BRIEF REPORT

Brivaracetam as Early Add-On Treatment in Patients with Focal Seizures: A Retrospective, Multicenter, Real-World Study

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ABSTRACT

Introduction: In randomized controlled trials, add-on brivaracetam (BRV) reduced seizure frequency in patients with drug-resistant focal epilepsy. Most real-world research on BRV has focused on refractory epilepsy. The aim of this analysis was to assess the 12-month effectiveness and tolerability of adjunctive BRV when used as early or late adjunctive treatment in patients included in the BRIVAracetam add-on First Italian netwoRk Study (BRIVAFIRST).

Methods: BRIVAFIRST was a 12-month retrospective, multicenter study including adult patients prescribed adjunctive BRV. Effective-
ness outcomes included the rates of sustained seizure response, sustained seizure freedom, and treatment discontinuation. Safety and tolerability outcomes included the rate of treatment discontinuation due to adverse events (AEs) and the incidence of AEs. Data were compared for patients treated with add-on BRV after 1–2 (early add-on) and ≥ 3 (late add-on) prior antiseizure medications.

**Results:** A total of 1029 patients with focal epilepsy were included in the study, of whom 176 (17.1%) received BRV as early add-on treatment. The median daily dose of BRV at 12 months was 125 (100–200) mg in the early add-on group and 200 (100–200) mg in the late add-on group (\( p < 0.001 \)). Sustained seizure response was reached by 97/161 (60.3%) of patients in the early add-on group and 286/833 (34.3%) of patients in the late add-on group (\( p < 0.001 \)). Sustained seizure freedom was achieved by 51/161 (31.7%) of patients in the early add-on group and 91/833 (10.9%) of patients in the late add-on group (\( p < 0.001 \)). During the 1-year study period, 29 (16.5%) patients in the early add-on group and 241 (28.3%) in the late add-on group discontinued BRV (\( p = 0.001 \)). Adverse events were reported by 38.7% and 28.5% (\( p = 0.017 \)) of patients who received BRV as early and late add-on treatment, respectively.

**Conclusion:** Brivaracetam was effective and well tolerated both as first add-on and late adjunctive treatment in patients with focal epilepsy.

**Keywords:** Antiseizure medication; Brivaracetam; Focal seizures; Epilepsy

### Key Summary Points

Brivaracetam (BRV) improved seizure frequency both as first add-on and late adjunctive treatment in patients with focal epilepsy.

- The median daily dose at 12 months was 125 mg and 200 mg in the early and late add-on groups.
- Sustained seizure frequency reduction was greater and retention rate was higher for BRV as an early add-on treatment.
- Adjunctive BRV was generally well tolerated in clinical practice and most adverse events were mild.
- The most common adverse events included somnolence, nervousness and/or agitation, vertigo, and fatigue.

### INTRODUCTION

Brivaracetam (BRV) is a rationally developed compound characterized by high-affinity binding to synaptic vesicle protein 2A (SV2A) and chemical structure similar to levetiracetam (LEV) [1]. In Europe, BRV is authorized for the adjunctive treatment of focal-onset seizures, including focal to bilateral tonic–clonic seizures, in patients over 2 years of age [2].

In randomized, placebo-controlled trials, BRV reduced seizure frequency when added to pre-existing antiseizure medications (ASMs) in patients with drug-resistant focal epilepsy [3].
Most real-world research on BRV has focused on refractory epilepsy and only a few studies have provided preliminary insights about BRV use in special populations [4–6] and in the early stages of treatment [7]. There is, hence, little information about the effectiveness of BRV when it is administered as a first or second add-on therapy.

The BRIVAracetam add-on First Italian netwoRk Study (BRIVAFIRST) investigated the use of adjunctive BRV in a large population of patients with focal epilepsy treated according to daily clinical practice over a 1-year period [8, 9]. BRIVAFIRST represents the largest real-world study of BRV, and the size of the cohort allows for sub-analyses to be performed.

The aim of this analysis was to explore the effectiveness and tolerability of adjunctive BRV when used as early add-on or later adjunctive treatment in patients included in BRIVAFIRST.

**METHODS**

**Participants**

BRIVAFIRST was a retrospective study conducted across 62 Italian centers [8, 9]. Adult patients attending participating centers who were prescribed to BRV (March 2018–March 2020) and were on stable treatment with at least one ASM during the prior 90 days were retrospectively identified. Only patients with focal epilepsy and with 12-month follow-up after initiating BRV were included in the current analysis. Data on demographics, clinical history, type of seizures and epilepsy [10], etiology, previous/concomitant ASMs, and baseline seizure frequency (monthly seizure frequency during the 3 months before starting BRV) were collected. Patients in the early add-on group were treated with BRV as add-on therapy after one or two prior ASMs; the late add-on group consisted of patients who received BRV as add-on therapy after three or more prior ASMs.

Data on seizure occurrence, adverse events (AEs), and drug withdrawal were retrieved from patient seizures diaries and clinical records; visits at 3, 6, and 12 months were performed as standard practice when a new ASM is initiated. Exclusion criteria were history of alcoholism, drug abuse, conversion disorders, or other non-epileptic ictal events.

Effectiveness outcomes included sustained seizure response (SSR) and sustained freedom (SSF); seizure worsening (greater than 25% increase in monthly seizure frequency relative to baseline) and treatment discontinuation at 12 months were also considered. Sustained seizure response (freedom) was defined as a reduction of at least 50 (100%) in baseline seizure frequency that continued without interruption from the first time it was achieved through the 12-month follow-up without BRV withdrawal in patients with at least one seizure during the 3 months before introducing BRV; the time of achievement of SSR and SSF was established using data at visits at 3, 6, and 12 months [11].

Safety and tolerability outcomes included the rate of treatment discontinuation due to AEs and the incidence of AEs considered BRV-related by participating physicians.

**Statistical Analysis**

Values were presented as median [interquartile range] for continuous variables and number (percentage) of subjects for categorical variables. In this sub-analysis, demographic and baseline characteristics and study outcomes were compared between early-add on and late add-on patient groups. Comparisons were made using the Mann–Whitney test or chi-squared test, as appropriate. Simple and multivariable logistic regression models were performed to identify baseline characteristics of patients associated with SSR and SSF. Selected independent variables were age, number of concomitant ASMs, concomitant use of sodium channel blockers (SCBs), baseline monthly seizure frequency, and early add-on treatment with BRV [11, 12]. Carbamazepine, phenytoin, lamotrigine, oxcarbazepine, eslicarbazepine acetate, lacosamide, and rufinamide were classified as SCBs; patients in the SCB group were those receiving at least one SCB, whereas those in the no-SCB group did not take any SCB. Results were considered significant for \( p \) values less than 0.05 (two sided).
Table 1 Baseline characteristics of patients

| Characteristics                              | Early add-on (n = 176) | Late add-on (n = 852) | p value |
|----------------------------------------------|------------------------|-----------------------|---------|
| Age, years                                   | 45 (30–61)             | 45 (33–55)            | 0.883   |
| Male sex                                     | 85 (48.3)              | 402 (47.1)            | 0.778   |
| Age at epilepsy onset, years (N)              | 176                    | 852                   | < 0.001 |
| Median                                       | 23 (11–47)             | 12 (5–22)             |         |
| Duration of epilepsy, years (N)              | 176                    | 852                   | < 0.001 |
| Median                                       | 11 (5–25)              | 27 (16–39)            |         |
| Type of seizure                              |                        |                       | 0.832   |
| N                                            | 157                    | 759                   |         |
| Focal onset                                  | 114 (72.6)             | 565 (74.4)            |         |
| Focal to bilateral tonic–clonic              | 32 (20.4)              | 139 (18.3)            |         |
| Focal onset and focal to bilateral tonic–clonic | 11 (7.0)               | 55 (7.3)              |         |
| Etiology                                     |                        |                       | 0.918   |
| Structural                                   | 98 (55.7)              | 455 (53.3)            |         |
| Genetic                                      | 6 (3.4)                | 34 (4.0)              |         |
| Immune                                       | 1 (0.6)                | 10 (1.2)              |         |
| Infectious                                   | 2 (2.3)                | 24 (2.8)              |         |
| Unknown                                      | 67 (38.1)              | 330 (38.7)            |         |
| Number of previous ASMs (N)                  | 176                    | 847                   | < 0.001 |
| Median                                       | 2 (1–2)                | 7 (4–9)               |         |
| Number of concomitant ASMs                   | 1 (1–2)                | 2 (2–3)               | < 0.001 |
| Concomitant use of SCB(s) at baseline (N)    | 166                    | 735                   | < 0.001 |
| Patients                                     | 128 (77.1)             | 643 (87.5)            |         |
| baseline monthly seizure frequency (A)       | 3 (1–6)                | 7 (3–20)              | < 0.001 |

Data are median (IQR) for continuous variables, and n (%) for categorical variables. 
ASM antiseizure medications, IQR interquartile range, SCB sodium channel blocker, N total number of patients for whom data in question were available. 
*Based on the number of seizures during the 90 days before starting adjunctive BRV.
Data analysis was performed using STATA/IC 13.1 (StataCorp LP, TX, USA). The study is reported according to STROBE guidelines [13].

**Standard Protocol Approval**

BRIVAFIRST was approved by the ethics committee at any participating site and conducted in accordance with the Declaration of Helsinki. Prior to participation in the study, informed consent (e.g., explanation of the purposes of the research, information about handling of personal data and results of the research, description of the procedures adopted for ensuring data protection) was obtained from any patient or from one of the parents or from the legal representative.

**RESULTS**

Out of 1325 patients initially identified, 71 patients were excluded as diagnosed with generalized, combined, or unknown epilepsy and 225 because follow-up after initiating BRV was less than 1 year at time of the current analysis. Accordingly, 1029 patients with focal epilepsy fulfilled the inclusion/exclusion criteria and were included, of whom 176 (17.1%) received BRV as early add-on treatment. Patients who

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Fig. 1 Sustained seizure response and sustained seizure freedom with brivaracetam according to early-add on treatment

Fig. 2 Time to sustained seizure response with brivaracetam according to early-add on treatment

Fig. 3 Time to sustained seizure freedom with brivaracetam according to early-add on treatment

Fig. 4 Sustained seizure response according to the number of lifetime antiseizure medications

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received BRV as add-on therapy after one or two prior ASMs were older at time of epilepsy diagnosis, had a shorter duration of epilepsy, were treated with a lower number of concomitant ASMs, and had a lower seizure frequency at baseline in comparison to patients who received BRV as late add-on therapy after more than two prior ASMs. Baseline characteristics of participants are summarized in Table 1.

The median daily dose of BRV at 3 months was 100 (100–150) in the early add-on group and 100 (100–200) in the late add-on group \((p = 0.087)\); it was 100 (100–150) mg in the early add-on group and 150 (100–200) mg in the late add-on group \((p < 0.001)\) at 6 months, and it was 125 (100–200) mg in the early add-on group and 200 (100–200) mg in the late add-on group \((p < 0.001)\) at 12 months.

During the 1-year study period, SSR was reached by 97/161 (60.3%) of patients in the early add-on group and 286/833 (34.3%) of patients in the late add-on group \((p < 0.001)\); SSF was achieved by 51/161 (31.7%) of patients in the early add-on group and 91/833 (10.9%) of patients in the late add-on group \((p < 0.001)\) (Fig. 1). Among patients who received BRV as early add-on treatment, 59 (36.6%) were sustained seizure responders from day 1, 26 (16.1%) from month 4, and 12 (7.5%) from month 7; in the late add-on group, SSR was reached by 177 (21.2%) patients from day 1, 68 (8.2%) patients from month 4, and 41 (4.9%) patients from month 7 (Fig. 2). In the early add-on group, 19 (11.8%) patients achieved SSF from day 1, 20 (12.4%) from month 4, and 12 (7.5%) from month 7; among patients who received BRV as late add-on treatment, 53 (6.4%) were seizure free from day 1, 26 (3.1%) from month 4, and 12 (1.4%) from month 7 (Fig. 3). The overall rates of SSR and SSF according to the number of prior ASMs are illustrated in Figs. 4 and 5.

Age, the number of concomitant ASMs, the concomitant use of SCBs, the baseline monthly seizure frequency, and the timing to add BRV

| Dependent variable | Unadjusted | p value | Adjusted a | p value |
|--------------------|------------|---------|------------|---------|
| Age                | 1.02 (1.01–1.02) | < 0.001 | 1.01 (1.00–1.02) | 0.011 |
| Number of concomitant ASMs | 0.69 (0.60–0.80) | < 0.001 | 0.75 (0.64–0.89) | 0.001 |
| Concomitant use of SCBs | 1.57 (1.03–2.39) | 0.037 | 2.05 (1.30–3.21) | 0.002 |
| Baseline monthly seizure frequency | 0.98 (0.98–0.99) | < 0.001 | 0.99 (0.98–0.99) | 0.001 |
| Brivaracetam early add-on | 2.90 (2.05–4.10) | < 0.001 | 2.13 (1.45–3.14) | 0.005 |

Values are from logistic regression models
ASM antiseizure medications, CI confidence interval, OR odds ratio, SCB sodium channel blocker
aAdjustment for age, number of concomitant ASMs, concomitant use of SCBs, baseline monthly seizure frequency, and treatment with brivaracetam as early add-on

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within lifetime ASMs were independent predictors of SSR and SSF with older age, the lower number of lifetime ASMs, the concomitant administration of SCBs, the lower baseline seizure count, and the use of BRV as early add-on treatment being associated with a higher likelihood to achieve SSR (Table 2) and SSF (Table 3).

There were no differences in the rates of seizure worsening between the early and late add-on groups at 3-month (early add-on 2.3%, late add-on 4.8%; \( p = 0.134 \)), 6-month (early add-on 3.4%, late add-on 3.1%; \( p = 0.802 \)), and 12-month (early add-on 0.6%, late add-on 2.6%; \( p = 0.100 \)) follow-up visits.

During the 1-year study period, 29 (16.5%) patients in the early add-on group and 241 (28.3%) in the late add-on group discontinued BRV (\( p = 0.001 \)). The reasons for treatment withdrawal were insufficient efficacy [early add-on \( n = 16 \) (9.1%), late add-on \( n = 144 \) (16.9%); \( p = 0.009 \)], AEs [early add-on \( n = 13 \) (7.4%), late add-on \( n = 90 \) (10.6%; \( p = 0.203 \)], and a combination of both [early add-on \( n = 0 \), late add-on \( n = 5 \) (0.6%; \( p = 0.309 \)]; in one case, BRV was discontinued because of the patient’s request and one patient died as a result of a cause unrelated to treatment.

Adverse events were reported by 38.7% and 28.5% (\( p = 0.017 \)) of patients who received BRV as early and late add-on treatment, respectively, and they were rated as mild (75.4%), moderate (24.2%) and severe (0.4%) in intensity. The most common AEs observed in both study groups included somnolence, nervousness and/or agitation, vertigo, and fatigue (Table 4).

**DISCUSSION**

In this exploratory post hoc analysis of BRIVA-FIRST data, BRV was associated with a greater sustained seizure frequency reduction measured as SSR and SSF and a higher retention rate when added as an early add-on treatment in patients with focal onset seizures than in patients receiving the drug as a late add-on therapy.

Thus far, very limited evidence in small groups of patients exists that has directly compared the effects of adjunctive BRV at different stages of epilepsy treatment. In BRIVA-LIFE, a multicenter retrospective study aimed to evaluate the use of BRV in clinical practice, patients with fewer lifetime ASMs were more likely to respond to treatment [7]. The rates of seizure freedom were 50.0% in 2 patients with a history of one ASM, 42.9% in 14 patients with a history of two ASMs, and 40.0% in 40 patients with a history of three ASMs. The seizure freedom rates progressively declined with the increased number of prior ASMs and reached 2.6% in patients who had used 12 ASMs [7]. These findings are consistent with data from other studies with
different ASMs that evaluated the impact of the number of lifetime drugs and demonstrated better responses in the early add-on setting [14, 15].

In BRIVAFIRST, patients had a reduction of baseline seizure frequency also when BRV was added as a late add-on therapy and had the chance to reach the status of SSF even they had tried more than 10 medications before for epilepsy treatment. These figures indicate the efficacy of BRV to control seizures when added to the pre-existing therapeutic regimen in patients with difficult-to-treat epilepsy and matched previous real-world evidence [7, 16–23].

Importantly, the maintenance of seizure frequency reduction over time is crucial for patients with epilepsy. In this regard, it is not clear whether the short-term efficacy of an ASM observed during the treatment phase of regulatory trials is a predictor of long-term drug effects. Further, missing data of patients who discontinue the medication before the end of the treatment period are generally imputed from the last available visits to estimate the seizure freedom rate. This approach can result into the risk of inflating the drug efficacy and providing a view that is not truly representative of the actual treatment response. In addition, although 50% response rate and change in median seizure frequency are typically used to measure whether trial participants successfully respond to treatment, individual seizure rates

Table 4  Adverse events with brivaracetam according to early add-on treatment

| Patients with adverse events | Early add-on | Late add-on |
|-----------------------------|-------------|-------------|
| N                           | 137         | 740         |
| n (%)                       | 53 (38.7)   | 211 (28.5)  |

Most frequently reported adverse events*

|                           | Early add-on | Late add-on |
|--------------------------|--------------|-------------|
| N                        | 136          | 716         |
| Somnolence, n (%)        | 11 (8.1)     | 45 (6.3)    |
| Nervousness and/or agitation, n (%) | 12 (8.8) | 38 (5.3) |
| Vertigo, n (%)           | 5 (3.7)      | 26 (3.6)    |
| Fatigue, n (%)           | 8 (5.9)      | 18 (2.5)    |
| Headache, n (%)          | 5 (3.7)      | 17 (2.4)    |
| Aggressiveness, n (%)    | 2 (2.2)      | 18 (2.5)    |
| Mood change, n (%)       | 5 (3.7)      | 15 (2.1)    |
| Dizziness, n (%)         | 3 (2.2)      | 16 (2.2)    |
| Sleep disturbances, n (%)| 4 (2.9)      | 11 (1.5)    |
| Memory disturbance, n (%)| 5 (3.7)      | 9 (1.3)     |
| Anxiety                  | 2 (2.2)      | 3 (0.4)     |
| Nausea/vomiting          | –            | 8 (1.1)     |
| Disturbances in attention/concentration | 3 (2.2) | 3 (0.4) |

N total number of patients for whom data in question were available

AEs reported by < 1% of patients: tremor (all n = 8), stomach pain (n = 7), diplopia/blurred vision (all n = 5), weight increase (n = 4), skin disorders, hair loss (all n = 3), fever, pharyngodynia, hyporexia (all n = 2), urinary disturbances, weight decrease, psychosis, tics, confusion, tinnitus, constipation, abdominal pain (all n = 1)

*Reported by ≥ 1% of patients in each group

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are highly volatile, with large fluctuations from month to month that may simply reflect the natural course of the disease itself [24, 25]. In this context, sustained efficacy outcomes that exclude patients who withdrew the treatment or had only a transient reduction in seizure frequency represent more reliable and informative measures of drug efficacy and more nuanced approaches to measuring individual treatment response. In the current subgroup analysis of BRIVAFIRST, the SSR and SSF were observed in around 60% and 32% of patients when BRV was given as the first- or second add-on treatment; the corresponding figures in patients who received BRV as a later therapeutic option were 35% and 11%. Of note, sustained seizure frequency reduction was obtained on the first day of treatment in most cases, supporting the evidence that BRV can have an early, sustained onset of action, with potential utility when rapid onset of action is necessary [26, 27]. The lack of need for titration with initiation at target dose and the fast entry of BRV into the central nervous system may contribute to explain the early onset of action. The increase in the rates of SSR and SSF over time suggests that BRV efficacy can be sustained even in patients who respond later, although the shorter follow-up available for these patients needs to be acknowledged.

The concomitant use of SCBs was an independent predictor of SSR and SSF, supporting the notion that favorable combinations usually consist of ASMs with different mechanisms of action [8, 28]. Further research is warranted to confirm this preliminary evidence and explore how BRV can be better combined in clinical practice within the frame of so-called rational polypharmacy.

The burden of concomitant medications and the baseline seizure frequency can act as surrogate markers of the intrinsic disease severity, and the inverse relationship found between the response to adjunctive BRV and these baseline characteristics is consistent with prior studies [12, 29]. Likewise, age was an independent predictor of sustained seizure frequency reduction, with older age being associated with a greater likelihood to achieve SSR and SSF; the better response to BRV in older versus younger patients is also in line with prior evidence [5, 7, 30]. Remarkably, ASMs are generally found to be more efficacious in elderly than younger patients when outcomes are stratified by age, and differences across the age groups can largely be explained by differences in baseline characteristics of participants [31, 32].

Since patients with epilepsy require long-term therapy, treatment discontinuation represents an important clinical concern. During the 1-year study period, the overall rate of treatment discontinuation was about 25%, which substantially overlapped the rates found in retrospective non-interventional studies of BRV [7, 16–23] and newer ASMs in clinical practice [32–35]. Further, fewer patients in the early than in the late add-on group discontinued BRV and the difference was mainly driven by the lower rate of treatment withdrawal due to insufficient efficacy.

The differences found in effectiveness outcomes between the early and late add-on groups were not unexpected. Patients in the late add-on group had a younger age at epilepsy onset and a longer duration of epilepsy in comparison to patients in the early add-on group, who developed epilepsy later in life. Although the actual prevalence of drug resistance across the study cohort was not available, patients who received BRV as late adjunctive treatment had a higher number of lifetime and concomitant ASMs. Further, patients in the late add-on group had a higher baseline seizure frequency and received a higher dose of BRV. All these features suggest that the two groups may comprise different epilepsy subtypes and patients who received BRV as late add-on treatment had a long-standing and more difficult to treat epilepsy.

Adverse events were reported by around 30% of the patients and were generally mild to moderate in intensity. Patients who received BRV as early add-on therapy reported AEs more frequently, while there was no significant difference in the rate of treatment discontinuation due to tolerability issues in comparison to late add-on patients’ group. In this regard, early add-on patients had a lower seizure frequency at baseline and the number of seizures during the last year has been shown to be inversely
associated with the likelihood to experience adverse drug effects [36]. It may be hypothesized that patients who have more frequent seizures may worry more about the disease than adverse drug effects and consider the AEs as symptoms of the epilepsy, whereas patients with better seizure control are more likely to attribute symptoms to the drugs that they are taking [36]. It is also possible that patients with a shorter disease duration and a lower number of lifetime ASMs may be more prone to report to physicians the occurrence of untoward drug effects in comparison to patients with a longer disease duration and a greater number of prior ASMs, who instead may be more usual and in a certain sense accustomed to experience AEs.

Somnolence, vertigo, and fatigue were the most frequent AEs and substantially overlap the profile of side effects of the majority of ASMs [37]; nervousness and agitation were the most common psychiatric AEs. These findings confirmed the overall favorable tolerability profile of BRV when added to concomitant ASMs irrespective of treatment stage and matched data from prior randomized and non-randomized studies [7, 16–23, 38, 39].

The main strengths of BRIVAFIRST included the recruitment at multiple sites and the large cohort of included patients, which allowed exploratory subgroup analyses. The real-world setting, which reflects the treatment approach employed by physicians according to the usual healthcare practice, can increase the external validity of the findings and the generalizability to other real-world populations with similar baseline characteristics. Further, the SSF and SSR as metrics of treatment efficacy offer insights into the clinical response to treatment from a novel perspective. Some limits need to be also acknowledged. The main limitation of the study is the lack of a control group or comparison with other therapeutic options, which prevented any definitive conclusions about the comparative efficacy and tolerability of BRV with other ASMs. The open-label and retrospective design may have introduced potential sources of bias. Further, the collection of AEs as recorded during clinical visits rather than by standardized questionnaires might have resulted in underreporting.

**CONCLUSION**

Brivaracetam was effective and well tolerated both as first add-on as well as late adjunctive treatment in patients with focal epilepsy. The best response to BRV was obtained in early-stage treatment and was associated with higher rates of sustained seizure frequency reduction and retention. Even some patients at the late stage of treatment who had received more than 10 prior ASMs could become free from seizure with the addition of BRV. Further research is warranted to explore the potential of BRV in specific etiologies and epilepsy syndromes to provide additional guidance for clinical decisions.

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**Compliance with Ethics Guidelines.** BRIVAFIRST was approved by the ethics committee at any participating site and conducted in accordance with the Declaration of Helsinki. Prior to participation in the study, informed consent (e.g., explanation of the purposes of the research, information about handling of personal data and results of the research, description of the procedures adopted for ensuring data protection) was obtained from any patient or from one of the parents or from the legal representative.

**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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