

# **Pharmacokinetic-Pharmacodynamic Modelling of Allopurinol, Its Active Metabolite Oxypurinol and Biomarkers Hypoxanthine, Xanthine and Uric Acid in Hypoxic-Ischemic Encephalopathy Neonates**

Wan-Yu Chu<sup>1\*</sup>, Kim V. Annink<sup>2\*</sup>, A. Laura Nijstad<sup>1</sup>, Christian A. Maiwald<sup>3</sup>, Michael Schroth<sup>4</sup>, Loubna el Bakkali<sup>5</sup>, Frank van Bel<sup>2</sup>, Manon J.N.L. Benders<sup>2</sup>, Mirjam M. van Weissenbruch<sup>5</sup>, Anja Hagen<sup>4</sup>, Axel R. Franz<sup>3</sup>, Thomas P.C. Dorlo<sup>6</sup>, Karel Allegaert<sup>7,8\*\*\*</sup>, and Alwin D.R. Huitema<sup>1,6,9\*\*</sup> on behalf of the ALBINO Study Group

<sup>1</sup> Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

<sup>2</sup> Department of Neonatology, University Medical Center Utrecht Brain Center, Utrecht University, Utrecht, the Netherlands

<sup>3</sup> Center for Pediatric Clinical Studies and Department for Neonatology, University Hospital Tuebingen, Tuebingen, Germany

<sup>4</sup> Cnops Children's Hospital, Department of Neonatology and Pediatric Intensive Care, Nuremberg, Germany

<sup>5</sup> Department of Neonatology, Emma Children's Hospital, Amsterdam UMC, location VUmc, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands

<sup>6</sup> Department of Pharmacy & Pharmacology, Netherlands Cancer Institute, Amsterdam, the Netherlands

<sup>7</sup> Department of Development and Regeneration, and Pharmaceutical and Pharmacological Sciences, KU Leuven, Belgium

<sup>8</sup> Department of Clinical Pharmacy, Erasmus MC, Rotterdam, the Netherlands

<sup>9</sup> Department of Pharmacology, Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands

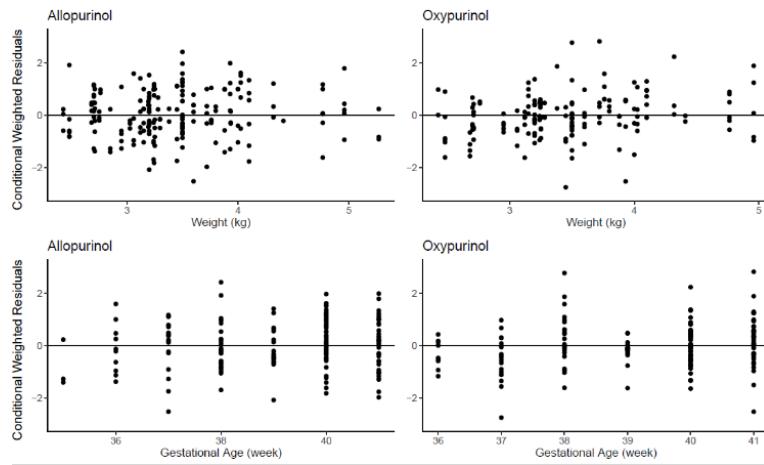
\* shared first authors

\*\* shared last authors

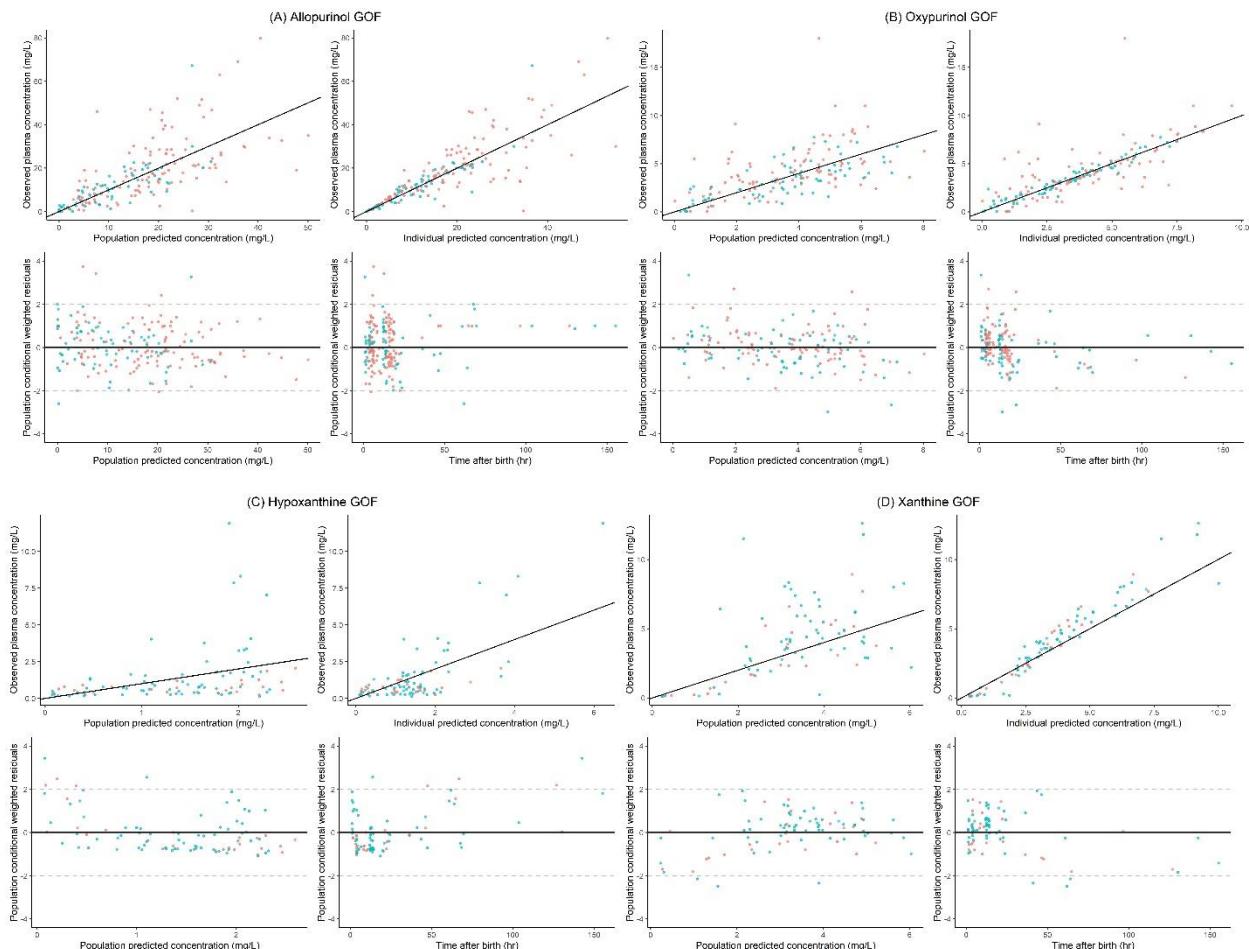
\*\*\* the ALBINO coordinating investigators are Axel R Franz (University Hospital Tübingen, Germany); Mario Rüdiger (University Hospital CG Carus, Medizinische Fakultät der TU Dresden, Germany). The beneficiaries and national coordinators are Axel R Franz and Christian F Poets (Tübingen, Germany), Mario Rüdiger (Dresden, Germany), Manon Benders and Frank van Bel (Utrecht, the Netherlands), Karel Allegaert and Gunnar Naulaers (Leuven, Belgium), Dirk Bassler (Zurich, Switzerland), Katrin Klebermass-Schrehof (Vienna, Austria), Maximo Vento (Valencia, Spain), Hercilia Guimaraes (Porto, Portugal), Tom Stiris (Oslo, Norway), Isabella Mauro (Udine, Italy), Marjo Metsäranta (Helsinki, Finland), Sampsa Vanhatalo (Helsinki, Finland), Jan Mazela (Poznan, Poland), Tuuli Metsvaht (Tartu, Estonia), Yannique Jacobs (ACE Pharmaceuticals, Zeewolde, the Netherlands).

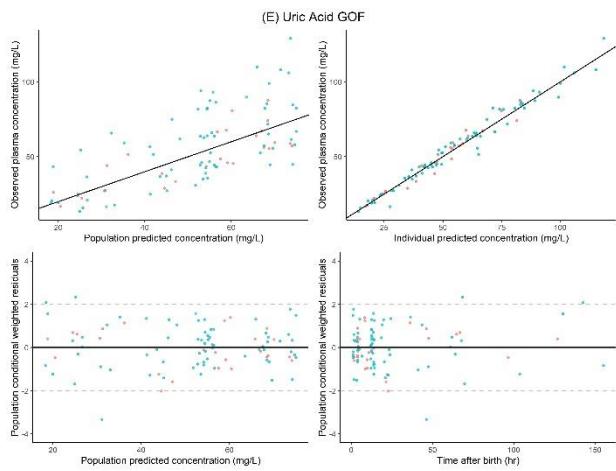
## Supplementary Information

### S1. Population conditional weighted residuals against BW and GA plots for allopurinol and oxypurinol



**S2. Goodness-of-fit (GOF) plots of (A) allopurinol (B) oxypurinol (C) hypoxanthine (D) xanthine and (E) uric acid. Data from therapeutic hypothermia (TH) and non-TH patients were colored in blue and red, respectively.**





S3. Normalized prediction distribution errors (NPDE) of (A) allopurinol (B) oxypurinol (C) hypoxanthine (D) xanthine and (E) uric acid. DV, concentration; npd, normalized prediction distribution errors.

