



Universiteit
Leiden
The Netherlands

Does size matter? : bridging and dose selection in paediatric trials

Cella, M.

Citation

Cella, M. (2011, October 12). *Does size matter? : bridging and dose selection in paediatric trials*. Retrieved from <https://hdl.handle.net/1887/17924>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/17924>

Note: To cite this publication please use the final published version (if applicable).

Acknowledgements

Some say that we are what we eat. I'd rather say we are who we meet.

The work described in this thesis was possible only because of the direct and indirect contribution of many people. Without their support and assistance this thesis would have remained only an abstract idea.

I would like to start with the staff, post-doc and PhD colleagues at the division of Pharmacology of LACDR: everybody was very friendly, enthusiastic and willing to help. Tuesday's seminars *in primis*, but informal discussions too, were all a great opportunity of sharing ideas and having feedback on my research from people with different experience. Pharmacology, statistics, R and NONMEM coding were blended with jokes and laughters. I am very thankful to Anne (because she knows things), Tarj (although we still have to win a tennis match...), Jasper (I owe you a West-vleteren, master!), Chiara, Joost, Stephan, Roos, Iba, Vincent, Vincenzo, Maurice, Amit and Stina: you made my days at the Gorlaeus well worth to be spent there.

The massive amount of simulations performed in Chapter 3 would have been impossible without the R-based platform created *ad hoc* by Gijs Santen. Also, some of the nicest plots you can find in this thesis were created by Hugo Maas and Tarj Sahota, true R geniuses. The help from Linda Smith (especially for all the administrative work required to submit a PhD thesis) and Ine Goedegebuur (when I moved to London) was incredible.

I was very lucky to have bright and motivated students: Frederick Gorter de Vries did the majority of technical work on abacavir, at a time when Bayesian analysis and NONMEM did not go along very well. Even though Frank Klopprogge was a bit too prone to take revenge targeting me with tennis balls, he contributed a lot with the modelling of atovaquone and proguanil. I would also like to acknowledge the work done on diclofenac by Jona Mijalkovic and Francesco Bellanti (one day we will be able to model it, I swear!).

In 2007 I participated in the ULLA Summer School held in Leiden. There I met Joe Standing (mio fratello farmacocinetico) and Donato Teutonico (who a few years later would have helped me with half of the L^AT_EX editing of this thesis).

I am very grateful to Stefano Canti, who designed the cover of this book and solved all graphical problems I had in the last five years, and to Andrea Zanelotti, who spent a few evenings hunting for typos.

During my PhD I was invited to spend nine months at GlaxoSmithKline, Greenford, UK, and there I met the persons that are now my colleagues in the

CPMS group in Stockley Park: Monica, Alienor, Chao, Stefano, Guy, Shuying, Daren, Alex, Isabelle, Claire and Sophie they all contributed in making a great experience even better. Lorenzo, Chris and Georgios (who helped me with the other half of the L^AT_EX typesetting) joined later, but they are also part of the Tech&Dev team.

My experience in Leiden was not only about work: when I moved to The Netherlands I realised how different was my social and cultural background, not to speak of the language. I am very grateful to Rianne and her social dinners, a great opportunity to meet people and make new friends. Since there can't be *mens sana sine corpore sano*, I'd like to thank coach Humphrey, Alvaro, Frank, Julio and the rest of the LUSV basketball club: you know how much I like competition, and at the Sport Centre I found a lot of it (and winning the International Tournament was the icing on the cake). Likewise, I enjoyed being part of the London Westside squad with coach Frank, coach Erwin and a couple of hundreds of other players from all corners of the world. It may be hard to believe, given my idiosyncrasy to football, but I also appreciated very much the wednesdays playing as a goalkeeper for De Dream Team alongside Oliver, Daniel, Bram, Ding and the other members of DDT.

It is a special pleasure to mention two persons in particular who supported me in a number of ways since the very start of my journey into PhD life. Robert, you were always on my side, whether it was cooking german potato balls, going play some hoops, teaching me how I could safely have more than just two beers, hair-drying climbing boots and many more stories now stored in my memory. Elke, thanks for being... Elke: probably you are the person with whom I have mostly agreed on our disagreements, yet you made me think about a lot of things I was previously giving for granted. You also provided the dutch translation of this thesis. Thanks to you both for your friendship.

Un grande ringraziamento va anche agli amici di Lodi (e Oslo e Baku), che mi hanno supportato (e sopportato) in questi anni con tutti i mezzi a loro disposizione. Che fosse un blog, messenger, skype o facebook, le distanze si accorciavano e la nostalgia non faceva in tempo a far presa. Ad ogni rientro mi avete fatto sentire come se non fossi mai partito. In particolare, voglio ringraziare i membri del Gruppo Trekking Lodi, con cui, indomiti e invitti, abbiamo scalato negli anni decine di cime alpine.

A mamma Mariangela, papà Giuseppe e Daniele, perché avete sopportato le mille domande di un bambino curioso, perché mi avete insegnato che le novità vanno esplorate, non temute, e perché avete sempre assecondato le mie scelte.

Infine, tra tutte queste persone speciali, ce n'è una che è un po' più speciale delle altre: mia moglie Claudia. Vicina o lontana, il tuo supporto e la tua fiducia in me hanno sempre rappresentato la spinta per superare le difficoltà. Questa tesi non può che essere dedicata a te.

Curriculum vitæ

Massimo Cella was born on the 13th of November 1978 in Lodi, Italy. He attended the Liceo Scientifico (High School) “G.Gandini” in Lodi, where he obtained his scientific diploma in 1997. Subsequently he started his undergraduated training in Pharmaceutical Chemistry and Technology at the Università di Pavia, where he obtained his MSc in January 2004, followed by a 2nd level University Master degree in Pre-formulation and Drug Development in 2005 and another 2nd level University Master degree in Regulatory Affairs in 2007. In June 2004 he started a research fellowship at the Consorzio per le Valutazioni Biologiche e Farmacologiche (CVBF) in Pavia, under the supervision of Prof. Adriana Ceci. Here he worked on designations and registration dossiers for orphan and paediatric drugs. At the same time he was actively involved in the research activities of the Task Force in Europe for Drug Development for the Young (TEDDY), a Network of Excellence funded under the Sixth EU Framework Programme for Research and Technological Development.

In November 2005 Massimo started his PhD research programme at the division of Pharmacology of the Leiden-Amsterdam Center for Drug Research in Leiden, with Dr. Oscar Della Pasqua as co-promoter and Prof. Meindert Danhof as promoter, which led to this thesis. From September 2009 to May 2010 he was invited to GlaxoSmithKline in Greenford, UK, to work on PK modelling of drug combinations in children.

Since May 2010 Massimo Cella is a post-doc fellow at the Clinical Pharmacology - Modelling and Simulation group of GlaxoSmithKline, Stockley Park, UK, where he is part of the Innovative Medicine Initiative (IMI) funded project *PharmaCog*. Among other tasks, he has taken responsibility for the development of translational and disease progression models in Alzheimer's Disease.

List of publications

M. Cella, W. Zhao, E. Jacqz-Aigrain, D. Burger, M. Danhof and O. Della Pasqua. Paediatric drug development: are population models predictive of pharmacokinetics across paediatric populations? *Br. J. Clin. Pharmacol.* 2011 **72**(3): 454-464.

M. Cella, C.A. Knibbe, M. Danhof and O. Della Pasqua. What is the right dose for children? *Br. J. Clin. Pharmacol.* 2010 **70**(4): 597-603.

M.Y. Peeters, K. Allegaert, H.J. Blussé van Oud-Alblas, **M. Cella**, D. Tibboel, M. Danhof M and C.A. Knibbe. Prediction of propofol clearance in children from an allometric model developed in rats, children and adults versus a 0.75 fixed-exponent allometric model. *Clin. Pharmacokinet.* 2010 **49**(4): 269-275.

M. Cella, F. Gorter de Vries, D. Burger, M. Danhof and O. Della Pasqua. A model-based approach to dose selection in early pediatric development. *Clin. Pharmacol. Ther.* 2010 **87**(3): 294-302.

E.H. Krekels, J.N. van den Anker, P. Baiardi, **M. Cella**, K.Y. Cheng, D.M. Gibb, H. Green, A. Iolascon, E.M. Jacqz-Aigrain, C.A. Knibbe, G.W. Santen, R.H. van Schaik, D. Tibboel and O. Della Pasqua. Pharmacogenetics and paediatric drug development: issues and consequences to labelling and dosing recommendations. *Expert Opin. Pharmacother.* 2007 **8**(12): 1787-1799.