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ORIGINAL ARTICLE

Efficacy of naloxone in reducing hypoxemia and duration of immobility following focal to bilateral tonic–clonic seizures

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Abstract

Objective: Evaluating the efficacy of an opioid antagonist, naloxone (NLX), to reduce the severity of post-ictal hypoxemia and immobility after focal to bilateral tonic–clonic seizures (FBTCS).

Methods: ENALEPSY is a double-blind placebo (PCB)-controlled trial conducted in patients with focal epilepsy undergoing long-term video-EEG monitoring (LTM). Patients with a FBTCS during LTM were randomized 1:1 to receive intravenous NLX or PCB within the 2 min following the end of FBTCS. After database lock, a discrepancy between the allocated arm and the received treatment was detected, resulting in a 4:1 NLX:PCB ratio. To further explore the efficacy of NLX, we used historical control (HC) data collected in patients included in the REPO$_2$MSE study whose characteristics matched those of patients randomized in ENALEPSY. The efficacy of NLX was then assessed versus PCB and versus HC. The primary endpoint was the delay between the end of the seizure and recovery of $SpO_2 \geq 90\%$. Secondary efficacy outcomes included desaturation nadir and duration of the post-ictal immobility.

Results: 33 patients contributed to the NLX group, 7 to the PCB group, and 43 to the HC group. The proportion of FBTCS type 1 or 3 was 84% in NLX, 100% in PCB, and 84% in HC. NLX did not improve the delay of recovery of $SpO_2 \geq 90\%$ or the desaturation nadir. By contrast, the duration of the post-ictal immobility

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differed across groups. The time to mobility recovery within the first 5 min post-ictal was very similar in the PCB (200.3 ± 215.8 s) and HC (194.4 ± 192.0 s) groups, and significantly shorter in the NLX group (128.9 ± 151.1 s) when compared to HC (Hazard Ratio, 1.84; 95% CI, 1.11–3.05; $p = 0.021$).

Significance: NLX did not prevent post-ictal respiratory dysfunction but might reduce the duration of post-ictal immobility. Confirmation of this effect and its impact on SUDEP risk will require additional studies.

Plain Language Summary: Release of endogenous opioids might participate in the severity of post-ictal hypoxemia and immobility after focal to bilateral tonic–clonic seizures (FBTCS). We conducted a multicenter double-blind randomized placebo-controlled trial evaluating the efficacy of an opioid antagonist, naloxone (NLX), administered within 2 min following the end of FBTCS. The efficacy of NLX was further explored with a comparison with historical control. NLX did not improve the delay of recovery or the severity of post-ictal hypoxemia. Post-ictal immobility was significantly shorter in the NLX group when compared to historical control. The impact of these results on SUDEP prevention will require additional studies.

KEYWORDS

epilepsy, generalized convulsive seizures, naloxone, post-ictal EEG hypoxemia, post-ictal immobility, SUDEP

1 | INTRODUCTION

Currently, there is no effective treatment to prevent sudden unexpected death in epilepsy (SUDEP),[1] aside from optimizing antiseizure medications (ASM),[1,2] epilepsy surgery, or vagal nerve stimulation.[3] The exact mechanisms leading to SUDEP remain unknown,[4] but central respiratory dysfunction is believed to play an important role.[2,4] Indeed, in most observed SUDEP cases, apnea will first occur within 1–3 min after the termination of a generalized tonic–clonic seizures,[5] followed by a terminal respiratory then cardiac arrest.[5]

Several factors might contribute to post-ictal respiratory dysfunction, such as a brainstem spreading depolarization, but also possibly a release of endogenous opioid peptides.[6] Indeed, both animal and human studies have shown that such peptides are released during seizures, possibly to help abort seizures.[7–9] Yet, given the rich concentration of opioid receptors in brainstem respiratory centers,[10] an excessive release of endogenous opioid peptides could also promote post-ictal respiratory dysfunction as observed in opioid overdose.[11] If this was the case, opioid antagonists could offer a potential strategy to prevent SUDEP.

In order to test this hypothesis, we performed a proof-of-concept study that tested the acute effect of intravenous naloxone on post-ictal respiratory dysfunction and hypoxemia in patients with refractory focal epilepsy, when administered immediately after a focal to bilateral tonic–clonic seizures (FBTCS) during video-EEG monitoring.

Key points

- The ENALEPSY trial evaluated the efficacy of intravenous naloxone to reduce the severity of post-ictal complications after focal to bilateral tonic–clonic seizures.
- Naloxone did not improve the delay of recovery of $SpO_2 \geq 90\%$ or the desaturation nadir.
- The time to mobility recovery was significantly shorter in the NLX group when compared to historical control.
- Impact of these results on SUDEP prevention will require additional studies.

2 | METHODS

2.1 | Study design

The ENALEPSY study (NCT02332447) is a multicenter, double-blind, randomized placebo-controlled trial

conducted in patients with focal epilepsy undergoing long-term video-EEG monitoring (LTM) in 15 epilepsy monitoring units in France (see Appendix S1 for the list of investigators and Appendix S2 for CONSORT checklist).[12] Because patients who will develop a FBTCS during the LTM cannot be individualized a priori, we used a two-step design: All eligible patients were included in the study at the beginning of the LTM, equipped with a peripheral venous catheter and continuously monitored. Then, only those with a FBTCS during the LTM were randomized 1:1 to receive intravenous naloxone (NLX) or placebo (PCB) within the 2 min following the end of a FBTCS.

However, after completion of the planned recruitment, database lock and unblinding, a discrepancy between the allocated arm defined by randomization and the treatment actually received was detected in 20 of the 49 randomized patients. Specifically, 17 patients randomized to the PCB group actually received NLX, whereas 3 randomized to the NLX group received PCB. Overall, while the randomization should have resulted in NLX administration in 24 patients and PCB in 25, 38 patients were eventually treated with NLX and 11 with PCB. The internal audit conducted by the coordination team (SR and ML), the biostatistics team (CM and PRoy) and the representatives of the study sponsor (Hospices Civils de Lyon) revealed that this major protocol violation had resulted from a mismanagement of the treatment batches preparation by the pharmaceutical department of Hospices Civils de Lyon, which had introduced a shift in the randomization. Given that the randomization was stratified by center and balanced by block (see below), this offset ultimately led to decorrelation with the randomization list and 4:1 NLX:PCB ratio.

In this context, and prior to any statistical analysis of the data, the study steering committee (SR, PR, CM, PRoy, and PI of each participating center) concluded that the number of subjects who received placebo was too low to offer an appropriate statistical power, and that the efficacy of NLX shall be further explored through a comparison with a historical control (HC) group which did not receive treatment, using the data collected in patients included in the REPO$_2$MSE study and previously reported.[13] The rationale for this approach was the similarities of patients' characteristics between REPO$_2$MSE and ENALEPSY studies, whose inclusion criteria and recruitment modalities were mostly similar. The original statistical plan was revised to integrate this combined analysis but without any modification of the primary or secondary endpoints which were analyzed in the HC group using the same approach as that predefined for the ENALEPSY trial. Overall, the data presented in the current manuscript are therefore the combination of the ENALEPSY trial (NLX vs. PCB) and of an exploratory complementary analysis comparing NLX with a group of patients included in the REPOMSE study who had received no pharmacological intervention.

2.2 | Standard protocol approvals, registrations, and patient consents

Both ENALEPSY and REPOMSE were approved by the ethics committee (CPP Sud Est II n°2014–853 and CPP Sud Est II n°2010-006-AM6) and the competent authority (ANSM n° 141241A-31 and ANSM B100108-40), and all patients gave written informed consent. ENALEPSY was registered with ClinicalTrials.gov (NCT02332447) on 2015-01-05. The most recent Protocol and Statistical Analysis Plans are available in Appendices S3 and S4, respectively.

2.3 | Design of the ENALEPSY trial

2.3.1 | Inclusion criteria

The first patient was enrolled on June 26, 2015, and the recruitment was completed on July 08, 2020, using the following inclusion criteria: (i) Adult patient (≥18 years) suffering from drug-resistant focal epilepsy according to ILAE definitions and (ii) undergoing long-term video-EEG or video-stereo-electroencephalography (SEEG). Patients with a history of severe heart disease or addiction to opioids, heroin, or any similar substance were excluded. Temporary administration of an immediate-release opioid agonist to manage acute pain resulted in temporary ineligibility for randomization during the 12 h following the last opioid administration, whereas chronic opioid treatment was an exclusion criterion.

2.3.2 | Study drugs

NLX consisted of dihydrous hydrochloride naloxone (0.4 mg/mL) packaged in 1 mL vials. The dose of 0.4 mg corresponds to the recommended starting dose for the treatment of acute opioid overdose where the delay between intravenous injection and awakening ranges from 30 s to 2 min.[11] PCB was isotonic sodium chloride prepared in 1 mL vials.

2.3.3 | Blinding and randomization

Randomization was centralized, stratified by center, and balanced by block of patients to ensure a 1:1 ratio between NLX and PCB. The pharmaceutical department of Hospices Civils de Lyon prepared both NLX and PCB in indistinguishable vials and numbered batches

according to the randomization list. The batches were then distributed to each participating center and stored in their respective pharmaceutical department. However, because the treatment needed to be immediately available upon the occurrence of a FBTCS, one or more batches were permanently stored in the epilepsy monitoring unit (EMU). In case of the occurrence of a FBTCS, the supervising nurse or physician took the first available batch in respect to batch numbers (i.e., batch 1 before batch 2, before batch 3).

2.3.4 | Primary endpoint

The original primary endpoint was the proportion of patients with a pulse oximetry (SpO_2) < 90% during at least 5 s between 30 s and 5 min after the onset of intravenous injection of the study drug in the immediate aftermath of a FBTCS.[12] However, in 10/2019, while the recruitment was still ongoing and before any analysis of the available data, the primary outcome was modified to the time to recovery of $SpO_2 \geq 90\%$ after the end of the FBTCS. This amendment of the original statistical plan, validated by the study steering committee, the independent Data and Safety Monitoring Board, and the ethics committee, was justified by published data which showed that transient hypoxemia was much more frequent than previously reported,[14] observed in up to 86% of FBTCS.[13]

2.3.5 | Secondary endpoints

The main other efficacy outcomes were: (i) SpO_2 nadir; (ii) number of patients with $SpO_2 < 90\%$ 30 s or 120 s after the end of the FBTCS; (iii) number of patients with post-ictal central apnea (PCCA); (iv) number of patients in whom O_2 administration was performed; (v) number of patients in whom cardiorespiratory rescue procedure was performed; (vi) time from end of the seizure to first voluntary movement; (vii) time from end of the seizure to patient's ability to handshake; (viii) occurrence and duration of Post-ictal Generalized EEG Suppression (PGES), as defined previously.[15]

The main safety outcomes were: (i) number of patients who have a second FBTCS within 120 min after the intravenous injection; (ii) report of adverse events observed throughout the study.

2.3.6 | Study conduct

All included patients benefited from continuous monitoring of SpO_2 and were equipped with a peripheral venous catheter throughout the video-EEG/SEEG monitoring.

All participating centers had long experience in presurgical evaluation. Patients were thus continuously supervised by one to two nurses specialized in long-term EEG/SEEG monitoring during daytime in all 15 participating centers. Six of the centers (40%) had the same organization over 24 h, whereas in the others, the organization of nurse supervision during nighttime did not ensure the immediate intervention required by the protocol. In the absence of immediate nurse intervention, FBTCS did not result in randomization, and the patient remained eligible for randomization if another FBTCS later occurred during monitoring. The management of the presurgical evaluation, including antiseizure drugs withdrawal, was not modified by participation in the study.

Upon the occurrence of a FBTCS, treatment (NLX or PCB) was administered by the supervising nurse or physician, using direct intravenous injection within the 2 min following the end of the FBTCS. Importantly, treatment was never administered before the clinical cessation of the clonic jerks. In the immediate post-ictal period, SpO_2, heart, and respiratory rates were carefully monitored by the supervising nurse or physician. Considering the objectives of the study, oxygen administration using a high concentration breathing mask (15 L/min) was only recommended in patients who showed $SpO_2 < 85\%$ for more than 2 min after the injection of the study drug. Investigators were also asked to specifically assess the ability to meet one single verbal command (handshake) in order to evaluate recovery of consciousness.

All digital data (video, EEG, SpO_2) were centralized at Hospices Civils de Lyon.

2.3.7 | Analysis of seizure-related clinical data

The coordinator investigator (SR) reviewed all raw video-EEG data to: (i) confirm the times of seizure onset, onset of FBTCS, end of FBTCS, and treatment injection; (ii) analyze the FBTCS semiology using the classification previously published[15]; (iii) determine the end of post-ictal immobility, defined as the first spontaneous movement observed on the video. Isolated myoclonic jerks that might occur after the end of a FBTCS or modifications of the patient's position by the nurses (i.e., lateral safety position) while the patient was still in post-ictal coma were not considered spontaneous movements. Administration of oxygen was considered early when performed during the seizure or within the first 5 s after seizure termination.[15]

2.3.8 | Analysis of SpO_2 data

The evolution of the SpO_2 during the 3 min preceding seizure onset, the seizure itself, and the 10 min following the

end of the FBTCS was assessed blindly to other data both by the coordinating investigator (SR) and the statisticians (FC and PRo) using a complementary approach. In both cases, post-ictal hypoxemia was defined as $SpO_2 < 90\%$ during at least 5 s. As previously reported,[13] the SpO_2 signal synchronized with the video was analyzed to determine the period(s) during which SpO_2 was not informative because of the patient's movements or because the oximetry sensor was not appropriately positioned on the patient's finger. In parallel, the statistician team extracted the SpO_2 signal from the video-EEG files and applied an objective analysis of SpO_2 values using a specific in-house detection algorithm that allowed automatic detection and quantification of SpO_2 variations. Data collected with the two approaches were then combined. When the duration of the post-ictal hypoxemia differed by ±5 s between the two approaches, the value identified with the automatic detection was preferred. In case of larger differences, data were reanalyzed by both the coordinating investigator and the statisticians (CM and FC) to reach a consensus. In all analyses, the SpO_2 nadir was the lowest available value of the SpO_2.

2.3.9 | Analysis of post-ictal central apnea

Previous studies assessed post-ictal apnea by combination of visually inspected thoracoabdominal excursions and EEG breathing artifact,[5] completed in some of them by inductance plethysmography.[16,17] Here, in the absence of inductance plethysmography, the presence of post-ictal apnea was searched independently by two investigators (VR and SR) using EEG breathing artifact and visual inspection of thoracoabdominal excursions on the video from the end of the clonic phase up to the patient's first voluntary movements.[16] In case of disagreement, the investigators discussed to reach consensus. Post-ictal central apnea (PCCA) was defined as a lack of breath for a period >5 s. PCCA was considered immediate if no breath was taken during the 5 s following seizure end.[17]

2.4 | Historical control (HC)

2.4.1 | Patients' and FBTCS selection

For HC, we used the data from patients who participated in the $REPO_2MSE$ study and whose SpO_2 data following FBTCS were previously published.[13] All centers involved in the ENALEPSY trial had participated in the $REPO_2MSE$ study. According to their comparable epilepsy-related inclusion criteria, virtually all patients included in the $REPO_2MSE$ study would have been eligible for inclusion in the ENALEPSY study. It should be noted, however, not that a history of severe heart disease or addiction to opioids, heroin, or any similar substance was not exclusion criteria in the REPOMSE study. However, none of the patients from REPOMSE who contributed to the HC group suffered from those diseases. Similarly, none of them received chronic opioid treatment. Temporary administration of an immediate-release opioid agonist was not monitored in REPOMSE. However, this antalgic drug is typically used in the EMU in the context of SEEG-related pain, especially during the first days after electrode implantation. Because the HC from the REPOMSE study did not include patients undergoing SEEG, the risk of undocumented temporary administration of immediate-release opioid agonist in REPOMSE patients contributing to the HC was low.

We then reviewed the video of the 107 available FBCTS to determine those which would have fulfilled criteria for randomization in the ENALEPSY trial, with a specific attention to the lack of early administration of oxygen and quality of video to assess the duration of post-ictal immobility and coma (Figure 1). Patients with early administration of oxygen (during the seizure or within the first 5 s after seizure termination) or whose duration of post-ictal immobility could not be assessed were thus excluded from the HC. When several FBCTS from the same patient fulfilled these criteria, only the first FBCTS recorded during the hospital stay was included in the HC group. Data extraction for HC was performed using the same methodology as that described above for patients recruited in the ENALEPSY trial.

2.5 | Statistical analyses

2.5.1 | Sample size of the ENALEPSY trial

We based our hypothesis on our previously reported SpO_2 findings following FBTCS with and without O_2 therapy, showing that the proportion of patients who recovered $SpO_2 \geq 90\%$ at 30, 60, and 120 s post-FBTCS was 17%, 52%, and 88% without O_2 administration, and 48%, 79%, and 92% with O_2 administration.[13] We hypothesized that the size of the NLX effect to reduce the recovery time to $SpO_2 > 90\%$ would be similar to that of oxygen therapy, with a hazard ratio of 2.4. Accordingly, using a log-rank test with a two-sided alternative hypothesis (significance level of 5%), 40 events needed to be observed to reject the null hypothesis in 80% of cases. Assuming that about 10% of patients with drug-resistant focal epilepsy who undergo long-term video-EEG monitoring develop at least one FBTCS,[13] inclusion of a total of 554 patients had been planned.

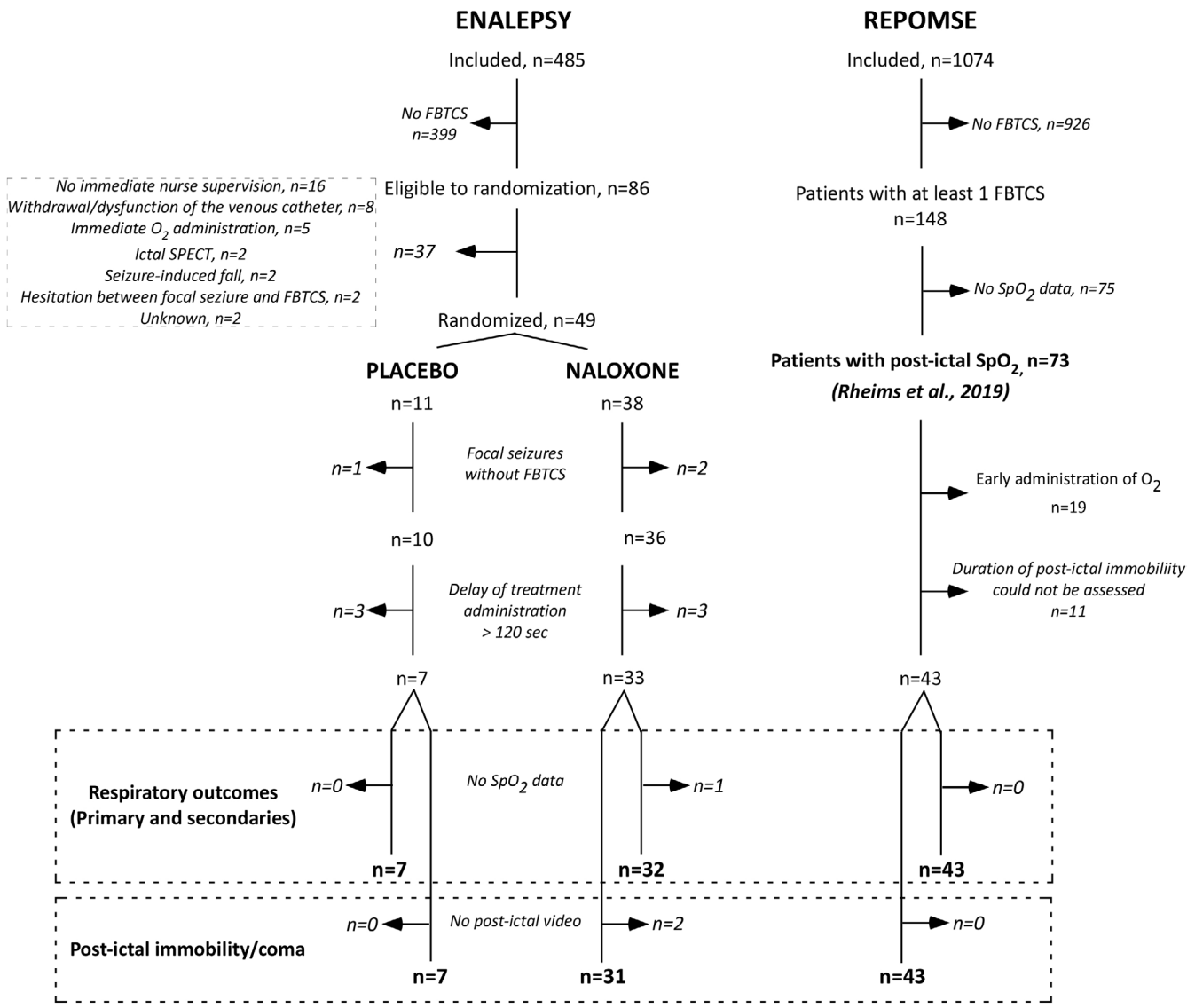

FIGURE 1 Flowchart of the study.

2.5.2 | Populations

Because of the major protocol violation related to the mismanagement from the pharmaceutical department, intention-to-treat analysis could not be performed. All efficacy analyses were therefore performed in the per-protocol population (ENALEPSY PP) defined as all randomized patients with FBTCS in whom the study drug was administered within the 2 min following the end of the FBTCS. The safety population corresponded to all randomized patients.

2.5.3 | Primary endpoint

The Kaplan–Meier estimator was used to estimate the evolution of the probability of recovery of $SpO_2 \geq 90\%$ between the end of the FBTCS and 5 min post-ictal. An accelerated failure time model considering a Weibull distribution was used to estimate the hazard ratio (HR) of NLX vs. PCB and NLX vs. HC effects.[18]

2.5.4 | Secondary endpoints

SpO_2 nadir and proportion of FBTCS associated with PCCA or PGES were compared between groups using Mann–Whitney or Fisher test. Time to first voluntary movement and to the patient's ability to handshake was analyzed from the end of the seizure to 5 min post-ictal with the same survival analysis as for the primary endpoint.

In all analyses, treatment effect estimates are presented with 95% confidence intervals (CIs). Two-sided p values <0.05 were considered significant. All analyses were performed using SAS®version 9.4 or further (SAS Institute

Inc., Cary, NC, USA) or R version 4.0.2 or further (R Core Team, 2012).

3 | RESULTS

3.1 | Populations

3.1.1 | ENALEPSY trial

The flowchart of the study is detailed in Figure 1. Among the 485 patients included in ENALEPSY, 86 had at least one FBTCS and were eligible for randomization. However, mainly because of a lack of immediate nurse supervision or a lack of available catheter, only 49 patients were eventually randomized. No difference was observed between eligible patients who were eventually randomized and those who were not (Table S1). Among the 49 randomized patients, 11 received PCB and 38 NLX. After exclusion of patients with protocol violations (i.e., delay of treatment administration >120 s), 40 patients (7 PCB and 33 NLX) were included in the per-protocol population (ENALEPSY PP).

3.1.2 | Historical control

After exclusion of patients who had received oxygen during all their FBTCS ($n = 19$) and those in whom post-ictal coma could not be assessed ($n = 11$), 43 of the 73 patients from the REPO$_2$MSE cohort[13] were included in the HC group (Figure 1).

3.2 | Patients' and seizures' characteristics

The detailed characteristics of the patients and the FBTCS are presented in Tables 1 and 2. Patients' characteristics were comparable between the ENALEPSY PP study and the HC group. The two exceptions were the FBTCS frequency over the last 12 months, with a greater proportion of patients with ≥1 FBTCS/month in ENALEPSY PP than in the HC group. The type of FBTCS was also comparable across groups, with 51.2%, 16.3%, and 32.6% of FBTCS type 1, 2, and 3, respectively, in the HC group and 57.9%, 13.2%, and 28.9% in ENALEPSY PP. Immediate nurse intervention during the initial phase of the seizure, before the onset of the bilateral tonic–clonic phase, and maintained in the post-ictal period was observed in all FBTCS in ENALEPSY PP and in all but three (93%) in the HC group. For these later, nurse intervention during the FBTCS was not maintained in the post-ictal period in one, whereas there was no intervention in the two others. In a patient, A total of 22 FBTCS (51.2%) occurred during sleep in the HC group, versus 11 (27.5%) in ENALEPSY PP. A transient loss of SpO_2 signal was observed in 26 (66%) FBTCS in ENALEPSY PP and in 28 (65%) in the HC group, with a mean duration of the period without informative SpO_2 ± SD of 50.5 ± 48.3 and 18.1 ± 21.2 s, respectively.

The mean ± SD time from termination of FBTCS to study drug or placebo injection was 44.2 ± 32.2 s (range 0–118), without difference between the NLX group (44.9 ± 32.0 s) and the PCB group (44.4 ± 35.6 s). However, SpO_2 was already ≥90% in 9 patients when the treatment was administered, including 8 NLX (24%) and 1 PCB (14%). Due to the FBTCS usual management protocol in one of the centers, a patient in NLX systematically received intravenous midazolam in the immediate post-FBTCS period.

3.3 | Efficacy of NLX

3.3.1 | Respiratory endpoints

The mean time ± SD from the termination of FBTCS to recovery of SpO_2 ≥ 90% was 85.5 ± 41.7 s with NLX, 93.9 ± 57.7 s with PCB, and 70.2 ± 54.1 s in the HC group (Table 3). Administration of NLX did not accelerate recovery of SpO_2 ≥ 90% in comparison with PCB (HR (95% CI): 1.33 (0.59–3.01), $p = 0.497$) or with HC (HR (95% CI): 0.88 (0.55–1.41), $p = 0.607$, Figure 2). The results remained similar when time from treatment administration to recovery of SpO_2 ≥ 90% was considered (71.1 ± 33.2 s with NLX and 68.5 ± 42.0 s with PCB). Similarly, the SpO_2 nadir was similar in NLX, PCB, and HC groups (Table 3). Occurrence of PCCA was similar across groups (29% in NLX, 14.3% in PCB and 30.2% in HC; Table 3), including when only delayed PCCA were considered (12.9% in NLX, 14.3% in PCB and 16.3.2% in HC). Similarly, the mean ± SD duration of PCCA did not differ across groups (Table 3). All PCCA were observed in patients in whom SpO_2 was <90% since the end of the FBTCS. No cardiorespiratory rescue procedure was required in any of the randomized patients.

3.3.2 | Other secondary endpoints

The mean time ± SD from the termination of FBTCS to the first voluntary movement was similar in the PCB (200.3 ± 215.8 s) and HC groups (194.4 ± 192 s) but lower in the NLX group (128.9 ± 151.1 s). Accordingly, an

TABLE 1 Characteristics of patients included in ENALEPSY PP and in the HC group.

	ENALEPSY study (PP population)			REPOMSE study (HC group) (*N* = 43)
	All patients (*n* = 40)	Placebo (*N* = 7)	Naloxone (*N* = 33)	
Age, mean (SD)	35.6 (11.6)	34.71 (18.4)	35.76 (9.95)	33.98 (10)
Sex, *n* (%)				
Female	18 (45.0%)	4 (57.1%)	14 (42.4%)	20 (46.5%)
Epilepsy duration, years, mean (SD)	16.1 (9.5)	16.71 (14.27)	15.94 (8.42)	16.82 (10.16)
Seizure frequency, *n* (%)				
≥1/day	5 (12.5%)	2 (33.3%)	3 (9.1%)	4 (9.3%)
<1/day but ≥1/week	15 (37.5%)	2 (33.3%)	13 (39.4%)	13 (30.2%)
<1/week	20 (50%)	3 (42.8%)	17 (51.5%)	25 (58.1%)
Unknown	0 (0%)	0 (0%)	0 (0%)	1 (2.3%)
FBTCS frequency, *n* (%)				
≥1/month	15 (37.5%)	1 (14.3%)	14 (42.4%)	5 (11.6%)
<1/month but ≥1/year	6 (15%)	2 (33.3%)	4 (12.1%)	15 (34.9%)
<1/year	15 (37.5%)	4 (57.1%)	11 (33.3%)	19 (44.2%)
None	0 (0%)	0 (0%)	0 (0%)	0 (%)
Unknown	4 (10%)	0 (0%)	4 (12.1%)	4 (9.3%)
Past epilepsy surgery, *n* (%)	5 (12.5%)	0 (0%)	5 (15.2%)	3 (7%)
Sleep apnea syndrome, *n* (%)	1 (2.5%)	0 (0%)	1 (3.0%)	1 (2.3%)
Treatment by VNS, *n* (%)	1 (2.5%)	0 (0%)	1 (3.0%)	3 (7%)
Number of ASM, *n* (%)				
0	0 (0%)	0 (0%)	0 (0%)	2 (4.7%)
1	7 (21.9%)	2 (33.3%)	5 (19.2%)	5 (11.6%)
2	15 (46.9%)	2 (33.3%)	13 (50.0%)	22 (51.2%)
≥3	10 (31.2%)	2 (33.3%)	8 (30.8%)	14 (32.6%)
Treatment with SSRI, *n* (%)	0 (0%)	0 (0%)	0 (0%)	3 (7.1%)
Seizure focus, *n* (%)				
Temporal	23 (57.5%)	6 (85.7%)	17 (51.5%)	21 (48.9%)
Extra-temporal	16 (40%)	1 (14.3%)	15 (45.5%)	19 (44.2%)
Unknown	1 (2.5%)	0 (0%)	1 (3.0%)	3 (6.9%)

Abbreviations: ASM, antiseizure medication; FBTCS, focal to bilateral tonic–clonic seizure; SSRI, selective serotonin recapture inhibitor; VNS, vagal nerve stimulation.

acceleration of the time of occurrence of the first voluntary movement was observed with NLX (Figure 3), which was significant when compared with no treatment (HR (95% CI); 1.84 (1.11–3.05), $p = 0.021$). By contrast, the duration of post-ictal coma did not differ across groups (Table 3). PGES could be assessed in 6 PCB, 25 NLX, while not available in nine patients, seven of whom underwent SEEG and two whose scalp EEG electrodes became detached during the FBTCS. Neither the rate of occurrence nor the mean duration of PGES differed between groups (Table 3).

3.4 | Safety of NLX

No serious adverse event was reported in the ENALEPSY study. A FBTCS recurrence within the 2h following treatment administration was reported in four patients who received NLX (12.1%), including one in whom recurrence was treated with intravenous clonazepam, one patient who received PCB (14.3%), and five patients from the HC group (11.6%). Pain following the post-ictal coma did not differ across groups. The mean ± SD score of the visual analog scale

TABLE 2 Characteristics of FBTCS.

	ENALEPSY study (PP population)			REPOMSE study (HC group) (*N* = 43)
	All patients (*n* = 40)	Placebo (*N* = 7)	Naloxone (*N* = 33)	
Recording modalities				
SEEG	7 (17.5%)	1 (14.3%)	6 (18.8%)	0 (0%)
Seizure type[a]				
I	22 (57.9%)	2 (33.3%)	20 (62.5%)	22 (51.2%)
II	5 (13.2%)	0 (0%)	5 (15.6%)	7 (16.3%)
III	11 (28.9%)	4 (66.7%)	7 (21.9%)	14 (32.6%)
Duration of tonic phase, s, mean (SD)[a]	13.2 (7.6)	17 (8.02)	12.5 (7.47)	12.3 (7.28)
Duration of tonic–clonic phase, s, mean (SD)[a]	55.5 (13.4)	64.33 (14.31)	53.84 (12.8)	51.74 (12.39)
State of wakefulness				
Asleep	11 (27.5%)	2 (28.6%)	9 (27.3%)	22 (51.2%)
Administration of O_2				
Early administration	2 (5%)	0 (0%)	2 (6.1%)	0 (0%)
Delayed administration	1 (2.5%)	0 (0%)	1 (3.0%)	5 (11.6%)
Nurse intervention during seizure	40 (100%)	7 (100%)	33 (100%)	40 (93%)

Abbreviation: FBTCS, focal to bilateral tonic–clonic seizure.

[a]Data available in 32 patients in the naloxone group and 6 in PCB group.

was 1.89 ± 2.95 with NLX (*n* = 27) and 2.83 ± 3.19 with PCB (*n* = 6).

4 | DISCUSSION

Results from the ENALEPY trial and comparison with historical controls suggest that post-ictal administration of NLX does not decrease the severity of post-FBTCS respiratory dysfunction but might be associated with a reduction in the duration of post-ictal immobility.

These conclusions must be tempered by the methodological limitations of the study. Due to an error in the preparation of batches by the pharmacy resulting in a major imbalance in treatment allocation, the ENALEPSY trial could no longer be analyzed on an intention-to-treat basis. Additionally, the sample size of the group that eventually received PCB was too small to ensure sufficient statistical power. For these reasons, we changed the design of this double-blind RCT into an exploratory study, whereby patients who received NLX were compared both with PCB and with an untreated group of patients whose data were collected in the previously reported REPO$_2$MSE cohort.[13] Importantly, patients' and FBTCS characteristics were similar between the ENALEPSY population and the control HC group, whose data were collected from the same EMUs. Accordingly, the primary and secondary endpoints also proved similar between the ENALEPSY PCB group and the HC group, particularly the duration of post-ictal immobility.

Post-ictal respiratory dysfunction was primarily evaluated by monitoring the occurrence of peri-ictal hypoxemia using SpO_2 and video analysis of thoracoabdominal excursions to detect post-ictal central apneas. Although this video-based approach was used previously,[5,16] its precision remains lower than inductance plethysmography. However, the frequency of PCCA in our study (14.3% in PCB, in 29% in NLX and 30% in HC) was similar to the one reported in previous studies that used full respiratory monitoring (i.e., 22% in[17]). We did not observe a period of $SpO_2 < 90\%$ during this 3-min duration pre-seizure baseline. However, because we did not have access to all the video-EEG and SpO_2 data recorded over 24 h, we could not formally exclude that some patients might have experienced periods of $SpO_2 < 90\%$ in absence of seizure, especially during sleep. Furthermore, we did not determine whether some patients had sleep-related apneas and, if so, compared their profile with that of PCCA. We did not have access to the exact ASM regimen on the day of randomization, and consequently, we could not exclude that ASM withdrawal might affect the study outcomes.

The lack of observable impact of NLX on hypoxemia could be due to a too low dose of NLX. In case of morphine overdose, the initial NLX dose is 0.4 mg, as in our study, but dose escalation up to 15 mg can then be performed based on clinical response, with NLX efficacy defined by increase in respiratory rate.[11] A higher dose of NLX might thus have shown efficacy on our primary endpoint. Yet, the effect of NLX on the duration of post-ictal

TABLE 3 Primary and secondary endpoints.

	ENALEPSY study (PP population)					Historical control (REPOMSE)			
			NLX vs. HC (Weibull AFT model estimates)		NLX vs. PCB (Mann–Whitney or Fischer exact test), *p* value		NLX vs. HC (Weibull AFT model estimates)		NLX vs. HC (Mann–Whitney or Fischer exact test), *p* value
	Placebo (*N* = 7)	Naloxone (*N* = 33)	Hazard ratio (CI95)	*p* Value		HC group (*n* = 43)	Hazard ratio (CI95)	*p* Value	
Primary endpoint									
Time from FBTCS end to recovery of $SpO_2 \geq 90\%$, sec, mean (SD)	93.86 (57.66)	85.5 (41.72)	1.33 (0.59–3.01)	0.5		70.2 (54.1)	0.88 (0.55–1.41)	0.61	
Respiratory secondary endpoints									
SpO_2 nadir, %, mean (SD)	74.83 (5.04)	71.96 (9.46)			0.482	70.95 (13.08)			0.749
Patients with $SpO_2 < 90\%$ 30 s after the end of the FBTCS, *n* (%)	5 (71.4)	30 (93.8)			0.141	35 (81.4)			0.174
Patients with $SpO_2 < 90\%$ 120 s after the end of the FBTCS, *n* (%)	2 (28.6)	8 (25)			1	6 (14)			0.247
PCCA, *n* (%)[a]									
All	1 (14.3%)	9 (29.0%)			0.649	13 (30.2%)			1
Immediate	0	7 (22.6%)			0.308	8 (18.6%)			0.772
Delayed	1 (14.3%)	4 (12.9%)			1	7 (16.3%)			0.752
Duration of PCCA ≥5 s; mean (SD; range)									
All	6	12.6 (5.4; 7–22)			–	12.5 (6.0; 5–27)			–
Immediate	na	14 (5.9; 7–22)			–	14.88 (6.1; 7–18)			–
Delayed	6	9 (1.4; 8–11)			–	8.1 (1.5; 7–11)			–

(Continues)

TABLE 3 (Continued)

	ENALEPSY study (PP population)					Historical control (REPOMSE)			
			NLX vs. HC (Weibull AFT model estimates)		NLX vs. PCB (Mann–Whitney or Fischer exact test), *p* value		NLX vs. HC (Weibull AFT model estimates)		NLX vs. HC (Mann–Whitney or Fischer exact test), *p* value
	Placebo (*N* = 7)	Naloxone (*N* = 33)	Hazard ratio (CI95)	*p* Value		HC group (*n* = 43)	Hazard ratio (CI95)	*p* Value	
Other secondary endpoints									
Time from FBTCS end to first voluntary movement, s, mean (SD)	200.29 (215.76)	128.93 (151.11)	1.85 (0.72–4.77)	0.2		194.44 (191.98)	1.84 (1.11–3.05)	0.02	
Time from FBTCS end to patient's ability to handshake, s, mean (SD)	334.86 (192.52	396.83 (338.48)	0.70 (0.30–1.60)	0.39		316.61 (224.94)	1.31 (0.75–2.26)	0.350	
Post-ictal generalized EEG[b]									
Yes, *n* (%)	4 (66.7%)	19 (76.0%)			1	27 (62.8%)			0.813
Duration, mean (SD)	63.5 (26.3)	53.5 (23.4)			–	44.3 (12.0)			0.13

Abbreviations: FBTCS, focal to bilateral tonic–clonic seizure; PCCA, post-ictal central apnea.

[a]Data available in 31 patients in the NLX group, 7 in the PCB group, and 43 in the HC group.

[b]Data available in 25 patients in the NLX group, 6 in the PCB group, and 43 in the HC group.

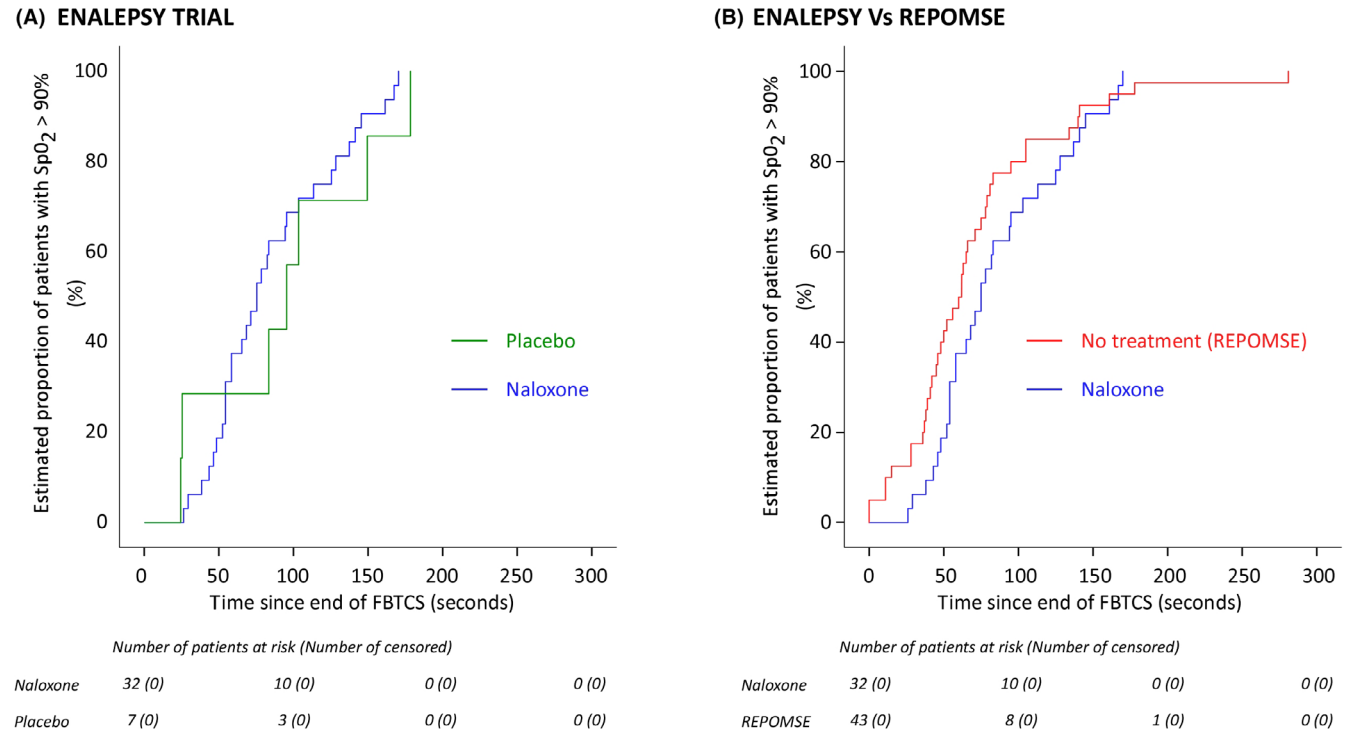

FIGURE 2 Time to recovery of $SpO_2 \geq 90\%$ from the end of the seizure to 5 min post-ictal.

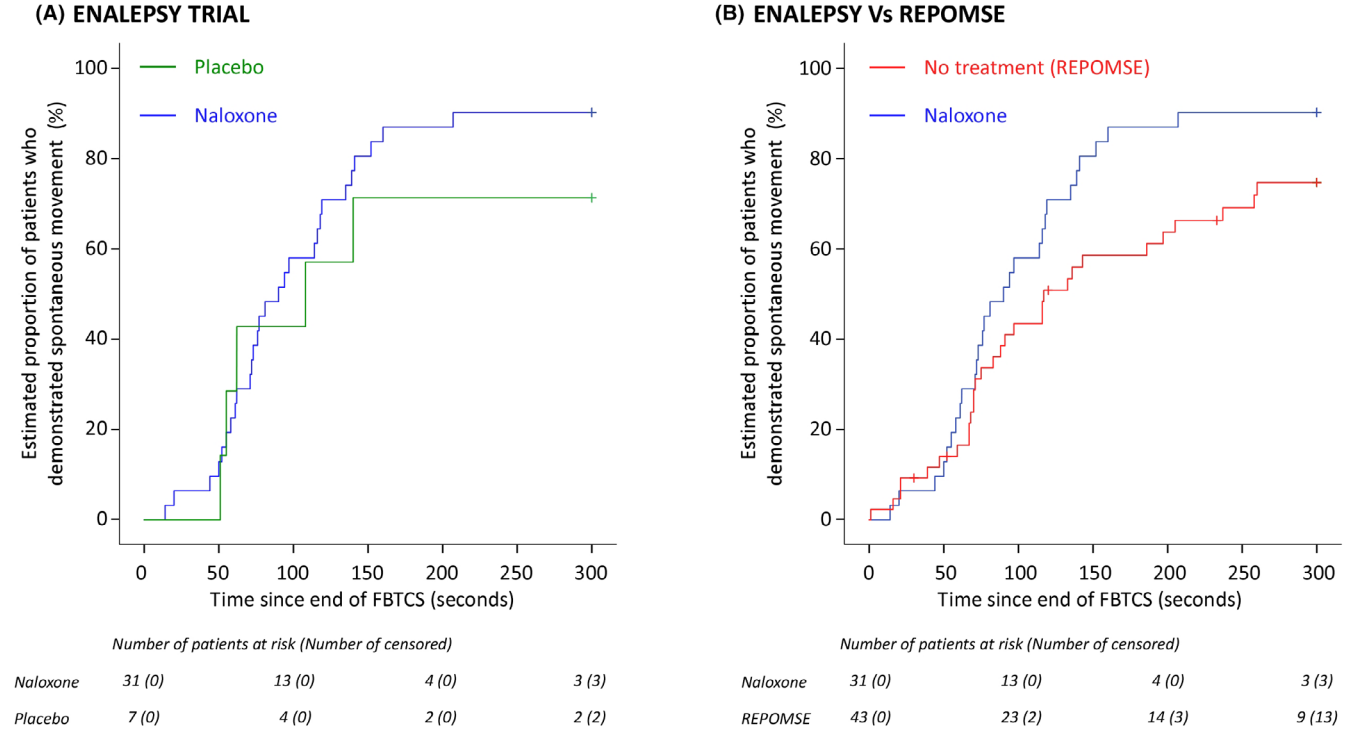

FIGURE 3 Time to first voluntary movement and to the patient's ability to handshake was analyzed from the end of the seizure to 5 min post-ictal.

immobility suggests that 0.4 mg was sufficient to produce a biological effect. According to its pharmacokinetics,[19] NLX effect is expected between 30 s and 2 min after intravenous administration, and its apparent duration of action is 20–90 min.[11] In this context, a NLX effect could not be expected for endpoints evaluated within the first 30 s after the end of the clonic phase, including immediate PCCA and PGES occurrence. The delay from termination

of FBTCS to injection of NLX might have also reduced the probability to detect the impact of NLX on other respiratory endpoints. However, the mean time to recovery of $SpO_2 \geq 90\%$ in the 14 patients (42.4%) who received NLX within the first 30 s (85 ± 38 s) was comparable to that of patients who received NLX after a longer delay (85.9 ± 45.7 s), suggesting that the impact of NLX on SpO_2 recovery did not depend on this delay.

Although current data argue for a predominant role of central apnea in the pathophysiology of SUDEP, the role of post-ictal coma severity must also be considered.[20] The duration of post-ictal immobility has been reported to be associated with the risk of PGES occurrence and the severity of respiratory dysfunction.[21] Moreover, it can be speculated that a longer duration of post-ictal immobility might increase the risk of prolonged post-ictal prone position and associated obstructive respiratory disorder. This issue might be particularly important for seizures occurring during sleep, which represent an independent risk factor for SUDEP. Several mechanisms might participate in this association, including alteration of arousal reactivity in drug-resistant epilepsy,[22] especially asphyxia-induced arousal[23] and increased severity of post-ictal coma.[24] Considering the impact of opioids on vigilance states,[11] naloxone might promote a faster awakening, clinically manifested by a reduction in the duration of post-ictal immobility. In our study, sleep-onset FBTCS were more frequent in the HC group (51.2%) than in ENALEPSY PP (27.5%), reflecting more frequent randomizations during daytime. Some studies thus suggested that PGES are more frequent after sleep than day-time FBTCS,[25] though this observation remains debated.[15] On the contrary, neither post-FBTCS respiratory dysfunction[13,16,25] nor the duration of post-ictal immobility[25] was reported to differ between sleep-onset and wake-onset FBTCS.

Because of the role of endogenous opioids in post-ictal seizure inhibition, administration of NLX might have increased the risk of an early recurrence of FBTCS. Our data showed that this was not the case. However, we cannot exclude that higher doses of NLX might have a different safety profile.

In conclusion, although our study failed to meet its primary endpoint, with no efficacy of NLX on post-FBTCS respiratory dysfunction, it suggests a potential role for opiate antagonists in mitigating other post-ictal disorders that might contribute to FBCTS-induced SUDEP. In the event that this acute effect of NLX would be confirmed, another long-acting opioid antagonist, naltrexone, could be tested as a chronic therapy to reduce the risk of SUDEP in persons with frequent FBCTS. Naltrexone has proved a safe drug in very large cohorts of patients with chronic alcoholism who are often at risk of breakthrough generalized convulsive seizures, without reports suggesting an increased risk of such seizure, in line with the lack of increased risk of seizure recurrence with NLX in our study.

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CONFLICT OF INTEREST STATEMENT

No author has a conflict of interest related to this study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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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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