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Proceedings of the 2020 Epilepsy Foundation Pipeline Conference: Emerging Drugs and Devices

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ABSTRACT

From August 27–28, 2020 the Epilepsy Foundation hosted the Pipeline Conference, exploring emerging issues related to antiepileptic drug and device development. The conference featured epilepsy therapeutic companies and academic laboratories developing drugs for focal epilepsies, innovations for rare and ultra-rare diseases, and devices both in clinical trials and approved for use. In this paper, we outline the virtual presentations by the authors, including novel data from their development pipeline.

1. Introduction

From August 27–28, 2020 the Epilepsy Foundation hosted the Pipeline Conference, exploring emerging issues related to antiepileptic drug and device development with authors presenting their work through live presentations. The conference focused on therapeutics in the preclinical stage through those undergoing clinical trials. Following the conference, summaries were created by two authors (CMB and SNG) based on the virtual presentations given at the conference; these summaries were then sent to the speakers for their approval. In the following document, we outline the numerous emerging initiatives in the epilepsy pipeline.

2. Diagnosis and detection devices

2.1. SeizeIT, Byteflies

2.1.1. Presented by Benjamin Vandendriessche, PhD and Gergely Vertes, MBA

The teams from UCB and Byteflies presented data on SeizeIT, a multicenter trial evaluating clinical use cases for Sensor Dot, a wearable EEG device. Given there is poor concordance between patient-reported seizure frequency and seizures recorded with more objective measures, clinicians are often making management decisions based on limited or erroneous data [1]. As a result, there is currently an unmet need for seizure detection outside of the hospital setting, for both optimizing treatment effect and for monitoring drug adjustments. Wearable devices for seizure detection have been produced, including Empatica, which detects generalized tonic-clonic seizures. The SeizeIT study intends to demonstrate that non-tonic-clonic seizures, including absence and focal seizures, can also be detected by wearable devices. Patients have been involved in designing proof-of-concept devices to detect seizures, including wearable technology for behind the ear EEG, which was then validated in a pilot study. A clinical validation study, with a plan for integrating into UCB clinical trials, is currently recruiting. In total, the SeizeIT2 Study aimed to recruit more than 500 patients across Europe and evaluate the clinical use for 2-channel EEG monitoring in specific types of epilepsy.

The wearable device used in SeizeIT2 is Sensor Dot, which monitors 2-channel EEG placed behind the ears and actigraphy placed on the neck, as well as in some cases 1-channel ECG, EMG and actigraphy. These data are manually reviewed by epileptologists and concurrent video-EEG data are also reviewed and independently annotated. The results are then compared to patient's seizure diaries. Data were compared for all patients, adults, and children between vEEG and Sensor Dot system for absence sei-

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zures. Among 7 patients with 155 seizures in total, the Sensor Dot achieved a sensitivity of 96% in detecting absence seizures and comparing Sensor Dot to seizure diary showed fivefold greater sensitivity. One patient had 12 of 12 seizures identified on vEEG correctly identified with Sensor Dot, though all 12 were missed by seizure diary. Another cohort of 6 patients with 46 seizures in total was investigated to determine the ability to detect focal seizures. Across focal aware and focal unaware semiologies in both temporal and frontal origin, the Sensor Dot achieved a sensitivity of 83% and was found to be 9.5 times more sensitive than manual seizure diaries. When the ECG/EMG sensor dot on the chest is added to the 2-channel EEG system, results improved to 93% sensitivity. Authors note this was limited by retrospective approach to data analysis, and the fact that only 2 of 6 patients with focal epilepsy underwent ECG/EMG sensing. Unfortunately, the team also notes that a pause on data collection was necessary due to the COVID-19 pandemic in Spring 2020, but data collection remains ongoing at this time.

2.2. Embrace platform and device

2.2.1. Presented by Matteo Lai

Empatica last presented at the Epilepsy Pipeline conference in 2018. They have developed the Embrace device, an FDA-approved wristwatch for detecting epileptic generalized tonic-clonic seizures. This device runs an algorithm based on wristwatch movements and sends an alert to caregivers when a seizure is detected to allow for intervention. The FDA cleared Empatica in January 2018 for adults, and the product has been co-promoted with Eisai in the US since 2019 with caregivers reporting improved peace of mind. As the COVID-19 pandemic progressed, the need for remote monitoring became apparent leading to the development of additional features and channels for data analysis and use.

First, the alert app for detecting seizures is now joined by a connected app called "Mate," an electronic seizure diary that allows patient capture of events with automatic cloud data uploading and raw data export, allowing for easy remote monitoring. An alarm has also been developed for medication reminders that can be customized for individual medications. These reports can then be exported monthly for physician review.

Another novel development is the diagnostic algorithm for detecting generalized tonic-clonic seizures using data from the Empatica device. The Alert App runs inside each Embrace device, whereas this diagnostic algorithm runs in the cloud with greater sensitivity due to extra processing capability. The False Alert Rate (FAR) over 24 h has been tracked closely since 2016 and at present is approaching 0%, while sensitivity has remained high with 95% sensitivity in the recent cloud algorithm. The FAR has been decreased 100 times, going from once per day in 2016 to 0.01% of the time at present.

Finally, the team has developed a new product geared toward supporting pharmaceutical companies and patients enrolled in clinical trials, the Research Portal. Data flow from sensors to real-time dashboards, offering actionable insights for patients and pharmaceutical companies.

Future directions for Empatica include detection and differentiation of nonepileptic seizures from epileptic seizures, detection of myoclonic seizures, and detection of focal-onset seizures.

2.3. Epihunter tracker

2.3.1. Presented by Dirk Loeckx

Epihunter is a consumer EEG headset that pairs via bluetooth with a smartphone algorithm and cloud platform to work as a diary for seizure detection to identify clinical absence seizures. When a seizure is detected, the app uploads data into a cloud platform that can be downloaded for patient or physician review. A seizure can also be video recorded on the smartphone. Prior validation studies were presented at the International Epilepsy Congress in Bangkok in 2019 with 8 subjects and 141 h of recording for annotated clinical vEEG, and the 2nd International Congress on Mobile Devices and Seizure Detection in Epilepsy in Lausanne in 2019 with 5 subjects and 27 h of recording, with expert annotations on wearable EEG. The algorithm was trained using only Fp1/F7 lead data, corresponding roughly to the Epihunter detection leads. These two validation studies were notable for high sensitivity (99.6% on the clinical video-EEG and 95.6% on the wearable EEG) and a positive predictive value (PPV) of 94.9% the clinical and 91.0% on the wearable EEG, respectively. Each of these arms included data from the annotated clinical vEEG versus the wearable EEG, respectively.

At this year's pipeline meeting, investigators presented data on a prospective clinical trial comparing in-hospital vEEG with Epihunter seizure detection in 40 subjects expected to have absence seizures across four sites in the US and Europe. The capacity to detect seizures was compared between Epihunter and expert review of vEEG, specifically looking at spike-wave discharges greater than 5 s (SW5) and electroclinical seizures of spike-wave longer than 1 s accompanied by clinical symptoms (ECS). Interim results are available for 18 subjects at 2 centers, excluding 5 subjects with poor wearable recording. In sum there were 13 subjects with 42 h of data included in the analysis, capturing 74 SW5 and 85 ECS. Epihunter was found to have 98.4% PPV for SW5 and 98.1% PPV for ECS. In this analysis, only 1 false seizure detection occurred. Sensitivity for SW5 was 82.4%, but for ECS was only 62.4%, perhaps due to very short electrical discharges accompanying clinical symptoms in ECS. Recruitment and data collection are ongoing for this study with plan for expansion to additional centers. The team is considering incorporating an 'awareness test' in the app, which will ask patients whether they sense having had a seizure after the algorithm has detected one. Plans are also in order to expand to other seizure types beyond absence.

2.4. Nelli seizure monitoring tool

2.4.1. Presented by Kaapo Annala

Nelli provides objective epilepsy outcome measures using machine learning by analyzing behavior and sounds produced by patients. Data are gathered by camera and microphone, and algorithms gather these data and produce an interactive report that is interpretable by a clinician, which improves as the tool is exposed to more seizures. There are three potential scenarios for use of Nelli: real-time monitoring, diagnostic usage based on semiology, and reviewing and validating models with the help of clinical experts.

Nelli uses semiology data to differentiate seizure types within each individual patient. Data can be collected on tonic movement, clonic movement, sounds, and oscillations within individual patient movements to elucidate a patient's various seizure types. In one patient two independent reviewers evaluated the video-recorded individual seizures as compared to the Nelli output, and the results demonstrated greater than 90% sensitivity for each reviewer. The false detection rate (FDR) for severe seizures was 0.015 per hour and 0.71 per hours for minor tonic seizures. Another patient using Nelli at home who reported zero seizures in their self-reported seizure diary was found to have 288 confirmed seizures through the Nelli system over the course of four weeks, allowing that patient to receive the medical interventions necessary to reduce their seizure frequency.

Nelli's current annotated library contains more than 2000 patients and more than 55,000 seizures, with 75% of the cohort being adults. Validation has taken place both in Epilepsy Monitoring Units (EMUs) and in the home environment using independent reviewers of video data. Investigators with Nelli have divided sei-

Table 1
Sensitivity and false-positive rate of the Nelli system in detecting Major Motor Seizures, Prominent Motor Seizures, and Subtle Motor Seizures.

Seizure Type	Sensitivity	False Positives per night
Major Motor Seizures (Tonic-clonic, hyperkinetic, clonic)	98%	0.08–0.15
Prominent Motor Seizures (Tics, automatisms)	94%	2.8–4.5
Subtle Motor Seizures (Spasm, myoclonic)	80%	4.8–5.7

zures into three seizure types, with Major Motor Seizures detected with 98% sensitivity, Prominent Motor Seizures with 94% sensitivity, and Subtle Motor Seizures with 80% sensitivity. Clinical studies are being planned for the United States (Table 1).

2.5. TMS-EEG

2.5.1. Presented by Isabella Premoli, PhD

Investigators aimed to use Transcranial Magnetic Stimulation (TMS) as a platform to assess brain response to new anti-seizure medications (ASMs) in trials. TMS is a non-invasive and painless technique to exogenously stimulate the human brain by production of electro-magnetic pulse inducing currents in the cortex [2]. TMS responses can be measured using electrodiagnostic techniques like electromyography (EMG). TMS-Electroencephalography (TMS-EEG) is a powerful technique that can be used to detect TMS-evoked EEG potentials (TEPs). TMS-EEG contains a characteristic constellation of evoked responses resulting from TMS; peaks in EEG potentials at specific timepoints correspond to specific components of the cortical response in healthy volunteers, allowing for the assessment of axonal excitability, GABA-A receptors, and GABA-B receptors [3]. By evaluating responses of specific TMS-EEG measures, investigators can offer information about mechanisms of specific ASMs.

TMS-EDMs (electrodiagnostic markers including resting motor threshold and TEP) were used in a recent first-in-human trial of XEN1101, a novel formulation of the potassium channel modulator retigabine, at doses of 10, 15 and 20 mg. TMS-EEG responses were recorded at three time points for each group: before dose, two hours post-dose and four hours post-dose. The results showed an increase in resting motor threshold (RMT) with the 20-mg dose of XEN1101, which was twice the effect appreciated of retigabine at 400 mg (twenty times the dose). This increase in resting motor potential indicates reduced corticospinal activity, supporting the efficacy of this ASM. With regard to TEP outcome, the 20-mg dose showed the strongest significant modulation at four hours after drug administration. Another study included dosing of XEN1101 at 20 mg in healthy volunteers and measured the RMT across time, finding an increase in RMT that was greater for XEN1101 than placebo, and that correlated tightly with serum level of XEN1101 concentration [4]. TMS-EEG similarly showed suppression of TEP amplitude, indicating suppression of cortical reactivity.

Future goals include development of specific TMS-EDM libraries for individual ASMs with discrete synaptic targets. In future drug trials, TMS-EDMs could be used to assess pharmacodynamics endpoints for new therapeutics, choose the most efficacious dose to enter late-stage clinical trials thereby increasing safety for trial participants, and provide pharmacokinetic relationships to help design the optimal therapeutic regimen.

2.6. 24/7 EEG™ SubQ, UNEEG Medical

2.6.1. Presented by Jonas Duun-Henriksen, PhD

For patients with infrequent or suspected unrecognized seizures, conventional EEG techniques may not provide the required timeframe to answer the clinical questions surrounding seizure occurrence. Ultra-long-term recording of EEG allows for the capture of all events, providing the clinicians with a new tool to assess the patient. The 24/7 EEG™ SubQ solution aims to make this possible by capturing up to 15 months of continuous EEG by placement of a subcutaneous implant under local anesthesia. Once connected to an external device, EEG is recorded from two channels with a sampling frequency of 200 Hz.

On top of supplying the raw EEG, the solution includes dedicated review software, highlighting potential seizure activity in the EEG data. In addition, patient self-reporting by tapping the external device enables markers in the EEG data. A cloud-based solution will ensure that latest data are always available and support remote management of patients.

At present, more than 100 implantations have been completed with the subcutaneous wire. A patient feedback survey of 490 days of recording showed that no patients felt constrained in their work or leisure activities, with no device related serious adverse events occurring [5]. The UNEEG solution is also helpful for delineating circadian or ultradian rhythms of seizures within individual patients, leading to seizure forecasting that could allow individuals to prepare for seizure occurrence or take additional doses of medication to mediate the risk of forthcoming seizures [6]. The COVID-19 Pandemic limited patient enrollment in UNEEG protocols at Kings College London and elsewhere, but more recently the pace of enrolling patients has increased.

2.7. Epi-Minder sub-scalp system

2.7.1. Presented by Mark Cook, MD

The Epi-Minder system was initially funded by the Epilepsy Foundation Shark Tank competition in 2015. This system was designed with the clinical need for long-term EEG recording in mind and has important applications in epilepsy diagnosis, therapy and forecasting. The device is implantable under the scalp using a single electrode with four contacts, allowing for coverage of both hemispheres. The implantation itself is an outpatient procedure well tolerated thus far. A behind ear unit of the Cochlear system is joined by an induction coil to the subscalp implant to transfer data, which are then recorded on a Smartphone App and subsequently uploaded into the Cloud. After analytics are performed in the cloud, data are sent to the end-user platform for review by clinicians.

A clinical trial is currently underway for Epi-Minder with 10 units currently implanted, some for over 1 year. Recruitment was slowed by the pandemic, but is increasing now through the involvement of multiple sites. The primary endpoints of this trial are safety, participant retention, and feasibility of implantation of the unit. Secondary endpoints include comparison of sub-scalp EEG against seizure diaries, scalp EEG signal, and the gold standard of video with 10–20 EEG arrays. Inpatient studies of implanted subjects relative to 10–20 array scalp EEG are occurring for seven days total at both the beginning and the end of the study period, and these preliminary data have captured a disparity between recorded and discovered events. Preliminary analysis of long-term data from the implantable system indicates seizure forecasting is feasible with these devices.

2.8. Epilog wearable device

2.8.1. Presented by Mark Lehmkuhle, PhD

Epilog is discreet single-channel sensor that uses a disposable, hydrogel sticker that attaches to the scalp below the hairline either behind the ear or on the forehead. Epilog was studied alongside scalp video-EEG in the epilepsy monitoring units for entrainment at Boston Children's, NYU and the University of Colorado. 872 EEG recording days were captured on 108 children and 78 adult participants with 347 total seizures captured. A machine learning algorithm was then trained from this dataset using all available electrographic seizure information.

NYU then enrolled 15 patients who were previously diagnosed with focal-onset seizures or generalized absence seizures to wear Epilog at home for three weeks and keep a conventional seizure diary. There were 33 self-reported seizures in the diaries, and 190 days of EEG were collected. The seizure detection algorithm was then run, with thresholds set for high sensitivity at the expense of a potentially high false detection rate, to create "event markers" on the chronic EEG recording. These event markers, along with the self-reported seizures, were added as simple annotation flags in the EEG record. Epileptologists were asked to review the EEG to determine if electrographic seizures had occurred in the Epilog EEG near the annotation marker times. Of 206 events detected by the algorithm, 30 were confirmed to be electrographic seizures by epileptologist review that were not self-reported by patients. Ten events were detected by both the algorithm and self-reported but were not identified as seizures by the epileptologist. Two events were self-reported and verified by the epileptologist that the algorithm has missed. There were 165 events that were detected by the algorithm during this period that were neither reported by the patient nor identified as an electrographic seizure by the epileptologist, confirming a tendency for false positives expected with elevated sensitivity. The team also surveyed patients about tolerability of the device and found some individuals experienced mild itching and discomfort with the Epilog sticker, but were overall comfortable wearing the device in sleep and in public. Furthermore, they found the stickers easy to replace and would wear the sensors again.

2.9. Cathodal Transcranial Direct Current Stimulation (tDCS), neuroelectrics

2.9.1. Presented by Alexander Rotenberg, MD PhD

Cathodal Transcranial Direct Current Stimulation (tDCS) is a method for focal noninvasive cortical stimulation where direct electrical current is conducted to the cortex by scalp electrodes. During tDCS, suppression of cortical excitability near the cathodal portion of the circuit outlasts the stimulation train. The Boston Children's Hospital and Neuroelectrics team recently completed an open-label clinical trial of tDCS for focal seizure suppression. The team asked epileptologists to offer a clinical impression of the seizure-onset zone location. This information was then mapped onto a standardized or customized brain template and targeted with tDCS by placing anodes and cathodes on the scalp to deliver a specific amount of cathodal current to the seizure focus. This trial included individuals from ages 9 to 65 years with persistent focal seizures despite two or more ASM trials and with a single seizure focus accounting for at least eighty percent of electroclinical seizures. Patients with prior craniotomy and those with significant malformations of cortical development were specifically included, and, of note, tolerated cathodal tDCS well. The team's models also predicted that no significant amount of electrical current was shunted intracranially in patients with pre-existing skull defects, with careful electrode placement. The primary outcome measure was change in seizure frequency at eight-week follow up as percentage of baseline. The study protocol consisted of an initial baseline of seizure monitoring, then two weeks of daily stimulation for 30 minutes daily, then seizure diary use and finally seizure frequency at eight-week follow-up. In a minority of patients seizures increased, but the majority of participants had less frequent seizures for a mean reduction of 44% of seizure frequency for the total cohort of participants [7] (Fig. 1). Investigators note that other interventions in this cohort have failed, including medications and surgery.

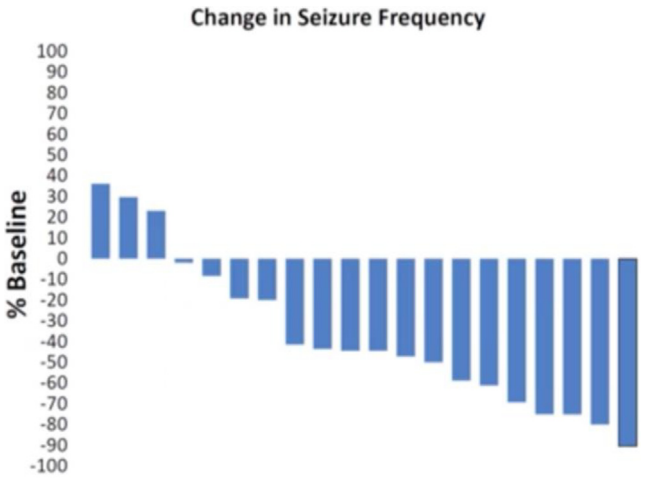

Fig. 1. Results from an open-label clinical trial of Cathodal Transcranial Direct Current Stimulation for focal seizure suppression. Epileptologists were asked to estimate the seizure-onset zone in a cohort of 20 patients with drug-resistant epilepsy and focal-onset epilepsy. The primary outcome measure was change in seizure frequency at 8-week follow-up, depicted in each individual. In a minority of patients seizures increased, but the majority of participants had less frequent seizures for a mean reduction of 44% of seizure frequency for the total cohort of participants.

To improve cathodal tDCS efficacy, in vitro preparations of isolated mouse and human postoperative cortex plated on microelectrode arrays are being investigated concurrently by the Boston Children's Hospital group. In these preparations, when direct current stimulation is passed through the sample the depression of the cortex is incomplete. Investigators hypothesize that variability in orientation of neuronal polarity causes some neurons to perceive signal as anodal even if it is coming from the cathodal direction. This team notes improved cortical suppression with NMDA receptor blockade, which leads to clean and full suppression of cortical excitability and improved seizure control in a mouse model [8]. These findings provide a rationale for drug-device coupling to treat refractory epilepsy.

2.10. DyNeuMo implantable device and platform

2.10.1. Presented by Timothy Denison, PhD (Oxford) with Martin Tisdall, MD (GOSH) and Antonio Valentin, MD, PhD (KCL)

The Picostim-DyNeuMo is an investigational research platform resulting from an industry-academic partnership. The Picostim-DyNeuMo aims to expand access to implantable neuromodulation devices for the research community and is applicable to multiple disease states. The first generation of the DyNeuMo research toolkit is built off the Picostim DBS device, which is a cranially mounted, rechargeable, bi-directional "brain-machine-interface." Potential advantages of the cranial location include mitigation of common artifacts (ECG, motion) found in subclavicular implants, and the elimination of tunneling in the neck; the trade-off is that the implant does require a cranial pocket similar to cochlear implants. The DyNeuMo research toolkit enables longitudinal

physiologic measurement and closed-loop algorithm prototyping. The system is currently being evaluated for whether circadian patterns and motion changes can be used to optimize neurostimulation in preclinical studies. Great Ormond Street Hospital, King's College London, and Oxford are collaborating to plan a study of centromedian nucleus of the thalamus stimulation in DBS for Lennox–Gastaut patients; the Royal Academy of Engineering is funding the pilot study, which is in the final planning stages at this moment.

3. Drugs for focal epilepsy

3.1. 2-Deoxy-d-Glucose (2DG)

3.1.1. Presented by Thomas Sutula MD, PhD

2-Deoxyglucose (2DG) is a glucose analogue that reversibly inhibits glycolysis in response to neural activity. The compound, made from removal of a single oxygen atom at the 2 position of glucose, cannot undergo isomerization to 5-carbon fructose-6-P, blocking the subsequent steps of glycolysis. Acutely, 2DG protects against seizures evoked by 6-Hz stimulation and status epilepticus invoked by kainic acid and pilocarpine [9]. Chronically, it leads to 2-fold slowing of kindling progression evoked from different brain sites and is effective against seizure progression when administered up to 10 min after a seizure [10]. Given the unique mechanisms of 2DG including presynaptic reduction of excitatory synaptic currents, decreased seizure induced gene expression and activity-dependent delivery in vivo by neurovascular coupling, it is potentially useful for the prevention of post-traumatic epilepsy and post-traumatic stress disorder.

Recently, Koenig and colleagues demonstrated that in a controlled cortical impact model of TBI, in vitro 2DG administration attenuated cortical hyperexcitability normally seen 3–5 weeks following TBI. Moreover, one week of in-vivo 2DG treatment immediately following the TBI was sufficient to prevent the development of epileptiform activity, suggesting a disease modifying effect [11]. Currently the toxicology of 2DG is being explored further as dose-dependent reversible cardiac toxicity has been found in five studies of 2DG in dogs and mice. The present goal is for 2-DG to receive FDA approval for orphan indications of status epilepticus, with next steps focusing on IV safety and tolerability studies, a phase II dose ranging study in ER and ICU patients with status epilepticus, and a phase III study in ER and ICU patients with status epilepticus.

3.2. Inhibitory interneuron cell therapy

3.2.1. Presented by Cory R. Nicholas, PhD

Medial ganglionic eminence (MGE) interneuron cell therapy holds promise in the treatment of temporal lobe epilepsy (TLE). A clinical-grade human pluripotent stem cell line is used to derive GABAergic inhibitory cells that express markers consistent with post-mitotic MGE cortical/hippocampal-type interneurons. Preclinical evaluation of the human interneurons has demonstrated decreased seizure frequency when grafted into the hippocampus in chronic TLE mouse models. In an intra-hippocampal kainite model of mesial temporal lobe epilepsy in mice, the human interneurons led to an 80–90% reduction in mean focal electrographic seizure frequency, with seizure events eliminated in 67% of animals. Notably, the human interneuron transplants reduced dentate granule cell dispersion in the sclerotic hippocampus. Dose response evaluations have uncovered minimum effective and maximum feasible doses, none of which have been associated with behavioral abnormalities. Of the approximately 200 animals studied, no tumors, teratomas, or ectopic tissues have developed, underscoring the lack of residual pluripotent cells in the final cell product. Given this data, Neurona is planning a first-in-human phase I/IIa dose escalation study for drug-resistant mesial TLE. While the study will focus on safety, efficacy endpoints will also be explored. Human interneuron cell therapy may provide a non-destructive alternative that restores local inhibitory tone for drug-resistant focal epilepsies.

3.3. Revivo-5061

3.3.1. Presented by Doug Cowart, PharmD

Nomethiazoles (NMZM) are a class of small molecules derived by the addition of a nitrate group to the Methylthiazole pharmacophore of the neuroprotectant clomethiazole (CMZ) [12]. This allows NMZMs to both potentiate GABA and decrease inflammation through their CMZ effect while also harnessing the neuromodulatory effects of nitric oxide. Revivo has developed a novel NMZM, Revivo-5061, which has broad activity in mice providing protection in both MES (electroshock) and scMET (Metrazol chemical) screens for anticonvulsant activity (Fig. 2). Oral administration to rats has demonstrated sustained activity against chemically induced seizures, with preliminary data to support that it is also active against kindling-induced seizures. Interestingly, the binding site for RIV-5061 appears to be the same as that for etomidate, and its GABA potentiating effect occurs at a site separate from that of diazepam or pentobarbital.

Revivo-5061 has both pro-cognitive and neuroprotective effects. In the step through adaptive avoidance animal model, where mice learn to avoid a chamber associated with an electric shock, the memory deficit induced by the amnesic agent scopolamine was reversed through the administration of NMZM. The agent also reversed the scopolamine-induced depression in pulse spike amplitude, in line with its pro-cognitive effects. In an ApoE4 amyloid mouse model, the administration of NMZM led to reactivation of CREB, restoration of synaptic plasticity, and reduction in levels of TNF, providing support for the neuroprotective effects of NMZM [13]. The compound is being advanced into a phase 1 program throughout 2021 and 2022, ultimately hoping to reach the target population of patients with epilepsy.

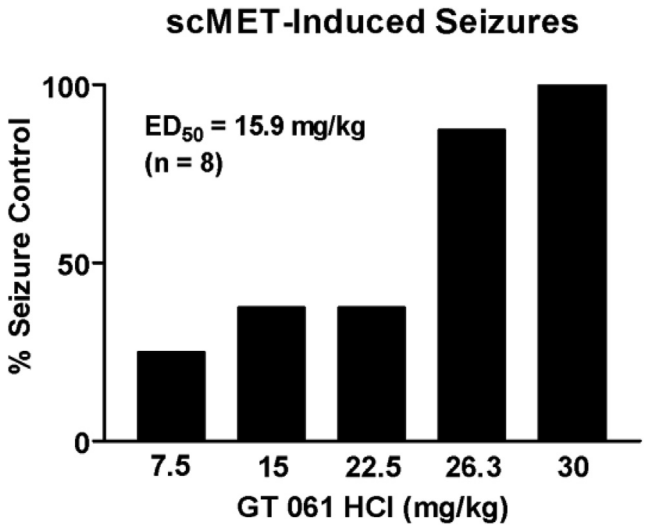

Fig. 2. Dose-dependent anticonvulsant activity of RIV-5061 in Metrazol chemical seizure models in rats. Drug was administered orally by gavage, and anticonvulsant activity against chemically induced seizures was determined 30 min later. Data are the mean for 8 animals at each dose.

3.4. Cenobamate and Carisbamate

3.4.1. Presented by William Rosenfeld, MD

Cenobamate is FDA-approved for the treatment of focal seizures and is currently being studied, but is not yet approved, for the treatment of patients with primary generalized tonic-clonic seizures. It is a tetrazole alkyl carbamate derivative that is thought to mediate its antiepileptic effects through dual mechanisms of preferential inhibition of the persistent current of voltage-gated sodium channels [14] and allosteric modulation of the gamma-aminobutyric acid ($GABA_A$) ion channel. Two pivotal double-blind, placebo-controlled studies were conducted to establish the efficacy of cenobamate. The first, C013, randomized 222 cases to a 6-week titration phase and a 6-week maintenance phase of 200-mg cenobamate [15]. In this study, the median baseline seizure frequency in 28 days was 6.5, and the median percent reduction in seizures was found to be 34% greater in the cenobamate group than the placebo group. The second trial, C017, included 437 patients randomized to a 6-week titration phase and a 12-week maintenance phase, evaluating doses of 100 mg, 200 mg, and 400 mg [16]. In this cohort the median seizure frequency in 28 days was 9.5, and the 100-mg dose led to a 12% greater median seizure reduction, while 200-mg and 400-mg doses both led to a 31% greater median seizure reduction. While the dose responses appear to be plateauing, the study authors note that the titration of the 400 mg had to be slowed throughout the study, and as a result the efficacy appears to plateau but in actuality increases later in the maintenance phase (Fig. 3). In the early clinical development program, 3 cases of drug reaction with eosinophilia and systemic symptoms (DRESS) were noted (2 among healthy volunteers and 1 in a patient with epilepsy) [17]. In the CO21 phase 3 study among 1339 patients, utilizing a low and slow titration, starting at 12.5 mg and increasing the dose every 2 weeks, as compared to weekly or faster, none developed DRESS. This suggests that a low and slow titration was successful in mitigating this risk.

Carisbamate is an investigational compound being studied as a potential treatment option for Lennox-Gastaut Syndrome. This agent inhibits the voltage-gated brain-type sodium channel with weak calcium channel inhibition and has demonstrated anticonvulsant activity in several animal seizure models including the genetic absence epilepsy rat from Strasbourg and the LTG-resistant kindled rat [18]. Carisbamate exhibited dose-related antiepileptic effects in the photosensitivity model. Carisbamate pharmacokinetics and safety are presently being studied in adult and pediatric patients with Lennox–Gastaut Syndrome.

3.5. Kv7 potassium channel modulators for the treatment of epilepsy

3.5.1. Presented by Ernesto Aycardi, MD

Despite the myriad number of antiseizure medications available, no currently approved medications directly target the voltage-gated potassium channel. While ezogabine modulated potassium channels and proved efficacious in adults with partial onset seizures, this medication was pulled from the market in 2017 given concerns for retinal abnormalities and pigmentations changes in patients. Despite this adverse effect, several case studies reported notable responses to the agent in KCNQ2 epileptic encephalopathy (KCNQ2-EE), with improvements in both seizure burden and children's development and cognition [19,20]. Given this initial response, XEN 496 and XEN1101 were developed to target the voltage gated sodium channel while avoiding the complications of previous formulations. XEN 496, specifically formulated in sprinkle capsules for the pediatric population, has shown rapid activity in vitro, and in preclinical studies does not require changes in dosage despite the different formulation from the previously approved ezogabine. The FDA has indicated it is acceptable to study XEN 496 in infants and children up to four years of age with KCNQ2-DEE with appropriate safety monitoring, and a single pivotal trial may be considered adequate to demonstrate efficacy in KCNQ2-DEE. XEN 496 is entering Phase 3 with a randomized, double-blind, placebo-controlled trial starting in 2020. XEN 1101, the adult formulation, has the same mechanism as ezogabine, but with once daily dosing, improved tolerability, and low concern for pigmentation changes given the agent does not dimerize to form pigmented molecules. Investigations using TMS have shown XEN1101 decreases cortical excitability, making it a promising therapeutic. XEN 1101 is currently in phase 2 for treatment of adult focal seizures, with results anticipated in 2021.

Xenon has also developed numerous strategic alliances within epilepsy, including the 'Behind the Seizure' collaboration with Invitae, BioMarin, and Stoke which offers free genetic testing to children under the age of 8 with an unprovoked seizure. Xenon also works closely with the KCNQ2 foundation, allowing them to incorporate the voices of the patients and caregivers in study design and feasibility. This relationship allowed xenon to explore the disability associated with KCNQ2-EE, finding that patients experience an average of 10 seizures per day. Among those that were able to try ezogabine in the past, the caregiver comments highlighted improvements in not just seizure burden but also development, cognition and social interactions.

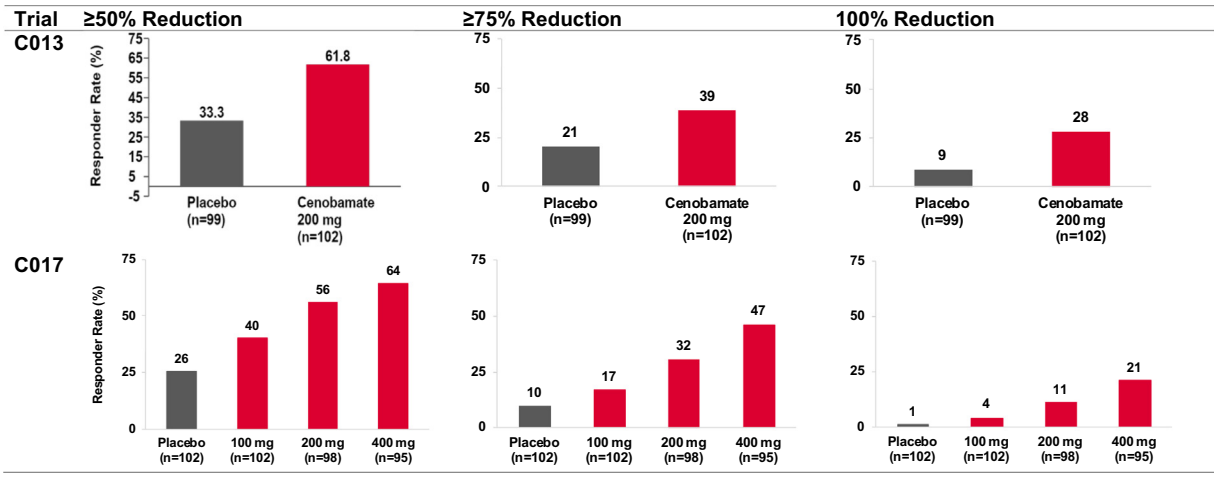

Fig. 3. Reductions observed in the maintenance phase of trials C013 and C017, double-blind, placebo-controlled trials to establish the efficacy of Cenobamate.

3.6. Darigabat (CVL-865), Cerevel Therapeutics

3.6.1. Presented by Rachel Gurrell

$GABA_A$ receptors are ligand gated ion channels that control chloride flux and dampen down neuronal excitability. The receptor is a pentameric complex commonly composed of two alpha subunits, a beta subunit, and a gamma subunit and, importantly, only $GABA_A$ receptor subtypes containing α1, α2, α3, and α5 subunits form a benzodiazepine binding site. Non-selective benzodiazepines are positive allosteric modulators (PAMs) of the $GABA_A$ receptor subtypes containing α1, α2, α3, and α5 subunits, leading to increased frequency of chloride channel influx and an increased inhibitory post-synaptic potential [21]. However, the anticonvulsant activity of these PAMs is believed to be mediated by only the α1 and α2 subunits, with the α1 subunits believed to be responsible for many of the undesired effects of benzodiazepines, such as somnolence, cognitive impairment, addiction and loss of efficacy [21,22].

Cerevel has developed darigabat (also known as CVL-865), a novel selective α2/3/5-$GABA_A$ receptor modulator with minimal activity at α1 subunits, thereby designed to minimize adverse effects and potential loss of efficacy associated with benzodiazepine use. The potent anticonvulsant effects are preserved via allosteric modulation of α2 subunits at high receptor occupancy, as exemplified by the broad spectrum preclinical efficacy of darigabat in the pentylenetetrazol and amygdala kindling mouse models as well as in the generalized absence epilepsy rat [23]. The safety profile of darigabat was recently explored in a phase 1 multiple ascending dose study in healthy volunteers at doses achieving greater than 80% receptor occupancy [24]. All side effects were mild and there were no reports of somnolence after titration. A proof-of-principle phase 2a study assessed response to darigabat in 7 photosensitivity patients, and 6 out of 7 patients experienced abortion of epileptiform discharges, indicating its anticonvulsant potential [25]. Cerevel Therapeutics has initiated a Phase 2 double-blinded randomized-controlled trial, the REALIZE trial, and accompanying open-label extension trial, enrolling adult patients with drug resistant focal epilepsy (NCT04244175, NCT04686786).

3.7. mGlu2 PAM JNJ-40411813 and Levetiracetam: a potential rational polypharmacy treatment

3.7.1. Presented by Marc Ceusters

Combination treatment of patients with refractory epilepsy occurs by trial and error, leading to limited therapeutic benefit. However, compelling preclinical data support strong synergy between mGlu2-positive allosteric modulators (PAM) and Leveteracitam (LEV), which could lead to the first rational polypharmacy medication in epilepsy. The mGLu2 autoreceptor is located in numerous brain regions associated with epilepsy, and it acts presynaptically to decrease glutamate release [26,27]. In the presence of a positive allosteric modulator, mGLu2 autoreceptor activity is further increased allowing for normalization of neurotransmission during states of hyper-glutamatergic activity [28]. In the 6-Hz animal model, mGlu2 PAMS show efficacy, though not in MES and s.c. PTZ animal models. However, this efficacy is greatly increased when the mGlu2 PAM is given in combination with LEV. In corneal kindled mice, the combination of JNJ-40411813 and LEV led to a reduction in seizure severity greater than that observed with either agent alone [29]. This positive synergy is specific to JNJ-40411813 and LEV, as other epileptic agents in combination only show modest reductions. In the nine Phase I clinical studies so far, the agent JNJ-40411813 has been well tolerated in single dose and multiple dose studies [28]. JNJ-40411813 will soon be advanced into Phase 2 clinical studies, with a randomized, double-blind, placebo-controlled adaptive dose-finding investigations to study the efficacy and safety of JNJ-40411813 added to LEV in focal-onset seizures.

3.8. NeuCyte platform

3.8.1. Presented by Thomas Portman, PhD

NeuCyte uses iPSC-derived human neural in vitro platforms for preclinical drug discovery. Pure populations of neuronal cell types can be differentiated from iPS cells, and then flexible co-culture systems combining multiple populations create flexible assay substrates for drug discovery. The platform is built around technology that involves creating inducible neurons (IN), both inhibitory GABAergic and excitatory glutamatergic, using specific transcription factors. In this setting, neurons rapidly form neural networks within three to five weeks including mature electrophysiological properties like action potential firing. These substrates are then combined with multi-electrode array recording to assess the activity of specific compounds on in-vitro networks. Investigators note that each compound, even those with overlapping mechanisms of action such as specific GABA receptor antagonism, lead to a specific signal captured in the microelectrode array, thus enabling rapid drug development.

At present, one model that is a focus for NeuCyte is created with picrotoxin (PTX), a GABA-A antagonist. This system approximates an acute seizure and the NeuCyte team is testing this model and creating rescue epileptogenic phenotypes by ASM. This system has been tested with 18 ASMs that are already approved for use in humans. This would help improve the lengthy and inefficient process of drug discovery. The next step will be to pursue Ca++ imaging as a sensitive proxy for neural activity to do high throughput screening for candidate compounds to develop new ASMs.

3.9. STK-001, Stoke Therapeutics

3.9.1. Presented by Barry Ticho, MD, PhD

Stoke Therapeutics focuses on creating antisense oligonucleotides (ASO) which bind to the nonsense mediated decay (NMD) exons of mRNA transcripts, preventing mRNA degradation and increasing target protein expression [30]. Currently, they have engineered an ASO directed at the NMD exon of the SCN1A gene in order to treat patients with Dravet Syndrome. This leads to increased levels of Nav1.1 expression, which can have positive effects not just on seizure control but also other sequelae of Dravet including intellectual disability, behavioral abnormalities and sleep abnormalities. In Dravet Syndrome mice, injection of this agent, STK-001, led to restoration of normal levels of Nav1.1 in the brain for up to 14 weeks. In these models, mice that received STK-001 had an 80% reduction in seizure, and experienced significant reductions in mortality compared to Dravet Syndrome mice who did not receive the injection, with 97% of the mice still alive at 90 days [31]. In single and multiple dose GLP toxicity studies in monkeys, no adverse effects where noted at the highest doses tested, with no alterations in renal or hepatic function and no adverse pathology noted in the brain. STK-001 has entered phase 1/2a and is enrolling patients in an open-label study to characterize the safety, tolerability and pharmacokinetics of STK-001 in humans, with a secondary endpoint of change in seizure frequency over 12 weeks.

3.10. ETX101, Encoded Therapeutics

3.10.1. Presented by Stephanie Tagliatela

In Dravet Syndrome, approximately 85% of cases are caused by loss-of-function mutations in a single allele of the *SCN1A* gene, which encodes the sodium ion channel Nav1.1– the primary

sodium channel used by GABAergic neurons to generate actions potentials [32]. Impairment of Nav1.1 results in decreased GABAergic tone and uncontrolled cortical excitation leading to seizures and neurodevelopmental manifestations of Dravet. Encoded Therapeutics is currently developing a gene therapy approach to treat Dravet Syndrome, by introducing an engineered transcription factor (eTF) that targets a conserved DNA region regulating *SCN1A*. The transgene encoding this eTF is introduced through an AAV9 capsid and the eTF transgene expression is restricted to GABAergic neurons. To reduce the dosing requirements and increase transduction in forebrain structures mediating the disease, ETX101 uses one-time intracerebral ventricular delivery (ICV). In SCN1A heterozygous mice, administration of ETX101 normalizes survival and prevents hyperthermia induced seizures up to 300 days, and in non-human primates, a single ICV administration of ETX101 led to broad distribution throughout the CNS without adverse histopathological observations. ETX101 is now on track to enter clinical trials in 2021.

4. Rare and ultra-rare diseases

4.1. Soticlestat, Takeda pharmaceuticals

4.1.1. Presented by Mahnaz Asgharnejad, PhD

Soticlestat (TAK-935/OV935) is a potent, selective CNS acting inhibitor of cholesterol 24-hydroxylase (CH24H). CH24H converts cholesterol to 24*S*-hydroxycholesterol (24HC), which is a positive allosteric modulator of N-methyl-D-aspartate (NMDA) receptors in the brain [33]. Thus, soticlestat administration can modulate neural glutamate activity leading to decreased hyper-excitability in the brain. In a model of Dravet Syndrome (DS) with $Scn1a^{+/-}$ mice, soticlestat treatment led to a significantly greatly proportion of seizure-free mice compared to controls, and also decreased frequency of generalized tonic-clonic seizures and seizure severity [34].

Soticlestat has been studied in healthy volunteers in a multiple-rising dose phase I trial which showed dose-dependent serum plasma levels and decrease in plasma 24HC levels. This dose-dependent and time-dependent decrease in 24HC may be a potential biomarker for target engagement [35]. In the Phase 2 ELEKTRA Trial, a global multicenter, randomized, double-blind, placebo-controlled study with enrollment of 141 patients ages 2–17 with DS or Lennox Gastaut syndrome (LGS), soticlestat demonstrated a 27.8% median reduction from baseline in seizure frequency (convulsive for DS and drops for LGS) compared to a 3.1% median increase in patients taking placebo during the 12-week maintenance period (median placebo-adjusted reduction = 30.5%; $p = 0.0007$) [36]. In the DS cohort ($n = 51$), patients treated with soticlestat demonstrated a 33.8% median reduction in convulsive seizure frequency compared to a 7.0% median increase in patients taking placebo during the full 20-week treatment period of the study (median placebo-adjusted reduction in seizure frequency is 46.0%; $p = 0.0007$). In the LGS cohort ($n = 88$), patients treated with soticlestat demonstrated a 20.6% median reduction in drop seizure frequency compared to a 6.0% median reduction in patients taking placebo during the full 20-week treatment period of the study (median placebo-adjusted reduction in seizure frequency is 14.8%; $p = 0.1279$). Soticlestat was well tolerated, and safety data were consistent with findings in previous studies. A phase 3 study in LGS was registered in July of this year.

4.2. UX-068, Ultragenyx

4.2.1. Presented by Melanie Brandabur, MD

Creatine Transporter Deficiency (CTD) is an X-linked recessive disorder secondary to mutations in SLC6A8, leading to severe developmental delay, particularly related to speech, language, and intellectual delay, as well as seizures, behavioral and autistic manifestations in many patients. In these patients, brain creatine levels range from undetectable to 20% of normal by MR spectroscopy [37]. Ultragenyx has taken over the Vigilan CTD natural history study to identify clinical characteristics and potential assessment tools and biomarkers. They have developed a lead compound, UX068, a prodrug that traverses the blood brain barrier and releases creatine to the neurons. In preclinical studies, UX068 was delivered to creatine transporter knockout mice leading to widespread delivery of creatine throughout the brain [38]. The ultimate goal is to use this small molecule approach to replenish cerebral creatine.

4.3. VAL-0417 and VAL-1221, Parasail Therapeutics

4.3.1. Presented by Matthew Gentry, PhD

Lafora disease is a severe progressive myoclonic epilepsy caused by an autosomal recessive mutation that results in hyperphosphorylated glycogen deposits in the central nervous system. These Lafora bodies accumulate in neurons and glia, leading to toxicity and rapid neurologic decline [39]. Both mutations in the malin and laforin genes on chromosome six led to the development of Lafora Disease [40]. In collaboration with Parasail Therapeutics, the agent VAL-4017 was developed, an antibody-amylase compound that uses a Fab fragment to enter cells and carries an amylase to break down the Lafora bodies. In laforin knockout mice VAL-4017 administration led to degradation of Lafora bodies throughout the brain, and the metabolic profile of these treated mice mirrors that of wild-type mice [41]. Recently, the agent has been reformulated for primate brain administration, and Parasail is currently determining the dosage and establishing biomarkers.

4.4. Epidiolex for tuberous sclerosis

4.4.1. Presented by Farhad Sahebkar, MD

Epidiolex is a plant-derived cannabinoid with a novel, though poorly understood, mechanism of action. Epidiolex is indicated for the treatment of seizures associated with Lennox–Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex (TSC) in patients 1 year of age and older, with side effects including somnolence, decreased appetite, diarrhea, pyrexia, convulsion, hepatic toxicity and suicide [42,43]. The clinical development plan consisted of 5 randomized double-blind placebo-controlled phase 3 trials including 1 that lead to the recent FDA approval of Epidiolex in TSC-associated seizures. This study met its primary endpoint with statistically significant and clinically significant seizure reductions in both the 25-mg and 50-mg dosage groups [44]. The most common adverse side effects were diarrhea, somnolence, and decreased appetite. Supplemental new drug application for TSC indication was approved in July 2020.

4.5. ZX008, Zogenix

4.5.1. Presented by Glenn Morrison, MSc, PhD

Fenfluramine (Fintepla) is a selective serotonin reuptake inhibitor recently FDA approved for patients with Dravet Syndrome. Two positive Phase 3 trials support this approval, which both found that the addition of fenfluramine to a patient's existing ASM regimen led to significant increases in median percent seizure reduction from baseline [45]. A Phase 3 study of fenfluramine for the treatment of Lennox–Gastaut Syndrome also met its primary endpoint, with patients taking fenfluramine experiencing a 26.5% median reduction in monthly drop seizures, compared to 7.8% in those taking placebo [46]. Moreover, patients given fenfluramine were significantly more likely to be rated by clinicians as "much or very

much improved" on the clinical global impression scale. Common adverse events included decreased appetite, diarrhea, and vomiting, and there were no cases of valvular heart disease or pulmonary artery hypertension observed. Given the efficacy and safety in patients with LGS, fenfluramine may be a useful anti-seizure medication for this patient population.

4.6. ANAVEX2-73, Anavex Life Sciences

4.6.1. Presented by Walter E. Kaufmann, MD

ANAVEX2-73 is a sigma-1 receptor (SIGMAR1) agonist capable of modulating neuroinflammatory, neurodevelopmental and neurodegenerative processes. Normally, activation of microglia leads to glutamate release, which can result in excitotoxity and developmental impairment. Activation of SIGMAR1 attenuates this inflammatory response leading to decreased glutamate release and increased astrocyte uptake of glutamate, ultimately resulting in restored physiologic neuronal function [47]. Preclinical studies suggest that activation of sigma-1 receptors (SIGMAR1) can restore cellular homeostasis and thus attenuate seizures and other types of neurologic dysfunction. Guo and colleagues investigated the SIGMAR1 allosteric modulator SKF83959 in three mouse models of epilepsy, MES, PTZ, and kainic acid-induced status epilepticus, and found that SKF83959 both had an anti-seizure effect and led to decreased cortical epileptiform activity without altering motor function [48]. Moreover, the dextromethorphan analog dimemorfan, which has a high affinity for SIGMAR1 receptors, reduced seizures in a dose-dependent manner in kainic acidinduced status epilepticus mouse models [49].

ANAVEX2-73 has been explored in a phase 2 trial of safety, tolerability, and efficacy in young adults with Rett syndrome, with primary endpoints including the caregiver administered Rett Syndrome Behavioural Questionnaire (RSBQ), a scale that evaluates abnormal behaviors and motor and autonomic symptoms influenced by behavior, as well as the clinician administered Clinical Global Impression - Improvement (CGI-I) Scale. The drug showed no serious adverse events and only three low grade adverse events. Both the RSBQ and the CGI showed significant decreases in scores between week 0 and week 7 (end-of-treatment), and improvements in both RSBQ and CGI correlated significantly. Given the possibility of bias, and because of its importance in Rett syndrome pathogenesis, glutamate was used as a biomarker for a more objective analysis of efficacy. Glutamate also decreased significantly from week 0 to week 7, and these changes were correlated with improvements in efficacy endpoints. Overall, the agent appears promising for the treatment of Rett syndrome.

4.7. AE1, Aeovian Pharmaceuticals

4.7.1. Presented by Stelios Tzannis, MS, PhD

Mammalian target of rapamycin (mTOR) is a protein kinase involved in numerous physiological functions including regulation of cell growth, apoptosis, and metabolism [50]. Its upregulation, as a consequence of upstream genetic mutations, leads to the development of numerous acquired epilepsies. mTOR inhibitors have been approved for the treatment of patients with Tuberous Sclerosis Complex (TSC); however they exhibit toxicity that limits their clinical utility [51]. While inhibition of aberrant mTORC1 activity is primarily responsible for the disease reversal and prevention, the toxic side effects of current mTOR inhibitors are mediated by mTORC2, the other subclass of the mTOR pathway. Aeovian has capitalized on this by developing a new generation of compounds that selectively inhibit mTORC1, with the potential to circumvent the adverse effects arising from mTORC2 inhibition. One such exploratory compound, AE1, significantly reduces seizures and normalizes mTORC1 activity, to a similar degree as rapamycin in the Tsc1-cKO mouse model of TSC-related epilepsy [52]. Further, it does not inhibit mTORC2, as assessed by biomarker analysis and confirmed by the lack of induction of immunosuppression. These novel, highly selective mTORC1 inhibitors may offer significant advantages by increasing the treatment therapeutic window, possibly improving treatment efficacy without the dose-limiting side effects of the current non-selective mTOR inhibitors.

4.8. PRAX-330, Praxis Precision Medicines

4.8.1. Presented by Kris Kahlig, PhD

While a large, transient voltage-gated sodium current initiates the classical action potential, a small component of sodium current, the persistent sodium current, remains and substantially contributes to subthreshold neuronal excitability and hyperexcitability in a number of disease states [53]. Selective persistent sodium current blockers such as PRAX-330/GS458967/GS967 target this persistent sodium current, allowing for the preservation of action potential amplitude while selectively decreasing the underlying hyperexcitability. In the maximal electric shock mouse model of generalized tonic-clonic seizures, administration of persistent sodium current blockers, such as PRAX-330 or PRAX-562, led to robust anti-convulsant activity at well-tolerated doses. PRAX-330 was also active across a number of SCN8A variants, readily inhibiting the persistent sodium current, decreasing seizures, and early mortality in animal models of epileptic encephalopathies [54]. Given this early evidence, selective inhibition of persistent sodium current has substantial potential as a precision medicine approach for sodium channel developmental and epileptic encephalopathies.

4.9. NBI-921352, Neurocrine Biosciences

4.9.1. Presented by Dietrich Haubenberger, MHSc, MD

The sodium channel Nav1.6 is encoded by the gene SCN8A and expressed throughout the brain in a number of excitatory pathways. Children born with gain-of-function mutations in the SNC8A gene present with SCN8A Developmental and Epileptic Encephalopathy (SCN8A-DEE) [55]. Current ASMs lack the therapeutic index needed to achieve seizure freedom in many of these patients. NBI-921352 is a novel ASM that selectively inhibits the Nav1.6 sodium channel, while maintaining a high therapeutic index and tolerability. In an SCN8A-DEE mouse model, NBI-921352 completely suppresses seizures in a modified 6-Hz assay with a greater than one-hundred-fold potency compared to phenytoin, carbamazepine, and lacosamide. In Phase I studies, the pharmacokinetics were dose proportional in healthy subjects, with no severe adverse effects and no adverse effects leading to subject withdrawal. In a single center, open-label, randomized study of the interaction between NBI-921352 and phenytoin, coadministration of phenytoin increased the peak plasma concentration of NBI-921352 by 22%, though the terminal elimination half-life did not change. No deaths or serious adverse events were noted in the study, and overall NBI-921352 has been well tolerated when coadministered with phenytoin. A pediatric granule formulation has also been explored in a single center, open-label, randomized, crossover study comparing the granules to adult immediate release tablets. This granule formulation was bioequivalent to the adult formulation. Neurocrine Biosciences received a license in 2020 to begin a clinical trial of NBI-921352 in patients with SCN8A-related epilepsy.

5. Reformulated drugs and other therapies

5.1. Diazepam buccal film, Aquestive Therapeutics

5.1.1. Presented by Michael A. Rogawski MD, PhD

Diazepam buccal film (DBF) is a novel delivery system for the benzodiazepine diazepam that is under development as a "when needed" treatment for acute repetitive seizures (seizure clusters). The DBF formulation is a rectangular (roughly 2 cm × 4 cm, or smaller) thin polymer-based film incorporating uniformly dispersed diazepam. Upon placement on the buccal mucosa inside the cheek, the film adheres, hydrates, and dissolves, rapidly releasing diazepam [56]. Several other benzodiazepine formulations are FDA approved for the treatment of acute repetitive seizures, including diazepam rectal gel (DRG; Diastat™), which has been available for more than twenty years, as well as diazepam nasal spray, which became available in 2020. DBF is packaged in a foil laminate pouch only slightly larger than the film dosage unit, which can be carried discretely by the patient and renders the product stable at body temperature and resistant to water damage. In clinical studies, DBF was easily administered by patients themselves as well as by caregivers.

Two clinical studies of DBF were conducted in patients. The first study used a crossover design and compared the bioavailability of diazepam under interical and ictal/perictal (within 5 min of a seizure) conditions in adults with generalized tonic-clonic or focal impaired awareness seizures. Among 21 subjects who participated in both study phases, within-patient comparisons showed that diazepam exposures (C_{max} and AUC) were similar when DBF was administered under the two conditions. The results indicate that use of DBF within close proximity to a seizure does not alter the absorption of diazepam. The second study compared the diazepam plasma levels achieved with DBF (dosed according to a weight-based regimen) and the legacy DRG product (dosed on a weight basis as recommended in the label). The treatments were administered following a moderate fat meal. Thirty-one patients with epilepsy were enrolled and 28 subjects (13 males, 15 females) had available pharmacokinetic profiles for both DBF and DRG. There was a 28-day washout period between doses. Both the rectal gel and film performed similarly from a pharmacokinetic standpoint, but the geometric mean C_{max} values for DBF were more consistent across weight groups than for DRG (Fig. 4). Also, in aggregate, the overall variability of C_{max} values was less for DBF than for DRG, suggesting that DBF will provide more reliable performance than the legacy product. In a long-term safety and usability study in 72 patients in which DBF was administered 1240 times, DBF was successfully placed 99.6% of the time.

5.2. Staccato alprazolam

5.2.1. Presented by Jouko Isojarvi, MD, PhD

Staccato alprazolam is in development for rapid cessation of seizures. It is not currently approved in any region. The staccato inhaler is an aerosolization device that allows drugs to be delivered deeply into the lung tissue for rapid systemic exposure. A phase 2a proof-of-concept study showed that Staccato alprazolam rapidly suppressed epileptiform activity in photosensitive patients [57]. An in-patient phase 2b study explored feasibility of dosing and efficacy of Staccato alprazolam in patients with predictable seizure patterns. This phase 2b double-blind study enrolled 116 adult patients with a diagnosis of focal or generalized epilepsy and documented history of predictable seizure episodes. Prior to randomization, patients must have experienced more than four seizure episodes with predictable pattern during the preceding four weeks. The Epilepsy Study Consortium (ESC) screened seizures for inclusion, and patients were randomized on day 1 of admission to the EMU to either 2-mg or 1-mg doses of Staccato alprazolam or placebo. A single predictable seizure episode was treated for each subject. EMU length of stay ranged from 2 to 8 days. The primary endpoint of the study was the proportion of responders in each treatment arm. A responder was defined as seizure activity cessation within 2 min and no recurrence of seizure activity within 2 h after dosing. Demographic characteristics of each group and seizure type and background ASM profile prior to trial enrollment were similar. Responder rate was statistically significantly higher for both Staccato alprazolam doses versus placebo (Fig. 5). Mean time to seizure cessation after dosing with Staccato alprazolam was 33.9 s, supporting rapid systemic absorption and onset of efficacy of Staccato alprazolam. Treatment-emergent adverse events were more frequent with Staccato alprazolam than with placebo but were predominantly mild or moderate in intensity. Overall treatment was well-tolerated and there were no serious or severe adverse events. Sedation and alertness scores on a visual analog scale were not notably different across three groups. These results support the efficacy and safety of *Staccato* alprazolam in treating acute seizure episodes and warrant further study.

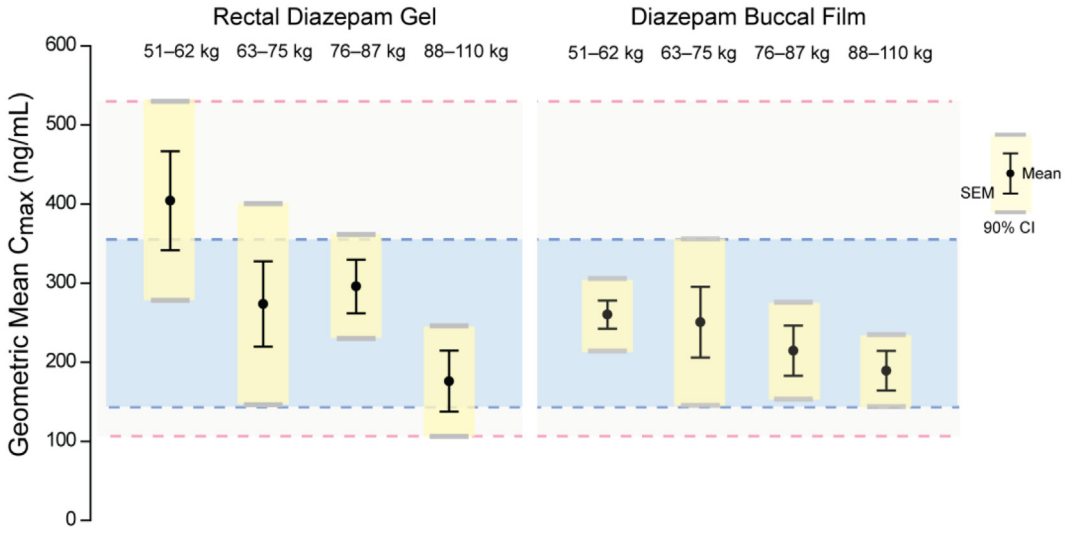

Fig. 4. Pharmacokinetics of diazepam rectal gel versus diazepam buccal film following weight-based dosing.

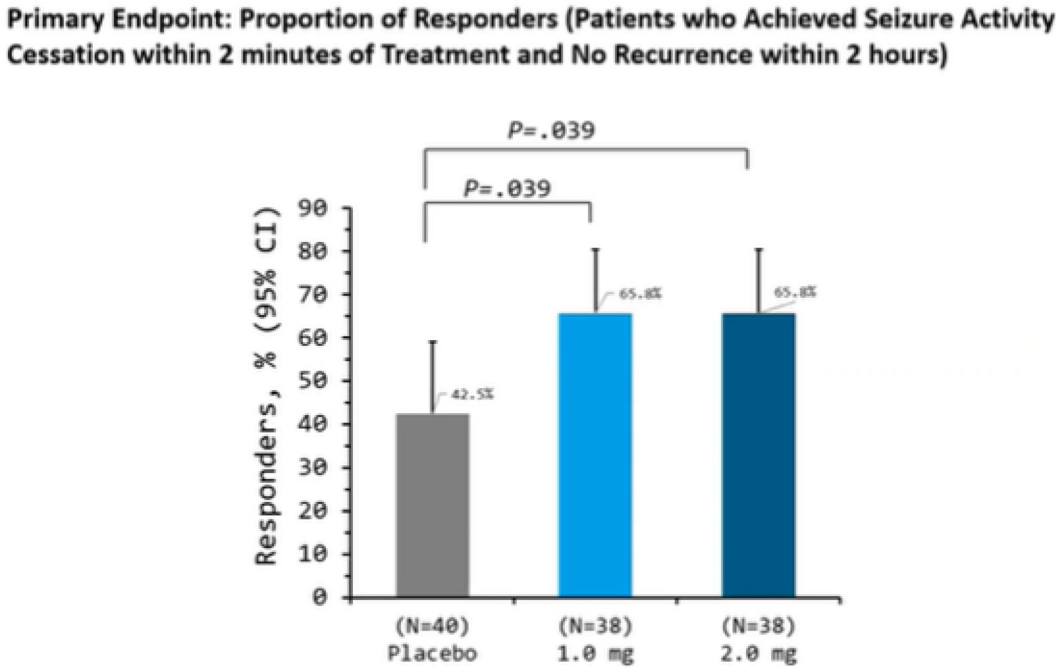

Fig. 5. Proportion of responders to Staccato Alprazolam aerosolized inhaled following a single predictable seizure episode. A responder was defined as seizure activity cessation within 2 min and no recurrence of seizure activity within 2 h after dosing.

5.3. Novel intramuscular diazepam, XP-0863

5.3.1. Presented by Anh Nguyen, MD; Khaled Junaidi, MD

Xeris reformulates drugs that are difficult to store or use into easily portable and deliverable mechanisms. One technical approach pursued by the firm has been to replace water with non-aqueous bio-compatible liquids that improve ease of use of pharmaceutical products. The formulation of diazepam is of particular interest in this context, given the variability of diazepam delivery mechanisms based on clinician and patient preference, and on seizure type. The Xeris solution (Xeris XP-0863) is 20 times more concentrated than other formulations, so that a smaller volume injection can provide full dose drug delivery.

The first Phase 1a study was a comparative pharmacokinetic study that investigated XP-0863 after subcutaneous (SC) and intramuscular (IM) administration, relative to rectal administration of commercially available diazepam gel. The dose administered was 10 mg across all conditions. This study showed that pharmacokinetic profiles were most similar between XP-0863 IM and per-rectum formulations. SC administration exhibited a less similar PK profile to IM and per-rectum formulations, specifically within the first 8 h after administration (Fig. 6). A follow-up Phase 1b study was performed as a three-treatment, three-way crossover study in healthy adults with the goal of comparing pharmacokinetic profiles of two different IM doses of XP-0863 and standard weight-based dosing of commercially available rectal diazepam gel. The maximum concentration demonstrated dose proportionality between the two doses of XP-0863, and the AUC parameters of larger dose of the novel agent were greater than that of the smaller dose and rectal diazepam gel.

Overall, XP-0863 (0.25 mg/kg) showed comparable maximum concentration to that of rectal gel, but an increased overall exposure due to longer time of increased drug concentration. XP-0863 also showed dose-proportionality, and recently Xeris underwent successful FDA interaction that can inform a Phase 3 registration study. The team envisions this work creating a ready-to-use prefilled and premeasured device for delivery of diazepam, analogous to the EpiPen for epinephrine administra-

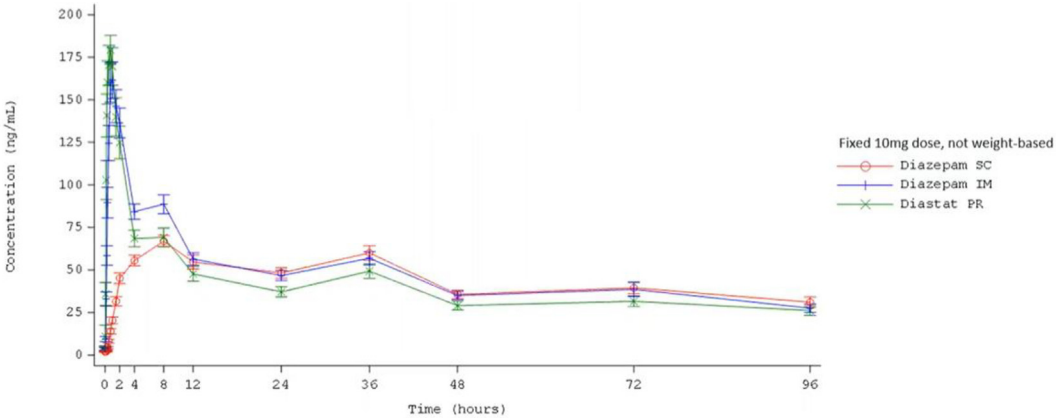

Fig. 6. Phase 1a comparative pharmacokinetic profile of XP-0863 after subcutaneous (SC) and intramuscular (IM) administration, relative to rectal administration of commercially available diazepam gel.

tion. Next steps include seeking a development partner and performing the Phase 3 study.

5.4. Ct-010

5.4.1. Presented by Dan Abrams, MD

Cerebral Therapeutics develops specialized drugs for medically refractory epilepsy. CT-010 is a specialized formulation of sodium valproate developed for intracerebroventricular (ICV) delivery by a proprietary implantable infusion system (Fig. 7). Continuous ICV delivery of valproate, at substantially lower doses than when administered orally or IV, improves efficacy while reducing systemic side effects of this medication.

A recent Phase IIa study evaluated five subjects who were implanted with an infusion system to continuously deliver ICV valproate following a 30-day seizure baseline period. Doses were evaluated during a blinded phase of 15–60 mg/day administration, focusing on safety and pharmacokinetics. Following the blinded period, there was an open-label follow-up period evaluating safety and efficacy, with doses between 80 and 200 mg/day. Four subjects were female, one was male, with monthly median baseline seizures of 28. All subjects had severe refractory epilepsy with temporal component, their seizures had failed at least six oral AEDs including oral valproate, and were unable to work and perform activities of daily living. Responses at 160 mg/day dosing are captured in Fig. 8, as are average percent seizure reduction by daily dose for each of the five subjects. Patients have experienced prolonged improvement with the therapy. The median seizure reduction at month 24 was 79 percent.

A Phase IIb blinded, randomized placebo-controlled study of CT-010 is currently enrolling and will include up to 70 subjects for 52 evaluable subjects in Australia, Israel, and the United States. The primary endpoint is seizure frequency with secondary endpoints including responder rate, reduction in seizure severity, and psychometric scales among others.

Fig. 7. Cerebral Therapeutics mechanism for intracerebroventricular (ICV) delivery of a specialized formulation of sodium valproate.

Delivering therapeutics across the blood-brain barrier has been a major obstacle to successful drug development in CNS diseases, and it is critical to enabling safe and effective treatments. Cerebral Therapeutic's ICV therapy development pipeline includes work in other refractory epilepsy subtypes, as well as drug candidates for other CNS indications such as Parkinson's Disease and ALS.

5.5. The gut–brain axis and epilepsy

5.5.1. Christopher Reyes, PhD

A complex ecology exists in the GI tract and links the gut and the central nervous system. This link manifests via both neurochemical circuitry and neuroinflammation. Broadly, this gut–brain axis can be investigated by looking at microbes in the gut and their influence on metabolites, as well as genes and neurophenotypes. Bloom is focused on this biology because of the opportunity to meet a high need level of therapy for neurologic conditions. Microbiome-based drugs that are genetically optimized have significant advantages over naturally isolated bacterial strains. One important platform is the GOLD platform (Genetically Optimized Living Drugs). This approach breaks down clinical or experimental biologic samples into key commensal species and key metabolites. Engineering approaches then open doors to therapeutic development opportunities including gut microbiomes capturing commensal bacteria with functionality optimized for biopharma properties.

In epilepsy, prototype strains BL-001 have generated significant effects in multiple animal models. The presumed mechanism of action includes changes in neurochemical circuitry via enhanced enzymatic inhibition or pharmacokinetics via increased engraftment. One epilepsy-specific area of work relates to the ketogenic diet. Propensity for two specific classes of bacteria are enriched in response to this diet in mice, offering a plausible mechanism for its anti-epileptogenic effect [20]. Another initiative in 200 healthy volunteers giving stool samples for culture, indicates that those on the ketogenic diet have similar abundance of these same two species, Akkermansia and Parabacteroides. The team from Bloom Science is currently in the process of doing fecal mouse transplant experiments where fecal samples from patients pre- and post- ketogenic diet are implanted into 6-Hz seizure mouse model. In the first three patient samples, a significant response from post-KD transplant is seen.

5.6. Ganaxolone IV

5.6.1. Presented by Joe Hulihan, MD

Ganaxolone is a synthetic analog of allopregnanolone. Investigations with the IV formulation are focused in status epilepticus, with studies of the oral formulation being conducted in rare pediatric epilepsies. The mechanism of action of ganaxolone is allosteric modulation of both synaptic and extrasynaptic GABA-A receptors, in contrast to conventional GABA-A agonists which act only synaptically [58]. Unlike synaptic GABA-A receptors, extrasynaptic receptors are not internalized during status epilepticus and therefore represent a plausible site of action for cessation of ongoing seizures. Pharmacokinetically, IV ganaxolone is rapidly absorbed with time to maximal serum concentration occurring within minutes. Brain penetration is also rapid and occurs within ten minutes as shown in animal pharmacokinetic and human pharmocodynamic studies.

Status epilepticus (SE) occurs along a clinical continuum ranging from initial presentation to established SE (benzodiazepine failure), refractory SE (failure at least one second-line ASM) and super-refractory SE (failure of anesthetic wean). An open-label,

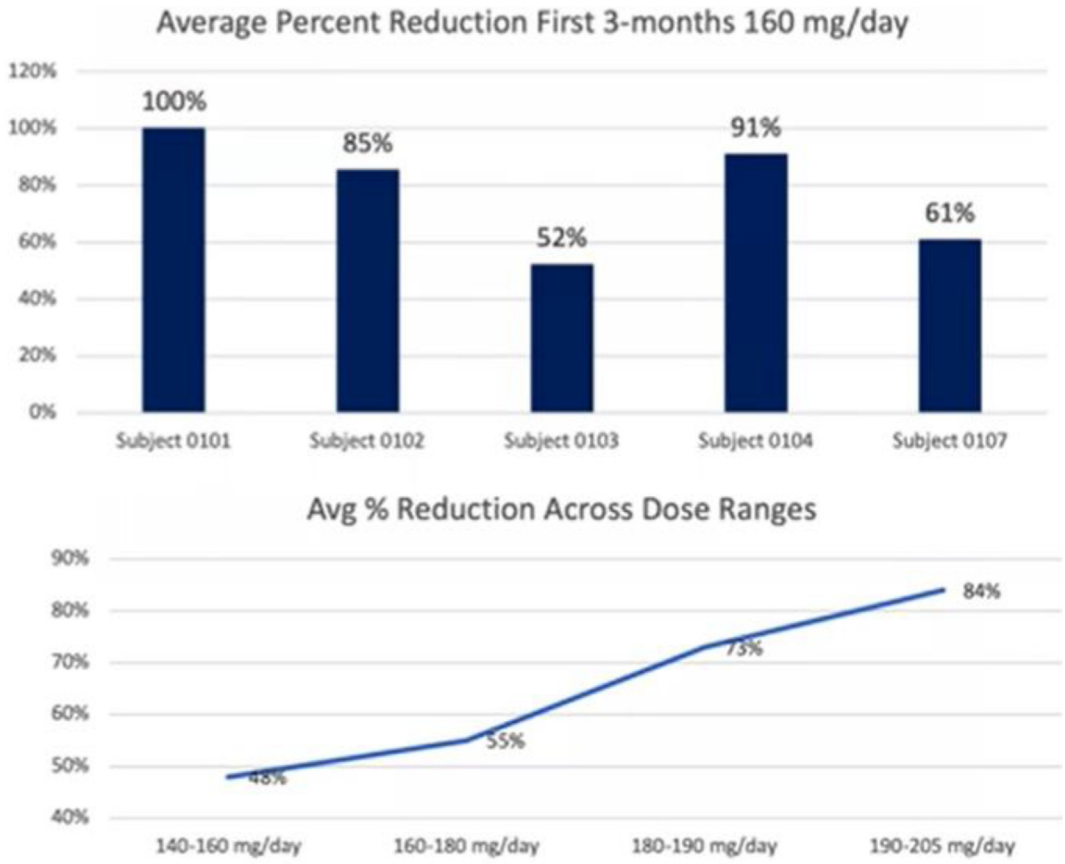

Fig. 8. Phase IIa study results of Cerebral Therapeutics ICV system for delivery of sodium valproate, displaying average percent reduction of seizures in three months and average percent reduction across dose ranges.

Phase 2 study of Ganaxolone (NCT03350035) in refractory SE enrolled 17 patients whose seizures had failed at least one second-line IV ASM. The primary endpoint was no escalation to IV anesthesia within 24 h. The study assigned patients to one of three dose levels – 500 mg/day, 650 mg/day and 713 mg/day of IV ganaxolone. All patients received a bolus followed by continuous infusion. In addition to total daily dose, the groups also differed in the duration at which the target concentration of 500 ng/mL was maintained: 4 h for the low-dose group, 0 h for the mid-dose group and 8 h for the high-dose group. Five of the 17 enrolled patients presented in convulsive SE and 12 in non-convulsive SE. The mean number of failed ASMs was 2.9 (including benzodiazepines), and seizures of 14 of 17 patients had failed two or more second-line ASMs. None of the patients progressed to IV anesthesia within 24 h and all but one was free of status epilepticus by investigator report through 24 h from infusion initiation. There was a dose-dependent trend towards avoiding escalation to IV anesthetics through 72 h, with no patients in the high-dose group and 2 of 5 patients in the low-dose group requiring this intervention. Median time to status cessation was five minutes. With regard to safety, 50 adverse events occurred in 16 patients. The most common adverse events were hypotension and somnolence. Two patients developed sedation, a serious adverse event assessed as treatment-related. On post hoc EEG review, patients in the mid-dose group (who did not reach the target ganaxolone concentration after the initial bolus) had the lowest reduction in EEG seizure burden of the three dose groups.

Two upcoming Phase 3 studies, one in the US and one in Europe, will evaluate ganaxolone versus placebo added to standard of care in refractory SE. Study participants will receive an IV bolus followed by a 48-h infusion that includes a 12-h taper. Target enrollment is 124 patients for the US study and 70 patients in Europe. The US study will have co-primary endpoints of (1) the proportion of participants with cessation of status epilepticus within 30 min of study drug initiation and (2) the proportion with no progression to anesthesia for 36 h. Endpoints for the European study are being finalized and will also encompass the attributes of onset and durability of effect.

5.7. NRL-3

5.7.1. Presented by Adrian Rabinowicz, MD

Seizure emergencies typically occur in the community setting without oversight from trained medical personnel. Out-of-hospital treatments may reduce admissions and therefore healthcare costs. Intranasal delivery of drug is one potentially important avenue to improve out-of-hospital care given ease of use. Diazepam nasal spray development for seizure clusters demonstrated that this mechanism of delivery is feasible with the inclusion of Intravail. In developing NRL-3 for intranasal administration, the product must prove itself to be active, soluble with an effective spray volume, and bioavailable in an amount that would have an effect on seizure activity.

Intravail is a proprietary alkylsaccharide derivative that is a potent permeation enhancer for delivery of peptide and protein drugs. Intravail has also been shown to have transient activity on mucosal membranes on the order of 30–40 min. A number of existing products used in clinical neurology currently use the intravail system, including sumatriptan for migraine and nalmefene for synthetic opioid overdose. NRL-3 is a pipeline asset from Neurelis in the initial stages of formulation development that aims to use intravail to provide an alternative to intravenously administered medication, with preclinical studies forthcoming.

6. Conclusions

Despite the numerous obstacles presented by the COVID-19 pandemic, the above talks outline the continued dedication toward advancing epilepsy therapy throughout the community. Numerous trials halted in 2020 have since resumed with increasing availability of vaccination, and it is clear many innovations are on the horizon. Numerous preclinical models present novel drug targets, while remote seizure monitoring continues to gain reliability. As COVID has highlighted innumerable barriers to care for patients, these advances are critical to ensuring people with epilepsy are consistently monitored and appropriately treated.

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Conflict of interest

The authors have no competing interests.

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