Supplementary Material

Overview of Clinical Trial Data Sources

Pediatric Data Sources
Pediatric data sources are shown in → Table S1.

Adult Data Sources
The previously developed adult models\(^1\) were based upon dense phase 1 data that investigated idarucizumab in the presence of dabigatran plasma exposure in 79 healthy males, and 18 males with mild-to-moderate chronic kidney function who were otherwise in relatively good health (NCT01688830 [N = 51 healthy males] and NCT01955720 [n = 28 healthy males and n = 18 males with renal impairment]).\(^2,3\) Only data from treatment periods when no idarucizumab was taken were considered.

The phase 3 RE-COVER study (NCT00291330) was the main adult patient comparator study as it enrolled patients with objectively diagnosed venous thromboembolism.\(^4\) Observed dabigatran concentration and corresponding activated partial thromboplastin time (aPTT) and ecarin clotting time (ECT) data were used in the graphical exploration for comparison with the pediatric and adult healthy subject data. As no diluted thrombin time (dTT) measurements were obtained in the graphical exploration for comparison with the pediatric and adult healthy subject data. As no diluted thrombin time (dTT) measurements were obtained in the RE-COVER study, dTT (and aPTT) adult patient data from the phase 3 RE-NOVATE study (NCT00657150) investigating the primary prevention of venous thromboembolism in adults following hip arthroplasty were used.\(^5\)

Clotting Assays
Clotting assays (performed using 10-channel coagulometers [MERLIN medical MC10PLUS]) have been described previously, and were performed in one central laboratory (menal GmbH, Emmendingen, Germany) to minimize variability between assay methods and laboratories.\(^1\)

For dTT, plasma samples (50 μL) were diluted with 0.9% sodium chloride (350 μL), and 50 μL of diluted sample was added to 100 μL of normal pooled human plasma and incubated at 37°C for 2 minutes. Human calcium thrombin (100 μL) was added to initiate clotting, and the time to clot formation recorded as the dTT.

For aPTT, plasma samples (75 μL) were combined with 75 μL of kaolin–cephalin reagent and incubated with continuous stirring at 37°C for 3 minutes. Clotting was initiated by the addition of 75 μL of 0.025 M calcium chloride, and the time to fibrin clot formation recorded as the aPTT.

For ECT, plasma samples (75 μL) were incubated for 2 minutes at 37°C with 75 μL of imidazole/veronal buffer. Ecarin solution (75 μL) was added to initiate clotting, and the time taken for clot formation recorded as the ECT.

Population Model Development
Data Exclusion and Handling of Missing Data and Outliers
Matching plasma samples, collected at the same time point, were used in the analysis. For pretreatment baseline clotting time measurements, missing dabigatran plasma concentrations were imputed with 0 ng/mL. Posttreatment clotting-time records associated with missing values were excluded from the parameter analysis but retained and used for the graphical analysis. For patients enrolled in both the DIVERSITY (NCT01895777) and NCT02197416 study, only baseline values from DIVERSITY were used.

Potential outliers (defined as data points in the datasets that appeared to be outside the norm for that dataset) were identified based on inspection of the raw data or the output from an overall satisfactory model fit. Specifically, observations that were associated with conditional weighted residuals >5 could be regarded as outliers. In this analysis, potential outliers were included throughout model building for a robust assessment.

Model Building
Refinement (modification of the basic relationships between dabigatran plasma concentration and laboratory coagulation parameters, and the relationship between baseline clotting time and treatment response) of the previously published model\(^1\) was considered if initial model evaluation using graphical diagnostics indicated any misspecification with the prior model structure. To begin with, interindividual variability (IIV) was included in the models in a similar fashion to the Maas et al analysis.\(^3\) During the course of model development, IIV parameters were tested on other model parameters that were likely to vary between individuals. Additive, proportional, and additive plus proportional residual error models were explored on the observed (untransformed) dabigatran plasma concentrations.

Base models were those that best described the data without showing unacceptable trends in the goodness-of-fit plots. Time-independent covariates used the screening value (or the value at the first dose if the screening value was missing), and time-dependent covariates (body weight, age) used the actual covariate value at the time of the observation. The age in years (for those aged >1 year), months (for those aged <1 year), and the postmenstrual age (postnatal age plus 40 weeks) were considered to be able to detect potential differences. Age in months was used in the final models and as there appeared to be a correlation between age and weight, weight was not evaluated. Once the structural model was established, additional nonstructural covariates were added. If apparent study differences were not sufficiently
explained by other covariates, study-specific covariates were considered.

Covariate model building used the stepwise covariate model (SCM) building procedure (in two stepwise phases) in Perl-speaks-NONMEM. The forward selection p-value was set to 0.05 and the backward elimination p-value to 0.01. Categorical covariate relationships were generally coded as a fractional difference to the most common category, and continuous covariate relationships were generally coded as power models. The SCM models were further refined by reassessing the IIV parameters supported in the base model, resulting in the final models. Outcomes were evaluated based upon graphical analysis (goodness-of-fit plots and visual predictive checks) and changes in objective function value derived by NONMEM. Parameter estimates of the final aPTT, dTT, and ECT models are shown in Table S2. Visual predictive checks of the final aPTT, dTT, and ECT models versus dabigatran plasma concentrations stratified by age group are shown in Fig. S2.
Supplementary Fig. S1 Graphical visualization of the relationships between observed aPTT, dTT, and ECT, and dabigatran total plasma concentrations, across studies. aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; sec, second. *Includes 58 children who rolled over from the DIVERSITY trial. †Includes 57 children who rolled over from the DIVERSITY trial. In the aPTT plot, squares represent observed data from adult patients in the RE-COVER and RE-NOVATE II studies. In the dTT plots, squares represent observed data from adult patients in the RE-NOVATE II study. In the ECT plot, squares represent observed data from adult patients in the RE-COVER study. In all plots, circles are observed data from the five pediatric studies, and the dashed lines represent a model-based 95% prediction interval in healthy adults.

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Supplementary Fig. S2 Visual predictive checks of the final aPTT, dTT, and ECT models versus dabigatran plasma concentrations, stratified by age group. aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; sec, second. Red lines represent the median (solid line), 10th percentile (lower dashed line), and 90th percentile (upper dashed line) of the observations. Shaded areas represent the 95% confidence interval of the median (red shading), 10th percentiles (lower blue shading), and 90th percentiles (upper blue shading) predicted by the model.
Supplementary Fig. S3 Graphical visualization of the relationships between observed aPTT, dTT, and ECT, and dabigatran total plasma concentrations in the DIVERSITY study only by age group. aPTT, activated partial thromboplastin time; CV, coefficient of variation; dTT, diluted thrombin time; ECT, ecarin clotting time; g, geometric; sec, seconds. *Randomized, \( n = 11 \) (included 5 neonates/young infants [four were 0 month old, and one was 1 month old]) and one protocol deviation preterm patient (gestational age at birth <37 weeks or with body weight <3rd percentile but the patient was 8 months old when entered in the study and related neither to the neonate subgroup nor to the subgroup <6 months old). Trough gMean (gCV) plasma dabigatran concentration = 52.9 ng/mL (49.1%) \( (n = 9) \). #Randomized, \( n = 11 \). Trough gMean (gCV) plasma dabigatran concentration = 64.4 ng/mL (41.0%) \( (n = 11) \). $Randomized, \ n = 155 \) (one adolescent withdrew before treatment). Trough gMean (gCV) plasma dabigatran concentration = 87.4 ng/mL (50.2%) \( (n = 144) \).
**Supplementary Table S1  Pediatric data sources**

| Design | Phase 2a | Phase 2b/3 |
|--------|----------|------------|
|        | NCT02223260<sup>8</sup> | NCT01083732<sup>9</sup> | NCT00844415<sup>10</sup> | DIVERSITY (NCT01895777)<sup>11</sup> | NCT02197416<sup>12,a</sup> |
| Children treated with dabigatran, n | 8 | 18 | 9 | 176<sup>9</sup> | 213<sup>9</sup> |
| Prior treatment | Had completed SOC therapy for VTE | Had completed SOC therapy for VTE | Had completed SOC therapy for VTE | Initial treatment for 5–21 days with SOC | Had completed SOC therapy for VTE |
| Age, y | Birth to <1 | 1 to <12<sup>b</sup> | 12 to <18 | Birth to <18<sup>e</sup> | 3 months to <18 |
| Dabigatran treatment | d<sup>d</sup> | d<sup>d</sup> | bid for 3 days<sup>c</sup> | d<sup>d</sup> | d,f<sup>d</sup> |
| Capsules only, n | – | – | 9 | 119<sup>9</sup> | 179<sup>9</sup> |
| Pellets only, n | – | – | – | 42<sup>9</sup> | 34<sup>9</sup> |
| Capsules then pellets, n | – | – | – | 1<sup>9</sup> | – |
| Oral solution only, n | 8<sup>h</sup> | 18<sup>i</sup> | – | 13<sup>9</sup> | – |
| Oral solution then pellets, n | – | – | – | 1<sup>9</sup> | – |
| Matching samples, n | 4 | 3 | 5 | 171<sup>9</sup> | 213<sup>9</sup> |

Abbreviations: bid, twice daily; PD, pharmacodynamic; SOC, standard of care; VTE, venous thromboembolism.

<sup>a</sup>Includes 58 children who rolled over from the DIVERSITY trial.

<sup>b</sup>Included children in successive groups (those aged 2 to <12 years followed by those aged 1 to <2 years).

<sup>c</sup>Included five neonates/young infants and one protocol deviation preterm patient.

<sup>d</sup>Dosed according to an age and weight dosing algorithm.

<sup>e</sup>The first dose was given at 80% of the adult dose (1.71 mg/kg) adjusted for the patient’s weight. Thereafter, the dose corresponded to the full adult dose (2.14 mg/kg) adjusted for the patient’s weight.

<sup>f</sup>One dose adjustment (up- or down-titration) was allowed during the study if plasma concentrations were <50 ng/mL or ≥250 ng/mL.

<sup>g</sup>Final unpublished trial data.

<sup>h</sup>Single dose.

<sup>i</sup>Three patients aged 2 to <12 years received oral solution twice daily for 3 consecutive days. Nine patients aged 2 to <12 years, and six patients aged 1 to <2 years received a single dose of oral solution.

<sup>j</sup>The number of patients with matching dabigatran plasma concentration and PD samples drawn during the study period.
### Supplementary Table S2

Parameter estimates of the final aPTT, dTT, and ECT models

| Parameter | Final aPTT model | Final dTT model | Final ECT model |
|-----------|-----------------|----------------|----------------|
| Baseline, s | Value | RSE (%) | Value | RSE (%) | Value | RSE (%) |
| Baseline, s< 5.8 mo, s | | | | | | |
| Age at baseline, mo | | | | | | |
| EC50, ng/mL | | | | | | |
| Slope, ng/mL/C0 | | | | | | |
| Emax | | | | | | |
| IIV baseline, CV | | | | | | |
| IIV Emax, CV | | | | | | |
| Prop RUV, CV | | | | | | |

Abbreviations: aPTT, activated partial thromboplastin time; CV, coefficient of variation; dTT, diluted thrombin time; ECT, ecarin clotting time; Emax, maximum response (fold-increase from baseline); EC50, dabigatran concentration where half the maximum response is achieved; IIV, inter-individual variability; RSE, relative standard error; RUV, residual unexplained variability; SD, standard deviation.

Note: The RSEs for IIV and RUV parameters are reported on the approximate SD scale. Correlations between IIV parameters were described by omega block. For ECT, the slope parameter describes the drug effect in a 9-year-old reference patient.

### References

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