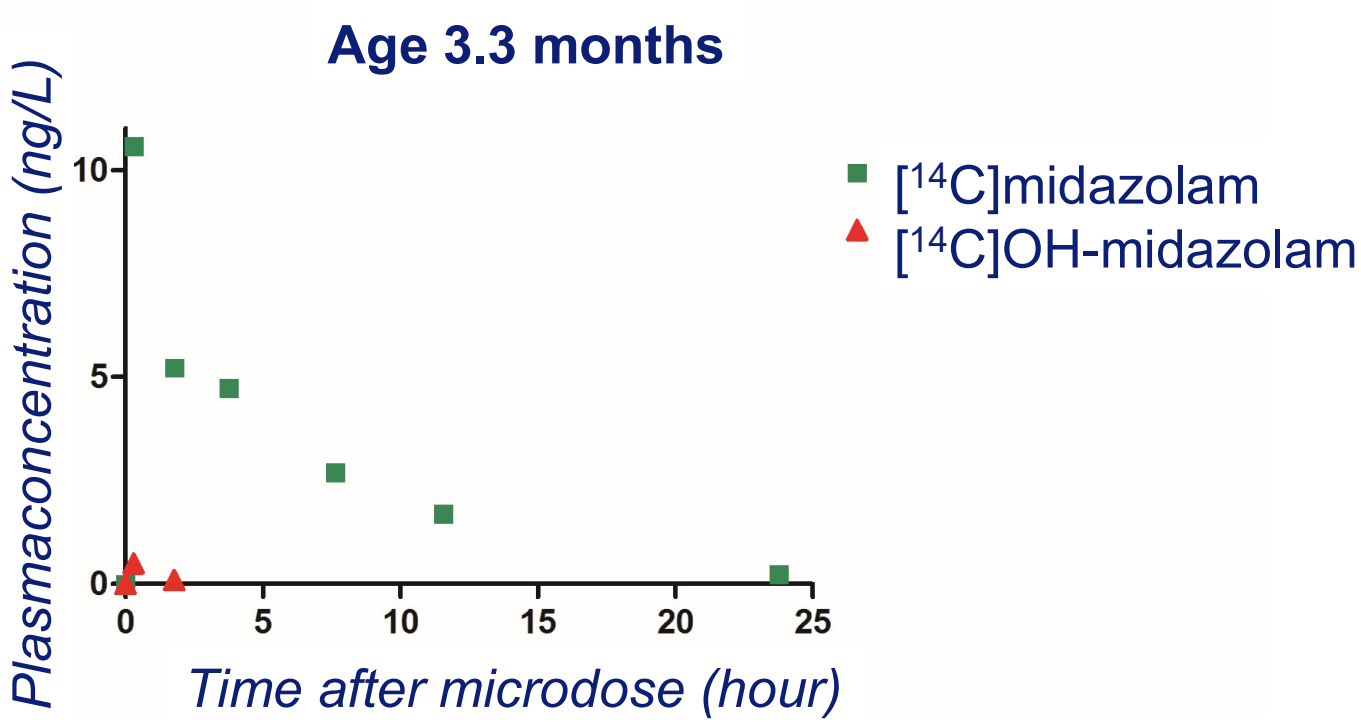
Preliminary results - example



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Dose linearity?

Our study	Reed et al
0-6 yrs	6 mth – 16 yrs
PICU patients	Healthy (ASA1)
Dose normalized to 0.25 mg/kg	Dose 0.25 mg/kg
Cmax Mida **99.8 (17.6-287.1) ng/ml**	Cmax Mida **55.6 ± 30.2 ng/ml**
Cmax OHM: **12.5 (6.0-98.0) ng/ml**	Cmax OHM: **35.6 ± 19.7 ng/ml**

2 fold difference: due to age and disease state?

1: Reed et al. J Clin Pharmacol, 2001.

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Conclusion

Conclusion so far:

- Microdosing 14C-midazolam is feasible
- Preliminary results are promising

Next step:

- Effect of age on oral bioavailability
- Determine intestinal vs hepatic metabolism (IV midazolam)

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Acknowledgements

Prof. Dr. S.N. de Wildt
Prof. Dr. D. Tibboel
Prof. Dr. K.M. Allegaert
Dr. M.G. Mooij
Dr. P.J.J.M. Janssen
Dr. L.M. Hanff
Dr. B.C.P. Koch
L.H. van Voorwinden
Edwin Spaans, PharmD

Dr. W. Vaes
Dr. E. van Duijn
Dr. R. de Ligt

Prof. Dr. S.N. de Wildt

Prof. Dr. C.A.J. Knibbe

Prof. Dr. N.H. Hendrikse
Dr. A.D. Windhorst

Preliminary results/Spare slide

[^{14}C]midazolam (n=9)	
C_{max}	7.5 (1.5-22.2) ng/L
T_{max}	0.5 (0.3-3.1) h
$T_{1/2}$	4.6 (1.1-14.0) h
CL/F	0.4 (0.2-5.3) L/h/kg
V_{ss}/F	3.1 (1.7-10.7) L/kg

[^{14}C]midazolam normalized to a dose of 0.25mg/kg (n=9)	
C_{max}	99.8 (17.6-287.1) ng/ml

Oral midazolam dose of 0.25mg/kg[1] in 6 mnths-16yrs old	
C_{max}	55.6 ± 30.2 ng/ml

1: Reed et al. J Clin Pharmacol, 2001.

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