Conference Proceedings

The Epilepsy Foundation's 4th Biennial Epilepsy Pipeline Update Conference

Jacqueline A. French a, Steven C. Schachter b,c,d,⁎, Joseph Sirven e, Roger Porter f,g

a Department of Neurology, New York University Langone Medical Center, New York, NY, USA
b Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA, USA
c Department of Neurology, Harvard Medical School, Boston, MA, USA
d Consortium for Improving Medicine Through Innovation and Technology, Boston, MA, USA
e Department of Neurology, Mayo Clinic Scottsdale, Scottsdale, AZ, USA
f Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA
g Department of Pharmacology, USUHS, Bethesda, MD, USA

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A B S T R A C T

On June 5 and 6, 2014, the Epilepsy Foundation held its 4th Biennial Epilepsy Pipeline Update Conference, an initiative of the Epilepsy Therapy Project, which showcased the most promising epilepsy innovations from health-care companies and academic laboratories dedicated to pioneering and advancing drugs, biologics, technologies, devices, and diagnostics for epilepsy. Speakers and attendees included emerging biotech and medical technology companies, major pharmaceutical and device companies, as well as investigators and innovators at the cutting-edge of epilepsy. The program included panel discussions on collaboration between small and large companies, how to get products in need of funding to the marketplace, who is currently funding epilepsy and CNS innovation, and how the NIH facilitates early-stage drug development. Finally, the conference featured the third annual “Shark Tank” competition. The presentations are summarized in this paper, which is followed by a compilation of the meeting poster abstracts.

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1. Introduction

On June 5 and 6, 2014, the Epilepsy Foundation (EF), based in Landover, Maryland, USA, held its 4th Biennial Epilepsy Pipeline Update Conference, an initiative of the Epilepsy Therapy Project, at the Hyatt Regency in San Francisco, California. SHOWCasing the most promising epilepsy therapies from health-care companies and academic laboratories dedicated to pioneering and advancing drugs, biologics, technologies, devices, and diagnostics for epilepsy, this conference also featured the third annual “Shark Tank” competition. On the day following the Pipeline conference, a day-long program was held for people with epilepsy, families, and advocates.

The Pipeline Update Conference brought together decision-makers with shared interests in epilepsy treatment and diagnosis and product development. Speakers and attendees included emerging biotech and medical technology companies, major pharmaceutical and device companies, as well as investigators and innovators at the cutting-edge of epilepsy and advances in treatment of central nervous system (CNS) diseases.

The program also included panel discussions on topics such as the role of collaboration between small and large companies, how to get products in need of funding to the marketplace, who is funding epilepsy and CNS innovation today, and how the NIH facilitates early-stage drug development.

“The Epilepsy Foundation’s Pipeline Conference is recognized as the premier business and scientific forum for driving innovation in the field of epilepsy and neurology,” said Philip M. Gattone, President and CEO of the Epilepsy Foundation. “Each year, this conference brings together great minds in R&D, clinical thought leaders, investors, and industry leaders who are focused on accelerating epilepsy drug and device development.”

“This conference has grown to attract an impressive audience. Companies are recognizing the need for and promise in developing potential new therapeutics for epilepsy,” said Jacqueline French, MD, Professor of Neurology, New York University.

The “Shark Tank” competition, held on the second day of the conference, is designed to spur breakthroughs that will change the lives of people living with epilepsy. Over the past two years, entrepreneurs, scientists, clinicians, industrial design engineers, and members of the epilepsy community have been recognized for their truly inventive product concepts, which have ranged from promising new therapeutics or technologies to new products that improve the quality of life for people living with epilepsy. At the 2014 Epilepsy Pipeline Conference, the...
winner was selected by live audience vote from the epilepsy community and a panel of distinguished reviewers. The Shark Tank award recipients received international recognition and cash prizes totaling $200,000 to fund the development of novel ideas.

The authors of this report attended the conference and wrote the text based on hearing the presentations at the conference as well as reviewing the meeting recordings (http://www.epilepsy.com/information/professionals/epilepsy-foundation-events-webcasts), which are recommended to readers interested in more details as well as the question-and-answer sessions. Most but not all of the presentation summaries were reviewed for accuracy by speakers. The affiliations and titles of authors are accurate as of the date of their presentation, but may have since changed.

2. Session 1: introduction and keynote address

2.1. Introduction. Philip Gattone, President and Chief Executive Officer, Epilepsy Foundation; Warren Lammert, Chairman, Board of Directors, Epilepsy Foundation

Mr. Phillip Gattone, CEO and President of EF, opened the conference. Mr. Gattone remarked that this Pipeline Conference is the first to be webcast (http://www.epilepsy.com/information/professionals/epilepsy-foundation-events-webcasts) and streamed live over Epilepsy.com. He welcomed all participants and stressed the importance of this conference, which helps to uniquely unify the epilepsy community with active participation from patient advocates, venture capitalists, basic scientists, pharmaceutical and device industry companies, and clinicians. Mr. Gattone then introduced Mr. Warren Lammert, Chairman of the Epilepsy Foundation Board of Directors. Mr. Lammert also welcomed all participants to this unique conference and highlighted how this conference further the vision of the Epilepsy Foundation research mission in order to help bolster the translation of novel ideas into new treatments for patients with epilepsy in an expedited manner.

2.2. The annual state of the drug pipeline — keynote. Jacqueline French, MD, Professor of Neurology, New York University; Co-director, Epilepsy Research and Epilepsy Clinical Trials, NYU Comprehensive Epilepsy Center; President, Epilepsy Study Consortium

Dr. French highlighted the fact that although there are many treatments that have become available for epilepsy, there is still a paucity of treatment for those who have drug-resistant epilepsy and for numerous epilepsy syndromes. In particular, she pointed out that a better way to predict the effectiveness of various drugs is needed. There are still too few options for newly diagnosed patients as many of the advances in epilepsy management are directed to those with drug-resistant epilepsy. In addition, there is a paucity of treatments for the comorbidities of epilepsy. Even more importantly, there are no therapies that truly prevent the disease. Most treatments are geared towards the concept of preventing further seizures but we do not have any antiepileptogenic or disease-modifying therapies. Even when a drug is approved, neither animal models nor clinical trials predict if a drug will be successful in day-to-day clinical practice. Despite many new approved antiepileptic drugs (AEDs), there are few in phase II trials [1]. Dr. French summarized her presentation by reminding the audience that so much more work is needed to discover new AEDs with the ability to truly help patients.

2.3. Annual state of the device pipeline — keynote. Robert Fisher, MD, PhD, Muslah Saal Professor of Neurology, Director, Stanford Comprehensive Epilepsy Program

Dr. Fisher divided his comments into different categories of devices. Specifically, he discussed seizure alerts or predictors; adherence monitors; clinical information systems; optical control or optogenetics; new ways of drug delivery; focal energy such as radiosurgery, laser, and ultrasound; and neurostimulation.

Regarding seizure alerts, SmartWatch and EpiAlert are currently available. These devices alert caregivers of seizures via wireless mobile phones or PDAs. Novel systems that alert patients and caregivers to their seizures are being devised. These systems operate on seizure detection by electrodermal responses, muscle activity by electromyography, or electroencephalography (EEG) patches [2–4]. For seizure prediction, a device is in trials in which implantable EEG leads are placed in the area of a seizure focus which attach to a personal advisory device that alerts patients when a seizure is likely to occur [5].

Adherence monitors are compliance-alerting devices with the ability to instantly provide information about pill-taking, blood test readouts of AED levels, or even when a pill reaches the stomach. Related to compliance devices are seizure diaries with three currently available online epilepsy diaries: My Epilepsy Diary, SeizureTracker.com, and Patients Like Me.

These diary applications help to better provide information to health-care practitioners and to the patients themselves as self-management tools.

Optogenetics is a promising technique where light-induced signals can either excite or inhibit neuronal activity, carrying with it the promise of enhancing epilepsy management. One of the provided examples was the idea of using a yellow light that activates a rhodopsin gene, which in turn opens a chloride channel, hyperpolarizing a transfected neuron and rapidly stopping the neuron from firing [6].

There are a number of therapeutic devices with the ability to deliver treatment by novel approaches including inhalation, buccal absorption, and infusion pumps. Focal energy can also be delivered to ablate epileptic tissue, such as with stereotactic radiosurgery or thermal ablation [7]. Focused ultrasound is a very new potential treatment with some promise. Lastly, various neuromodulatory techniques, including vagus nerve stimulation, transcranial magnetic brain stimulation, trigeminal nerve stimulation, thalamic deep brain stimulation, and responsive neurostimulation, are either currently available or being trialed [8,9].

3. Session 2: what was better in 2013 than 2012 — progress in epilepsy therapy

3.1. FDA and epilepsy trials: past, present, and future. Russell Katz, MD, Consultant, Epilepsy Study Consortium

Dr. Russell Katz, consultant to the Epilepsy Study Consortium and former Food and Drug Administration (FDA) official, discussed the FDA and epilepsy trials: past, present, and future. He noted that in particular, there are four areas in which the FDA is considering new forms of acceptable data: monotherapy indication, pediatric indication, design of add-on trials, and controlled released products.

Monotherapy claims are difficult to obtain because of the ethical concerns about performing trials where standard of care is withdrawn for the drug being studied, and further, it has been difficult to extrapolate information from add-on trials. He pointed out problems with not accepting equivalence trials, yet companies want to have a monotherapy claim. A white paper has been drafted, and the FDA is reviewing it in order to address these issues and look for novel ways to approve a monotherapy indication, including possibly extrapolating from add-on studies, if proper dosing information is available.

Pediatric claims have always required that a clinical trial be performed in pediatric patients. However, pediatric claims based on adult clinical trials can be made, assuming the disease is similar in both the adults and children in a sufficient manner that one could make that claim in a reliable and safe manner, and that pediatric dosing could be provided. However, to date, these criteria have not been considered to have been met. Therefore, the FDA is working on finding novel ways to establish those claims, including the possibility that extrapolation from adult data might be acceptable.

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Add-on trials themselves are now being rethought as a result of a recent meta-analysis by Ryvlin [9.5] in which SUDEP risk was shown to be lower in clinical trials for those who were randomized to effective drugs compared to those randomized to placebo. This led to the concern that the current add-on trial design is not ethically viable. Therefore, the FDA is working on new ways to assess novel endpoints, such as time to the nth seizure as opposed to the current manner in which the studies are assessed.

Dr. Katz also addressed approval of controlled release products, specifically the requirement that controlled trials need to be done in order to show that a controlled release product is effective. Recently, a study of an extended release topiramate was able to show that at all points during the day (not just at Cmax and total AUC), the plasma levels and partial AUCs met bioequivalence criteria compared to the levels of immediate release Topamax (topiramate). This led to the approval of the controlled released product. Dr. Katz summarized by saying that the FDA continues to work to find better ways to assess drugs and improve the approval process for AEDs.

3.2. Why industry should keep investing in epilepsy. Christopher Gallen, MD, PhD, President and Chief Executive Officer, SK Biopharmaceuticals, SK Life Sciences

Dr. Christopher Gallen, President and Chief Executive Officer, SK Biopharmaceuticals, SK Life Sciences, stated the case for why industry should keep investing in epilepsy, noting that the short answer to the question is that “we can succeed”. He said that the success rates of CNS therapeutics are relatively low when compared to other disease states like infectious diseases because those areas are comparatively simple with core pathology largely internal to a single cell. Nervous system disorders involve far more complex systems, composed of many cells, transmitters, and regulatory systems and a core pathology involving systems of cells—consequently, these disorders are not as amenable to simple target-oriented in vitro or cellular screening models, and they are better addressed by targeting modulation of pathophysiological processes rather than point targets.

Epilepsy, he pointed out, is not simple. Existing animal predictive models have limitations in that they test specific pathophysiological mechanisms in a complex system but do not mimic the entirety of any human pathology. But the animal and human screening models have significant predictive utility even with their limitations, more so than almost any other CNS area. Of critical importance, in epilepsy, when the drug works, high quality clinical trials typically work. Trial success is much more problematic in many CNS areas such as depression where even known effective drugs often fail in large clinical trials. This makes epilepsy a great first indication to assess the effectiveness of certain novel medication mechanisms.

He also noted that while existing AEDs are useful, epilepsy remains a great market with a major unmet medical need—particularly to move from reduction of numbers of seizures to the goal of complete seizure cessation. He pointed out that economic growth in Asia and elsewhere from the changing demographics together with the spread of capitalism is driving the availability of modern medicine to billions of people in new corners of the world, opening the opportunity to serve a huge new market that will ultimately exceed all existing markets combined. In terms of prescription number, nervous system disorders are the largest therapeutic area. The emergence of genuinely superior next generation proprietary therapies will overcome crowded markets, pricing pressure, and generic erosion, and their commercial success will fuel the development of future generations of ever-improving therapeutics until the scourge of epilepsy is contained. Epilepsy is a large initial market, and the fact that drugs proven useful in epilepsy often prove to be useful in other nervous system disorders opens even larger markets.

As he finished his presentation, he noted that “The logic of winning is attacking where competitors are absent. Many large pharma companies have abandoned nervous system development because it was too hard. This opens the opportunity for smaller competitors with novel approaches to drug invention to pick an initial serious indication like epilepsy where animal models, human models, and clinical trials in concert work to find effective therapeutics, displace older less effective therapeutics, then expand to additional indications. Epilepsy is a place where you can win”.

3.3. The NINDS ASP: yesterday, today, and tomorrow. John Kehne, PhD, Program Director, National Institutes of Health, National Institute of Neurological Disorders and Stroke; H. Steve White, PhD, Professor and Director, Anticonvulsant Drug Development Program, University of Utah

Dr. John Kehne and Dr. H. Steve White discussed the National Institute of Neurological Disorders and Stroke (NINDS) Anticonvulsant Screening Program (ASP). Dr. Kehne is a Program Director at NINDS and Head of the ASP, and Dr. White is Professor and Director of the Anticonvulsant Drug Development (ADD) Program at the University of Utah. Dr. Kehne started the presentation by pointing out that the ASP provides free compound testing to academia and industry through a contract between NINDS and the University of Utah. Since it was established in 1975, the ASP has contributed to nine “third generation” marketed AEDs.

He then provided an overview of the ASP testing workflow. In the initial identification phase, compounds are tested against maximal electroshock seizures, the 32–mA 6–Hz test, the cornel–kindled mouse, and on a behavioral toxicity test. Active compounds are further tested for initial differentiation using pharmacoresistance models, e.g., the 44–mA 6–Hz test, the bursting hippocampal slice, and the lamotrigine-resistant kindled rat, and for effects on seizure threshold using the IV pentylentetrazole test. Active compounds advance to full differentiation, which currently includes efficacy in a post-status epilepticus (SE) epileptic rodent model and evaluation for effects on cognition in a long-term potentiation test and in the Morris water maze assay. In addition to this “standard track” serial screening protocol, a new “special projects” track allows flexibility for assessing novel therapeutic mechanisms. Lastly, Dr. Kehne highlighted the PANACHE (Public Access to Neuroactive and Anticonvulsant Chemical Evaluations) Data Sharing Initiative; a publicly accessible database for nonconfidential data and information from the ASP developed as a tool to further stimulate epilepsy drug discovery. The database was released at the December 2013 annual meeting of the American Epilepsy Society and currently contains 150 literature reference compounds [10].

Dr. H. Steve White’s lecture provided a snapshot of models under evaluation by the ASP. Specifically, he highlighted the intrahippocampal kainite mouse model for mesial temporal lobe epilepsy, as well as a battery of tests to evaluate cognitive liability. He focused on Theiler’s virus mouse model of encephalitis-induced epilepsy and then the novel stress-free approach to the chronic delivery of AEDs to “newly diagnosed” epileptic rats using a recently designed automated feeder system. Dr. White summarized the presentation by stating that the mesial temporal lobe epilepsy mouse, Theiler’s murine encephalomyelitis virus model, and the battery of cognitive tests, once fully implemented, will aid in the differentiation of promising investigational drugs submitted to the ASP. Moreover, the automated feeder system provides a unique and stress-free mechanism for the chronic delivery of a drug to epileptic rats and provides a novel solution to chronic oral-dosing studies. New models and approaches are directly addressing the recommendations of the 2012 NINDS working group report and expanding the testing armamentarium of the ASP.

3.4. Epilepsy therapies: accomplishments and challenges. Roger J. Porter, MD, Chief Scientific Officer, Epilepsy Foundation

Dr. Roger J. Porter, EF CSO, discussed the challenges of trying to guide a compound to a successfully approved drug that can help patients with epilepsy. He started by defining the valley of death. This is
basically the time in a compound’s development between its screening for potential use in epilepsy to a clinical trial. He highlighted that the Epilepsy Foundation has helped by funding 60 of 123 potential epilepsy compounds through its Epilepsy Therapy Pipeline initiative. He then asked the question, are we taking enough risks? He noted that in comparison to other conditions, epilepsy has $5.3 million with regard to annual research compared to $61 million for Parkinson’s disease and $40 million for multiple sclerosis and muscular dystrophy — two other diseases that affect far fewer patients. Clearly, the epilepsy community needs to drive clinical research. Mechanisms exist and we are well primed to take advantage of this, but we need to invest in platform partnerships and even consider crowdfunding. He finished the talk by reminding the audience that there is a massive underserved population of persons with epilepsy that needs our help.

4. Session 3: early stage drug pipeline: proof of principle through IND

The conference then moved to discussion of treatments in the early stage of the pipeline, with 12 presentations by companies with products that are currently in the stage of development between proof of principle and clinical trials.

4.1. Intellimedix. Novel approaches to drug discovery with applications to epilepsy and mitochondrial disease. Jeffrey Skolnick, PhD, Scientific Advisor, Intellimedix; Director of the Integrated Biosystems Institute at Georgia Institute of Technology

Jeffrey Skolnick, PhD, who is the Director of the Center for the Study of Systems Biology at the Georgia Institute of Technology, presented on behalf of Intellimedix. This system is a high throughput screening approach currently being used for epilepsy with specific emphasis on Dravet syndrome and mitochondrial disorders. He noted the strategy of using computational analysis as a screening tool and then moving to zebrafish models and on to small-scale clinical trials. He emphasized the importance of this tool by citing successful examples such as the screening of progesterone using the zebrafish Dravet model as well as mifepristone. Moreover, the company is utilizing calcium imaging to classify seizure type and testing to assess antiepileptic mechanism of action.


Dr. Cynthia Rask of Asklepios BioPharmaceutical discussed galanin gene delivery for mesial temporal lobe epilepsy. This company is developing gene delivery technology based on adeno-associated virus (AAV) to deliver therapeutic genes. Because galanin has been shown to attenuate seizures and cell death in multiple animal models, they are working to utilize efficient viral vectors to deliver the galanin gene to a seizure focus in the temporal lobe. Their goal is to achieve optimal transduction of cells constituting a localized expression of the inhibitory factor, galanin. Delivery of the gene transfer product is achieved by stereotactic injection into a defined seizure focus to attenuate local seizure activity. There are three classes of galanin-signaling receptors, and she pointed out in the early studies that infusion of galanin into the CNS significantly attenuated seizure activity in a number of animal models [11–13]. Proof-of-concept studies are in the public domain, and dose escalation studies to determine the upper limit that can be delivered are completed [14–17]. Currently, the company is evaluating a delivery system with Medtronic. Preliminary nonhuman primate and sheep studies are completed. Definitive dosing studies (in rodents and nonhuman primates), as well as the toxicology and biodistribution studies that are required prior to conducting studies in humans, are currently being planned.

4.3. AurimMed Pharma, Inc. AMPX-0079. Amir Pesyan (presented by Roger J. Porter, MD in Dr. Pesyan’s absence), Chairman and Chief Executive Officer, AurimMed Pharma, Inc.

Amir Pesyan, Chairman and CEO of AurimMed Pharma, Inc., discussed the compound AMPX-0079. AMP-X-0079 has been shown in vivo studies to be orally and parenterally bioavailable, fast-acting (rapid oral absorption within 15 min), with a reasonably long pharmacological half-life in animal models, and able to pass through the blood-brain barrier, thereby manifesting its pharmacological effects directly in the CNS. This compound has been tested using Cerep® Full-BioPrint. It has no significant activity at any Cerep® targets. It is a CYP450 substrate with no P-glycoprotein inhibition. The chemical lacks side effects associated with any Cerep® targets, suggesting a novel mechanism of action.

AMP-X-0079 is effective in the only two validated models for partial epilepsy, MES and kindling. In addition, AMP-X-0079 is effective in virtually all other models of epilepsy, including the lamotrigine-resistant amygdala-kindled rat and, most recently, in the mesial temporal lobe epilepsy (MTLE) mouse, in which classical AEDs are ineffective, implying substantial broad-spectrum activity.

The immediate plans for this product are phenotypic screening and prediction of sedative side effect. The company will determine whether AMPX-0079 exhibits a functional similarity to known sedative compounds. If yes, at what concentration does it exhibit a functional similarity to known sedative compounds? Their future plans are to create IND-enabling studies for genetic, general, toxicology, analytical, and safety pharmacology. There are development challenges with regard to funding, and the company is looking for help with this.

4.4. BioCrea GmbH. LT GABA PAMs for refractory epilepsy. Norbert Hoeftgen, PhD, Vice President Discovery, BioCrea Germany

Dr. Hoeftgen presented LT GABA PAMs for the treatment of refractory epilepsy. GABA PAM has a novel GABA beta mechanism of action. The long-term effective site of action for GABA PAM is different than the benzodiazepine receptor site. This compound interfaces at the alpha beta 2-receptor site. GABA PAM shows activity at extrasynaptic GABA receptors, which are resistant to benzodiazepine action. Thus, these compounds could be useful for treating refractory epilepsy, refractory status epilepticus, and Rett syndrome. Moreover, these drugs are highly differentiated from traditional benzodiazepines and may be synergistic with existing therapeutic compounds. Hoeftgen stated how these compounds appear to have a broad-spectrum anticonvulsant efficacy in animal models, superiority in models of refractory epilepsy, and relative freedom from the development of tolerance with twice-daily dosing [18–20]. The data support a therapeutic value of long-term GABA PAMs for the long-term treatment of epilepsy with excellent efficacy, lack of tolerance, good therapeutic index, good oral availability, and low risk of drug interaction. He further stated that the lack of development of tolerance together with activity at the extrasynaptic GABAA receptors suggests potential as a prime treatment for status epilepticus, and the company is looking for partners to help bring this compound to market.

4.5. Epalex. Inhaled treatment for refractory epilepsy. Michael Rogawski, MD, PhD, Professor, Department of Neurology, University of California, Davis

Dr. Michael Rogawski provided information on an inhaled treatment to stop seizures once they start in the brain but before they spread to become more severe, which is being developed in collaboration with Epalex Corp. Propofol hemisuccinate (PHS), a proprietary propofol prodrug, has been formulated for pulmonary delivery by nebulization. The concept is that PHS would be self-administered during a seizure aura to prevent the localized seizure discharge from progressing to a full-blown seizure or by a caregiver to terminate seizure clusters or
status epilepticus. Animal studies have shown that intrapulmonary PHS has potent, broad-spectrum antiseizure activity [21]. Inhalation toxicity studies in rats demonstrated that intratracheal PHS does not cause histopathological changes in the lung. In collaboration with NINDS and NIH’s National Center for Advancing Translational Sciences (NCATS), clinical-grade PHS has been manufactured, and a proprietary clinical formulation has been developed. Nonclinical studies are being completed that will enable PHS to enter clinical trials. This work is partly supported through the NCATS BirDS (Bridging Interventional Development Gaps) program.

4.6. Fluorinova Pharma Inc. FV-082: a safer orally active broad-spectrum antiepileptic drug candidate. Malik Slassi, PhD, President and Chief Scientific Officer, Fluorinova Pharma Inc.

Dr. Malik Slassi, President and CSO of Fluorinova Pharma, discussed the progress of one of their three lead AED candidates, FV-082, an orally active broad-spectrum AED. He emphasized that FV-082 was a unique chemotype with a novel mechanism of action. This chemical displays a broad spectrum of efficacy profile and is very well tolerated in multiple epilepsy animal models. Dr. Slassi noted that FV-082 exhibits a superior preclinical safety profile when compared with leading AEDs [18,22,23]. It also demonstrated robust activity in amygdala-kindled rats, suggesting potential clinical efficacy for the treatment of complex partial seizures. FV-082 selectively modulates the Nav1.8 channel, androgen receptor (AR), and MAOB region with no activity in over 100 related targets. Further studies are ongoing. Preliminary safety data on this compound show lack of typical deep sedation, and it is well tolerated in different species up to 1000 mg/kg with only very mild clinical signals reported. There were no abnormalities in terms of liver function enzyme elevations and no weight gain, and other neurological signals were similar to vehicle controls. Besides its broad spectrum AED potential, the compound has robust efficacy in models of inflammatory and neuropathic pain.

Dr. Slassi summarized by saying that this compound is a new AED chemically unrelated to current AEDs with an excellent safety profile in the mouse, rat, and dog. The drug inhibits the voltage-gated sodium channel Nav1.8 and interacts with AR and MAOB. It has an excellent PK profile in rats and dogs. In animal seizure models, it possesses a broad-spectrum profile, and it demonstrated efficacy in models of neuropathic and inflammatory pain. The plans for testing this compound in human clinical trials are underway.

4.7. NeuroGate Therapeutics, Inc. Extended neuroamides. Harold Kohn, PhD, Kenan Distinguished Professor, Division of Chemical Biology and Medicinal Chemistry, University of North Carolina; Eshelman School of Pharmacy and Department of Chemistry, University of North Carolina–Chapel Hill; Founder, NeuroGate Therapeutics, Inc.

Harold Kohn, PhD, Kenan Distinguished Professor, the Division of Chemical Biology and Medicinal Chemistry at the UNC Eshelman School of Pharmacy and Department of Chemistry, provided information about extended neuroamides (ENAs). Extended neuroamides are novel drug candidates for epilepsy and pain that control neuronal hyperexcitability [22,24]. He noted that ENAs strategically combine pharmacophores found in functionalized amino acids (FAAs), such as lacosamide (Vimpat®), with α-aminoamides (AAAs), such as safinamide and ralfinamide. Both FAAs and AAAs are potent anticonvulsants. It is believed that the targets for ENAs are sodium channels with potential benefit for pathological states such as seizures, pain, and other neurological conditions. The ENAs exhibit excellent activities in multiple, validated animal seizure models and displayed minimal neurotoxicity at high doses. They also displayed good drug properties with high bioavailability, low clearance rates, and high brain-to-plasma ratios. He emphasized the lower development risk for these drugs as they were designed using validated pharmacophores and that these molecules served as functional inhibitors of sodium channels that potently transition sodium channels to the slow inactivated state and show frequency use-dependent inhibition at therapeutically accessible concentrations, thus providing greater control of neuronal hyperexcitability.

4.8. NeuroGenomeX, Inc. 2DG. Thomas P. Sutula, MD, PhD, Founder, Chief Technical Officer and Director, NeuroGenomeX, Inc.

Dr. Sutula, Professor and Chair of the Department of Neurology at the University of Wisconsin and the Founder and CTO of NeuroGenomeX, Inc., discussed the novel anticonvulsant disease-modifying antiepileptic and neuroprotective effects of 2-deoxyglucose (2DG) with therapeutic opportunities for epilepsy and traumatic brain injury. The 2DG is a glucose analog with novel neuroprotective and anticonvulsant disease modifying effects on plasticity [25]. Preclinical efficacy studies in epilepsy are completed. Delivery of 2DG to neurons and circuits is activity dependent, which is a novel advantageous property for an anticonvulsant. Currently, the company has two US patents issued for epilepsy and a US patent for traumatic brain injury. The drug has favorable animal toxicity and human toxicity. Potential clinical uses include intractable epilepsy, seizure clusters, status epilepticus, and traumatic brain injury. The company is funded by the Epilepsy Therapy Project–Epilepsy Research Foundation for an initial clinical trial to assess tolerability and efficacy of 2DG in intractable epilepsy.

4.9. INSYS Therapeutics, Inc. Synthetic CBD. Mark W. Davis, Senior Director, Clinical, INSYS Therapeutics, Inc.

Mr. Davis, Senior Director, Clinical, INSYS Therapeutics, Inc., explained the use of pharmaceutical cannabidiol (CBD) for epilepsy. He introduced INSYS Therapeutics and noted recent successful anecdotal cases of marijuana usage with a high ratio of CBD for multiple indications in epilepsy. They have filed (and since received) orphan drug designations in two indications — Lennox–Gastaut syndrome and Dravet syndrome. The company will be conducting clinical studies in epilepsy and is currently working with leading universities and researchers on pilot studies to investigate cannabidiol usage across a variety of indications. INSYS’s cannabidiol is produced via synthetic reaction and HPLC purification for a product that is >99.5% cannabidiol. There is no use of plant-based materials. It is consistently reproducible and manufactured in the United States. Other INSYS products currently available include generic dronabinol and Subsys® (fentanyl sublingual spray).

4.10. NeuroAdjuvants, Inc. Galanin receptor 2-based therapy. H. Steve White, PhD, Professor and Director, Anticonvulsant Drug Development Program, University of Utah

Dr. H. Steve White provided a synopsis of galanin receptor 2-based therapy. The specific highlighted compound was NAX 810–2, a novel galanin receptor 2 preferring neuropeptide analog for the treatment of epilepsy and pain. This modified neuropeptide is metabolically stable and blood–brain barrier permeable. Unlike galanin receptor 1-preferring compounds, the preclinical profile of NAX 810–2 shows no effect on plasma glucose levels at therapeutic doses. Moreover, NAX 810–2 possesses a favorable CYP induction and inhibition profile with potent analgesic activity in several animal models. Several preclinical development activities are planned including broad receptor screening and dose-ranging toxicity and pharmacokinetic studies in rats. A pre-IND meeting with the FDA is also planned. The goal for this drug is to be parenterally available.

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Dr. D’Agostino reviewed the use of the high fat/carbohydrate-restricted ketogenic diet (KD) and its importance for the metabolic management of seizures through the elevation of specific ketone bodies. Ketone supplementation represents a strategy to circumvent the dietary restriction associated with the KD and produces a therapeutic ketosis independent of carbohydrate restriction [26]. Ketone supplements have been created that can produce rapid (15 min) and sustained (>8 h) nutritional ketosis [27]. Ketone esters and ketone mineral salts are pending FDA Generally Recognized as Safe (GRAS) approval and there is a phase I pilot study planned within one year.

4.12. SciFluor Life Sciences LLC. SF0034: a potent and selective KCNQ2/3 activator as a potential antiepileptic drug. Scott Edwards, PhD, Vice President and General Manager, SciFluor Life Sciences LLC

Dr. Edwards, Vice President and General Manager of SciFluor Life Sciences, introduced SF0034, a potent and selective KCNQ2/3 activator. This potential AED was created by strategic incorporation of fluorine to modulate binding properties. Specific fluorine substituents result in a compound with significantly increased potency and selectivity for KCNQ2/3, potentially eliminating the urinary retention and cardiac safety issues of ezogabine and which is much less susceptible to blue discoloration than ezogabine. This proprietary new chemical entity has an extensive preclinical dataset, including assessment by the NINDS ASP, and a 12-month path to the IND. The key development challenge is to show that this new chemical entity has mitigated the skin and eye toxicity that resulted in recent label restrictions for ezogabine. The company has established several academic collaborations to further assess SF0034 and is looking for development and partnering opportunities to bring the compound to market for epilepsy.

4.13. Sage Therapeutics. SAGE 547 for status epilepticus. Jeffrey M. Jonas, MD, Chief Executive Officer, Sage Therapeutics

Dr. Jonas, CEO of Sage Therapeutics, introduced SAGE-547 injection (allopregnanolone), a novel compound for the management of super-refractory status epilepticus. SAGE-547 has displayed activity in benzodiazepine-resistant seizure models targeting the alpha-4 subunit of the GABA_A receptor. A phase 1/1 study in refractory status epilepticus is currently underway with 20 participating clinical sites. Preliminary data from the first four patients with severe status epilepticus, arising from varying conditions, revealed promising clinical activity.

5. Session 4: early-stage diagnostic devices and product pipeline: new concepts and initial findings

This session consisted of six presentations by representatives of companies with devices under development or that are available commercially for the detection of seizures. The presentations were followed by a panel session on user perspectives of seizure detection and alerting devices.

5.1. Cyberonics. ProGuardian REST™: an innovative, in-home device system designed to monitor, detect, and log night-time seizure activity. Laurie Groven, Global Medical Device/Diagnostic Marketing and Sales Executive, Cyberonics

Laurie Groven, Global Medical Device/Diagnostic Marketing and Sales Executive and Program Head of ProGuardian at Cyberonics, presented ProGuardian REST™, a device currently under investigation. The ProGuardian system is based on similar cardiac-based seizure detection technology that is found in the company’s AspireSR™ generator for VNS therapy, which received CE Mark approval in February 2014. The technology has been further modified to provide caregivers, such as parents of children with epilepsy, an in-home nocturnal seizure detection system. Based on Cyberonics’ data showing a correlation between generalized seizures and ictal tachycardia, ProGuardian was designed to monitor changes in heart rate. It also monitors motion. Algorithms have been designed to determine whether a particular pattern of heart rate changes and movement could represent a seizure and if so, audible and visual notifications are generated for the caregiver. Sensitivity settings for both heart rate and movement detection can be adjusted by the end user. Operationally, before the patient goes to sleep, a sensor will be attached to a flexible, single-use patch that is applied to the chest, after which the sensor automatically begins to monitor heart rate and establish a communication link with a hub to which seizure notifications are sent upon algorithmic confirmation for the caregiver. The hub needs to be within 30 ft of the patient — if the caregiver is further away, an optional Android smartphone app will be able to send notifications throughout a wi-fi-enabled home. Confirmed seizures are electronically logged within the hub, which can generate a report for later review. Daytime seizures can be manually added to make the reports more comprehensive.

5.2. Brain Sentinel™. EMG-based convulsive seizure detection and warning system. José E. Cavazos, MD, PhD, Vice President, Medical Affairs, Brain Sentinel, LGCH, Inc.

Dr. Cavazos, VP, Medical Affairs, and Co-Founder, LGCH, Inc. dba Brain Sentinel™, discussed the Brain Sentinel™ seizure detection, analysis, and warning system, which is intended for use in the home, seizure monitoring units, and long-term care facilities such as nursing homes. It aims to detect seizures based on using surface electromyogram (EMG) recording of the biceps muscle to detect patterns consistent with muscular contractions during seizures such as generalized tonic–clonic seizures. It is currently undergoing evaluation in a multicenter, phase III, pivotal clinical trial of its sensitivity and false detection rate compared to multiple reviews of the same subjects’ video–EEG recordings. The device consists of an EMG sensor that communicates via wi-fi with a base station, which in turn alerts caregivers nearby when a seizure is detected based on algorithmic analysis of the surface EMG. The system includes a microphone to record sounds occurring during seizures. Alerts can also be sent via phone, text, or email to caregivers or to summon emergency services. All EMG recordings, including marked periods of ictal EMG, will be saved and stored in near real-time in the cloud, which could assist the patient’s clinician in the determination of seizure semiology (e.g., tonic, clonic, or tonic–clonic) and hence potentially in the selection of therapy.

5.3. Epitel, Inc. Wireless EEG patch. Mark Lehmkuhle, PhD, Chief Executive Officer, Chief Technology Officer, Epitel, Inc., Research Assistant Professor, Department of Neurosurgery, University of Utah

Dr. Lehmkuhle, CEO, CTO, Epitel, Inc., Research Assistant Professor, Department of Neurosurgery, University of Utah, described a wireless EEG patch under development by Epitel, Inc. The goal of the EEG patch is to augment patient self-report of seizure occurrence in diaries with a quantitative, electrographic report of when seizures occurred and how long they lasted. The current prototype is based on flexible circuit boards, has two gold electrodes that are attached on the scalp (at locations guided by an individual patient’s prior EEG studies), is covered by flexible urethane, and logs and transmits EEG data for over three days. The prototype is currently being evaluated in the neurocritical care unit at the University of Utah, and recordings have demonstrated clean and artifact-free EEG. Once applied to the scalp, it begins to log and transmit EEG data immediately. Multiple devices could be placed on the scalp if needed. Efforts are now underway to make a disposable EEG patch that is 1” by 1” by 0.25” with the two electrodes separated.
by 24 mm, extend recording time to seven days, and make it waterproof with polyamide encapsulation. The technical challenge of making the electrode–scalp interface watertight over the duration of the recording and at the same time ensuring that the electrode gel does not dry out can be addressed by adding a nonstandard adhesive for the part of the patch not occupied by the electrodes. Candidate adhesives have been identified which can be removed with acetone at the conclusion of the recording. The company plans to test this new design in patients in the home setting.


Dr. Picard, Chief Scientist, Empatica, and Mr. Lai, CEO, Empatica, discussed two sensor products worn on the wrist. The “E3” is a device available today for researchers, and the “Embrace” is a consumer-facing device under development. Both sensors measure motion, temperature, and autonomic activity. Autonomic activity captures both branches of the autonomic nervous system: the sympathetic branch through measurement of electrodermal activity (EDA) and the parasympathetic branch through measurement of blood volume pulse, from which heart rate and heart-rate variability are computed. Dr. Picard cited data from a 90-patient study at Boston Children’s Hospital showing that EDA was elevated more than 2 standard deviations above preictal levels in 100% of generalized tonic–clonic seizures and in 86% of complex partial seizures [28]. She presented other findings showing that combining EDA data with motion sensing increased accuracy in detecting generalized tonic–clonic seizures compared with motion sensing alone [29]. In a study of 73 children with active epilepsy recorded for a total of 3525 h, using a nonpersonalized detection algorithm, 77% of the children had zero false detections, while 23% had one. The findings are expected to better understand and treat ictal events. The Embrace will be the first comfortably wearable seizure-alerting device to collect clinical quality autonomic data in patients with epilepsy while providing an important biomarker correlated to postictal EEG suppression.

5.5. Smart Monitor. Automated seizure tracking and recording. Anoo Nathan, Chief Executive Officer, Smart Monitor

Ms. Nathan, CEO, Smart Monitor, provided an update of SmartWatch, a device that detects and alerts upon the repetitive shaking motions caused by generalized tonic–clonic seizures (GTCSs). The SmartWatch is available with a monthly subscription-based pricing model. Sixty percent of current users are under the age of 21 years. In addition to functioning as a wristwatch by telling time and the date, SmartWatch utilizes algorithms to continuously monitor and analyze motion and to determine if a pattern of repetitive shaking movements may be representative of a GTCS. Upon detecting patterns of abnormal movement that may be representative of seizures, and in conjunction with a companion smartphone, an alert is issued as a text message and/or phone call that are automatically sent to caregivers or other designated alert recipients, providing the location of the patient based on GPS. These alerts go out within seconds after the onset of repetitive shaking motion. A panic button on the watch can be pressed by the patient in case of an emergency or if they feel that they are about to have a seizure. The SmartWatch supports additional functionality such as giving the patient medication reminders, analyzing sleep duration and quality, recording audio during seizure episodes, and providing analytics and reporting/seizure tracking for physicians after data transmission to back-end cloud-based servers. Seizure-related data provided to physicians include duration of the episode, severity (amplitude and frequency of the shaking movements), frequency, time of occurrence, and associated audio. Detailed tracking and counting of episodes and informative user dashboards provide a quick longitudinal overview of the individual’s episodic activity. A provided push-button allows the patient to input when a non-GTCS (such as a complex partial seizure) has occurred and when medication was taken. Ms. Nathan mentioned that five pilot and field studies are underway and planned, including a pediatric study at LeBonheur Children’s Research Hospital, a study at Stanford to integrate the SmartWatch-generated data with My Epilepsy Diary, a study at University of Virginia focused on reduction of adolescent anxiety and successful transition to adulthood in an outpatient setting, an inpatient study at Boston Children’s Hospital of ictal autonomic biomarkers to assess SUDEP risk, and a study at New York University of the usefulness of the data for ongoing outpatient clinical care of patients with epilepsy. A submission to the FDA for 510(k) clearance is under preparation.

5.6. RTI International. esap. Kristin H. Gilchrist, PhD, Research Scientist, Electronics and Applied Physics Division, RTI International

Dr. Gilchrist, Research Scientist, Electronics and Applied Physics Division, RTI International, discussed esap, a system that detects seizures based on a multi-parametric approach and an adaptive algorithm. esap senses heart-rate patterns as recorded by electrocardiogram (ECG) as well as movement and respiration. An initial study of 28 patients at Children’s National Medical Center completed in 2012 using postprocessing analysis demonstrated high detection accuracy for generalized seizure types and 50% detection for partial seizures. In late 2013, NIH funding was secured for trials at Children’s National Medical Center using less burdensome hardware and technology capable of real-time detection. The current prototype consists of a sensor (the Zephyr Biopatch) that is worn on the chest and which communicates via Bluetooth to a processing module. An adaptive algorithm that “learns” from its successes and mistakes for a particular patient is being developed and will eventually be integrated into the sensor to send an alarm locally or remotely.

5.7. Panel session: seizure detection and alerting devices: are they ready for prime time?

Panel: Daniel Friedman, MD, Moderator, Assistant Professor of Neurology, New York University, Comprehensive Epilepsy Center; Tom Stanton, Executive Director, Danny Did Foundation; Michelle Welborn, PharmD, President, Intractable Childhood Epilepsy (ICE) Alliance; Catherine Jacobson, PhD, Post-doctoral Fellow, Pediatric Epilepsy, University of California, San Francisco

Dr. Friedman, Assistant Professor of Neurology, New York University, moderated a panel discussion that addressed the roles that noninvasive seizure detection devices may play in the management of epilepsy and seizure safety, the benefits of various detection methods and form factors for different patient populations, the seizure types that are a priority for detection, and optimal performance characteristics of these devices. The panel participants were Tom Stanton, Executive Director, Danny Did Foundation; Michelle Welborn, PharmD, President, Intractable Childhood Epilepsy (ICE) Alliance; Dr. Friedman, Assistant Professor of Neurology, New York University; Catherine Jacobson, PhD, Post-doctoral Fellow, Pediatric Epilepsy, University of California, San Francisco; and Catherine Jacobson, PhD, Post-doctoral Fellow, Pediatric Epilepsy, University of California, San Francisco, and also a parent of a child with epilepsy.
Dr. Jacobson stressed the importance of multiparametric systems for detecting nonconvulsive seizures; especially systems that have a low false-negative rate and which alert caregivers, particularly parents whose children have nocturnal seizures. Her child, for example, experiences severe, nocturnal nonconvulsive seizures that last up to 15 min and can be associated with cessation of breathing, and so, on a nightly basis, she is very concerned about the possibility of SUDEP. Dr. Welborn’s daughter also has a preponderance of seizures during sleep. She expressed the need for a system that could accurately predict when a seizure was going to occur so that interventions could be developed and used to prevent seizures before they started; consequently, seizure-related complications, including SUDEP, would also be prevented. She too commented on the need for systems to detect seizures other than generalized tonic–clonic seizures.

Mr. Stanton, whose nephew Danny died from SUDEP in 2009, works through the Danny Did Foundation to educate parents and increase awareness about the available seizure-detection systems. In his experience, parents want to know which device they should use, how much particular devices cost, what kinds of data are captured, and which parameters for seizure activity are measured. He said many parents use video- and audio-based baby monitors (and Dr. Jacobson said that she does as well so that she can see her son and assess if he is having a seizure or not). Mr. Stanton feels it is important for medical professionals to share information with parents and adults with epilepsy about devices in the same manner that they present options related to medicine, surgery and diet, with the understanding that there is, currently, no one-size-fits-all device solution.

Regarding cost, Dr. Welborn said ideally the costs should be covered by insurance. She also encouraged clinicians to consider recommending private-duty nursing services for children with catastrophic epilepsies who are at high risk for SUDEP from nocturnal seizures.

6. Session 5: late-stage and approved devices—what is new?

This session consisted of 6 presentations about late-stage devices for the treatment of epilepsy.

6.1. Medtronic, Inc. DBS therapy for epilepsy. Jon Gifakis, PhD, Senior Principal Scientist, Medtronic Neuromodulation

Dr. Gifakis, Senior Principal Scientist, Medtronic Inc., talked about deep brain stimulation (DBS). Deep brain stimulation therapy for epilepsy is approved in various geographies outside of the U.S. In the U.S., DBS therapy for epilepsy is under investigation and remains unapproved for commercialization. The device consists of an implantable pulse generator connected to stimulating electrodes placed in the anterior nucleus of the thalamus (ANT) bilaterally. The SANTE trial, which evaluated DBS therapy for epilepsy, was published in 2010 [31]. Enrolled patients have continued to be followed. Five years of data collection has been completed and submitted for publication. Discussions continue with the FDA on options for regulatory approval in the U.S. Medtronic is developing a new neurostimulation device that is currently in human studies and which has a built-in accelerometer to monitor motion, patient-specific seizure detection algorithms, and the capability to both stimulate and sense brain activity concurrently. Further, it can perform evoked potentials to determine if there is neural connectivity between a therapy electrode and another remote electrode, such as an electrode in the hippocampus, and the extent of excitability of that remote site, which can in turn be modulated by stimulations by the ANT electrode [32–34].

6.2. NeuroSigma, Inc. eTNS. Christopher DeGiorgio, MD, Professor of Neurology, University of California, Los Angeles

Dr. DeGiorgio, representing NeuroSigma, addressed noninvasive trigeminal nerve stimulation with the eTNS™ system as an epilepsy therapy. He characterized this approach as neuromodulation, without implantation, of neural structures involved in seizures, mood, and attention. Mechanism-of-action studies using positron emission tomography have suggested that eTNS reduces metabolism in the temporal-parietal cortex and the mesial temporal regions and increases metabolism in the mesial frontal lobe, a region associated with mood and attention [35]. A phase II, randomized, double-blind trial of eTNS was conducted in 50 patients with drug-resistant epilepsy who were randomized to active treatment or sham stimulation [36]. A 40% responder rate was seen in the active treatment group at 18 weeks compared with a 16% responder rate in the control group. The within-group change in responder rate was statistically significant in favor of active treatment (p = 0.0136), and the between-groups change in responder rate approached but did not quite meet statistical significance (p = 0.078). There were also significant within-group and between-groups improvement in mood associated with active treatment. His impression was that improvement in mood typically occurs before the improvement in seizure frequency. Plans are underway for a pivotal phase III, multicenter trial as adjunctive therapy for drug-resistant complex partial seizures in up to 350 patients, which will exclude data from the first 4 weeks of treatment (induction phase), during which epilepsy device trials have historically not shown significant efficacy compared to placebo. The planned primary endpoint is percent change in seizure frequency from baseline to end of 12 weeks of continued treatment, which begins after the 4-week induction period. Secondary endpoints include responder rate, RRATIO, mood, and quality-of-life measures. The company is pursuing additional potential indications, including attention-deficit hyperactivity disorder, major depressive disorder, and posttraumatic stress disorder.

6.3. University of California, Los Angeles. Ultrasound for seizure modulation. John Stern, MD, Department of Neurology; Director, Epilepsy Clinical Program and Co-Director, Seizure Disorder Center, University of California, Los Angeles

Dr. Stern, Director of the Epilepsy Clinical Program at UCLA, discussed low-intensity focused ultrasound (LIFUP) for the treatment of temporal lobe epilepsy (TLE). As opposed to high-intensity focused ultrasound (HIFU), low-intensity ultrasound modulates brain activity without imparting significant thermal energy to bone or brain tissue. The mechanism is presumed to be exerted by a biomechanical effect on neuronal membranes which impacts excitability in one direction or another depending on the pulse width and frequency that are used, as demonstrated in animal studies with functional MRI [37–39]. An advantage of this technique over transcranial magnetic stimulation is that deep brain structures can be targeted. In a rodent PITZ model of acute seizures, LIFUP decreased seizures compared to controls, and histological analysis of the treated brains showed no evidence of tissue destruction, as compared to HIFU, which ablates brain tissue [40]. Dr. Stern’s group plans to study the safety of LIFUP using an MRI-compatible LIFUP device in patients with TLE who are candidates for standard anterior temporal lobe resection. This patient group was identified in part because the bone overlying the target is relatively thin. Study subjects will undergo LIFUP with simultaneous fMRI, and will also have an EEG obtained prior to and after LIFUP and neuropsychological testing after LIFUP. After a period of approximately 1 week, the study subjects will undergo the planned anterior temporal lobe resection. Resected tissue will be examined histologically to evaluate for any potential histopathologic effects of LIFUP.

6.4. Visualase, Inc. Laser ablation in neurosurgery. Ashok Gowda, PhD, Founder and Chief Operating Officer, Visualase, Inc.

Dr. Gowda, Founder and COO of Visualase, provided an update on their Visualase device, which is cleared for marketing as a surgical tool for soft tissue ablation in neurosurgery. Visualase entails a real-time, MRI-guided, laser-based thermal ablation technique that targets the...
brain tissue that has been identified as a patient’s seizure focus. The disposable laser applicator, 1.65 mm in diameter, consists of a laser-diffusing fiber and an outer cooling catheter, and is inserted through a small access hole that is made in the skull. Therefore, unlike resective surgery, this device does not require a craniotomy. A workstation generates the 980-nm diode laser and interfaces with an MRI machine to provide real-time thermal feedback during the procedure to enable the surgeon to limit tissue damage to the intended structure. Patients typically remain in the hospital for one night. The technology, originally developed to target brain tumors, has been used in patients with difficult-to-access deep-seated lesions, such as hypothalamic hamartomas, and approximately 70 patients have been treated as of this presentation. Dr. Gowda said that the neurosurgeon who has performed the largest number of procedures on these lesions has publicly reported a 93% seizure-free rate among his treated patients. Other targets for this therapy have included mesial temporal structures (amygdala and hippocampus), focal cortical dysplasias, and tubers, including multiple tubers treated in the same patient, either during the same session or serially. In total, over 400 patients with epileptic foci have undergone the Visualase procedure as of this presentation, and about half are adults and the other half children. Outcome results are being collected by a number of investigators, though they have not yet been analyzed.

6.5. Swedish Neuroscience Institute. MRI-guided focused ultrasound for treatment of mesial TLE. John Snell, PhD, Technical Director—Brain Program, Focused Ultrasound Foundation, Swedish Neuroscience Institute

Dr. Snell, Technical Director—Brain Program, Focused Ultrasound Foundation, discussed MRI-guided focused ultrasound as a therapy for mesial TLE. The device thermally ablates brain tissue and is also currently under evaluation for the treatment of essential tremor, Parkinson’s disease, and other CNS disorders where the targets are deep, such as the thalamus. A study using cadaver skulls filled with gel-mimicking phantom material suggests that clinically significant heating can be produced in regions corresponding to the hippocampus and amygdala. In these experiments, significant heating of the bone underlying the region corresponding to the hippocampus was observed, especially the petrous bone, and particularly with 30-second sonication. A shielding technique has been devised to lessen skull floor heating. Based on this feasibility work, plans are underway to proceed with clinical development and to move towards lower-frequency transducers and better focusing techniques for lateral targets.

6.6. Boston Children’s Hospital. Transcranial magnetic stimulation. Alexander Rotenberg, MD, PhD, Director, Neuromodulation Program, Associate Professor of Neurology, Boston Children’s Hospital, Harvard Medical School

Dr. Rotenberg, an epileptologist at Boston Children’s Hospital, presented transcranial magnetic stimulation (TMS) for the treatment of epilepsy. Transcranial magnetic stimulation is a method for focal brain stimulation with small intracranial electrical currents that are generated by a powerful magnetic field. Uniquely among brain stimulation methods, TMS has robust diagnostic and therapeutic capacities that are relevant to the study and management of epilepsy. Transcranial magnetic stimulation protocols can be divided into three categories: repetitive TMS (rTMS), which modulates brain excitability; single-pulse TMS (spTMS), which evokes a motor response or other observable change in cortical function; and paired-pulse TMS (ppTMS), which is a means to assess the excitation/inhibition ratio [41,42]. In common spTMS and ppTMS protocols, a hand-held electromagnetic coil is positioned next to the scalp and generates a brief, approximately 2-Tesla, magnetic field, which induces an electrical current in the nearby cortex [41]. When the motor cortex is targeted, the resultant limb movement can be quantified with surface EMG, which serves as confirmation that the motor cortex has been stimulated or as a measure of motor cortex excitability. Both clinical and preclinical epilepsy research with TMS are ongoing in Dr. Rotenberg’s Neuromodulation Program [43]. Clinically, his group uses TMS to localize motor and language function to help the neurosurgeon plan the extent of resection for epilepsy surgery candidates whose seizure focus is close to motor or language cortical areas. He is also studying the effects of TMS in patients with unilateral or bilateral TLE using customized magnetic coils that can induce electrical currents deeper in the brain than is achievable with conventional coils. Preliminary data are encouraging in terms of efficacy, tolerability, and safety (adverse events and memory function).

7. Session 6: Nonprofit Organizations, Government, and Crowdfunding—Grants, Awards and Funding to Advance Research to the Next Critical Stage

Panel: Roger J. Porter, MD, Moderator, Chief Scientific Officer, Epilepsy Foundation; Jan Buelow, RN, PhD, Vice President, Programs and Research, Epilepsy Foundation; Rajesh Ranganathan, PhD, Director, Office of Translational Research, National Institute of Neurological Disorders and Stroke; H. Steve White, PhD, Research Director, Citizen’s United for Research in Epilepsy (CURE), Professor and Director, Anticonvulsant Drug Development Program, University of Utah; Bre DiGiammarino, Citizen’s Director, Indiegogo

Dr. Porter, CSO, Epilepsy Foundation (EF), chaired a panel session that addressed funding mechanisms to advance epilepsy-related research to the next critical stage of development.

Dr. Buelow presented the new approach to research funding at the EF which resulted from the merger of EF with the Epilepsy Therapy Project. The EF is moving from traditional research grants to a strategy of driving research to bring treatments to patients more quickly. To achieve this strategy, successful programs such as new therapies grants are continuing. New funding mechanisms are being introduced, including support for postdocs working in innovative environments and rolling seed grants to address timely topics. In addition, working cooperatively with other key stakeholders through partnerships is a major focus. The overall goal of EF, as an organization that advocates for patients with epilepsy and their families, is to be a leader in cutting-edge research to benefit the community.

Dr. Ranganathan outlined the changes underway at NINDS to support translational research. Based on the concept that translation begins and ends with the patient, their guiding principles are to get therapeutics to people; establish a fail-early, fail-fast approach to portfolio management; and work with partners to hand off de-risked projects for downstream funding. Two programs have supported the bulk of their translational research efforts: Cooperative Program in Translational Research (U01) and the trans-NIH Blueprint Neurotherapeutics (BPN). The NINDS is now evolving these programs to achieve an integrated vision to further advance small molecules, biologics and biotech products, and devices. Announcements from NIH about these new programs were released in July 2014, with the first grants awarded starting in June 2015.

Dr. White discussed CURE’s research programs, which are based on CURE’s mission to find a cure for epilepsy and to raise awareness of the prevalence and devastation caused by epilepsy — in short, no seizures, no side effects, no exceptions. As the largest nongovernmental funder of epilepsy research ($20,802,464 in 174 awards between 2000 and 2014), CURE has four priority research areas: the basic mechanisms of epileptogenesis, the multifaceted causes of epilepsy, the pediatric epilepsy syndromes, and new animal models of epilepsy. There is a concerted effort to invest in high-risk, scientifically sound research proposals that have the potential of being transformative. The most recent initiative, launched in May 2014, is the Epilepsy Genetics Initiative. The goal is to develop an exome/genome sequence database of clinical generated sequences and associated phenotyping data. The data will be analyzed every six months and findings reported back to patients’ physicians in an effort to identify the cause of a patient’s epilepsy. In
addition, the database will serve as a resource for scientists to drive further research.

Ms. DiGiammarino defined crowdfunding as the collective effort of individuals who network and pool their money, usually via the internet, to support efforts initiated by other people or organizations. Indiegogo was founded in 2008 and is the world’s largest crowdfunding platform. Organizations run campaigns on the platform to amplify their existing support, demonstrate interest in the organization, spread their message and raise awareness, and engage the community. The EF, for example, has already partnered with Indiegogo to increase funding for SAMI, an innovative movement monitor that previously received the EF Shark Tank award.

The session concluded with H. Steve White, PhD receiving the Lifetime Accelerator Award, with remarks lauding his accomplishments offered by Warren Lammert, Chair of the EF Board of Directors; Evelyn Nussbaum, a member of the CURE Board of Directors; Roger J. Porter, MD, Chief Scientific Officer, EF; and Jacqueline French, Professor of Neurology, New York University. Dr. White then expressed his profound thanks and appreciation to the many people who have supported him over his career.

8. Session 7: new directions and opportunities in epilepsy research

In this session, scientists and representatives of the drug and device private sector provided insight on the trends for the future of epilepsy therapeutics.

8.1. New directions in epilepsy research. Daniel Lowenstein, MD, Robert B. and Ellinor Aird Professor and Vice-Chair of Neurology, Director, UCSF Epilepsy Center, University of California, San Francisco

Dr. Lowenstein gave the audience an exciting look into his personal view of the major advances likely to make a significant impact in the epilepsy field in the relatively near term. The first area he highlighted was that of optogenetics. This technology uses light-sensitive proteins called “opsins” to control seizures. Scientists can tie the opsin genes to a promoter that allows them to be incorporated into specific neurons. Once this is done, light can selectively activate specific cells and alter their excitability. Dr. Lowenstein described an experiment carried out by Dr. Jeanne Paz and colleagues in which inhibitory opsin were placed in the thalamic neurons of animals that had seizures due to a focal cortical stroke [44]. The investigators then created a closed-loop system that turned on the light when the EEG showed a seizure, which inhibited the thalamic neurons and instantly aborted the seizure. This is a very exciting technology that may allow seizure control without medication.

He next discussed the future impact of the explosion of knowledge about epilepsy genetics. He reminded us that in the “first era” of epilepsy genetics, the majority of genes discovered that were associated with epilepsy were genes encoding ion channels. This era has been termed the “channelopathy era” by Dr. Ingo Helbig [45]. Recently, copy number variation (CNV) has come to the forefront as a culprit in epileptic encephalopathies [46]. Now, Dr. Lowenstein believes, as a result of a number of large genetic scientific collaborations, that we are on the verge of a new era of genomic discovery. For example, recent large-scale efforts have led to the recognition of de novo mutations explaining upwards of 15% of epileptic encephalopathies [46]. In the near future, the Epilepsy Genetic Initiative (EGI), sponsored by the nonprofit Citizens United for Research in Epilepsy (CURE) and the NINDS, will allow individuals to “donate” their genetic data so that genes can be studied and restudied.

Next, Dr. Lowenstein highlighted the field of pluripotential stem cell research, which has now made it feasible to obtain cells from a patient’s skin biopsy, grow out fibroblasts, and then drive the cells to become inducible pluripotential stem cells [47]. If the patient has a gene mutation, one could theoretically correct the mutation and thus modify the cells to a “healthy state” and put them back in the patient. Also, the cells could be differentiated into neurons, which would create an assay system for the identification of specific drugs that might be effective for the individual from whom the cells were derived. A research team led by Dr. Jack Parent has demonstrated that pluripotent stem cells derived from patients with Dravet syndrome and differentiated into neurons have abnormal firing, a result the team has labeled “human seizures in a dish” [48].

Dr. Lowenstein also discussed the potential of drug screening in zebrafish. Dr. Scott Baraban and his colleagues have successfully shown that it is feasible to take a specific genetic mutation, such as the SCN1A mutation that leads to Dravet syndrome, place it in zebrafish, and observe the epilepsy phenotype [49]. This elegant system allows for a very effective, high-throughput system for screening candidate drugs, and this has already led to the discovery of some novel compounds that may soon be studied clinically.

He then discussed some remarkable studies that have demonstrated the ability of transplanted inhibitory interneurons to prevent epileptogenesis and associated comorbidities [48,50] and ended by briefly describing the Human Epilepsy Project (HEP), a multicenter observational cohort study of patients with recently diagnosed focal epilepsy that will look for biomarkers of disease activity and treatment resistance [51].

8.2. Improving delivery of therapies in people who need them: an industry perspective. Mark Evenstad, Chief Executive Officer, Upsher-Smith

Mark Evenstad, the CEO of a privately held and family-owned pharmaceutical company that has a large focus on epilepsy, spoke about the complexity of the current system of getting medication to patients and observed that physician decisions to treat patients with a certain AED do not always translate into the patient actually getting the drug due to issues of access and cost. He fears that this can often become a “system of no”, where patients are unable to get optimal therapy. This has motivated Upsher-Smith to implement a new business model designed to improve access to effective treatments and reduce health-care costs. He encouraged the epilepsy community to work towards greater access opportunities coupled with a focus on outcomes-driven health care.

8.3. The role of corporate and government partnerships in developing new epilepsy products

Panel: Roger J. Porter, MD, Moderator, Chief Scientific Officer, Epilepsy Foundation; Santiago Arroyo, MD, PhD, Vice President, Head of Clinical Research and Chief Medical Officer, Pharmatherapeutics, Worldwide Research & Development, Pfizer, Inc.; Roy E. Twyman, MD, Vice President and Head, Alzheimer’s Disease Area, Janssen Pharmaceuticals R&D LLC; Michael Gold, MD, Vice-President and Head of the CNS Practice, UCB, Inc.; Frank Fischer, Chief Executive Officer, NeuroPace, Inc.

Dr. Roger J. Porter moderated a panel of four representatives of drug and device companies that have been or are currently focused on epilepsy development.

Dr. Santiago Arroyo, VP, Head of Clinical Research & CMO, Pharmatherapeutics, Worldwide Research & Development, for Pfizer Inc., discussed what big pharma looks for in a new drug for epilepsy. He stated that the top needs were for superior efficacy, differentiation, improved safety and tolerability, no need for titration, broad-spectrum activity, and – ideally – disease modification. He went on to say that neurologists in the U.S. and Europe believe efficacy is the #1 concern. Usually, drugs produce 50% responders; but achieving 100% responders is more critically important. Because epilepsy is heterogeneous, he feels that there is a need for better understanding of who will be a responder, through biomarkers, or a better understanding of genetic variation. Unfortunately, one may need tens of thousands of patients to determine this. Echoing Dr. Lowenstein’s previous talk, he discussed the possibility of treating patients with rare disorders through the use of pluripotent stem cells or as a “disease in a dish”. He announced that Pfizer and
Intellimedix are in an agreement to look at children with rare epilepsies. He is hopeful for individualized therapies.

Roy E. Twyman, MD, VP and Head, Alzheimer's Disease Area, Janssen Pharmaceuticals R&D LLC, spoke next. He reported that unlike in the past, epilepsy is not now a priority at Janssen. Because “the world of yesterday is not the world of tomorrow”, “me too” drugs now have difficulty being reimbursed. For this reason, the therapies of tomorrow will need to be innovative, but timelines will be long. What is innovative today still needs to be innovative at the time of launch—which means one needs to be forward thinking. Clearly in epilepsy, there is an unmet need, and there is access to the market. He feels that targeted medicine is the future. There is an opportunity also to improve the overall risk–benefit. There is a need for differentiation. In his opinion, our current animal models do not differentiate drugs, and for this reason, the 20 recently developed AEDs are in turn not differentiated. Other CNS areas have moved away from animal models. He feels that epilepsy should turn more to molecular targets. He gave the example of Alzheimer's disease, where 230 genetic mutations have been identified, potentially providing molecular targets. He also feels that there is a need for models that are more translatable to humans, that allow early differentiation, and that could couple with early proof-of-concept studies, which would make attractive opportunities for pharma. There also needs to be a path to development. He feels the discussions with the FDA on new development pathways will pique the interest of pharma. On the negative side, he targeted the competitive landscape in epilepsy therapy as an issue. The economic driving force is to try cheaper drugs first, and there are many generics on the market. This makes differentiation even more important when competing for price.

Michael Gold, MD, VP and Head of the CNS Practice, UCB, highlighted that UCB is still looking for new opportunities in epilepsy. UCB encourages investigators to inform them of any new discoveries that might lead to new therapies. Like the previous speakers, he emphasized that in a generalized market, they are not excited about “me-too” opportunities. In his opinion, one issue is that payers (e.g., insurance companies) do not understand epilepsy. They see a lot of AEDs on the market and think that the market is satisfied. In contrast, patients want a cure, and they do not have it yet. Moreover, patients feel that the tradeoff between side effects and seizure control is not good. Dr. Gold discussed the struggle to individualize therapy and get the right drug to the right patient and gave several examples: in refractory status, some standard AEDs do not work because of the downregulation of GABA receptors; so here you could match a drug with a specific patient population. Neuroinflammation is another potential target. If you could find markers of inflammation in a patient, you could target an antiinflammatory drug to that patient. These might be opportunities UCB would consider for development. In contrast, they would not develop a drug just because it has a novel mechanism of action or because it works in every animal model. They also would not develop a drug in the hopes that its clinical value became apparent later (like levetiracetam and lamotrigine) and do not believe that a philosophy of “build it and they will come” is likely to fly anymore. He put out a novel consideration: that we could suggest to payers a scheme to get a drug out for 3–5 years with a discounted price, and a bump if there is differentiation, or a high price for 3–5 years that gets discounted if no differentiation is found.

Frank Fischer, CEO, NeuroPace, Inc., spoke from the perspective of a device manufacturer. First, he addressed the question of why a company would choose to develop a medical device to treat epilepsy. An established company already in the epilepsy space may want to broaden their product line or a company not in the epilepsy space may have an existing technology that is being sold for other indications that can be brought to a new market (e.g., the Visualase laser). In his opinion, outside of these scenarios, epilepsy devices will likely be developed by a start-up, and this will be driven by venture capital perception of unmet medical need, a novel and proprietary solution, no freedom-to-operate issues, a technical approach that will address the unmet need, a good business plan, and a good understanding of timelines and returns. There will also have to be a thorough analysis and favorable outlook for adequate reimbursement.

In summary, all speakers emphasized innovation, a well-delineated development pathway, and a departure from “business as usual”.

9. Session 8: clinical stage drugs

The conference then moved to discussion of treatments in the clinical stage of development.

9.1. Ultragenyx Pharmaceutical Inc. Triheptanoin. Emil D. Kakkis, MD, PhD, Chief Executive Officer, Ultragenyx Pharmaceutical Inc.

Dr. Kakkis, CEO, Ultragenyx Pharmaceutical Inc., discussed triheptanoin, which is being developed as a treatment for Glut1 deficiency, a genetic deficiency in glucose transportation. Glut1 deficiency causes blockage of glucose transport into the brain and leads to a chronic state of energy deficiency in the brain. The most classic phenotype involves seizures, developmental delay, and movement disorders and often presents in infancy or early childhood [52]. This condition was considered to be rare, but recently, it has become apparent that there are many more undiagnosed patients and variable phenotypic expression at different stages of disease. It is likely that the condition is underdiagnosed and may account for a subset of patients with chronic or refractory epilepsy. It has been reported that possibly 1% of all idiopathic generalized epilepsy and 10% of early-onset absence epilepsy may be undiagnosed Glut1 deficiency. To help enhance the diagnosis of patients with Glut1 deficiency, Ultragenyx will be supporting a free sequencing program for the Glut1 DS mutation.

In children with Glut1 deficiency, traditional AEDs are relatively ineffective, but the ketogenic diet has been effective in controlling seizures because ketone bodies can cross the blood–brain barrier and provide a source of energy, even though glucose is blocked. However, the ketogenic diet is difficult to maintain for some families, and there may be other nutritional and safety issues with prolonged use of a high-fat diet.

Triheptanoin is a triglyceride of medium-chain fatty acids with an odd number chain length of 7 carbons. Once in the body, triheptanoin is broken into heptanoate and later metabolized to 4 and 5 carbon ketone bodies. Both the heptanoate and the ketone bodies eventually provide multiple energy substrates to the brain that are also anaplerotic, i.e., they help restore the Kreb's cycle and gluconeogenesis [53]. A phase II study of this compound in Glut1 deficiency is underway in children who do not respond to the ketogenic diet and who are randomized to triheptanoin or control oil. The company is also supporting investigator-initiated trials of triheptanoin in other patient subsets with Glut1 deficiency and in refractory epilepsy.

9.2. Alexza Pharmaceuticals, Inc. Inhaled alprazolam. James V. Cassella, PhD, Chief Scientific Officer and Executive Vice President, R&D

Dr. Cassella, CSO and EVP, R&D for Alexza Pharmaceuticals, Inc., discussed inhaled alprazolam as a potential novel treatment for acute repetitive seizures (ARS). The current available therapies for ARS consist of rectally and intranasally administered benzodiazepines. Alexza has developed a technology called the Staccato system to deliver the benzodiazepine alprazolam to the lung in a single breath, with no coordination required. With this system, expirient-free pure drug is transformed (through heating) into fine aerosolized particles to get into the deep lung. Vaporization takes ~1 s and results in high bioavailability and IV-like pharmacokinetics. Peak plasma concentrations from a phase I study show $C_{\text{max}}$ within 2 min which is dose independent. This is a much faster $C_{\text{max}}$ compared to intranasal or rectal routes of administration. Alexza has one product on the market with this technology — loxapine for agitation. They have an active IND and have
studied about 100 patients to date with alprazolam. They are planning a proof-of-concept study using the photosensitometry model.

9.3. GW Pharmaceuticals. Epidiolex in pediatric epilepsy. Alice Mead, JD, Vice President, Professional Relations

Ms. Mead, VP, Professional Relations, GW Pharma, presented cannabidiol (CBD; Epidiolex) for pediatric epilepsy, as well as cannabidiol (CBDV; GW42006). Extensive clinical and preclinical data exist on cannabinoïd compounds as a class that suggest that some are anticonvulsant, antiinflammatory, antioxidant, and potentially neuroprotective [54–56]. GW has performed over 7 years of research into CBD, CBDV, and other non–THC cannabinoïds in the field of epilepsy. Epidiolex is a liquid form of highly purified (>98%), plant-derived CBD. The processes of purification and removal of THC are very highly controlled and performed under GMP conditions.

GW Pharma has secured orphan designation for Epidiolex in both Dravet syndrome and Lennox–Gastaut syndrome, as well as fast track designation from the FDA. They expect to seek breakthrough designation in due course. Epidiolex is already being used on a compassionate use basis under FDA-approved investigator-led, expanded access INDs. GW has an IND open with FDA and is in advanced preparations for pivotal phase II and III randomized controlled trials in the second half of 2014. There have already been approximately 600 weeks of exposure (up to 60 consecutive weeks) in investigator INDs.

Cannabidiol has a different antiepileptic preclinical profile than CBD. Phase I is completed for this compound, and GW intends to commence a phase II trial in early 2015.

9.4. Insero Health, Inc. Huperzine. Stephen D. Collins, MD, PhD, President and Chief Executive Officer, Insero Health, Inc.

Dr. Collins, President and CEO, Insero Health, Inc., said the company has a strategy of taking traditional compounds from around the world and improving them for pharmaceutical use. Their lead compound is a synthetic form of huperzine (INS-001), which has been used in China for hundreds of years and which is a potent acetylcholinesterase inhibitor with unique properties. It is very potent in the 6-Hz seizure model (57× more than levetiracetam) and appears to aid in cognition. The compound has also demonstrated strong activity in an SCN1A (Dravet) mouse genetic model. Complete seizure suppression was obtained in many animals at clinically relevant doses. The first indication will be for Dravet syndrome.

9.5. Marinus Pharmaceuticals, Inc. Ganaxolone. Gail M. Farfel, PhD, Chief Clinical Development & Regulatory Officer

Dr. Farfel, Chief Clinical Development & Regulatory Officer, Marinus Pharmaceuticals, discussed the development of ganaxolone, a neurosteroid that is a synthetic analog of allopregnanolone. Allopregnanolone is a byproduct of progesterone metabolism and can be enzymatically back-converted to a substrate for nuclear hormone receptors, whereas ganaxolone cannot. Ganaxolone is a positive allosteric modulator of the GABAA receptor. Ganaxolone is active at synaptic and extrasynaptic receptors. Activation of extrasynaptic receptors by neurosteroids is by a mechanism of diffusion into the postsynaptic membrane to interact with transmembrane domains of the receptor. Marinus has issued patents covering their nanoparticulate technology and manufacturing method used to formulate ganaxolone in oral capsules and liquid suspension.

Marinus has 4 open INDs and has completed all preclinical safety and toxicology studies except two-year carcinogenicity. The compound appears to be very safe. Ganaxolone is metabolized by CYP 3A4/5 and in a midazolam probe does not seem to be an inhibitor or inducer of CYP 3A4/5 enzymes. Ganaxolone has the potential advantage in that there is no evidence of reproductive toxicity, no weight gain, and interactions with oral contraceptive pills are not expected.

A phase II study has been completed in drug-resistant partial onset seizures. One hundred forty-seven adult subjects were enrolled, with 98 on ganaxolone (oral suspension, 1500 mg/day). There was a statistically significant seizure reduction seen in patients randomized to drug. The median reduction was 26% on ganaxolone vs 10% for placebo. Dizziness, fatigue, and somnolence were seen in >5% of patients.

A presurgical proof-of-concept monotherapy study was conducted in 52 subjects using the oral suspension (1875 mg/day). This study did not show a significant difference between groups (p = 0.08), but there was a trend in favor of ganaxolone [57].

Marinus has completed development of a new BID capsule formulation of ganaxolone. A pharmacokinetic study of this formulation at medium and high doses (1200, 1600, and 2000 mg/day) showed that proportionality is essentially maintained from 1200 to 1600 mg/day but not between 1600 and 2000 mg/day. A phase IIb double-blind, randomized study in adults with drug-resistant partial onset seizures is underway at 30 sites in the U.S. and Russia using the BID capsule. Subjects are treated for 4 weeks at 1200 mg/day followed by 4 weeks at 1800 mg ganaxolone or matching placebo. The study is expected to complete in 2015.

In addition to their work in adult and pediatric epilepsy, Marinus has undertaken proof-of-concept studies in fragile X syndrome and post-traumatic stress disorder (PTSD).

9.6. SK Life Sciences, Inc. YKP3089. Christopher Gallen, MD, PhD, President and Chief Executive Officer, SK Biopharmaceuticals, SK Life Sciences, Inc.

Dr. Gallen, President and CEO, SK Biopharmaceuticals, SK Life Sciences, Inc., presented YKP3089, a new investigational AED with a potentially unique mechanism of action and a pharmacokinetic profile suited to once-daily dosing.

The first randomized, double-blind, placebo-controlled study to assess efficacy and tolerability in patients with refractory partial epilepsy has been completed. Adults with partial-onset seizures (>3/28 days during an 8-week baseline despite 1–3 AEDs) were randomized to placebo or to adjunctive 200-mg YKP3089 which was titrated over 6 weeks (50-mg increments at 2-week intervals) and maintained for 6 weeks. The primary endpoint was the 28-day median % seizure reduction from baseline. Secondary endpoints included % patients with >50% seizure reduction (responder rate); % of study completers with no seizures in maintenance; and median % seizure reduction by seizure type.

Patient characteristics were similar at baseline (YKP3089, N = 113; placebo, N = 108). Median % seizure reduction was 56% on YKP3089 vs 22% on placebo (p < 0.0001). Twenty-eight percent of patients on YKP3089 were seizure-free during the maintenance phase compared to 9% on placebo. A statistically significant difference favored YKP3089 over placebo across all partial-onset seizure types. The most common adverse events were somnolence (22% YKP3089 vs 12% placebo), dizziness (21% vs 17%), fatigue (11% vs 6%), headache (11% vs 11%), and nystagmus (10% vs 0%). Nervous system/GI adverse events included balance disorder (8% vs 1%), tremor (6% vs 2%), constipation (5% vs 0%), diarrhea (5% vs 0%), and vomiting (5% vs 2%).

YKP3089 was highly effective vs placebo in reducing partial-onset seizures in patients with refractory epilepsy. No unexpected safety or tolerability issues were identified. A randomized double-blind placebo-controlled dose–response study examining 100 mg, 200 mg, and 400 mg is underway.

9.7. UCB, Inc. Brivaracetam. Joseph D’Souza, PhD, Senior Global Medical Director, UCB, Inc.

Dr. D’Souza, Senior Global Medical Director, UCB, Inc., provided an update on brivaracetam, an optimized SV2a ligand. Brivaracetam has a
strong affinity to SV2A, with high lipophilicity and rapid blood–
brain barrier uptake. There is a quick onset of action in animal models
[58–62]. There is complete absorption and dose-proportional PK,
which are not affected by food. Protein binding is 20%. There are no
oral contraceptive interactions [63–66]. The T1/2 is 8 h. Two phase III
studies have been completed [67,68]. Study N01253 met its primary ef-
ficacy, whereas study N01253 did not achieve statistical significance.
The most common adverse events were headache, somnolence, and
dizziness.

In total, 8 phase II/III trials have been performed. Two thousand pa-
patients have been exposed to brivaracetam, equating to 6000 patient-
years of exposure. A phase III study was just completed, using 100 and
200 mg of brivaracetam vs placebo.

9.8. Vertex Pharmaceuticals. VX-765. Jacqueline French, MD, Professor of
Neurology, New York University, Co-Director Epilepsy Research and
Epilepsy Clinical Trials, NYU Comprehensive Epilepsy Center; President,
Epilepsy Study Consortium

Dr. French, Professor of Neurology, NYU; Co-Director Epilepsy
Research and Epilepsy Clinical Trials, NYU Comprehensive Epilepsy Cen-
ter; President, ESC, presented VX-765. Animal and human data strongly
implicate cytokines and inflammation in the development and perpetu-
ation of epileptic foci. VX-765 works by modulation of proinflammatory
cytokines via inhibition of interleukin-converting enzyme. Preclinical
studies indicated that the compound could reduce seizures in achrono-
sically seizing mouse model of epilepsy [69]. The first proof-of-concept
study enrolled patients with treatment-resistant focal epilepsy (48
patients in the active arm and 12 in the placebo arm). The study had a
6-week baseline followed by randomization and then 6 weeks of treat-
ment, after which the drug was discontinued. Seizures were tracked for
another 6 weeks [70,71]. There was minimal seizure reduction during the
T1/2. However, seizures appeared to be reduced (20.5% after placebo subtraction) in a post hoc analysis during a “hybrid” period
consisting of the last 2 weeks of treatment and the first 2 weeks post-
treatment (with the consideration that an antiinflammatory therapy
may have a delayed onset of action, and the effect may outlast treat-
ment, through disease modification). A second study intended to con-
firm this finding was terminated after only 55 patients were enrolled
because of the company changing its priorities. VX-765 is not currently
in development.

9.9. Sapienza University, University of Utrecht. Pitolisant, a histamine 3
receptor antagonist, in the human photosensitivity model. Dorothee
Kastelein-Nolst Trenité MD, PhD, MPH, Professor of Neuroscience
at Sapienza University, Rome, Italy, Sr. Researcher Medical Genetics,
University of Utrecht, The Netherlands

Dr. Kastelein-Nolst Trenité from Sapienza University and University
of Utrecht presented a proof-of-concept photosensitivity study of
pitolisant, a histamine 3 receptor (H3R) antagonist. The study was funded
by Bioproject. Histamine 3 receptor is a presynaptic auto-
receptor that inhibits the release of histamine in the brain, as well as
other neurotransmitters [72–77]. It is found with high expression in
the prefrontal cortex, hippocampus, and hypothalamus [74]. Histamine
1 and 2 receptor antagonists are used in patients with allergy and
gastric ulcer [72–79]. Histamine 3 receptor antagonists are not yet on
the market but may have benefits for learning, alertness, and memory
improvement. There have been phase II studies with pitolisant that
demonstrated improvement in refractory daytime sleepiness in patients
with other neurologic diseases [80,81]. There are reasons to believe that
this compound would be beneficial in epilepsy. For example, there are
reports of seizures after antihistamine use [82–85], and low histamine
has been found in children with febrile seizures [86]. Pitolisant is a
non-imidazole-based histamine receptor inverse agonist/antagonist.
Preclinically, it was effective in the GAERs, kainite, and MES animal
models. Up to 120 mg, the Tmax was between 1 and 3 h, and there was
a clear dose–response relationship. The photosensitivity human phase
IIA study was performed with single doses of 20, 40, and 60 mg. Four-
teen patients (with diverse EEG profiles, some with frontal or
corticoparietal occipital discharges) were studied. Results showed sig-
nificant reduction or abolition of photopileptiform discharges in 64%
with a clear dose–response relationship [87]. Time of onset was 2 h
postdose, and duration of effect at the highest dose was up to 28 h.

9.10. IzumiBiosciences, LLC. Elacridar. Ton Bunt, MD MBA, founder,
President and Chief Executive Officer, IzumiBiosciences, LLC

Dr. Bunt, founder, President and CEO of IzumiBiosciences, LLC, pre-
sented elacridar, an oral pharmacoenhancer (PE). As epilepsy pro-
gresses in patients, two ABC gatekeepers (ABC1 or PCP and ABCG2 or
BCRP) are upregulated and work together synergistically to “vacuum”
AEDs out of the epileptic lesions, leading to subtherapeutic AED levels
and causing drug resistance [88,89]. The PE is a potent and selective
blocker of these two ABC pumps. It is not a drug in itself, but if given
concomitantly with an AED, it can enhance its penetration into epileptic
lesions and potentially reduce seizures in patients with drug-resistant
epilepsy. In 3 rat models of epilepsy, ABC inhibitors combined with
AEDs significantly reduced seizures. In those models, the increase in
AED concentrations was targeted at the epileptic lesions, while there
was an insignificant increase in serum and brain concentrations, boding
well for clinical safety and efficacy [90–92].

Previously, ABCB1 inhibitors showed good safety upon chronic dos-
ing in 5773 cancer patients, yet they lacked efficacy as they did not block
ABCG2. Elacridar showed good safety and tolerability in four phase I
studies, but also varying pharmacokinetic properties. There is regula-
try precedent of using pharmacoenhancers (with a different mechanism
of action) in HAART therapy for HIV/AIDS. The company proposes a
combination therapy of its proprietary PE with an AED and would like
to partner with a company to further develop and market such a differ-
entiated AED for patients with drug-resistant epilepsy.

9.11. Brabant Pharma. Twenty-two years of clinical data using low-dose
fenuramine to treat Dravet syndrome. Rick Stewart, Director, Brabant
Pharmaceuticals

Rick Stewart, Director, Brabant Pharmaceuticals, discussed the
company’s efforts to develop fenuramine for patients with Dravet syn-
drome. They have accrued up to 26 years of clinical data from a series
of patients who have been treated since 1988. The patients that were
followed had an average of 6 years of seizure freedom on the drug,
with an average treatment period in excess of 13 years. Ninety-two per-
cent are currently experiencing seizure freedom or >75% reduction
from baseline.

The company has met with both the FDA and the European Medi-
cines Agency, who have given them direction on the regulatory path-
way. They expect to commence two phase III clinical trials towards
the end of 2014. They have orphan designation in the U.S. and Europe,
and it is pending in Japan. They feel they have the potential for break-
through status from FDA.

Treatment of the series of patients with fenuramine started in 1988
and is continuing. The first publication was in 1996, reporting an 8-year
follow-up, and there was a more recent publication in 2012 [93,94].

Brabant conducted a longitudinal study of the long-term data,
looking at each patient before fenuramine treatment and at every
assessment point while on the drug. There were minimal cardiac side
effects, which they believe was due to a substantially reduced dose com-
pared to what was used in the past for weight loss (when problems with
cardiac valves were identified). The talk ended with a comparison of the
oldest and most recent patient treated with fenuramine. The oldest
patient was first treated in 1988 and has been on the drug for
26 years. She went from 12 convulsive seizures per year to having her

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last convulsion 9 months ago. The most recent patient was first treated in 2011 at age 14 months. Prior to treatment, she had 25 convulsive seizures in a 9-month period, with 11 hospitalizations, but on fenfluramine, her most recent seizure was 5 months ago.


Paige Figi, the mother of a child with Dravet syndrome and spokesperson and co-founder of the Realm of Caring, talked about Charlotte’s web, a cannabis-based oil from a plant that is high in cannabidiol and very low in THC. She placed her 5-year-old child on this, who became seizure-free after the first dose (compared to 300 convulsive seizures/week previously). The oil was renamed “Charlotte’s web”. Two and a half years later, Charlotte is not on any other AED and no longer needs a wheelchair, feeding tube, or supplemental oxygen. In August 2013, when 40 to 50 other children had taken Charlotte’s web through the Realm of Caring and there had been a number of exceptional responses, Ms. Figi reported it to the media. The compound is lab-tested, and they prepare a specific mg/ml infusion. She feels the media hype has created an unmanageable expectation, and families have moved to Colorado in order to access Charlotte’s web through her organization. She reported that seizures in some patients do not respond while others have a good response. She expressed frustration that the treatment is still considered “anecdotal” and urges that clinical trials be commenced as soon as possible. She believes the children who need this are out of time and out of options. She stated that a multicenter, blinded, placebo-controlled trial is planned in the near future in Uruguay because of the difficulty in performing such a trial in the U.S. due to schedule I designation of the drug.

10. Session 8: who is investing in epilepsy and CNS therapy research and innovation today? Funding beyond angels, grants, and awards

Panel: Casey Lynch, Moderator, Managing Director of NeuroInsights, LLC, Neurotechnology Industry Organization (NIO), and Chief Executive Officer of Cortemyme, Inc.; Greg Simon, Chief Executive Officer, Poliwogg; Manuel O. Lopez-Figueroa, PhD, Vice President, Bay City Capital, Scientific Liaison, Pritzker Neuropsychiatric Disorders Research Consortium; Sigrid Van Bladel, PhD, Venture Partner, Aberdare Ventures; Samuel Wu, Managing Director, MedImmune Ventures

This panel session was chaired by Warren Lammert, EF Chairman, and moderated by Casey Lynch, Managing Director of NeuroInsights, LLC, NIO, and CEO of Cortemyme, Inc.

Following an introduction of the panel members by Mr. Lammert, Ms. Lynch provided data on neuroscience investment, which is now at an annual rate of $1.4B with the pharmaceutical sector especially active. The first discussion related to the need to segment the epilepsy population in anticipation of personalized medicine. The panel noted that we are able to differentiate focal and generalized disease and that genetically defined populations were slowly emerging. Genetic differentiation is being led by the oncology field, with tailored treatments for cancer; the epilepsy community could learn from this example as well as from the segmentation of patients with asthma.

Another concept considered by the panel was the concept of incremental improvements as opposed to breakthrough therapies. Many companies, especially smaller companies, have done well with incremental improvements to existing therapies, much as in the field of cancer, where small incremental gains gradually improve the outlook of patients. In CNS, the small company Civitas, with its proposed inhaled treatment for Parkinson’s disease, was cited as a good example. Some panel members disagreed, citing that reformulations, for example, were no longer going to be supported by the marketplace, especially if the benefit to the patient was marginal.

The discussion then revolved around funding of exciting research projects. The company Poliwogg has engaged with EF on two projects and is available for investors interested in playing a role in health-care financing. The questions usually asked are 1) is the company investable?, 2) does it have the right kind of Board?, 3) does the investor have a high tolerance for failure, as no one can predict the winners, and 4) are multiple “shots on goal” available? The proponents claim that the “Valley of Death” is replaced by the “Bridge to Life.” Leveraging Poliwogg was emphasized as an alternative to failed efforts to get VC funding. Other investment funds have been created, such as for regenerative disorders and stem cells.

Turning to the device market, everyone noted the recent approval of the NeuroPace system, suggesting that new life may be coming to devices for epilepsy. One unanswered question was “Where are the device IPOs?” In the usual cycles of skepticism and optimism, companies are often bought out before an IPO can occur. One must be careful investing early, as later needs for capital can “wash out” early, smaller investments. On the regulatory side, whereas the EU was noted to be more device-friendly, the FDA has proven to be very tough. Finally, the question “What is a blockbuster device?” was asked. Examples outside the CNS area include pacemakers and stents.

The final conclusions of one of the panel members were 1) genetic therapies are the wave of the future, 2) noninvasive technologies (such as ultrasound) are moving rapidly, and 3) unexpected technological developments from other fields will have a huge influence in the next two decades.

11. Shark Tank competition

This session was chaired by Joseph Sirven, MD, Chair of Neurology at Mayo Clinic in Arizona and Editor-in-Chief of Epilepsy.com. The Shark Tank competition is based on a popular TV program and was adapted by EF, primarily through the efforts of Dr. French.

During the competition, novel and exciting ideas are presented either by persons or by small start-up companies (the presenters) to a group of business and medical experts (the sharks). The presentations are limited to 5 min, followed by vigorous questioning by the sharks for about 10 min. All of this takes place in front of the audience, who have a substantial influence on the distribution of the funds. In 2012, $50,000 was awarded and in 2013, $100,000 was awarded to the best project. These two awardees presented brief project updates.

11.1. Charles Anderson, Owner, HiPass Design LLC

The 2012 Shark Tank winner was Charles Anderson with HiPass Design LLC for the SAMi sleep activity monitor. This video-based monitor detects nocturnal seizures by looking for movement. The alarm does not work well with active sleepers or children that sleep with pets. SAMi does not connect to the Internet and is not yet approved for insurance reimbursement. Nevertheless, the device is available to patients. More than 90 units have been sold and shipped. Plans for a 3rd-generation camera should make the device less expensive; new and different sensors are also being evaluated. A U.S. patent on the system has been granted. An Indiegogo campaign is underway. At the end of the presentation, Phil Gattone, President and CEO of EF announced an anonymous $25K match for the Indiegogo campaign—with much to the delight of the audience.

11.2. Utkan Demirci, MS, PhD, Bio-Acoustic MEMS in Medicine Labs, Brigham and Women's Hospital, Harvard Medical School, Harvard-MIT Health Sciences and Technology; Steven C. Schachter, MD, Professor of Neurology, Harvard Medical School; Chief Academic Officer, Consortia for Improving Medicine through Innovation and Technology

The 2013 Shark Tank award went to Utkan Demirci, MS, PhD and Steven Schachter, MD for their AED Drug Levels on a Chip Project. The concept is to determine blood levels of AEDs using a finger stick device, which employs color change as an indicator for drug levels. The aim is to
develop a rapid, easy-to-use, and accurate platform to monitor AED levels and to decrease the cost and time factor (eliminating the need to go to the hospital or laboratory) for patients with epilepsy. For patients on polytherapy, this platform will also contain multiple microchannels whereby serum concentrations of different AEDs are simultaneously detected, as well as other components of whole blood, such as WBC counts and liver function tests. The current reader costs about $500 and the chip only a few dollars. The technology is also capable of measuring AED levels from saliva.

### 11.3. 2014 Shark Tank presenters and sharks

The moderator for the 2014 Shark Tank competition was Jacqueline French, MD.

For 2014, 58 applications were received. Six finalists were chosen by members of the Scientific and Business Advisory Boards of EF to present to five expert sharks. The prize money was increased from $100K to $200K. Some of the rules were the same as in previous years. Each presenter was given 5 min, followed by 10 min of intense questioning by the sharks. No audience questioning was allowed, as before. The sharks (not the audience) were provided with additional information in advance of the contest.

However, new rules were laid down by EF for 2014. Each of the five sharks would have $25K at his/her disposal for their favorite project. The audience (voting on smartphones) was allocated $75K. The sharks would choose their favorites in public, but no project could receive less than $50K (no “lone sharks”). The sharks would be required to resolve their differences in public before the audience vote. In essence, this meant that the five shark allocations would result either in one project getting $125K or two projects would share the shark award at $50K and $75K, respectively. The audience award of $75K was completely independent; the audience did not vote until the shark decisions were final.

The 2014 sharks were Jim Abrahams, Founder and Executive Director of The Charlie Foundation; Ari Mackler, PhD, MBA, VP, Clinical Development, POM Wonderful—Paramount Farms; Martha Morrell, MD, CMO, NeuroPace and Clinical Professor, Neurology and Neurological Sciences, Stanford School of Medicine; Andrew Smith, Healthcare Investment Banking Analyst, Credit Suisse; and Elson So, MD, Professor of Neurology, Mayo Clinic and President, American Epilepsy Society.

### 11.3.1. Jon Davis, inventor. Shower Power, a bathing safety monitoring system

Shower Power is a safety device for the shower. In 2008, the U.S. had 22 million hospital visits for bathroom injuries. Of the total, bathing and showering accounted for about 30% of all injuries. In February 2014, the inventor’s daughter was diagnosed with epilepsy after her first seizure which occurred in the shower. Essentially, the device discreetly monitors for upright posture in the shower; it shuts off the water and initiates alarms (local + smartphone) when an upright showering posture is not maintained. The system is designed to allow independence, safety, and peace of mind for the patient and their caregiver. The device may also be helpful for people needing additional showering safety, like patients with Parkinson’s disease and the elderly. The project is in the initial stages, but a $200 price point for the shower safety monitoring system is the target.

### 11.3.2. Nirav Sheth, Head of Medical Development, MC10, Inc. “Biostamp” wearable sensors

The inventor addressed the need for automatic monitoring of seizure activity. In a video, both patients and parents speak about the need for more information about seizures and medications, and the effect of each on the patient. The company has expertise in sensors and algorithm development. A wearable skin patch with sensors was passed to the sharks for inspection. The data are delivered directly to a smartphone with option for onboard memory as well. Existing sensing modalities are centered on motion and muscle activation, including EMG, accelerometer, and gyroscope functionality. Feasibility of monitoring temperature, respiration, and heart rate is also proven. Theoretical future sensors could include ECG and EEG. MC10 is looking for partners to assemble an epilepsy-appropriate portfolio of sensing modalities and algorithms for both research and patient empowerment applications.

### 11.3.3. Sandra L. Helmers, MD, MPH, Professor of Neurology and Pediatrics, Emory University School of Medicine. WebEase—Y: enhancing youth epilepsy management behaviors

Web Epilepsy Awareness, Support, and Education (WebEase) is a free, internet-based, interactive, evidence-based, HIPPA-compliant, self-management program that is currently available for adults with epilepsy. It provides the skills that adults need to take charge of their epilepsy. With this new product, the developers aimed to adapt the existing software for 12- to 17-year-olds to assist with their transition to independence, daily management of their epilepsy. The WebEase-Y is designed to empower youth to set goals, engage in healthy coping skills, and successfully transition to independence.

### 11.3.4. Oren Knopfmacher, PhD, Avails Medical, Inc. In-home and inexpensive AED monitoring device using saliva

Robert Fisher, MD, PhD, started the presentation and details were then provided by Dr. Knopfmacher. The concept is to dip a disposable chip in saliva and obtain a read-out of AED levels. The eventual plan is for the system to work with blood, urine, or saliva. Saliva reflects the unbound fraction of the drug levels, presenting a possible advantage. The planned prototype is for levetiracetam, to be followed by other drugs. The device should eventually be able to measure multiple drug levels simultaneously. This is not an optical device like the previous Shark Tank winner but instead uses inexpensive and portable methodology. The specificity of the strips is extremely precise. Data can be sent to other devices or to a customized feedback program on the web. The plan is to seek 510K, with the aim of correlating saliva levels to plasma levels and thereby develop a way to track levels of medications before onset of seizures or toxicity.

### 11.3.5. Ahmed Helmy, Associate Professor, Computer and Information Science and Engineering (CISE) Department, University of Florida and his 13-year-old son, Amir Helmy, Co-Designer and Developer. Seizario app—software to detect seizures using smartphones

The unique feature of this seizure detection concept is that it does not use any external device. It is entirely new software for smartphones—basically a mobile application. It can detect seizures or emergencies. Help is summoned by the smartphone, which contains data such as location. The main features of the system are that it 1) detects an emergency, 2) provides communication to others, and 3) is capable of recording data automatically. The program contains a sophisticated app to detect seizures; the user can turn off false alarms. A panic button is included. The user has full control of the program, which is designed to improve self-management as well as provide better communication between patient and relatives.

### 11.3.6. Michell Lundell of M Object Oriented Software Engineering AB. Ketonix breath ketone analyzer

The concept is to measure ketones in the breath to reflect the desired ketogenic state during implementation and maintenance of a ketogenic diet. The device is a breath analyzer that measures the ketones and gives a read-out. The Ketonix device was initiated after the current CEO had seizures and decided to try the ketogenic diet because of adverse drug effects. When he switched from drugs to the diet, he wanted a good way to indicate his ketosis. He first used blood and urine but thought that there must be a better way. He could not find a device to measure breath ketones, so he developed this device. The process is simple:
1) plug it in, 2) wait for calibration, 3) blow into it, and 4) watch for different colors as blood levels of ketosis, but it reliably measures the generation of ketones (ketosis). The device can be used by people on ketogenic diets to manage epilepsy, diabetes, and cancer. It can also be used by athletes who wish to access fat for energy instead of carbohydrates.

Since single votes (lone sharks) were not permitted, Dr. French asked all the single voters to reconsider. The final vote for the sharks was three for the salvia drug detection device ($75K) and two for the Shower Power ($50K).

The audience then voted by smartphone, with the tally displayed on the screen for all to see. The audience (by a substantial margin) voted for the Seizario app—software to detect seizures using smartphones ($75K).

12. Closing Remarks

Philip Gattone, President and CEO, EF, gave the final remarks following the last session. He stated that the Foundation is privileged to have hosted this incredible pipeline event. He also announced new collaborations between EF, Intellimedix, and Pfizer as well as between EF and Epilepsy & Behavior. Mr. Gattone thanked the audience as the agents for change and thanked all the participants for their steadfast commitment to epilepsy research as we move towards a better life for persons with epilepsy.

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Conflict of Interest

S. Schachter is inventor on a patent for the use of huperzine for treatment of epilepsy, which is licensed by Harvard Medical School to Insero Health, Inc., in which he holds less than 5% equity and for which he serves as chair of the scientific advisory board. R. Porter is a paid consultant to AurimMed, Astellas, Medivation, and Upsher-Smith. He has an equity position in AurimMed.

J. French is President of the Epilepsy Study Consortium. All consulting is done on behalf of the consortium, and fees are paid to the consortium. The NYU Comprehensive Epilepsy Center receives salary support from the consortium. She has acted as a consultant for Acorda, Biotie, Brabant Pharma, Eisai Medical Research, GlaxoSmithKline, GW Pharma, Impax, Johnson and Johnson, Marathon Pharmaceuticals, Marinus, Neusentis, Novartis, Pfizer, Sage, Sunovion, SK Life Sciences, Supernus Pharmaceuticals, Takeda, UCB, Upsher-Smith, Ultragenyx, Vertex, Zynera; has received grants and research from Acorda, Alexza, LCGH, Eisai Medical Research, Lundbeck, Pfizer, SK Life Sciences, UCB, Upsher-Smith, Vertex; and has received grants from NINDS, Epilepsy Therapy Project, Epilepsy Research Foundation, Epilepsy Study Consortium. She is on the editorial board of Lancet Neurology, Neurology Today, and Epileptic Disorders, and an associate editor of Epilepsia.

Meeting presenters discussing commercial or commercializable products should be considered to have a conflict of interest unless they have no affiliation with the company.

References


