Appendix 1: description of pharmacokinetic and pharmacodynamic model development and rationale for proposed doses in study D5136C00009.

| Drug Substance | Date       |
|----------------|------------|
| Ticagrelor     | 19 May 2017|

Description of pharmacokinetic and pharmacodynamic model development and rationale for proposed doses in study D5136C00009
1. DESCRIPTION OF PHARMACOKINETIC AND PHARMACODYNAMIC MODEL DEVELOPMENT AND RATIONAL FOR DOSE SELECTION IN PHASE 3

This document provides a summary of the population PK and PKPD modelling and simulation used to guide the dose selection for the planned ticagrelor Phase III study in children ≥2 to <18 years of age with sickle cell disease.

Pooled population PK and PKPD models were developed using available PK and platelet inhibition data from a total of 45 paediatric and 84 young adult sickle cell disease patients in the studies D5136C00007 and D5136C00008. The objective was to characterize the dose-exposure-response relationship in the target patient population including the potential influence of relevant demographic covariates that might necessitate dose adjustment.

The models was subsequently used to simulated PK and platelet inhibition data to guide selection of appropriate doses.

Summary of results:

- The PK model using allometric scaling for clearances and volumes by bodyweight and the proportional direct effect inhibition PKPD model provided adequate description of the observed ticagrelor plasma concentration and PRU platelet inhibition data.

- The overall ticagrelor exposure supports weight-based dosing at the dose levels of 15 mg, 30 mg, and 45 mg bd for the bodyweight cohorts 12 to 24 kg, >24 to 48 kg, and >48 kg.

- The proposed doses of 15, 30, and 45 mg with associated bodyweight cohorts 12 to 24 kg, >24 to 48 kg, and >48 kg are estimated to result in >35% platelet inhibition with few patients showing PRU <85 for extended time.

2. METHODS

2.1 Derivation of dataset

A pooled dataset from studies D5136C00007 and D5136C00008 was built by AstraZeneca programming for analysis using NONMEM. A total of n=625 ticagrelor plasma concentration and n=648 PRU platelet inhibition measurements from a total of n=129 (n=28 placebo) subjects were included in the analysis. Relevant demographic and disease related covariates were included for each individual patient, see Table 1 for summary of the patients included in
the analysis. Graphical display of the ticagrelor plasma concentration and PRU platelet inhibition are included in the appendix.

### Table 1  Demographic summary

| Study No. | D5136C00007 | D5136C00008 | Total |
|-----------|-------------|-------------|-------|
| Clinical Phase | Phase 2a | Phase 2b |  |
| Patient population | Sickle cell disease | Sickle cell disease |  |
| No. Individuals | 45 | 84 | 129 |
| No. Males | 21 (47%) | 38 (45%) | 59 (46%) |
| Age distribution (years) | 11 [3-17] | 22 [18-30] | 18 [3-30] |
| Bodyweight distribution (kg) | 38 [17-82] | 56 [29-97] | 50 [17-97] |
| No. Race equal to Black | 35 (78%) | 45 (54%) | 80 (62%) |

Mean and [range] for respective parameter is shown.

#### 2.2 Nonlinear Mixed Effects modeling in NONMEM

NONMEM V7.3.0 was used to perform model building simulations. NONMEM was complemented by Perl-speaks-NONMEM (PsN) version 3.5.3 to automate NONMEM model executions, bootstraps and VPC runs. Post-handling of modeling output and generation of graphs were done in RStudio version 1.0.136 and R version 3.2.4

#### 3. PK MODEL

The PK model was a 2-compartment disposition model with absorption characterized using an Erlang–type absorption model where a fixed number of absorption transit compartments (n=5) are step-wise added to the model and the first order transfer-rate constant, KTR was estimated (Rousseau et al 2004). The structure of the model is displayed in Figure 1. Inter-individual variability (IIV) was added sequentially on multiple parameters and the succeeding models were evaluated based on drop in the objective function value (OFV drop > 3.84 points) and assessment of the goodness of fit plots. IIV was estimated for oral clearance (CL/F), central volume of distribution (Vc/F), relative bioavailability (Frel) and the mean absorption transit time (MTT) in the base model.

Clearance and volume parameters were scaled allometrically to the individual baseline bodyweight, normalized around the median bodyweight in the dataset (50 kg) and with the exponent fixed to 0.75 and 1 for clearance and volume parameters respectively. The inclusion of fixed allometric exponents resulted in a drop in OFV >3.84 points, and was included in the
Appendix 1

base PK model. Estimation of the allometric exponents was evaluated but render an unstable model with highly correlated parameters and was not included.

**Figure 1** Final structural PK model for studies D5136C00007 (pediatric study) and D5136C00008 (young adult study)

A covariate forward inclusion-backward elimination procedure (\(\alpha =0.05\) for inclusion and \(\alpha=0.01\) for elimination) was performed and identified: sex, race, and study as significant predictors of PK variability.

Graphical display for the model good-ness of fit including VPCs are included in the appendix and the estimated model parameters with and without the identified covariates are shown in Table 2.

**Table 2** Base and final PK model parameters

| Parameter                        | Final model (run304) | Base model (run300) |
|----------------------------------|----------------------|--------------------|
|                                  | (OFV= 5643)          | (OFV= 5670)        |
| Estimate                         | (CI)                 | (CI)               |
| IIV (CV%)                        | (CI)                 | (CI)               |
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| Parameter (WT/50) | Final model (run304) | Base model (run300) |
|------------------|----------------------|---------------------|
| Clearance (CL/F; L/h) | 29.9 (27-32) | 18.4 (7.6-25) | 31.1 (28.3-33.2) | 14.5 (5.3-26) |
| Central Volume (Vc/F; L) | 172 (97-156) | 30.5 (13-37) | 188 (160-211) | 33.8 (14-40) |
| Peripheral Volume (Vp/F; L) | 186 (129-882) | | 177 (130-894) | |
| Inter-compartment clearance (Q/F; L/h) | 23.1 (14-40) | | 25.4 (14-47) | |
| Mean transit time (MTT; h) | 0.67 (0.49-0.89) | 61.0 (42-86) | 0.74 (0.54-0.99) | 58.0 (38-87) |
| Bioavailability (Frel) | 1 (FIXED) | 25.4 (19-33) | 1 (FIXED) | 32.7 (27-39) |
| Covariate 1: Vc increase in Study D5136C00007 | 48.4% (19-89%) | |
| Covariate 2: Frel decrease in males | -22.8% (-33 to -15%) | |
| Covariate 4: CL decrease in non-Blacks | -23.2% (-33 to -12%) | |
| Proportional residual error | 40.1% (37-43%) | 39.9% (37-43%) |

OFV: Objective function value.

a The diagonal element from the omega matrix, estimated during the NONMEM run. This number, for a log-normal parameter distribution, is approximately the square of the CV%.
b CI: Confidence intervals were obtained from 695 respective 728 successful runs, out of 1000 bootstrap replicates, with the respective model, using the quantile function in R (with the type = 6 algorithm).

4. PKPD MODEL

A sequential PKPD analysis method was performed in which empirical Bayes estimates (EBEs) of individual PK parameters were used to predict individual concentrations, which were then linked to the observed absolute scale PRU time-course. The PRU data at time of randomization (TIME=0) were used to establish a suitable baseline PRU model and the placebo data were used to characterize the placebo-PRU response and variability. Ticagrelor PK and PRU data was then used to derive the base PKPD model (fixed and random effects model) that ultimately yielded the final PKPD drug model by incorporation of covariate relationships on structural model parameters.

The structure of the PKPD model was a proportional direct effect model where ticagrelor concentrations inhibit platelet aggregation as measured by the VerifyNow™ P2Y12 reaction units (PRU) assay in a sigmoid E\textsubscript{max} type model:

\[
PRU_t = PRU_{\text{baseline}} \times \left(1 - \frac{E_{\text{max}} \times C_t^\gamma}{EC_{50}^\gamma + C_t^\gamma}\right)
\]

where PRU\textsubscript{t} is the platelet inhibition at given time point, PRU\textsubscript{baseline} is the baseline PRU value at TIME=0, EC\textsubscript{50} is the concentration at half-maximum effect, E\textsubscript{max} is the maximum effect, \(\gamma\) is the sigmoid slope factor and C\textsubscript{t} is the individual predicted ticagrelor plasma concentration.
A covariate forward inclusion-backward elimination procedure (α =0.05 for inclusion and α=0.01 for elimination) was performed and identified: sex, race, and study as significant predictors of PK variability.

A covariate forward inclusion-backward elimination procedure (α =0.05 for inclusion and α=0.01 for elimination) was performed and identified higher baseline PRU (10.4%) in the pediatric study compared to young adult patients. There were thus no covariates identified for the exposure response relationship of platelet inhibition from baseline.

Graphical display for the model good-ness of fit including VPCs are included in the appendix and the estimated model parameters with and without the identified covariates are shown in Table 3.

Table 3  PD Model Parameters – base and final model

| Parameter: | Final model (run403) | Base model (run401) |
|------------|----------------------|---------------------|
|            | Estimate (CI)b | IIV (CV%)* | Estimate (CI)b | IIV (CV%)* |
| Baseline PRU (BASE, PRU) | 252 (242-259) | 31.4c (24-37)c | 262 (256-268) | 34.4c (28-40)c |
| Concentration at Half-maximum effect (EC50, mmol/L) | 203 (180-234) | 59.2 (47-71) | 196 (172-224) | 58.7 (46-70) |
| Maximum effect (EMAX) | 1 FIXED | 1 FIXED | 1 FIXED | 1 FIXED |
| Sigmoid factor (GAM, ) | 1.15 (1.06-1.30) | 1.16 (1.07-1.31) | 1.16 (1.07-1.31) | 1.16 (1.07-1.31) |
| Covariate 1: Baseline PRU increase in D5136C00007 | 10.4% (6.7-17) | 10.4% (6.7-17) | 10.4% (6.7-17) | 10.4% (6.7-17) |
| Additive Residual Error (SD, PRU) | 41.0 (38-44) | 41.0 (37.4-44.1) | 41.0 (37.4-44.1) | 41.0 (37.4-44.1) |

a  The diagonal element from the omega matrix, estimated during the NONMEM run. This number, for a log-normal parameter distribution, is approximately the square of the CV%.

b  CI: Confidence intervals were obtained from 894 respective 915 successful out of 1000 bootstrap replicates, with the respective model, using the quantile function in R (with the type = 6 algorithm).

c  Presented as the standard deviations.

5. DOSE SELECTION IN PHASE 3

Simulations were used to guide the selection of doses that would render platelet inhibition at the target level (>35%), but not associated with too high platelet inhibition (>80%) for an extended time period. Various age or bodyweight adjusted dose levels and varying age or bodyweight cut-offs were evaluated, as well as dosing frequencies.

The individual parameter estimates from the final PKPD model in children ≥2 to <18 years of age (n=45) were resampled (with replacement) to generate a fictive study population of
100 individuals. This procedure was then repeated 100 times to generate 100 studies, and a final simulation dataset with 10000 individuals in total. Data from young adults was excluded, as these patients are outside the intended age range for the Phase III population.

The pediatric population in study D5136C00007 is considered to be representative of the intended Phase III study population with regards to demographic and disease-related characteristics. The resampling of the study population was set to generate 25% of patients below 12 years of age in each resampled study.

Bodyweight-based dosing algorithms showed overall less variability in the PRU response compared with age-based dosing algorithms.

More frequent dosing, than the proposed twice daily, was evaluated given the within dosing interval fluctuations in PRU response to ticagrelor. Even if the PRU peak-to-trough ratio may be reduced with more frequent dosing (eg, three or four times daily), the risk of reduced compliance (both too high or too low exposure) with dosing every 8 or 6 hours was deemed not feasible for the patient population.

The bodyweight based dosing algorithm of: 15, 30, and 45 mg with bodyweight cut-off at 12-24 kg, >24-48 kg, and >48 kg was simulated and the output from the simulations are summarized below, in Figure 2 & 3.

The simulation results show that with the proposed body weight-adjusted dosing algorithm of 15 mg, 30 mg, and 45 mg, the ticagrelor exposure is well within the range that has been observed during the Phase II program. Exposure across the weight cohorts 12 to 24 kg, >24 to 48 kg, and >48 kg, is reasonably well distributed. Moreover the simulated sequent PRU response is within acceptable limits to balance efficacy and the increased bleeding risk associated with high levels of platelet inhibition.
Figure 2  
Simulated ticagrelor exposure after dosing pediatric sickle cell disease patients (left) and the derived population mean AUC in each of the weights cohorts

(Left) Represents the simulated ticagrelor exposure at steady state using the proposed bodyweight adjusted dosing algorithm of 15, 30 and 45 mg. The dashed line represents simulated median concentration and the grey shaded area the 5th and 95th percentiles of the simulation (n=10 000). (Right) Represents the ticagrelor AUC using the proposed bodyweight adjusted dosing algorithm of 15, 30 and 45 mg and based on the population predicted CL/F from the final PK model, allometrically scaled to bodyweight.

Figure 3  
Simulated absolute and relative PRU response with the final PKPD model.
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(left) Represents the simulated PRU response at steady state using the proposed bodyweight adjusted dosing algorithm of 15, 30 and 45 mg. The dashed line represents simulated median concentration and the grey shaded area the 5th and 95th percentiles of the simulation. (right) Represents the subsequent relative PRU inhibition.

6. SUMMARY

The presented population PKPD modelling and simulation to guide the dose selection for the planned ticagrelor Phase III study in children ≥2 to <18 years of age with sickle cell disease support the following conclusions:

- The overall ticagrelor exposure supports weight-based dosing at the dose levels of 15 mg, 30 mg, and 45 mg bd for the bodyweight cohorts 12 to 24 kg, >24 to 48 kg, and >48 kg.

- The proposed doses of 15, 30, and 45 mg with associated bodyweight cohorts 12 to 24 kg, >24 to 48 kg, and >48 kg are estimated to result in >35% platelet inhibition with few patients showing PRU <85 for extended time.

7. APPENDIX: SUPPORTING TABLES AND FIGURES
**Figure 4**  
Bodyweight distribution in studies D5136C000007 and D5136C000008. The dashed line (---) represents the median bodyweight in the respective study.

![Bodyweight distribution in study D5136C000007](image1.png)  
![Bodyweight distribution in study D5136C000008](image2.png)

**Table 4**  
Summary of study-specific and overall dosing and key covariate information in the PK dataset used in the base and final model

| Study No.              | D5136C00007 | D5136C00008 | Total |
|------------------------|-------------|-------------|-------|
| Clinical Phase         | Phase 2a    | Phase 2b    |       |
| Patient population     | Sickle cell disease | Sickle cell disease |       |
| No. PK samples (>LLOQ) | 471         | 154         | 625   |
| No. Individuals        | 45          | 56          | 101   |
| No. Males              | 21 (47%)    | 25 (45%)    | 46 (46%) |
| Administration Route   | Oral (mg/kg)| Oral (mg)   |       |
| Dose range (in mg)     | [2-139.5]   | [10-45]     |       |
| Dosing frequency       | SD/BD       | BD          |       |
| Planned study duration (weeks) | 3+1(+4) | 12 |     |
| Age distribution (years) | 11 [3-17] | 23 [18-30] | 18 [3-30] |
| Bodyweight distribution (kg) | 38 [17-82] | 56 [29-82] | 48 [17-82] |
| No. Race equal to Black | 35 (78%)    | 31 (55%)    | 66 (65%) |
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| Study No.          | D5136C00007 | D5136C00008 | Total |
|-------------------|-------------|-------------|-------|
| No. Cholecystectomy | 10 (22%)    | 10 (18%)    | 20 (20%) |

LLOQ: Lower Limit of Quantification of the bioanalysis method (0.96 nmol/L); SD: Single Dose; BD: Twice daily.

**Figure 5** Individual observed ticagrelor plasma concentration and time profile after single dose in study D5136C00007 (dose range: 0.125 to 2.25 mg/kg)
**Figure 6** Individual observed steady-state plasma concentrations in study D5136C00007 at first steady-state visit (visit 4) (doses: 0.563 mg/kg or 0.75 mg/kg BD) and at the second steady-state visit (visit 8) (dose: 0.125 mg/kg BD)

![Graph showing plasma concentration over time for visits 4 and 8.]

**Figure 7** Individual observed ticagrelor plasma concentrations at 2 hours post dose and at trough in study D5136C00008 (doses: 10 mg or 45 mg bd)

![Graph showing ticagrelor plasma concentrations over time.]
Figure 8 Baseline distribution of platelet reactivity measured by VerifyNow™ P2Y12 PRU-assay. Dashed line (---) represent the median PRU in the respective study.
Figure 9  Individual observed PRU versus time profiles after a single ticagrelor dose in study D5136C00007 (Dose range: 0.125 to 2.25 mg/kg)

Figure 10  Individual steady-state PRU observations in study D5136C00007 at Visit 4 (doses: 0.563 mg/kg or 0.75 mg/kg bd) and Visit 8 (dose: 0.125 mg/kg bd)
Figure 11  Individual PRU observations at Visits 2 (single dose) and 3 (steady-state) in study D5136C00008 (doses: 10 or 45 mg bd)

Figure 12  Individual PRU observations at Visits 2 and 3 in study D5136C00008 (Placebo arm)
### Table 5  Summary of data in the PKPD dataset

| Study No. | D5136C00007 | D5136C00008 | Total: |
|-----------|-------------|-------------|--------|
| Clinical Phase | Phase 2a | Phase 2b | |
| Patient population | Sickle cell disease | Sickle cell disease | |
| No. Individuals | 45 | 84 | 129 |
| No. PRU samples | 341 | 307 | 648 |
| Planned study duration (weeks) | 3+1(+4) | 12 | |
| No. Males | 21 (47%) | 38 (45%) | 59 (46%) |
| Age distribution (years) | 11 [3-17] | 22 [18-30] | 18 [3-30] |
| Bodyweight distribution (kg) | 38 [17-82] | 56 [29-97] | 50 [17-97] |
| No. Race equal to Black | 35 (78%) | 45 (54%) | 80 (62%) |
| Mean baseline PRU | 279 [212-372] | 252 [151-416] | 262 [151-416] |

Mean and [range] for each respective parameter.
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Figure 13  Individual ticagrelor exposure versus PRU-response in studies D5136C00007 (pediatric study) and D5136C00008 (young adult study)
Figure 14  Estimated oral clearance (CL/F) versus baseline bodyweight.

(●) Represent the individual predicted oral clearance values with the final PK model (run304), the dashed line represents the population mean clearance prediction across bodyweights.
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**Figure 15**  VPC plot (single dose) showing suitability of the final population PK model (run304)

Study: D5136C00007, single dose, Age: 2 to 18 years

(+) Observed data. The black solid line represents the median observed data and the broken lines the observed 10th and 90th percentiles. The gray shaded area represents the 95% confidence interval around the median and respective percentiles. Prediction correction was used.

**Figure 16**  Age stratified VPC plots (single dose) for the final PK model (run304)

Study: D5136C00007, single dose, Age: ≤9 years  
Study: D5136C00007, single dose, Age: > 9 to ≤18 years

(+) Observed data. The black solid line represents the median observed data and the broken lines the observed 10th and 90th percentiles. The gray shaded area represents the 95% confidence interval around the median and respective percentiles. Prediction correction was used.
Figure 17   VPC plots (steady-state D5136C00007; all data D5136C00008) for the final PK model (run304).

(+ ) Observed data. The black solid line represents the median observed data and the broken lines the observed 10th and 90th percentiles. The gray shaded area represents the 95% confidence interval around the median and respective percentiles. Prediction correction was used.
Figure 18  VPCs of the final Model absolute and relative PRU response (run403)

(+) Observed data. The black solid line represents the median observed data and the broken lines the observed 10th and 90th percentiles. The gray shaded area represents the 95% confidence interval around the median and respective percentiles. Prediction correction was used.
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Figure 19  VPC plots of the final model age and study stratified (run403)

Study: D5136C00007, single dose, Age: 2 to 18 years  Study: D5136C00007, steady-state, Age: 2 to 18 years

(+) Observed data. The black solid line represents the median observed data and the broken lines the observed 10\textsuperscript{th} and 90\textsuperscript{th} percentiles. The gray shaded represent the 95\% confidence interval around the median and respective percentiles. Prediction correction was used.
Figure 20  
VPCs of the final Model after single and repeated dosing (run403)

Study: D5136C00008, single dose, Age: 18 to 30 years

Study: D5136C00008, steady-state, Age: 18 to 30 years

(+ ) Observed data. The black solid line represents the median observed data and the broken lines the observed 10th and 90th percentiles. The gray shaded represent the 95% confidence interval around the median and respective percentiles. Prediction correction was used.

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