Single-Agent Ibrutinib for Rituximab-Refractory Waldenström Macroglobulinemia: Final Analysis of the Substudy of the Phase III Innovate™ Trial

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ABSTRACT

Purpose: The first report from the open-label substudy of the phase III iNNOVATE study (PCYC-1127; NCT02165397) demonstrated that single-agent ibrutinib was efficacious and well tolerated in patients with heavily pretreated, rituximab-refractory Waldenström macroglobulinemia. Results from the final analysis are now reported.

Patients and Methods: Ibrutinib 420 mg was administered once daily to patients ($N = 31$) who failed to achieve at least a minor response (MR) or who relapsed <12 months after their last rituximab-containing therapy. Endpoints included progression-free survival (PFS) and overall response rate (ORR; MR or better) per independent review committee, hemoglobin improvement, overall survival (OS), and safety; serum IgM was also assessed.

Results: After a median follow-up of 58 months (range: 9–61), median PFS was 39 months [95% confidence interval (CI): 25–not

evaluable]; 60-month PFS rate was 40%. In MYD88^{L265P}/CXCR4^{WT} and MYD88^{L265P}/CXCR4^{WT} subtypes, median PFS was 18 months and not reached, respectively. In all patients, ORR was 87%; responses deepened over time with major response ($\geq$ partial response) rates increasing from 61% at 6 months to 77% at 60 months. Median OS was not reached. Seventeen of 21 patients (81%) with baseline hemoglobin ≤ 11.0 g/dL had sustained hemoglobin improvement. Improvements in serum IgM levels were sustained, reaching a maximum median change of -37 g/L at 54 months. Ibrutinib maintained a manageable safety profile, with no new safety signals identified. There were no events of major hemorrhage or atrial fibrillation.

Conclusions: In the final analysis from iNNOVATE, single-agent ibrutinib continued to show sustained efficacy in patients with heavily pretreated, rituximab-refractory Waldenström macroglobulinemia.

Introduction

Waldenström macroglobulinemia is a rare lymphoproliferative disorder classified as an indolent non-Hodgkin B-cell lymphoma (1). For patients with Waldenström macroglobulinemia, current treatments include alkylating agents, anti-CD20 mAbs, proteasome inhibitors, nucleoside analogues in combination with rituximab, as well as ibrutinib (2). While rituximab-based regimens are most commonly used for the treatment of symptomatic Waldenström macroglobulinemia, most patients will eventually develop resistance to rituximab (3). For patients with rituximab-refractory Waldenström macroglobulinemia, effective treatment options are limited (2). Experience with ibrutinib in this patient population remains limited.

Ibrutinib is the only once-daily Bruton's tyrosine kinase (BTK) inhibitor approved as either a single agent or in combination with rituximab for patients with Waldenström macroglobulinemia across all lines of therapy and is the only BTK inhibitor approved for the treatment of Waldenström macroglobulinemia (4). Ibrutinib was originally identified as a potential treatment for Waldenström macroglobulinemia based on the high prevalence of MYD88 mutations in patients with Waldenström macroglobulinemia (5). More than 90% of patients carry the MYD88^{L265P} point mutation, and nearly one third of these patients also have a frameshift or nonsense mutation in CXCR4 (6). Mutations in MYD88 and CXCR4 are associated with important differences in disease presentation, including serum IgM levels and symptoms at diagnosis (5). Mutations in both CXCR4 and MYD88 are associated with constitutive activation of the BTK pathway (7), making BTK inhibitors an attractive therapeutic option (5). Results from a pivotal phase II study demonstrated high response rates

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

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Translational Relevance

Rituximab resistance is commonly observed in patients with Waldenström macroglobulinemia due to its widespread and repeated use as either monotherapy or in a combination regimen. Results from the first report of the phase III iNNOVATE substudy showed that single-agent ibrutinib was effective and well tolerated in patients with previously treated, rituximab-refractory Waldenström macroglobulinemia. Here we present results from the final analysis after up to 5 years of follow-up (median: 58 months; range: 9–61). Patients were heavily pretreated, receiving a median of 4 prior lines of therapy. Continuous treatment with single-agent ibrutinib led to sustained response, durable progression-free survival and overall survival, and an acceptable safety profile. Importantly, sustained improvements in hemoglobin and serum IgM and clinically meaningful improvements in patient-reported outcomes were also demonstrated. Our findings support single-agent ibrutinib as an effective chemotherapy-free treatment option for patients with rituximab-refractory Waldenström macroglobulinemia, a population with limited treatment options.

with single-agent ibrutinib in patients with relapsed Waldenström macroglobulinemia (8).

In the phase III randomized iNNOVATE study (PCYC-1127; NCT02165397), ibrutinib demonstrated superior progression-free survival (PFS) in combination with rituximab versus single-agent rituximab in patients with Waldenström macroglobulinemia (9). In the open-label substudy of iNNOVATE for patients with heavily pretreated, rituximab-refractory Waldenström macroglobulinemia, single-agent ibrutinib demonstrated sustained efficacy and was well tolerated (10, 11). With a median follow-up of 18 months, the estimated 18-month PFS rate per investigator assessment was 86%, and the overall survival (OS) rate was 97% (10). Median PFS was still not reached after a median of 39 months of follow-up in a subsequent analysis (11).

Here we present results from the final analysis of the iNNOVATE substudy of single-agent ibrutinib in patients with rituximab-refractory Waldenström macroglobulinemia, representing up to 5 years of follow-up, an additional 40 months since the first report.

Patients and Methods

Study design

The iNNOVATE substudy was an international, multicenter, single-arm, open-label trial designed to assess the efficacy and safety of single-agent ibrutinib in patients with rituximab-refractory Waldenström macroglobulinemia. Study design details have been previously published (10). In brief, eligible patients had centrally-confirmed Waldenström macroglobulinemia defined per criteria from the Second International Workshop on Waldenström macroglobulinemia (IWWM) and had failed to achieve at least a minor response to their last rituximab-containing therapy or relapsed less than 12 months after their last rituximab-containing therapy. Patients received once-daily ibrutinib 420 mg until unacceptable toxicity or progressive disease (PD). iNNOVATE was approved by institutional review boards or independent ethics committees at each institution and was conducted according to the principles of the Declaration of Helsinki and the

Good Clinical Practice guidelines from the International Conference on Harmonization. All patients provided written informed consent prior to enrollment.

Endpoints and assessments

The primary endpoint was PFS per independent review committee (IRC). Other endpoints included response per IRC, hematologic improvement as measured by change in hemoglobin, OS, safety, and patient-reported outcomes (10). Change in serum IgM was also assessed.

Efficacy, safety, and response assessments were conducted as described previously (10). Briefly, responses were assessed according to the modified consensus criteria from the sixth IWWM. The proportion of patients with an overall response was defined as the proportion of patients who achieved a minor response (MR; $\geq 25\%$ but $< 50\%$ reduction of serum IgM from baseline) or better. Major response was defined as a partial response (PR; $\geq 50\%$ reduction of serum IgM concentrations from baseline) or better.

Adverse events (AE), regardless of attribution, were collected by investigators throughout the study and graded per National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

Genotype analysis

Bone marrow aspirates were collected to assess *MYD88* and *CXCR4* mutational status using the Personalis ACE Extended Cancer Panel with $> 500\times$ mean coverage depth. Calls of somatic variants for *MYD88* and *CXCR4* used the Personalis Cancer Panel DNA pipeline operating in the tumor-only mode with no matched normal samples.

Patient-reported outcomes

Patient-reported outcomes and disease-related symptoms were measured according to the Functional Assessment of Cancer Therapy-Anemia (FACT-An) and the EuroQoL 5-Dimension Questionnaire (EQ-5D-5L[®]; copyright of EuroQol Research Foundation; EQ-5D is a trademark of the EuroQol Research Foundation), as previously described (10). A clinically meaningful improvement in FACT-An was defined as an increase of ≥ 7 points in the total score or ≥ 6 points in the anemia-subscale score. A clinically meaningful improvement in EQ-5D-5L was defined as an increase of ≥ 7 points in the visual analog scale (VAS) or ≥ 0.08 points in the utility score.

Statistical analysis

The open-label substudy provided a descriptive analysis of the efficacy, safety, and patient-reported outcomes of single-agent ibrutinib for the treatment of patients with rituximab-refractory Waldenström macroglobulinemia and was not designed to provide statistical comparisons. Analyses included all patients who received at least one dose of ibrutinib.

Kaplan–Meier estimates of PFS, OS, time to next treatment, and duration of response (DOR) were calculated. For overall response rate (ORR; MR or better) and major response rate (PR or better), 95% confidence intervals (CI) were provided. Sustained hematologic improvement was defined as improvement in hemoglobin of ≥ 2.0 g/dL (intent-to-treat population) or an increase to > 11.0 g/dL with improvement of ≥ 0.5 g/dL (patients with baseline hemoglobin ≤ 11.0 g/dL) for ≥ 56 days. DOR was defined as the duration from the date of initial documentation of response to the date of first documented evidence of PD or death for responders.

Results

Patient demographics and characteristics

Thirty-one patients were enrolled; their detailed baseline characteristics were previously reported (10). Patients had received a median 4 prior lines of systemic therapy (range: 1–7), and more than one third of patients (39%) had at least 5 prior treatments (Table 1). Median baseline hemoglobin was 10.3 g/dL (range: 6.4–14.6), and 68% of patients had hemoglobin $\leq$ 11.0 g/dL. Mutational data were available

Table 1. Patient demographics and baseline characteristics.

Characteristics	Patients, N = 31
Median age, years (range)	67 (47–90)
IPSSWM, n (%)	
Low	7 (23)
Intermediate	11 (35)
High	13 (42)
Median Hgb, g/dL (range)	10.3 (6.4–14.6)
Baseline Hgb $\leq$ 11.0 g/dL, n (%)	21 (68)
Median serum IgM, g/L (range)	39 (9–107)
Median bone marrow involvement, %	
Cellularity	75
Intertrabecular space	53
Median prior therapies, n (range)	4 (1–7)
Number of prior systemic therapies, n (%)	
1–2	9 (29)
3–4	10 (32)
$\geq$ 5	12 (39)
Prior autologous stem-cell transplant, n (%)	2 (6)
Types of prior therapy, n (%)	
Rituximab	31 (100)
Alkylating agent	28 (90)
Corticosteroids	27 (87)
Purine analog	16 (52)
Vinca alkaloids	15 (48)
Proteasome inhibitor	14 (45)
Anthracyclines	12 (39)
Immunomodulating agent	3 (10)
Nucleoside analogue (cytarabine)	2 (6)
Other	8 (26)
Genotype, n (%)	
MYD88 ^{L265P} /CXCR4 ^{WT}	17 (68)
MYD88 ^{L265P} /CXCR4 ^{WHIM}	7 (28)
MYD88 ^{WT} /CXCR4 ^{WT}	1 (4)
Unknown	6 ^a
Most common concomitant medications, n (%)	
Antibacterials	26 (84)
Analgesics	17 (55)
Antivirals	16 (52)
Anti-inflammatory and antirheumatic agents	14 (45)
Medications for acid-related disorders	13 (42)
Antithrombotic agents	12 (39)
Anti-anemic preparations	12 (39)
Vitamins	11 (36)
Ophthalmologicals	10 (32)
Most common reasons for treatment initiation, n (%)	
Fatigue	22 (71)
Constitutional symptoms	13 (42)
Hgb $\leq$ 10 g/dL	13 (42)
Lymphadenopathy	7 (23)

Abbreviations: Hgb, hemoglobin; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinemia.

^aGenotype data available for 25 patients; percentages were calculated using 25 as the denominator.

for 25 of 31 patients (81%); 6 were missing due to lack of tumor sample or low tumor yield. Of those with available mutational data, 17 patients (68%) had the MYD88^{L265P}/CXCR4^{WT} genotype, 7 (28%) had the MYD88^{L265P}/CXCR4^{WHIM} genotype, and 1 (3%) had the MYD88^{WT}/CXCR4^{WT} genotype.

Patient disposition

The final analysis was performed at the time of study closure, and the median follow-up was 58 months (range: 9–61). Treatment discontinuations during the study were due to PD ($n = 13$; 42%), AEs ($n = 2$; 6%), and withdrawal by patient ($n = 2$; 6%). Median duration of treatment was 41 months (range: 0.3–61). At study closure, 14 patients (45%) were still receiving ibrutinib: 8 patients opted to enroll in a treatment extension study and 6 continued to receive commercial ibrutinib. Twelve patients (39%) in total received subsequent treatment; subsequent treatments included alkylating agent ($n = 7$), anti-CD20 antibody therapy ($n = 6$), corticosteroids ($n = 6$), proteasome inhibitor ($n = 3$), vinca alkaloids ($n = 2$), anthracyclines ($n = 1$), immunomodulator ($n = 1$), nucleoside analog ($n = 1$), and other ($n = 4$; including 2 patients who received ibrutinib). Median time to next treatment was not reached [95% CI: 42–NE (not evaluable)].

PFS

At the time of the final analysis, median PFS was 39 months (95% CI: 25–NE); 18 patients had PD or died, and the estimated 60-month PFS rate was 40% (Fig. 1). Median PFS was not reached (95% CI: 27–NE) in patients with the MYD88^{L265P}/CXCR4^{WT} genotype ($n = 17$) and was 18 months (95% CI: 3–28) in patients with the MYD88^{L265P}/CXCR4^{WHIM} genotype ($n = 7$). The single patient with the MYD88^{WT}/CXCR4^{WT} genotype progressed at 6 months.

Response

At the final analysis, the ORR per IRC was 87%; 29% of patients ($n = 9$) achieved a best response of very good partial response (VGPR), 48% ($n = 15$) achieved a best response of PR, and 10% ($n = 3$) had a best response of MR. Three patients (10%) had stable disease, and 1 patient was not evaluable due to a lack of follow-up assessments after week 1. Over time, a deepening of response was observed with major response rates increasing from 61% at 6 months to 71% at 18 months and 77% at 60 months (Fig. 2A). The median time to overall response (MR or better) was 1 month (range: 1–20), and the median time to major response (PR or better) was 2 months (range: 1–52). In patients who achieved a response, the median DOR per IRC was 33 months (range: 2–60+).

ORRs were similar between the MYD88^{L265P}/CXCR4^{WT} (88%) and MYD88^{L265P}/CXCR4^{WHIM} (86%) genetic subtypes (Fig. 2B). However, a larger proportion of patients with the MYD88^{L265P}/CXCR4^{WT} genotype achieved a VGPR (41% vs. 14%). The 1 patient with MYD88^{WT}/CXCR4^{WT} genotype had a best response of stable disease. Median time to MR or better was 1 month (range: 1–4) in patients with the MYD88^{L265P}/CXCR4^{WT} genotype and 1 month (range: 1–2) in those with the MYD88^{L265P}/CXCR4^{WHIM} genotype. Median time to major response (PR or better) was 1 month (range: 1–50) and 4 months (range: 1–7) in patients with MYD88^{L265P}/CXCR4^{WT} and MYD88^{L265P}/CXCR4^{WHIM} genotypes, respectively.

Hemoglobin and IgM levels

At baseline, median hemoglobin was 10.3 g/dL (range: 6.4–14.6). Improvements in hemoglobin were generally rapid (median +1.7 g/dL increase from baseline to week 9) and reached a maximum median

Figure 1.

PFS as assessed by IRC in all patients and by genetic subtype. The single patient with MYD88^{WT}/CXCR4^{WT} genotype is not shown; this patient progressed at 5.6 months.

change of +3.5 g/dL at 35 months (Fig. 3). In patients who had baseline hemoglobin levels ≤ 11.0 g/dL, the maximum median increase from baseline was +4.3 g/dL (range: 1.2–8.9) at month 50. In total, 22 of 31 patients (71%) exhibited sustained hemoglobin improvement, including 17 of 21 patients (81%) who had baseline hemoglobin levels ≤ 11.0 g/dL.

Likewise, improvements in IgM were generally rapid and sustained. Median serum IgM was 39 g/L (range: 9–107) at baseline. The median change reached –20 g/L at week 9, and reached the maximum –37 g/L at 54 months (Fig. 3).

OS

Median OS was not reached (95% CI: NE–NE), and the 60-month OS rate was 73% (Fig. 4). Median OS was not reached for all subgroups evaluated by number of prior lines of therapy (Fig. 4). When analyzed by genotype, median OS was not reached (95% CI: NE–NE) in patients with the MYD88^{L265P}/CXCR4^{WT} genotype ($n = 17$) and was 50 months (95% CI: 11–NE) in patients with the MYD88^{L265P}/CXCR4^{WHIM} genotype ($n = 7$). The single patient with the MYD88^{WT}/CXCR4^{WT} genotype died at 9 months.

Safety

Patients had received single-agent ibrutinib for a median of 41 months (range: 0.3–61). Overall, 30 patients (97%) experienced a treatment-emergent AE (TEAE), and 25 patients (81%) had a grade ≥ 3 TEAE. The prevalence of TEAEs of clinical interest of any grade (occurring in >2 patients) during the last 2 years of treatment were infections (years 3–4: 47%, 8/17; years 4–5: 50%, 7/14), hypertension (years 3–4: 29%, 5/17; years 4–5: 36%, 5/14), and diarrhea (years 3–4: 24%, 4/17; years 4–5: 7%, 1/14). The prevalence of grade ≥ 3 AEs of clinical interest generally declined over time with ibrutinib treatment (Fig. 5). Notably, no patients experienced major hemorrhage or atrial fibrillation. Of 3 patients with grade ≥ 3 hypertension during the study, all had hypertension at baseline. Grade ≥ 3 neutropenia and grade ≥ 3 thrombocytopenia primarily occurred during the first year of treatment, with 1 patient each experiencing these AEs in subsequent years. Five patients experienced a total of 7 AEs requiring dose reduction (diarrhea, $n = 2$; arthralgia, $n = 1$; maculopapular rash, $n = 1$; nausea, $n = 1$; constipation, $n = 1$; and fecalith, $n = 1$); all 7 AEs resolved following dose reduction, and 1 patient was able to

resume treatment at the full ibrutinib dose. Two patients experienced a TEAE leading to discontinuation of ibrutinib (grade 2 diarrhea and grade 3 constipation; $n = 1$ each). No deaths occurred due to TEAEs.

Patient-reported outcomes

Patients reported clinically meaningful improvements in quality-of-life measures. FACT-An score, anemia-subscale score, and EQ-5D-5L VAS improved from baseline. At the time of final analysis, most patients had a clinically meaningful improvement in total FACT-An score (77%; $n = 24$) and anemia-subscale score (84%; $n = 26$; Supplementary Fig. S1). Clinically meaningful improvements in EQ-5D-5L VAS and utility score were also reported by 71% of patients ($n = 22$) each.

Discussion

In this final analysis of the open-label substudy of the phase III iNNOVATE trial, once-daily, single-agent ibrutinib demonstrated sustained efficacy in patients with heavily pretreated, rituximab-refractory Waldenström macroglobulinemia. With a median follow-up of 58 months, representing approximately 40 months of additional follow-up since the initial analysis, single-agent ibrutinib continued to demonstrate durable clinical benefit. Response deepened over time, driven by an increase in VGPR from 16% at month 6 to 23% at month 18 and 29% at month 60. Additionally, responses were durable with a median DOR of 33 months. After a median 58 months of follow-up and regardless of the number of prior therapies, median OS was not reached. Median hemoglobin increased and serum IgM levels decreased rapidly and were sustained with treatment. Correspondingly, clinically meaningful improvements in patient-reported outcomes were reported by most patients and were sustained over time.

The long-term results of our study suggest that single-agent ibrutinib offers durable clinical benefit for patients with rituximab-refractory Waldenström macroglobulinemia, a population with few effective treatment options. Other recent trials in previously treated patients with Waldenström macroglobulinemia have reported similar results to those reported here. In a phase II study by Treon and colleagues of 63 patients with relapsed Waldenström macroglobulinemia treated with single-agent ibrutinib, the median 5-year PFS rate

Figure 2.

ORR. **A**, Cumulative best response over time in all patients. ORRs are shown at the top of each bar, and major response rates are shown next to brackets for each bar. **B**, Best overall response per IRC in all patients and by genetic subtype. The single patient with $MYD88^{WT}/CXCR4^{WT}$ genotype is not shown; this patient had a best response of stable disease. MR, minor response; ORR, overall response rate; PR, partial response; VGPR, very good partial response.

was not reached and the 5-year OS rate was 87% (12). Overall and major response rates were 90.5% and 79.4%, respectively, after a median follow-up of 59 months (12); this is highly concordant with the 87% overall and 77% major response rates reported here after a median follow-up of 60 months. Consistent with previous observations that patients with $MYD88$ wild-type Waldenström macroglobulinemia have shorter survival and a lower probability of response than those with a $MYD88$ mutation (13) and that mutations in $CXCR4$ are associated with a lower likelihood of achieving a major response compared with patients with $CXCR4$ wild-type disease (6), results from Treon and colleagues showed that efficacy responses were genotype dependent. In patients with $MYD88$ wild-type Waldenström macroglobulinemia, the median PFS was 0.4 years, whereas those with $MYD88^{Mut}/CXCR4^{WT}$ and $MYD88^{Mut}/CXCR4^{Mut}$ genotypes had a median PFS of not reached and 4.5 years, respectively (12).

In addition to studies with ibrutinib, another BTK inhibitor, zanubrutinib, has been evaluated as a treatment for Waldenström macroglobulinemia. In the phase III ASPEN study investigating ibrutinib versus zanubrutinib in both previously untreated and previously treated patients with $MYD88^{L265P}$ Waldenström macroglobulinemia, the primary endpoint of superiority of zanubrutinib was not met; 84% of patients treated with ibrutinib and 85% treated with zanubrutinib were progression-free at 18 months, and major response rates were 78% (ibrutinib) and 77% (zanubrutinib; ref. 14). In the ASPEN single-arm cohort conducted in patients with the $MYD88$ wild-type genotype, estimated 18-month PFS and OS rates were 68% and 88%, respectively, after treatment with zanubrutinib (median PFS and OS were not reached with a median follow-up of 17.9 months; ref. 15). Interestingly, in an earlier report (median 19 months on treatment) of the above study by Treon and colleagues, the ORR in

Ibrutinib was well tolerated, and no new safety signals emerged over more than 5 years of follow-up. Consistent with observations from other studies, AEs were generally most common during the first year of ibrutinib treatment and decreased over time (17–20). No major hemorrhage or atrial fibrillation events occurred during the entire study. Most AEs were low grade, and few patients ($n = 2$) discontinued treatment due to an AE. Notably, grade ≥ 3 neutropenia and thrombocytopenia were observed in a small number of patients, primarily during the first year of treatment. This contrasts with a previous report that neutropenia and thrombocytopenia were more common in heavily pretreated patients (12). All AEs that led to an ibrutinib dose reduction resolved following dose

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Figure 5.

Prevalence of grade ≥ 3 AEs of clinical interest by yearly interval. ^aCombined terms.

reduction, suggesting that many AEs can be managed effectively with dose modification.

In conclusion, single-agent ibrutinib remains an effective treatment for patients with heavily pretreated, rituximab-refractory Waldenström macroglobulinemia. This regimen provides sustained efficacy, is well tolerated, and provides clinically meaningful improvements in quality of life in a population of patients who have few effective treatment options.

Data sharing statement

Requests for access to individual participant data from clinical studies conducted by Pharmacyclics LLC, an AbbVie Company, can be submitted through Yale Open Data Access (YODA) Project site at <http://yoda.yale.edu>.

Authors' Disclosures

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Authors' Contributions

J. Trotman: Conceptualization, data curation, investigation, writing—original draft, writing—review and editing. **C. Buske:** Data curation, investigation, writing—review and editing. **A. Tedeschi:** Data curation, investigation, writing—review and editing. **J.V. Matous:** Data curation, investigation, writing—review and editing. **D. MacDonald:** Data curation, investigation, writing—review and editing. **C.S. Tam:** Data curation, investigation, writing—review and editing. **O. Tournilhac:** Data curation, investigation, writing—review and editing. **S. Ma:** Data curation, investigation, writing—review and editing. **S.P. Treon:** Data curation, investigation, writing—review and editing. **A. Oriol:** Data curation, investigation, writing—review and editing. **J. Ping:** Data curation, formal analysis, validation, writing—review and editing. **E.M. Briso:** Data curation, writing—review and editing. **I. Arango-Hisijara:** Writing—review and editing. **M.A. Dimopoulos:** Data curation, investigation, writing—review and editing.

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