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RESEARCH ARTICLE

Long-term safety and efficacy of adjunctive brivaracetam in pediatric patients with epilepsy: An open-label, follow-up trial

Lieven Lagae[1] | **Kerstin Alexandra Klotz**[2] | **András Fogarasi**[3] | **Florin Floricel**[4] | **Christoph Reichel**[4] | **Jan-Peer Elshoff**[4] | **Sofia Fleyshman**[5] | **Harriet Kang**[6]

[1]Department of Development and Regeneration, Pediatric Neurology Section, University Hospitals Katholieke Universiteit Leuven, Leuven, Belgium

[2]Department of Neuropediatrics and Muscle Disorders, Medical Center, University of Freiburg, Freiburg, Germany

[3]Department of Neuropediatrics, Bethesda Children's Hospital, Budapest, Hungary

[4]UCB Pharma, Monheim am Rhein, Germany

[5]UCB Pharma, Morrisville, North Carolina, USA

[6]Department of Neurology, Icahn School of Medicine at Mount Sinai Hospital, New York, New York, USA

Correspondence
Lieven Lagae, Department of Development and Regeneration, Pediatric Neurology Section, University Hospitals Katholieke Universiteit Leuven, UZ Herestraat 49–box 7003, Leuven 3000, Belgium.
Email: lieven.lagae@uzleuven.be

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Abstract

Objective: This study was undertaken to evaluate the long-term safety, tolerability, and efficacy of adjunctive brivaracetam (BRV) treatment in pediatric patients with epilepsy.

Methods: A phase 3, open-label, multicenter, long-term follow-up trial (N01266; NCT01364597) was conducted on patients (aged 1 month to <17 years at core trial entry; direct enrollers aged 4 to <17 years) treated with BRV. Outcomes included treatment-emergent adverse events (TEAEs), behavior assessments (Achenbach Child Behavior Checklist [CBCL], Behavior Rating Inventory of Executive Function [BRIEF]/BRIEF-Preschool version [BRIEF-P]), and efficacy outcomes (percent change in focal seizure frequency, 50% responder rate for all seizure types for patient subgroups <2 years and ≥2 years of age using daily record card data).

Results: Of 257 patients with ≥1 dose of BRV (141 [54.9%] male; mean age = 8.0 years [SD = 4.5]), 36 patients were <2 years of age, and 72.0% of patients had a history of focal seizures. Mean BRV exposure was 3.2 patient-years. At least one TEAE occurred in 93.4% patients, and 32.3% had serious TEAEs. Seven patients died during the trial; no deaths were considered treatment-related. Patients ≥2 years of age had a median decrease in 28-day adjusted focal seizure frequency of 62.9%, and 50.9% had a ≥50% response in all seizures. Patients <2 years of age had a median decrease in 28-day adjusted focal seizure frequency of 96.9%, and 68.2% had a ≥50% response in all seizures. Kaplan–Meier estimated treatment retention was 72.7%, 64.5%, 57.8%, 53.3%, 50.1%, and 44.8% at 1, 2, 3, 4, 5, and 6 years, respectively. Mean changes (baseline to last evaluation) for all Achenbach CBCL and BRIEF-P/BRIEF subscale scores were negative, reflecting stability/slight improvement.

Significance: Long-term adjunctive BRV treatment was generally well tolerated and efficacious in reducing seizure frequency, and had high retention rates, with generally stable cognitive/behavioral scores in pediatric patients with epilepsy.

KEYWORDS

antiseizure medication, adolescents, children, focal seizures

1 | INTRODUCTION

Epilepsy is estimated to affect 3.2–5.5 of 1000 children in developed countries and 3.6–44.3 of 1000 children in underdeveloped countries, with annual incidence rates ranging from 41–187 of 100 000 children.[1] As epilepsy generally requires long-term treatment, it is critical to determine the long-term safety and efficacy of antiseizure medications (ASMs).

Brivaracetam (BRV) is currently indicated for adjunctive treatment of focal (partial onset) seizures in patients ≥2 years of age in the European Union,[2] and as monotherapy and adjunctive treatment in patients ≥1 month of age in the United States.[3]

Here, we report data from an open-label, long-term follow-up (LTFU) trial (N01266 [ClinicalTrials.gov: NCT01364597]) of adjunctive BRV in pediatric patients with epilepsy. This trial enrolled patients who completed a core trial of adjunctive BRV (N01263,[4] N01349 [NCT03325439],[5] or EP0065 [NCT03405714][6]) and directly enrolled patients ≥4 years to <17 years of age with focal seizures only. The primary objective was to document the long-term safety and tolerability of BRV. The secondary objective was to assess the efficacy of BRV during long-term exposure.

Key Points

- Safety/tolerability of long-term adjunctive BRV in patients aged ≥1 month to <17 years was consistent with that in adults
- Seizure frequency, responder rates, and seizure freedom improved with long-term adjunctive BRV treatment in pediatric patients
- Behavioral and cognitive functioning scores were stable/slightly improved in pediatric patients during long-term adjunctive BRV therapy
- Kaplan–Meier estimates supported high 1- and 2-year retention rates of adjunctive BRV during long-term treatment of pediatric patients
- The trial lasted >10 years (August 1, 2011 to February 3, 2022), following patients with up to 9.5 years of BRV exposure

2 | MATERIALS AND METHODS

2.1 | Trial design

N01266 was a phase 3, open-label, single-arm, multicenter, long-term trial that evaluated the long-term safety, tolerability, and efficacy of BRV as adjunctive treatment in children with epilepsy. LTFU patients enrolled in N01266 from one of the core trials: N01263, EP0065, or N01349. Those from core BRV trial N01263 or EP0065 were ≥1 month to <16 years of age upon entry into the core trial and had a diagnosis of epilepsy (localized, generalized, or undetermined focal or generalized epileptic syndrome or other symptomatic generalized epilepsy), whereas LTFU patients from core BRV trial N01349 were term or preterm neonates ≤27 days of postnatal age who had ≥2 min of cumulative electroencephalographic neonatal seizures (ENS), or three or more identifiable ENS before entering the evaluation period. Additionally, N01266 allowed patients who had not participated in a core trial to directly enroll (i.e., direct enrollers) if they were ≥4 years to <17 years of age and had a clinical diagnosis of focal onset seizures. LTFU patients entered directly into the evaluation period and continued BRV treatment at the individualized dose received at the completion of their core trial. Direct enrollers entered N01266 at the screening visit and participated in up to 3 weeks of an uptitration period. If a direct enroller demonstrated, in the opinion of the investigator, acceptable tolerability and seizure control on the same daily dose of BRV (≥1 mg/kg/day) for 7 ± 2 days during the uptitration period, the patient entered the evaluation period on that dose.

BRV was provided as tablets or oral solution to be administered twice daily (bid) in two equally divided doses, to a maximum BRV dose of 5 mg/kg/day (2.5 mg/kg bid), not to exceed 200 mg/day. BRV dose adjustments during the uptitration period were made in accordance with protocol-specified guidelines; dose adjustments of BRV and any concomitant ASMs were allowed at any time based on clinical judgment.

All concomitant ASMs were permitted during the study; levetiracetam (LEV) was allowed after the entry visit, and felbamate was allowed if a stable dose was

maintained during the core study for LTFU patients, or during the screening and uptitration periods for direct enrollers.

Patients received BRV treatment for ≥3 years, until BRV was approved for pediatric patients in their age range, a managed access program was established, patients transitioned to another BRV trial, or the investigational product development in the related age range was stopped by the sponsor, whichever came first. Study completion required the status on the study termination form to be marked as completed, indicating all planned visits had taken place. Planned visits were dependent on whether a patient discontinued the study, entered into another study, or received marketed drug after their final visit. The end of the study was the date of the last visit of the last patient in the study. Evaluation period definitions and visit sequences are reported in Data S1.

This trial was conducted in compliance with the International Council for Harmonisation–Good Clinical Practice and the Declaration of Helsinki, and with the Health Insurance Portability and Accountability Act for US sites. The trial protocol and amendments were approved by local institutional review boards/independent ethics committees, as defined in local regulations. Written informed consent was obtained for all study participants.

2.2 | Eligibility criteria

In addition to age criteria, LTFU patients needed a confirmed diagnosis of epilepsy. Direct enrollers were required to have a clinical diagnosis of focal (partial onset) seizures according to the current International League Against Epilepsy (ILAE) classification at the start of the trial (ILAE 1981)[7] and an electroencephalogram (EEG) compatible with this diagnosis; to have uncontrolled focal seizures after an adequate course of treatment with at least one ASM; to have at least one focal seizure during the 3 weeks before screening; and to be taking at least one ASM. All ASMs needed to be at a stable dose for at least 7 days before screening. Vagal nerve stimulator use (stable for at least 2 weeks before screening) and benzodiazepines taken more than once per week (for any indication) were considered a concomitant ASM. Females of childbearing age had to have a negative pregnancy test and use contraception or not be sexually active.

Patients were excluded if they had severe medical, neurological, or psychiatric disorders or laboratory values; had planned participation in a clinical study of another investigational drug or device; had any medical condition that in the investigator's opinion warranted exclusion; had chronic liver disease; had an exclusionary level of transaminase; or were pregnant or breastfeeding. Other exclusion criteria are presented in Data S1.

Patients were withdrawn from the trial if they developed an illness that, in the opinion of the investigator, would have interfered with their continued participation or been detrimental to their physical/mental health; took prohibited concomitant medications; became pregnant; or had an episode of convulsive status epilepticus, prolongation of seizure duration, worsening of seizure frequency, or emergence of a new type, which was considered by the investigator to require intervention.

2.3 | Outcome measures

The primary variables were treatment-emergent adverse events (TEAEs) and serious TEAEs.

The secondary variables assessed efficacy. For patients <2 years of age (based on EEG data [recorded for at least 24 h]), variables included the absolute and percent change in average daily frequency of focal seizures (patients with focal seizures only), and the 50% responder rate for all seizures (all seizure types). Secondary variables for patients ≥2 years of age (based on daily record card [DRC] data) were the absolute and percent change in 28-day adjusted focal seizure frequency from baseline to the end of the evaluation period (patients with focal seizures only), and the 50% responder rate (a responder was defined as having ≥50% reduction in seizure frequency compared with baseline) for all seizures (all seizure types). Seizure assessments were performed for patients with evaluable data. Patients with no seizures at baseline and postbaseline were regarded as "not evaluable" for the responder assessment, because they already had the minimum possible number of seizures.

Other variables (additional efficacy outcomes, behavioral and cognitive assessments, estimated retention on BRV) are described in Data S1.

2.4 | Statistical methods

Descriptive statistics were used to summarize outcomes; no statistical hypothesis testing was planned. Patients were categorized as focal seizure patients or primary generalized seizure patients at screening if those seizures were entered on the ILAE Seizure Classification History electronic case report form (eCRF) page at screening, or if they had been reported on the Historical Seizure Count eCRF page for the last 3 weeks before screening with a nonzero value. Patients who could not be categorized into any of the above categories were classified as

uncategorized. Patients who had been rolled over from core trial N01263 had already been categorized as focal seizure or primary generalized seizure patients within the core analysis dataset. This categorization was taken over for trial N01266.

Safety analyses were performed on the safety set (all enrolled patients who took at least one dose of trial medication); seizure data analyses were performed on the full analysis set (all patients in the safety set who had at least one completed postbaseline DRC or EEG). Analyses were also performed for the subgroup of patients with focal seizures.

No formal sample size calculation was performed for this trial, as no formal statistical testing was needed. It was initially planned that approximately 600 patients would be enrolled, assuming that 90% of patients having completed a core trial would continue into this trial, including up to 100 direct enrollers. However, changes to planned, enrolling studies resulted in a revised anticipated enrollment of approximately 270. Specifically, an enrolling study eventually received its own open-label extension and those participants did not enter N01266. Furthermore, two planned studies were canceled because efficacy goals to support label extension <16 years of age were achieved with extrapolation of efficacy data from adults.[8–10]

3 | RESULTS

3.1 | Patients

This trial was conducted between August 1, 2011 and February 3, 2022 at 46 sites in North America, Latin America, and Europe. A total of 264 patients were enrolled; 257 patients received at least one dose of BRV and were included in the safety set and full analysis set. A total of 120 (46.7%) patients were direct enrollers, and 137 (53.3%) were LTFU patients. One hundred twenty-four (48.2%) patients completed the trial, and 133 (51.8%) discontinued, most commonly (≥10% of patients) due to lack of efficacy (39 [15.2%]), adverse event (32 [12.5%]), and withdrawn consent (29 [11.3%]). Discontinuation due to lack of efficacy was reported for 27 of 185 (14.6%) and 12 of 68 (17.6%) patients with focal and primary generalized seizures, respectively. No association was observed between seizure type or syndrome and discontinuation due to lack of efficacy.

Baseline characteristics are reported in Table 1. Thirty-six (14.0%), 15 (5.8%), 141 (54.9%), and 65 (25.3%) patients were aged <2, ≥2 to <4, ≥4 to <12, and ≥12 to 17 years, respectively (Table S1). A total of 185 (72.0%), 68 (26.5%), and four patients, respectively, were categorized as having focal seizures, primary generalized seizures, and uncategorized (i.e., did not satisfy criteria for focal or primary generalized seizure classification; Table S2). Among patients with focal seizures, four patients had nonspecific etiology. Most patients (202 [78.6%]) had taken at least one ASM before trial entry.

3.2 | Exposure and retention on BRV

A total of 257 patients were exposed to at least one dose of BRV for a mean of 3.2 patient-years. Of these, 209 (81.3%), 184 (71.6%), 151 (58.8%), 133 (44.0%), 88 (34.2%), 74 (28.8%), and 50 (19.5%) patients completed a treatment duration of >6, >12, >24, >36, >48, >60, and >72 months, respectively (Figure 1). Kaplan–Meier estimated retention on BRV at 12, 24, 36, 48, 60, and 72 months was 72.7%, 64.5%, 57.8%, 53.3%, 50.1%, and 44.8%, respectively. One patient remained in the trial for 114.3 months.

3.3 | Safety and tolerability

3.3.1 | TEAEs and discontinuations

A total of 240 (93.4%) patients had at least one TEAE during the trial (Table 2). The incidence of TEAEs was higher in the first 3 months of treatment (195/257 [75.9%] patients) than in Months 4–6 (113/227 [49.8%] patients), as well as subsequent 3-month time intervals (range = 16.0%–49.4%; trend similar over time; only time intervals with ≥20 patients [up to 87 months] were considered; Figure 2). TEAEs that were considered drug-related by the investigator were reported by 79 (30.7%) patients, most commonly (≥3% of patients) somnolence (12 [4.7%]), decreased appetite (11 [4.3%]), aggression (10 [3.9%]), and fatigue (nine [3.5%]). The incidence of drug-related TEAEs was highest in the first 3 months of treatment and decreased thereafter (Figure 2).

Serious TEAEs were reported by 83 (32.3%) patients, most commonly (≥2% of patients) seizure, status epilepticus, pneumonia, and pyrexia. Most patients experienced TEAEs with a maximum intensity of mild (60 [23.3%]) or moderate (136 [52.9%]). A total of 44 patients (17.1%) experienced severe TEAEs, most commonly (at least three patients) seizure (seven patients [2.7%]), pneumonia (seven patients [2.7%]), and status epilepticus (five patients [1.9%]).

A total of 31 (12.1%) patients had TEAEs leading to discontinuation, most frequently during the first 3 months of the study. The largest change in discontinuations due to TEAEs occurred between the ≤3-month ($n = 31$) and >3-month ($n = 22$) exposure duration

TABLE 1 Baseline demographics, epilepsy characteristics, and antiseizure medications (safety set).[a]

	Patients with focal seizures, $n=185$	Patients with primary generalized seizures, $n=68$	All patients, $N=257$[b]
Age, mean (SD), years	8.7 (4.3)	6.7 (4.6)	8.0 (4.5)
Male, *n* (%)	107 (57.8)	34 (50.0)	141 (54.9)
Weight, mean (SD), kg	32.9 (20.1)	25.3 (19.3)	30.4 (20.2)
Epilepsy duration, mean (SD), years	5.2 (3.8)	3.9 (3.4)	4.8 (3.8)
Age at diagnosis, mean (SD), years	3.6 (3.3)	2.8 (3.4)	3.3 (3.3)
Previous and ongoing medical history conditions[c] reported by ≥5% of all patients, *n* (%)			
Developmental delay	29 (15.7)	7 (10.3)	36 (14.0)
Mental retardation	13 (7.0)	13 (19.1)	26 (10.1)
Attention deficit/hyperactivity disorder	20 (10.8)	4 (5.9)	24 (9.3)
Gastroesophageal reflux disease	12 (6.5)	8 (11.8)	22 (8.6)
Constipation	13 (7.0)	8 (11.8)	21 (8.2)
Cerebral palsy	15 (8.1)	4 (5.9)	20 (7.8)
Psychomotor retardation	12 (6.5)	8 (11.8)	20 (7.8)
Hypotonia	11 (5.9)	5 (7.4)	18 (7.0)
Mental impairment	9 (4.9)	9 (13.2)	18 (7.0)
Microcephaly	9 (4.9)	9 (13.2)	18 (7.0)
Asthma	12 (6.5)	5 (7.4)	17 (6.6)
Strabismus	13 (7.0)	2 (2.9)	15 (5.8)
Hemiparesis	13 (7.0)	0	13 (5.1)
Number of prior ASMs[d]			
Prior ASMs, median (range)	3.0 (0–16)	3.0 (0–12)	3.0 (0–16)
0–1, *n* (%)	50 (27.0)	24 (35.3)	76 (29.6)
2–4, *n* (%)	89 (48.1)	24 (35.3)	115 (44.7)
≥5, *n* (%)	46 (24.9)	20 (29.4)	66 (25.7)
Concomitant ASMs[e] taken by ≥10% of all patients, *n* (%)			
At least one ASM	184 (99.5)[f]	67 (98.5)[f]	255 (99.2)[f]
Valproate	79 (42.7)	50 (73.5)	129 (50.2)
Clobazam	48 (25.9)	24 (35.3)	72 (28.0)
Diazepam	50 (27.0)	16 (23.5)	68 (26.5)
Topiramate	48 (25.9)	13 (19.1)	62 (24.1)
Lamotrigine	43 (23.2)	18 (26.5)	61 (23.7)
Phenytoin	45 (24.3)	11 (16.2)	56 (21.8)
Carbamazepine	51 (27.6)	2 (2.9)	53 (20.6)
Oxcarbazepine	45 (24.3)	4 (5.9)	50 (19.5)
Lacosamide	34 (18.4)	3 (4.4)	38 (14.8)
Clonazepam	24 (13.0)	5 (7.4)	29 (11.3)
Phenobarbital	13 (7.0)	11 (16.2)	26 (10.1)
Vigabatrin	12 (6.5)	12 (17.6)	26 (10.1)

Abbreviations: ASM, antiseizure medication; BRV, brivaracetam; LTFU, long-term follow-up.

[a]Information collected at time of entry into the core trial for LTFU patients, or at time of entry into N01266 for direct enrollers.

[b]Four patients included in the total population could not be categorized into seizure categories.

[c]Medical Dictionary for Regulatory Activities version 18.1 preferred term (version 18.1 was the most recent version at the start of the trial, and terms may have changed over time).

[d]ASMs taken at any time before entry and discontinued before trial entry (into the previous BRV trial for LTFU patients and into N01266 for direct enrollers).

[e]ASMs taken concomitantly for ≥1 day during the trial period.

[f]Two patients from trial EP0065 (one in the subgroup of patients with focal seizures) did not take any concomitant ASMs during the trial.

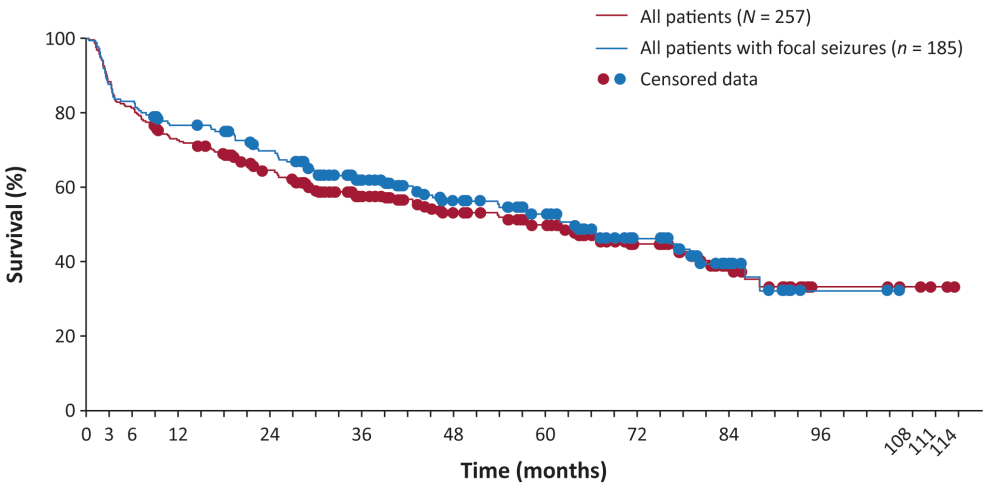

FIGURE 1 Kaplan–Meier estimated retention on brivaracetam (BRV; safety set), showing Kaplan–Meier estimates of the percentages of patients completing the specified durations of treatment. Patients who permanently discontinued from the trial were analyzed as events on the final day of treatment with BRV; patients who completed the trial were censored on the final day of treatment with BRV.

cohorts, whereas subsequent duration cohorts had fewer discontinuations (ranging from zero to three). Of those discontinuing within the first 3 months, four (11.1%), five (33.3%), 15 (10.6%), and seven (10.8%) patients were <2, ≥2 to <4, ≥4 to <12, and ≥12 to 17 years of age. TEAEs most commonly (at least two patients) leading to discontinuation were suicidal ideation (four patients) and pneumonia, simple partial seizures, status epilepticus, pregnancy, and circulatory collapse (two patients each). Seven patients died during the trial; none of these deaths was considered treatment-related by the investigator (Table S3). The incidences of overall, drug-related, and serious TEAEs in the focal seizure subgroup were comparable with those observed in the overall population.

No clinically relevant mean changes from baseline after BRV treatment were observed for hematology, clinical chemistry, endocrinology parameters, vital signs, or 12-lead electrocardiographic values.

3.3.2 | Behavioral and cognitive outcomes

Achenbach Child Behavior Checklist

Mean changes from baseline to last evaluation in raw scores were negative for all Achenbach Child Behavior Checklist (CBCL) subscales, reflecting stability or slight improvement (Table S4). The largest improvements in scores were observed for "aggressive behavior" and "anxious/depressed" in both age groups (1.5–5 years and 6–16 years), and "other problems" for patients 1.5–5 years of age.

Most patients had no shift in T-score category from baseline to last evaluation for each Achenbach CBCL subscale (between "normal" and "borderline or clinical range"; Figure 3A).

Behavior Rating Inventory of Executive Function (BRIEF)/BRIEF-Preschool version subscales

Mean changes from baseline to last evaluation in raw scores were negative for all Behavior Rating Inventory of Executive Function (BRIEF)/BRIEF-Preschool version (BRIEF-P) subscales, reflecting stability or slight improvement (Table S5). The largest improvements in scores were observed for "inhibit" and "working memory" in both age groups (<5 years and 5–16 years), and "emotional control" for patients <5 years of age.

Most patients had no shift in T-score category from baseline to last evaluation for each BRIEF-P/BRIEF subscale (between "normal" and "potential clinical significance"; Figure 3B).

3.4 | Efficacy

The efficacy variables below are presented by age (patients <2 years and ≥2 years of age) and by whether analyses were based on DRC or EEG (no EEG data were available for patients ≥2 years of age). Outcomes are also presented for the subgroup of patients with focal seizures.

3.4.1 | Change in seizure frequency

Median change in 28-day adjusted focal seizure frequency for patients <2 years and ≥2 years old (DRC data) and median change in average daily focal seizure frequency for

TABLE 2 Summary of TEAEs (safety set).

	Patients, *n* (%)		
	Patients with focal seizures, *n* = 185	**Patients with primary generalized seizures, *n* = 68**	**All patients, *N* = 257[a]**
Any TEAEs	175 (94.6)	61 (89.7)	240 (93.4)
Serious TEAEs	56 (30.3)	25 (36.8)	83 (32.3)
Severe TEAEs	29 (15.7)	13 (19.1)	44 (17.1)
Drug-related TEAEs	60 (32.4)	19 (27.9)	79 (30.7)
Drug-related serious TEAEs	2 (1.1)	3 (4.4)	5 (1.9)
TEAEs leading to discontinuation	16 (8.6)	15 (22.1)	31 (12.1)
Deaths	3 (1.6)	4 (5.9)	7 (2.7)
TEAEs[b] reported by ≥10% of all patients			
Nasopharyngitis	52 (28.1)	23 (33.8)	75 (29.2)
Pyrexia	42 (22.7)	21 (30.9)	65 (25.3)
Pharyngitis	46 (24.9)	13 (19.1)	59 (23.0)
Vomiting	37 (20.0)	17 (25.0)	55 (21.4)
Upper respiratory tract infection	28 (15.1)	17 (25.0)	46 (17.9)
Seizure	34 (18.4)	8 (11.8)	42 (16.3)
Headache	31 (16.8)	8 (11.8)	39 (15.2)
Diarrhea	26 (14.1)	10 (14.7)	36 (14.0)
Pharyngotonsillitis	31 (16.8)	5 (7.4)	36 (14.0)
Cough	27 (14.6)	5 (7.4)	32 (12.5)
Gastroenteritis	20 (10.8)	11 (16.2)	31 (12.1)
Decreased appetite	21 (11.4)	8 (11.8)	30 (11.7)
Influenza	21 (11.4)	8 (11.8)	29 (11.3)
Bronchitis	20 (10.8)	8 (11.8)	28 (10.9)
Somnolence	22 (11.9)	5 (7.4)	27 (10.5)
Serious TEAEs[b] reported by ≥3 patients			
Seizure	13 (7.0)	3 (4.4)	16 (6.2)
Status epilepticus	10 (5.4)	0	11 (4.3)
Pneumonia	5 (2.7)	2 (2.9)	8 (3.1)
Pyrexia	2 (1.1)	4 (5.9)	6 (2.3)
Epilepsy	4 (2.2)	1 (1.5)	5 (1.9)
Dehydration	2 (1.1)	3 (4.4)	5 (1.9)
Generalized tonic–clonic seizure	0	5 (7.4)	5 (1.9)
Somnolence	3 (1.6)	1 (1.5)	4 (1.6)
Gastroenteritis	2 (1.1)	2 (2.9)	4 (1.6)
Vomiting	1 (.5)	2 (2.9)	3 (1.2)

Abbreviation: TEAE, treatment-emergent adverse event.

[a]Four patients included in the total population could not be categorized into seizure categories.

[b]Medical Dictionary for Regulatory Activities version 18.1 preferred term (version 18.1 was the most recent version at the start of the trial, and terms may have changed over time).

patients <2 years of age (EEG data) are reported in Table 3, alongside results for the subgroups with focal seizures. The median decrease in 28-day adjusted frequency for all seizures in the overall and focal seizures subgroups,

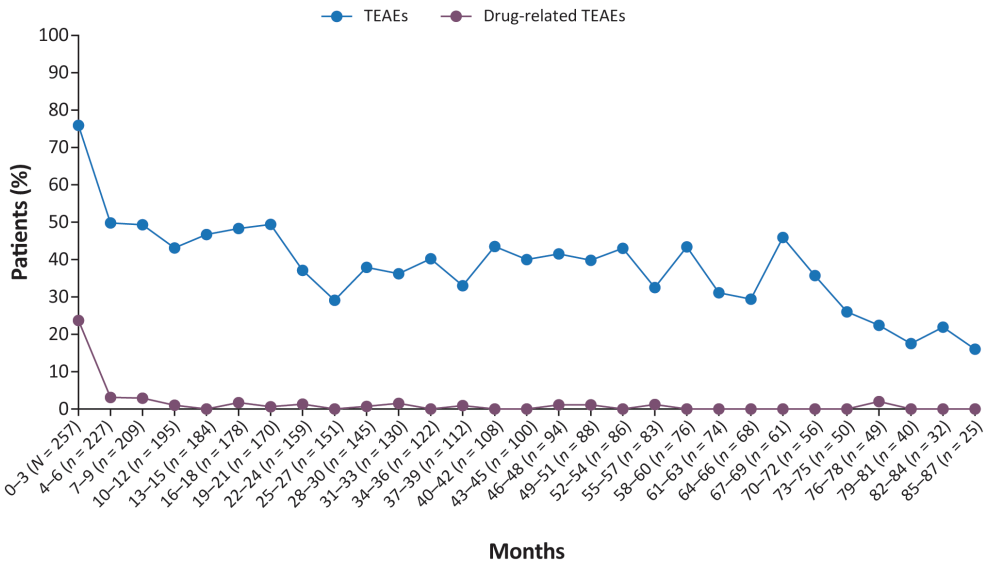

FIGURE 2 Incidence of treatment-emergent adverse events (TEAEs) and drug-related TEAEs (safety set). Figure presents the percentage of patients reporting TEAEs or drug-related TEAEs with a start date within the specified time interval. Patients were included in a 3-month interval if they were receiving brivaracetam at any time during that interval.

respectively, was 87.7% and 96.9% for patients <2 years of age and 60.3% and 63.0% for patients ≥2 years of age (DRC data; Table S6). The median decrease in average daily frequency for all seizures was 98.4% and 100%, respectively, in patients <2 years of age and the subgroup of patients <2 years of age with focal seizures (EEG data [recorded for at least 24 h];Table S6).

3.4.2 | Responder rates

In total, 15 of 22 (68.2%) and 81 of 159 (50.9%) patients <2 years and ≥2 years of age, respectively, had a ≥50% response in all seizures based on DRC data. In the subgroup with focal seizures, nine of 10 (90.0%) and 61 of 126 (48.4%) patients <2 years and ≥2 years of age had a ≥50% response in all seizures. Furthermore, 10 of 13 (76.9%) and 65 of 145 (44.8%) patients <2 years and ≥2 years of age had a ≥50% response in focal seizures based on DRC data. In the subgroup with focal seizures, nine of 10 (90.0%) and 60 of 126 (47.6%) patients <2 years and ≥2 years of age had a ≥50% response in focal seizures.

Based on EEG data, six of eight (75.0%) and five of six (83.3%) patients <2 years of age had a ≥50% response in all seizures and in focal seizures, respectively. In the subgroup with focal seizures, four of four (100%) and three of three (100%) patients had a ≥50% response in all seizures and in focal seizures.

Because patients with no seizures at baseline were counted as nonresponders despite having no room for improvement, analyses were also performed for the subset of patients with seizures at baseline; results are reported in Table S7.

3.4.3 | Seizure freedom

Based on DRC data, five of 36 (13.9%) and 18 of 218 (8.3%) patients <2 years and ≥2 years of age, respectively, were seizure-free for all seizures. For the subgroup with focal seizures, three of 18 (16.7%) and 16 of 164 (9.8%) patients <2 years and ≥2 years of age, respectively, were seizure-free for all seizures. Based on EEG data, 12 of 20 (60.0%) patients <2 years of age were seizure-free for all seizures; in the subgroup of patients <2 years of age with focal seizures, eight of nine (88.9%) patients were seizure-free for all seizures.

The median proportion of seizure-free days during the evaluation period for both age groups and the subgroups with focal seizures is reported in Table S8.

3.4.4 | Seizure worsening

Median percent worsening in average daily frequency of primary generalized seizures using EEG data, and in 28-day adjusted frequency for primary generalized seizures using DRC data for patients <2 years of age is reported in Table S9. For the overall study population, a total of 59 patients had seizure worsening (an increase in 28-day adjusted seizure frequency during the evaluation period vs. baseline); there was no association between seizure worsening and any particular seizure or syndrome type.

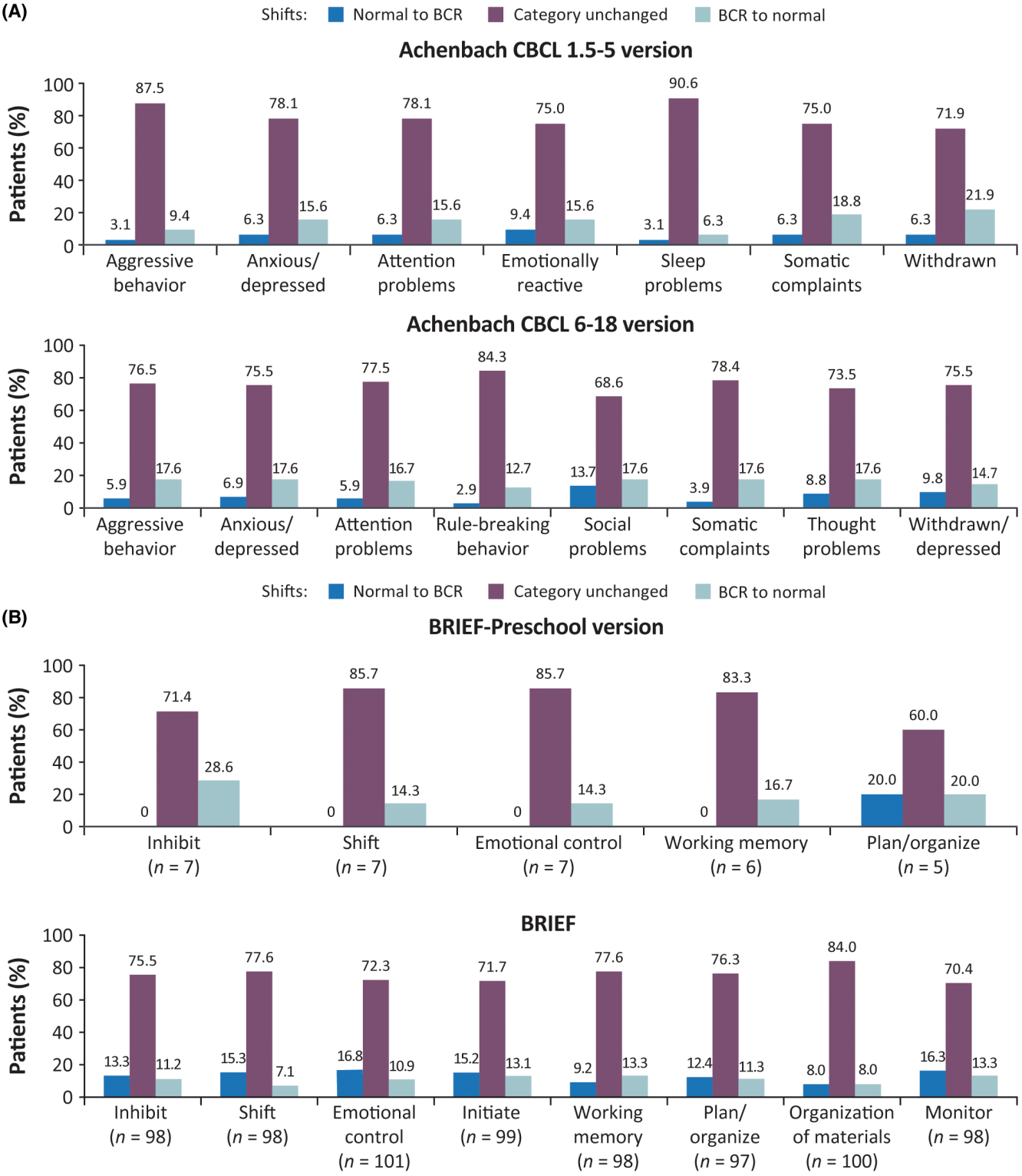

FIGURE 3 Shifts in T-score categories in (A) Achenbach Child Behavior Checklist (CBCL) subscales and (B) Behavior Rating Inventory of Executive Function (BRIEF) subscales from baseline to last evaluation in patients with focal seizures (safety set). Only patients providing data at both baseline and last evaluation were included. Baseline data were obtained from the core trial (N01263) screening visit. Median time to last CBCL evaluation: 9.5 months (patients 1.5–5 years of age, $n = 32$), 34.8 months (patients 6–16 years of age, $n = 102$). Median time to last BRIEF-Preschool version/BRIEF evaluation: 6.8 months (patients <5 years of age, $n = 7$), 40.7 months (patients 5–16 years of age, $n = 101$). BCR, borderline or clinical range.

TABLE 3 Change in 28-day adjusted frequency (DRC data) and average daily frequency (EEG data) of focal seizures from baseline to the end of the evaluation period (full analysis set).

		Absolute change		Percent change	
	Mean baseline ASF/ADF	*n*	Median (min, max)	*n*	Median (min, max)
DRC data					
Patients <2 years of age	181.39	22	16.37 (−19.8, 1248.1)	12	91.34 (−19.8, 100.0)
Patients <2 years of age with focal seizures	384.58	10	39.60 (32.7, 1248.1)	10	96.86 (45.4, 100.0)
Patients ≥2 years of age	63.71	167	3.93 (−7075.3, 721.9)	115	62.52 (−693.7, 100.0)
Patients ≥2 years of age with focal seizures	62.37	134	7.09 (−7075.3, 721.9)	105	62.92 (−693.7, 100.0)
EEG data					
Patients <2 years of age	3.64	14	0 (−1.0, 20.7)	5	98.41 (92.6, 100.0)
Patients <2 years of age with focal seizures	2.63	8	0 (0, 12.5)	3	100.00 (96.2, 100.0)

Note: Patients from core trials EP0065 and N01349 did not have appropriate baseline data and were excluded from these analyses. No data were available for patients ≥2 years of age based on EEG data. Change is defined as decrease in 28-day ASF compared with baseline or decrease in ADF compared with baseline. Because percent change cannot be calculated for patients with 0 seizures at baseline, the *n* values for absolute change and percent change may differ.

Abbreviations: ADF, average daily frequency; ASF, adjusted seizure frequency; DRC, daily record card; EEG, electroencephalographic; max, maximum; min, minimum.

4 | DISCUSSION

As expected in a trial spanning >10 years and following a population of children with epilepsy over a long exposure period (mean = 3.2 patient-years), the incidence of TEAEs was high (93.4%). Although the TEAE rate is somewhat higher than reported (84.5%) in a 5-year study in adults,[11] 5-year retention rates in these studies were similar (50.1% vs. 54.4% in adults), and the current study duration was considerably longer, increasing the likelihood for TEAEs. The incidences of TEAEs (93.4%) and TEAEs leading to discontinuation (12.1%) were highest during the first 3 months of BRV exposure and decreased thereafter. This decreased incidence with exposure duration may reflect adaptation to BRV.[12] The most common TEAEs (≥20% of patients) were nasopharyngitis, pyrexia, pharyngitis, and vomiting, and have been commonly reported in other pediatric trials of ASMs.[13–24] These TEAEs may partially reflect the higher incidence of infectious diseases, including the common cold, in a pediatric population.[25] Pooled safety and tolerability data from phase 2/3 trials and LTFU studies of adjunctive BRV 50–200 mg/day in adults with epilepsy reported the most common TEAEs (≥10%) were headache (20.9%), dizziness (17.5%), somnolence (15.2%), nasopharyngitis (13.2%), fatigue (11.3%), and convulsion (10.6%).[11] Headache, dizziness, somnolence, and fatigue occurred in the current study at lower incidences. The overall incidence of drug-related TEAEs (30.7%, most frequently somnolence, decreased appetite, aggression, and fatigue) was lower than the incidence reported in the adult population (54.2%).[11] Changes to patients' concomitant ASM regimens were allowed, which may have affected the incidence of TEAEs.

A previous report of BRV treatment in patients of age 1 month to <16 years showed a higher incidence of TEAEs in patients of age 1 month to <2 years versus ≥2 years but a lower incidence of drug-related TEAEs versus the older age group.[4] In the present study, the 1 month to <2 years group had the highest incidence of TEAEs (34/36, 94.4%), but the ≥2 to <4 years age group had the highest incidences of serious TEAEs (8/15, 53.3%), severe TEAEs (6/15, 40.0%), TEAEs leading to discontinuation (5/15, 33.3%), and drug-related TEAEs (7/15, 46.7%) versus other age groups, which likely reflect the disproportionate effect of a very small sample size of patients in the ≥2 to <4 years age group. Sudden unexpected death in epilepsy, which has an incidence of 1.2 per 1000 patient-years in the general epilepsy population,[26] did not occur during this study.

In clinical studies of BRV in adults, 13% and 8% of BRV-treated (50–200 mg/day) and placebo-treated patients experienced a psychiatric adverse reaction, and discontinuation due to psychiatric adverse events was low (1.7% and 1.3% of BRV- and placebo-treated patients, respectively).[3] In the present study, aggression was the most common behavioral TEAE ($n = 10$, 3.9% of patients) and suicidal ideation was the most common TEAE leading to discontinuation ($n = 4$). A systematic literature review reporting behavioral adverse events of BRV, LEV, perampanel, and topiramate in adults with epilepsy found that incidences of aggression were 2.5%,

2.6%, 4.4%, and .5%, respectively, whereas incidences of aggression leading to discontinuation were .8%, 2.4%, 9.2%, and 1.2%.[27]

BRV was generally efficacious over the long term as shown by improvements from baseline to the end of the evaluation period in seizure frequency, responder rates, and seizure freedom. Interpretation of some efficacy outcomes is limited by the small sample size, particularly in the group <2 years of age. EEG data were analyzed only for patients <2 years of age, and baseline EEG data were missing for many patients. There were several protocol amendments over the course of this long-term (>10 years) trial, some of which affected EEG assessments. When interpreting data during the evaluation period, the differences between DRC (continuous assessment) and EEG (spot check assessment, overrepresenting early trial periods) data should be considered. However, concordance between DRC and EEG data was observed for patients <2 years of age in average daily frequencies, suggesting that DRC could provide a reliable, more practical option than EEG when assessing improvement in average daily seizure frequency. Efficacy data were presented as medians, because the data distribution was skewed. Limitations can also be attributed to the open-label design, which subjected the study to possible selection bias, as patients who completed the core trials could enroll if they expected to show a reasonable benefit from long-term BRV administration. The very long study duration also may complicate interpretation, as treatments available and treatment guidelines changed over the course of the study.

Kaplan–Meier estimated treatment retention rates were consistent with reported BRV retention rates (79.8%, 1 year; 68.1%, 2 years; 54.4%, 5 years) from previous follow-up phase 2/3 studies in adults.[11] These rates were similar to 1-year but not necessarily 2-year retention rates, respectively, of other third-generation ASMs in adults with focal seizures—lacosamide (75.4%; 61.7%), perampanel (75.3%; 35.9%), and eslicarbazepine acetate (72.5%; 2-year data not available)[28]—but higher than overall 1-year retention rates for first- and second-generation ASMs (26.1% and 26.5%) in pediatric patients.[29] Pediatric retention rates (without addition of another ASM) at 1 year for first-generation ASMs were 31.4%, carbamazepine; 21.2%, phenobarbital; 17.2%, phenytoin; and 26.2%, valproate,[29] and somewhat higher for second-generation ASMs: 32.4%, lamotrigine; 30.2%, LEV; and 33.3%, oxcarbazepine.[29,30]

An additional study interest was to assess the cognitive and behavioral outcomes of long-term BRV treatment in pediatric patients. Studies have reported an increased risk for cognitive[31] and behavioral[32] problems in children with epilepsy, with many abnormalities present near the time of epilepsy diagnosis. Variable effects of ASMs on cognitive function in children have been reported.[33] In the current study, results from BRIEF-P/BRIEF assessments reflected no change or improvement with BRV treatment. A similar lack of negative cognitive sequelae was observed in a study in adults of the neurocognitive effects of BRV and LEV versus a drug known to adversely affect cognition (lorazepam), which reported that BRV and LEV had similar profiles as placebo.[34] Improvements in cognitive measures without changes in behavioral aspects (i.e., mood, aggression) were found with up to 25 weeks of adjunctive BRV treatment in a clinical setting.[35] Additionally, few changes on behavioral scales were observed in an interim report of BRV studies in children.[36] In the current study, changes in Achenbach CBCL subscales reflected stability or slight improvement in behavioral categories, with the largest decreases in scores observed for "aggressive behavior." These results further support studies demonstrating that BRV has minimal/positive effects on cognitive and behavioral outcomes, although further research in the pediatric population is warranted.

5 | CONCLUSIONS

In this LTFU trial, adjunctive BRV therapy was well tolerated in children, with a safety profile in patients <17 years of age at individualized doses up to 2.5 mg/kg bid (maximum of 200 mg/day) that was consistent with the known safety profile of BRV in adults. Safety and tolerability improved over time after the first 3 months of treatment. BRV treatment reduced seizure frequency and maintained high retention rates. Behavior and cognitive functioning scores were generally stable or slightly improved (including aggressive behavior and anxious/depressed subscales) in both age groups. These findings support the long-term use of adjunctive BRV to treat pediatric patients with epilepsy.

AUTHOR CONTRIBUTIONS

Kerstin Alexandra Klotz, Christoph Reichel, and Harriet Kang contributed to the acquisition of data. Lieven Lagae, Kerstin Alexandra Klotz, Florin Floricel, Christoph Reichel, Jan-Peer Elshoff, Sofia Fleyshman, and Harriet Kang analyzed and interpreted the data. András Fogarasi interpreted the data. All authors critically reviewed the manuscript and approved the final version for publication.

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CONFLICT OF INTEREST STATEMENT

L.L. has served as a paid consultant/speaker for Eisai, GW/Jazz Pharmaceuticals, LivaNova, Novartis, Shire, and UCB Pharma and holds a patent for fenfluramine for the treatment of Dravet syndrome and infantile epilepsies, which is assigned to his institution and licensed to Zogenix/UCB Pharma. K.A.K. (currently employed by University Hospital Bonn, Bonn, Germany) was an employee of the University of Freiburg at the time the research was conducted, and has received honoraria for lectures and advice from Eisai, GW Pharmaceuticals, Neuraxpharm, and Zogenix. H.K. has served as a paid consultant for UCB Pharma. A.F. reports no conflicts of interest. F.F., C.R., and J.-P.E. are employees of UCB Pharma, and S.F. was an employee of UCB Pharma at the time the research was conducted.

ORCID

Lieven Lagae https://orcid.org/0000-0002-7118-0139
Kerstin Alexandra Klotz https://orcid.org/0000-0002-1601-5384
András Fogarasi https://orcid.org/0000-0001-8397-8706
Christoph Reichel https://orcid.org/0009-0001-8145-2767
Harriet Kang https://orcid.org/0009-0009-9717-2530

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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