Primary immunodeficiency diseases (PI) comprise more than 200 rare genetic diseases characterized by increased susceptibility to serious and recurrent infections as a result of an individual’s compromised immune system. Awareness and diagnosis of PI has increased over the last 40 years, and in 2007, results from a survey suggested that the estimated prevalence of diagnosed PI in the United States (US) is approximately 1 in 1200 persons. Clinical symptoms generally include recurrent or difficult-to-treat infections, poor growth or weight loss, recurrent deep abscesses of the organs or skin, and swollen lymph glands or an enlarged spleen. Patients with PI experience significantly higher hospitalization rates, as well as increased limitations on physical, school, and social activities. For example, in 2011, the Jeffrey Modell Centers Network reported that the average patient with PI in the US had a significant burden of 12 physician, emergency department, or hospital visits and 5 days of hospitalization annually in the year following diagnosis. Annual infection-related costs are estimated to be $18,368 among patients with PI. In addition, more than 50% of PI are associated with antibody deficiencies (often resulting in recurrent serious bacterial infections of the respiratory tract) that negatively impact patients’ life expectancy and put patients at increased risk of comorbidities such as autoimmune diseases and inflammatory and lymphoproliferative disorders.

Immunoglobulin G (IgG) replacement therapy can be administered to the patient either intravenously (IVIG) or subcutaneously (SCIG), with the 2 routes demonstrating equivalent efficacy in preventing bacterial and other infections, such as pneumonia, sinusitis, and otitis media. Both therapies may also help prevent hospitalizations due to infection, as well as improve other important quality-of-life-related outcomes. In addition, SCIG is associated with lower rates of systemic adverse reactions and provides easier patient access to treatment as it is self-administered and does not require a visit to the clinic for infusion. SCIG has been shown to be generally more cost-effective than IVIG, largely due to fewer lost work or school days. As demonstrated in previous studies, the net cost savings after switching from IVIG to SCIG at a dose ratio of 1:1 was studied and approved for the European Union (EU). The dose-adjustment ratio used by prescribers in real-world US clinical practice is unknown.

OBJECTIVES: To examine real-world Hizentra 20% SCIG-to-IVIG dose ratios in the US after PI patients are switched from IVIG to 20% SCIG (Hizentra).

METHODS: A retrospective longitudinal study was conducted using prescription shipment data of patients with PI from specialty pharmaceutical and service providers from 2011 to 2016. Patients who had at least 1 shipment of IVIG prior to switching to 20% SCIG (Hizentra) and subsequently received at least 1 more 20% SCIG (Hizentra) shipment in the following 6 months were included. Monthly 20% SCIG (Hizentra) doses following a switch from IVIG were calculated for each 2-month interval by summing daily doses that were estimated by dividing shipped volume by days between shipments. Mean monthly IVIG dose was calculated from the total volume shipped prior to switch. Per-patient dose ratios of Hizentra 20% SCIG-to-IVIG were calculated by dividing monthly 20% SCIG (Hizentra) dose by monthly IVIG dose during each 2-month interval. To minimize the influence of outliers, median dose ratios were reported. Dose ratios at months 2 to 4, 4 to 6, and 6 to 8 were compared with the dose ratio at months 0 to 2 using the Wilcoxon signed rank test. A sensitivity analysis excluding pediatric patients was conducted to assess the impact of changes in weight.

RESULTS: Data from 278 patients who met the inclusion criteria showed that median Hizentra 20% SCIG-to-IVIG dose ratios were 1.14:1 at 0 to 2 months post switch, 1.09:1 at 2 to 4 months, and stabilized at 1.05:1 at 4 to 6 and 6 to 8 months post switch. Median dose ratios at months 2 to 4, 4 to 6, and 6 to 8 were statistically significantly lower than the median dose ratio at 0 to 2 months post switch (all P <.001). Similar results were seen in the sensitivity analysis excluding pediatric patients.

CONCLUSIONS: Real-world data indicate that patients were switched to 20% SCIG (Hizentra) from IVIG at dose ratios lower than recommended by US prescribing information but similar to prescribing information in the EU. The initial dose ratio of 1.14:1 at 0 to 2 months stabilized to 1.05:1 at 4 to 6 and 6 to 8 months, which was consistent with reports of dose-equivalent switching patterns used in management of PI in clinical practice in the US.

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1:1.5 dose ratio is between $755 and $4115 per patient, depending on the cost that is considered to be saved for having successfully avoided infections.7,8

Hizentra (Immune Globulin Subcutaneous [Human] 20% Liquid; 20% SCIG) is the first 20% SCIG therapy indicated for PI in adults and pediatric patients 2 years of age and older.9 It was approved after 2 pivotal trials in the US and Europe, which had durations greater than 60 and 40 weeks, respectively. Its higher concentration of 20%, as compared with 10% and 16% products, was formulated for lower-volume subcutaneous administration.10 In addition, 20% SCIG (Hizentra) is also self-administered and can be stored at temperatures up to 25°C.11,12

Due to differences in pharmacokinetics between IVIG and SCIG preparations (i.e., differences in bioavailability, as measured by the area under the serum concentration–time curve [serum AUC]), the FDA requires manufacturers to calculate a dose-adjustment coefficient between the 2 treatment routes that ensures equivalent systemic exposure within margins of 80% to 125%.9 Specifically, a pharmacokinetic study of 20% SCIG (Hizentra) indicated that the monthly dose of SCIG that provides equivalent systemic exposure to IVIG was 1.53 times the dose of IVIG.11 In January 2015, the FDA approved reduction of the dose adjustment factor to 1.37 on the basis of data from pharmaco-economic modeling and simulations. This dose-adjustment factor is consistent with the class of SCIG therapies, except the 10% SCIG human hyaluronidase and immune globulin. As such, current prescribing information for 20% SCIG (Hizentra) in the US recommends that patients switching from IVIG therapy to 20% SCIG (Hizentra) are dosed at 1.37 times their previous IVIG dose.12 However, prescribing information in the European Union (EU) recommends equivalent dosing between IVIG and 20% SCIG (Hizentra).4 An analysis of cross-sectional data from a major home care provider showed that dosing patterns may vary across patient populations or route of administration, with lower doses prescribed for patients on SCIG than with IVIG.12 Previous research also indicates that treatment with 20% SCIG (Hizentra) at equivalent doses to IVIG (i.e., at a 1:1 ratio) is well-tolerated and effective in protecting against infections in patients with PI.13 As a result, a number of studies have raised questions about whether dose-adjustment coefficients are needed.10,11,12,15

The objective of this study was to evaluate and provide real-world evidence of dose ratios in the US after patients with PI were switched from IVIG to 20% SCIG (Hizentra).

**Methods**

**Study Design and Patient Selection**

A retrospective longitudinal study was conducted using shipment data on prescriptions dispensed from specialty pharmaceutical and service providers (SPs) from 2011 to 2016. SPs fill prescriptions for specialty drugs, such as IgG replacement therapy, that are not available at local retail pharmacies, due to higher costs or complexity of handling and administration. The database contained information from more than 40 different SPs and included data on patient diagnoses; details about the drugs shipped, such as strength, volume, vial quantity, and mode of administration; prescriber specialty; patient weight; and patient demographics, including age, sex, and geographic region. Shipped volume (in grams) was used to calculate the dose in this study because volume prescribed or consumed is not available in the data. The study, therefore, implicitly assumes that patients were administered the total volume of therapy shipped. There are no strong reasons to believe that patients were administered a volume different than that shipped. Even if patients were not administered all of the shipments they received, it is unlikely that this phenomenon would impact calculations of SCIG and IVIG dose differentially. Moreover, if patients were administered only a portion of volume shipped, the current study would tend to overestimate the SCIG-to-IVIG dose ratios.

The study design scheme is presented in Figure 1. The study population included PI patients who switched from IVIG therapy to 20% SCIG (Hizentra). PI patients were identified using ICD-9-CM (279) or ICD-10-CM (D80-D84) diagnosis codes. Patients who switched from IVIG to 20% SCIG (Hizentra) were identified as patients who had at least 1 IVIG shipment prior to the first 20%
SCIG (Hizentra) shipment observed in the database. All patients were required to have at least 2 shipments of 20% SCIG (Hizentra), including the first 20% SCIG (Hizentra) shipment, which defined the switch date, and at least 1 shipment of 20% SCIG (Hizentra) at least 6 months after the switch date. Patients were also required to be at least 2 years old at 6 months before the switch date and have no claims for IVIG during the 6 months following the switch.

**Treatment, Outcomes, and Covariates**

Baseline demographic, provider, and payer characteristics were assessed at the time of switch; these included sex, weight, geographic location of provider, type of PI diagnosis, specialty of provider, and payer type. Age was assessed at 6 months prior to switch.

The outcomes of interest were within-patient Hizentra 20% SCIG-to-IVIG monthly dose ratios at months 0 to 2 (0-60 days), 2 to 4 (61-120 days), 4 to 6 (121-180 days), and 6 to 8 (181-240 days) after the patient switched to 20% SCIG (Hizentra) from an IVIG therapy.

**Statistical Analysis**

Baseline demographic, provider, and payer characteristics were described with frequency distributions for categorical variables and with means, standard deviations (SDs), medians, and interquartile ranges (IQRs) for continuous variables.

Mean daily IVIG dose (g/day) prior to the switch to 20% SCIG (Hizentra) was calculated as the total volume of IVIG therapy shipped to the patient prior to the switch date divided by the number of days between the first and the last IVIG shipment date plus 30 days to account for time associated with the last shipment (based on the median number of days between shipments observed in the database). The mean daily IVIG dose was multiplied by 30 to calculate the average monthly IVIG dose (g/month).

The data show that shipments of 20% SCIG (Hizentra) were sent to patients in variable intervals (mean, SD, and mode of the duration of time between shipments were 27, 19, and 28 days, respectively). This observed nonuniformity in shipment intervals could have implications on the calculation of mean monthly 20% SCIG (Hizentra) dose because a simple aggregation of shipments by month could result in the mean monthly dose being automatically inflated or deflated based on the frequency of shipments. Therefore, to assess the volume of 20% SCIG (Hizentra) that was intended for treatment of each patient, mean monthly 20% SCIG (Hizentra) dose was calculated assuming that the duration of time between shipments reflected the number of days that a particular prescription shipment was used by the patient (as noted above, the mean duration between 20% SCIG (Hizentra) shipments was 27 days). Specifically, daily 20% SCIG (Hizentra) doses (g/day) were first estimated by dividing the shipped volume in each shipment by the number of days to the next shipment. These estimated daily doses were aggregated for each 2-month period following the switch date, and average monthly doses (g/month) were calculated by dividing the aggregated daily doses by 2 months.

For each patient, Hizentra 20% SCIG-to-IVIG dose ratios were calculated for each 2-month period post switch by dividing the patient’s mean monthly 20% SCIG (Hizentra) dose by his or her mean monthly IVIG dose prior to the switch. If a patient did not have a shipment in a given 2-month period, the patient’s dose ratio from the last period was carried forward. This last observation carried forward approach for imputing missing data is commonly used in health outcomes research.16

Median (IQR) dose ratios at each 2-month interval were then calculated in order to minimize the impact of outliers and were plotted for the study population. Dose ratios at 2 to 4, 4 to 6, and 6 to 8 months were compared with the dose ratio at 0 to 2 months using the Wilcoxon signed rank test to account for the paired nature of the data.

**Sensitivity Analysis**

Patient weight was available for only 82% of the study population and was not regularly recorded for each shipment. Because healthcare providers prescribe SCIG and IVIG dose based on patient weight, mean monthly dose ratios were calculated assuming that patient weight did not change substantially over the course of the 8-month observation period. Although this is a reasonable assumption to make for adults, it may not be valid for
pediatric patients. Therefore, a sensitivity analysis was conducted excluding pediatric patients younger than 8 years of age from the study population to reduce the effects of changes in patient weight on dose calculations.

Results
Baseline Demographic, Provider, and Payer Characteristics
A total of 278 patients met the inclusion criteria for the study; baseline characteristics are reported in Table 1. The study population was 66.2% female, and mean age and weight were 38.6 years (SD, 21.6; median, 42.0; IQR, 17.5-57.5) and 61.3 kg (SD, 36.0; median, 58.0; IQR, 35.5-79.0). Provider locations were similarly distributed across all geographic regions, with the highest proportion of providers in the South (30.6%) and Northeast (27.7%) regions. The most common PI diagnosis was immunodeficiency of humoral immunity (ICD-9-CM 279.0 and ICD-10-CM D83, 80.2%), followed by disorders involving the immune system (ICD-9-CM 279, 12.9%). Most shipped prescriptions were prescribed by providers specializing in allergy and immunology (81.3%), followed by pediatrics (9.7%). More than 80% of patients were covered by a commercial payer; approximately 20% of patients were covered by a federal payer.

Median Dose Ratios Over Time
Figure 2 presents the median Hizentra 20% SCIG-to-IVIG dose ratio for each 2-month period following the patients’ switch date. The initial median (IQR) Hizentra 20% SCIG-to-IVIG dose ratio was 1.14:1 (0.92:1-1.45:1) at 0 to 2 months post switch, a level lower than the dose ratio of 1.37:1 specified in the current US prescribing information. The median dose ratio was 1.09:1 (0.79:1-1.36:1) at 2 to 4 months and stabilized to 1.05:1 (0.75:1-1.34:1) at 4 to 6 months and 1.05:1 (0.70:1-1.34:1) 6 to 8 months post switch. As shown in Table 2, median dose ratios at months 2 to 4, 4 to 6, and 6 to 8 were all statistically significantly different from the median dose ratio at 0 to 2 months post switch (all P <.001).

Results From Sensitivity Analysis Excluding Pediatric Patients
A total of 25 pediatric patients younger than 8 years of age were excluded in the sensitivity analysis sample. As shown in Figure 3,

### Table 1. Baseline Demographic, Provider, and Payer Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>38.6 ± 21.6</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>184 (66.2)</td>
</tr>
<tr>
<td>Male</td>
<td>94 (33.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Patient weight (kg), mean ± SD</td>
<td>61.3 ± 36.0</td>
</tr>
<tr>
<td>Geographic US location of provider site, n (%)</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>55 (19.8)</td>
</tr>
<tr>
<td>Midwest</td>
<td>57 (20.5)</td>
</tr>
<tr>
<td>Northeast</td>
<td>77 (27.7)</td>
</tr>
<tr>
<td>South</td>
<td>85 (30.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>Type of PI diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Deficiency of humoral immunity</td>
<td>223 (80.2)</td>
</tr>
<tr>
<td>Disorders involving the immune mechanism</td>
<td>36 (12.9)</td>
</tr>
<tr>
<td>Deficiency of cell-mediated immunity</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Other immunodeficiencies</td>
<td>13 (4.7)</td>
</tr>
<tr>
<td>Other autoimmune diseases</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Specialty of provider who prescribed 20% SCIG (Hizentral), n (%)</td>
<td></td>
</tr>
<tr>
<td>Allergy and immunology</td>
<td>226 (81.3)</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>Other</td>
<td>27 (9.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>15 (5.4)</td>
</tr>
<tr>
<td>Payer type, n (%)</td>
<td></td>
</tr>
<tr>
<td>Commercial</td>
<td>223 (80.2)</td>
</tr>
<tr>
<td>Federal</td>
<td>55 (19.8)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; PI, primary immunodeficiency disease; SCIG, subcutaneous immunoglobulin G; SD, standard deviation; US, United States.

IVIG indicates intravenous immunoglobulin G; SCIG, subcutaneous immunoglobulin G.
results from the sensitivity analysis were nearly identical to those from the main analysis, demonstrating that the main study results were robust to the assumption of constant patient weight over time. The initial median (IQR) Hizentra 20% SCIG-to-IVIG dose ratio excluding the pediatric population was 1.15:1 (0.88:1-1.45:1) at 0 to 2 months post switch. Median dose ratios were 1.09:1 (0.78:1-1.37:1) at 2 to 4 months, 1.06:1 (0.74:1-1.34:1) at 4 to 6 months, and 1.07:1 (0.70:1-1.34:1) at 6 to 8 months post switch. As observed in the main analysis, the median dose ratios at months 2 to 4, 4 to 6, and 6 to 8 were all statistically significantly different from the median dose ratio at 0 to 2 months post switch (all \(P < .001\)).

**Discussion**

Results from this study of real-world US data indicate that many patients switching to 20% SCIG (Hizentra) from IVIG began treatment at dose ratios lower than the Hizentra 20% SCIG-to-IVIG dosing ratio of 1.37:1 recommended in the current US 20% SCIG (Hizentra) prescribing information. The median dose ratio subsequently reached approximately 1.1:1 after 2 months post switch and remained relatively stable through 8 months post switch. The median dose ratio at 0 to 2 months was statistically significantly different from dose ratios at later bimonthly intervals (2 to 4, 4 to 6, and 6 to 8 months). Hence, patients receive 20% SCIG (Hizentra) at a dose that is approximately equivalent to their IVIG dose, as recommended in the EU. These results are not surprising, because previous research has shown that 20% SCIG (Hizentra) is well-tolerated and effective in doses equivalent to IVIG. In fact, in 1 of the first studies of 20% SCIG (Hizentra), it was stated that a dose ratio of 1.5:1 may not be necessary, because doses of SCIG that were equivalent to previous IVIG doses resulted in a 17.7% increase in serum IgG levels. Furthermore, stabilization of the dose ratio at approximate equivalency is consistent with reports from PI clinical experts on their approach to management. Because the FDA recommends that SCIG doses be modified based on the patient’s clinical condition, results from this study may reflect the fact that similar doses of IVIG and SCIG are prescribed to reduce the rate of infection in patients with PI.

The conclusions of this study also held for the sensitivity analysis excluding pediatric patients from the study sample. Since the dose of 20% SCIG (Hizentra) is expected to increase over time with increasing weight for pediatric patients, it is expected that the dose ratio would also increase over time. However, the opposite trend was observed, and potential changes in patient weight did not impact stabilization of the postswitch dose ratio to approximately 1.1:1.

Real-world dosing evidence presented in this study may also have implications on the expected costs of treatment associated with 20% SCIG (Hizentra). Although 20% SCIG (Hizentra) is more costly than IVIG, it has been shown to be cost-effective or cost-saving at a Hizentra 20% SCIG-to-IVIG dose ratio of 1:1 and cost-saving even at a dose ratio of 1.5:1 as a result of lower healthcare resource utilization and, therefore, lower costs for hospital care. The need for medical supervision and administration of IVIG infusions at healthcare centers is one of the main drivers of the cost differences between IVIG and SCIG treatment. A number of international studies have shown that switching from IVIG to SCIG also reduces healthcare costs incurred by payers as a result of decreased hospital personnel labor costs, increased healthcare personnel productivity, and less use of healthcare facilities. The convenience of administering SCIG at home, avoiding time spent at infusion centers, and reduced productivity loss resulting from short infusion times also provides indirect cost savings to patients. Improvements in patient quality of life are observed among pediatric and adult patients who switch from IVIG to SCIG, and

**TABLE 2. Comparison of Monthly Hizentra 20% SCIG-to-IVIG Dose Ratios**

<table>
<thead>
<tr>
<th></th>
<th>Median differencea</th>
<th>95% CI</th>
<th>Wilcoxon signed rank test (P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 month versus 6-8 month dose ratio</td>
<td>-0.08</td>
<td>[-0.12 to -0.05]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>0-2 month versus 4-6 month dose ratio</td>
<td>-0.08</td>
<td>[-0.11 to -0.05]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>0-2 month versus 2-4 month dose ratio</td>
<td>-0.06</td>
<td>[-0.08 to -0.04]</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; IVIG, intravenous immunoglobulin G; SCIG, subcutaneous immunoglobulin G.

*aMedian differences and CI were calculated based on the Hodges-Lehmann estimator for medians.

**FIGURE 3. Median Monthly Hizentra 20% SCIG-to-IVIG Dose Ratio Over Time Excluding Pediatric Patients**

IVIG indicates intravenous immunoglobulin G; SCIG, subcutaneous immunoglobulin G.
dose ratios of approximately 1:1 are likely to be sufficient to achieve these positive outcomes. Specifically, patients treated with home-based SCIG reported improved treatment satisfaction, greater freedom and flexibility, and better school and social functioning among children. Given patient preference for home therapy, equal efficacy of SCIG and IVIG therapy in protecting against infections, and the relative safety of SCIG administration, it is not surprising that 90% of patients who switched from IVIG to SCIG therapy in a previous study remained on SCIG and 95% of newly diagnosed patients who chose SCIG over IVIG remained on SCIG.

Thus, in addition to showing that the dose of 20% SCIG (Hizentra) needed to achieve positive clinical and quality-of-life outcomes is lower than the level currently recommended in the US, the potential implications of the lower, real-world dose ratio include reduced direct and indirect costs. These cost savings are certainly a benefit to patients and payers.

This analysis of real-world prescription data suggests that, for most PI patients, stable dose ratios close to 1:1 were achieved after 2 months following the switch, providing economic benefits to patients and lower costs to payers. As such, our findings indicate the current prescribing information–recommended dose ratio of 1.37:1 may be excessive and result in higher drug costs to the patient than necessary. Additional research is needed to confirm the results of our study.

Limitations

This study has several limitations. First, data on patient weight was not available for all patients and thus could not be factored into the calculation of dose ratios. Since prescribed dose for IVIG and SCIG therapy depend on weight, changes in weight over time may potentially affect dose ratios and render monthly doses over time incomparable. However, exclusion of pediatric patients, whose weight is likely to be the least stable, demonstrated that the same conclusions from the main study population hold, suggesting that study results were robust to potential changes in weight.

Second, the calculated doses for 20% SCIG (Hizentra) and IVIG are based on volume shipped and not volume prescribed or consumed by the patient, because this information is not regularly available from SP shipment data, to which this study was limited. Thus, it was assumed that the volume shipped was equal to the volume administered to the patient. However, a method that estimated monthly dose by calculating daily doses first was applied to ensure that dose estimates were as accurate as possible. The availability of additional data fields may enhance the ability to address objectives of the current study. Currently, few datasets would allow for such an investigation. In addition, the nonuniformity of shipment intervals and missing dose ratios in consecutive 2-month periods (addressed using the last observation carried forward imputation method, which may increase bias) are also limitations of this study.

Lastly, as with all retrospective observational studies, these results may be subject to selection bias. Data on the patient’s clinical condition (e.g., comorbidities and infection history) prior to and following switch, IgG serum levels, and clinical outcomes were lacking from the SP database used in this study. Although the objective of this analysis was to calculate monthly dose ratios, these interesting findings may warrant a future study to examine clinical and quality-of-life outcomes associated with different dose ratios, and to examine the economic impact of lower dose ratios.

Conclusions

Real-world data show that patients switching from IVIG began SCIG therapy with 20% SCIG (Hizentra) at dose ratios lower than the current prescribing information–recommended dose ratio in the US. Stabilization of the Hizentra 20% SCIG-to-IVIG dose ratio close to 1:1 is consistent with reports of clinical management of PI and with the dosing ratio used in the EU. In previous research, serum IgG levels with SCIG have been shown to be higher than with IVIG, and this raises the possibility that the dose adjustment factor recommended in the current prescribing information in the US may be too high or unnecessary.

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Authorship information: Concept and design (RHB, ALB, MD, MSD, BE, GK, JKL); acquisition of data (DL); analysis and interpretation of data (RHB, ALB, MD, MSD, BE, GK, DL, JKL); drafting of the manuscript (RHB, MD, BE, GK, JKL); critical revision of the manuscript for important intellectual content (RHB, ALB, MD, MSD, BE, GK, JKL); statistical analysis (RHB, MD, BE, DL, JKL); obtaining funding (MDS); and supervision (MDS).

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REFERENCES


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