A Once-Daily Dasatinib Dosing Strategy for Chronic Myeloid Leukemia

George Bryant, ND, ACNP-BC, ANP-BC, AOCNP®

The BCR-ABL inhibitor imatinib is standard first-line therapy for patients with chronic myeloid leukemia (CML) and has revolutionized treatment of the disease. However, resistance and intolerance to the agent have emerged as major clinical complications. Dasatinib is the first and only dual BCR-ABL/SRC family kinase inhibitor approved by the U.S. Food and Drug Administration for the treatment of patients with CML in any phase or Philadelphia chromosome–positive acute lymphoblastic leukemia who are resistant to or intolerant of imatinib. The agent is well tolerated and has shown clinical activity in such patients. As with other oral tyrosine kinase inhibitors, nonadherence to the prescribed dasatinib treatment regimen could obstruct a successful outcome. A new recommended dose of 100 mg once daily has been approved for patients with chronic phase CML. That dosing regimen, combined with appropriate management of dasatinib-related adverse events, may help patients adhere to their prescribed treatment and achieve maximum therapeutic benefit. This article highlights recent changes to the dasatinib label, including results with the 100 mg once-daily starting dose for patients with chronic phase CML, and discusses nursing strategies for the successful management of adverse events in patients receiving dasatinib.

At a Glance
✦ Imatinib, a first-line treatment for chronic myeloid leukemia (CML), is associated with resistance and intolerance, necessitating second-line treatment options.
✦ A new 100 mg once-daily dose of dasatinib, the first available second-line CML treatment, has demonstrated similar efficacy and improved safety as other doses in patients with chronic phase CML.
✦ Dasatinib 70 mg twice daily remains the approved dosing regimen in patients with advanced CML or Philadelphia chromosome–positive acute lymphoblastic leukemia.

Despite significant improvements in the physical function, well-being, and quality of life of patients with CML treated with imatinib (Hahn et al., 2005), resistance and intolerance to this agent have emerged as substantial clinical issues (Ramirez & DiPersio, 2008). In the pivotal phase III Immediate Risk-Stratification

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Digital Object Identifier:10.1188/09.CJON.316-323
Improves Survival (IRIS) Study of patients with newly diagnosed CP CML, approximately 25% of patients were initially refractory to imatinib (primary resistance). Relapse and progression (acquired resistance) occurred in approximately 17% and 7% of patients after five years of treatment, respectively (Druker et al., 2006; Hughes & Branford, 2006; O’Brien et al., 2003). Resistance to imatinib is more common among patients with advanced-stage CML, and 51% of patients in blast crisis or AP who initially respond to imatinib therapy eventually relapse (Jabbour, Cortes, Giles, O’Brien, & Kantarjian, 2007; Lahaye et al., 2005; Soverini et al., 2006). Imatinib intolerance was observed in the IRIS trial: 4% of patients discontinued imatinib as a result of adverse events (AEs) after a median follow-up of 60 months (Druker et al., 2006).

Another concern with oral tyrosine kinase inhibitors as well as other oral cancer treatments is nonadherence to medication, particularly with long-term treatments for patients with chronic conditions, especially in the absence of overt disease (i.e., asymptomatic patients) (Partridge, Avorn, Wang, & Winer, 2002). Deviating from treatment guidelines can hamper or even prevent the achievement of therapeutic goals and may result in worsening of disease and death (Osterberg & Blaschke, 2005). Thus, the importance of adherence to treatment guidelines is clear.

Several factors can contribute to nonadherence, including numerous psychological variables (Osterberg & Blaschke, 2005), age (Partridge et al., 2002), and a patient's understanding of the risks and benefits of taking medication (Osterberg & Blaschke). The complexity of a treatment regimen also can affect adherence (Claxton, Cramer, & Pierce, 2001; Osterberg & Blaschke). Claxton et al. confirmed that adherence decreases with increased dosing frequency per day (see Figure 1). Additionally, the incidence and severity of AEs can have an impact on adherence (Druker et al., 2006; Hamdan et al., 2007). As mentioned previously, 4% of patients in the IRIS trial discontinued imatinib after five years of follow-up as a result of an AE (Druker et al., 2006). A retrospective analysis of patients with CML identified in the medical and pharmacy claims in the HealthCore Managed Care Database found that imatinib therapy was suspended in 62 (29%) patients, most often because of anemia (11%) or thrombocytopenia (11%). Treatment was discontinued permanently by 7% of patients (Hamdan et al.). Furthermore, the incidence and severity of imatinib-related AEs increase with higher doses (Druker et al., 2001). Although a study has not been performed to evaluate the association, a decreasing adherence rate also is noted (Sun, Fincher, Wang, Lee, & Buchner, 2007) (see Table 1).

The U.S. Food and Drug Administration’s 2006 approval of dasatinib (Sprycel®, Bristol-Myers Squibb), a BCR-ABL/SRC family kinase (SKF) inhibitor, has provided another option for patients with all phases of CML or those with Ph-positive acute lymphoblastic leukemia (Ph+ ALL) who are resistant to or intolerant of imatinib. However, nonadherence remains a potential barrier to successful treatment. This article discusses dosing strategies for the successful management of AEs in patients receiving dasatinib and highlights the 2007 changes to the dasatinib label, including results with the 100 mg once-daily starting dose for patients with CP CML, which may help with adherence.

Nilotinib (Tasigna®, Novartis Pharmaceuticals) is another tyrosine kinase inhibitor clinically available for patients with CP or AP CML who are resistant to imatinib (Kantarjian et al., 2006; le Coutre, 2008). Nilotinib is more potent than its parent compound, imatinib, but does not target SFKs like dasatinib. Nilotinib is taken orally, and the approved schedule calls for a twice-daily regimen with a fasting period of at least two hours before and one hour after each administration. Black-box warnings explain that QT prolongation and sudden death are associated with nilotinib, which should be considered prior to administration (Novartis Pharmaceuticals, 2008).

Dasatinib

Dasatinib has shown 325-fold greater activity in vitro against unmutated BCR-ABL compared with imatinib, representing an enhanced binding affinity that could be important in overcoming resistance in mutated forms of BCR-ABL that have been described (O’Hare et al., 2005). Dasatinib also is effective against all imatinib-resistant BCR-ABL mutations, which are the most common causes of imatinib resistance in patients with CML (Hochhaus, Erben, & Mueller, 2007; O’Hare et al.; Shah et al., 2004). The exception to this is the T315I “gatekeeper” mutation, which confers a structural modification to BCR-ABL such that all currently available tyrosine kinase inhibitors are no longer effective. Furthermore, the activity of dasatinib against SFKs may contribute to its clinical efficacy, as these kinases have been implicated in the development and progression of CML and Ph+ ALL (Hu et al., 2006; Lionberger, Wilson, & Smithgall, 2000; Meyn et al., 2006). Preclinical studies have shown that dual BCR-ABL/SRC inhibition with dasatinib significantly prolongs the survival of mice with CML compared with BCR-ABL inhibition alone with imatinib (Hu et al., 2006).
Dasatinib was approved based on its efficacy demonstrated in a series of multicenter, open-label, phase II clinical studies (the START program [SRC/ABL Tyrosine Kinase Inhibition Activity Research Trials of Dasatinib]) (Cortes et al., 2007; Guilhot, Apperley, Kim, Bullorsky, et al., 2007; Hochhaus, Kantarjian, et al., 2007; Ottmann et al., 2007). Across the START program, dasatinib was administered orally at a dose of 70 mg twice daily and showed marked efficacy in heavily pretreated patients. Longer-term results from the studies were reported at the 2007 annual meeting of the American Society of Hematology (Gambacorti et al., 2007; Guilhot, Apperley, Kim, Rosti, et al., 2007; Kantarjian, Rousselot, et al., 2007; Stone et al., 2007) (see Table 2). Hematologic response, achieved when leukocyte and thrombocyte counts return to normal, were durable in patients taking dasatinib. More importantly, cytogenetic response, which is a more robust sign of disease remission, was observed in patients harboring all imatinib-resistant BCR-ABL mutations except T315I. Importantly, dasatinib showed undiminished activity in patients with mutations in the P loop, a catalytically important region of the BCR-ABL kinase domain, which can become highly resistant to imatinib and is associated with a poor prognosis (Branford et al., 2003).

The new dasatinib prescribing information includes results from a randomized study (START-R trial) comparing dasatinib (70 mg twice daily) with high-dose imatinib (800 mg per day) for the treatment of patients with CP CML who were resistant to first-line imatinib (400–600 mg per day). At a median follow-up of 15 months, complete cytogenetic responses were achieved in 40% of patients (n = 101) treated with dasatinib compared with 16% of patients (n = 49) treated with high-dose imatinib (Kantarjian, Pasquini, et al., 2007; Shah et al., 2006). The median time-to-treatment-failure was not yet reached for dasatinib and was 3.5 months for high-dose imatinib (95% confidence interval 3.3–3.8) (Kantarjian, Pasquini, et al.). Overall risk-benefit assessment significantly favored dasatinib for patients with CP CML who are resistant to conventional doses of imatinib (Bristol-Myers Squibb Company, 2008; Kantarjian, Pasquini, et al.; Shah et al., 2006).

### Tolerability

Most AEs observed across clinical trials with dasatinib were mild to moderate (grade 1 or 2) and resolved spontaneously or with appropriate management (Shah et al., 2007). An article titled, “Practical Management of Dasatinib for Maximum Patient Benefit” on pages 329–335 describes AEs associated with dasatinib and their effective management. Although the AEs typically resolve with dose interruption or reduction, they can recur upon rechallenging with dasatinib. No evidence exists of cumulative toxicity with long-term therapy (Hochhaus, Kantarjian, et al., 2007), and dasatinib had a similar tolerability profile in patients who were resistant to or intolerant of imatinib (Cortes et al., 2007). The rate of dasatinib discontinuation because of drug-related AEs was 9% in CP, 0% in AP, 11% during myeloid blast crisis, and 2% during lymphoid blast crisis. This low rate of discontinuation indicates that dasatinib is not cross-intolerant with imatinib (Cortes et al.; Guilhot, Apperley, Kim, Bullorsky, et al., 2007; Hochhaus, Kantarjian, et al.).

### Table 1. Adherence Rates by Imatinib Dose Among Patients With Chronic Myeloid Leukemia

<table>
<thead>
<tr>
<th>DOSE (MG PER DAY)</th>
<th>ADHERENCE RATE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 400</td>
<td>66.9</td>
</tr>
<tr>
<td>400 to less than 600</td>
<td>65.7</td>
</tr>
<tr>
<td>600 to less than 800</td>
<td>52.1</td>
</tr>
<tr>
<td>800 or more</td>
<td>48.1</td>
</tr>
</tbody>
</table>

**Note.** Sample consisted of patients with chronic myeloid leukemia who filled imatinib prescriptions at a national retail pharmacy chain from August 1, 2006, to March 31, 2007. Adherence was measured with the medication possession ratio (total number of days of medication supplied / number of days from index date to the end of the study period). Sample size was not stated. **Note.** Based on information from Sun et al., 2007.

### Table 2. Efficacy of Dasatinib 70 mg Twice Daily in Phase II Clinical Studies

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>N</th>
<th>FOLLOW-UP (MONTHS)</th>
<th>CHR</th>
<th></th>
<th>MCyR</th>
<th></th>
<th>CCyR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic phase (START-C)</td>
<td>387</td>
<td>15.2</td>
<td>351</td>
<td>91%</td>
<td>230</td>
<td>59%</td>
<td>189</td>
<td>49%</td>
</tr>
<tr>
<td>Accelerated phase (START-A)</td>
<td>174</td>
<td>14.1</td>
<td>78</td>
<td>45%</td>
<td>67</td>
<td>39%</td>
<td>55</td>
<td>32%</td>
</tr>
<tr>
<td>Myeloid blast phase (START-B)</td>
<td>109</td>
<td>12 or more*</td>
<td>NR</td>
<td>NR</td>
<td>36</td>
<td>33%</td>
<td>28</td>
<td>26%</td>
</tr>
<tr>
<td>Lymphoid blast phase (START-B)</td>
<td>48</td>
<td>12 or more*</td>
<td>NR</td>
<td>NR</td>
<td>25</td>
<td>52%</td>
<td>22</td>
<td>46%</td>
</tr>
<tr>
<td>Ph+ ALL (START-L)</td>
<td>46</td>
<td>12 or more*</td>
<td>15</td>
<td>33%</td>
<td>26</td>
<td>57%</td>
<td>25</td>
<td>54%</td>
</tr>
</tbody>
</table>

* Minimum follow-up

CCyR—complete cytogenetic response; CHR—complete hematologic response; MCyR—major cytogenetic response; NR—not reported; Ph+ ALL—Philadelphia chromosome—positive acute lymphoblastic leukemia; START—SRC/ABL Tyrosine Kinase Inhibition Activity Research Trials of Dasatinib

**Note.** Based on information from Gambacorti et al., 2007; Guilhot, Apperley, Kim, Rosti, et al., 2007; Kantarjian, Rousselot, et al., 2007; Porkka et al., 2007; Soverini et al., 2006; Stone et al., 2007.
Table 3. Phase III Dose-Optimization Study of Dasatinib in Patients With Chronic Phase Chronic Myelogenous Leukemia (CA180-034)∗

<table>
<thead>
<tr>
<th>DOSE</th>
<th>RESPONSES (%)</th>
<th>INCIDENCE OF ADVERSE EVENTS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHR</td>
<td>MCyR</td>
</tr>
<tr>
<td>100 mg once daily (n = 165)</td>
<td>90</td>
<td>59</td>
</tr>
<tr>
<td>50 mg twice daily (n = 167)</td>
<td>92</td>
<td>54</td>
</tr>
<tr>
<td>140 mg once daily (n = 163)</td>
<td>86</td>
<td>56</td>
</tr>
<tr>
<td>70 mg twice daily (n = 167)</td>
<td>87</td>
<td>55</td>
</tr>
</tbody>
</table>

∗ Minimum follow-up was six months.
CCyR—complete cytogenetic response; CHR—complete hematologic response; MCyR—major cytogenetic response
Note. Based on information from Bristol-Myers Squibb Company, 2008.

New Dasatinib Dosage

Although dasatinib 70 mg twice daily was the chosen dose in the phase II study, results of a phase III dose-optimization study have led to the approval of a new dasatinib dose in patients with CP CML (Shah et al., 2007). In that study, 670 patients with CP CML who were resistant to or intolerant of imatinib were randomized to receive dasatinib 100 mg once daily, 50 mg twice daily, 140 mg once daily, or 70 mg twice daily. Similar hematologic and cytogenetic responses were observed across all four arms (see Table 3). A difference was found, however, in safety profiles: The 100 mg once-daily dose was associated with reduced incidence of grade 3 or 4 cytopenias and pleural effusions, suggesting that this dosing regimen is more tolerable than the 70 mg twice-daily schedule. Overall, the results of the study indicate that the 100 mg once-daily regimen offers a more favorable risk-benefit assessment compared with twice-daily dasatinib.

Based on the findings, 100 mg once-daily dasatinib (administered in the morning or evening) is now the recommended starting dose for patients with CP CML who are resistant to or intolerant of imatinib. The reduced frequency of serious AEs associated with the once-daily treatment regimen may improve patient adherence. Data show that fewer treatment interruptions, dose reductions, and discontinuations were associated with the 100 mg once-daily dose compared with the 70 mg twice-daily dose (Shah et al., 2007). One additional advantage of dasatinib with respect to adherence is the lack of a fasting requirement, which is necessary with nilotinib. Studies of adherence with antiviral and bisphosphonate agents have reported that patients had difficulty adhering to fasting requirements and that hunger from such requirements is a primary cause of nonadherence (da Silva et al., 2003; Gallant & Block, 1998; Papaioannou et al., 2007). The recommended dose for patients with advanced-phase CML (i.e., AP and BP CML) and Ph+ ALL remains 70 mg twice daily.

Management of Adverse Events

Although most AEs that occur with dasatinib are mild to moderate, pleural effusion, cytopenias, and cardiac abnormalities must be managed promptly to ensure that patients can remain on therapy and achieve maximum therapeutic benefit. Additionally, patients should be informed of the AEs that can arise during therapy and educated about the benefits of early reporting, in addition to adhering to their prescribed treatment regimens. (Partridge et al., 2002).

Across all clinical trials of dasatinib, the most commonly occurring nonhematologic grade 3 or 4 AEs were fluid retention (8%), hemorrhage (6%), pleural effusion (5%), dyspnea (4%), diarrhea (3%), and fatigue (2%) (Bristol-Myers Squibb Company, 2008). Those AEs generally occurred at comparable rates in all phases of CML; however, the incidences of grade 3 or 4 neutropenia (73.6% versus 46%), thrombocytopenia (75.4% versus 41%), and anemia (58% versus 18%) were higher in patients with advanced-phase CML or Ph+ ALL.

During dasatinib treatment, patients should be monitored closely for signs and symptoms of cytopenias and pleural effusions. Recommended monitoring and management techniques for patients with these and other dasatinib-related AEs are listed in Table 4 (Bristol-Myers Squibb Company, 2008; National Comprehensive Cancer Network, 2008). Cytopenias can be related to the disease (particularly in the advanced phase) and may be an indication of therapeutic benefit. In such cases, treatment with dasatinib should not be interrupted and dose escalation may be warranted (National Comprehensive Cancer Network, 2008). (Also see “Practical Management of Dasatinib for Maximum Patient Benefit” on pages 329–335.)

Drug Interactions

Because dasatinib is a CYP3A4 substrate, use of CYP3A4 inhibitors (e.g., ketoconazole) during dasatinib treatment should be avoided, as it may increase exposure to dasatinib (see pages 329–335). If co-administration is unavoidable, toxicity should be monitored closely and dose reduction of 20–40 mg daily should be considered (Bristol-Myers Squibb Company, 2008). Furthermore, CYP3A4 inducers (e.g., rifampin) may decrease dasatinib plasma concentrations. In clinical trials, co-administration of dasatinib with rifampin resulted in a five-fold decrease in dasatinib plasma concentrations. In patients who require CYP3A4
Table 4. Monitoring and Management of Hematologic and Nonhematologic Adverse Events

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>MONITORING RECOMMENDATION</th>
<th>PHASE OF DISEASE</th>
<th>MANAGEMENT TECHNIQUES</th>
</tr>
</thead>
</table>
| Cytopenias (neutropenia, thrombocytopenia) | Because cytopenias usually occur within the first one or two months of treatment, particular care should be taken during that time. Also, because cytopenias tend to occur more frequently in patients with advanced disease (probably because of a high incidence of pancytopenia prior to starting therapy), care should be taken in such cases as well. Complete blood counts should be performed weekly for the first two months and monthly thereafter or as clinically indicated. | Chronic phase | • Stop dasatinib until absolute neutrophil count (ANC) is 1.0 x 10^9/L or higher and platelets are 50 x 10^9/L or higher.  
• Resume treatment with dasatinib at the original starting dose if recovery occurs in seven days or less.  
• If platelets are lower than 25 x 10^9/L or recurrence of ANC is lower than 0.5 x 10^9/L for more than seven days, repeat step 1 and resume dasatinib at a reduced dose of 80 mg once daily (second episode) or discontinue (third episode). |
| | | Advanced disease | • Check if cytopenia is related to leukemia.  
• If unrelated to leukemia, stop dasatinib until ANC is 1.0 x 10^9/L or higher and platelets are 20 x 10^9/L or higher, and resume at the original starting dose.  
• If cytopenia recurs, repeat step 1 and resume dasatinib at a reduced dose of 50 mg twice daily (second episode) or 40 mg twice daily (third episode).  
• If cytopenia is related to leukemia, consider a dose escalation to 100 mg twice daily. |
| Congestive heart failure or cardiac dysfunction | Exercise caution when treating patients who have or may develop QTc prolongation. Monitor for any changes in QTc. | Any | Hypokalemia or hypomagnesemia should be corrected prior to dasatinib administration. Temporarily interrupt dasatinib administration and monitor the patient carefully until symptoms resolve. |
| Diarrhea | Question patients during therapy. | Grade 3 | For mild to moderate adverse events, use anti-diarrheal medications. In case of nausea, patients can benefit from eating after initial fasting periods. |
| | | Grade 4 | In the case of severe gastrointestinal adverse events that are not responsive to therapy, dose should be withheld. Following resolution of the event, a dose reduction may be prudent (not less than 300 mg). |
| Gastrointestinal bleeding | Perform regular blood count testing (weekly for the first two months of treatment). Patients should be informed of the importance of notifying their physicians of any bleeding or bruising. Patients requiring anticoagulants are at increased risk, and extra care should be taken to monitor them. | Any | Dasatinib dose modifications may be performed when patients experience thrombocytopenia (previously described). In case of severe gastrointestinal hemorrhages, treatment must be interrupted, and transfusion may be appropriate. |
| Gastrointestinal upset | Symptoms may include nausea, belching, heartburn, cramping, and abdominal distention. | Any | • Antiemetics for nausea and vomiting  
• Intensive fluid management  
• Dasatinib should be taken with a meal or a large glass of water. |
| Headache | Symptoms may include head pain, blurred vision, nausea, vomiting, impaired hearing, irritability, and malaise. | Any | Pain relief (e.g., nonsteroidal anti-inflammatory drugs, acetaminophen) |
| Pleural effusion | Symptoms suggestive of pleural effusion, such as dyspnea or dry cough, should be evaluated by chest x-ray. Severe pleural effusion may require thoracentesis and oxygen therapy. | Grade 3 | Standard management approach is to use diuretics or dose interruption. If patient has significant symptoms, a short course of steroids can be administered; when resolved, reduce one dose level. |
| | | Grade 4 | Hold dasatinib until grade 1 or better, then consider resuming at decreased dose level. |
| Rash | Symptoms may include itching, swelling, and change in color. | Any | • Apply topical or systemic steroids.  
• Dasatinib dose should be reduced, interrupted, or discontinued. |

Note: Based on information from National Comprehensive Cancer Network, 2008.
inducers, alternate agents with lower enzyme induction potential should be used, if possible; however, if the use of a CYP3A4 inducer is necessary, dasatinib dose escalation in 20 mg increments is recommended (Bristol-Myers Squibb Company).

The solubility of dasatinib is pH-dependent, according to preclinical data, suggesting that concomitant administration of dasatinib and antacids could decrease the absorption of dasatinib (Bristol-Myers Squibb Company, 2008). Therefore, antacids should be taken at least two hours before or after dasatinib administration (Bristol-Myers Squibb Company). The use of proton pump inhibitors should be avoided entirely as it is likely to reduce exposure to dasatinib. Antacids should be used in place of proton pump inhibitors (Bristol-Myers Squibb Company).

Additionally, dasatinib may affect the plasma concentration of certain drugs. Caution should be used when administering CYP3A4 substrates that have a narrow therapeutic index during concomitant dasatinib treatment (Bristol-Myers Squibb Company, 2008). The article on pages 329–335 offers a listing of drugs whose plasma concentrations may be altered by dasatinib.

Special Populations

Dasatinib is not recommended for use by women who are pregnant or who are contemplating pregnancy; women should not breast-feed while taking dasatinib (Bristol-Myers Squibb Company, 2008). Although no differences have been observed in the safety and efficacy of dasatinib in clinical studies between patients who were older than 65 years and those who were younger, some older patients may have greater sensitivity to dasatinib (Bristol-Myers Squibb). Additionally, the safety and efficacy of dasatinib have not been established in patients younger than 18 years (Bristol-Myers Squibb Company).

Conclusion

Imatinib resistance and intolerance have emerged as significant clinical issues in the treatment of CML and Ph+ ALL. Dasatinib is highly effective in patients with CML who are resistant to or intolerant of imatinib, and it offers a positive prospect for such patients. The new 100 mg once-daily dosing regimen for patients with CP CML may benefit treatment adherence through simpler dosing and improved tolerability. Additionally, appropriate management of AEs associated with treatment may help patients adhere to their prescribed treatment regimens, thus ensuring that patients achieve maximum therapeutic benefit.

The author takes full responsibility for the content of this article but thanks Jonathan C. Maher and Josh Collis of Gardiner-Caldwell U.S., supported by Bristol-Myers Squibb Company, for medical writing support. The author served on Millennium Pharmaceuticals, Inc., and Celgene Corporation speakers bureaus. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the author, planners, independent peer reviewers, or editorial staff.

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