FOURTEENTH EILAT CONFERENCE ON
NEW ANTIEPILEPTIC DRUGS AND DEVICES
(EILAT XIV)
Madrid, Spain, May 13-16, 2018

PROGRAM

AND

ABSTRACTS

Under the auspices of
The Hebrew University of Jerusalem, Israel

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CONFERENCE ORGANIZERS
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ACKNOWLEDGEMENTS

The Organizing Committee wishes to acknowledge the following companies and organizations whose generous support has made this Conference possible.

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GENERAL INFORMATION

VENUE
Meliá Castilla Hotel & Convention Center
Poeta Joan Maragall 43 - 28020 (formely Capitán Haya, 4328020)
Madrid, Spain
Tel. (34) 91 567 50 77
Fax (34) 91 567 50 66

LANGUAGE
The Conference will be conducted in English.

REGISTRATION / HOSPITALITY / INFORMATION
A desk will operate at the Meliá Castilla Hotel as follows:

Sunday, May 13	from 13:00 - 20:00
Monday, May 14	from 08:00 and during session times
Tuesday, May 15	from 08:00 and during session times
Wednesday, May 16	from 07:30 and during session times

NAME BADGE
Your name badge is included in the material which you received upon registration. Please wear your badge to all conference sessions and events.

SPEAKER PRESENTATIONS
Computer projection is available. Please see the technician before the beginning of your session.

POSTERS
Posters will be on display in the lecture hall for the duration of the conference. Presenters are requested to refer to the program book to find the board number assigned to them. Posters should be mounted as of Sunday, May 13 afternoon, and must be removed by the end of the conference. Please note that the organizers cannot be held responsible for posters that are not removed on time.

GET-TOGETHER RECEPTION
SUNDAY, MAY 13, 2018 - 19:30
An informal get-together to renew acquaintances and meet new colleagues will take place at the Meliá Castilla Hotel by the swimming pool.
All registered participants are invited to attend.

CONFERENCE PROGRAM

SUNDAY, MAY 13, 2018

16:00 – 16:15	**OPENING SESSION**
	OPENING REMARKS AND GREETINGS **Meir Bialer**, Organizing Committee, Jerusalem, Israel
	GREETINGS **Emilio Perucca**, Organizing Committee and ILAE Past-President, Pavia, Italy
16:15 – 19:10	**PLENARY LECTURES: NEW APPROACHES TO PRECLINICAL AED DISCOVERY**
	Chairs: **Arne Schousboe**, Denmark **Henrik Klitgaard,** Belgium
16:15	**A LECTURE IN HONOR OF H. STEVEN WHITE** ANIMAL MODELS OF SEIZURES AND EPILEPSY: PAST, PRESENT AND FUTURE ROLE FOR THE DISCOVERY OF AEDs **Wolfgang Löscher,** University of Veterinary Medicine, Hannover, Germany
16:40	Discussion
16:50	UPDATE ON THE NINDS/NIH EPILEPSY THERAPY SCREENING PROGRAM (ETSP) **John Kehne**, National Institutes of Health, Bethesda, MD, USA
17:10	Discussion
17:20	TRANSLATIONAL ASPECTS OF RATIONAL DRUG DISCOVERY IN EPILEPSY **Rafal Kaminski,** UCB Pharma, Brussels, Belgium
17:45	Discussion

SUNDAY, MAY 13, 2018 (Continued)

17:55	TESTING DISEASE MODIFICATION IN THE CLINIC: HAS THE TIME COME? **Henrik Klitgaard,** UCB Pharma, Brussels, Belgium and **Roy Twyman**, Amron Neuroscience, LLC, Darby, MT, USA
18:20	Discussion
18:30	ORPHAN DRUGS: WHERE POLITICS AND ECONOMICS COLLIDE **Michael Drummond**, University of York, York, UK
19:00	Discussion
19:30	*Get-Together Reception*

MONDAY, MAY 14, 2018

08:30 – 09:00	**UPDATE ON SEIZURE AND EPILEPSY MODELS: DEBATE**
	Chairs: **Emilio Perucca**, Italy **H. Steven White,** USA
08:30	THE HUMAN PHOTOSENSITIVITY MODEL FOR THE DEVELOPMENT OF DRUGS FOR FOCAL ONSET SEIZURES: A DEBATE ***Pro:*** **Dorothee Kasteleijn-Nolst Trenite,** University of Rome, "Sapienza" II, Rome, Italy ***Con:*** **Roger Porter**, University of Pennsylvania, Philadelphia, PA, USA
08:50	Discussion
09:00 – 11:00	**PLENARY LECTURES**: **UPDATE ON SEIZURE AND EPILEPSY MODELS**
	Chairs: **Emilio Perucca**, Italy **H. Steven White,** USA
09:00	RELEVANCE OF ACUTE PRECLINICAL EFFICACY STUDIES TO THE TREATMENT OF A CHRONIC DISEASE: A NOVEL APPROACH TO CHRONIC DRUG DELIVERY **H. Steven White,** University of Washington, Seattle, WA, USA
09:20	Discussion
09:30	GENETIC MODELS OF EPILEPTIC ENCEPHALOPATIES: HOW WILL THEY INFORM CLINICAL DEVELOPMENT? **Jeffrey Noebels,** Baylor College of Medicine, Houston, TX, USA
09:50	Discussion

MONDAY, MAY 14, 2018 (Continued)

09:00 – 11:00	**PLENARY LECTURES**: **UPDATE ON SEIZURE AND EPILEPSY MODELS (Continued)**
10:00	PRECLINICAL EVIDENCE FOR SEIZURE SUPPRESSION THROUGH NEUROMODULATION **Kristl Vonck***,* Ghent University Hospital, Ghent, Belgium
10:20	Discussion
10:30	TIME TO EVENT MODEL FOR EARLY EFFICACY SIGNAL DOSE FINDING **Filip De Ridder**, Janssen R&D, LLC, Raritan, NJ, USA
10:50	Discussion
11:00	*Coffee break*
11:30 – 13:35	**DRUGS IN DEVELOPMENT SESSION 1**
	Chairs: **Svein I. Johannessen**, Norway **Torbjörn Tomson,** Sweden
11:30	ACETONE ANALOGS **John Andrews***, Ketogen Pharma Inc.,* Toronto, Canada
11:55	ADENOSINE **Detlev Boison**, Legacy Research Institute, Portland, OR, USA
12:20	AMPA RECEPTOR ANTAGONISM via MEDIUM CHAIN FATTY ACIDS **Robin S.B. Williams**, Royal Holloway University of London, UK
12:45	AMPA TARP-γ8 NEGATIVE MODULATORS **Marc Ceusters**, *Janssen R&D,* Beerse, Belgium
13:10	ANAKINRA Presented by **Elaine Wirrell***, The Mayo Clinics,* Madison, WI, USA

MONDAY, MAY 14, 2018 (Continued)

13:35	*Lunch*

14:35 – 16:15	**DRUGS IN DEVELOPMENT SESSION 2**
	Chairs: **Meir Bialer,** Israel **Simon D. Shorvon**, UK
14:35	BUMETANIDE and its DERIVATIVES Presented by **Wolfgang Löscher**, University of Veterinary Medicine, Hannover, Germany
15:00	CANNABIDIOL *GW Pharmaceuticals* Presented by **Kevan VanLandingham,** *Greenwich Biosciences Inc*, Carlsbad, CA, USA
15:25	CANNABIDIVARIN *GW Pharmaceuticals* Presented by **Volker Knappertz,** *Greenwich Biosciences Inc*, Carlsbad, CA, USA
15:50	TAK-935 *Takeda/ Ovid Therapeutics*, USA Presented by **Matthew During***, Ovid Therapeutics*, Cambridge, MA, USA
16:15	*Coffee Break*

MONDAY, MAY 14, 2018 (Continued)

16:45 – 18:50	**DRUGS IN DEVELOPMENT SESSION 3**
	Chairs: **Emilio Perucca**, Italy **Torbjörn Tomson**, Sweden
16:45	OV329 **Matthew During***, Ovid Therapeutics*, Cambridge, MA, USA
17:10	CERLIPONASE ALFA (BMN 190) *BioMarin Pharmaceutical Inc.,* USA Presented by **Nicola Specchio**, Bambin Gesù Children Hospital, Rome, Italy
17:35	NEW APPROACHES TO THE MEDIUM CHAIN TRIGLYCERIDE DIET *Vitaflo,* UK Presented by **Matthew Walker**, University College London, London, UK
18:00	2-DEOXY-(D)-GLUCOSE **Thomas Sutula**, University of Wisconsin, Madison, WI, USA
18:25	FENFLURAMINE **Gail Farfel***, Zogenix Pharmaceutical*, San Diego, CA, USA

TUESDAY, MAY 15, 2018

08:30 – 10:35	**DRUGS IN DEVELOPMENT SESSION 4**
	Chairs: **Meir Bialer,** Israel **Rene H. Levy**, USA
08:30	GANAXOLONE **Lorianne Masuoka***, Marinus Pharmaceuticals Inc,* Radnor, PA, USA
08:55	HUPERZINE A (BIS-001) **Stephen D. Collins***, Biscayne Neurotherapeutics,* Miami, FL, USA
09:20	IMEPITOIN *Boehringer-Ingelheim,* Germany Presented by **Wolfgang Löscher**, University of Veterinary Medicine, Hannover, Germany
09:45	JNJ-40411813 and mGluR2 PAMs **Roy Twyman**, Amron Neuroscience, LLC, Darby, MT, USA
10:10	Novel mTOR-inhibitors *PIQUR Therapeutics,* Switzerland Presented by **Wolfgang Löscher**, University of Veterinary Medicine, Hannover, Germany

TUESDAY, MAY 15, 2018 (Continued)

10:35	*Coffee Break*

11:00 – 13:00	**DRUGS IN DEVELOPMENT SESSION 5**

Chairs: **Svein I. Johannessen**, Norway
H. Steven White, USA

11:00	OXYNYTONES **Michael Poulter**, *OB Pharmaceuticals,* Toronto, Canada
11:25	PADSEVONIL **Konrad J. Werhahn**, *UCB Pharma,* Brussels, Belgium
11:50	VALNOCTAMIDE and sec-BUTYLPROPYLACETAMIDE (SPD) Presented by **Meir Bialer**, The Hebrew University of Jerusalem, Israel
12:15	XEN1101 **Y. Paul Goldberg**, *Xenon Pharmaceuticals Inc.*, Burnaby, Canada
12:40	XEN901 **Charles Cohen**, *Xenon Pharmaceuticals Inc.*, Burnaby, Canada
13:00	*Lunch*

TUESDAY, MAY 15, 2018 (Continued)

14:00 – 16:50	**PROGRESS REPORT ON SECOND-GENERATION TREATMENT**
	Chairs: **Piero Perucca**, Australia **Cecilie Johannessen Landmark**, Norway
14:00	BRIVARACETAM **Jan-Peer Elshoff***, UCB Pharma,* Brussels, Belgium
14:25	ESLICARBAZEPINE ACETATE *Bial, Portugal* Presented by **Vicente Villanueva***,* Hospital Universitario y Politécnico La Fe, Valencia*,* Spain
14:50	EVEROLIMUS *Novartis,* Switzerland Presented by **Paolo Curatolo,** "Tor Vergata" University Hospital, Rome, Italy
15:15	LACOSAMIDE **Robert Roebling***, UCB Pharma,* Brussels, Belgium
15:40	PERAMPANEL **Stella Ngo***, Eisai Inc.,* Woodcliff Lake, NJ, USA
16:05	PREGABALIN **Lloyd Knapp***, Pfizer Inc.,* New York, NY, USA
16:25	STIRIPENTOL *Biocodex, France* Presented by **Elaine Wirrell***,* The Mayo Clinic*,* Rochester, MN, USA
16:50	*Coffee Break*

TUESDAY, MAY 15, 2018 (Continued)

17:15 – 19:20	**PROGRESS REPORT ON DEVICES FOR SEIZURE DETECTION AND TREATMENT**
	Chairs: **Matthias Koepp**, UK **Kristl Vonck**, Belgium
17:15	RESPONSIVE CORTICAL STIMULATION **Martha Morrell***, NeuroPace*, Mountain View, CA, USA
17:40	NEUROMODULATION, MONITORING AND MRI GUIDED LASER ABLATION **Jon Giftakis***, Medtronic Brain Therapies,* Minneapolis, USA
18:05	SEIZURE RESPONSIVE VAGUS NERVE STIMULATION *LivaNova,* Belgium Presented by **Kristl Vonck**, University of Ghent, Ghent, Belgium
18:30	TECHNOLOGY-ENABLED SEIZURE DETECTION AND REPORTING:THE EPILEPSY NETWORK PROJECT **Rupert Page**, Poole Hospital, Poole, UK
18:55	EMBRACE AND E4: DEVICES FOR SEIZURE DETECTION AND ADVANCING RESEARCH **Matteo Lai,** *Empatica*, Milan, Italy

WEDNESDAY, MAY 16, 2018

08:00 – 09:30	**DEVICES FOR THE TREATMENT OF EPILEPSY: TRIAL DESIGNS AND REGULATORY REQUIREMENTS**
	Chairs: **Paul Boon,** Belgium **Matthias Koepp,** UK
08:00	REGULATORY REQUIREMENTS FOR MEDICAL DEVICES IN EUROPE **Ivana Hayes,** *European Medicines Agency*, London, UK
08:25	TRIAL DESIGNS: THE INDUSTRY PERSPECTIVE **Maxine Dibué-Adjei**, *LivaNova*, Munich, Germany
08:50	ACADEMIC DEVICE TRIALS: CHALLENGES AND OPPORTUNITIES **Paul Boon**, Ghent University Hospital, Ghent, Belgium
09:15	PANEL DISCUSSION
09:30 – 10:20	**PROGRESS REPORT ON TREATMENT DEVICES (continued)**
	Chairs: **Matthias Koepp,** UK **Matthew Walker**, UK
09:30	LESSONS TO LEARN FROM TRANSCUTANEOUS VAGUS NERVE STIMULATION (tVNS) **Hajo Hamer**, University Hospital, Erlangen, Germany
09:55	AUTONOMIC BIOFEEDBACK THERAPY **Yoko Nagai***,* Brighton & Sussex Medical School, Brighton, UK
10:20	*Coffee Break*

WEDNESDAY, MAY 16, 2018 (Continued)

10:50 – 13:30	**INNOVATIVE EMERGENCY TREATMENTS**
	Chairs: **Simon D. Shorvon**, UK **Eugen Trinka**, Austria
10:50	NEUROMODULATION FOR REFRACTORY STATUS **Eugen Trinka,** The Christian Doppler University Hospital, Salzburg, Austria
11:15	PROPOFOL PRODRUG (EPALEX-102) *Epalex,* USA Presented by **Michael A. Rogawski**, University of California, Davis, CA, USA
11:40	INTRANASAL DIAZEPAM **Enrique J. Carrazana**, *Neurelis*, San Diego,CA, USA
12:05	BRIVARACETAM **Jean-Marie Nicolas,** *UCB Pharma,* Brussels, Belgium
12:30	INTRANASAL MIDAZOLAM (NAYZILAM™ USL261) **William E. Pullman***, Proximagen*, Plymouth, MN, USA
12:55	STACCATO ALPRAZOLAM **Gregory Mayes***, Engage Therapeutics*, New Jersey, USA
13:20	End of Conference and Concluding Remarks
	Light Lunch

POSTER PRESENTATIONS

Board No.

1. HYBRID COMPOUNDS IN THE SEARCH FOR THE NEW HIGHLY EFFECTIVE ANTICONVULSANTS
Michał Abram[1], Anna Rapacz[2], Szczepan Mogilski[2], Gniewomir Latacz[3], Bartłomiej Szulczyk[4], Kamil Kuś[5], Maria Walczak[5], Krzysztof Kamiński[1]
[1]Department of Medicinal Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, Kraków, Poland, [2]Department of Pharmacodynamics, Faculty of Pharmacy, Jagiellonian University Medical College, Kraków, Poland, [3]Department of Technology and Biotechnology of Drugs, Faculty of Pharmacy, Faculty of Pharmacy, Jagiellonian University Medical College, Kraków, Poland, [4]Department of Drug Technology and Pharmaceutical Biotechnology, Medical University of Warsaw, Warsaw, Poland, [5]Department of Toxicology, Faculty of Pharmacy, Jagiellonian University Medical College, Kraków, Poland

2. RECENT TRENDS IN UTILISATION OF ANTIEPILEPTIC DRUGS IN NORWAY
Arton Baftiu[1], Pål G. Larsson[2], Svein I. Johannessen[3,4], Cecilie Johannessen Landmark [1,3,4]
[1]Department of Life Sciences and Health, Oslo Metropolitan University, Oslo, Norway, [2]Department of Neurosurgery, Oslo University Hospital, Oslo, Norway, [3]The National Center for Epilepsy, Oslo University Hospital, Sandvika, Norway, [4]Department of Pharmacology, Oslo University Hospital, Oslo, Norway

3. DESIGN AND COMPARATIVE EVALUATION OF THE ANTICONVULSANT PROFILE, CARBONIC-ANHYDRATE INHIBITION AND TERATOGENICITY OF NOVEL CARBAMATE DERIVATIVES OF BRANCHED ALIPHATIC CARBOXYLIC ACIDS WITH 4-AMINOBENZENSULFONAMIDE
David Bibi[1], Hafiz Mawasi[2], Alessio Nocentini[3], Claudiu T. Supuran[3], Bogdan Wlodarczyk[4], Richard H. Finnell[4], Meir Bialer[2]
[1]Department of Pharmaceutical Sciences, School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, Israel, [2]School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, Israel, [3]Neurofarba Dept., Università Degli Studi Di Firenze, Florence, Italy, [4]Department of Pediatrics, The University of Texas at Austin, Texas, USA

POSTER PRESENTATIONS (Continued)

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4. CONCOMITANT MEDICATIONS IN PATIENTS WITH EPILEPSY
Magdalena Bosak[1], Bryan Song[2]
[1]Neurology, Jagiellonian University, Krakow, Poland, [2]School of Medicine in English, Jagiellonian University Medical College, Krakow, Poland

5. ZEBRAFISH-BASED DISCOVERY OF ANTISEIZURE COMPOUNDS FROM THE RED SEA
Daniëlle Copmans[1], Mostafa Rateb[2,3], Jioji N. Tabudravu[2], Mercedes Pérez-Bonilla[4], Nina Dirkx[1], Riccardo Vallorani[1], Caridad Diaz[4], José Pérez del Palacio[4], Alan J. Smith[2], Rainer Ebel[2], Fernando Reyes[4], Marcel Jaspars[2], Peter A. M. de Witte[1]
[1]Laboratory for Molecular Biodiscovery, Department of Pharmaceutical and Pharmacological Sciences, University of Leuven, Leuven, Belgium, [2]Marine Biodiscovery Centre, Department of Chemistry, University of Aberdeen, Aberdeen, UK, [3]Faculty of Pharmacy, Pharmacognosy Department, Beni Suef University, Beni Suef, Egypt, [4]Fundación Medina, Centro De Excelencia en Investigación De Medicamentos Innovadores en Andalucía, Granada, Spain

6. EFFICACY AND TOLERABILITY OF ADJUVANT LACOSAMIDE: THE ROLE OF CLINICAL CHARACTERISTICS AND MECHANISMS OF ACTION OF CONCOMITANT AED
Wendyl J. D'Souza[1], Andrew Neal[1,2], Nicholas Lawn[3], Graham Hepworth[4], Mark Cook[5,2], Armin Nikpour[6,7]
[1]Department of Medicine, St Vincent's Hospital, The University of Melbourne, Melbourne, Australia, [2]Neurology, St Vincent's Hospital Melbourne, Melbourne, Australia, [3]Western Australian Adult Epilepsy Service, Sir Charles Gardiner Hospital, Perth, Wa, Australia, [4]Statistical Consulting Centre, The University of Melbourne, Melbourne, Australia, [5]The Department of Melbourne, St Vincent's Hospital, The University of Melbourne, Melbourne, Australia, [6]Sydney Medical School, University of Sydney, University of Sydney, Sydney, Australia, [7]Department of Neurosciences, Royal Prince Alfred Hospital, Sydney, Australia

POSTER PRESENTATIONS (Continued)

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7. SUSCEPTIBILITY GENES FOR VPA-INDUCED CONGENITAL MALFORMATIONS
Richard H Finnell, Yunping Lei, Robert Cabrera, Bogdan Wlodarczyk
Molecular and Cellular Biology, Baylor College of Medicine, Houston, USA

8. ALTERNATIVE NKCC1-INHIBITORS FOR TREATMENT OF SEIZURES? PHARMACOKINETIC PROPERTIES OF BUMETANIDE VS. TORASEMIDE AND AZOSEMIDE
Philip Hampel[1,2], Kerstin Römermann[1], Wiebke Theilmann[1], Wolfgang Löscher[1,2]
[1]Department of Pharmacology, Toxicology and Pharmacy, University of Veterinary Medicine, Hannover, Germany,
[2]Center for Systems Neuroscience, University of Veterinary Medicine, Hannover, Germany

9. THE NOVEL, SPECIFIC, BRAIN PENETRANT MTOR AND PI3K/MTOR INHIBITORS PQR620 AND PQR530 PREVENT EPILEPTIC SEIZURES IN A TSC MOUSE MODEL
Petra Hillmann[1], Denise Rageot[2], Alexander Sele[2], Florent Beaufils[2,3], Paul Hebeisen[1], Anna Melone[2], Thomas Bohnacker[2], Jean-Baptiste Langlois[2], Chiara Borsari[2], Wofgang Löscher[4], Matthias P Wymann[2], Doriano Fabbro[1]
[1]Preclinical Biology, Piqur Therapeutics, Basel, Switzerland,
[2]Department of Biomedicine, University of Basel, Basel, Switzerland,
[3]Current Address, Spiro Chem, Basel, Switzerland,
[4]Department of Pharmacology, Toxicology, and Pharmacy, University of Veterinary Medicine, Hannover, Germany

10. TOLERABILITY, EFFICACY AND RETENTION RATE OF BRV IN PATIENTS PREVIOUSLY TREATED WITH LEV
Martin Hirsch, Andreas Schulze-Bonhage
Epilepsy Center, Clinic for Neurosurgery, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

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11. IMPLEMENTATION OF THERAPEUTIC DRUG MONITORING TO STUDY PHARMACOKINETIC VARIABILITY OF LACOSAMIDE IN CHILDREN AND ADOLESCENTS
Margrete Larsen Burns[1], Arton Baftiu[2], Andre Gottås[1], Marina Nikaronova[3], Jan B Rasmussen[4], Svein I Johannessen[5], **Cecile Johannessen Landmark[6,5,2]**
[1]Dept of Pharmacology, Oslo University Hospital, Oslo, Norway, [2]Programme for Pharmacy, Dept of Life Sciences and Health, Oslo Metropolitan University, Oslo, Norway, [3]Dept of Pediatry, The Danish Epilepsy Hospital, Dianalund, Denmark, [4]Dept of Clinical Pharmacology, The Danish Epilepsy Hospital, Dianalund, Denmark, [5]The National Center for Epilepsy and Dept of Pharmacology, Oslo University Hospital, Oslo, Norway, [6]Programme for Pharmacy, Dept of Life Sciences and Health, Oslo and Akershus University College, Oslo, Norway

12. HYBRID COMPOUNDS BASED ON THE PYRROLIDINE-2,5-DIONE SCAFFOLD AS CANDIDATES FOR NEW BROAD-SPECTRUM ANTICONVULSANTS
Krzysztof Kamiński[1], Michał Abram[1], Anna Rapacz[2], Martyna Sojka[1], Gniewomir Latacz[3], Jolanta M. Obniska[1], Marcin Jakubiec[1]
[1]Department of Medicinal Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, Krakow, Poland, [2]Department of Pharmacodynamics, Faculty of Pharmacy, Jagiellonian University Medical College, Krakow, Poland, [3]Department of Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College, Krakow, Poland

13. ANTICONVULSANT ACTION OF CANNABIDIOL IN IMMATURE RATS
Hana Kubova[1], Libor Uttl[1,2], Tomas Hložek[3], Pavel Mares[1]
[1]Developmental Epileptology, Inst.physiology Czech Academy of Sciences, Prague, Czech Republic, [2]Neurophysiology, National Instiute of Mental Health, Klecany, Czech Republic, [3]Forensic Medicine and Toxicology, 1st Medical Faculty, Charles University, Prague, Czech Republic

POSTER PRESENTATIONS (Continued)

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14. FINDING A LOST SLEEP MIGHT BE MORE REJOICING: A REAL-WORLD EXPERIENCE WITH PERAMPANEL IN THE PATIENT WITH SUPER-REFRACTORY FOCAL EPILEPSY
    Soonhak Kwon, Su-Kyeong Hwang, Yun-Jeong Lee
    Pediatric Neurology, Kyungpook National University Children's Hospital, Daegu, Korea

15. ANTICONVULSANT ACTION OF PREGNANOLONE SULFATE AND PREGNANOLONE GLUTAMATE IN IMMATURE RATS
    Pavel Mares[1], Hana Kubova[1], Eva Kudova[2], Hana Chodounska[2], Karel Vales[3]
    [1]Developmental Epileptology, Inst.physiology Czech Academy of Sciences, Prague, Czech Republic, [2]Dept.steroid Inhibitors, Inst.organic Chemistry and Biochemistry, Czech Academy of Sciences, Prague, Czech Republic, [3]Dept.experimental Neurobiology, National Instiute of Mental Health, Klecany, Czech Republic

16. RETENTION RATE AND OUTCOME-RELATED FACTORS OF PERAMPANEL: A REAL-LIFE POPULATION STUDY
    Sara Matricardi[1], Sabrina Siliquini[1], Simona Lattanzi[2], Claudia Cagnetti[2], Francesco Deleo[3], Andrea Stabile[3], Francesca Ragona[4], Elena Freri[4], Elisabetta Cesaroni[1], Gaia Anibaldi[1], Nicoletta Foschi[2], Flavio Villani[3], Tiziana Granata[4], Nelia Zamponi[1]
    [1]Department of Neuropsychiatry, Children's Hospital "G. Salesi", Ospedali Riuniti Ancona, Ancona, Italy, [2]Department of Experimental and Clinical Medicine, Neurological Clinic, Marche Polytechnic University, Ancona, Italy, [3]Clinical and Experimental Epileptology Unit, Foundation Irccs Neurological Institute ''C. Besta'', Milan, Italy, [4]Department of Pediatric Neuroscience, Foundation Irccs Neurological Institute ''C. Besta'', Milan, Italy

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17. MAY PSYCHIATRIC DISORDERS PREDICT THE RESPONSE TO ANTIEPILEPTIC DRUGS?
Gonzalo Mazuela[1], Manuel Quintana[2], Estevo Santamarina[1], Sonia Cazorla[1], Jose Angel Mauri[3], Xiana Rodríguez-Osorio[4], Francisco Javier Lopez-González[4], María Gómez-Eguilza[5], Marian Barcala[6], Patricia Esteve[7], Juan Jose Baiges[7], Javier Abril-Jaramillo[8], Juan Rodríguez-Uranga[8], María Dolores Castro-Vilanova[9], Laura Abraira del Fresno[1], Javier Salas-Puig[1], Manuel Toledo[1]
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18. SYNTHESIS AND ANTICONVULSANT ACTIVITY OF NEW HYBRID COMPOUNDS DERIVED FROM 5,5-DISUBSTITUTED OR 5-SPIRO-IMIDAZOLIDINE-2,4-DIONE CORE AND MORPHOLINE MOIETY
Jolanta Maria Obniska[1], Anna Czopek[2], Hanna Byrtus[2], Małgorzata Góra[2], Krzysztof Kamiński[2], Anna Rapacz[3]
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Michèle Partoens[1], Daniëlle Copmans[1], Gert Steurs[2], Rik Verschueren[2], Annelii Ny[1], Wim De Borggraeve[2], Peter A. M. de Witte[1]
[1]Laboratory for Molecular Biodiscovery, Department of Pharmaceutical and Pharmacological Sciences, University of Leuven, Leuven, Belgium, [2]Laboratory of Organic Synthesis, Chemistry Department, University of Leuven, Leuven, Belgium

20. EFFICACY AND SAFETY OF ORAL CANNABIDIOL AS ADJUNCTIVE TREATMENT FOR PEDIATRIC SUBJECTS WITH EPILEPTIC ENCEPHALOPATHY
Nicola Pietrafusa, Marina Trivisano, Luca De Palma, Ilaria Pizzolorusso, Alessandro Ferretti, Federico Vigevano, Nicola Specchio
Neurosciences and Neurorehabilitation, "Bambino Gesù" Children's Hospital Irccs, Rome, Italy

21. STATUS EPILEPTICUS AFTER EXPERIMENTAL TRAUMATIC BRAIN INJURY: A NOVEL IN VIVO PLATFORM FOR TESTING TREATMENTS
Ivette Banuelos, Pedro Andrade, Niina Lapinlampi,
Xavier Ekolle Ndode-Ekane, **Asla Pitkanen**
A.I. Virtane Institute, University of Eastern Finland, Kuopio, Finland

22. AEDS REDUCE THE UPPER PHOTOSENSITIVITY LIMIT MORE THAN THE LOWER IN PHOTOSENSITIVE PATIENTS WITH EPILEPSY – INCLUDING THOSE ON CARBAMAZEPINE.
Ronald Charles Reed[1], Dorothee Kasteleijn Nolst-Trenite[2]
[1]Pharmacy Practice, Husson University, School of Pharmacy, Bangor, USA, [2]Epilepsy, University Medical Center Utrecht, Utrecht, Netherlands

23. DRUG DISCOVERY PROGRAMS FOR THE DEVELOPMENT OF NEW ANTIEPILEPTIC DRUGS USING THE MTLE MOUSE AND THE GAERS MODELS
Corinne Roucard, Céline Ruggiero, Carine Dumont,
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Venceslas Duveau
Synap Cell Sas, Bâtiment Synergy, Saint Ismier, France

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24. PROGRESS TOWARDS INTRANASAL DIAZEPAM DELIVERY USING AN AQUEOUS PRODRUG/ENZYME COMBINATION
Ronald A Siegel[1], Davin Rautiola[2], Narsihmulu Cheryala[3], Kathryn Nelson[3], Gunda Georg[3], Jared Fine[4], Aleta Svitak[4], Katherin Faltesek[4], Leah Hanson[4], Usha Mishra[5], Lisa Coles[5], Patricia Maglalang[5], James Cloyd[5]
[1]Pharmaceutics and Biomedical Engineering, University of Minnesota, Minneapolis, Mn, USA, [2]Pharmaceutics, University of Minnesota, Minneapolis, USA, [3]Medicinal Chemistry, University of Minnesota, Minneapolis, USA, [4]Neuroscience Research, Health Partners Institute, St. Paul, USA, [5]Experimental and Clinical Pharmacology, University of Minnesota, Minneapolis, USA

25. FV-082: A SAFER ORALLY ACTIVE BROAD SPECTRUM ANTI-EPILEPTIC DRUG CANDIDATE
Malik Slassi[1,2], Peter Dove[3]
[1]R&D, Trillium Therapeutics, Mississauga, Canada ,
[2]R&D, Fluorinov Pharma Inc., Toronto, Canada ,
[3]Discovery Research, Trillium Therapeutics Inc., Mississauga, Canada

26. FV-137: NOVEL, ORALLY ACTIVE BROAD SPECTRUM DRUG CANDIDATE WITH UNIQUE MOA FOR EPILEPSY AND PAIN
Malik Slassi[1,2], Peter Dove[3]
[1]R&D, Trillium Therapeutics, Mississauga, Canada , [2]R&D, Fluorinov Pharma Inc., Toronto, Canada , [3]Discovery Research, Trillium Therapeutics Inc., Mississauga, Canada

ABSTRACTS:

ORAL PRESENTATIONS

UPDATE ON THE NINDS/NIH EPILEPSY THERAPY SCREENING PROGRAM (ETSP)

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The mission of the NINDS Epilepsy Therapy Screening Program (ETSP) is to facilitate the discovery and characterization of novel therapeutic agents for addressing the significant remaining unmet medical needs in epilepsy, most notably treatment-resistance, and disease prevention and modification. The ETSP builds on the success of the longstanding NINDS/NIH Anticonvulsant Screening Program (ASP) which for over 40 years screened over 32,000 compounds from >600 participants from around the world and contributed to numerous marketed antiseizure drugs. The current prime contractor for the ETSP is the University of Utah (Karen Wilcox, Ph.D., P.I.). Based on input from expert working groups, and with ongoing feedback provided by members of an External Consultant Board (ECB), the ETSP has implemented significant enhancements in its testing strategies. These include the development of a refined two-stage flow chart to evaluate the potential of compounds for clinically-differentiated treatments for drug refractory epilepsy. In this workflow, an initial "Identification" phase utilizes two acute seizure models in neurologically-intact rodents, the maximal electroshock (MES) seizure test, and the mouse 6 Hz 44 mA model of pharmacoresistant seizures. The Identification phase has two additional assays with "disease-like" characteristics, corneal kindled seizures and an in vitro spontaneous electrical bursting slice model. The inclusion of these two models is to help identify mechanistically-novel agents that interact with aberrant processes in the epileptic brain and therefore may not be detected by acute seizure tests. With suitable activity, compounds advance to a subsequent "Differentiation" phase which utilizes three advanced disease models: the lamotrigine-resistant amygdala-kindled rat model; mouse mesial Temporal Lobe Epilepsy (mTLE) model, and chronically-epileptic rat model with video/EEG recording. Data are compared to marketed antiseizure drugs, which show varying levels of pharmacoresistance in these models. The ETSP currently has other models of special epilepsy populations including a mouse model of viral-induced encephalitis [Theiler's murine encephalitis virus (TMEV) model], and a rat model of benzodiazepine pharmacoresistant status epilepticus. Compounds can be assessed for potential antiepileptogenic activity using the mTLE mouse and chronic epileptic rat models.

Finally, the ETSP established the publicly-accessible PANAChE database that provides information on ETSP methodologies and a searchable repository for non-confidential data generated on compounds tested by the ETSP to encourage further discovery efforts by external investigators. The overall goal of these ETSP efforts is to identify promising agents that will comprise the next-generation of pharmacological treatments that will significantly reducing the burden of epilepsy.

Website links:

ETSP: ~~ (http://www.nind.nih.gov/ETSP)

PANAChE publicly accessible database: ~~(http://panache.ninds.nih.gov)

TRANSLATIONAL ASPECTS OF RATIONAL DRUG DISCOVERY IN EPILEPSY

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Recent decades of antiepileptic drug (AED) discovery have led to the development and approval of many compounds providing significant therapeutic benefit for patients with epilepsy. In fact, when compared to other neurological diseases, the epilepsy field has enjoyed one of the highest rates of success when it comes to progression of preclinical drug candidates into clinical development and regulatory approval. This is largely due to the generally high predictability of preclinical seizure models, which were instrumental for drug discovery approaches based on phenotypic in vivo screening. However, a large proportion of patients still remain without adequate seizure control, driving the need to further improve the AED discovery and development process. One potential way forward would be a stronger focus on rational drug discovery and precision medicine in epilepsy. Future therapies should be designed for specific patient subpopulations based on strong biological rationales. Furthermore, such approaches would enable an even better translation of preclinical results into well-informed and optimized clinical development programs. This presentation will discuss some recent examples of rational drug design in epilepsy with an emphasis on selection of clinical doses based on target engagement biomarker studies.

TESTING DISEASE MODIFICATION IN THE CLINIC: HAS THE TIME COME?

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No disease-modifying treatment has yet navigated the path from preclinical proof-of-concept to clinical success in epilepsy, despite an accumulation of preclinical studies reporting on the antiepileptogenic activity of a variety of mechanisms. This emphasizes an increasing need to define preclinical validation strategies and to optimize clinical trial designs in an effort to guide potential preclinical and clinical investigations towards success. Signals that the time has come for testing disease modification in the clinic include the following: i) evidence of disease modification in preclinical models that require testing in human studies to confirm, ii) suggestive clinical evidence for breakthrough disease-modifying treatment in human epilepsy based on preclinical evidence or repurposing, and iii) safe, feasible and economically sound clinical trial designs in human epilepsy. This presentation discusses some of the known limitations and hurdles for moving compounds found effective in animal models to applicability in human clinical practice. We hope this information will facilitate the identification of preclinical validation strategies, translational approaches and the design of optimal clinical “learn and confirm” studies that can effectively identify new disease-modifying agents.

ORPHAN DRUGS: WHERE POLITICS AND ECONOMICS COLLIDE

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Orphan drugs (drugs for rare diseases) pose political and economic challenges. Politicians often prefer to make them available on emotional grounds, but economists point out that they are extremely expensive in relation to the gains in health they provide. Manufacturers argue that the high prices (often in excess of €500k per annum) are justified, given the small number of patients available to allow them to recoup their research expenditure. Some researchers have argued that pharmaceutical manufacturers prey on politician's emotions in order to make excessive profits and that, when asked, the general public do not want to pay a premium for rarity. Given this situation what is the best way forward? Specifically, how might one determine a fair price for an orphan drug? This presentation will discuss these issues, with examples from epilepsy.

DEBATE:

THE HUMAN PHOTOSENSITIVITY MODEL FOR THE DEVELOPMENT OF DRUGS FOR FOCAL ONSET SEIZURES (PRO)

D. Kasteleijn Nolst-Trenite[1,2]

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Epileptiform EEG discharges evoked by intermittent photic stimulation (IPS) in epilepsy patients can be used as biomarker for determination of efficacy of a potential antiepileptic drug (AED). An international community-driven and standardized stimulation protocol of repeated IPS over a three-day period (a baseline placebo IPS day #1, an investigational AED, single dose, on Day #2, followed by a third IPS day to determine the AED's duration of effect) has been accepted by the scientific community as a valid method for determining an AED's pharmacologic effect in epilepsy. This Phase IIa, Proof of Principle (PoP) Study procedure has been designated the 'Photosensitivity Model'. This 'Photosensitivity Model' has repeatedly shown its' value in the development of new AEDs, as demonstrated by the number of original publications using this PoP protocol and subsequent AED approvals granted having utilized the Model in early clinical development. A premiere example of the drug-development utility of the Model is Levetiracetam (LEV), a first-line AED in new-onset focal epilepsies. LEV showed dose-dependent efficacy in the 'Photosensitivity Model' and was then developed as an AED, primarily owing to its' dramatic effect in the Model. Many other AEDs for focal epilepsies have also been detected using the Model; this is not surprising since PPRs occur in about 15% of patients with focal epilepsies. In addition, patients may exhibit signs and symptoms during PPRs that are focal.

Based on data gathered over the past 30 years, there is every reason to accept that PPRs, as observed in the uniform PoP Photosensitivity Model, can be used to successfully identify new AEDs for patients with focal epilepsy.

DEBATE:
THE PHOTOSENSITIVITY MODEL IS NOT A MODEL FOR PARTIAL (FOCAL) SEIZURES (CON)

R. J. Porter
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The search for new and better anti-seizure medications is an obsession for many of us who despair that cures for the epilepsies are not likely in the near future. But when we are sufficiently fortunate not only to have safely reached the stage where a potential new drug is ready for human testing, but passed through Phase I and now need confirmation in human epilepsy, the dilemma is considerable. Should we proceed to an expensive Phase IIA/B study, or is there a shortcut that will give us valuable information about efficacy and save us time and money? For sure, we want our clinical shortcut to predict important characteristics of partial seizures.The difficult question is whether we can evaluate drug efficacy in a single human model of neuronal hyperexcitability and extrapolate to all epilepsy syndromes. Most of the work on the PPR model in epilepsy, a type of hyperexcitability model, has been accomplished by the Dorothee Kasteleijn Group (DKG) in the Netherlands, extending back at least to 1986--an excellent and amazing accomplishment. Among the unchallengeable contributions of the DKG are analysis and standardization of the procedure itself. However, the photosensitivity model has been proposed as a model to evaluate drugs for partial seizures. The following arguments suggest that this proposal is inaccurate and and potentially misleading:

1. The prevalence of photic sensitivity in epilepsy is overestimated.
2. The prevalence of partial epilepsy with photic sensitivity has been overestimated.
3. The PPRs recorded by the DKG group may actually be seizures.
4. False-positive results for PPR predictions of efficacy for partial seizures are already available.
5. False-negative results for PPR predictions of efficacy for partial seizures are already available.
6. The only double-blind study by the DKG was the negative study of carbamazepine.
7. The PPR model sometimes finds a PK/PD relationship.
8. The PPR model sometimes finds the minimal effective dose for partial seizures.

The PPR human model is an excellent model for predicting efficacy of drugs against photosensitive epilepsy. Photic sensitivity in partial seizures is exceedingly rare. Use of the model for predicting efficacy against partial seizures is fraught with the danger of both false positive and false negative results. The latter is potentially the most damaging; a new drug with great potential for partial seizures--but which, like

carbamazepine, is ineffective in the PPR model--may be inappropriately abandoned by the industry sponsor.

RELEVANCE OF ACUTE PRECLINICAL EFFICACY STUDIES TO THE TREATMENT OF A CHRONIC DISEASE: A NOVEL APPROACH TO CHRONIC DRUG DELIVERY

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Since the introduction of phenytoin for the treatment of epilepsy in 1938, the early identification and characterization of investigational anti-seizure drugs (ASDs) has relied largely on acute testing in well-characterized animal seizure and epilepsy models. This approach has been highly successful in bringing over 20 new drugs to the patient with epilepsy since 1993. However, despite this success, there is still a large unmet need for more efficacious therapies for those patients whose seizures remain largely uncontrolled. One limitation with the current approach is that it does not typically employ chronic efficacy testing in an etiologically relevant epilepsy model. This is largely because chronic oral dosing of animals with epilepsy is stressful to the animal and extremely labor intensive as ASDs typically have short half-lives in rodents and require multiple; e.g., four or more, daily administrations to achieve chronic steady state blood and brain levels. In recent years, we have developed a highly reliable computer-controlled automated drug-in-food delivery system for the chronic delivery of ASDs to rats with epilepsy (1). Importantly, this system removes the stress associated with repeated, chronic oral gavage. In the present investigation, we describe the results of a proof-of-concept carbamazepine (CBZ) pharmacokinetic study following acute and chronic (75 mg/kg, p.o., q.i.d.) to naïve Sprague Dawley rats using this newly described automated system. The results of this investigation demonstrate that CBZ blood levels reach steady state therapeutic levels (4-12 µg/mL) within 24 hours and despite the presence of auto-induction; i.e., increased conversion of CBZ to CBZ-epoxide, CBZ blood levels remain within the therapeutic range for the duration of the 10 day study. In addition, results from proof-of-concept efficacy studies with chronic CBZ administered to rats with newly diagnosed epilepsy using this feeder system that demonstrate the overall feasibility of this system for chronic oral delivery of ASDs to assess chronic efficacy of investigational ASDs in etiologically relevant animal epilepsy models will be discussed (2). Importantly, the proposed chronic dosing approach addresses an inherent limitation of current ASD testing.

1) Thomson KE, White HS. A novel open-source drug-delivery system that allows for first-of-kind simulation of nonadherence to pharmacological interventions in animal disease models. *J Neurosci Methods.* Dec 30; 238-105-11, 2014.
2) Thomson KE, Modi AC, Glauser TA, Rausch JR, White HS. The impact of nonadherence to antiseizure drugs on seizure outcomes in an animal model of epilepsy. *Epilepsia.* 58(6):1054-1062, 2017.

GENETIC MODELS OF EPILEPTIC ENCEPHALOPATHIES: HOW WILL THEY INFORM CLINICAL DEVELOPMENT?

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In the last five years, well over 100 novel genes have been implicated in pediatric epilepsies, most of them corresponding to more severe forms of life-long seizures. The pharmcoresistance of many of these disorders emphasizes the emerging opportunity to discover and develop gene-guided therapies for uncommon, but urgently needed treatments.

The genes identified provide striking evidence of the biological diversity of brain pathways contributing to epileptogenesis. Interestingly, although the first 10 genes identified for epilepsy were all ion channels, a favored target of frontline antiseizure drugs, channels now constitute only about one third of the list, and the remainder appear to be involved in complex developmental programs regulating the growth, migration, and maturation of synaptic networks in the developing brain. While patients carrying mutations in these genes can be easily stratified for clinical trials, it is unclear whether the genes themselves constitute drug targets, or simply point toward still unknown mechanistic defects which are druggable yet poorly defined. Fortunately, powerful tools, including genetic engineering of mouse models with human mutations and neurons derived from induced pluripotent stem cells obtained from patients are now in wide use to search for targets and evaluate treatments for epilepsy and its co-morbidities, including SUDEP.

TIME TO EVENT MODEL FOR EARLY EFFICACY SIGNAL DOSE FINDING

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Time to-event endpoints have been proposed as alternatives to establish the effect of anti-epileptic drugs in clinical trials. These endpoints may reduce exposure to placebo or ineffective treatments, thereby facilitating trial recruitment and improving safety. Time to baseline seizure count is defined as the number of days until a subject experienced a number of seizures equal to the baseline seizure count. A post hoc analysis of completed Phase III trails with perampanel showed that an analysis of the time to baseline count endpoint is consistent with the classical endpoints (median % seizure rate reduction, percentage of patients achieving a 50% or greater reduction in seizure frequency)[1].

We investigated the performance of the time to baseline seizure endpoint by (1) a post hoc analysis of topiramate and carisbamate clinical trial data and (2) clinical trial simulation using a longitudinal model for daily seizures counts. This model included key features of daily seizure count data, such as a large between subject variability in baseline seizure rate and drug response, a large variability of the number of seizures per day and clustering of seizures over time.

The re-analysis of topiramate and carisbamate clinical trial data confirmed the relationship between the median time to baseline seizure count and the classical endpoint of median % seizure rate reduction that was observed with perampanel. In addition, the observed relationship agreed with the one that was predicted by the simulation model.

Clinical trial simulations were used to investigate the performance of a proof-of-concept study design using the time to baseline seizure count endpoint. The study consisted of a 4-week prospective baseline, followed by a 4-week double blind treatment period, after which subjects would exit the study if they had reached or exceeded their baseline seizure count, or would continue for another 8-weeks. These simulations showed that (1) with relatively small sample sizes (~ 20/arm) the design is able to identify clinical relevant treatment effects (30% - 50% seizure rate reduction); (2) a 4-week baseline period provides enough information on the baseline seizure count and (3) the length of exposure of subjects to placebo or an inactive treatment is strongly reduced as compared to a classical design.

[1]French JA, Gil-Nagel A, Malerba S, Kramer L, Kumar D, Bagiella E. (2015) Time to prerandomization monthly seizure count in perampanel trials: A novel epilepsy endpoint. Neurology 84(20):2014-2020.

KETONES IN ANTI-CONVULSIVE THERAPY: KETONE ENHANCED ANTIEPILEPTIC DRUGS (AED'S)

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The KD is clinically effective in treating both children and adults with refractory epilepsy; however, its use is limited due to its unpalatable nature and potential cardiovascular risks. Ketones, such as acetone, are known to display similar anticonvulsant activity in models to the KD and earlier research had indicated that some AED's can be potentiated by some ketones. However, acetone and other ketones are not likely to be useful as stand-alone AED's given their stability and the concentration required for sufficient penetration into the CNS and site of action. Ketogen has designed several series of "multivalent" new chemical entities (NCEs) that incorporate active and effective AED components linked to a ketone-generating group (KGG). The AED acts as an active carrier to bring the KGG into the CNS and provides a unique way to reduce side effects and body load of ketones, while improving tolerability and the overall benefit-risk. The combined KGG/AED demonstrate unique anticonvulsant properties in a range of models where the parent motifs are either inactive or poorly active. The choice of KGG and AED motifs can have a dramatic effect on efficacy. For example, KG-110, KG-130 and KG131 all use the same AED motif but have different KGGs and correspondingly different profiles across a range of models such as PTZ, 6Hz and MES, in some cases an AED inactive in some models will become active when combined with an appropriate KGG. In addition to efficacy, the duration of action also differs substantially dependent on the KGG. In contrast to the KD, the potentiating effects on anti-seizure activity are seen immediately and not after several days. Moreover, the activity in the model does not correlate strongly with measurements of BHB in the blood, taken to indicate the occurrence of ketosis. These data suggest that the ketone enhanced anticonvulsant activity does not have to rely only on the presumed metabolic changes occurring with the KD. Several drug-refractory paediatric disorders show some response to the KD. This suggests that they are ketone sensitive and could serve as a focussed and enriched population for testing the efficacy of these NCEs and may help in developing tailored treatment options.

ADENOSINE AND ADENOSINE KINASE INHIBITORS

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The purine ribonucleoside adenosine is a well-characterized endogenous anticonvulsant and seizure terminator of the brain. New findings from our laboratory show that epilepsy and its progression can be prevented by the transient therapeutic augmentation of adenosine, which can most effectively be achieved by pharmacologically blocking the major adenosine metabolizing enzyme adenosine kinase (ADK). ADK exists in a cytoplasmic isoform ADK-S, which regulates extracellular levels of adenosine and adenosine receptor activation, and a nuclear isoform ADK-L, which acts as a regulator of DNA and histone methylation. We have initiated medicinal chemistry efforts with the goal to move an ADK-L inhibitor into therapeutic development. Our clinical target is to prevent temporal lobe epilepsy (TLE) and its progression. Our approach is based on solid evidence (i) that overexpression of ADK within an epileptogenic brain area is a biomarker and pathological hallmark for epileptogenesis, and (ii) that a transient dose of adenosine delivered to the brain either directly, via brain implants, or pharmacologically, via an ADK inhibitor, effectively prevents epileptogenesis and disease progression long-term. As regulators of DNA methylation, ADK inhibitors are uniquely suited to reprogram the DNA methylome and thereby to interrupt molecular processes implicated in epileptogenesis. ADK inhibitors designed to enhance adenosine receptor activation via augmentation of extracellular adenosine (based on inhibiting ADK-S) in brain tissue were previously considered for anticonvulsive therapy, but eventually failed due to lack of specificity and adverse events. We propose to develop novel ADK inhibitors that block the specific nuclear isoform ADK-L to capitalize on adenosine's epigenetic effects for the new indication 'antiepileptogenesis'. We have initiated iterative processes to pursue our overarching goal to identify and rigorously test an antiepileptogenic ADK-L inhibitor as a candidate for clinical trials. We developed a lead compound, MRS4203, with demonstrated ADK-L inhibition and epigenetic efficacy in vitro and in the brain; importantly, and in contrast to inhibitors that affect ADK-S, a systemic dose of MRS4203 is not associated with any overt adverse events. Because ADK is overexpressed in the epileptic brain and associated with epileptogenesis, there is a strong rationale for the clinical development of ADK inhibitors that restore normal adenosine function. The development and validation of new ADK inhibitors that mobilize long-lasting antiepileptogenic epigenetic effects through transient ADK-L inhibition will enhance the contribution of desirable epigenetically-based antiepileptogenic effects of adenosine.

AMPA RECEPTOR ANTAGONISM via MEDIUM CHAIN FATTY ACIDS

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Ketogenic diets, involving a low carbohydrate and high fat intake, are broadly considered to function through the metabolism of fats to generate ketones that then giving rise to seizure control. However, despite many years of research, the mechanism of ketones in seizure control remain largely unclear, and ketone levels correlate poorly with seizure control. To investigate the medium chain triglyceride (MCT) ketogenic diet we initially assessed the role of ketones and the two major fats provided in the diet, octanoic acid and decanoic acid. We show that only decanoic acid reduced seizure like activity in two acute ex vivo rat hippocampal slice models of epileptiform activity. Using whole cell patch clamp recordings from CA1 pyramidal neurons, we further show that decanoic acid reduces EPSCs, consistent with an effect on postsynaptic excitatory (AMPA) receptor. To investigate a direct effect of medium chain fatty acids, we expressed various AMPA receptor subunit combinations (from GluA1, 2 and 3) in Xenopus oocytes, to characterise direct inhibitory against AMPA receptor generated currents following agonist induction. We show decanoic acid (IC50=0.52±0.02mM) was more potent that related octanoic acid (IC50=3.82±0.03mM), suggesting decanoic acid-dependent inhibition of endogenous AMPA receptor signalling at brain concentrations found in mouse model following dietary MCT treatment. This inhibition was non-competitive to glutamate, greater for GluA2/3 than GluA1/2 receptors, and was enhanced under depolarised conditions suggesting stronger inhibitory activity during seizures. In silico docking analysis suggested decanoic acid binds to AMPA receptors on the M3 helices within the channel region, providing a distinct binding site to that proposed for perampanel – a currently licensed treatment for partial onset and primary generalised tonic-clonic seizures. Several in vivo studies have shown seizure control following decanoic acid treatment. Following a single bolus gavage dose, decanoic acid treatment showed resistance in both MEST and 6Hz mouse models, and in dietary treatment with decanoic acid medium chain triglycerides in the 6Hz and flurothyl model. A range of novel derivatives of medium chain fatty acids, have also been shown to work through the same mechanism with improved in vivo activity compared to decanoic acid in a multiple models. These data therefore suggest that decanoic acid provided in the MCT ketogenic diet, functions through AMPA receptor inhibition to provide seizure control.

AMPAR TARP-γ8 NEGATIVE MODULATORS

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The a-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA) subtype of ionotropic glutamate receptors mediates the majority of fast synaptic transmission within the mammalian brain. The ubiquitous expression of the primary subunits of AMPA receptors (AMPARs), and the lack of pharmacological selectivity amongst them, preclude regional or neuronal subtype specificity. In vivo, AMPARs are associated with a variety of accessory proteins. One such family, designated Transmembrane AMPA-receptor Regulatory Proteins (TARPs), shows an intriguing expression pattern in the brain. In particular, TARP-g8 is highly expressed in the hippocampus, part of the limbic circuitry that putatively is overactive in recurrent mood disorders.

Using high-throughput screening we discovered compounds that selectively modulate AMPARs containing TARP-g8. Subsequent medicinal chemistry efforts were used to improve potency and pharmacokinetics of the hits. Assays were developed to measure target occupancy and functional effects of the compounds in vivo.

These compounds possess a novel mechanism-of-action consistent with a partial attenuation of the interaction between the TARP and the pore-forming subunits of the channel. Lead molecules with oral bioavailability and high brain penetration allowed demonstration of a strong relationship between pharmacokinetics and pharmacodynamics and has resulted in a compound that has progressed to clinical development. The compounds show anticonvulsant profiles in rodent. In preclinical species molecules in this class provide large safety margins relative to non-specific AMPAR inhibitors due to the improved regional specificity of TARP-g8 modulators.

Negative modulation of AMPA receptors with a molecule selective for TARP-g8 offers the possibility of selectively reducing excitatory transmission within brain circuits associated with neuropsychiatric or neurologic disorders. Such an agent could be a useful therapeutic in pathologic conditions characterized by hyperactivity within the hippocampus—for example, temporal lobe epilepsy. This approach could mitigate the side-effect profile attributed to nonselective AMPAR antagonists.

ANAKINRA

E. Wirrell
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Anakinra (Kineret®) is a recombinant human interleukin-1 (IL-1) receptor antagonist that is approved for the treatment of rheumatoid arthritis and several inflammatory conditions. It does not modulate neuronal excitability, but due to anakinra's ability to block IL-1β, it presents a novel therapy to attenuate maladaptive neurogenic inflammation (via activation of the IL-1/Toll Like Receptor 4 system) which contributes to epileptogenesis. IL-1β and high mobility group box 1 are the main ligands involved in neurogenic inflammation and directly affect neuronal excitability by rapid post-transcriptional effects on receptors and ion channels, and induce Src kinase-dependent phosphorylation of the NR2B subunit of the NMDA receptor, increasing calcium influx.

Anakinra is administered by subcutaneous injection, had a half-life of 4-6 hours and is renally excreted. Its main side effects include injection site reactions, headache, nausea, vomiting, pyrexia and hypersensitivity. Rarely, serious infection or malignancy (predominantly lymphoma) may occur. Immunogenicity appears in approximately 2% of patients after 12 weeks of treatment.

Animal studies have documented that anakinra blocks the ongoing neuronal injury and blood-brain barrier leakage induced by seizures and IL-1β. Furthermore, anakinra may ameliorate memory impairment due to ongoing seizures.

There is abundant evidence for an inflammatory contribution to human epilepsy, with evidence of neurogenic inflammation in epilepsy surgery specimens, and elevated proinflammatory cytokines in various types of seizures including febrile and neonatal seizures. Febrile Infection-Related Epilepsy Syndrome (FIRES) is a devastating disorder, in which a previously well child presents with refractory status epilepticus following a febrile illness. Mortality is high and survivors are typically left with intractable multifocal epilepsy and moderate to severe intellectual disability. Studies have documented markedly elevated levels of proinflammatory cytokines and chemokines in the CSF of children with FIRES, suggesting a fulminant inflammatory response in the brain is responsible for this condition. A single published case report and two abstracts have documented that anakinra therapy markedly reduces seizures in the acute phase, although how much this improves long-term outcome is unclear. Further studies are in the planning stage.

BUMETANIDE AND ITS DERIVATIVES

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Bumetanide is a potent, fast-acting loop diuretic, which has been used clinically for many decades. Its diuretic effects result from blocking the renal Na-K-2Cl-cotransporter (NKCC2). In addition to NKCC2, bumetanide blocks NKCC1, which is ubiquitously expressed in many tissues, including the brain, and plays a major role in the regulation of intracellular chloride ion concentration. In brain neurons, NKCC1 is thought to be involved in deranged cellular chloride homeostasis in several brain diseases, such as neonatal seizures, epilepsy, autism, and ischemic and traumatic brain injury (TBI). This has sparked considerable interest in using bumetanide for treating such disorders, which are often refractory to standard therapies. However, use of bumetanide for treating brain diseases is hampered by its poor brain penetration, which is ascribed to its high plasma protein binding (~97–98%) and extensive ionization (>99%) at physiologic pH, which limits its ability to enter the brain by passive diffusion. Brain concentration of bumetanide is further reduced by organic anion transporters actively facilitating brain efflux of the compound upon entrance. Bumetanide concentrations found in the brain are less than 1–2% of those in plasma, meaning that tolerable systemic doses of bumetanide yield brain concentrations far below those required to affect neuronal NKCC1. This is a likely explanation for the disappointing negative results of the first clinical phase I/II trial (NEMO) with bumetanide in newborn infants with seizures, in which bumetanide was not effective and increased the risk of hearing loss. Over the past ~12 years, we explored several strategies to improve the use of bumetanide or its derivatives for the treatment of brain disorders such as epilepsy. These strategies included, among others, (1) development of lipophilic, bumetanide prodrugs (such as BUM5) that enter the brain before cleavage to bumetanide and (2) evaluation of a large series of bumetanide derivatives for brain permeability and effects on NKCC1 vs. NKCC2, resulting in the recent discovery of BUM13 (bumepamine). The latter drug is much more effective than bumetanide to potentiate the anti-seizure effect of phenobarbital in chronic rodent models of epilepsy and is currently further characterized. Next, we started to characterize various clinically approved loop diuretics from different chemical categories, most of which has not previously been tested for inhibitory effect on NKCC1. Interestingly, the basic (nonacidic) loop diuretic azosemide was 4-times more potent to inhibit NKCC1 than bumetanide. We currently evaluate whether azosemide has advantages vs. bumetanide for treatment of brain diseases with deranged neuronal chloride homeostasis.

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CANNABIDIOL

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Cannabidiol is the second most abundant phytocannabinoid derived from the Cannabis sativa plant with positive therapeutic effects in preclinical models of antiepileptiform activity, seizure, and epilepsy; and more recently anti-seizure effects in clinical trials of childhood onset epilepsies. While the precise mechanisms of action by which cannabidiol exerts its anti-convulsant effect in humans are unknown, cannabidiol lacks appreciable interaction with cannabinoid receptors (CB1 or CB2), likely accounting for its apparent lack of euphoric side effects. Cannabidiol is known to reduce neuronal hyperexcitability and inflammation through modulation of intracellular calcium via G protein-coupled receptor 55, transient receptor potential vanilloid type 1 channel, and adenosine mediated signaling.

GW Pharmaceuticals has initiated a pre-clinical and clinical development program investigating the potential therapeutic application of cannabinoids across a wide range of disease states. GW and its US subsidiary Greenwich Biosciences are involved in six phase II/III studies evaluating the safety and efficacy of a plant-derived pharmaceutical formulation of cannabidiol (Epidiolex), as add-on treatment, across four drug-resistant epilepsy conditions: Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS), tuberous sclerosis complex (TSC), and infantile spasms (IS). Epidiolex is currently under review by both the US and European regulatory authorities and if approved, will be a first-in-class antiepileptic drug for the treatment of drug-resistant seizures associated with DS and LGS.

In comparison to valproic acid, ethosuximide, and phenobarbital, cannabidiol did not produce any motor deficits or neurotoxicity in tolerability assays and repeated cannabidiol treatment reduced epilepsy-induced motor and cognitive deficits in rats. Across the cannabidiol development program, common adverse reactions are somnolence, decreased appetite, diarrhea, pyrexia, fatigue, lethargy, rash, nasopharyngitis, and pneumonia. Adverse events were of mild or moderate severity in the majority of patients and treatment was generally well tolerated with few discontinuations. Dose-related reversible elevation of liver transaminases without meeting Hy's law criteria was observed with cannabidiol treatment.

Three completed phase III trials (randomized, double-blind, placebo-controlled, multicenter) demonstrated that GW's pharmaceutical formulation of purified cannabidiol was significantly superior to placebo, as add-on treatment, in reducing seizure frequency over a 14-week treatment period in patients with DS and LGS.

Three similar trials are ongoing: a phase III dose-ranging study in DS, a phase III study in TSC, and a phase II study in IS. Eligible patients from these studies are participating in ongoing open label extension trials. Other indications in epilepsy are being considered for future studies.

CANNABIDIVARIN

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Cannabidivarin is the propyl analog of cannabidiol and is an active constituent derived from the Cannabis sativa plant. Cannabidivarin has shown antiepileptic properties in both in vitro models of epileptiform activity and in vivo models of seizures; however, the precise mechanisms of action underlying these effects remain unknown. Similar to cannabidiol, cannabidivarin lacks appreciable interaction with cannabinoid receptors CB1 and CB2 at physiologically achievable concentrations. As part of the cannabinoid development program, GW Pharmaceuticals and its US subsidiary, Greenwich Biosciences, are investigating the potential therapeutic applications of cannabidivarin across a range of disease states, including epilepsy.

A large body of preclinical toxicological evidence suggests that cannabidivarin has a wide safety margin between the proposed clinical dose and the dose at which the No-Observed-Adverse-Effect-Level was observed in the nonclinical studies. Pharmacokinetic trials have confirmed that 7-hydroxy-cannabidivarin and 7-carboxy-cannabidivarin are circulating metabolites of cannabidivarin, but the clinical relevance of the abundance of metabolites has yet to be established.

A phase I randomized, double-blind, placebo-controlled trial in healthy subjects showed that cannabidivarin was well-tolerated at even the highest tested dose (800mg, q.d.) and no significant adverse events were observed. A two-part phase II study to investigate the potential antiepileptic effects of adjunctive cannabidivarin for the treatment of inadequately controlled focal seizures has been completed. Part A evaluated the safety and pharmacokinetics of cannabidivarin in the presence of concomitant antiepileptic drugs and indicated that there were no appreciable differences in the pharmacokinetics and safety profile of cannabidivarin when given concomitantly. Part B involved a 4-week baseline period and an 8-week treatment period (2-week titration starting with 400 mg, b.i.d., up to 800 mg, b.i.d. plus 6-week maintenance) followed by a 12-day taper period. The primary endpoint is the change from baseline in focal seizure frequency in patients taking add-on cannabidivarin compared with add-on placebo.

In preclinical models cannabidivarin is a promising antiseizure agent and has thus far demonstrated a favorable toxicological profile. Its clinical development will include targeting patients with seizure disorders, Rett syndrome, and autism spectrum disorder.

TAK-935 (OV935): A FIRST IN CLASS CHOLESTEROL 24-HYDROXYLASE INHIBITOR

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TAK-935 (OV935) is a new chemical entity that potently and selectively inhibits cholesterol 24-hydroxylase (CH24H) activity, thereby decreasing 24S-hydroxycholesterol (24HC). Preclinical studies show that TAK-935 has anti-epileptic, and pro-survival activity. In a pentylenetetrazole-induced kindling model, TAK-935 suppressed seizure progression in direct correlation ($r = -0.68$; $p<1x10-4$) to the degree of brain 24HC lowering, suggesting that its effects on kindling retardation are mediated via CH24H inhibition. TAK-935 was also evaluated in the Scn1a mutant mouse model of Dravet Syndrome (DS), a subtype of epileptic encephalopathy (EE) which is susceptible to febrile seizures. TAK-935 significantly raised the threshold temperature for hyperthermia-induced seizures, significantly reduced the frequency of spontaneous seizures, and strongly protected mice from sudden death. A similar pro-survival effect was observed in a genetic mouse model of tuberous sclerosis complex (TSC) and amyloid precursor protein and presenilin-1 double transgenic mice (APP/PS1-Tg) in which epilepsy relevant deficits are observed. These activities are likely mediated by the reduction in 24HC, the most potent endogenous positive allosteric modulator of N-methyl-D-aspartate (NMDA) receptors identified to date. TAK-935 clinical development includes the completion of four Phase 1 safety and tolerability studies in healthy adult subjects. Of note, TAK-935 target engagement has also been confirmed in human brain with a proprietary positron emission tomography ligand. Target occupancy in humans correlates with plasma 24HC levels, validating the use of 24HC as a soluble biomarker to monitor TAK-935 activity in the brain. TAK-935 was well tolerated in these Phase 1 studies with single-rising doses up to 1350 mg and multiple-rising doses up to 400 mg once daily for 14 days. Currently, a Phase 1b/2a study in adult subjects with EE is underway. This study and future efforts will evaluate whether TAK-935 may have therapeutic benefit in developmental and epileptic encephalopathies which remain an important therapeutic challenge.

OV329: A NEW AND HIGHLY POTENT INACTIVATOR OF γ-AMINOBUTYRIC ACID AMINOTRANSFERASE (GABA-AT)

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Although inhibition of GABA-AT is effective in selected epilepsies, progressive and irreversible visual loss in a substantial proportion of vigabatrin (VGB) treated individuals has limited the use of this compound and diminished interest in its target. Described here are results for (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (aka OV329), a new chemical entity with inhibitory activity more than two orders of magnitude greater than VGB, and the potential for an improved risk-benefit profile. A recently published description of OV329 (Silverman, R. B. and coworkers, J. Am. Chem. Soc. 2018, 140, 2151-2164) shows good target specificity, favorable drug-like properties, and, consistent with in vivo target engagement, complete suppression of reward-evoked striatal dopamine release. To evaluate OV329 as a potential treatment for infantile spasms (IS), we looked at the effect of pre-treatment on NMDA-induced seizures and motor deficits. These studies determined that juvenile mice treated with ≥0.01 mg/kg 30 minutes ahead of a proconvulsant dose of NMDA showed a significant reduction in seizure severity relative to vehicle treated animals ($p<0.001$). Moreover, the significant NMDA-induced coordination deficits seen at 7 days in an ACTH-treated positive control group were not observed in mice treated with OV329. An acute NOAEL of 6 mg/kg, a dose 600-fold greater than the lowest effective dose tested in the IS model, was determined by evaluating behavioral neurotoxicity in naïve adult mice. Administration of OV329 at 1 mg/kg/day for 45 days in a separate cohort showed the compound to be well tolerated with no reduction in body weight gain relative to control, gross behavioral deficits, or impact on retinal function. These findings stand in contrast to those obtained in a head to head comparison with VGB, where a dose with considerably less GABA-AT inhibitory activity resulted in a marked effect on weight and abnormal retinal function. More specifically, whereas mice in the Vehicle and OV329 groups showed similar day to day increases in weight over the course of treatment (8.7 and 9.0% average respectively; $p=0.97$), such gains were significantly reduced in VGB treated animals (0.2% average; $p<0.0001$ vs. Vehicle or OV329). With regard to retinal function, baseline and end of study stimulus-ERG response curves from Vehicle and OV329 treated animalswere indistinguishable (99.8% probability).

In contrast, comparison of baseline and end of study recordings from VGB treated mice showed a significant separation of curves (99.9% probability). Taken together, these data suggest that VGB's impact on retinal function is not a GABA-AT class effect. Moreover, the excellent tolerability of OV329 vs. VGB suggests that higher target engagement and hence greater efficacy may be possible. With the goal to develop an effective alternative to existing therapeutic options, IND-enabling studies are in progress.

LONG-TERM SAFETY AND EFFICACY OF INTRACEREBROVENTRICULAR ENZYME REPLACEMENT THERAPY WITH CERLIPONASE ALFA IN CHILDREN WITH CLN2 DISEASE: TWO YEAR RESULTS FROM AN ONGOING MULTICENTER EXTENSION STUDY

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Background: CLN2 disease, a rare, inherited, pediatric, neurodegenerative lysosomal storage disorder caused by TPP1 deficiency, is characterized by seizures, language and motor function loss, blindness and early death. A phase 1/2 study (NCT01907087) demonstrated that intracerebroventricular (ICV) infusion of 300 mg cerliponase alfa, a recombinant human TPP1 enzyme, every other week for 48 weeks slowed deterioration in motor and language function. This extension study (NCT02485899) assesses the long-term safety and efficacy of ICV-administered cerliponase alfa in children with CLN2 disease for up to 240 weeks.

Design: Subjects who completed the phase 1/2 study continued receiving 300 mg cerliponase alfa qow in this open-label extension study. Cumulative data from both studies were used to evaluate long-term safety (assessed by adverse events (AEs) frequency) and efficacy (assessed by changes in the CLN2 clinical rating scale motor and language (ML) domains).

Results: 24 subjects were initially treated with cerliponase alfa in the phase 1/2 study (9 male, 15 female, mean (SD) age 4.3 years (1.24)); 23 subjects enrolled in the extension study (96 to 161 weeks total exposure, median 116 weeks). All had AEs; most were Grade 1-2. Common AEs included pyrexia, vomiting, and convulsion. Twenty (83%) subjects had at least one serious AE, which were mostly consistent with neurodegenerative disease in a pediatric population. Significant attenuation of the rate of decline in ML score (mean (95% CI): 0.27 (0.12, 0.42) points/ 48 weeks, $p<0.0001$) was observed compared with a rate of decline of 2.0 points/48 weeks in untreated patients. The responder (<2 point loss per 48 weeks) rate at 96 weeks (100%, $p <0.0001$) was improved compared to that observed at 48 weeks, suggesting a persistent treatment effect.

Conclusions: These data suggest that enzyme replacement therapy with ICV-administered cerliponase alfa has an acceptable safety profile and a sustained treatment effect over time.

2DG: ANTICONVULSANT ACTIONS, NEUROPROTECTION, AND PREVENTION OF POST-TRAUMATIC EPILEPSY AND DELAYED CONSEQUENCES OF TBI

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2DG (2-deoxy-D-glucose) is a reversible inhibitor of glycolysis currently in preclinical development for therapeutic indications including epilepsy and traumatic brain injury (TBI). 2DG has acute anticonvulsant actions as demonstrated in multiple in vivo and in vitro seizure models, and has the unique property of activity-dependent uptake into focal brain regions in response to increased local energy demands during seizures and in response to brain injury. 2DG also has chronic antiepileptic 'disease-modifying' actions consisting of 2-fold slowing of kindling progression in rats when administered as long as 15 minutes after repeated evoked seizures as a consequence of enhanced postictal delivery into neural circuits by neurovascular coupling. 2DG reduces secondary damage progression measured by MRI/DTI following controlled cortical impact (CCI) in rats, and prevents frequent post-traumatic focal and generalized seizures in ~ 50% of kindling-susceptible rats after CCI. 2DG also favorably reduces fear conditioning at 1 month and preserves spatial context fear memory formation at 6 months after CCI. The mechanisms and therapeutic actions of 2DG against seizures, epilepsy progression, and consequences of TBI are distinctive compared to currently marketed anticonvulsants. 2DG's acute anticonvulsant mechanisms include activity-dependent reduction in synaptic currents by a presynaptic mechanism. The chronic actions of 2DG involve glycolytic metabolic regulation of seizure-induced and injury-induced gene expression by the transcriptional repressor Neuron Restrictive Silencing Factor (NRSF) and its redox sensor Carboxy-terminal Binding Protein (CtBP). Preclinical toxicological studies of 2DG in rats have confirmed dose-dependent, reversible cardiac myocyte vacuolation with features of reversible autophagy at high doses. Cardiac toxicity has not been observed in dogs and appears to be species-specific. These toxicological observations and human oncology studies demonstrating safety and tolerability of 45 mg/kg/day doses for 14 days and longer support potential use of 2DG for therapeutic indications including status epilepticus, seizure clusters, combination with device therapy, and as a neuroprotectant to prevent or reduce delayed adverse consequences after TBI including post-traumatic epilepsy, PTSD, and consequences of concussion.

FENFLURAMINE

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Dravet syndrome is a rare and severe epilepsy syndrome which firsts presents in infancy and is refractory to conventional anti-epileptic drugs (AEDs). Current treatment of patients with DS usually involves multiple AEDs, including combination therapy with valproate, clobazam, topiramate, stiripentol, and others, but despite the use of these multi-AED therapies, 45% of patients continue to experience ≥4 tonic-clonic seizures per month. ZX008 (low dose fenfluramine HCl) is being developed as an oral solution for the add-on treatment of seizures in Dravet syndrome. The anti-seizure efficacy of fenfluramine was initially demonstrated in two cohorts of Dravet syndrome patients in Belgium who have now been treated for between 1 and 29 years. The results of the initial Phase 3, randomized, double-blind, placebo-controlled clinical trial of ZX008 for the treatment of Dravet syndrome have been reported. The study met its primary objective by demonstrating that ZX008 at 0.8 mg/kg/day was superior to placebo as adjunctive therapy. Compared to placebo, subjects treated with ZX008 0.8 mg/kg/day demonstrated a 63.9% greater reduction in monthly frequency of major motor seizures ($P<0.001$). In addition, 70% of subjects treated with ZX008 0.8 mg/kg/day demonstrated ≥50% reduction in monthly frequency of major motor seizures compared with 7.5% in the placebo group ($P<0.001$). Non-cardiovascular adverse events reported in ≥10% of subjects in ZX008 treatment groups were diaarhea (7.5%, 30.8%, and 17.5% in placebo, ZX008 0.2 mg/kg, and ZX008 0.8 mg/kg, respectively), weight decreased (0%, 12.8%, 5%), decreased appetite (5%, 20.5%, 37.5%), constipation (0%, 2.6%, 10.0%), and lethargy (5%, 10.3%, 17.5%). Fenfluramine had originally been marketed as an anorectic agent for the treatment of obesity in adults, but was withdrawn from global markets after an association with incidence of cardiac valvulopathy and primary pulmonary hypertension emerged. No cases of pulmonary hypertension were seen in the Phase 3 study. Trace mitral regurgitation (MR) or aortic regurgitation (AR) are not considered medically meaningful but were captured on the echocardiogram during the Phase 3 study. At least one finding of trace mitral and/or trace aortic valve regurgitation was observed in 5 (12.5%), 7 (17.9%), and 9 (22.5%) subjects in the placebo, ZX008 0.2 mg/kg/day, and ZX008 0.8 mg/kg/day groups, respectively. ZX008 appears to have potential as a new treatment for uncontrolled seizures in Dravet syndrome.

GANAXOLONE

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Background: Ganaxolone (GNX) is a strategically modified neurosteroid, which allosterically modulates GABAA receptors to increase inhibition in the brain. Unlike the endogenous progesterone metabolite, allopregnanolone, GNX lacks nuclear progesterone receptor activity, and is appropriate for chronic oral dosing. GNX activates both synaptic and extrasynaptic GABAA receptors at sites distinct from benzodiazepine or barbiturate binding and is not associated with development of tolerance. GNX has anticonvulsant activity with good safety and tolerability at doses up to 1800 mg daily in adults and children.

Activity in Epilepsy: GNX has been studied in a variety of epileptic conditions including West Syndrome, focal onset seizures, PCDH19 epilepsy, Lennox Gastaut Syndrome and CDKL5 Deficiency Disorder (CDD). GNX demonstrates the anticonvulsant activity in the most refractory epilepsies such as patients requiring the most treatment intensive regimens or those with genetic epileptic encephalopathies. This may be partially explained by the need for a new mechanism of action to address these highly treatment resistant patients.

In the phase 2 study of girls with PCDH19 epilepsy, treatment with GNX reduced seizure frequency at 6 months in approximately half the cohort (54%-100% in 4/11, 26%-33% in 2/11). In the cohort of children with Lennox Gastaut Syndrome, eight patients with severe, treatment-resistant generalized tonic-clonic and/or drop seizures, experienced a median percent reduction in seizures at 6 months of 32%. The median percent increase in seizure-free days was 33%. In the CDD cohort, the 7 subjects experienced a median percent reduction in seizures at 6 months of 43% and a median percent increase in seizure-free days of 78%. Subjects from all three cohorts, including 4 of the 7 CDD children enrolled into the 52-week extension study due to continued good long-term seizure control.

Current GNX Studies in Epilepsy: A phase 2 study of GNX in second-line refractory status epilepticus is being conducted in the US. A pivotal phase 3 study of GNX in children and young adults with CDKL5 Deficiency Disorder is being initiated globally in 2018.

HUPERZINE A (BIS-001)

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BIS-001 (Huperzine A) is a natural acetylcholinesterase inhibitor being developed by Biscayne Neurotherapeutics, Inc. for difficult-to-treat adult and childhood seizure disorders. BIS-001 has a long-standing human-use history in China to treat cognitive-related disorders. More recently, BIS-001 has been shown to display potent anti-seizure capabilities in highly predictive animal models of refractory seizures, as well as genetic mutant mouse models for Dravet Syndrome and General Epilepsy with Febrile Seizures plus (GEFS+). A prior Phase I with the immediate release (IR) formulation identified Tmax/Cmax-related nausea and vomiting that were dose limiting, demonstrating the IR formulation is not adequate for seizure control due to its peak-related side effects. Furthermore, BIS-001 in the IR form would require dosing 4-6 times a day, which is not compatible with sustained, effective compliance. Given the data demonstrating the effectiveness of BIS-001 in multiple seizure models, Biscayne developed a novel extended release formulation of BIS-001 to eliminate the rapid pharmacokinetics of the current immediate-release formulation. In a recently completed Phase Ib clinical trial in healthy subjects, BIS-001ER demonstrated a dramatic reduction in adverse events from the immediate release preparation. The Phase Ib testing showed that approximately double the dose predicted for significant seizure control was attainable; yielding much higher, stable plasma levels of BIS-001 given on a twice/day schedule, and achieved drug plasma levels predicted to provide significant seizure protection in patients with adult and childhood intractable epilepsies. Accordingly, we believe BIS-001 will be a safe, effective therapy for children and adults afflicted with difficult-to-treat seizure disorders, and will be entering a proof-of-concept clinical trial in early 2018.

IMEPITOIN

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Although benzodiazepines (BZDs) offer a wide spectrum of antiepileptic activity against diverse types of epileptic seizures, their use in the treatment of epilepsy is limited because of loss of efficacy (tolerance) and dependence liability. BZDs act as positive allosteric modulators of the inhibitory neurotransmitter GABA by binding to the BZD recognition site ("BZD receptor") of the GABAA receptor. Traditional BZDs such as diazepam or clonazepam act as full agonists at this site, so that one strategy to resolve the disadvantages of these compounds would be development of partial agonists with lower intrinsic efficacy at the BZD site of the GABAA receptor. Several partial or GABAA receptor subtype selective compounds, including bretazenil, abecarnil or alpidem, have been developed as anxioselective anxiolytic drugs, but epilepsy was not a target indication for such compounds. More recently, the imidazolone derivatives imepitoin (ELB138) and ELB139 were shown to act as low-affinity partial agonists at the BZD site of the GABAA receptor, and imepitoin was developed for treatment of epilepsy. Imepitoin displayed a broad spectrum of anti-seizure effects in diverse seizure and epilepsy models at tolerable doses, and, as expected from its mechanism of action, lacked tolerance and abuse liability in rodent and primate models. In addition to anti-seizure activity, imepitoin and ELB139 exerted anxiolytic effects in various rodent models. The more favorable pharmacokinetic profile of imepitoin in dogs vs. humans led to the decision to develop imepitoin for treatment of canine epilepsy. Based on several randomized controlled trials that demonstrated antiepileptic efficacy and high tolerability and safety in epileptic dogs, the drug was approved for this indication in Europe in 2013 and is marketed by Boehringer-Ingelheim (BI) under the trade name Pexion®. Preliminary findings in epileptic dogs indicated that, in addition to suppressing seizures, imepitoin also suppresses some of the behavioral abnormalities, including anxiety, associated with epilepsy in dogs. Indeed, a recent study in nonepileptic dogs indicated the potential value of imepitoin for the rapid alleviation of signs of fear and anxiety in dogs, and BI is currently exploring this effect in more detail. In addition to dogs, imepitoin is currently evaluated in epileptic cats, and a first pilot trial indicated safety and efficacy in this species. Hopefully, the favourable profile of imepitoin for treatment of canine epilepsy will reactivate the interest in partial BZD site agonists as novel treatments for human epilepsy, too. Indeed, in a recently published proof-of-concept clinical study, abecarnil was demonstrated to exert anti-seizure efficacy in patients with photosensitive epilepsy.

JNJ-40411813 and mGluR2 PAMs

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The metabotropic glutamate receptor subtype 2 (mGluR2) is expressed in the frontal cortex and limbic structures and modulates glutamatergic excitatory synaptic transmission. Metcalf et al. (Epilepsia 2017, Epilepsia in press 2018) have previously described the anti-seizure properties of both orthosteric agonists and positive allosteric modulators (PAMs) in traditional and refractory epilepsy animal models. The studies also implicate a potential pharmacodynamic interaction between levetiracetam (LEV) and mGluR2 PAMs for improved efficacy in 6 Hz 44 mA and kindling epilepsy models without increasing adverse effects as measured by rotarod performance. Specifically, isobolographic analysis in the 6 Hz 44 mA model of refractory epilepsy revealed a strong multi-fold efficacy synergy between LEV and mGluR2 PAMs and suggested potency of the mGluR2 PAM as the most significant contributor of synergy. Similar isobolographic studies with other anticonvulsants did not reveal a strong synergy in the 6 Hz 44 mA model. These observations implicate a possible pre-synaptic pharmacodynamic interaction and support a rational polypharmacy concept for epileptic patient treatment. This presentation summarizes the data for the mGluR2 PAMs and considers a time to event proof of concept study for efficient and safe efficacy signal determination and dose ranging.

NOVEL mTOR INHIBITORS

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The mTOR signaling pathway has emerged as a possible therapeutic target for epilepsy. Clinical trials have shown that mTOR inhibitors such as everolimus reduce seizures in tuberous sclerosis complex (TSC) patients with intractable epilepsy. Furthermore, accumulating preclinical data suggest that mTOR inhibitors may have anti-seizure or anti-epileptogenic actions in other types of epilepsy. However, the chronic use of rapalogs such as everolimus is limited by poor tolerability, particularly by immunosuppression, poor brain penetration and induction of feedback loops which might contribute to their limited therapeutic efficacy. Here we describe two novel, brain-permeable small molecule 1,3,5-triazine derivatives, the mTORC1/C2 inhibitor PQR620 and the dual pan-PI3K/mTOR inhibitor PQR530. The anti-seizure potential of these ATP-competitive inhibitors was determined by evaluating their effect on the electroconvulsive seizure threshold in normal and epileptic mice. Furthermore, experiments were performed in a TSC mouse model. Both compounds rapidly entered the brain, reaching brain:plasma ratios of ~1.6, and significantly decreased phosphorylation of S6 ribosomal protein in the hippocampus of normal and epileptic mice, demonstrating effective mTOR inhibition at well tolerated doses. PQR620 and PQR530 significantly increased seizure threshold, and the effect of PQR620 was more marked in epileptic vs. nonepileptic mice. In the TSC mouse model, both compounds markedly suppressed seizures at nontoxic doses. Overall, the novel compounds described here have the potential to overcome the disadvantages of rapalogs for treatment of epilepsy and other brain diseases.
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OXYNYTONES A NEW CLASS OF AED THAT ATTENUATES HFO ACTIVITY IN KINDLED AND TRAUMATIC BRAIN INJURY RATS

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We have produced more than 100 new chemicals entities (NCE) that block sodium channel activity to varying degrees. Using a novel screening procedure employing voltage sensitive dye imaging (VSDI) we were able to assay both potency and the pharmacodynamics of these NCEs. A number of our compounds have been shown to have high potency and a preference to block high frequency synaptic activation of the piriform cortex circuitry in vitro. The two most studied are TD561 and 562 which inhibit fast sodium channel recovery with an IC50 in pM range. By contrast, block of resting channel activity could not be achieved with concentrations of up to 10 microM. TD561/562 (20mg/kg) prevents the induction of seizures by amygdala kindling and seizures in fully kindled rats. TD561 blocks fast ripples that occur during the kindling process, thus we believe the major mechanism of action is the prevention of this activity during the kindling procedure. We also tested our compounds in a traumatic brain injury model where a stressor was applied. In untreated rats an acute stressor generated a very strong electrographic response that included the generation of HFOs (ripples and fast ripples). TD561 blocks HFO generation in this model. Phenytoin exacerbated these responses, producing more HFOs. This suggests the use of TD561/562 in the prevention post traumatic seizures and perhaps post traumatic epilepsy. TD561/562 blocks activation of human brain slices obtained for drug resistant epilepsy patients, having a better profile than CBZ and levetiracetam. PK studies show high (near 100%) oral bioavailability and no liver metabolism. TD561 is rapidly de-esterified becoming TD562. TD562 is excreted unchanged (t1/2 = 6 hrs). An acute LD50 could not be established as doses of up 1g/kg produced no mortality. At therapeutic doses immobility, poor gait and sedation were not observed. At doses 30 times higher no behavioural effects were seen only a small reduction in body temperature was observed Off target binding was evaluated using a panel of 44 ion channels, GPCRs and other neuronal receptors and no significant binding was observed. An Aimes test was negative and block of hERG channel activity was insignificant. Histopathological analyses of heart, kidney and liver show that in rats treated with therapeutic dose for 25-30 days no toxicity was evident. Both TD561 and 562 have no chiral centres. In summary our data shows Oxynytones reduce epileptiform activity in rat and human brain, have excellent PK profile with low or no off target binding nor behavioural effects.

PADSEVONIL

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Padsevonil (PSL, UCB0942) is a rationally designed antiepileptic drug (AED) candidate with a unique mechanism of action, combining presynaptic activity (equally high affinity to all three synaptic vesicle 2 [SV2] isoforms) with postsynaptic enhancement of GABAergic inhibition (moderate affinity at benzodiazepine site of GABAA receptor). PSL acts as a partial agonist at the GABAA receptor and may therefore display reduced potential for tolerance induction. PSL has shown potent antiseizure activity in numerous acute seizure models, with greater protection against seizures than a simple combination of AEDs that target SV2A and GABAAreceptors at doses resulting in similar target occupancies. Further, PSL provided full seizure protection in the amygdala kindling model of chronic epilepsy.
PET studies in humans demonstrated quantifiable coverage for both molecular targets, and indicated that the 400 mg twice daily (bid) dose selected for the proof-of-concept trial achieves desired target occupancies. For SV2A, there is sustained high level (>90%) receptor occupancy at PSL doses of ≥100 mg bid, while for GABAA, there is transient low but quantifiable receptor occupancy at doses of ≥200 mg bid (200 mg bid: 6.4%; 400 mg bid: 13.4%). This target occupancy was consistent with the in vivo target occupancy associated with anticonvulsant efficacy in the amygdala kindling model. Pharmacokinetic data from Phase I trials in healthy volunteers supported bid dosing.
A randomized, double-blind, placebo-controlled Phase II trial of PSL (NCT02495844) has recently been completed. This proof-of-concept trial enrolled adult patients with frequent focal-onset seizures (≥4 per week), who had failed ≥4 AED schedules of adequate dose and duration. Randomized patients (n=55) had a median baseline seizure frequency of 8.24 observable seizures/week (more than three times the frequency generally observed in AED clinical trial programs), and 75% had failed ≥8 prior AEDs (including AEDs at baseline). In these severely affected patients, adjunctive treatment with PSL (400 mg bid) was associated with clinically meaningful reductions in focal seizure frequency compared with PBO. During the first 2 weeks of treatment, 8/26 (30.8%) patients on PSL vs 3/27 (11.1%) on PBO had a ≥75% reduction in focal seizure frequency from baseline (odds ratio: 4.14; p=0.0679). Median percent reduction (MPR) in weekly focal seizure frequency was 53.7% with PSL and 12.5% with PBO (median difference 34.0; 95% CI: 3.0, 67.5; p=0.026 [not adjusted for multiplicity]). Two patients on PSL and one on PBO were seizure-free.

During the last 4 weeks of the trial, 16/51 (31.4%) patients were ≥75% responders, and the MPR was 55.2%. No patients were seizure-free for the entire trial. Overall, 50/55 (90/9%) of patients reported treatment-emergent adverse events with PSL, most commonly somnolence (25 [45.5%]), dizziness (24 [43.6%]), headache (14 [25.5%]), and fatigue (13 [23.6%]). There was no consistent effect on laboratory parameters, vital signs, weight, or electrocardiogram evaluations. 50 patients completed the trial. Adjunctive PSL treatment had an overall positive benefit-risk balance.

A long-term open-label extension to the proof-of-concept trial (NCT02625090) and Phase II/III trials (NCT03373383, NCT03370120) are evaluating efficacy and long-term safety of adjunctive PSL in patients with drug-resistant focal-onset seizures.

UCB Pharma-sponsored.

VALNOCTAMIDE AND SEC-BUTYLPROPYLACETAMIDE (SPD): SECOND GENERATION DRUGS TO VALPROIC ACID (VPA)

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Valnoctamide (VCD) is a chiral constitutional isomer of valproic acid (VPA) corresponding amide valpromide and sec-butylpropylacetamide (SPD) is a one-carbon homologue of VCD. The activity of VCD and SPD has been assessed in comparison to VPA a model of status epilepticus (SE) in which seizures were induced by tetramethylenedisulfotetramine (TETS), a highly lethal neurotoxic rodenticide that acts as a noncompetitive GABAA receptor antagonist. SPD at doses of 54 and 100 mg/kg terminated SE within ~4 and ~2 min, respectively, and protected 65% and 100% of animals from mortality for >7 days. VCD at doses 50 and 100 mg/kg terminated SE within, ~7 and ~2 min, respectively, and protected 62.5 and 90% of animals from mortality. Both SPD and VCD produced sedation in treated animals, which was especially pronounced at the dose of 100 mg/kg. VPA (100 mg/kg) terminated TETS SE transiently in 80% of animals and only 20% animals survived. A high VPA dose (200 mg/kg) terminated SE within ~8.8 min and protected 80% of animals from mortality. Thus, both SPD and VCD effectively terminate TETS-induced behavioral SE and protect animals from mortality and are more potent and more rapidly acting than VPA.

In another study the efficacy of SPD, VCD and phenobarbital was studied in pediatric rats. Female and male post-natal day (PND) 21 and 28 and PND 70 adult control rats were implanted with electroencephalographic (EEG) headpieces and were exposed to seizure-inducing doses of the nerve agents: sarin or VX. Five minutes after seizure onset, animals were treated with SPD, VCD or phenobarbital. The up-down method was used to determine the anticonvulsant- ED50 of each of the three drugs. SPD-ED50 values in the VX model were: PND 21, 53 mg/kg (male) and 38mg/kg (female); PND 28, 113mg/kg (male) and 43mg/kg (female); PND 70, 102mg/kg (male), 40mg/kg (female). SPD-ED50 values in the sarin model were: PND 21, 33 mg/kg (male) and 56mg/kg (female); PND 28, 79mg/kg (male) and 34 mg/kg (female); PND 70, 53mg/kg (male), 53mg/kg (female). VCD-ED50 values in the VX model were: PND 21, 43mg/kg (female); PND 28, 173mg/kg (male) and 59mg/kg (female); PND 70, 87 mg/kg (male) and 91mg/kg (female). VCD-ED50 values in the sarin model were: PND 21, 45mg/kg (male); PND 28, 78mg/kg (female); PND 70, 97mg/kg (male), 79mg/kg (female). Phenobarbital- ED50 values in the VX model were: PND 21, 43mg/kg (male) and 18mg/kg (female); PND 28, 48mg/kg (male) and 114mg/kg (female).

Phenobarbital- ED50 values in the sarin model were: PND 21, 34mg/kg (male) and 32mg/kg (female); PND 28, 58mg/kg (male) and 74mg/kg (female). Anticonvulsant-ED50 values for phenobarbital could not be reliably determined in either the VX or sarin models for PND 70 animals since the phenobarbital tested dose was high and resulted in early toxicity.

In a head-to-head comparison between VCD and VPA, VCD, in contrast to VPA, was found to be non-teratogenic in three species; mice, rats and rabbits. Consequently, the efficacy and safety of VCD monotherapy was evaluated in comparison to placebo in the treatment of patients in an acute manic episode. Risperidone was used as an active control to verify the validity of the trial. The study was a three-week, double-blind, randomized, placebo and risperidone controlled, parallel group trial was conducted on 173 patients in an acute manic episode. Patients were randomized to receive VCD 1500 mg/day given tid (n=71), risperidone 6 mg/day (n=32), or matching placebo (n=70). The primary outcome measures was the change in Young Mania Rating Scale (YMRS) score. In order to get an overall impression of change, the Clinical Global Impression Scale for bipolar Disorder (CGI-BP) was also utilized. VCD did not differ significantly from placebo on any of the study endpoints. However, the per-protocol for changes in total YMRS scores showed a trend of significance ($p=0.17$) in favor of VCD. Mixed models for repeated measures showed that risperidone was produced significantly more improvement than placebo in the overall bipolar disorder clinical global impression (CGI) severity scale ($p=0.036$), and the CGI severity scale for mania ($p=0.021$). However, resperidone (like VCD) was not superior to placebo at the YMRS score changes compared to baseline ($p=0.320$). The good tolerability of a high VCD dose (1,500 mg/day) coupled with the unmet need for a non-teratogenic VPA derivative emphasizes the potential of VCD in epilepsy as a non-teratogenic CNS-active follow-up compound to VPA suitable for women of childbearing age as well as for therapy-resistant patients with epilepsy.

XEN1101, A NOVEL SMALL MOLECULE KV7.2/7.3 POSITIVE ALLOSTERIC MODULATOR FOR THE TREATMENT OF EPILEPSY

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XEN1101, is a novel small molecule Kv7.2/7.3 opener currently in phase 1 development for the treatment of focal epilepsy. The Kv7.2/7.3 heterotetrameric M-current channel represents a highly validated target for the treatment of epilepsy both from genetic (KCNQ2-encephalopathy) and pharmacological perspectives (ezogabine). Pre-clinically, XEN1101 has demonstrated improved oral pharmacokinetics (potential for once-a-day dosing), as well as enhanced potency and selectivity compared to ezogabine, the first generation Kv7.2/7.3 opener. To support patient trials, toxicology/safety studies up to 4 months in rats and monkeys have been completed.

The phase 1 first-in-human clinical trial is an adaptive design to evaluate the safety, tolerability and pharmacokinetics of both single and multiple doses of different formulations in either the fed or fasted state. The trial also includes a transcranial magnetic stimulation (TMS) sub-study, which is designed to noninvasively assess XEN1101's effects on cortical excitability by observing changes in TMS-evoked EEG potentials and/or EMG metrics. Preliminary results have confirmed the PK profile and enabled dose selection and sample size estimation for a placebo-controlled, double-blind, cross-over TMS study. In a recently reported placebo-controlled, double-blind, clinical trial, ezogabine (400 mg PO) significantly increased TMS-EMG parameters including resting motor threshold, and active motor threshold compared to placebo (1).

XEN1101 was evaluated in recombinantly expressed human Kv7 channels to assess its potency. The positive control, ezogabine (30 μM), shifted the voltage dependence of channel activation to more negative voltages for Kv7.2/7.3, Kv7.3/7.5 and Kv7.4 by 33.1, 28.4 and 12.3 mV, respectively, demonstrating pharmacological sensitivity of each cell line and assay run. EC50 values for XEN1101 were 0.027, 0.094 and 0.113 μM for Kv7.2/7.3, Kv7.3/7.5 and Kv7.4, respectively.

XEN1101, in this in vitro study, exhibited an EC50 value in the low nM range for the primary channel, Kv7.2/7.3, with approximately 4-fold selectivity over Kv7.4. This in vitro potency has translated to an increase in potency in the rat MES model compared to ezogabine, with an ED50 value of 0.86 mg/kg for XEN1101 vs 3.1 mg/kg

for ezogabine. Planning is underway for a phase 2 safety and efficacy trial in patients with focal seizures.

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XEN901, A FIRST-IN-CLASS SUBTYPE SELECTIVE INHIBITOR OF NAV1.6 VOLTAGE GATED SODIUM CHANNELS.

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XEN901 is a potent inhibitor of NaV1.6 (encoded by the SCN8A gene) and is unique as a sodium channel blocker as it is >100-fold selective against all other sodium channel subtypes. XEN901 provides protection from electrically-induced seizures in rodent models (MES and 6 Hz) at plasma levels with wide exposure margins from the NOAEL obtained in GLP safety pharmacology and toxicology studies in rats and dogs. XEN901 recently entered a phase 1 first-in-human trial.

Inhibitors of voltage gated sodium channels (NaV) have long been a mainstay of the anti-seizure pharmacopeia. Drugs that work by inhibiting NaV channels, such as phenytoin and carbamazepine, are indicated for the treatment of focal seizures, but their utility is reduced by relatively narrow therapeutic indices. Unlike XEN901, classic NaV inhibitors are not selective; they block all NaV subtypes indiscriminately which contributes to their narrow therapeutic window. While NaV1.6 and NaV1.2 are highly expressed in excitatory glutamatergic pyramidal neurons, NaV1.1 (SCN1A) is primarily expressed in GABAergic inhibitory interneurons. Hence, inhibition of NaV1.1 is pro-convulsant, as indicated by the seizure phenotype of SCN1A heterozygous null patients with Dravet syndrome. Inhibition of NaV1.5, the cardiac sodium channel, introduces additional risk for non-selective compounds. We created a small molecule drug that effectively inhibits NaV1.6 without inhibiting other sodium channels, particularly NaV1.1 and NaV1.5, and that we believe will provide greater potential for efficacy and an improved therapeutic index.

XEN901 inhibits human NaV1.6 current with an IC50 <100 nM and is >100-fold selective against all other human voltage gated NaV subtypes (NaV1.1-1.7). Inhibition is highly state-dependent with >1000-fold more potency against open or inactivated channels than for channel resting state.

XEN901 is efficacious in a mouse model of Early Infantile Epileptic Encephalopathy type 13, EIEE13, that was created by introducing a patient identified heterozygous mutation (N1768D) in SCN8A leading to a gain-of-function in NaV1.6 channels. These N1768D+/- mice were protected from electrically (6Hz) induced seizures by brain concentrations of XEN901 approximately 1000-fold lower than concentrations of phenytoin required for the same efficacy. Similarly, XEN901 was effective at brain concentrations about 1000-fold lower than needed for phenytoin in the maximal

electroshock (MES) assay in wild type mice, a model that predicts efficacy against human focal seizures.
XEN901 represents a novel precision treatment for patients with NaV1.6 gain-of-function variants (EIEE13) and an improved treatment option for focal seizures with the potential for greater efficacy and therapeutic indices relative to current AED's.

BRIVARACETAM

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Brivaracetam is a rationally designed, selective high-affinity ligand for synaptic vesicle protein 2A (SV2A) that rapidly penetrates the blood-brain barrier. Brivaracetam is approved as treatment for focal (partial-onset) seizures in patients aged ≥16 or ≥18 years (depending on country) with a therapeutic dose range of 50–200 mg/day. Evidence for the efficacy and tolerability of brivaracetam 50–200 mg/day as adjunctive therapy (without up-titration) for focal seizures came from three phase III, randomized, double-blind, placebo-controlled, fixed-dose, multicenter studies in patients aged ≥16 years (N01252, NCT00490035; N01253, NCT00464269; N01358, NCT01261325).1 The percentages of patients with a ≥50% reduction in focal seizure frequency were 34.2%, 39.5%, and 37.8% for 50 mg/day, 100 mg/day, and 200 mg/day, respectively, vs 20.3% for placebo. The most common treatment-emergent adverse events (TEAEs) (≥10% patients) vs placebo were somnolence (15.2% vs 8.5%) and dizziness (11.2% vs 7.2%).

Epilepsy is the most common chronic neurological condition in childhood, affecting 0.5–1% of children,2 and can adversely affect educational achievement, potentially leading to poorer socioeconomic outcomes. Additional treatment options that provide seizure control with low side effects, especially treatments that do not impair cognitive development and academic achievement, are needed for children with epilepsy.

The pathophysiology of focal seizures in children aged ≥4 years is believed to be similar to that of adults. Consequently, it has been proposed that efficacy results from studies of antiepileptic drugs (AEDs) in adults can predict efficacy in children. A recent systematic review of clinical trial data indicated that effect measures for a range of AEDs are comparable in children aged 2–18 years and adults with partial onset seizures, supporting extrapolation of efficacy data from adults to children.3 Brivaracetam pharmacokinetics have been shown to be similar in children and adults;4 as such, a similar exposure in children compared with adults would be expected to lead to a similar effect. The Food and Drug Administration and European Medicines Agency accept extrapolation of efficacy data from adults to children aged ≥4 years with focal seizures under certain circumstances.

The safety profile of an AED can be different in adults and children, particularly the potential effects on growth, development, and cognition, and hence cannot be fully extrapolated from adults. In a recent pooled interim analysis with data from short-term (N01263, NCT00422422) and long-term (N01266, NCT01364597) open-label, single-arm, multicenter trials, adjunctive brivaracetam treatment (0.8–5 mg/kg/day)

was generally well tolerated in children with epilepsy aged 1 month–<17 years.5 The most common (≥5% patients) drug-related TEAEs were somnolence (6.8%) and decreased appetite (6.4%). Somnolence has also been associated with brivaracetam treatment in adults.5 Together with the extrapolation of efficacy data from adults to children, these safety findings support brivaracetam's development as a potential new therapy for children aged ≥4 years with focal seizures.

An open-label study to evaluate the pharmacokinetics, efficacy, and safety of brivaracetam in neonates with repeated electroencephalographic seizures is currently ongoing (N01349, NCT03325439).

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Table. Summary of the ongoing trials in the brivaracetam pediatric clinical development program

Trial	Estimated completion	Description
NCT03405714 (EP0065)	Q1 2020	Phase II, multicenter, open-label study to evaluate the pharmacokinetics, safety, and tolerability of intravenous brivaracetam in patients 1 month to <16 years of age with epilepsy
NCT01364597 (N01266)	Q4 2021	Phase III open-label, single-arm, multicenter, long-term study to evaluate safety and efficacy of brivaracetam used as adjunctive treatment in patients ≥4 to <17 years of age with focal epilepsy
NCT03325439 (N01349)	Q4 2020	Phase II/III, open-label, single-arm, multicenter study to evaluate the pharmacokinetics, efficacy, and safety of brivaracetam in neonates with repeated electroencephalographic seizures

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REAL-WORLD DATA ON THE EFFECTIVENESS, SAFETY AND TOLERABILITY OF ESLICARBAZEPINE ACETATE MONOTHERAPY IN CLINICAL PRACTICE

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Rationale: Eslicarbazepine acetate (ESL) is approved in Europe and the US for the treatment of partial-onset seizures as monotherapy or adjunctive therapy. Real-world clinical practice data complement evidence from clinical trials by providing information on patients who are more diverse in terms of clinical characteristics than those recruited for clinical trials. The Euro-Esli study investigated the real-world effectiveness, safety and tolerability of ESL when used in everyday clinical practice in Europe. We present a subanalysis of Euro-Esli data from patients who were treated with ESL as initial monotherapy or converted to ESL monotherapy following ESL adjunctive therapy.

Methods: Euro-Esli was a pooled analysis of 14 European clinical practice studies. Effectiveness assessments included responder rate (≥50% seizure frequency reduction) and seizure freedom rate (seizure freedom at least since prior visit), assessed after 3, 6 and 12 months of ESL treatment, and at last visit. Safety and tolerability were assessed by evaluating adverse events (AEs) and ESL discontinuation due to AEs, respectively. Data were compared for patients treated initially with ESL monotherapy versus adjunctive therapy, and for patients treated at last visit with ESL monotherapy versus adjunctive therapy.

Results: Of the 2058 patients included in Euro-Esli, the number of concomitant AEDs used at baseline and last visit was known for 2045 and 1340 patients, respectively. ESL was used as monotherapy in 88/2045 (4.3%) patients initially and in 229/1340 (17.1%) patients at last visit. At 12 months, responder and seizure freedom rates were higher in patients treated initially with ESL monotherapy versus adjunctive therapy, and in patients treated at last visit with ESL monotherapy versus adjunctive therapy. The overall incidence of AEs was similar in patients treated initially with ESL monotherapy and adjunctive therapy, and in patients treated at last visit with ESL monotherapy and adjunctive therapy. The rate of discontinuation due to AEs was not markedly different in patients treated initially with ESL monotherapy versus adjunctive therapy, but the rate was lower in patients treated at last visit with ESL monotherapy versus adjunctive therapy.

Conclusions: In Euro-Esli – the largest ESL clinical practice study conducted to date – ESL was shown to be more effective when used as monotherapy, compared with adjunctive therapy. ESL safety and tolerability were generally comparable when used as monotherapy or adjunctive therapy. These data support the use of ESL as monotherapy, as well as adjunctive therapy, for partial-onset seizures in clinical practice, complementing evidence from clinical trials.

EVEROLIMUS

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Everolimus is a selective inhibitor of the mTOR (mechanistic/mammalian target of rapamycin) complex, specifically targeting mTORC1.
Preclinical research has demonstrated that everolimus could exert both an anticonvulsant action and an antiepileptogenic effect in models of genetic and acquired epilepsy.
Preliminary clinical evidence from a phase I/II trial and different clinical series reported good efficacy of everolimus on TSC-related epilepsy with at least 50% of responders.
A phase I/II clinical trial evaluating the efficacy of everolimus in medically refractory TSC related epilepsy reported a >50% seizure frequency reduction in 12/20 patients. The 4-year final analysis of this first prospective open label human clinical trial for individuals with TSC related refractory epilepsy treated with everolimus adjusted for a target serum range of 5-15 ng/mL provided evidence that improved seizure control is maintained in 72% of patients.
A phase III randomized, double-blind, placebo-controlled study (EXIST3) evaluated the efficacy and safety of two trough-ranges of everolimus (3-7 ng/ml and 9-15 ng/ml) given as adjunctive therapy for patients with refractory partial-onset seizures. This consisted of an 8 week baseline phase, 6 week titration phase, and 12 week maintenance phase, followed by an extension phase of 48 weeks. 366 patients aged 2-65 years have been enrolled in this multicentre study. The response rate at the end of the maintenance phase, appeared to be 15.1% in the placebo group, 28.2% in the low-exposure everolimus group, and 40% in the high exposure everolimus group. Overall adverse events, including mouth ulcerations, upper respiratory tract infections and stomatitis, were usually mild and self-limited. Grade 3 or 4 adverse events were reported with placebo vs low-exposure/high-exposure in 10.9% vs 17.9/23.8%; serious adverse events were reported in 2.5% vs 13.7/13.8%. Adverse events led to treatment discontinuation in 1.7% vs 5.1/3.1%. Preliminary evidence from the extension phase revealed a sustained seizure reduction over time with acceptable safety profile. Taking into consideration the positive results of the EXIST3 study, everolimus was approved by both FDA and EMA for refractory epilepsy related to TSC in patients aged at least 2 years.

LACOSAMIDE

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Lacosamide (LCM, Vimpat®) is indicated for the treatment of focal (partial-onset) seizures in patients 4 years of age and older in the European Union and the United States.

The long-term tolerability of LCM as monotherapy in adults with newly-diagnosed epilepsy was investigated in a Phase III double-blind extension (SP0994; NCT01465997) of the active-controlled, non-inferiority trial SP0993 (NCT01243177). 279/445 (62.7%) patients randomized to LCM and 270/443 (60.9%) randomized to carbamazepine controlled-release (CBZ-CR) continued in SP0994. 181/279 (64.9%) patients on LCM and 182/269 (67.7%) on CBZ-CR reported treatment-emergent adverse events (TEAEs); 12 (4.3%) vs 21 (7.8%) discontinued due to TEAEs. LCM monotherapy was well tolerated over a median of ~2 years of treatment and seizure control was maintained.

An open-label Phase III conversion-to-monotherapy trial (EP0057; NCT02124564) of LCM in Japanese adults with focal seizures has recently been completed. An open-label extension trial (EP0009; NCT01832038) to evaluate long-term safety and efficacy of adjunctive LCM in Chinese and Japanese adults with focal seizures is ongoing; interim analyses showed long-term adjunctive treatment with LCM was generally well tolerated, and seizure control was maintained over time.

Extension of the LCM licensing to pediatrics (≥4 years) was based on extrapolation of efficacy data from Phase III trials in adults, on safety and tolerability data from open-label trials in children and adolescents, and on pharmacokinetic modelling and simulation data to support weight-based dosing. Several pediatric trials are ongoing (Table).

In a double-blind, placebo-controlled trial (SP0969; NCT01921205), 343 patients (≥4 to <17 years) with uncontrolled focal seizures were randomized (1:1) to adjunctive LCM or placebo (PBO). Adverse events were the most common reason for discontinuation during the Treatment period (Titration and Maintenance) (LCM: 7 [4.1%]; PBO: 10 [5.8%]). Percent reduction for LCM vs PBO in focal seizure frequency/28 days from Baseline to Maintenance was 31.7% (p=0.0003). During Maintenance, median percent reduction in focal seizure frequency/28 days was 51.7% for LCM and 21.7% for PBO. 50% responder rates (patients with ≥50%

reduction in focal seizure frequency) were higher with LCM than PBO (52.9% [90/170] vs 33.3% [56/168]; odds ratio 2.17; p=0.0006). 116/171 (67.8%) patients on LCM and 100/172 (58.1%) on PBO reported TEAEs during Treatment. The most common TEAEs with LCM were somnolence (LCM: 24 [14.0%]; PBO: 9 [5.2%]) and dizziness (18 [10.5%]; 6 [3.5%]). Adjunctive LCM was effective in reducing seizure frequency and was generally well tolerated, with a favorable tolerability profile similar to that observed in adults.

Interim data in 283 children and adolescents who transitioned from SP0969 to the ongoing extension trial (EP0034) showed long-term adjunctive LCM had a safety profile consistent with that in adults, with a low incidence of behavior-related TEAEs, no memory-related TEAEs, and no overall worsening of behavioral/cognitive measures (Achenbach Child Behavior Checklists and Behavior Rating Inventory of Executive Function). These results further support use of LCM in pediatric patients (≥4 years) with focal seizures. A double-blind, placebo-controlled trial (SP0967) is being conducted to evaluate the efficacy and safety of adjunctive LCM in young children (1 month to <4 years) with focal seizures.

UCB Pharma-sponsored.

PERAMPANEL

S. Ngo

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Perampanel, a selective, non-competitive AMPA receptor antagonist, is approved for adjunctive treatment of partial seizures, with or without secondarily generalised seizures, and primary generalised tonic-clonic seizures (PGTCS) in patients with epilepsy ≥12 years. In the USA, perampanel is also approved for use as monotherapy for partial seizures in patients with epilepsy ≥12 years. Approval was based on efficacy and safety data from randomised, double-blind, placebo-controlled, Phase III trials of adjunctive perampanel in patients with partial seizures (Studies 304 [NCT00699972], 305 [NCT00699582], 306 [NCT00700310]) or idiopathic generalised epilepsy and PGTCS (Study 332 [NCT01393743]). A consistent perampanel efficacy and safety profile was found in patients with partial seizures from Asia Pacific (Study 335 [NCT01618695]). Long-term adjunctive perampanel treatment appeared efficacious and well tolerated in open-label extension (OLEx) studies in patients with partial seizures (Studies 307 [NCT00735397], 335 OLEx [NCT01618695]) or PGTCS (Study 332 OLEx [NCT02307578]). In adolescents (12-<18 years) with partial seizures, adjunctive perampanel showed no long-term, clinically meaningful, overall effects on Cognitive Drug Research system global cognition score (Study 235 double-blind and OLEx [NCT01161524]). Based on the recent acceptance by the Food and Drug Administration (FDA) to extrapolate data from antiepileptic drug (AED) adjunctive trials to the monotherapy setting for partial seizures, efficacy and safety data were extrapolated from Studies 304, 305 and 306 to evaluate perampanel monotherapy. Perampanel was efficacious and well tolerated, regardless of Baseline concomitant AED use, suggesting similar outcomes in monotherapy and adjunctive settings. Perampanel monotherapy was generally well tolerated in seven patients who converted to monotherapy during clinical trials and 60 patients who received perampanel as primary/secondary monotherapy during a retrospective, non-interventional study (Study 504 [NCT02736162]). Together, these data formed part of the FDA submission, supporting approval of perampanel for monotherapy use for partial seizures. Due to ethical concerns for AED trials in children, the FDA deemed it acceptable to extrapolate efficacy data from adults with partial seizures to children (≥4 years). To support extrapolation of AED efficacy data in adults with PGTCS to children (4-12 years), a meta-analysis of published trials found similar AED efficacy profiles in adults and children. Such extrapolation is being utilised in Study 311 (NCT02849626) to evaluate the tolerability and pharmacokinetics of adjunctive perampanel oral suspension in children (4-<12 years) with partial seizures or PGTCS. These data will be important to determine perampanel use in paediatric patients (≥4 years). Future studies will further explore perampanel use in different patient populations.

STIRIPENTOL

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Stiripentol is a structurally unique, antiepileptic agent which has several mechanisms of action: (1) positive allosteric modulator of the GABAA receptor, acting at both the gamma-containing (BZD-sensitive) and the delta-containing (BZD-insensitive) receptors; (2) inhibits LDH which leads to reduced levels of ATP, enhanced K+ efflux with greater neuronal hyperpolarization, and thus reduces neuronal excitability; (3) inhibits CYP p450 enzymes leading to pharmacokinetic interactions with many AEDs, most importantly significant elevation of both clobazam and its active metabolite, N-desmethylclobazam; (4) neuroprotective effects in the Li-Pi seizure model, as well as when administered either pre or post-exposure to glutamate, and pre-exposure to oxygen-glucose deprivation. This neuroprotective effect is likely due to the ability of stiripentol to block Ca++-permeable NMDA-sensitive glutamate receptors and voltage-sensitive Na+ and Ca++ channels.

Stiripentol exhibits more rapid metabolism in younger children. In a study evaluating stiripentol pharmacokinetics in 35 children with Dravet syndrome receiving 50 mg/kg divided into 2 or 3 doses, the apparent clearance and apparent volume of distribution were related to body weight, and the AUC increased by 300% when the body weight increased from 10-70 kg (Peigne et al. 2017). These findings confirm the dose-dependent, non-linearity seen in adults, and suggest that lower stiripentol doses are appropriate for weight >30 kg, with further possible dose adjustment during adolescence.

Clinically, the most significant use of stiripentol has been in Dravet syndrome. In the pivotal randomized, placebo-controlled, add-on STICLO study, 67-71% achieved a >50% reduction in frequency of convulsive seizures. Large, open-label, add-on studies have shown similar efficacy, and documented that response is maintained in the majority of patients long-term. A French cohort, cross-sectional study showed that 96% maintained stiripentol therapy after a median of 8 years, although most continued to have brief, convulsive seizures (De Liso et al. 2016). Efficacy may be somewhat lower when STP is started during adolescence or adulthood, with responder rates of 23% at 36 months (Balestrini et al. 2017). Stiripentol may have greater efficacy in children with a documented pathogenic SCN1A mutation than those without this finding (72.5% vs 50.6%, p=0.004) (Cho et al. 2017).

Epilepsy of infancy with migrating focal seizures (EIMFS) is a rare disorder, beginning in the first months of life, with exceedingly frequent, multifocal seizures and severe intellectual disability. Many infants are found to have a genetic etiology, but causes are heterogenous. Several small, open-label, add-on studies suggest that stiripentol may significantly reduce seizure burden.

Stiripentol may also have a role in super-refractory status epilepticus, as demonstrated in one small open label study in 5 adults and another case report of an adult with anti-NMDA receptor encephalitis.

NEUROMODULATION, MONITORING AND MRI GUIDED LASER ABLATION

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The Circuit of Papez has been widely studied as a neural network, due to its demonstrated involvement in seizure generation and propagation, and its critical role in learning and memory. This network has been targeted for therapeutic intervention with Deep Brain Stimulation (DBS) in patients with epilepsy, and more recently investigated in pilot studies of MRI-guided LASER ablation technology. The present work investigates advanced therapy concepts related to use of DBS, laser ablation, and brain monitoring in this network.

Preliminary pre-clinical data on Medtronic's next generation rechargeable platform (Medtronic Activa RC+S), incorporating brain and motion sensing features for epilepsy, will be described. This platform is in early-phase development, and thus, the data presented here are from research prototypes evaluating potential use cases for epilepsy. Proof of concept for a new monitoring paradigm, based on use of evoked potentials (EPs) as a biomarker for changes in brain excitability, during therapeutic interventions (electrical stimulation, anti-epileptic drugs) and seizure states, is provided. First demonstrations of chronic seizure detection, performed in real-time using on-board event detectors and remotely captured via ORCA (ORganize Copy Annotate), a cloud-based device data collection system for physiologic data monitoring, are also described. Examples from ORCA will illustrate seizure review and event trending of seizure counts.

Lastly, a status update of Medtronic's epilepsy therapy development program will be provided. This includes: (1) Next clinical steps related to evaluation of minimally invasive sub-cutaneous brain monitoring for seizure diagnosis; and, (2) Clinical activities related to MRI-guided LASER ablation technology as a possible treatment for mesial temporal lobe epilepsy (MTLE). These technologies will be discussed in reference to elements of a proposed epilepsy portfolio with emphasis on the care continuum.

TECHNOLOGY-ENABLED SEIZURE DETECTION AND REPORTING:THE EPILEPSY NETWORK PROJECT.

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Traditional models of epilepsy care provision have not changed substantially in more than a century, despite rapid recent changes in computing, technology and materials science. One consequence has been a near universal prevalence of smartphones. These devices provide a coalescence of digital computing and communication tools that offer a new way to detect, report and communicate about seizures.

We have developed a smartphone-based application for patients and cares which allows real-time reporting of seizures securely to the relevant epilepsy care team. In addition, an algorithm has been developed for seizure detection using linked data from a consumer-grade wrist worn device with a multi-sensor array, which also captures lifestyle information. The information from these devices is stored securely in patient-held cloud-based storage. Relevant information, such as seizure notifications, are sent securely to the epilepsy care team in real time. Live alerts for notification of emergency attendance or admission to the hospital for patients known to have epilepsy are also configured automatically. Tailored specialist advice following notification is provided along traditional lines.

This novel platform for epilepsy care has been piloted for the last year in Dorset. Compared to the preceding 12 month period the interval between seizure occurrence in the community and notification of the specialist team has reduced by 3 weeks, with faster response times in terms of advice. There has been a 30% reduction in admissions for patients with epilepsy and 10% reduction in length of stay. Patients using the technology report an increased feeling of empowerment. Machine based learning approaches have also been applied to the anonymized data sets.

This model of care has several challenges and requires modification of existing working practices if benefits for patients are to be fully realised. The benefits and challenges of technology-enabled care in are discussed from the perspective of the experience from development to clinical deployment.

EMBRACE AND E4: DEVICES FOR SEIZURE DETECTION AND ADVANCING RESEARCH

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There is a growing need for new devices providing continuous monitoring of epileptic seizures, especially those carrying a higher risk of sudden unexpected death in epilepsy (SUDEP), namely generalized tonic-clonic seizures (GTCS). Wearable automated seizure detectors may improve existing practice by providing continuous, unobtrusive ambulatory monitoring, potentially more accurate seizure counts, and real-time alerts to bring caregiver intervention.

The Embrace and E4 wristbands (Empatica) are the first commercially available multimodal smartwatches which were designed to measure important physiological changes caused by GTCS, and which received medical clearance (E4 from EU CE, Embrace from EU CE and US FDA). Both devices contain motion (accelerometers, ACM) and electrodermal activity (EDA) sensors. The E4 platform allows real-time recording and visualization of sensor signals (but no real-time alerts), whereas the Embrace runs an on-board seizure detection algorithm and is paired with a mobile app ("Alert") to automatically trigger calls to caregivers when a GTCS is detected. A second mobile app "Mate", used with Embrace, aggregates seizures, and quantifies sleep and physical activity to operate as an innovative electronic diary. The only known risk in using Empatica E4 and Embrace devices is a very low rate of contact dermatitis, which is reduced by keeping the sensors cleaned regularly.

A machine learning algorithm able to recognize ACM and EDA signatures of GTCS-like events was trained on E4 data, labeled using gold-standard video-EEG examined by epileptologists in clinical centers, and now runs in real-time on Embrace. While keeping an elevated sensitivity to GTCS (95%), algorithm improvements and growing data availability led to lower false alarm rate (FAR) from the initial ~2 down to 0.2 false alarms per day (55 GTCS, 69 patients). Algorithm adjustment to better discriminate real-life physical activities from GTCS, has brought the initial FAR of ~6 on Embrace outpatient data to values comparable to best-case clinical settings (FAR<0.5), with sensitivity ranging from 95% to 99%.

Beyond seizure detection, the multimodal sensing has proven effective to also quantify seizure autonomic dysfunction, based on EDA surge which has previously been correlated with the duration of post-ictal generalized EEG suppression, a biomarker found in 100% of monitored SUDEP cases. EDA surges, together with abnormal motor duration based on ACM, can help the objective characterization of seizures.

Future technological developments will be centered around the detection of additional seizure types, algorithm personalization based on individual seizure semiology, and the detection of autonomic activations (e.g., autonomic arousal and stress).

REGULATORY REQUIREMENTS FOR MEDICAL DEVICES IN EUROPE

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The European Medicines Agency (EMA) is responsible for the scientific evaluation, supervision and safety monitoring of human and veterinary medicinal products in the EU. EMA does not approve medical devices; however, EMA has a role in medicinal product and medical device combinations and medical devices containing ancillary substances.

Medical devices within the European Union must carry a "Conformité Européenne" (CE) mark verifying that a device meets all regulatory requirements set forth in the three current EC Medical Device Directives: Directive 93/42/EEC on General Medical Devices, Directive 90/385/EEC on Active Implantable Medical Devices, and Directive 98/79/EC on In Vitro Diagnostic Medical Devices. For low risk devices a CE mark can be placed on the device after the manufacturer writes up a statement to declare that the device meets the requirements of the relevant directive. For medium and high risk devices a specially designated body known as a 'Notified Body' must carry out a conformity assessment to approve the device meets the requirements of the relevant directive. Once a Notified Body certification is received the manufacturer can place a CE mark on the device.

As per Directive 93/42/EEC, it is compulsory for the notified body of a medical device that includes a medicinal product with an ancillary substance or human blood or plasma derivative to consult a medicinal product competent authority or the EMA prior to CE certification as appropriate. EMA evaluates marketing authorisations for medicinal products with an integrated or co-packaged device component (i.e. drug delivery devices) which fall under the pharmaceutical legislation.

The medical devices landscape in Europe is undergoing significant changes at the moment. The three directives are being replaced by two new regulations: Regulation 2017/745 on Medical Devices (MDR) and Regulation 2017/746 on In Vitro Diagnostic medical devices (IVDR).

The MDR and IVDR have bestowed additional important responsibilities on the EMA, including a new consultation of substance based medical devices that are systemically absorbed, a new consultation on companion diagnostics, and a consultation on borderline products.

This presentation will focus on the EMA's roles and responsibilities for medical devices, specifically the consultation on ancillary medicinal products and considerations when marketing a medicinal product with an integrated or co-packaged medical device.

LESSONS LEARNED FROM TRANSCUTANEOUS VAGUS NERVE STIMULATION (tVNS)

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Transcutaneous vagus nerve stimulation (tVNS) is a newly developed method which intends to overcome the disadvantage of surgical implantation of the stimulation device. The auricular branch of the vagus nerve (ABVN) supplies the cymba conchae. The ABVN can be stimulated using an external device with a bipolar electrode attached to the skin of the left ear conch. A pilot studie showed seizure reduction of up to 50%.

One randomized, double-blind controlled trial has been performed which fully disclosed the stimulation technique to assess efficacy and safety of 20 weeks of tVNS in patients with drug-resistant epilepsy. Primary objective was to demonstrate superiority of add-on therapy with tVNS (stimulation frequency 25 Hz, n = 39) versus active control (1 Hz, n = 37) in reducing seizure frequency over 20 weeks. With treatment adherence over >80% in both groups, mean seizure reduction per 28 days at end of treatment was –2.9% in the 1 Hz group and 23.4% in the 25 Hz group (p = 0.146). Adverse events were usually mild or moderate and comprised headache, ear pain, application site erythema, vertigo, fatigue, and nausea. In summary, the study failed to show superiority of 25 Hz tVNS over 1 Hz tVNS. However, there was a moderate but considerable seizure reduction rate of 23.4% within the 25 Hz group and overall, tVNS treatment was well tolerated in both groups. Therefore, these results justify further trials with larger patient numbers. Since treatment effect appeared to increase after 20 weeks of treatment, longer observation periods are desirable in upcoming studies.

In conclusion, the clinical value of tVNS cannot be finally evaluated at this point and the results of further studies must be awaited.

AUTONOMIC BIOFEEDBACK THERAPY

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Nagai and her colleagues first started research into biofeedback to modulate sympathetic activity (Galvanic Skin Response: GSR or Electrodermal activity: EDA) in patients with drug resistant epilepsy in 1997. The therapy was established based on a series of neuroscientific studies characterizing an inverse relationship between electroencephalographic (EEG) indices of cortical neural excitability (slow cortical potentials) and peripheral sympathetic arousal (indexed by GSR activity). An increase in sympathetic activity reduces cortical excitation. The therapy is termed as Autonomic Cognitive Rehabituation Training (ACRT) and the training is composed of twelve consecutive 45 minutes session over the period of four weeks.

The first randomized controlled trial (2004) demonstrated a robust positive effect of ACRT therapy in that 60% of patients in the therapy group reduced seizure 50% or more. The group also identified that ventromedial prefrontal cortex (VMPFC) activity is inversely correlated to the tonic level of GSR suggesting that this part of the brain is an important hub for modulation of sympathetic activity.

In the recent clinical trial, we recruited 40 patients with drug resistant temporal lobe epilepsy (TLE) (N= 20 Therapy group, N = 20 Control). Neuroimaging (fMRI) was used to investigate functional connectivity changes before and after the ACRT therapy intervention. There was a significant difference in reduction of seizure frequency between the therapy and control groups ($p < 0.001$). A month of therapy training, elicited a significant reduction in the patients' seizure frequency ($p<0.001$), with average seizure reduction of 43% and response rate of 45%. Neuroimaging analysis revealed that post-therapy seizure reduction was linearly correlated with enhanced functional connectivity between amygdala and the orbitofrontal cortex (OFC) indicating role of Uncinate Fasiculus in generation and suppression of seizures in patients with TLE.

Our combined clinical trial and neuroimaging study demonstrates the potential of ACRT therapy as an effective, non-invasive and cost saving technology-driven therapy that can be globally offered for patients with drug resistant epilepsy in the near future.

PROPOFOL PRODRUG EPALEX-102 FOR THE TREATMENT OF ACUTE REPETITIVE SEIZURES

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The propofol prodrug EPALEX-102 is being developed as an oral agent for the treatment of acute repetitive seizures (ARS). ARS is a condition occurring in people with drug refractory epilepsy characterized by the occurrence of a series of seizures grouped consecutively, typically with short (or shorter than normal) interictal periods. More generally, ARS represents an increase in the frequency or severity of seizures. ARS may be associated with injury, negative social and economic impact, and status epilepticus, which may lead to permanent neurological impairment and death. All novel ARS treatments currently in clinical use or under investigation represent different benzodiazepine dosage forms. These include nasal, buccal and inhaled forms of diazepam, midazolam, lorazepam and alprazolam. There is a need for improved ARS treatments that are more efficacious than current treatments and that are better accepted by caregivers and patients. Propofol is a highly effective antiseizure agent that terminates benzodiazepine-refractory seizures but it is available only for intravenous administration. Propofol is not orally bioavailable. In rats, EPALEX-102 is absorbed orally and rapidly converts to propofol. High doses of EPALEX-102 cause sedation whereas lower doses that do not cause sedation are associated with elevation of pentylenetetrazol seizure threshold. Single oral dose administration of EPALEX-102 in healthy male volunteers resulted in adequate exposures to propofol, and single ascending dose administration resulted in a linear dose-dependent increase in propofol Cmax and AUC. Low doses of EPALEX-102 in the ascending dose study were well-tolerated whereas higher doses led to lethargy and somnolence. We conclude that adequate exposures to propofol can be achieved in humans with oral dosing of EPALEX-102, and that there is a therapeutic window between exposures believed to be associated with seizure protection and those causing sedation and other adverse effects. EPALEX-102 is a promising agent for advancement to clinical trials as a treatment of ARS.

BRIVARACETAM: POTENTIAL FOR TREATMENT OF ACUTE SEIZURES

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Brivaracetam (BRV) is approved as treatment for focal (partial-onset) seizures in patients aged ≥16 or ≥18 years (depending on the country). BRV has an analog chemical structure of levetiracetam (LEV) but represents an advancement of the racetam class; BRV was rationally designed to have a higher affinity and selectivity for synaptic vesicle protein 2 (SV2A). Controlled clinical studies in adult patients with focal seizures showed that adjunctive therapy with BRV was efficacious and well-tolerated. Of particular interest, BRV showed an early and sustained onset of action in patients, with efficacy measured from the first day of treatment. BRV exhibits a favorable pharmacokinetic profile with low inter-individual variability, rapid and complete oral absorption, a 7-8 h elimination half-life, and low clinically significant drug-drug interactions. The BRV bolus intravenous injection was found to be bioequivalent to the BRV 50 mg and 100 mg oral tablets. Further, the intravenous BRV formulation is well tolerated when given by bolus or infusion, regardless of whether the intravenous formation is given initially, or after conversion from oral administration.

In vitro, BRV shows a more favorable lipophilicity degree and cell permeability than LEV. This results in a faster distribution into the brain tissue in vivo as well as a quicker onset of action in animal models of epilepsy. BRV was also shown to be devoid of active transport mechanisms (e.g. P-glycoprotein) that impair the blood brain barrier permeability and potentially the efficacy of a number of AEDs.

The above data triggered brain PET studies in non-human primates and, subsequently, in human volunteers. These studies consistently demonstrated that the faster brain penetration of BRV translates into a faster occupancy of the SV2A pharmacological target. After intravenous dosing to human subjects, BRV binds to brain SV2A in few minutes (equilibrium half-time of 8.5 min after 100 mg iv, to be compared with about 20 min for 1500 mg LEV iv).

Overall, the above data suggested that BRV might be a candidate for further investigation in the treatment of acute seizures with a fast onset of action in animals, favorable tolerability (via intravenous and oral dosing), no clinically major risk of drug interaction, and no evidence of tolerance mechanisms. These attributes are reinforced by recent data in animal models of status epilepticus where BRV is highly efficacious by itself but also markedly potentiates the anticonvulsant activity of diazepam. The potential of BRV in the treatment of acute seizure is actually under investigation in clinical trial EP0087/NCT03021018 “A Study to Assess the Efficacy and Safety of Brivaracetam as Treatment for Increased Seizure Activity in an Epilepsy Monitoring Unit”.

CHARACTERIZATION OF NAYZILAM™ (USL261; MIDAZOLAM NASAL SPRAY) FOR TREATMENT OF ACUTE REPETITIVE SEIZURES: A COMPREHENSIVE DEVELOPMENT PROGRAM

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Nayzilam™ (USL261; midazolam nasal spray) has been developed as an alternative to rectal diazepam, the only FDA-approved non-intravenous treatment for patients with intermittent bouts of increased seizure activity (ie, acute repetitive seizures [ARS], seizure clusters [SC]). As a drug/device combination product, the novel nasal spray formulation of midazolam provides convenient, easy-to-use, non-invasive (nasal applicator) drug administration in the outpatient setting by caregivers or medical personnel. The pharmacokinetics, pharmacodynamics, safety and efficacy of Nayzilam have been evaluated in a comprehensive Clinical Development Program. Following IN administration of Nayzilam, rapid achievement of maximal plasma concentrations (within 15 minutes post dose) and distribution into the central nervous system was observed; peak effects on PD measures of sedation and psychomotor performance occurred by 30 to 60 minutes post dose. Consistent with the short plasma half-life of MDZ, PD effects returned to near baseline values by approximately 4 hours post dose. In the pivotal trial, ARTEMIS-1, subjects with a history of SC receiving a stable regimen of antiepileptic drugs (AED) were randomized (2:1) to receive Nayzilam 5 mg or placebo (PBO). Upon completion, patients were eligible to proceed to an open-label safety experience trial. Of the 262 subjects randomized to treatment, 201 treated a SC with double-blind study drug (n=134 Nayzilam; n=67 PBO). The proportion of subjects with Treatment Success was significantly greater with Nayzilam as compared with PBO (effect size 19%; p=0.0109). The time to next seizure with a start time >10 minutes after study drug administration was statistically significant (p=0.0124) with clear separation between the Nayzilam and PBO groups within 1 hour and maintained for the duration of the 24-hour observation period. Subjects who did not respond to the initial 5 mg dose of Nayzilam could take a second 5 mg dose to treat the ongoing SC. For all doses, Nayzilam demonstrated 71% overall Treatment Success. None of the randomized subjects discontinued from the study due to an AE. The overall incidence of treatment emergent AEs (TEAEs) in ARTEMIS-1 were 28% (Nayzilam) and 22% (PBO), with the majority reported as mild-to-moderate in intensity. Nasal discomfort, somnolence, lacrimation increased, product taste abnormal, and throat irritation were the most commonly reported treatment-related TEAEs throughout the study and were consistent with route of administration. No deaths were reported. Two (1.0%) subjects reported at least one treatment-emergent serious AE, of which none

were Respiratory depression or considered related to study drug. Nayzilam continued to demonstrate good efficacy and safety during long-term open-label follow-up where 1998 SC were treated; aggregate efficacy of >80% was observed. There were no new safety findings. The Nayzilam development program demonstrated that Nayzilam (midazolam nasal spray) was efficacious for the treatment of SC, and significantly terminated seizure activity and prevented seizure recurrence for 24 hours. Nayzilam also appeared to be safe and well-tolerated in subjects with seizure clusters. These data suggest that Nayzilam may provide a significant benefit to patients with epilepsy.

STACCATO ALPRAZOLAM

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Staccato Alprazolam (STAP-001) is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery by inhalation of a thermally generated aerosol of alprazolam. STAP-001 represents a new dosage form for alprazolam and is based on the proprietary Staccato delivery system developed by Alexza Pharmaceuticals. STAP-001 is delivered orally to the deep lung for systemic delivery, and the pharmacokinetics are similar to what is achieved with drug delivery by IV injection. The Staccato delivery system is user-friendly and easy to use. Device actuation, aerosol formation, and delivery of the aerosolized drug to the deep lung are all accomplished with a single, normal breath by the subject. Achievement of peak plasma levels within 2 minutes via a simple, user-friendly delivery system makes STAP-001 ideal for the acute treatment of seizures.

STAP-001 was assessed in a phase 2a study using the Intermittent Photic Stimulation (IPS) model in subjects with photosensitive epilepsy. This study was conducted to establish proof of concept for STAP-001 as an acute treatment for seizures and to establish the dose range for subsequent clinical trials in epilepsy. Five patients were enrolled and completed all treatment arms (0.5mg, 1 mg, 2 mg of STAP-001, and two doses of placebo). All doses of STAP-001 decreased the mean standardized photosensitivity range (SPR), with maximal or near-maximal effect occurring by 2 minutes post dose, and the reduction in SPR was observed out to the 6 hours of observation. Sedation was the most common adverse event. It was dose related and most common with the 2mg dose of STAP-001. Overall the STAP-001 treatment was well tolerated and no serious adverse events were reported.

The next study in the STAP-001 clinical program for epilepsy is a phase 2b study (StATES = Staccato Alprazolam Terminates Epileptic Seizures) that will be conducted in an in-patient setting. The StATES study will enroll adult subjects with predictable patterns of seizure episodes. The patients will be randomized to 0.5 or 1 mg of Staccato Alprazolam or to placebo. One predictable seizure episode per patient will be treated. The primary endpoint is proportion of responders defined as seizure episode cessation within 2 minutes and no seizure recurrence in 2 hours. The study has just been initiated and will be conducted in 40 centers across the US.

ABSTRACTS:

POSTER PRESENTATIONS

HYBRID COMPOUNDS IN THE SEARCH FOR THE NEW HIGHLY EFFECTIVE ANTICONVULSANTS

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The current development of new drugs for the treatment of multifactor illnesses, such as e.g. Alzheimer's disease or epilepsy, is focused on the multifunctional drugs which possess usually hybrid structure. Hybrid molecules are defined as chemical entities with two or more structural domains having different biological functions (1). That determines broad activity in preclinical studies and giving hope for a comprehensive and effective therapy for a particular disease. Linking of different molecular mechanisms maybe especially beneficial in the treatment of disease with the high-risk of drug resistance development, such as epilepsy. It should be emphasized that in the case of the aforementioned disease, in nearly 30% of patients pharmacotherapy does not produce expected improvement (2).

Bearing in mind the assumptions of multi-target strategy and with the aim of obtaining new highly effective and broad-spectrum anticonvulsants, we have developed integrated hybrid molecules derived from the pyrrolidine-2,5-dione ring (3,4). These compounds were designed by applying the fragment-based approach, thus they overlap on the common structural framework the chemical fragments of three chemically and pharmacologically diversified ADEs such as ethosuximide, levetiracetam and lacosamide. As a result, the hybridization process yielded substances with potent and broad-spectrum anticonvulsant activity that joined pharmacological properties of all AEDs creating hybrid structures. The most active was compound KA-104, which showed potent anticonvulsant activity in different animal models of epilepsy, ED50 (MES)=23.7 mg/kg, ED50 (6 Hz, 32 mA)=22.4 mg/kg, ED50 (6 Hz, 44 mA)=73.2 mg/kg, ED50 (scPTZ) = 59.4 mg/kg in mice. In addition, KA-104 demonstrated effectiveness by decreasing pain responses in formalin-induced tonic pain, in capsaicin-induced neurogenic pain, and notably in oxaliplatin-induced neuropathic pain in mice. Compound KA-104 underwent only a minor metabolic transformation due to the activity of recombinant human liver microsomes (HLMs), and affected slightly (at high concentration of 100 μM) the activity of CYP2D6 and

CYP3A4 cytochromes in the in vitro assays. This molecule inhibited the sodium current in rat prefrontal cortex pyramidal neurons.

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RECENT TRENDS IN UTILISATION OF ANTIEPILEPTIC DRUGS IN NORWAY

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Purpose: In recent years, several newer antiepileptic drugs (AEDs) as brivaracetam, eslicarbazepine, lacosamide, retigabine, rufinamide, stiripentol and perampanel have become available in Norway as mono- and as add-on therapy in patients with epilepsy. In addition, older AEDs as clobazam and sulthiame are experiencing a new era in patients with epilepsy. The aim of this study was to investigate changes in utilisation of the newest AEDs, as well as clobazam, and sulthiame in various patients groups in Norway in recent years.
Methods: Data regarding the utilisation of these AEDs consisted of all prescriptions of AEDs from the Norwegian Prescription Database (NorPD) from 2012 to 2016. Variables included age groups, sex and utilisation of AEDs as number of patients and defined daily doses (DDDs).
Results: The use of the newest AEDs has increased by 80% from 904 patients in 2012 to 1619 patients in 2016. In terms of DDDs, the increase was 2-fold, 0.13-0.26 DDDs/1000 inhabitants/day from 2012 to 2016 (approximately 2% of the total use of AEDs in Norway). Lacosamide was the most commonly used of the newest AEDs, 623 patients in 2016, closely followed by eslicarbazepine, 457 patients. Only 17 patients used retigabine in Norway in 2016 following its withdrawal from the marked. The number of patients using clobazam and sulthiame increased with 17 and 74%, up to 824 and 269 patients, respectively in 2016. This is reflected in clinical practice in refractory epilepsy at the National Center for Epilepsy. Clinical implications include increased awareness of interactions and including sulthiame into the TDM-repertoire. Overall, the gender distribution was 50/50, except for rufinamide which had twice as many male users compared to women. The use in children (<10 years) is still low, except for sulthiame, stiripentol and clobazam which have a high percentage of young users (20-63% of all users).
Conclusion: Newer AEDs, and old AEDs as clobazam and sulthiame are increasingly used in epilepsy in Norway. The use of NorPD is useful to study the changes and follow the utilisation of the drugs over time. Awareness of the increased exposure of AEDs to new groups of patients is of great importance and contributes to improved pharmacovigilance.

DESIGN AND COMPARATIVE EVALUATION OF THE ANTICONVULSANT PROFILE, CARBONIC-ANHYDRATE INHIBITION AND TERATOGENICITY OF NOVEL CARBAMATE DERIVATIVES OF BRANCHED ALIPHATIC CARBOXYLIC ACIDS WITH 4-AMINOBENZENSULFONAMIDE

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Epilepsy is one of the most common neurological diseases, with between 34 and 76 per 100,000 people developing epilepsy annually. Epilepsy therapy for the past 100+ years is based on the use of antiepileptic drugs (AEDs). Despite the availability of more than twenty old and new AEDs, approximately 30% of patients with epilepsy are not seizure-free with the existing medications. In addition, the clinical use of the existing AEDs is restricted by their side-effects, including the teratogenicity associated with valproic acid that restricts its use in women of child-bearing age. Thus, there is an unmet clinical need to develop new, effective AEDs. In the present study, a novel class of carbamates incorporating phenethyl or branched aliphatic chains with 6–9 carbons in their side-chain, and 4-benzenesulfonamide-carbamate moieties were synthesized and evaluated for their anticonvulsant activity, teratogenicity and carbonic anhydrase (CA) inhibition. Three of the ten newly synthesized carbamates showed anticonvulsant activity in the maximal-electroshock (MES) and 6 Hz tests in rodents. In mice, 3-methyl-2-propylpentyl(4-sulfamoylphenyl)carbamate(1),3-methyl-pentan-2-yl-(4-sulfamoylphenyl) carbamate (9) and 3-methylpentyl, (4-sulfamoylphenyl)carbamate (10) had ED50 values of 136, 31 and 14 mg/kg (MES) and 74, 53, and 80 mg/kg (6 Hz), respectively. Compound (10) had rat-MES-ED50 = 13 mg/kg and ED50 of 59 mg/kg at the mouse-corneal-kindling test. These potent carbamates (1,9,10) induced neural tube defects only at doses markedly exceeding their anticonvuslnat- ED50 values. None of these compounds were potent inhibitors of CA IV, but inhibited CA isoforms I, II and VII. The anticonvulsant properties of these compounds and particularly compound 10 make them potential candidates for further evaluation and development as new AEDs.

CONCOMITANT MEDICATIONS IN PATIENTS WITH EPILEPSY

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Purpose: Concomitant medication (CM) usage is common in patients with epilepsy due to the comorbidities which are often present in this population. Comedication may pose significant hazards due to potential interactions. The purpose of this study was to understand and quantify the exposure to CMs in patients with epilepsy.

Material and Methods: This one-year prospective single center study included 663 patients with the mean age of 35,1 years. Data on patients' characteristics and treatment were collected during consecutive three visits. OTC drugs were not included in this analysis. All CMs were classified according to The Anatomical Therapeutic Chemical (ATC) Classification System.

Results: The cohort comprised of 395 women (59.6%). Mean age at onset of epilepsy was 19.6 years. 361 patients (54,4%) were on antiepileptic drug (AED) monotherapy, 251 (37,9%) were in remission. The most frequently used (in monotherapy or polytherapy) AEDs were: valproate in 329 (49,6%) patients, levetiracetam in 225 (33,9%), lamotrigine in 148 (22,3%) and carbamazepine in 130 (19,6%). 127 (19,2%) patients took enzyme inducing AEDs. 265 (40%) patient used at least one CMs. 219 (33%) patients used somatic comedication, 95 (14,3%) used psychiatric medication. Cardiovascular drugs (30,1%), neurological drugs other than AEDs (23,2%), and systemic hormonal preparations exl. sex hormones and insulins (8,6%) were most commonly used. Of psychiatric comedication, 7,6% patients took psycholeptics, and 9,1% psychoanaleptics. The most commonly used single drugs were levothyroxine, metoprolol, simvastatin ,atorvastatin and acetylsalicylic acid. Total drug load including AEDs and CMs was 1 to 12 drugs per patient. Patients taking CMs were older ($p<0.001$) than patients not receiving any CMs, had earlier age at epilepsy onset ($p=0,021$), had more frequent seizures ($p=0,004$) and took more AEDs ($p=0,035$)

Conclusions: The results confirm that patients with epilepsy commonly take CMs. The patients in this study used up to 12 drugs, which indicates the need for close monitoring of potential pharmacodynamic and pharmacokinetic interactions, and should challenge clinicians to achieve a simpler pharmacotherapy.

ZEBRAFISH-BASED DISCOVERY OF ANTISEIZURE COMPOUNDS FROM THE RED SEA

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In search for novel antiseizure drugs (ASDs), the European FP7-funded PharmaSea project used zebrafish embryos and larvae as a drug discovery platform to screen marine natural products to identify promising antiseizure hits in vivo for further development. Within the framework of this project, 7 known compounds were isolated from a bioactive marine fungus from the Red Sea and their antiseizure activity was evaluated in the larval zebrafish PTZ seizure model. Compounds A and B were identified as antiseizure hits, while their close chemical analogues were inactive. Besides, electrophysiological analysis from the zebrafish midbrain demonstrated that compounds A and B also ameliorate PTZ-induced epileptiform discharges. Next, to determine whether these findings translate to mammalians, both compounds were analyzed in the mouse 6-Hz (44 mA) psychomotor seizure model. They lowered the seizure duration dose-dependently, thereby confirming their antiseizure properties and suggesting activity against drug-resistant seizures. Finally, in a thorough ADMET assessment, compounds A and B were found to be drug-like. Based on the prominent antiseizure activity in both species and the drug-likeness, we propose these antiseizure hits as lead compounds that are worth further investigation for the treatment of epileptic seizures. This study not only provides the first evidence of antiseizure activity of this compound class, but also demonstrates the value of the zebrafish model in (marine) natural product drug discovery in general, and for ASD discovery in particular.

EFFICACY AND TOLERABILITY OF ADJUVANT LACOSAMIDE: THE ROLE OF CLINICAL CHARACTERISTICS AND MECHANISMS OF ACTION OF CONCOMITANT AED

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Objective: To analyse the effectiveness and long-term tolerability of adjuvant lacosamide (LCM) in a multicentre cohort. We aim to assess outcomes of LCM-containing anti-epileptic drug (AED) combinations based upon 'mechanism of action' (MoA) and patient's clinical features.

Methods: Consecutive patients commenced on LCM, with focal epilepsy were identified from three Australian hospitals. 12-month efficacy endpoints were a greater than 50% reduction in seizure frequency (responders) and seizure freedom. Tolerability endpoints were cessation of LCM for any reason, cessation due to side-effects and censoring due to inefficacy. Outcomes were assessed according to concomitant AED according to their MoA and the clinical risk factor profile.

Results: 310 patients were analysed and followed for median 17.3 months. 299 (97%) had drug resistant epilepsy and 155 (50%) had tried more than 7 AEDs at LCM commencement. Adjuvant LCM was associated with responder and seizure freedom rate of 29% and 9% respectively at 12 months. Lower baseline seizure frequency, a prior 6-month period of seizure freedom at any time since epilepsy diagnosis and being on fewer concomitant AEDs were predictive of 12-month seizure freedom. Previous focal to bilateral tonic clonic seizures, lower baseline seizure frequency and concomitant AED reduction after LCM commencement were associated with improved LCM tolerability. No specific MoA AED combinations offered any efficacy or tolerability advantage.

Significance: Adjuvant LCM is associated with seizure freedom rates of 9% at 12 months after commencement and is predicted by lower prior seizure frequency, a period of 6 months or longer of seizure freedom since diagnosis and fewer concomitant AED. While the broad MoA of concomitant AED did not influence efficacy or tolerability outcomes, we have provided a framework that may be utilised in future studies to help identify optimal synergistic AED combinations.

SUSCEPTIBILITY GENES FOR VPA-INDUCED CONGENITAL MALFORMATIONS

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Ever since an association between in utero Depakote (Valproic Acid, VPA) exposure and an increased risk for neural tube defects (NTDs) was established 30+ years ago, efforts have been underway to identify susceptibility genes that place selected embryos at increased risk for congenital malformations. VPA is known to increase spina bifida risk in human populations by more than 10-fold. It is critically important to understand the underlying teratogenic mechanisms by which VPA increases the NTDs risk in order to prevent VPA exposure to high-risk mother-child pairs. Identifying which genes were responsible for sensitivity to VPA induced NTDs would have an immediate translational impact on patient care. However, determining which genes are responsible for the VPA induced NTDs remains unknown.

In mice, VPA increases the risk of exencephaly, an anterior NTD, and the degree of susceptibility depends on the genetic background of the mouse strain exposed. Since the early 1980s, we have developed two mice strains who respond differently to maternal VPA treatment. One strain (C57BL/6J) is resistant to VPA, with only a modest portion (10%) of the exposed embryos present with NTDs. The SWV/Fnn inbred mouse strain is highly sensitive to in utero VPA exposure, with 80% of the embryos having NTDs after the embryos are exposed to VPA at E8.5. Performing a series of linkage studies, we were able to map purported sensitivity genes to a 6Mb chromosomal region located on chromosome 7, which are responsible for VPA interactions in the SWV/Fnn embryos. To further this initial investigation, we performed whole genome sequencing (WGS) in VPA-exposed embryos from these two strains, and called genetic variants including both single nucleotide variants (SNVs) and copy number variants (CNVs) that differed between these strains. Using SNVs identified from WGS, we fine mapped a SNP in SOX6 which is we believe is associated with increasing the risk for VPA-induced NTDs. We demonstrated that SOX6 is downregulated in embryos 4-hours post-VPA injection. Allelic expression imbalance demonstrated that expression of the two alleles (C/T) for the SNP in question was significantly different.

This represents the first significant candidate sensitivity gene for VPA teratogenicity after some 30 years of experimentation. Our finding is important because VPA is not only increase risk for NTDs but also increase risk for other birth defects and autism. Knowing which genes and variants are responsible for the VPA induced birth defects will help to prevent these birth defects.

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ALTERNATIVE NKCC1-INHIBITORS FOR TREATMENT OF SEIZURES? PHARMACOKINETIC PROPERTIES OF BUMETANIDE VS. TORASEMIDE AND AZOSEMIDE

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The NKCC1 inhibitor bumetanide in combination with the GABA-enhancing anti-seizure drug phenobarbital proved to have better anticonvulsant efficacy than phenobarbital alone in an animal model of neonatal seizures (CLEARY et al., 2013). In a clinical trial the same combination, however, did not meet efficacy goals (PRESSLER et al., 2015). Because of its physicochemical properties and high plasma protein binding, bumetanide only poorly penetrates into the brain and, in addition, is substrate of efflux transporters at the blood-brain barrier (BBB). This study assessed the unbound fraction fu and the brain:plasma ratios Kp of bumetanide and two alternative NKCC1 inhibitors, azosemide and torasemide, which, in contrast to bumetanide, are not acidic. Furthermore, the unbound brain to unbound plasma concentration ratio Kp,uu was calculated (REICHEL, 2009). It was also examined whether the substances are substrates of probenecid-sensitive efflux transporters at the BBB.

In vitro, equilibrium dialysis was performed with plasma and homogenized brain tissue from female CD1-mice against PBS. Drug concentrations were quantified using HPLC after 4 hours when equilibrium was reached. In vivo, substances were injected i.v. (1 mg/kg and 10 mg/kg respectively), and drugs were analyzed in plasma and brain tissue with HPLC. To assess efflux from the brain, animals were injected with probenecid (150 µg) into the right cerebral ventricle during anesthesia with isoflurane, followed immediately by i.v. injection of either substance and decapitation 15 min thereafter, and quantification by HPLC.

The in vitro experiments indicate that all three drugs are highly bound to plasma proteins and brain lipids, which markedly reduces the free, functionally relevant drug levels in the brain. In vivo results up to this point indicate efflux-mechanisms at the BBB for all three tested substances (Kp-values <0.1). Compared to vehicle controls, brain concentrations were increased in animals that received probenecid by a factor of 1.52 for bumetanide, 1.47 for azosemide and 1.45 for torasemide respectively, showing that all substances are substrates of probenecid-sensitive efflux-transporters at the BBB.

In a Xenopus laevis oocyte expression system, torasemide was less effective than bumetanide to inhibit NKCC1 (IC50 6.18 vs. 0.945 µM), while azosemide was more effective than bumetanide (IC50 0.246 µM).

In conclusion, we characterized the NKCC1 inhibitory potency and brain kinetics of two clinically approved loop diuretics (azosemide, torasemide) that, in contrast to bumetanide, have not been previously used for treatment of brain diseases such as seizures or epilepsy. Clinically, azosemide has a much longer duration of action than bumetanide, which would be an advantage for treatment of brain diseases. We therefore plan to characterize the effects of azosemide and torasemide on the anti-seizure activity of phenobarbital in epileptic mice to further characterize whether any of these drugs may be an alternative to bumetanide for the treatment of neurological diseases.

THE NOVEL, SPECIFIC, BRAIN PENETRANT MTOR AND PI3K/MTOR INHIBITORS PQR620 AND PQR530 PREVENT EPILEPTIC SEIZURES IN A TSC MOUSE MODEL

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Tuberous Sclerosis Complex (TSC) is a genetic disorder that results from loss-of-function mutations in TSC1 and TSC2 genes causing tumor formation in different organs, but also epilepsy, developmental delay, and autism. Seizures are observed in 80-90% of TSC patients, most prominently during childhood.

Two ATP-competitive inhibitors of the mTOR pathway have been evaluated for their potential to reduce seizures in the Tsc1flox/flox-GFAP-Cre (TSC-GFAP [glial fibrillary acidic protein]) mouse model of TSC-induced epilepsy. PQR530 is a potent, selective dual PI3K/mTOR inhibitor exhibiting Kd values for mTOR and all class I PI3K isoforms in the low nanomolar range. PQR620 specifically binds to mTOR complex 1 and complex 2 (Kd=0.3 nM). Physicochemical properties of both compounds enable for good oral bioavailability and excellent brain penetration. Good tolerability has been observed for PQR620 (mouse MTD=150 mg/kg) and PQR530 (mouse MTD=25 mg/kg).

TSC-GFAP mice were implanted with EEG head-mounts, and EEG-video was monitored for electrographic seizures from postnatal day (PND) 21-53. Three groups of animals were treated with vehicle, PQR620 (100 mg/kg) or PQR530 (25 mg/kg) by oral gavage daily from PND 21-55. Vehicle-treated TSC-GFAP mice suffered robust electrographic seizures (n=150), mice treated with 25 mg/kg PQR530 or 100 mg/kg PQR620 showed significantly lower numbers of seizures (n=8, n=2, respectively). Survival and bodyweight of animals was not significantly altered within the timeframe of the study. The long-term impact of PI3K/mTOR therapy is currently under further investigation.

The novel mTOR inhibitor PQR620 and the PI3K/mTOR inhibitor PQR530 potently and specifically inhibit mTOR signaling via an ATP-competitive mode of action. Both compounds strongly suppress seizures in a TSC mouse model. Physicochemical and pharmacological properties of PQR620 and PQR530 allow for further preclinical development of the compounds.

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TOLERABILITY, EFFICACY AND RETENTION RATE OF BRV IN PATIENTS PREVIOUSLY TREATED WITH LEV

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We evaluated the potential for improvement of tolerability and efficacy by the use of Brivaracetam (BRV) in patients directly switched from Levetiracetam (LEV) and in patients who were treated witch LEV at some time in the past.
102 patients (49 male; mean age 42.5 y ± 15.8 y) treated with BRV at the Freiburg Epilepsy Center with a minimum follow up of 6 months or with prior end of treatment were included. 83 patients presented with structural epilepsy, 11 with genetic epilepsy, and 8 with epilepsy of unknown etiology. The mean duration of epilepsy was 17.6 y, the mean number of co-applied AED was 1.6, there had been pharmacoresistance to a mean of 4.9 prior AED treatments. 60 patients underwent an overnight switch from Levetiracetam (LEV; mean dosage: 2161 mg/day) and 42 patients were add-treated with other baseline AED but had LEV at some time in the past.
Mean target dose of BRV at the beginning of treatment was 115.3 mg/day (median, 100 mg/day), at last follow up 157.9mg/day (median, 150mg/day). 27 patients discontinued treatment with BRV after a mean follow up time of 117.8 (± 133.9) days. The mean duration of treatment for the remaining 75 patients was 367.8 (± 102.1) days.
Switching from LEV to BRV led to seizure relapse in 1 out of 15 patients who had been completely controlled before. For 46 patients seizures could be quantified for a 3 months baseline and a 6 months follow up period. 10 patients (21.7%) had an increase in seizures, 15 (32.6 %) had a decrease by more than 50% in seizure frequency yet were not completely controlled, and 10 patients (21.7%) were newly seizure-free.
49 (81.7 %) of patients switched overnight from LEV to BRIV had psychiatric side effects during treatment with LEV; after switch to BRV in 33 patients (67.3%) psychiatric symptoms were reported as improved. From the 42 patients with LEV in the past, 8 (19 %) had psychiatric side effects documented during treatment with BRV resulting in end of treatment in all cases. 4 of these patients had psychiatric side effects documented during prior exposure to LEV.
Overall, intolerability or ineffectiveness of prior treatment with LEV seems not to preclude a good response to BRV. BRV was substantially better tolerated than LEV and an overnight treatment change did not endanger a preexisting seizure freedom.

IMPLEMENTATION OF THERAPEUTIC DRUG MONITORING TO STUDY PHARMACOKINETIC VARIABILITY OF LACOSAMIDE IN CHILDREN AND ADOLESCENTS

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Background: Lacosamide is one of the most recently approved antiepileptic drugs (AEDs) with indication monotherapy and add-on in adults, adolescents and children from 4 years with focal epilepsy. Data on pharmacokinetic variability in young patients are scarce, since they are most often not included in clinical studies or exposed to drugs early after approval of new drugs. The purpose of this study was to characterise pharmacokinetic variability of lacosamide in children and adolescents by use of therapeutic drug monitoring (TDM)-data.

Method: Retrospective anonymous data from the TDM-database at two national centers for epilepsy, Norway and Denmark were collected (2012-2017). The serum samples were drawn at steady-state, drug-fasting in the morning. The study was approved by the regional ethics committee.

Results: There were 144 patients included, 4-17 years (56 girls/88 boys). The daily dose of lacosamide varied from 100 to 600 mg/day. Mean serum concentration was 22 (range 4-53) mmol/L. The concentration/dose-ratio varied 12-fold, from 0.015-0.187 mmol/L/mg. When the children were grouped by age, the variability was: 4-fold in children <8 years (n=7), 7-fold in children 8-12 years (n=38), and 10-fold in adolescents, 13-17 years (n=99). There were 84% of patients (n=123) with serum concentrations within the reference range (10-40 mmol/L), where we have previously shown that adults most often show efficacy. We observed less variability than previously in adults, which may indicate a closer follow-up in children.

Conclusion: There was extensive pharmacokinetic variability of lacosamide among children and adolescents. Most patients had serum concentrations within the reference range. Lacosamide was most widely used in older children and adolescents. Implementation of TDM for new drugs contributes to early characterisation of pharmacokinetic variability in special patient groups as children and individualisation of pharmacotherapy.

HYBRID COMPOUNDS BASED ON THE PYRROLIDINE-2,5-DIONE SCAFFOLD AS CANDIDATES FOR NEW BROAD-SPECTRUM ANTICONVULSANTS

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Since many years, the design of new multi-target compounds have generated considerable interest owing to their advantages in the treatment of multifactorial diseases (characterized by complex pathomechanism), and also health disorders linked to the issues of drug resistance. No doubt, epilepsy, which is recognized as the most common and debilitating neurological disorder, fulfills both the aforementioned conditions. It should be emphasized here that about one third of the patients with epilepsy show resistance to antiepileptic drugs (AEDs). Thus, the multifunctional (or multi-target) AEDs such as the valproic acid belong to the most often used anticonvulsants, especially valuable in case of different epilepsy types and epileptic seizures with undefined etiology (1).The combination of different mechanisms of action tends to be beneficial also in case of refractory epilepsy. Therefore, the multi-target pharmacology of AEDs seems to guarantee their wide spectrum of indications and high therapeutic utility compared with single-target drugs, which are dedicated for the treatment of some specific epilepsy types or syndromes. Taking assumptions of multi-target strategy into consideration and with the aim of obtaining new broad-spectrum anticonvulsants, in the previous studies, we proposed the structure of hybrid molecules derived from pyrrolidine-2,5-dione core. These hybrid molecules fuse on the single core structure the chemical fragments of different ADEs such as ethosuximide, levetiracetam, and lacosamide. As a result, the hybridization process yielded substances with potent and broad-spectrum anticonvulsant activity that joined pharmacological properties of all AEDs creating hybrid structures. Thus they were effective in the “classic” animal models of epilepsy, that is maximal electroshock seizure test (MES) and subcutaneous pentylenetetrazole seizure test (scPTZ), and also in the 6 Hz model (32 mA) of partial seizures (2,3).

Considering beneficial anticonvulsant properties of the aforementioned hybrids, in the current studies we have developed the new series of hybrid molecules based on the pyrrolidine-2,5-dione core fragment. These compounds revealed potent anticonvulsant activity in the MES, scPTZ, and 6 Hz (32 mA) seizure models as well as in the 6 Hz (44 mA) test, which is recognized as model of pharmacoresistant epilepsy.

Furthermore, these derivatives did not affect the activity of CYP2D6 and CYP3A4 cytochromes as well as were stable on human liver microsomes (HLMs) in the in vitro assays.

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ANTICONVULSANT ACTION OF CANNABIDIOL IN IMMATURE RATS

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Cannabinoids were demonstrated to have an anticonvulsant action in adult animals. To studÿ their effects in immature laboratory animals we tested an action of cannabidiol (CBD) and delta9tetrahydrocannabinol (THC) against pentylenetetrazol-induced convulsions in 12-day-old rat pups. In parallel, we studied also plasma and brain levels of CBD and THC for 24 hours after a single administration.

CBD was emulgated in PBS pH7.4 with 2% solution of Tween 80 using sonification at 50°C for one hour and injected ip at doses of 10 or 60 mg/kg. Controls received vehicle in corresponding volume Sixty minutes later pentylentetrazol (PTZ) was injected (100 mg/kg s.c.). Rats were observed in individual cages for 30 min after PTZ injection and incidence, type and latency of seizures were registered. In parallel, plasma and brain levels of CBD and its metabolite THC were assessed after administration of the same doses of CBD at 5 intervals from 30 min up to 24 hrs. To evaluate possible participation of THC in anticonvulsant effects of CBD, THC in doses of 1 or 5 mg/kg i.p. (i.e. doses that produce the comparable levels of THC in both plasma and brain as CBD in a dose of 60 mg/kg) was administered to additional groups of animals. Marked anticonvulsant action of CBD (abolition of the tonic phase of generalized seizures) was observed after the 60-mg/kg dose, lower dose as well as both doses of THC resulted in nonsignificant changes.

Plasma as well as brain levels of CBD were six times higher after the 60- than after the 10-mg/kg dose. A decrease was observed after the lower dose earlier in plasma than in brain but brain concentration (especially after the higher dose) remained stable for at least 4 hours but it was were never higher than plasma concentration. Both doses of THC resulted in higher brain than plasma levels one and two hours after administration, suggesting accumulation of THC in the brain of immature rats.

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FINDING A LOST SLEEP MIGHT BE MORE REJOICING: A REAL-WORLD EXPERIENCE WITH PERAMPANEL IN THE PATIENT WITH SUPER-REFRACTORY FOCAL EPILEPSY

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Add-on Perampanel (PER) treatment can achieve clinically significant improvement, or even seizure freedom, in more than one-third of the patients with refractory epilepsies. Previous studies showed PER achieved seizure freedom in about 5 to 10% of the patients. Putting aside the number, I would share my experience in a girl with super-refractory focal epilepsy. She is a 17 year old girl with focal epilepsy since February, 2012. She has been presenting with dialeptic seizures, which usually last about 10 minutes, several times a day. She was relatively good at school despite the daily seizures. Neurological exam was unremarkable. EEG showed frequent spike-and-wave discharges from fronto-central or temporal regions with right predominance. Brain MRI revealed a choroid fissure cyst with mass effect on the right hippocampal head. Six famous antiepileptic drugs have been tried without success. She was on levetiracetam, lamotrigine and clobazam and was very reluctant on epilepsy surgery, Vagus Nerve Stimulation or ketogenic diet. 2mg per day of PER was added, but was off all by herself due to dizziness in a few days. After the persevering persuasion for a few months, PER was started again and was increased to 4 mg per day by 2mg per month. She has been seizure free ever since. The seizure freedom surely changed her life. In real practice, we have to rejoice it when we find a lost one out of a hundred sheep who achieve the seizure freedom. A single life that has been completely changed from a certain treatment should not be overlooked.

ANTICONVULSANT ACTION OF PREGNANOLONE SULFATE AND PREGNANOLONE GLUTAMATE IN IMMATURE RATS

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Anticonvulsant action of neurosteroids (e.g.allopregnanolone) was described in adult as well as immature rats. We decided to study a possible anticonvulsant action of another neurosteroid pregnanolonsulfate (PS) and its analog pregnanolonglutamate (PG) in pentylenetetrazol (PTZ)-induced convulsions.
Two age groups (12 and 25 days old) were pretreated intraperitoneally with either neurosteroid at doses of 1, 5, 10, and 20 mg/kg. Twenty minutes later PTZ was injected subcutaneously at a dose of 100 mg/kg. Generalized tonic-clonic seizures (GTCS) were observed in both age groups, minimal clonic seizures only in 25-day-old animals. Latency and incidence of seizures were evaluated, seizure severity was calculated according to a 5-point scale.
Action of both drugs was more marked in 12-day-old than in older rats. The 5-mg/kg dose of either neurosteroid abolished the tonic phase of generalized seizures in the younger group, the 20-mg/kg dose completely suppressed generalized seizures. Latency of generalized seizures was significantly prolonged only by the 10-mg/kg dose of PG. Specific action on the tonic phase was not seen in 25-day-old animals, GTCS were abolished by the highest dose of PG, their incidence tended to decrease with the 10- and 20-mg/kg doses of PS. Severity of seizures decrease in relation to changes in GTCS. Minimal clonic seizures were not affected by either neurosteroid.
Stronger action of both drugs in 12- than in 25-day-old rats mirht be due to developmental differences in major neurotransmitter systems (GABA and glutamateergic). Immaturity of blood-brain barrier might also play a role.
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RETENTION RATE AND OUTCOME-RELATED FACTORS OF PERAMPANEL: A REAL-LIFE POPULATION STUDY

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Purpose: To evaluate the effectiveness of perampanel (PER) in adolescents and adults with drug-resistant epilepsy, using time to treatment failure as the outcome measure.

Method: Epileptic patients receiving PER from May 2015 to December 2017 were enrolled in this multicenter retrospective observational cohort study. Kaplan-Meier survival curves were made to assess the time to PER failure, defined as discontinuation of PER. The impact of other factors including age, epileptic syndrome, duration of epilepsy, concomitant and previous treatments, titration, dosage, and neuropsychological comorbidities were evaluated using Cox Proportional Hazard Methods.

Results: The series comprised 143 patients (65 females), with median age at epilepsy onset of 10 years (interquartile range [IQR]: 1 month-59 years) and a median time of disease duration prior PER of 19 years (IQR 11-32). The most frequent epileptic syndromes were: drug-resistant focal epilepsy (117 patients, 81.82%) and Lennox-Gastaut syndrome (20 patients, 14%). All patients received previous (median 6, IQR 4-9) and concomitant (median 2.5, IQR 2-3) treatments. The probability of remaining on PER was 61% at 12 months, and 47% at 24 months. PER was discontinued by 66 (46.15%) due to inefficacy (54%), side effects (28%), or both (16%). Nine patients (6%) achieved seizure freedom, and 24 (17%) gained significant (≥ 50%) seizure reduction. The presence of intellectual disability was significantly associated with PER failure (HR 1.71, 95% CI 1.04 – 2.81, p=0.03).

Conclusion: This study provides observational evidence for treatment persistence of PER in drug-resistant epilepsy using time to treatment failure. The presence of neuropsychological comorbidities should be kept in mind to optimize the use of PER in clinical setting.

MAY PSYCHIATRIC DISORDERS PREDICT THE RESPONSE TO ANTIEPILEPTIC DRUGS?

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Purpose: Psychiatric and behavioural adverse events related to antiepileptic drugs (AEDs) are a major concern due to the impact on efficacy. Moreover, they are more likely to occur in patients with psychiatric disorder background (PDB). The aim of this study is to evaluate the impact of PDB on the anger and mood status in patients with focal epilepsy that were switch to a new treatment.

Methods: Two databases from two prospective studies were unified to make a sub-analysis based on the psychiatric history. Patients with focal onset seizures, ≥18-year-old and ≤2AEDs at baseline were recruited. They started different AEDs at baseline and completed the State-Trait Anger with the Expression Inventory 2TM (Staxi-2TM), Hospital Anxiety and Depression Scale and Quality of Life in epilepsy inventory (QOLIE-10). The scale control was collected between three and six months later.

Results: We recruited 104 patients, 47.1% women, mean age 48.5 (range 18-84), mean age at seizure onset 35.3 years (standard deviation 21), and median epilepsy duration 5.5 years (range 0-64). 61.2% were focal epilepsy and 38.8% had secondarily generalized seizures; 45.1% had temporal lobe epilepsy; 46.5% were of unknown etiology.

28.2% reported previous psychiatric disorders, and 46% were switched to a new AED due to side effects or lack of efficacy (41.3%). Patients with and without PDB improved their seizures ($p<0.001$ and $p=0.001$, respectively). Only patients without PDB improved anger expression index ($p=0.003$), and also on anger trait ($p<0.001$). Anxiety and depression also improved only on those patients without PDB ($p<0.001$). Patients ≤50 year-old did a better performance on anger expression index ($p<0.001$) and QoLIE-10 ($p<0.001$) while older patients did not show differences.

Conclusions: The history of psychiatric disorder and age >50 are single factors that shows a worse anger, mood and quality of life outcomes related to AED treatment response.

SYNTHESIS AND ANTICONVULSANT ACTIVITY OF NEW HYBRID COMPOUNDS DERIVED FROM 5,5-DISUBSTITUTED OR 5-SPIRO-IMIDAZOLIDINE-2,4-DIONE CORE AND MORPHOLINE MOIETY

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Epilepsy is a common neurological disorder, affecting approximately 70 million people world-wide. It is characterized by unprovoked seizures, which can be focal or generalized in nature. Despite the ongoing advance in epilepsy research, about one-third of epileptic patients is refractory to pharmacotherapy. [1] Thus, new approach in designing new anticonvulsant molecules like multifunctional (hybrid) ligands is required to obtain more effective and safer drugs. In this approach, two or more different structural elements of active drugs are merged into one chemical entity and that could improve anticonvulsant activity and safety.

Searching for the new safer and more effective antiepileptic drug, we combine in one structure the core heterocyclic ring of imidazolidine-2,4-dione with morpholine moiety which is presented in new anticonvulsant drug imepitoin [2] The newly designed molecules differ in substituent at position-5 of the hydantoin (imidazolidine-2,4-dione) and the length of the linker (one or three methylene group) between imidazolidine-2,4-dione ring and morpholine moiety. The investigated compounds were prepared in Bucherer-Bergs cyclization followed by Mannich reactions or alkylation with 1-bromo-3-chloropropan and condensation with morpholine moiety.

The final compounds were evaluated for their anticonvulsant activity within the Antiepileptic Drug Development (ADD) Program in Epilepsy Branch, Neurological Disorders Program, National Institute of the Neurological and Communicative Disorders and Stroke (NIH/NINDS), Rockville, MD, USA, by using of the procedures described elsewhere [3]. The preliminary pharmacological screening revealed anticonvulsant activity in the MES and/or scPTZ tests. The most active were compounds with two substituents (cyklopropyl or cyclobutyl and phenyl rings) at position-5 of imidazolidine-2,4-dione and with one methylene group between hydantoin and morpholine nitrogen atoms.

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THE USE OF ZEBRAFISH AS A PROMISING PRE-RODENT MODEL IN ANTISEIZURE DRUG DISCOVERY

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Epilepsy is the most common neurological disease characterised by the presence of spontaneous, unprovoked seizures. About 70 million people worldwide suffer from epilepsy. Even though >25 anti-seizure drugs (ASDs) are on the market, seizures cannot be controlled in 30% of the patients due to pharmacoresistance (1). Despite the availability of the so-called new generation ASDs, the probability of achieving seizure freedom did not lower since the 70s (2). Besides, current ASDs often have adverse effects such as fatigue, gastrointestinal problems, hepatotoxicity, osteoporosis, and even cognitive impairment (1,3). These factors show that there is an acknowledged need for the development of new and safe ASDs that are more effective. To bridge this gap, our laboratory aims at developing a novel and proprietary class of ASD candidates, discovered in a recent collaboration with the laboratory of Organic Synthesis (KU Leuven) that showed a promising activity in two pharmacoresistant zebrafish models. Over the years, the zebrafish (Danio rerio) model has rapidly emerged as a cost-efficient and valid alternative for disease modelling and large-scale drug screening. 13 out of 21 compounds were active in the zebrafish pentylenetetrazole (PTZ) seizure model, a standard in preliminary ASD discovery due to a high level of translation to rodents (4), and 12 out of 21 compounds were active in the novel zebrafish ethyl ketopentenoate (EKP) model of pharmacoresistant seizures, with a novel mode-of-action (inhibition of glutamate decarboxylase) (5). The efficacy of promising hits will be further studied in a panel of acute mouse models of pharmacoresistant seizures, whereafter a drug lead will be selected. Afterwards, the molecular target(s) of the lead drug will be identified, and finally will be further evaluated in chronic (pharmacoresistant) rodent seizure and epilepsy models. This altogether will facilitate future preclinical drug development.

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EFFICACY AND SAFETY OF ORAL CANNABIDIOL AS ADJUNCTIVE TREATMENT FOR PEDIATRIC SUBJECTS WITH EPILEPTIC ENCEPHALOPATHY

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Purpose: to assess the efficacy and safety of cannabidiol (CBD) as an adjunctive treatment for pediatric subjects with Epileptic Encephalopathy.

Method: the trial will comprise a 4-week baseline period, 10 days of titration and the follow-up period. Patients were given oral purified CBD at 2-5 mg/kg per day, up titrated until intolerance or to a maximum dose of 20 mg/kg per day. The primary objective was to establish the safety and tolerability of CBD and the primary efficacy endpoint was asses the percentage change per 28 days from the 4-week baseline period in convulsive-seizure frequency during the follow-up period. Comparisons of the percentage change in frequency of motor seizures were done with a Mann-Whitney U test.

Results: 17 patients were enrolled; in 7 patients the EE was due to a genetic mutation (SCN1A, KCNQ2, GRIN2A, KCNB1, SCN8A, PIG-A), in 4 to a brain malformation and in the other 6 the etiology was unknown. The mean follow-up was 4.6 months. The adverse events were reported in 8 (47.0 %) above all somnolence (in 6) and diarrhea (in 4). No one discontinued treatment because of an adverse event. The median reduction in monthly motor seizures was 46.5%.

Conclusion: our findings suggest that CBD might reduce seizure frequency in pediatric patients with EE and might have an adequate safety profile.

STATUS EPILEPTICUS AFTER EXPERIMENTAL TRAUMATIC BRAIN INJURY: A NOVEL IN VIVO PLATFORM FOR TESTING TREATMENTS

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Background: Severe traumatic brain injury (sTBI) induces multiple seizures or status epilepticus (SE) in 20-30% of patients while monitored with EEG in intensive care unit at acute phase. We hypothesized that similar to sTBI in humans, sTBI in rats induced with lateral fluid-percussion injury (LFPI) will trigger post-impact SE.
Methods: Twenty-one adult Sprague-Dawley male rats were randomized into two groups: Sham-operated (n=5) or LFPI-induced severe TBI (n=16). Recording electrodes were implanted right after sTBI induction, and rats were monitored with video-EEG 24/7 for 1 month. Outcome measures included: post-impact electrographic patterns, latency to the first seizure, number and duration of electroencephalographic seizures, behavioural seizure types, and percentage of animals with SE.
Results: During the first 48 h post-TBI, all injured rats (16/16) had long-lasting epileptiform activity (spiking, periodic generalised epileptic discharges, generalised slow waves) and SE. During 120-144 h post-TBI, 25 % (4/16) were still presenting epileptiform activity. Ninety-nine percent of electrographic seizures were recorded 0-72 h post-TBI (7.6 ± 7.5 seizures, median 4.5, range 1-35). Mean latency to the first seizure was 19.6 ± 16.0 h (median 15.1, range 5.2-53.8). Mean duration of electrographic seizures was 92 ± 41 s (median 94, range 22-226). Mean behavioural seizure severity score in individual rats was 1.7 ± 2.0 (median 1, range 0-5, modified Racine scale). Thus, behaviour of the TBI animals appeared for the most of time "normal" although their EEG showed continuous epileptiform patterns. None of the Sham-operated experimental controls had SE. In the sham-group, however, we detected 20 electrographic seizures between 0-72 h post-surgery with a latency to the first seizure of 17.8 ± 0.2 h (median 17.8, range 17.7-17.9), mean seizure duration of 36 ± 10 s (median 35 s, range 17-62 s), and mean behavioural score of 1.5 ± 0.1 (median 2, range 0-3).
Conclusion: Our data demonstrates that TBI after LFPI results in post-injury long-lasting epileptiform activity and SE with minor behavioural manifestations, explaining why it has remained undiagnosed until now.

AEDS REDUCE THE UPPER PHOTOSENSITIVITY LIMIT MORE THAN THE LOWER IN PHOTOSENSITIVE PATIENTS WITH EPILEPSY – INCLUDING THOSE ON CARBAMAZEPINE.

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Introduction: The photosensitivity model is a well-known human model to determine antiepileptic properties of new AEDs as proof of principle (PoP) (Yuen ESM & Sims JR. Seizure 2014; Kasteleijn Nolst-Trenité DG, Genton P, Brandt C and Reed RC. Epilepsy Research 2017). It was clear from visual inspection of all individual photosensitivity cases treated with any AED (n = 152 patients on AEDs) that AED treatment (compared to placebo) produced a lowering of the upper photosensitivity limit, whereas the lower limit moved upwards marginally. We sought to determine whether or not a difference exists for the lower and upper photosensitivity limit when testing novel potential AEDs overall, and the magnitude of change for singular AEDs, including those dominantly prescribed for generalized and focal seizures.

Methods: Photic induced EEG responses (Photo-paroxysmal responses, PPRs) of 236 regular photosensitive patients (163 F; 69%), mean age = 20 + 10 yr (min 7, max 60 yrs) were analyzed. In all patients, standardized photic stimulation, 2 - 60 Hz, using a Grass PS 33plus had been performed with determination of upper and lower sensitivity ranges in 3 eye conditions. The PPRs for patients with vs. without AEDs were compared (t-test; Mann-Whitney; ANOVA regression analysis).

Results: Of the 236 patients with a PPR, 233 had a PPR on eye closure, 206 with eyes closed and 149 with eyes open. Most patients were on stable AEDs (152; 64%) and monotherapy (104; 44%), with VPA in 62 cases, CBZ in 18 and other AEDs in 24. Forty eight patients (20%) took 2-4 AEDs, with PB as most often prescribed drug in combination (18), followed by ESM (14), LTG (10), or one of the benzodiazepines DZP, CNZ or CLB (9), PHT (4) and VGB (1). The upper sensitivity limit decreased with AED(s) treatment; this was statistically significant in all eye conditions (for eye closure, $p = 0.002$, for eyes closed, $p = 0.008$ and for eyes open, $p = 0.04$). Similar movement in the upper threshold was seen for all AEDs tested, including CBZ.

Discussion: This phenomenon is also seen in individual cases participating in PoP studies of new AEDs, in which the same patient is investigated with and without trial medication. Determination of the upper limit may be sufficient in PoP new AED trials when rapid testing is required, which reduces the total number of photic stimulations by half. This has advantages for the patient and should reduce the costs of the PoP-trial.

Conclusion: The upper sensitivity limit of photosensitive patients is substantially lowered in patients with AED(s) treatment. Lowering of the upper sensitivity limit is also seen with CBZ-treated patients.

DRUG DISCOVERY PROGRAMS FOR THE DEVELOPMENT OF NEW ANTIEPILEPTIC DRUGS USING THE MTLE MOUSE AND THE GAERS MODELS

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Mesio temporal lobe epilepsy (MTLE) is one of the most prominent forms of focal drug resistant epilepsy. A better understanding of mechanisms underlying this resistance would help to identify new active compounds. The MTLE Mouse model is a chemically induced model of mesial temporal lobe epilepsy. A unique intrahippocampal injection of kainate induces a status epilepticus followed by a period of epileptogenesis of two to three weeks. Thereafter epileptic mice display non convulsive focal spontaneous recurrent hippocampal discharges, with rare generalisations (2-3 per week).

Epilepsy absence is a generalised epilepsy involving the thalamo-cortical loop and is characterised by the occurrence of Spike and Wave Discharges. The GAERS model is recognised as a true translational model for epilepsy absence as the pharmacology in the model is parallel to the one observed in human patients.

SynapCell has developed translational AED Discovery programs that has assessed more than 500 drug candidates in the last 13 years. A first step to validate the first application on the market for drug resistant focal epilepsies is proposed with the MTLE mouse model. The second step consists in the evaluation of AED candidates for their therapeutic or aggravating effects on epilepsy absence with the GAERS model.

A screening protocol was developed with the MTLE mouse model and is used to test a library of 6 compounds over 3 weeks in order to identify the most promising drugs based on their effect on hippocampal paroxysmal discharges. This elementary unit can be thereafter multiplied to enhance the screening capacity.

Then, several protocols allow the in depth study of the pharmacodynamic properties of lead compounds : the dose-response, the long term anti-epileptic effect and even the anti-epileptogenic effect of an AED candidate can be evaluated through dedicated protocols with this versatile model.

Finally, AED candidates are tested on the GAERS model to validate and de-risk the therapeutic potential in generalised epilepsy.

SynapCell offers with the MTLE mouse and the GAERS models powerful tools for preclinical evaluation and predictive clinical validation of new AEDs, using clinical like protocols and customized solutions.

PROGRESS TOWARDS INTRANASAL DIAZEPAM DELIVERY USING AN AQUEOUS PRODRUG/ENZYME COMBINATION

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Due to the time delay and objections, respectively, associated with iv and rectal benzodiazepine (BZD) therapy for seizure emergencies, there has been substantial interest in developing intranasal BZD formulations. A successful intranasal delivery system should be convenient and the vehicle should be nontoxic. Further, drug absorption should be complete and consistent, with an onset of effect that is more rapid than rectal diazepam. Presently, there are at least two intranasal formulations in Phase III or beyond in their development. These formulations contain organic solubilizing additives, which concentrate the drug in a small enough volume for a single dose to be administered intranasally. We contend that the use of organic vehicles poses two disadvantages. First, the organic components are likely to be irritating and potentially toxic to nasal and systemic tissues, or to brain tissue when there is direct nose-to-brain transport. Second, enhanced solubilization of drug will likely increase its residence time in the nasal cavity and delay absorption. To circumvent these issues, we propose a platform system for intranasal BZD delivery, in which water-soluble, open-ring peptide prodrugs are coadministered with a converting aminopeptidase. These components are stored in dry, nonreacting form but are rapidly mixed with an aqueous solution just before administration. Conversion of the prodrug to active compound then occurs during mixing and within the nasal cavity. Because conversion is rapid, the active drug is produced in a high concentration in a supersaturated state, which further promotes rapid absorption across the nasal mucosal membrane. We will report progress using avizafone (AVF), a lysil prodrug of diazepam (DZP), together with human aminopeptidase B (hAPB). We have demonstrated in vitro that hAPB converts AVF to DZP at a rate depending on hAPB concentration, and that DZP reaches concentrations greater than nine-fold above saturation, after which an amorphous precipitate appears. Crystallization of the amorphous precipitate requires days, so the precipitate is in rapid exchange with the aqueous DZP. The increased chemical activity of aqueous DZP enables proportionally accelerated transport across model monolayer membranes. We have also conducted a set of studies in rats, which

demonstrate both rapid absorption (tmax=2-20 min, Cmax=200-500 ng/ml following 1 mg/kg dose) and appearance of DZP in brain following intranasal administration (e.g. 110 ng/ml at 2 min following 1 mg/kg dose), with minimal acute intranasal histopathological toxicity. Finally, we have synthesized an analogous lysil prodrug of midazolam (MDZpro). The results of the in vitro studies with MDZpro/hAPB roughly parallel those obtained with AVF/hAPB. These studies support continued development of the proposed platform.

FV-082: A SAFER ORALLY ACTIVE BROAD SPECTRUM ANTI-EPILEPTIC DRUG CANDIDATE

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Introduction and rationale for development: Broad spectrum AEDs are valued for their potential to treat focal and generalized epilepsy syndromes and some of them have been employed for a variety of CNS diseases including migraine, bipolar disorder and neuropathic pain. However, the benefits of AEDs have been marred by unintended CNS side effects. Combining Fluorinov Pharma's proprietary chemistry platform with NIH's in vivo phenotypic screening strategy, three novel AED drug candidates were identified, including FV-082, exhibiting superior efficacy and preclinical safety profiles compared to prototypical AEDs. As such, FV-082 was selected by the NIH's Anticonvulsant Screening Program (ASP) as a promising lead drug candidate for the treatment of non-refractory and pharmacoresistant epilepsy.
Pharmacology: FV-082 was screened across all available in vitro and rodent seizure models at ASP, and was found to have broad spectrum anti-seizure activity and a safety profile superior to that of valproic acid, gabapentin and levetiracetam. FV-082 has an ED50 of 20.1 ± 0.7 (p.o.) in a rat MES model and 17.4 ± 0.6 mg/kg (i.p) in a mouse 6 Hz epilepsy model. FV-082 prevented seizures induced by sound in the Frings audiogenic seizure-susceptible mouse model with an ED50 value of 13.0 ± 2.0 mg/kg i.p. In addition, FV-082 displayed significant efficacy in corneal kindled mice, kindled rat amygdala and hippocampal seizures models. Importantly, FV-082 was also found to limit seizure spread and elevate seizure threshold in the Mesial Temporal Lobe Epilepsy (MTLE) acute model of pharmacoresistant epilepsy. Furthermore, administration of a single dose of FV-082 showed robust efficacy in models of neuropathic pain, such as spinal nerve injury (50 mg/kg i.p) and formalin induced inflammatory pain (71 mg/kg i.p).
Safety and toxicology: Safety assessment of FV-082 suggests no interaction with the major CYP isozymes when tested at concentrations up to 500 µM and no functional hERG activity when tested at concentrations up to 20 µM. A telemetry cardiopulmonary safety study, under GLP conditions, following oral dosing (120 mg/kg single dose) of FV-082 in female beagle dogs showed no evidence of cardiopulmonary pharmacological adverse effect. FV-082 exhibits a considerably broader CNS therapeutic index compared to currently available and marketed AEDs. FV-082 was well tolerated in a 28-day repeated oral dosing/14 day recovery study in rats. Dosing regimens ranged from 0–800 mg/kg/day. No immediate reactions were noted and all animals in the study survived the 28-day treatment period. There was

no indication of organ damage in gross pathology samples extracted from animals on day 29 (day after final dose) and day 43 (last day of recovery).

Pharmacokinetics: In-vivo pharmacokinetic studies in mouse, rat and dog at a dose of 20 mg/kg revealed that FV-082 has high oral bioavailability (100%, 84% and 34% in mouse, rat and dog, respectively), with corresponding half-life values of 1, 3, and 4 hrs in each of the aforementioned species. In addition, a linear relationship between dose and drug exposure, as measured by Cmax and AUC, was observed.

Mechanism(s) of action: Ion channel and G-protein coupled receptors profiling across 100 known ion channels, transporters suggest that several mechanisms contribute to the pharmacological profile of FV-082 but that no single mechanism is likely to be a major contributor. FV-082 inhibited voltage-gated Na+ channel Nav1.8, as well as androgen receptor (AR) and human recombinant enzyme monoamine-oxidase-B (MAO-B).

Planned studies: Ongoing studies are directed towards models of pharmacoresistant epilepsy using oral chronic dosing in a kainic acid-induced status epilepticus rat model. Furthermore, IND-enabling studies in higher species, such as non-human primates, are planned. Also, a convenient and cost effective manufacturing process for FV-082 has been developed, allowing for multi-kilogram scale synthesis.

FV-137: NOVEL, ORALLY ACTIVE BROAD SPECTRUM DRUG CANDIDATE WITH UNIQUE MOA FOR EPILEPSY AND PAIN

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Introduction and rationale for development: Broad spectrum AEDs are valued for their potential to treat refractory epilepsy and as general 'neurostabilizers' have been employed for a variety of neurological diseases including migraine, bipolar disorder and neuropathic pain. Combining Trillium' proprietary chemistry platform with NIH's in vivo phenotypic screening strategy, three novel AED drug candidates were identified, including FV-137, exhibiting superior efficacy and selectivity for target ion channels. This candidate has been granted Red Book status by NIH; additional studies have demonstrated safety and shown it to possess properties expected of a CNS development candidate. This drug candidate is a potential therapeutic option for pharmacoresistant epilepsy.

Pharmacology: is a structurally distinct and novel, orally bioavailable AED displaying promising preclinical efficacy and safety profiles. FV-137 was extensively screened across a battery of well-defined in vitro and in vivo murine seizure models at ASP, including pharmacoresistant epilepsy models, FV-137 was found to exhibit an excellent spectrum of anti-seizure activity and safety profiles superior to that produced by Depakote®, Neurontin® and Keppra®. FV-137 has an ED50 of 22.7 in the rat MES model upon p.o. dosing. Additionally, FV-137 showed strong efficacy in the 6-Hz electrical stimulus model of refractory partial seizures, exhibiting ED50 values of 48.5 and 91.1 mg/kg in traditional 32 mA and 44 mA stimulation conditions, respectively. FV-137 also increased seizure threshold in a dose–dependent manner, and prevented seizures induced by sound in Audiogenic Seizure-susceptible Frings mice (i.p), predictive of potential genetically-susceptible reflex seizures, with an ED50 value of 28.9 ± 3.0 mg/kg. ED50 values in electrically induced corneal kindled mouse, kindled rat amygdala, kindled rat hippocampal as well as lamotrigine (LTG)-resistant kindled rat seizures models were 70.4± 1.0, 50, 49.4 ± 1.47 and 32.6 ± 3.58 mg/kg, respectively. FV-137 also demonstrated efficacy in a Hippocampal Paroxysmal Discharges mouse model at a dose of 125 mg/kg i.p, which indicates its potential to relieve seizures in chronic pharmacoresistant Mesial Temporal Lobe Epilepsy (MTLE) patients. Additionally, FV-137 at a dose of 100 µM demonstrated robust efficacy in in vitro spontaneous electrographic bursting model of pharmacoresistance

Pharmacokinetics: In-vivo pharmacokinetic studies in mouse and rat revealed that FV-137 has high oral bioavailability (84% and 95%, respectively), with corresponding

T1/2 values of 3.2 and 0.7 hrs. in each of the aforementioned species. In addition, drug exposure as measured by Cmax and AUC was shown to be directly proportional to oral dose, ranging from 20 to 200 mg/kg.

Safety and Toxicology: Safety assessment of FV-137 suggests no interaction with the major CYP isozymes, except for 1A2 and 2D6 with IC50 values of 19 uM and 156 uM, respectively. No functional hERG activity was observed over a range of concentrations approaching 50 μM and toxicity studies suggest a MTD of greater than 500 mg/kg in both mice and rats. A large protective index (ratio between TD50 and ED50) of >22-fold was observed in rat following oral administration. Further, a 5-day safety study following oral dosing in the rat at doses of 100 and 200 mg/kg suggest that FV-137 is well tolerated.

Mechanism(s) of action: Mechanistically, FV-137 inhibited P/Q-type Ca2+ Channels, and voltage-gated Na+ channels with no significant inhibition up to 100 μM in other related channels. Importantly, no significant affinities were observed in a CEREP broad profiling screen. Furthermore, in models of neuropathic inflammatory pain, FV-137 showed robust efficacy.

Planned studies: Ongoing studies are directed towards models of pharmacoresistant epilepsy and post-kainic acid treated rat models of status epilepticus-induced spontaneous recurrent seizures. Furthermore, IND-enabling studies are planned, and a convenient and cost effective manufacturing process for FV-137 has been developed, allowing for multi-kilogram scale synthesis.

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