Using thrombocytopenia modeling to investigate the mechanisms underlying platelet depletion induced by pan-proteasome inhibitors

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Abstract
Pan-proteasome inhibitors (pPIs) significantly improve outcomes in patients with multiple myeloma; however, their indiscriminate inhibition of multiple proteasome and immunoproteasome subunits causes diverse toxicities, including thrombocytopenia. We investigated the mechanisms underlying the platelet depletion induced by the pPIs bortezomib, carfilzomib, and ixazomib. An established thrombocytopenia model was adapted for each compound (bortezomib, ixazomib, and carfilzomib) to compare the following two pharmacodynamic mechanisms: a reversible inhibition of new progenitor cell formation (the myelosuppression model) and a reversible effect on the function of megakaryocytes to bud new platelets (platelet formation model). Bortezomib, ixazomib, and carfilzomib plasma concentration profiles and platelet counts were extracted from the literature. Pharmacokinetic (PK) and thrombocytopenia models were developed to predict the PK of these drugs and to describe their effects on proliferating cells and platelet budding. The PK models reproduced the exposure of the three compounds at steady state well compared with those reported in the literature. Both the platelet formation and myelosuppression models seemed able to describe the platelet depletion caused by bortezomib, ixazomib, and carfilzomib. Estimated structural parameters in the myelosuppression model were in the range of the values reported in the literature, whereas the mean transit time estimated with the platelet formation model was 3-fold to 10-fold higher than the highest reported value. The model of drug-induced myelosuppression yielded estimates of structural parameters in the range of those previously reported. The platelet formation model captured the temporal variation reported in clinical studies.
INTRODUCTION

Multiple myeloma (MM) is an incurable hematological cancer distinguished by the clonal proliferation of neoplastic plasma cells.1 Most regulatory proteins in eukaryotic cells are degraded by the ubiquitin–proteasome pathway, rendering it critical for maintaining normal cellular homeostasis.2 With a higher level of proteasome activity than normal cells, MM cells are highly sensitive to proteasome inhibition, which induces an apoptotic cascade resulting in growth arrest and cell death.3 The use of proteasome inhibitors in MM treatment regimens has significantly improved patient outcomes.1

Bortezomib, ixazomib, and carfilzomib are pan-proteasome inhibitors (pPIs) approved for use in MM,4 with bortezomib and carfilzomib indiscriminately inhibiting multiple subunits of the constitutive proteasome and immunoproteasome.1 The mechanisms of action of pPIs in MM vary in terms of chemical class, enzyme binding kinetics, route of administration, and toxicity.5,6 The therapeutic applicability of these drugs is limited by the diverse toxicities arising from their constitutive proteasome inhibition in healthy tissues.1

Although pPIs have a manageable safety profile, hematological adverse effects are common, with all agents investigated to date associated with thrombocytopenia.1 The exact mechanisms by which pPIs induce thrombocytopenia are not yet fully understood1; one suggestion is that proteasome inhibition prevents nuclear factor kappa B (NF-κB) activation, leading to impaired platelet budding from megakaryocytes,7 which is in contrast to many other cytotoxic agents that cause myelosuppression through inhibiting new progenitor cell formation.8

Mathematical models to investigate drug effects on chemotherapy-induced myelosuppression have been previously developed9 and successfully adapted to investigate drug effects on thrombocytopenia.10–12

This report describes the adaptation of previously established thrombocytopenia models to investigate the following two alternative pharmacodynamic (PD) mechanisms of action on thrombocytopenia: a reversible inhibition of new progenitor cell formation (hereafter referred to as the myelosuppression model) and a reversible effect on the function of megakaryocytes to bud new platelets (hereafter referred to as the platelet formation model).7 The human exposure of approved pPIs (bortezomib, carfilzomib, and ixazomib) was described by pharmacokinetic (PK) models either adapted from published models or built based on exposure data extracted from the literature.

The myelosuppression and platelet formation models were fitted to platelet counts reported for bortezomib, carfilzomib, and ixazomib in the literature.5,7,13,14 Model validity was assessed based on graphical analysis, diagnostic plots, and comparison of the values estimated for the structural parameters describing platelet formation to values reported in the literature.10–12

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
The indiscriminate inhibition of multiple proteasome subunits by pan-proteasome inhibitors (pPIs) causes diverse toxicities, including thrombocytopenia.

WHAT QUESTION DID THIS STUDY ADDRESS?
This study investigated the mechanisms underlying the platelet depletion induced by currently approved pPIs using thrombocytopenia models.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
The developed PK models reproduced the exposure of the three compounds at steady state well versus those reported in the literature. The thrombocytopenia model of drug-induced myelosuppression yielded estimates of structural parameters in the range of those previously reported. The model of inhibition of platelet budding captured the temporal variation in clinical studies.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
Mechanism-based modeling can improve understanding of in vivo behavior following drug administration, an approach frequently used to support drug development and dosing. We show here that data modeling can be leveraged to test hypotheses on the mechanism of action behind pPI-induced thrombocytopenia. By better understanding the mechanisms of platelet depletion by pPI compounds, more targeted therapeutics may be developed.
**METHODS**

**Data sources**

Informed consent information is detailed in the respective publications from which data were extracted for use in this study. Data were extracted by digitization of the literature graphs using the web-based tool WebPlotDigitizer.

**Bortezomib**

Mean platelet count data were derived from reported data of patients with MM who were treated with 1.3 mg/m² bortezomib intravenously (i.v.) twice weekly (Days 1, 4, 8, and 11) for the first 2 weeks of each 3-week treatment cycle for up to eight cycles. PK data were extracted for comparison from Reece et al. and included bortezomib exposure data from Days 1 and 11 of Cycles 1 and 3 following i.v. administration of 1.3 mg/m² at Days 1, 4, 8, and 11 in 3-week cycles.

**Ixazomib**

Mean platelet counts after once weekly (2.97 mg/m² for 3 weeks in 4-week cycles) or twice weekly (2 mg/m² at Days 1, 4, 8, and 11 in 3-week cycles) oral dosing of ixazomib were derived from phase I trial data. Platelet counts were available for the maximum tolerated dose cohorts for each treatment regimen.

PK data were extracted from the same publications. PK profiles following once-weekly dosing were available for Days 1 and 15 after once-weekly oral dosing of 0.24, 0.48, 0.80, 1.20, 1.68, 2.23, 2.97, and 3.95 mg/m² ixazomib, but only profiles from 1.20 to 3.95 mg/m² were extracted as these are closer to the dose for which platelet data were available.

PK profiles following twice-weekly oral dosing were available for Days 1 and 11 after twice-weekly oral dosing of 0.24, 0.48, 0.8, 1.2, 1.68, 2.0, and 2.23 mg/m² of ixazomib, but only profiles from 0.8 to 2.23 mg/m² were extracted for analysis as these are closer to the dose for which platelet data were available.

**Carfilzomib**

Data regarding individual platelet counts were extracted from Alsina et al. During the dose expansion phase of the study, patients received either 20 or 27 mg/m² carfilzomib i.v. twice weekly on consecutive days (Days 1 and 2) for 3 weeks of a 4-week cycle.

PK data were extracted from Wang et al. Patients were administered 20 mg/m² carfilzomib i.v. for 2–10 min in combination with 4 mg dexamethasone on Days 1, 2, 8, 9, 15, and 16 in a 4-week cycle. Plasma concentration profiles were available from Days 1 and 16 of Cycle 1.

**Model development**

Modeling was performed in two steps for each of the three compounds (bortezomib, ixazomib, and carfilzomib). First, a relevant PK model was established either by fitting a compartmental PK model to the literature data or by adapting a PK model found in the literature and validating by comparison to published data. Platelet counts were subsequently modeled using the model structure presented in Bender et al., Tsuji et al., and Collins et al. Platelet count data were characterized by models describing either a reversible inhibition of new progenitor cell formation (the myelosuppression model) or by a reversible inhibition of the last transit step (new platelet budding; the platelet formation model).

**PK model development and analysis**

PK sampling, bioanalytical methods, and PK modeling approaches are as described in the respective articles from which data were captured. For bortezomib, a pediatric population PK model was adapted to the adult population using allometric scaling based on body surface area (BSA) and validated by comparison to digitized exposure data. Details of the pediatric model can be found in Table S1 in Supplementary Information S1. For scaling to adults, we used the following formula for each PK parameter (P) of the three-compartment model (clearance [CL], central volume of distribution [V₁], peripheral volume of distribution [V₂ and V₃], and intercompartmental clearance [Q₂ and Q₃]):

\[
P = a \times BSA^b \rightarrow P_{\text{adult}} = P_{\text{pediatric}} \times \left( \frac{\text{BSA}_{\text{adult}}}{\text{BSA}_{\text{pediatric}}} \right)^b
\]

- \(a = \) constant
- \(b = 1\), per agreement following author discussions
- \(\text{BSA}_{\text{pediatric}} = 1.30 \text{ m}^2\) per Hanley et al.
- \(\text{BSA}_{\text{adult}} = 1.62 \text{ m}^2\) per US Food and Drug Administration guidelines for estimating maximum safe starting doses

For ixazomib, concentration-time profiles and mean platelet count data were extracted by digitization of the graphs from the literature. Data were fitted to a
two-compartment PK model. A two-compartment model was chosen over a one-compartment model for ixazomib as this best fit the data.

For carfilzomib, a population PK model developed by Ou et al. was used to describe the exposure. The model was validated by comparison of predicted exposures to exposures reported in Wang et al.

### PD model development and analysis

A model to investigate drug effects on chemotherapy-induced myelosuppression was previously developed and successfully adapted to investigate drug effects on thrombocytopenia (Figure 1a). The model structure, equations, and parameters of significance have been described previously.

In the current study, the existing models were adapted, and for each compound, the myelosuppression and platelet formation models were investigated (Figure 1b).

Evolution of platelet count was described by a semimechanistic model composed of a compartment representing the progenitor cells (Prol) in the bone marrow, three transit compartments representing platelet maturation (Trans1, Trans2, and Trans3), and a compartment describing the circulating platelets (Circ). The proliferation of the progenitor cells is influenced by the ratio between circulating cells and initial baseline Circ0, with a strength γ. Transit between compartments is defined by the transit rate constant between transit compartments, Ktr. Circulating platelets are eliminated at a rate Kcic and Kprol denotes the rate of proliferation. The cell dynamics through the various compartments are described by the following equations:

\[
\frac{d\text{Prol}}{dt} = K_{\text{prol}} \times \text{Prol} \times \left( \frac{\text{Circ0}}{\text{Circ}} \right)^\gamma - K_{\text{tr}} \times \text{Prol} \quad (1)
\]

\[
\frac{d\text{Trans}_1}{dt} = K_{\text{tr}} \times \text{Prol} - K_{\text{tr}} \times \text{Trans}_1 \quad (2)
\]

\[
\frac{d\text{Trans}_2}{dt} = K_{\text{tr}} \times \text{Trans}_1 - K_{\text{tr}} \times \text{Trans}_2 \quad (3)
\]

\[
\frac{d\text{Trans}_3}{dt} = K_{\text{tr}} \times \text{Trans}_2 - K_{\text{tr}} \times \text{Trans}_3 \quad (4)
\]

\[
\frac{d\text{Circ}}{dt} = K_{\text{tr}} \times \text{Trans}_3 - K_{\text{cic}} \times \text{Circ} \quad (5)
\]

The mean transit time (MTT) is derived as \((n+1)/K_{\text{tr}}\), where \(n\) is the number of transit compartments. The number of transit compartments was set to three as it has been shown that it describes adequately the time course of platelet formation.

To describe the effect of the concentration \((C)\) of the pPI drugs on cell proliferation, Equation (1) was modified into the following:

\[
\frac{d\text{Prol}}{dt} = K_{\text{prol}} \times \text{Prol} \times \left( 1 - \text{slope}_{\text{pPI}} \times C \right) \times \left( \frac{\text{Circ0}}{\text{Circ}} \right)^\gamma - K_{\text{tr}} \times \text{Prol} \quad (6)
\]

To describe the effect of the pPIs on the budding of new platelets, Equations (4) and (5) were modified into the following respective equations:

\[
\frac{d\text{Trans}_3}{dt} = K_{\text{tr}} \times \text{Trans}_2 - K_{\text{tr}} \times \text{Trans}_3 \times \left( 1 - \text{slope}_{\text{pPI}} \times C \right) \quad (7)
\]

\[
\frac{d\text{Circ}}{dt} = K_{\text{tr}} \times \text{Trans}_3 \times \left( 1 - \text{slope}_{\text{pPI}} \times C \right) - K_{\text{cic}} \times \text{Circ} \quad (8)
\]

Modeling was performed using Phoenix WinNonLin version 6.4 (Certara). Both forms of the model were fitted to the data of each pPI separately, and models were assessed using diagnostic plots, Akaike’s information criterion/Bayesian information criteria, and comparison of simulated versus observed platelet counts. Additional information on the model evaluation can be found in Supplementary Information S2. Estimated parameters were compared with published values from similar models of myelosuppression.

### Results

#### Bortezomib

All of the patients had relapsed MM, and slightly more than half of the patients (55%–57%) were men, the median age was 59–62 years, and most were White/European American race (69%–81%). The mean baseline platelet count in the patients was 167.2 10^9/L. Mean plasma concentration profiles for bortezomib on Days 1 and 11 included data from 12 patients who received 1.3 mg/m² bortezomib. Estimated, scaled PK parameters for adults are shown in Table 1. A comparison of simulated versus observed plasma concentrations is shown in Figure 2a. The scaled PK model reproduced bortezomib exposures at steady state that were comparable with those reported in the literature.

Comparison of simulated versus observed platelet counts for bortezomib demonstrated that the myelosuppressive model captured the observed variations well (Figure 3). For the myelosuppressive model, the estimated
structural parameters (MTT and $\gamma$) were within the range of parameters reported in the literature (Table 2). The platelet formation model also captured the observed variations well (Figure 3), and $\gamma$ was within the range of parameters reported in the literature; however, estimated MTT was sixfold higher than the highest value reported in the literature (Table 2).

**Ixazomib**

All of the patients had relapsed/refractory MM, and slightly more than half of the patients (53%–55%) were men, the median age was 64–65 years, and most were White race (85%–90%). The mean baseline platelet count in patients was approximately 160 $10^9$/L (value extracted from a graph). In the study reported by Kumar et al., mean plasma concentration–time profiles on Days 1 and 15 included patients who received between 1.20 and 3.95 mg/m² ixazomib. In the study reported by Richardson et al., mean plasma concentration–time profiles on Days 1 and 11 included patients who received between 1.20 and 2.23 mg/m² ixazomib. A comparison of simulated versus observed plasma concentrations is shown in Figure 2b. Although there was a small overprediction of the exposure after the first dose, the PK model reproduced ixazomib exposures at steady state well versus those reported in the literature.
Comparison of simulated versus observed platelet counts demonstrated that the myelosuppressive model did not fully capture the observed variations (Figure 3); however, the estimated structural parameters (MTT and $\gamma$) were within the range of parameters reported in the literature (Table 2). The platelet formation model captured the observed variations well (Figure 3), but MTT was outside the range of parameters reported in the literature at 10-fold higher than the highest value reported in the literature (Table 2).

**Carfilzomib**

All patients had solid tumors or MM. The mean baseline platelet count in patients ranged approximately from 60 to $250 \times 10^9$ L in the 20 mg/m² cohort and from 60 to $205 \times 10^9$ L in the 27 mg/m² cohort (values extracted from graphs). Mean plasma concentration profiles for carfilzomib on Days 1 and 16 each included data from three patients who received 20 mg/m² carfilzomib. A comparison of simulated versus observed plasma concentrations is shown in Figure 2c. The model captured well the maximum exposure as reported in the literature but overestimated the exposure at later timepoints.

As individual profiles were available for carfilzomib, with large differences in the initial platelet count across patients, models were fitted considering interindividual variability in the initial platelet count. Comparison of simulated versus observed counts demonstrated that the myelosuppression model described the observed data well (Figure 3). The estimated structural parameters (MTT and $\gamma$) were in line with the values reported in the literature (Table 2). The platelet formation model could be fitted to the data; however, the estimated parameters (MTT and $\gamma$) were not biologically plausible. The parameter describing the effect of the compound was very high (Figure 3).

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**TABLE 1** Estimated pharmacokinetic parameter values for adults treated with bortezomib using allometric scaling of pediatric population pharmacokinetic parameters

| Parameter                  | Adult estimates |
|---------------------------|-----------------|
| CL (L/h/m²)               | 9.2             |
| $V_1$ (L/m²)              | 9.6             |
| $Q_1$ (L/h/m²)            | 24.7            |
| $V_2$ (L/m²)              | 31.2            |
| $Q_2$ (L/h/m²)            | 25.5            |
| $V_3$ (L/m²)              | 934.6           |

Abbreviations: CL, clearance; $Q_1$, intercompartmental clearance 1; $Q_2$, intercompartmental clearance 2; $V_1$, central volume of distribution; $V_2$, peripheral volume of distribution 1; $V_3$, peripheral volume of distribution 2.

**FIGURE 2** (a) Overlay of simulated (gray dots) bortezomib pharmacokinetics using a pharmacokinetic model scaled from a pediatric population pharmacokinetic model and observed (black line) bortezomib plasma concentrations at a dose of 1.3 mg/m² at Days 1, 4, 8, and 11 in 21-day cycles. (b) Overlay of simulated (gray dots) ixazomib pharmacokinetics using a fitted pharmacokinetic model and observed (black line) ixazomib concentrations at a dose of 2 mg/m² twice weekly. (c) Overlay of simulated (gray dots) carfilzomib pharmacokinetics using median values from population pharmacokinetic data derived by Ou et al. and observed (black line) carfilzomib concentrations at a dose of 20 mg/m².
FIGURE 3 Overlay of observed (black lines) and simulated (gray lines) platelet counts in patients treated with bortezomib 1.3 mg/m² at Days 1, 4, 8, and 11 in 3-week cycles (top row), ixazomib 2 mg/m² at Days 1, 4, 8, and 11 in 3-week cycles (middle row), or carfilzomib 20 or 27 mg at Days 1 and 2 for 3 weeks in 4-week cycles (bottom row). Simulations were performed using models of either myelosuppression (left) or inhibition of the formation of circulating platelets (right).
Inhibition of platelet budding

maximum plasma concentration were in line with the values reported in Wang et al.\textsuperscript{16}

Mechanism-based modeling can be used to improve understanding of in vivo behavior following drug administration, and this modeling approach is frequently used to support drug development and dosing.\textsuperscript{21}

A drug’s mechanism of action must be considered during model development to increase model reliability as this will affect outcomes when simulating different scenarios and dosing regimens. The model for pPI-induced thrombocytopenia was based on observed cyclical patterns of platelet reductions and shorter recovery times than for myelosuppressive cytotoxic agents\textsuperscript{5,13} in addition to the posited effects of pPIs on NF-\kappaB activation, leading to impaired platelet budding from megakaryocytes.\textsuperscript{7}

For bortezomib, a PK model could be fitted that described bortezomib exposure well after single and repeated dosing. The PK model developed for ixazomib slightly overpredicted the exposure after the first dose, but otherwise reproduced exposures at steady state that were comparable with those reported in the literature.\textsuperscript{5,13,15,16}

For carfilzomib, the overlay of PK data was not optimal, likely because we compared the median of a simulation made using a population PK model with mean data from a single dose level. Data after repeated doses should be better reproduced by the model. However, we could not find such data in the literature for validation. The data we used for the graphical comparison were part of the data set published with the population PK model by Ou et al.\textsuperscript{20} In addition, PK parameters derived by noncompartmental analysis of the exposure simulated with this model such as area under the curve and maximum plasma concentration were in line with the values reported in Wang et al.\textsuperscript{16}

The model of drug-induced myelosuppression yielded estimates of structural parameters that were in the range of those previously reported\textsuperscript{10–12} and were similar between drugs, supporting the validity of the model.

When looking at inhibition of platelet budding, the adapted model seemed to capture the temporal variation in clinical studies, especially for ixazomib.\textsuperscript{10–12} However, this variation may have been a result of the withdrawal of patients who experienced thrombocytopenia and/or other adverse effects. This could only be verified by having individual platelet profiles along with precise information on individual treatment. Further model development may reveal the validity of this output of the model. Structural parameter value estimates of the model of drug-induced inhibition of platelet budding were not consistent across compound data sets and differed significantly from the values reported in the literature for MTT.

A comparison of the two models indicates that the model with myelosuppression better describes the data. However, in general, the platelet budding model could be more biologically relevant as it better reflects the mechanism of action of the compounds. As such, its utility and the use of the parameter estimates in terms of explaining the biological events are more relevant.

Monoclonal plasma cells infiltrate bone marrow, resulting in the disruption of hematopoietic cell lines and causing MM-related thrombocytopenia independent of drug-induced thrombocytopenia.\textsuperscript{22} Therefore, the platelet formation dynamic could differ between patients with solid tumors and patients with hematological tumors; however, no data were available on platelet counts before treatment to support the investigation of the impact of the disease on platelet formation. Consequently, the thrombocytopenia models adapted in this study examined platelet variations taking place only from the initiation of pPI treatment. MM-related thrombocytopenia is accounted for by a low initial platelet count. If data were available both before treatment initiation and during the posttreatment recovery

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### Table 2

Parameters estimated for the thrombocytopenia model based on myelosuppression or inhibition of platelet budding for bortezomib, ixazomib, and carfilzomib

| Parameter | Myelosuppression effect\textsuperscript{a} | Inhibition of platelet budding\textsuperscript{a} | Published values: myelosuppression |
|-----------|-----------------|-----------------|-------------------------------|
| γ         | 0.38 (11.5)     | 0.33 (11.1)     | 0.35 (31.9) [53.3]            |
| MTT, h    | 99 (7.6)        | 95 (6.5)        | 82 (11.4)                     |
| Circ₀, 10\textsuperscript{9} p/L | 171 (4.5) | 188 (5.6) | 114 (16.4) |
| Slope    | 0.07 (11.2)     | 0.02 (8.8)      | 0.014 (25.3)                  |

\textsuperscript{a}Values presented are modeled estimates (coefficient of variation) and for carfilzomib [interindividual variability].

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**DISCUSSION**

Estimated MTT was around threefold higher than the values reported in the literature (Table 2).
phase, it would have been possible to model MM-related thrombocytopenia modulation through the antitumoral effect of the pPIs.

Bortezomib, ixazomib, and carfilzomib have different mechanisms of action, with bortezomib and ixazomib being reversible proteasome inhibitors and carfilzomib being an irreversible proteasome inhibitor. The investigated models were able to reproduce the drug-induced thrombocytopenia without taking this difference into account. However, more detailed data sets comprising individual platelet counts could reveal divergences in the impact on platelets of reversible versus irreversible proteasome inhibitors. It would then be necessary to integrate the specific mechanisms of action in the modeling.

**Limitations**

An important limitation of this study was the lack of individual patient data, both for PK and platelet counts. Platelet data were reported as the mean of the patient population. Mean platelet counts increased over time, likely as a result of the withdrawal of patients who experienced severe thrombocytopenia and/or other adverse effects. Therefore, the imputed data may not reflect an increase in platelet counts in individual patients.

**CONCLUSIONS**

The results of this study demonstrated that, via adaptation of existing models and in vivo data from clinical studies, the mechanisms of platelet depletion by pPI compounds can be elucidated. Both platelet formation and myelosuppressive models seemed to be able to describe the platelet depletion caused by bortezomib, ixazomib, and carfilzomib, and PK models reproduced the exposure of the three compounds at steady state well compared with those reported in the literature.

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**CONFLICTS OF INTEREST**

F.L., A.D.B., C.G., and F.R. are employees of The Healthcare Business of Merck KGaA, Darmstadt, Germany, and S.E.B. was an employee of The Healthcare Business of Merck KGaA, Darmstadt, Germany, at the time of the study.

**AUTHOR CONTRIBUTIONS**

F.L., A.D.B., C.G., F.R., and S.E.B. wrote the manuscript. F.L., A.D.B., C.G., F.R., and S.E.B. designed the research. F.L. performed the research. F.L., F.R., and S.E.B. analyzed the data.

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.

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