Model based estimation of posaconazole tablet and suspension bioavailability in hospitalised children using real–world therapeutic drug monitoring data in patients receiving intravenous and oral dosing

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ABSTRACT   Invasive fungal infections are a major cause of morbidity and mortality for immunocompromised patients. Posaconazole is approved for treatment and prophylaxis of invasive fungal infection in adult patients with intravenous, oral suspension and gastro-resistant/delayed-released tablet formulations available. In Europe posaconazole is used off-label in children and there is an urgent need for greater understanding of posaconazole pharmacokinetics in this special population.

A population pharmacokinetic model was developed using posaconazole therapeutic drug monitoring data following intravenous and oral dosing in hospitalised children, thus enabling estimation of paediatric suspension and tablet oral bioavailability. In total 297 therapeutic drug monitoring plasma levels from 104 children were included in this analysis. The final model was a 1-compartment model with first order absorption and non-linear elimination. Allometric scaling on clearance and volume of distribution was included *a priori*. Tablet bioavailability was estimated to be 66%. Suspension bioavailability was estimated to decrease with increasing dose, ranging from 3.8 to 32.2% in this study population. Additionally, concomitant use of proton pump inhibitors was detected as a significant covariate, reducing suspension bioavailability by 41.0%.

This is the first population pharmacokinetic study to model posaconazole data from hospitalised children following intravenous, tablet and suspension dosing simultaneously. Key to the credible joint estimation of tablet and suspension bioavailability has been incorporation of saturable posaconazole clearance into the model. To aid rational posaconazole dosing in children the model has been used alongside published pharmacodynamic targets to predict the probability of target attainment using typical paediatric dosing regimen.

KEYWORDS: Posaconazole; paediatric dosing; bioavailability; population pharmacokinetics.

INTRODUCTION

Invasive fungal infections (IFIs) present a serious risk for morbidity and mortality in immunocompromised patients undergoing both solid organ and stem cell transplantation. Posaconazole was first approved for use in Europe for adults in 2005, with Merck Sharp and Dohme (MSD) initially launching the oral suspension, followed by a gastro-resistant/delayed release tablet and then an intravenous (IV) formulation. Recently, in the US, a new posaconazole suspension has been approved for use in children above 2 years of age. (1). However, in Europe, paediatric posaconazole use is still off-label, with children often receiving the suspension product, due to inability to swallow tablets. As more formulation options are becoming available for posaconazole dosing in children, there is an urgent need for greater understanding of posaconazole pharmacokinetics (PK) and its formulation dependent absorption and absolute bioavailability (F) in this special population (2).

Posaconazole is lipophilic (logP=4.6), dibasic, poorly soluble, and highly plasma protein bound (97 to 99% bound, predominately to albumin) (3). Posaconazole PK after IV dose escalation (50, 100, 150, 200 and 300 mg) in healthy adults (n=9) follows bi–exponential distribution and elimination, with saturable clearance. Clearance decreased on dose escalation from 10.9 L/hr to 6.9 L/hr (determined by non-compartmental analysis, NCA) and inter-individual variability was 32%. Half-life increased from 19 hrs at 50 mg to 25 hours at 300 mg and the mean volume of distribution of posaconazole was 261 L (226-295 L) (4).

Posaconazole undergoes metabolism in healthy adults, primarily mediated by uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes (especially UGT1A4). The predominant route of elimination is through faecal excretion with only trace amounts of posaconazole measured in urine (5). Posaconazole is a substrate for P-gp efflux, and biliary and intestinal secretions are likely (6). The PK of the original posaconazole suspension has been extensively studied in both adult healthy volunteers and patients at risk of IFIs (7, 8, 9, 10, 11, 12).

Previous population PK analysis of paediatric posaconazole therapeutic drug monitoring (TDM) data has confirmed that exposure following suspension posaconazole dosing increases in a sub-proportional manner (13). This is thought to be due to a reduction in the fraction of dose absorbed with escalating dose, due to the poor intestinal solubility of posaconazole. As observed in adults, elevated gastric pH also reduces exposure in children following suspension dosing (13). The gastro-resistant/delayed release tablet formulation that was approved in Europe in 2014 was developed specifically to improve the extent of oral absorption relative to the suspension and to overcome issues such as the requirement for multiple daily dosing in conjunction with a high fat meal.

Here, we present the population PK analysis of real world posaconazole TDM data from hospitalised children receiving both IV and oral posaconazole. While previous studies have reported paediatric posaconazole PK data, simultaneous model based analysis of IV, suspension and tablet data to enable estimation of formulation dependant F in children has not previously been reported.

RESULTS

Pharmacokinetic model building for the paediatric population was informed by previously published adult dose escalation data in a first step. These results were then taken forward as initial estimates to inform the scaled paediatric model parameters. Subsequently, the paediatric TDM data was analysed.

87

88 **Pharmacokinetic model building - adult literature data** A two–compartment
89 model was found to be superior (difference in objective function value,- OFV, 24.95 for
90 two degrees of freedom, df) to a one–compartment model when using linear clearance
91 to describe the IV dose escalation (50-300 mg) data published by Kersemaker et. al. ([4]).
92 Introducing saturable clearance further improved the model (- OFV 34.82 for one df).
93 Saturable clearance is represented by parameters CL_{sat}, the maximum (or saturated)
94 rate of clearance and K_m, the concentration at which clearance is half its maximal
95 value. Figure [1]A presents the model predicted concentration-time profiles versus the
96 extracted observed data and Figure [1]B the estimated model parameters along with
97 visualisation of the impact of posaconazole concentration on adult adjusted clearance.
98 CL_{sat} is estimated to be 12.11 L/hr/70kg, total volume of distribution (Vss = V1 + V2)
99 is 260.2 L/70kg and Km is 0.49 mg/L (490 ng/mL, 0.7 μM). No inter–individual variability
100 (IIV) was estimated for these data as only the average concentration–time profiles were
101 available.

102 The clearance and volume of distribution parameter estimates were carried for-
103 ward to model adult tablet PK data taken from the control arm of the 5-way crossover
104 study published by Kraft et. al. (400 mg tablet, *n*=20 healthy adults) ([14]). With Ka_{tab}
105 fixed to the previously estimated value of 0.588 /hr ([15]) tablet F was estimated to be
106 0.59 (5.9% RSE) and visually C_{max} and $AUC_{f_…}$ were well described.

107

108 **Observed Pardiatric TDM and Covariate Data** The final paediatric dataset is
109 described in Table [1]. Age and body weight (BW) of patients in the study population
110 ranged from 0.4 to 16.8 years (median 6.2 years) and 4.3 to 86.1 kg (median 19.5 kg)
111 respectively.

112 Dose frequency varied between the formulations and doses ranged from 2.0 to
113 11.5, 1.6 to 10.6, 1.8 to 35.5 mg/kg for the IV, tablet and suspension formulations re-
114 spectively. Across all formulations, 69% percent of the plasma levels were collected
115 during periods of concomitant proton–pump inhibitor (PPI) administration and 49% of
116 levels during a period of diarrhoea. Non-surgical prophylaxis accounts for the majority
117 (43.7%) of in-patient poaconazole dosing.

118 The median [inter-quartile range, IQR] alanine aminotransferase (ALT) and plasma
119 protein albumin (ALB) concentrations in blood were 49 [33-83] U/L and 33 [30-36] g/L
120 respectively. Of the 297 plasma levels in the final data set 94.3% have an ALT concen-
121 tration measured within 24 hours, for ALB this is higher at 98.3%.

122 The measured plasma concentrations pooled by formulation and compared to
123 the calculated time after last dose (TALD) are presented in Figure [2]. Nineteen of the
124 297 plasma concentrations in this dataset (6.4%) are reported as below the limit of
125 quantification (BLOQ) these include 5 tablet and 14 suspension levels.

126 The paediatric data set included 47 plasma levels collected after IV dosing in 13
127 children. Cross over data (plasma levels following oral and IV dosing) was available for
128 7 of the 13 subjects. The IV data set includes data from children aged 2.8 to 13.8 years,
129 weighing 12.0 to 52.9 kg.

130

131 **Pharmacokinetic model building - paediatric real-world data** The base struc-
132 tural model was a one compartment model with linear clearance. IIV was introduced
133 only on clearance. A combined error model was used to describe residual unexplained
134 variability. Bioavailability was estimated for suspension and tablets separately. Al-
135 lometric weight scaling was included *a priori*. Base model parameter estimates are
136 presented in Supplementary Table S1. Tablet bioavailability estimated from this lin-

137 ear model was 1.39 (41.1% RSE). No improvement was seen with a two compartment
138 model. Adding dose-dependent bioavailability for the suspension improved the over-
139 all fit (- OFV 21.26) but tablet F remained above 1 (F_{tab} 1.36 with 33.4% RSE).
140   Non-linear clearance with parameters fixed to adult estimates increased OFV but
141 tablet F decreased below 1. A sensitivity analysis varying Km found a value of 2 mg/L to
142 adequately predict the observed data. Addition of IIV to volume, tablet F and suspen-
143 sion $D_†$. was tested in a next step, however, the data set only supported estimation of
144 IIV on CL_{sat} and volume of distribution .
145 Covariate analysis revealed PPI co-administration on F_{sus} to significantly improve the
146 model (- OFV 50.72 for 1 df). No further covariate effects were found to be significant
147 at a level of p<0.01 on backward elimination. Age was not tested in the model as no
148 relationship was detected with CL_{sat} using visual exploration of the base model, see
149 Figure 3.
150   The final paediatric population pharmacokinetic model consisted of a one-compartment
151 model with non-linear elimination. Bioavailability was estimated separately for tablet
152 and suspension data. A dose-dependent decrease in bioavailability could be detected
153 for suspension. Also, an effect of concomitant PPI use was estimated on suspension
154 bioavailability. Additive error was removed in the final model as it was estimated to
155 be zero.
156   Table 2 presents the final model parameter estimates. The NONMEM code is in-
157 cluded in supplementary material. Goodness of fit (GOF) plots and prediction-corrected
158 visual predictive checks (VPCs) split by formulation are presented in Figure 4. Com-
159 bined GOF plots can be found in supplementary Figure S1. Visualisation of covariate
160 effects alongside the effect of plasma concentration on clearance are visualised in Fig-
161 ure 5. The model estimated dose independent tablet bioavailability, was included in
162 Figure 5 for comparison.
163
164   **Pharmacokinetic simulations and probability of target attainment predic-**
165 **tions** The age and weight distributions of the full hypothetical population are pre-
166 sented in supplementary information Figure S2, the median (range) age and weight
167 were 4.5 years (0.51 to 16.0 years) and 19.1 kg (2.88 to 79.67 kg) respectively. The me-
168 dian age and weight in each simulation group are presented in Figure S3.
169   To visually assess the model predicted time to steady state for the different formu-
170 lations using 'typical' dosing regimens, 5 mg/kg QD tablet and IV simulations are com-
171 pared with 10 mg/kg TID suspension simulations (both with and without PPI). The me-
172 dian (50th percentile) concentration-time profiles for all age groups following 8 days of
173 dosing using these 'typical' regimens are presented in supplementary information Fig-
174 ure S4, while a comparison of the predicted 2.5th, 50th and 95th percentiles for each
175 regimen in the 4-6 year old age group on day 8 of dosing are compared in Figure S5.
176 The youngest child in the observed population to receive a posaconazole tablet was
177 8.9 years. However, visualisation of all formulations was conducted across all chosen
178 age groups to allow a theoretical comparison. That said, it is also acknowledge that
179 swallowing a tablet maybe challenging for most 4 year olds.
180   Figure 6 presents the probability of target attainment (PTA) for all ages groups. To
181 aid comparisons between the tablet and liquid formulations the red circle highlights
182 the probability of target attainment for the 4-6 year old group at a dose of 10 mg/kg
183 using either QD IV or tablet dosing and TID suspension dosing.

DISCUSSION

184 We describe the first intravenous and oral population PK model based on real–world
185 therapeutic drug monitoring data from immunocompromised children. This enabled
186 the first joint estimation of posaconazole tablet and suspension oral bioavailability in
187 children. It is also the first population PK model estimating the non-linear clearance
188 previously reported by Kersemaekers et. al.(4), which was key to a meaningful estima-
189 tion of tablet bioavailability.

190   The starting point for our model development was a one–compartment distri-
191 bution and elimination model with linear clearance. Indeed this model is used in
192 most published posaconazole models irrespective of the underlying study popula-
193 tion. (16, 17, 18, 19, 15) While an acceptable description of this sparse paediatric TDM
194 dataset could be achieved with a model employing linear clearance, it did not allow
195 meaningful estimation of both tablet and suspension F. Although this model was able
196 to reconcile the low exposures seen following suspension dosing, significantly improv-
197 ing predictions for tablet exposures was only achieved through estimation of a tablet
198 bioavailability > 1. Thus, our analysis suggests, that the poor exposure seen following
199 suspension dosing, is not simply due to poor intestinal posaconazole solubility but is
200 also compounded by a saturable clearance mechanism.

201   A comparison of different formulations and their NCA based parameters has been
202 published by Dekkers et al. (20). Volume of distribution for the IV formulation is re-
203 ported at 261 L, whereas V/F for tablet is stated at 394 L and oral suspension at 1774 L.
204 This agrees well with the adult estimated V of 250 L for IV and the derived Tablet V/F
205 of 379L when considering the estimated F of 66%. With an estimated oral suspension
206 bioavailablility of 18% at a common adult dose of 200 mg, V/F is calculated at 1406 L.

207   Our estimated adult CL_{sat} of 12 L/h/70kg would equal CL/F of 60 L/h/70kg for oral
208 suspension taking the model estimated median bioavailability of around 20%. At the
209 C_{avg} of 0.7 mg/L, CL is reduced to 10 L/h/70kg, which equivalent to 50 L/h/70kg for CL/F.
210 This agrees well with the range of CL/F of 30 to 113 L/h for oral suspension reported in
211 literature (16, 17, 18). For tablet data a CL/F is reported at 7.3 and 8 L/h (19, 15), which
212 is lower than a converted CL/F of 12.5 L/h at C_{avg} of 0.7 mg/L taking the estimated 80%
213 bioavailability into account.

214   The reason non-linearity of posaconazole CL has not previously been found in
215 suspension PK modelling is likely due to the fact that intestinal absorption is so poor
216 that nonlinear clearance was masked. The enhanced solubility of posaconazole in the
217 tablet combined with real world dosing in the fed state means tablet F is estimated to
218 be > 1 if clearance is assumed to be linear. Whilst this has not previously been reported
219 in human PK models, it has however been seen preclinically in IV/tablet crossover stud-
220 ies in dog (21).

221   When we tried to estimate K_m and CL_{sat} using this paediatric dataset, K_m would
222 go to the upper boundary essentially collapsing clearance back to a linear process.
223 F_{tab} would however be estimated well over 1. A value of 2 mg/L for the K_m was identi-
224 fied through parameter sensitivity analysis and rationalised since between 97-99% of
225 posaconazole is bound to plasma proteins (3). Thereby only small increases in plasma
226 protein binding moving from healthy adults to a sick paediatric population could lead
227 to commensurate increases in the free/unbound posaconazole K_m.

228   Tablet bioavailability estimated by this analysis is 66% (22.1% RSE). The fasted state
229 tablet F reported to the EMEA as part of clinical development was 54% (31.9 %CV) (22).
230 In addition an absolute bioavailability study in healthy adult Chinese subjects has been
231 published recently and after 300 mg IV/tablet crossover (*n*=18 Chinese subjects) in the
232 fasted state the geometric mean F of the tablet is 42.2%, Tmax 4.0 hours (range; 2-

234 6 hours). The authors also found that tablet exposure increased 2-fold in the fed state
235 (fed state F_{tab} = 87.1%) (23). Unfortunately for our real-world data, information on the
236 patients fed or fasted status was unavailable.

237 The suspension $D_{\dagger\bullet}$ has been estimated previously by Boonsathorn et. al. at
238 99 mg•m^f (13). Due to the lack of IV data availability at the time, this was estimated
239 relative to the tablet CL/F and thus, was estimated relative to tablet exposure. Figure 5
240 shows how estimated suspension bioavailability evolves across dose range evaluated
241 in this study population. With IV data available for this analysis, we estimate suspen-
242 sion $D_{\dagger\bullet}$ relative to IV exposure to be 43.25 mg•m^f (14.2% RSE).

243 Concomitant PPI dosing is known to be an important covariate in uencing suspen-
244 sion exposure (F_{sus}). Our analysis was able to re-con rm this nding with concomitant
245 PPI dosing on F_{sus} reducing suspension bioavailability by 41% (27.5% RSE). This is in
246 agreement with the e ect estimated by Boonsathorn et. al.; 42% and the 45% esti-
247 mated by Dolton et. al. in healthy volunteers (13, 16). Figure 5 shows, that at the
248 highest suspension dose evaluated (625 mg•m^f) only 3.8% of the posaconazole given
249 to the patient is estimated to reach the systemic circulation when administered along-
250 side a PPI.

251 While diarrhoea has previously been reported to be an important covariate on
252 Fsus (13), this covariate e ect was not retained when employing a 1% level of signi -
253 cance in the backward elimination step. However curating information regarding the
254 occurrence of diarrhoea is complex and also highly subjective relying on an individual's
255 interpretation of diverse patient history notes. It should also be of noted that the per-
256 centage of posaconazole levels in this modelling dataset identi ed as being collected
257 during periods of diarrhoea was higher; 49% as compared to the 20% of samples iden-
258 ti ed in the Boonsathorn dataset.

259 The construction of a population pharmacokinetic model further enabled us to
260 simulate di erent dosing regimen for the three formulations to allow a side-by-side ex-
261 posure comparison and evaluation against PKPD indices. This was expressed through
262 probability of target attainment calculations in Figure 6.

263 Pharmacodynamic target de nition varies across literature. Jang et. al. published
264 in 2010 on the posaconazole exposure-response relationship, which suggest C_{avg} of
265 > 700 ng/mL to yield adequate antifungal coverage (24). Posaconazole e cacy in pre
266 clinical models by Gastine et. al. found an $AUC_{f...}$ of 30 mg.h/L or C_{min} > 1 mg/L
267 to be relevant (25). While Groll et. al. report intravenous/PO crossover PK data us-
268 ing the 'new' posaconazole suspension in children and target an exposure window of
269 C_{avg} 500 ng/mL to 2500 ng/mL (26). Probability of Target attainment were therefore
270 performed for multiple indices: $AUC_{f...}$ of 30 mg.h/L; C_{avg} of > 500 ng/mL (which is
271 equivalent to an $AUC_{f...}$ of 12 mg.h/L) and a C_{min} of >1 mg/L, which was also sug-
272 gested by Gastine et. al. due to better monitoring feasibility during clinical practice.

273 PTA following suspension TID dosing irrespective of concomitant PPI treatment
274 suggests little di erence in PTA when applying the two targets previously described
275 by Gastine et. al. (25, 24). Considering the 4-6 year age group, with PPI the PTA at
276 steady state following a 10 mg/kg three times daily dosing regimen is 9.7% and 12.5%
277 for the AUC and trough target respectively. For the lower C_{avg} target of > 500 ng/mL
278 ($AUC_{f...}$ 12 mg.h/L) this increases to 46.6%.

279 The probability of target attainment following tablet once daily dosing is described
280 for multiples of the unit tablet strength (100 mg) rather than on a mg/kg basis as this
281 was considered to be more useful to clinicians. However, to allow direct comparison to
282 a suspension given at 10 mg/kg three times daily, and IV given at 10 mg/kg once daily a
283 200mg tablet dose to the 4-6 year old group is highlighted (equates to a 10 mg/kg once

284 daily tablet, in a 20 kg child.). Here, the probability of achieving a steady state $AUC_{f\ldots}$
285 30 mg.h/L is 72.4% and 52.0% for exceeding a trough of 1 mg/L. If the $AUC_{f\ldots}$ target
286 was reduced to 12 mg.h/L the 4-6 year old age group is predicted to exceed 90% PTA
287 after 200 mg tablet once daily and all age groups are predicted to exceed 75% PTA.
288 Thus, tablet administration is more likely to reach adequate exposures compared to
289 the currently available suspension in Europe.
290
291 Finally, following IV dosing the PTA results show that in contrast to the oral formu-
292 lations, it is easier to achieve the $AUC_{f\ldots}$ targets than the C_{min} target. Again, focusing
293 on a typical 4-6 year, 10 mg/kg once daily intravenous dosing is predicted to ensure
294 92.2% of children achieve an $AUC_{f\ldots}$ 30 mg.h/L and 74.4% would have a steady state
295 trough > 1 mg/L. However while this regimen is predicted to result in 74.4% of the pop-
296 ulation exceeding trough concentrations of 1 mg/L, it is also predicted that part of the
297 population is at risk of high exposures. For example the 95th percentile of trough con-
298 centrations (after 7 days prior dosing of 10 mg/kg QD IV to 4-6 year old's) is predicted
299 to be 51.6 mg/L, see Figure S6. With a recommended C_{avg} below 2.5 mg/L used by
300 Groll et. al., this highlights the estimated high inter individual variability in the underly-
301 ing population PK model. Therefore, therapeutic drug monitoring after posaconazole
302 administration with subsequent dose adaptation is warranted. If the $AUC_{f\ldots}$ target is
303 reduced to 12 mg.h/L (equivalent to a C_{avg} > 500 ng/mL) all age groups are predicted
304 to exceed 84.2% PTA after q24hr IV doses of 5 mg/kg or above. This is in good agree-
305 ment with the paediatric IV PK study results reported by Groll et. al. where the authors
306 found that after 7 days of dosing 4.5 and 6.0 mg/kg once daily, 90% of participants
307 achieved a C_{avg} > 500 ng/mL (26).
308 There are limitations to our analysis that stem from the retrospective assessment
309 of sparse real world TDM data combined with the relatively small number of patients
310 contributing IV and tablet PK levels to the dataset. Because of this the dataset did
311 not support estimation of Km and this parameter was xed based on ndings from
312 modelling of adult IV data ,and parameter sensitivity analysis performed using the
313 paediatric data.
314 The FDA granted regulatory approval of a new suspension posaconazole product
315 to MSD in May 2021(1) and hopefully this will also be available to children in Europe
316 in the near future. This new oral suspension combines the improved absorption char-
317 acteristics of the tablet with the added dosing exibility of a typical liquid paediatric
318 formulation.

319 CONCLUSION
320 From real world TDM data, more understanding of posaconazole PK in children can
321 be generated.
322 The model that has been presented successfully describes the bioavailability dif-
323 ferences seen following tablet and suspension dosing in children. Key to this has been
324 incorporation of saturable posaconazole clearance into the model. Due to the sparse
325 nature of posaconazole TDM data extrapolation of PK in adult populations informed
326 the base model. Covariate analysis con rmed previously reported dose-dependent
327 decreases in suspension bioavailability, which are then further reduced by concomi-
328 tant PPIs.
329 The model has been used to evaluate typical paediatric IV, tablet and suspension
330 dosing regimens using published PD targets. These simulations highlight, that both IV
331 and tablet formulations are capable of achieving adequate posaconazole exposures
332 across the pediatric population. However for the original/old suspension formulation,

333 that is still widely used across Europe, escalation of dose beyond 10 mg/kg is essen-
334 tially pointless and even with TID dosing many children are likely to be left with sub-
335 therapeutic posaconazole exposures.

MATERIALS AND METHODS

337 A retrospective analysis of posaconazole TDM data captured by a single specialist pae-
338 diatric hospital electronic health records (EHRs) between Jan 2017 and July 2021 was
339 performed. The study was approved by the London and South East Research Ethics
340 Committee under ref. no. 21/LO/0646.

341   Preparation of the PK modelling data le was performed in R (version 4.1) ([27]) us-
342 ing posaconazole dosing information (formulation type, dose, route of administration,
343 dose frequency and dose date/time). Corresponding posaconazole plasma concentra-
344 tion data were collected as part of routine TDM. Posaconazole bioanalysis was per-
345 formed by external laboratories working under Good clinical Laboratory Practice. The
346 assay's lower limit of quanti cation (LLOQ) ranged from 0.02-0.2 mg/L (20 to 200 mg/L)
347 and the respective value was accounted for each sample.

348   Time-varying covariate data incorporated into the modelling data le included age,
349 BW, PPI co administration, occurrence of diarrhoea, hepatic impairment surrogate
350 ALT and ALB. Last observation carried forward method was applied to handle missing
351 covariates. Information regarding episodes of diarrhoea were manually collated by a
352 hospital pharmacist from patient records. For IV dosing a nominal infusion time of 90
353 minutes as per the local guidance was used to calculate infusion rate (mg/hr).

355   Population PK modelling and simulation was undertaken using rst-order condi-
356 tional estimation method with interaction (FOCEI) in NONMEM version 7.4.3. During
357 data le preparation, posaconazole TDM levels that were reported as less than the
358 LLOQ were replaced with 1/2 the associated LLOQ. Only the rst value below LLOQ
359 during one dose cycle was retained in the data set (M6 method, ([28])).

360   Since published intravenous posaconazole pharmacokinetic data in healthy adults
361 demonstrated, that over a dose range of 50 to 300 mg (0.7 to 4.3 mg/kg assuming a
362 70 kg body weight) clearance is saturable ([4]) the decision was made to evaluate the
363 paediatric TDM data using both linear and non-linear clearance models. To help in-
364 form paediatric model parameterisation, published rich PK data following tablet ([14])
365 and IV dosing ([4]) in adult populations was extracted and modelled. Adult PK data ex-
366 traction was done using a web based application called WebPlotDigitizer version 4.5
367 ([29]).

369   Pharmacokinetic Model Development   One and two compartment models with
370 rst order absorption and either linear or non-linear clearance from the central com-
371 partment were evaluated. Inter individual variability (IIV) was tested on clearance and
372 volume of distribution assuming a log-normal distribution, and on tablet and suspen-
373 sion F using logistic transformation. A combined error model was tested initially and
374 separate additive or proportional models only employed if one component was esti-
375 mated to be negligible. For nested models, the likelihood ratio test was employed to
376 detect signi cant model improvement. Assuming the di erence in log likelihood be-
377 tween two nested modes was asymptotically Chi squared distributed, a drop in the
378 log likelihood ratio of >6.64 per degree of freedom was needed to be signi cant at
379 a level of $< \bullet : \bullet$, and >3.84 at a level of $< \bullet : \bullet \dagger$. For univariate forward selection
380 covariates were included if $p<0.05$ but removed from the combined covariate model
381 if $p>0.01$ on backward elimination.

382 Non-linear clearance was accounted for using a Michaelis Menten type function
383 as shown in Equation 1. This allows clearance to vary depending on the concentration
384 C in plasma based on two parameters CL_{sat}, the maximum (or saturated) rate of
385 clearance and K_m, the concentration at which clearance is half its maximal value.

$$CL = \frac{CL_{sat} \cdot C}{K_m + C} \tag{1}$$

387 Due to wide ranging body weight in the observed study population, allometric
388 scaling was included a priori using a fixed exponent of 0.75 on CLsat and linear scaling
389 on volume of distribution see Equation 2 and 3. A standard weight of 70 kg was used
390 to allow comparison of parameter estimates with previous studies.

$$CL_{sat_i} = CL_{satpop} \cdot \left(\frac{BW_i}{70}\right)^{0.75} \tag{2}$$

$$V_i = V_{pop} \cdot \left(\frac{BW_i}{70}\right)^{1} \tag{3}$$

393 Covariate effects were evaluated for dose, concomitant diarrhoea and PPI dosing
394 as these have previously been reported to be significant determinants of suspension
395 F (13, 30)
396 Posaconazole is known to undergo phase 2 metabolism (5) and to be highly plasma
397 protein bound (3). Due to metabolism being an important route of elimination for
398 posaconazole and in light of previous findings by Petitcollin et. al. (15) regarding a
399 potential association of ALT with posaconazole clearance, ALT was tested as a contin-
400 uous covariate on clearance. Finally, because posaconazole is highly plasma protein
401 bound, ALB was tested on the volume of distribution.
402 Continuous covariate effects were modelled using a power function centred on
403 the median value see Equation 4 and categorical covariates evaluated by estimation
404 of their fractional change of any given fixed effect see Equation 5.

$$COV_{continous} = \frac{COV_i}{COV_{median}} \tag{4}$$

$$COV_{categorical} = 1, \, 0 \tag{5}$$

407 The function described by Boonsathorn et. al. (13) was used to account for the
408 effect of dose on bioavailability, see Equation 6, where D is the dose in mg/m^f and D_{50}
409 is the dose at which F is 50%. IIV was tested on D_{50} assuming a log-normal distribution.
410 To calculate dose per body surface area (BSA) we used the Boyd method to estimate
411 BSA based solely on body weight (31, 32).

$$F = \frac{D}{D + D_{50}} \tag{6}$$

413 Due to the sparse nature of TDM data, absorption rate constants (Ka) for suspen-
414 sion (Ka_{sus}) and tablets (Ka_{tab}) were fixed based on prior adult estimates (33, 15). The
415 effect of BW on Ka was also tested using the approach previously employed by Boon-
416 sathorn et. al. using a fixed exponent of -0.25, see Equation 7.

$$Ka_i = Ka_{pop} \cdot \left(\frac{BW_i}{70}\right)^{-0.25} \tag{7}$$

418   Decisions during model development were made based on the likelihood ratio
419 test, goodness of t (GOF) plots and visual predictive checks (VPC) using n=1000 simu-
420 lations and visualised using Xpose4 (34, 35).

421

422   Pharmacokinetic Simulations and Target Attainment   Using the observed base-
423 line demographic information for the children included in the nal modelling dataset
424 the variance covariance matrix was calculated between log transformed age and weight.
425 From this, n=10,000 hypothetical children were simulated and categorized into age
426 based groups; 0.5-2, 2-4, 4-6, 6-9, 9-12, 12-16 years. Using body weight, the Boyd
427 method (31) was used to calculate body surface area. Simulations with or without PPI
428 were performed for suspension. Tablet simulations were performed at 100, 200, 300,
429 400 and 500 mg once daily (QD), IV simulations at 1, 2.5, 5, 7.5 and 10 mg/kg QD and
430 suspension simulations at 1, 5, 10, 20 and 30 mg/kg three times daily (TID). While tablet
431 dosing in children less than 6 years of age maybe impractical, all age groups were sim-
432 ulated for all formulations as this provides clinicians the most exibility when selecting
433 the appropriate formulation for a respective individual patient.

434

435   A full PK time course was simulated for 8 days (T_{last} = 192 hours) and $AUC_{f...}$ and
436 C_{min} from the last 24 hour period were used in calculation of the probability of target
437 attainment (PTA) using previously published PD targets of 30 mg.hr/L ($AUC_{f...}$ at steady
438 state) and 1 mg/L (C_{min} at steady state) (25). This proposed $AUC_{f...}$ of 30 mg.hr/L, corre-
439 sponds to a C_{avg} of 1250 ng/mL, which is higher than a previously suggested posacona-
440 zole C_{avg} target of 700 ng/mL(36, 37, 24). More recently a steady state C_{avg} of between
441 500 ng/mL (0.5 mg/L) and 2500 ng/mL (2.5 mg/L) has been used as an alternative PD
442 target (26) and as such a C_{avg} 0.5 mg/L (which is equivalent to an $AUC_{f...}$ at steady
443 state of 12 mg.h/L) was also included in the PTA assessments.

444

SUPPLEMENTAL MATERIAL

446 SupplementalMaterials.docx includes the model code of the nal paediatric posacona-
447 zole model, Figure S1 showing combined goodness-of- t plots, Figure S2 and Figure
448 S3 showing detailed graphical exploration of the virtual population used for simula-
449 tions and Figures S4 -S6 with plasma concentration time curves constructed from the
450 simulations. Table S1 presents the base model parameter estimates.

451

466 As such patients or their parents were not required to provide informed consent. The
467 study was approved by the London and South East Research Ethics Committee, refer-
468 ence 21/LO/0646.

REFERENCES

1. **Merck S, Corp D**. May 2021. NDA approval (214770) Noxafil Powder-Mix for delayed-release oral suspension https://www.accessdata.fda.gov/drugsatfda_docs/nda/ƒ•ƒ‚/ƒ‚…ˆˆ•Orig‚s•••Approv.pdf.

2. **Chen L, Krekels EHJ, Verweij PE, Buil JB, Knibbe CAJ, Brüggemann RJM**. 2020. Pharmacokinetics and Pharmacodynamics of Posaconazole. Drugs 80 (7):671–695. doi:10.1007/s40265-020-01306-y.

3. **Hens B, Pathak SM, Mitra A, Patel N, Liu B, Patel S, Jamei M, Brouwers J, Augustijns P, Turner DB**. 2017. In Silico Modeling Approach for the Evaluation of Gastrointestinal Dissolution, Supersaturation, and Precipitation of Posaconazole. Mol Pharm 14 (12):4321–4333. doi:10.1021/acs.molpharmaceut.7b00396.

4. **Kersemaekers WM, Van Iersel T, Nassander U, O'Mara E, Waskin H, Caceres M, Van Iersela MLPS**. 2015. Pharmacokinetics and safety study of posaconazole intravenous solution administered peripherally to healthy subjects. Antimicrob Agents Chemother 59 (2):1246–1251. doi:10.1128/AAC.04223-14.

5. **Krieter P, Flannery B, Musick T, Gohdes M, Martinho M, Courtney R**. 2004. Disposition of posaconazole following single-dose oral administration in healthy subjects. Antimicrob Agents Chemother 48 (9):3543–3551. doi:10.1128/AAC.48.9.3543-3551.2004.

6. **Merck Sharp Dohme**. Sep 2014. Noxafil IV Clin Pharm Review (NDA 205596) https://www.accessdata.fda.gov/drugsatfda_docs/nda/ƒ•‚…/ƒ•††Š‡Orig‚s•••ClinPharmR.pdf.

7. **Krishna G, Martinho M, Chandrasekar P, Ullmann AJ, Patino H**. 2007. Pharmacokinetics of oral posaconazole in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease. Pharmacotherapy 27 (12 I):1627–1636. doi:10.1592/phco.27.12.1627.

8. **Krishna G, Ma L, Vickery D, Yu X, Wu I, Power E, Beresford E, Komjathy S**. 2009. Effect of varying amounts of a liquid nutritional supplement on the pharmacokinetics of posaconazole in healthy volunteers. Antimicrob Agents Chemother 53 (11):4749–4752. doi:10.1128/AAC.00889-09.

9. **Krishna G, Moton A, Lei M, Medlock MM, McLeod J**. 2009. Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers. Antimicrob Agents Chemother 53 (3):958–966. doi:10.1128/AAC.01034-08.

10. **Krishna G, Ma L, Martinho M, O'Mara E**. 2012. Single-dose phase I study to evaluate the pharmacokinetics of posaconazole in new tablet and capsule formulations relative to oral suspension. Antimicrob Agents Chemother 56 (8):4196–4201. doi:10.1128/AAC.00222-12.

11. **Courtney R, Pai S, Laughlin M, Lim J, Batra V**. 2003. Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. Antimicrob Agents Chemother 47 (9):2788–2795. doi:10.1128/AAC.47.9.2788-2795.2003.

12. **Abutarif MA, Krishna G, Statkevich P**. 2010. Population pharmacokinetics of posaconazole in neutropenic patients receiving chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. Curr Med Res Opin 26 (2):397–405. doi:10.1185/03007990903485056.

13. **Boonsathorn S, Cheng I, Kloprogge F, Alonso C, Lee C, Doncheva B, Booth J, Chiesa R, Irwin A, Standing JF**. 2019. Correction to: Clinical Pharmacokinetics and Dose Recommendations for Posaconazole in Infants and Children (Clinical Pharmacokinetics, (2019), 58, 1, (53-61), 10.1007/s40262-018-0658-1). Clin Pharmacokinet 58 (1):141. doi:10.1007/s40262-018-0722-x.

14. **Kraft WK, Chang PS, Van Iersel MLPS, Waskin H, Krishna G, Kersemaekers WM**. 2014. Posaconazole tablet pharmacokinetics: Lack of effect of concomitant medications altering gastric pH and gastric motility in healthy subjects. Antimicrob Agents Chemother 58 (7):4020–4025. doi:10.1128/AAC.02448-13.

15. **Petitcollin A, Boglione-Kerrien C, Tron C, Nimubona S, Lalanne S, Lemaitre F, Bellissant E, Verdiera MC**. 2017. Population pharmacokinetics of posaconazole tablets and monte carlo simulations to determine whether all patients should receive the same dose. Antimicrob Agents Chemother 61 (11). doi:10.1128/AAC.01166-17.

16. **Dolton MJ, Brüggemann RJ, Burger DM, McLachlan AJ**. Nov 2014. Understanding variability in posaconazole exposure using an integrated population pharmacokinetic analysis. Antimicrob Agents Chemother 58 (11):6879–6885.

17. **Kohl V, Müller C, Cornely OA, Abduljalil K, Fuhr U, Vehreschild JJ, Scheid C, Hallek M, Rüping MJ**. Jan 2010. Factors influencing pharmacokinetics of prophylactic posaconazole in patients undergoing allogeneic stem cell transplantation. Antimicrob Agents Chemother 54 (1):207–212.

18. **Vehreschild JJ, Müller C, Farowski F, Vehreschild MJ, Cornely OA, Fuhr U, Kreuzer KA, Hallek M, Kohl V**. Jun 2012. Factors influencing the pharmacokinetics of prophylactic posaconazole oral suspension in patients with acute myeloid leukemia or myelodysplastic syndrome. Eur J Clin Pharmacol 68 (6):987–995.

19. **Peña-Lorenzo D, Rebollo N, Sánchez-Hernández JG, Zarzuelo-Castañeda A, Vázquez-López L, Otero MJ, Pérez-Blanco JS**. Jan 2022. Population pharmacokinetics of a posaconazole tablet formulation in transplant adult allogeneic stem cell recipients. Eur J Pharm Sci 168:106049.

20. **Dekkers BGJ, Bakker M, van der Elst KCM, Sturkenboom MGG, Veringa A, Span LFR, Alffenaar JC**. 2016. Therapeutic Drug Monitoring of Posaconazole: an Update. Curr Fungal Infect Rep 10:51–61.

21. **Kendall J, Papich MG**. 2015. Posaconazole pharmacokinetics after administration of an intravenous solution, oral suspension, and delayed-release tablet to dogs. Am J Vet Res 76 (5):454–459. doi:10.2460/ajvr.76.5.454.

22. **Merck S, Corp D**. Feb 2014. EMEA Assessment Report (EMA/159150/2014) https://www.ema.europa.eu/en/documents/variation-report/noxafil-h-c-‡‚•-x-••ƒ‰epar-scientific-discussion-extension_en.pdf.

23. **Li H, Wei Y, Zhang S, Xu L, Jiang J, Qiu Y, Mangin E, Zhao XM, Xie S**. 2019. Pharmacokinetics and Safety of Posaconazole Administered by Intravenous Solution and Oral Tablet in Healthy Chinese Subjects and Effect of Food on Tablet Bioavailability. Clin Drug Investig 39 (11):1109–1116. doi:10.1007/s40261-019-00833-1.

24. **Jang SH, Colangelo PM, Gobburu JV**. Jul 2010. Exposure-response of posaconazole used for prophylaxis against invasive fungal infections: evaluating the need to adjust doses based on drug concentrations in plasma. Clin Pharmacol Ther 88 (1):115–119.

25. **Gastine S, Hope W, Hempel G, Petraitiene R, Petraitis V, Mickiene D, Bacher J, Walsh TJ, Groll AH**. 2021. Pharmacodynamics of posaconazole in experimental invasive pulmonary aspergillosis: Utility of serum galactomannan as a dynamic endpoint of antifungal efficacy. Antimicrob Agents Chemother 65 (2). doi:10.1128/AAC.01574-

20.

26. **Groll AH, Abdel-Azim H, Lehrnbecher T, Steinbach WJ, Paschke A, Mangin E, Winchell GA, Waskin H, Bruno CJ**. 2020. Pharmacokinetics and safety of posaconazole intravenous solution and powder for oral suspension in children with neutropenia: an open-label, sequential dose-escalation trial. Int J Antimicrob Agents 56 (3):106084. doi: 10.1016/j.ijantimicag.2020.106084.

27. **R Foundation for Statistical Computing - Core Team**. 2013. R: A Language and Environment for Statistical Computing http://www.R-project.org.

28. **Bergstrand M, Karlsson MO**. Jun 2009. Handling data below the limit of quantification in mixed effect models. AAPS J 11 (2):371–380.

29. **Ankit Rohatgi**. WebPlotDigitizer version 4.5 https://github.com/ankitrohatgi/WebPlotDigitizer.

30. **Bentley S, Davies JC, Gastine S, Donovan J, Standing JF**. 2021. Clinical pharmacokinetics and dose recommendations for posaconazole gastroresistant tablets in children with cystic fibrosis. J Antimicrob Chemother doi:10.1093/jac/dkab312.

31. **Sharkey I, Boddy AV, Wallace H, Mycroft J, Hollis R, Picton S**. 2001. Body surface area estimation in children using weight alone: Application in paediatric oncology. Br J Cancer 85 (1):23–28. doi: 10.1054/bjoc.2001.1859.

32. **Boyd E**. 1935. The growth of the surface area of the human body. Milford, Univ. Minnesota Press.

33. **Ezzet F, Wexler D, Courtney R, Krishna G, Lim J, Laughlin M**. 2005. Oral bioavailability of posaconazole in fasted healthy subjects: Comparison between three regimens and basis for clinical dosage recommendations. Clin Pharmacokinet 44 (2):211–220. doi: 10.2165/00003088-200544020-00006.

34. **Jonsson EN, Karlsson MO**. Jan 1999. Xpose–an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. Comput Methods Programs Biomed 58 (1):51–64.

35. **Lindbom L, Pihlgren P, Jonsson EN, Jonsson N**. Sep 2005. PsN-Toolkit–a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed 79 (3):241–257.

36. **Cornely OA, Robertson MN, Haider S, Grigg A, Geddes M, Aoun M, Heinz WJ, Raad I, Schanz U, Meyer RG, Hammond SP, Mullane KM, Ostermann H, Ullmann AJ, Zimmerli S, Van Iersel MLPS, Hepler DA, Waskin H, Kartsonis NA, Maertens J**. 12 2017. Pharmacokinetics and safety results from the Phase 3 randomized, open-label, study of intravenous posaconazole in patients at risk of invasive fungal disease. J Antimicrob Chemother 72 (12):3501.

37. **Tissot F, Agrawal S, Pagano L, Petrikkos G, Groll AH, Skiada A, Lass-Flörl C, Calandra T, Viscoli C, Herbrecht R**. 03 2017. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica 102 (3):433–444.

38. **Merck Sharp Dohme Corp**. Jun 2022. FDA Noxafil Prescribing Information https://www.merck.com/product/usa/pi_circulars/n/noxafil/noxafil_pi.pdf.

39. **Wiederhold NP**. 2015. Pharmacokinetics and safety of posaconazole delayed-release tablets for invasive fungal infections. Clin Pharmacol Adv Appl 8:1–8. doi:10.2147/CPAA.S60933.

40. **Bhatnagar S, Mukherjee D, Salem AH, Miles D, Menon RM, Gibbs JP**. 2021. Dose adjustment of venetoclax when co-administered with posaconazole: clinical drug–drug interaction predictions using a PBPK approach. Cancer Chemother Pharmacol 87 (4):465–474. doi: 10.1007/s00280-020-04179-w.

41. **Lu Chen**. June 2022. PAGE2022 Abstract 10036: An integrated population pharmacokinetic analysis for posaconazole oral suspension, delayed-release tablet, and intravenous infusion in healthy volunteers https://www.page-meeting.org/default.asp?abstract=, ••„‡.

42. **Vaitkute G, Panic G, Alber DG, Faizura-Yeop I, Cloutman-Green E, Swann J, Veys P, Standing JF, Klein N, Bajaj-Elliott M**. 2022. Linking gastrointestinal microbiota and metabolome dynamics to clinical outcomes in paediatric haematopoietic stem cell transplantation. Microbiome. 10 (1):89. doi:10.1186/s40168-022-01270-7.

TABLES

TABLE 1   Study population demographic, formulation and bioanalytical information.

Population Variable	Formulation	Median (Range) or Number
Age at baseline observation (years)	IV	9.7 (2.8 - 13.8)
	Tablet	13.8 (8.9 - 16.8)
	Suspension	4.7 (0.4 - 16.5)
Weight at baseline observation (kg)	IV	35.0 (12.0 - 52.9)
	Tablet	44.0 (26.8 - 86.1)
	Suspension	16.2 (4.3 - 61.3)
Number of patients providing plasma levels	IV	13[1]
	Tablet	18[2]
	Suspension	83[2]
Dose (mg/kg)	IV	4.5 (2.0 - 11.5)
	Tablet	5.6 (1.6 - 10.6)
	Suspension	9.3 (1.8 - 35.5)
Plasma concentrations g/mL	IV	1.8 (0.1 - 5.4)
	Tablet	2.0 (0.01 - 11.4)
	Suspension	0.5 (0.01 - 9.3)
Number of plasma concentrations	IV	47
	Tablet	39
	Suspension	211

[1]Of which seven patients also provide oral plasma levels
[2]Of which three patients provide tablet and suspension plasma levels

TABLE 2   Final population pharmacokinetic model parameter estimates. All disposition terms are centred on a fully mature 70 kg individual using allometric scaling with exponents of 1 for volume and 0.75 on CL_{sat}. Condition number for the final model is 43.7 and 70% of bootstrap runs were successful. IIV %CV = (standard error $_i$• $_i$^{0} , ••

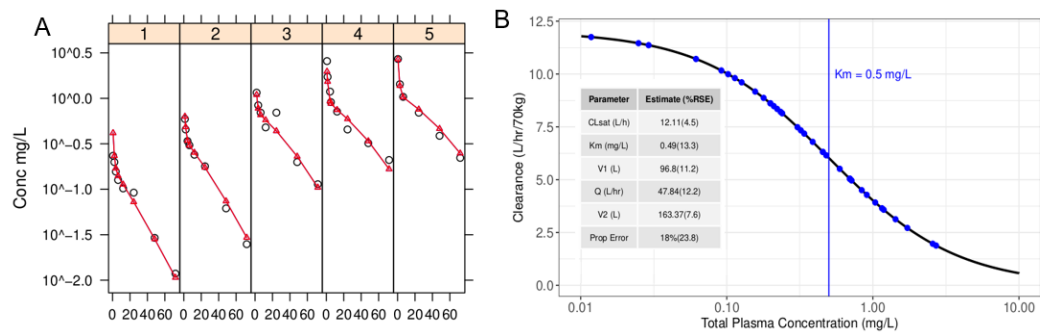| Parameter	Estimate (%RSE)	IIV %CV (%RSE)	Bootstrap 90% CI
CL_{sat} (L/hr/70kg)	13.47 (11.8)	57 (20.5)	11.2 - 15.7
K_m (mg/L)	2 (fixed)	-	-
V (L/70kg)	186.01 (37.6)	120 (33.1)	114 - 258
Ka_{tab} (/hr)	0.59 (fixed)	-	-
Ka_{sus} (/hr)	0.2 (fixed)	-	-
Tablet F	0.66 (21)	-	0.45 - 0.87
Suspension D_{50} (mg/BSA)	43.25 (14.2)	-	31.4 - 55.1
$_{ppi}$ on F_{sus}	-0.41 (27.5)	-	-0.54 - -0.28
Proportional Error (%)	63 (22.1)	-	0.5 - 0.74

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FIGURES

FIG 1 **Adult IV dose escalation modelling. (A) Observed model predicted concentration time profiles. Red line, model prediction; open black circles, observed concentrations. (B) Visualisation of the effect of posaconazole concentration on adult adjusted clearance. Blue circles; observed posaconazole concentrations.**
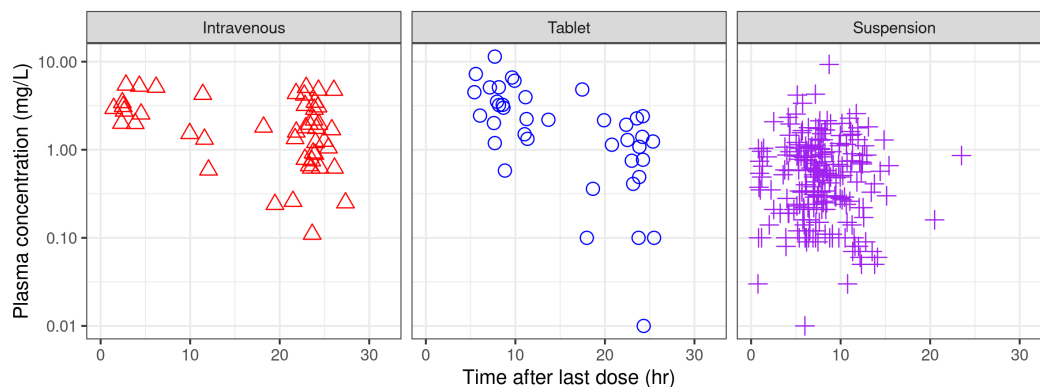

FIG 2 **Pooled plasma concentrations (TDM levels) versus calculated time after last dose (TALD) included in the final modelling dataset. Panels from left to right: IV, tablet and suspension data.**
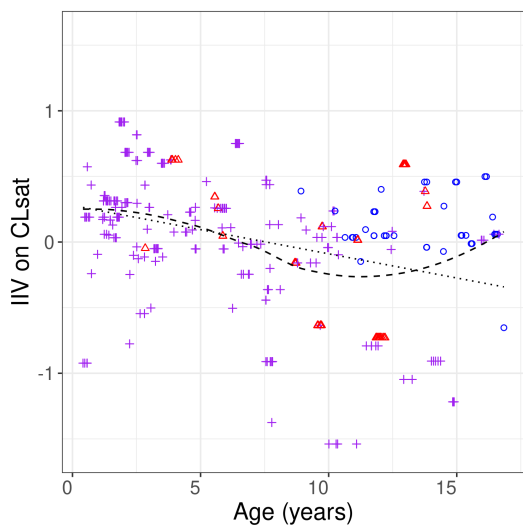

FIG 3 **Effect of age on clearance assessed using the base model. Points; IV - red triangle, tablet - blue circle, suspension - purple cross. Lines; loess smooth - black dashed line, linear regression - black dotted.**
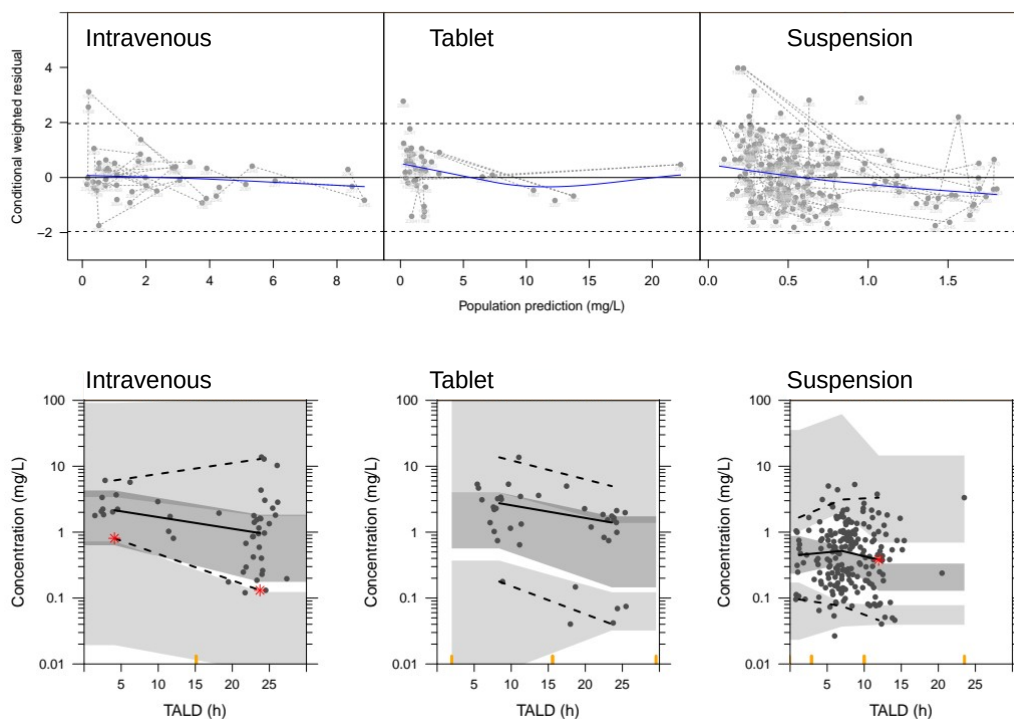
FIG 4 **Conditional weighted Residuals (CWRES) versus population prediction (top row) and prediction-corrected visual predictive check (VPC) plots stratified by formulation for the final model (bottom row). VPCs show the observed data (black circles), 2.5th, 50th and 97.5th percentiles of the observed data (black lines) compared with 95 percent confidence intervals of the corresponding simulations from the final model (shaded areas). TALD, time after last dose administered. In the VPCs a red asterisk highlights that the observed percentile is outside of the model prediction interval.**
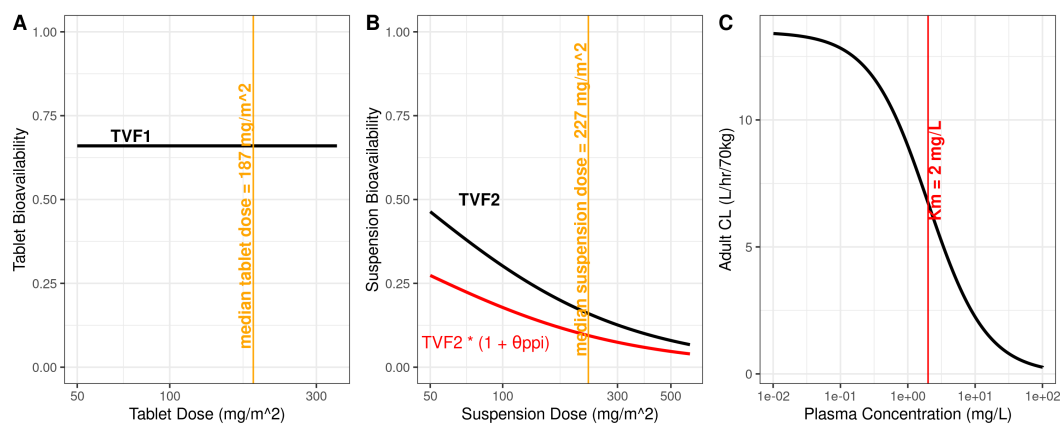

FIG 5 **Visualisation of the model estimated (A) Tablet bioavailability. (B) The covariates effecting suspension bioavailability. (C) The concentration dependence of clearance in the final model. TVF1: Typical value of tablet bioavailability. TVF2: Typical value of suspension bioavailability. $_{ppi}$: Fractional change in suspension bioavailability during concomitant PPI dosing.**