



UNIVERSITY OF CALGARY
CUMMING SCHOOL OF MEDICINE



HOTCHKISS
BRAIN INSTITUTE



TITLE: A Phase II Pilot Clinical Trial Testing the Safety and Efficacy of Vorinostat in Pediatric Patients with Medically Intractable Epilepsy

PROTOCOL NO.: VOR-17-2471

PRINCIPAL INVESTIGATORS: Dr. Jong Rho
Department of Pediatrics, Department of Physiology and Pharmacology, Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary
Department of Pediatrics, Alberta Children's Hospital, Alberta Health Services

Dr. Deborah Kurrasch
Department of Medical Genetics
Cumming School of Medicine
University of Calgary

CO-INVESTIGATORS: Dr. Luis Bello-Espinosa
Dr. JP Appendino
Department of Pediatrics, Cumming School of Medicine, University of Calgary
Department of Pediatrics, Alberta Children's Hospital, Alberta Health Services

VERSION 2: 2018-07-18

TABLE OF CONTENTS

| | |
|--|-----------|
| GLOSSARY OF ABBREVIATIONS | 5 |
| SECTION 1.0: BACKGROUND AND RATIONALE | 7 |
| 1.1 BACKGROUND | 7 |
| 1.1.1. DISEASE | 7 |
| 1.1.2 STUDY DRUG RATIONALE | 7 |
| 1.1.3 TOLERABILITY OF VORINOSTAT | 10 |
| 1.1.4 TOLERABILITY OF VORINOSTAT IN PEDIATRIC EPILEPSY PATIENTS | 15 |
| 1.2 RATIONALE FOR THE STUDY | 23 |
| SECTION 2.0: OBJECTIVES | 25 |
| 2.1 PRIMARY OBJECTIVES | 25 |
| 2.2 SECONDARY OBJECTIVES | 25 |
| SECTION 3: STUDY DESIGN | 26 |
| 3.1 OVERVIEW OF STUDY DESIGN AND DOSING REGIMEN | 26 |
| 3.1.1 DOSAGE | 26 |
| 3.1.2 PHASES OF STUDY | 27 |
| 3.1.2 END OF STUDY | 28 |
| 3.2 RATIONALE FOR STUDY DESIGN | 28 |
| 3.3 NUMBER OF SUBJECTS | 28 |
| SECTION 4: STUDY POPULATION | 29 |
| 4.1 OVERVIEW | 29 |
| 4.2 INCLUSION CRITERIA | 29 |
| 4.3 EXCLUSION CRITERIA | 29 |
| 4.4 DIAGNOSTIC CRITERIA FOR MEDICALLY INTRACTABLE EPILEPSY | 30 |
| 4.5 CONCOMITANT MEDICATIONS AND TREATMENTS | 30 |
| 4.5.1 PROHIBITED CONCOMITANT MEDICATIONS AND TREATMENTS | 30 |
| 4.5.2 PERMITTED CONCOMITANT MEDICATIONS | 31 |
| 4.6 CONTRACEPTION PROTECTION | 32 |
| 4.7 CRITERIA FOR PREMATURE WITHDRAWAL | 32 |
| 4.8 REPLACEMENT POLICY | 32 |
| SECTION 5: SCHEDULE OF ASSESSMENTS AND PROCEDURES | 34 |
| 5.1 PROCEDURES | 34 |
| 5.1.1 SCREENING EXAMINATION AND ELIGIBILITY SCREENING FORM – VISIT 1 | 35 |
| 5.1.2 ENROLLMENT VISIT – VISIT 2 | 36 |

| | |
|---|-----------|
| 5.1.3 ASSESSMENTS AND PROCEDURES DURING THE TREATMENT PERIOD..... | 37 |
| 5.1.4 SAFETY FOLLOWUP | 38 |
| 5.2 OUTCOMES ASSESSMENTS | 38 |
| 5.2.1 SAFETY AND TOLERABILITY ASSESSMENT | 38 |
| 5.2.2 EFFICACY ASSESSMENTS..... | 38 |
| 5.3 SAFETY MONITORING | 38 |
| 5.3.1 ADVERSE EVENTS..... | 39 |
| 5.3.2 SAFETY MONITORING..... | 39 |
| SECTION 6: INVESTIGATIONAL MEDICINAL PRODUCT..... | 41 |
| 6.1 FORMULATION, PACKAGING AND LABELING | 41 |
| 6.1.1 FORMULATION | 41 |
| 6.1.2 PACKAGING & LABELING | 41 |
| 6.1.3 STORAGE..... | 41 |
| 6.2 DOSE AND SCHEDULE OF STUDY MEDICATION..... | 41 |
| 6.2.1 DOSAGE RATIONALE..... | 41 |
| 6.2.2 DOSAGE..... | 41 |
| 6.2.3 DOSE INTERRUPTIONS..... | 42 |
| 6.3 ASSESSEMENT OF COMPLIANCE | 42 |
| 6.4 DESTRUCTION OF STUDY MEDICATION | 42 |
| SECTION 7: SAFETY INSTRUCTION AND GUIDANCE | 43 |
| 7.1 ADVERSE EVENTS AND LABORATORY ABNORMALITIES..... | 43 |
| 7.1.1 CLINICAL ADVERSE EVENTS..... | 43 |
| 7.1.2 LABORATORY TEST ABNORMALITIES..... | 44 |
| 7.1.3 TREATMENT AND FOLLOW UP OF AEs | 45 |
| 7.2 HANDLING OF SAFETY PARAMETERS | 46 |
| 7.2.1 REPORTING OF SERIOUS ADVERSE EVENTS | 46 |
| 7.2.2 EXEMPTION OF PROJECT SPECIFIC SERIOUS AEs FROM IMMEDIATE REPORTING TO HEALTH AUTHORITIES AND IRBs..... | 47 |
| 7.2.3. PREGNANCY..... | 47 |
| SECTION 8: STATISTICAL CONSIDERATION AND ANALYTICAL PLAN | 48 |
| 8.1 PRIMARY AND SECONDARY STUDY ENDPOINTS..... | 48 |
| 8.1.1 PRIMARY ENDPOINTS..... | 48 |
| 8.1.2 SECONDARY ENDPOINT | 48 |
| 8.2 STATISTICAL AND ANALYTICAL METHODS..... | 48 |
| 8.2.1 SAMPLE SIZE..... | 48 |
| 8.2.2 ANALYSIS..... | 48 |

SECTION 9: DATA COLLECTION & MANAGEMENT50
SECTION 10: ETHICAL ASPECTS51
SECTION 11: STUDY DOCUMENTATION, RECORD KEEPING, AND CONFIDENTIALITY OF TRIAL
 DOUCMENTS AND PARTICIPANT RECORDS.....52
 11.1 INVESTIGATOR'S FILES/RETENTION OF DOCUMENTS52
 11.2 CONFIDENTIALITY OF TRIAL DOUCMENTS AND PARTICIPANT RECORDS52
SECTION 12: REFERENCES54

GLOSSARY OF ABBREVIATIONS

| | |
|--------|--|
| 13 cRA | 13-cis-retinoic acid |
| ACH | Alberta Children's Hospital |
| AE | Adverse Event |
| AED | Anti-epileptic drug |
| ALL | Acute lymphoblastic leukemia |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| AST | Aspartate transaminase |
| BOR | bortezomib |
| BSA | Body surface area |
| BVC | Brivaracetam |
| CBZ | carbamazepine |
| CHREB | Conjoint Health Research Ethics Board |
| CRF | Case report form |
| CTCAE | Common Terminology criteria for adverse events |
| CTCL | Cutaneous T-cell lymphoma |
| DCF | Data collection form |
| DEC | decitabine |
| DLT | dose-limiting toxicity |
| DVT | deep vein thrombosis |
| ECG | Electrocardiogram |
| EDC | Electronic data capture |
| eDCF | Electronic data capture form |
| EOT | End of treatment |
| ESF | Eligibility screening form |
| ETSP | Epilepsy therapy screening program |
| ETX | Ethosuximide |
| FBM | Felbamate |
| FDA | Food and Drug Administration |
| GBP | Gabapentine |
| GCP | Good Clinical Practice |
| HDAC | Histone deacetylase |
| HDACi | Histone deacetylase inhibitor |
| ICH | International Conference on Harmonisation |
| ILAE | International League Against Epilepsy |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| KD | Ketogenic diet |
| LCM | Lacosamide |
| LEV | Levetiracetam |

| | |
|-----------|--|
| LTG | Lamotrigine |
| MIBG | metaiodobenzylguanidine |
| MO | Morpholino oligonucleotide |
| MTD | maximum tolerated dose |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NIH | National Institutes of Health |
| OXC | Oxcarbazepine |
| PK | pharmacokinetics |
| PMP | Perampanel |
| PTT | Prothrombin time |
| PTZ | pentylentetrazol |
| QoL | Quality of life |
| QTc | QT corrected |
| REB | Research ethics board |
| SAE | Serious adverse event |
| SFU | Safety Follow-up |
| TEM | Temozolomide |
| TPM | Topiramate |
| ULN | Upper limit of normal |
| vEEG | Video EEG |
| VNS | Vagal nerve stimulator |
| VOR | Vorinostat |
| VPA | Valproic acid |
| wt | wild type |
| ZNS | Zonisamide |

SECTION 1.0: BACKGROUND AND RATIONALE

1.1 BACKGROUND

1.1.1. DISEASE

Epilepsy is defined as the occurrence of two or more unprovoked seizures, caused by abnormal, excessive discharge of neurons, usually accompanied by behavioral or sensorimotor manifestations¹. An estimated 15,500 new patients are diagnosed with epilepsy each year in North America alone².

Several therapies are available for the treatment of seizures, including over 10 pharmaceutical agents, as well as surgical, neurostimulation, diet, and immunomodulatory interventions, with the goals of complete seizure remission, minimal or no adverse effects (AEs), and best quality of life (QoL)^{3, 4}. Despite these numerous available therapies, attainment of treatment goals continues to be elusive. Approximately 85% of patients are prescribed an anti-epileptic drug (AED) within one year of the first unprovoked seizure⁵; of those only 30 - 50% achieve seizure freedom^{5, 6}, and 30–60% experience drug-related AEs⁷. About a third have medically intractable epilepsy^{5, 8}, which is defined by the International League Against Epilepsy (ILAE) 2010 task force as “failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom”⁹.

Uncontrolled seizures in children can impose a deleterious impact on development, increase the risk of medical complications and injuries, contribute to poor QoL¹⁰, and significantly increase mortality rate (1.59% per year)^{10, 11}. Almost half of the children with medically intractable epilepsy may evolve some intellectual dysfunction or decline in cognitive function over the years¹²⁻¹⁴. Children with epilepsy are at particular risk for impaired QoL and psychological problems, and are among those with the poorest QoL and worst psychological adjustment during infancy and adolescence, compared to other chronic conditions not involving central nervous system conditions^{15, 16}. The risk of death in children with epilepsy is several-fold higher over the subsequent 10-20 years of life¹⁷; and lack of seizure freedom is the greatest risk factor for premature death in this population¹⁸. Furthermore, the associated medical care costs of sub-optimal control of seizures is exorbitant: while the direct and indirect costs of epilepsy are estimated to be \$9.6 billion (US data)¹⁹⁻²¹, the health care costs of patients with uncontrolled seizures or AEs are estimated to be twice as high²².

The incidence of medically intractable epilepsy remains unacceptably high and an unmet medical need exists for patients with uncontrolled seizures. Newly identified treatment targets to control seizures are clearly required, however typical drug development processes take greater than a decade to avail new treatment options. A strategy which identifies potential therapies that can be rapidly tested in the clinical setting is paramount.

1.1.2 STUDY DRUG RATIONALE

Vorinostat (VOR), a histone deacetylase (HDAC) inhibitor has been identified as a potential viable therapy for the treatment of seizures in epilepsy, via a metabolism based discovery platform by researchers at the University of Calgary. Dr. Kurrasch *et al.* have developed a novel, metabolism-based discovery platform, modelled on the

mechanistic underpinnings and therapeutic efficacy of the ketogenic diet (KD), to rapidly identify potential therapies and therapeutic targets.

The KD is a high-fat, low-carbohydrate treatment for patients who fail to respond to anti-seizure medications²³⁻²⁵. Although the underlying mechanisms of the KD remain unclear²⁶, proof of clinical efficacy has been demonstrated²³. A link appears to exist between the KD and alterations in bioenergetics, since patients who respond to the KD demonstrate underlying respiratory changes^{27, 28}. Derangements in cellular metabolism have been linked in part to the underlying aetiology of epilepsy, therefore it is possible that restoration of mitochondria-mediated bioenergetics may have disease-modifying effects²⁹. For this reason, alterations and restoration of cellular bioenergetics can serve as a framework for investigation of target identification and drug development, where pharmacological agents that exert similar neurometabolic effects might prove efficacious in controlling seizures.³⁰ Dr. Kurrasch *et al.* developed such a platform, which utilizes a combination of zebrafish genetics and in vivo bioenergetics functional readout assays to screen for therapeutic agents that improve mitochondrial health in single gene knockdown models of epilepsy. Efficacious compounds can be identified via this platform by screening commercially available chemical libraries of approved drugs.

The metabolism based discovery platform includes a multi-step process for screening and identifying potential viable drug therapies: behavioral assay screen; metabolic assay screen; and validation of positive compounds with spontaneously epileptic *Kcna1*-null mice (see Figure 1).

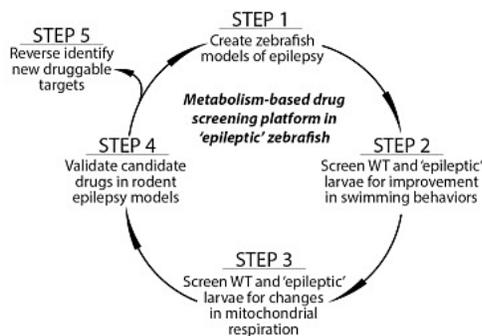


Figure 1: Schematic representation of the workflow for the 2-step drug screen.

1. Behavioral assay

First, a behavioral assay is conducted using a zebrafish genetic model of epilepsy to screen compounds from chemical libraries. Zebrafish are simple vertebrates that are highly amenable to genetic manipulation and share >70% genetic similarity with humans³¹⁻³³, thereby conserving many biological pathways common to zebrafish and humans. As such, zebrafish have rapidly become a key tool in epilepsy research and experimental therapeutics³⁴⁻³⁷. Two zebrafish models of 'epileptic' zebrafish were developed and validated for this purpose, the first was a pharmacological induction model utilizing pentylentetrazol (PTZ), termed the 'PTZ induction model'. The second, termed the 'kcna1-MO model' is a knockdown approach targeting the zebrafish orthologue of the human and murine potassium channel gene (*KCNA1* and *Kcna1* respectively), which encodes for the delayed rectifier potassium channel protein Kv1.1. This was done using a morpholino oligonucleotide (MO) that targeted the *kcna1a* ATG initiation site. The models were validated to demonstrate neuronal hyperexcitability consistent with a seizure model, and elevated basal, total mitochondrial and ATP-linked respiration. Compounds which reduced total locomotor activity by 40% or more in populations of these

models, without toxic effects, moved forward to the metabolic screen step. 870 compounds were screened in the behavioural assay; 120 compounds went on the next step.

2. Metabolic screen assay

To assess the efficacy of the compounds identified in the behavioral screen for improved bioenergetics, wild-type (wt) and *kcna1*-MO zebrafish were exposed to PTZ and/or drug identified in the behavioral assay. Compounds that reversed basal & mitochondrial respiration by >40% in both zebrafish models were considered 'active'.

The active compounds identified via the metabolic screen assay were then assessed to determine if the compound functions as an effective anti-epileptic compound. This includes a 3-pronged approach: i. extracellular field recordings in zebrafish; ii. video EEG (vEEG) recording in spontaneously epileptic *Kcna1*-null mice and; iii. acutely induced approaches in mice in collaboration with the United States National Institutes of Health-sponsored Epilepsy Therapy Screening Program (ETSP), which is the pre-eminent epilepsy screening program that, since 1975, has tested and made important contributions to nearly every anti-seizure drug developed over the past forty years. ETSP tested compounds across two mouse models of epilepsy – the 6Hz psychomotor and Maximal Electroshock Seizure (MES) models, which represent therapy resistant limbic seizures and tonic-clonic seizures respectively^{38, 39}

Of the compounds screened through this process, VOR was identified as a potent anti-epileptic compound. When measuring the extracellular field potentials from *kcna1*-MO zebrafish brains, repetitive high-frequency large amplitude spikes, indicative of hyperexcitability, were nearly completely abolished with VOR perfusion (Fig 2). Additionally, when *Kcna1*-null mice were treated with VOR, seizure frequency was significantly reduced by 60% (see Fig 3). Lastly, when the acute effect of VOR administration was tested on seizures in the 6 Hz psychomotor and MES models, mice from the 6 Hz model responded to all doses when dosed 30 minutes prior to the 6Hz test. However VOR was far less efficacious in the MES test, with only 2 animals responding when treated 2 hours prior to MES stimulation. These data suggests that VOR may not possess a broad-spectrum anti-seizure profile. However, anti-epileptic compounds that are principally effective in the MES model are voltage-gated sodium channel blockers with restricted efficacy in focal onset seizures. Furthermore, valproic acid (VPA), a commonly utilized anti-epileptic with known HDAC inhibitor activity, is considered a broad spectrum drug.



Figure 2: Figure shows representative extracellular field recordings obtained from the optic tectum of 6- days-post fertilization wild-type and *kcna1*-MO zebrafish larvae + VOR treatment

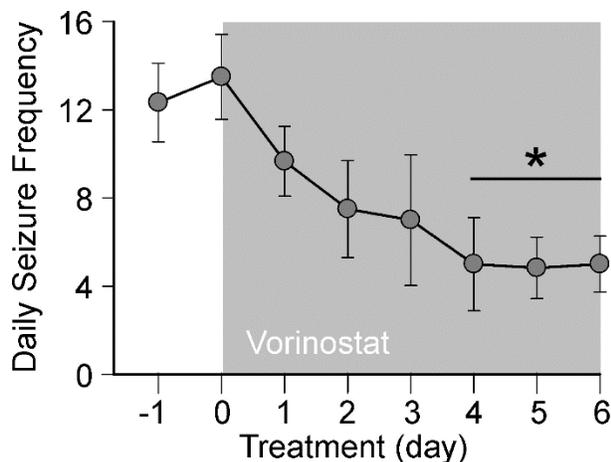


Figure 3: Representative electrographic seizure recorded in *Kcna1*-null mice. Bar graph of the mean number of seizures per day recorded from six *Kcna1*-null mice + VOR treatment. VOR treatment significantly reduced the number of seizures (two way ANOVA, $F=27.7$, $P<0.01$).

VOR is a potent inhibitor of histone deacetylases. These enzymes catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors⁴⁰. HDACs control various cellular functions by altering the dynamics of chromatin structure, which thereby affects gene transcription and can contribute to the pathogenesis of various diseases. The potential for HDAC inhibitors for the treatment of epilepsy was first proposed with the discovery of VPA's HDAC activity. VPA is broad anti-epileptic drug used as a first-line treatment in various seizures and epilepsies. It was originally thought to block voltage-dependent sodium channels and increase brain levels of γ -aminobutyric acid. However, more recently, VPA has been shown to also inhibit HDACs, and it is through this action that VPA is thought to offer its neuroprotective effects. VPA inhibits both Class I and Class IIa enzymes⁴¹, whereas VOR inhibits Class I, IIa, IIb, IV enzymes^{42,43}.

Currently, VOR is approved by Health Canada for the treatment of cutaneous manifestations in patients with advanced cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease subsequent to prior systemic therapies⁴⁰. The anti-neoplastic effect of VOR is attributed to the inhibition of HDAC activity and subsequent accumulation of acetylated proteins, including histones. Histone acetylation results in transcriptional activation of genes, including tumor suppressor genes, whose expression leads to induction of differentiation, apoptosis and/or inhibition of tumor growth⁴⁰.

1.1.3 TOLERABILITY OF VORINOSTAT

In Phase 1 studies, VOR has been generally well-tolerated with drug limiting toxicities (DLTs)⁴⁴⁻⁴⁷.

- According to the VOR product monograph⁴⁰, AEs reported at greater than 10% incidence at a dose of 400 mg/day were: **fatigue** (45.3%), **diarrhea** (46.5%), **nausea** (38.4%), **thrombocytopenia** (25.5%), **dysgeusia** (23.3%), **anorexia** (23.3%), **weight decrease** (19.8%), **dry mouth** (16.3%), **alopecia** (16.3%), **muscle spasms** (16.3%), **anemia** (12.8%), **blood creatinine increase** (12.8%), **vomiting** (11.6%), **decreased appetite** (11.6%), **constipation** (10.5%), **chills** (10.5%).

- Of these AEs, the following occurred with a severity of Grade 3-4 (moderate – life threatening): **thrombocytopenia** (5.8%), **nausea** (3.5%), **muscle spasms** (2.3%), **anemia** (2.3%), **fatigue** (2.3%), **anorexia** (2.3%), **weight decrease** (1.2%), **decreased appetite** (1.2%), **chills** (1.2%), **dizziness** (1.2%), and **abdominal pain** (1.2%).
- SAEs outlined included events of **pulmonary embolism** (4.7%) and **anemia** (2.3%), as well as single experiences (1% incidence rate each) of thrombocytopenia, death of unknown cause, ischemic stroke, deep vein thrombosis (DVT), gastrointestinal hemorrhage, streptococcal bacteremia, dehydration and syncope, increased serum creatinine, decreased appetite, hypokalemia, leukopenia, nausea, neutropenia, and vomiting. There were a total of 5 deaths in these studies, which included disease progression, untreated sepsis, ischemic stroke and unknown cause; these were all considered unrelated to VOR.
- Regarding dose modification, 10.5% of patients required a dose modification due to AEs. AEs included: increased serum creatinine, decreased appetite, hypokalemia, leukopenia, nausea, neutropenia, thrombocytopenia, and vomiting. 10.5% of patients discontinued VOR due to AEs, these included: anemia, angioneurotic edema, asthenia, chest pain, death, DVT, ischemic stroke, lethargy, pulmonary embolism and skin lesions.

It is recommended by the product monograph that patients on VOR be closely monitored for several particular events, namely, thromboembolic events, QT/QTc prolongation, increased heart rate, hyperglycemia, dehydration, and hematologic events. In addition, VOR should be used with caution in special populations.

- Thromboembolic events: a greater incidence of thromboembolic events appears to be associated with the use in VOR in adult patients with malignancies⁴⁸. In the pivotal study in patients with CTCL, the incidence rate of pulmonary embolism and DVT was 4.7%, and 1.2%, respectively⁴⁹. In all completed and ongoing studies in patients with CTCL, the proportion of patients with a venous thromboembolic event was 6.8%⁴⁸. In greater than a 1000 patients with hematologic malignancies and solid tumors who have been treated with VOR as monotherapy, or in combination with other chemotherapy agents, in completed and ongoing clinical studies, the proportion of patients that experienced a venous thromboembolic events was approximately 5.0%⁴⁸. In a double-blind study of patients with advanced non-small cell lung cancer who received VOR in combination with chemotherapy, there was an increase in the incidence of venous thromboembolic events as compared to patients who received chemotherapy alone; DVT and/or pulmonary embolism was reported in 6.5% (8/124) of patients in the VOR/chemo arm compared to 2.4% (3/124) in the placebo arm⁴⁸.
- QT/QTc prolongation: Use of VOR is reported to be associated with QT/QTc interval prolongation, which may lead to torsade de pointes; particular care should be exercised in patients with increased risk of experiencing torsade de pointes and patients on medications known to increase QT/QTc interval⁴⁸.
- Increased heart rate: Use of VOR is reported to be associated with increases in heart rate, which may lead to worsening of cardiac conditions in patients with history of cardiac problems⁴⁸.
- Hyperglycemia: Hyperglycemia is reported at an incidence rate of 4.7%⁴⁸ when using VOR.
- Dehydration: Reported as a common serious drug-related AE in clinical trials⁴⁸ with VOR.
- Hematologic events: Use of VOR is associated with dose-related thrombocytopenia and anemia⁴⁸.
- Special populations: VOR should with caution in patients with mild hepatic impairment; it is not recommended in patients with moderate hepatic impairment, and is contraindicated in patients with severe hepatic impairment.

The pivotal VOR studies reviewed above did not include a pediatric population, and currently VOR is not approved for use in children. As the proposed study design involves a pediatric population, it was elected to examine the tolerability profile of VOR in pediatric patients. Five Phase 1 studies utilizing VOR in a pediatric population were reviewed. These studies sought to investigate the efficacy, tolerability, and maximum tolerated dose (MTD) of VOR as a single agent and/or in combination therapy in pediatric populations with various malignancies. The first report reviewed was a Phase

1 trial investigating the use of VOR alone and in combination with 13-cis-retinoic acid (13 cRA), an antiangiogenic agent, in children with recurrent or refractory malignancies, namely solid tumors and leukemia⁵⁰. The second study was a Phase 1 trial investigating VOR in combination with Temozolomide (TEM) (an oral imidazotetrazine prodrug that undergoes spontaneous hydrolysis to the active metabolite MTIC, which methylates DNA at O6-guanine and other sites), in children with recurrent or refractory brain or spinal cord tumors⁵¹. The third was a Phase I trial investigating VOR in combination with bortezomib (BOR), (a selective inhibitor of the ubiquitin-proteasome pathway, which is essential for the degradation of most regulatory intracellular proteins), in children with recurrent or refractory solid tumors, including CNS tumors⁵². The fourth study was a pilot study investigating the combination of VOR and decitabine (DEC) (a cytidine anti-metabolite analogue that acts as a demethylating agent by incorporating itself into cellular DNA and covalently trapping DNA methyltransferase as a protein-DNA adduct), followed by standard re-induction chemotherapy to test the feasibility, tolerability and efficacy in patients with relapse or refractory acute lymphoblastic leukemia (ALL)⁵³. The final study was a Phase 1 trial to determine the MTD of VOR and ¹³¹I-metaiodobenzylguanidine (MIBG) (a systemic radiopharmaceutical), when used in combination in children with relapsed or refractory neuroblastoma.⁵⁴

There were a total of 110 patients with ages ranging from 12 months to 60 years of age with median age being 11.4 years of age. Three dosage levels of VOR were utilized in these studies, 180 mg/m²/d, 230 mg/m²/d; and 300 mg/m²/d. These dosages were utilized as single agents or in combination therapy with 160 mg/m²/d of 14cRA; 150 mg/m²– 200 mg/m² TEM; 1.3 mg/m²/d BOR; 15 mg/m² DEC; or 8 - 18 mCi/kg MIBG.

Adverse events

As these were oncology studies, with the majority attempting to determine MTD, AEs were typically graded according to the National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE) (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf).

Therefore the prevalence of reported AEs are presented utilizing this grading system. Briefly, Grade 1 refers to mild, asymptomatic; Grade 2 refers to moderate events, which may require non-invasive interventions; Grade 3 refers to events that are severe but not life-threatening; or required hospitalization or prolongation; Grade 4 refers to life-threatening events, and Grade 5 refers to events that lead to death.

The AE prevalence given below is for all patients in all reviewed studies evaluable for toxicity, at all doses of treatment for cycle 1 of treatment: (See Table 1 for all AEs reported)

- Across the five studies, there were a total of 378 AEs reported in 110 patients.
- Of the 378 AEs, 158 (42%) were rated as Grade 2; 145 (38%) as Grade 3; 72 (19%) as Grade 4; and 3 (0.8 %) were Grade 5.
- Grade 2-3 events: 45% of all Grade 2-3 AEs were hematologic type AEs; 27% were non-hematologic; less than 10% were laboratory abnormalities (see Table 1 for specific AEs); the most commonly reported Grade 2-3 AEs were **leukopenia** (38%); **lymphopenia** (23%); **thrombocytopenia** (17%); **neutropenia** (15%); and **anemia** (14%).
- Grade 4 events: 66% of all Grade 4 events were hematological; 26% were non-hematological; 7% were laboratory abnormalities (see Table 1 for specific AEs); the most commonly reported Grade 4 AEs were: **leukopenia** (32%); **lymphopenia** (26%); **thrombocytopenia** (22%); **nausea** (19%); **anemia** (18%); **neutropenia** (14%).
- Grade 5 events: there were 3 events that led to death: hemorrhage/bleeding event; hypoxia/acute respiratory distress, and CNS hemorrhage.

- DLT AEs: there were 36 AEs (10%) that met the criteria for DLTs; the most common DLT was thrombocytopenia (4%); severe DLTs included thrombosis (n=1), neuropathy (n=1), and hemorrhage (oral, n=1; CNS, n=1).

Severe and Serious AEs

DLTs were pre-defined in study protocols; they were typically divided into hematologic/non-hematologic categories and had to meet a severity Grade of 3 or 4. There were 3 events, which were considered as severe DLTs. The first was a case in which the patient developed a DVT in the iliac vein while on VOR monotherapy at a dose of 180 mg/m², the lowest dose group utilized in the study⁵⁰. The authors indicated that this was most likely not related to therapy, given that the patient was on oral contraceptives and had a vascular anomaly⁵⁰. The second was a case of Grade 2 sensory neuropathy at the highest dose level of the study (300 mg/m²/d VOR + 1.3 mg/m²/d BOR). The patient had stable disease but elected to stop therapy; the neuropathy progressed however to Grade 3, requiring intensive analgesia for pain and physical rehabilitation. This event was attributed to BOR therapy by the researchers since this is a known AE associated with BOR⁵². The third case involved Grade 3 oral bleeding in the setting of Grade 4 thrombocytopenia and evidence of platelet allosensitization⁵⁴.

There were 3 deaths during the course of these studies. The first involved a single toxic death which included a Grade 5 hemorrhage/bleed. This was attributed to the chemotherapy cocktail given after VOR/DEC therapy (230 mg/m² VOR + 15 mg/m² DEC)⁵³. The second death occurred in the same study in a patient who experienced Grade 5 hypoxia/acute respiratory distress and then died on day 4; this was attributed to disease progression⁵³. The third death involved Grade 5 central nervous system hemorrhage, in the setting of ongoing thrombocytopenia and coagulopathy⁵⁴. The patient was on the highest dose of the study 18 mCi/kg MIBG + 230 mg/m² VOR. This occurred in the same study as the Grade 3 oral bleeding event described above. The authors indicated these events were unanticipated, since bleeding is an unusual event for both VOR and MIBG when used as single agents and that perhaps this event was the result of an unanticipated interaction between VOR and MIBG.

There are similarities and differences between the adult studies (pivotal studies for FDA approval) to the reviewed pediatric studies. Comparing the Grade 3-4 events, it appears that children experience more hematologic events. For example, the incidence rate of thrombocytopenia in the pediatric studies was 29.1%, as compared to 5.8% in the adult studies; anemia was 12.7% in the pediatric studies, as compared to 2.3% in adults. Other hematologic events seen frequently in the pediatric studies were lymphopenia (34.5%), and leukopenia (29.1%); these were not reported in the adult studies. The highest non-hematologic event in children was nausea (24.5%), whereas in adults nausea was reported at 3.5%. Regarding serious adverse events (SAEs), DVT and bleeding/hemorrhage were reported in both adults and children, however in the pediatric studies, all SAEs were not attributed to VOR therapy. Discontinuation rates were higher in the pediatric studies than the adult studies (32.7% vs. 10.5%). Regarding the special cautionary AEs recommended for special monitoring in the product monograph, increased QT interval, hyperglycemia and dehydration had incidence rates of <1% each in the pediatric studies and there were no cases of increased heart rate. It is important to note that comparison of the adult studies and pediatric studies should be approached with the context that in the pediatric studies: patients with refractory/relapsed solid tumors, CNS tumors and leukemia also made up the tested population, in addition to refractory/relapsed CTCL patients; patients were heavily pre-treated prior to VOR treatment; and lastly the majority of patients were treated with a combination that included VOR as part of treatment.

TABLE 1: ADVERSE EVENTS IN 5 PHASE 1 REVIEWED PEDIATRIC STUDIES WITH VORINOSTAT (n=110)

| | GRADE 2 | GRADE 3 | GRADE 4 | GRADE 5 | TOTAL (ALL GRADES) | PERCENT INCIDENCE (ALL GRADES) |
|---|---------|---------|---------|---------|--------------------|--------------------------------|
| Leukopenia | 32 | 23 | 9 | | 64 | 15.5 |
| Lymphopenia | 14 | 19 | 19 | | 52 | 12.6 |
| Thrombocytopenia | 8 | 16 | 16 | | 40 | 9.7 |
| Nausea | 8 | 14 | 13 | | 35 | 8.5 |
| Neutropenia | 12 | 10 | 2 | | 24 | 5.8 |
| Anemia | 7 | 13 | 1 | | 21 | 5.1 |
| Vomiting | 9 | 4 | | | 13 | 3.1 |
| Hemoglobin | 8 | 1 | 1 | | 10 | 2.4 |
| Fatigue (asthenia, lethargy, malaise) | 8 | 1 | | | 9 | 2.2 |
| ALT | 5 | 3 | | | 8 | 1.9 |
| AST | 2 | 3 | | | 5 | 1.2 |
| Anorexia | 4 | 1 | | | 5 | 1.2 |
| Fever with neutropenia | | 5 | | | 5 | 1.2 |
| Infection (Blood) with neutropenia | | 3 | 2 | | 5 | 1.2 |
| infection With grade 3 or 4 neutrophils | 1 | 4 | | | 5 | 1.2 |
| Hyperglycemia | 1 | 2 | 1 | | 4 | 1.0 |
| Hypophosphatemia | 4 | | | | 4 | 1.0 |
| Diarrhea | 3 | 1 | | | 4 | 1.0 |
| Dry skin | 4 | | | | 4 | 1.0 |
| Infection with normal ANC or grade 1 or 2 neutrophils | | 4 | | | 4 | 1.0 |
| Pain (Abdomen NOS) | 1 | 3 | | | 4 | 1.0 |
| ANC | 2 | 1 | | | 3 | 0.7 |
| Alkaline phosphatase | 3 | | | | 3 | 0.7 |
| Hypokalemia | | 2 | 1 | | 3 | 0.7 |
| Hyponatremia | | 3 | | | 3 | 0.7 |
| Dehydration | 1 | 2 | | | 3 | 0.7 |
| Headache | 2 | 1 | | | 3 | 0.7 |
| Albumin | 2 | | | | 2 | 0.5 |
| Amylase elevation | | 2 | | | 2 | 0.5 |
| Back pain | 2 | | | | 2 | 0.5 |
| Constipation | 2 | | | | 2 | 0.5 |
| Dyspnea | 1 | | 1 | | 2 | 0.5 |
| Hypoxia/acute respiratory distress | | | 1 | 1 | 2 | 0.5 |
| Bicarbonate, serum low | 1 | | | | 1 | 0.2 |
| Creatinine | 1 | | | | 1 | 0.2 |
| Hyperbilirubinemia | 1 | | | | 1 | 0.2 |
| Hypercholesteremia | | | 1 | | 1 | 0.2 |
| Hypertriglyceiremia | | | 1 | | 1 | 0.2 |
| Lipase | | | 1 | | 1 | 0.2 |
| Low albumin | | 1 | | | 1 | 0.2 |
| Blood | | 1 | | | 1 | 0.2 |
| Cough | 1 | | | | 1 | 0.2 |
| Dysgeusia | 1 | | | | 1 | 0.2 |
| Fever | 1 | | | | 1 | 0.2 |
| Hemorrhage | | | | 1 | 1 | 0.2 |
| Hemorrhage, CNS | | | | 1 | 1 | 0.2 |
| Infection (Abdomen - NOS) with neutropenia | | 1 | | | 1 | 0.2 |
| Muscle weakness | 1 | | | | 1 | 0.2 |
| Neuro – Right hemiparesis | | 1 | | | 1 | 0.2 |
| Neutropenic fever | | | 1 | | 1 | 0.2 |
| Pain Extremity-limb | 1 | | | | 1 | 0.2 |
| Palpitations | 1 | | | | 1 | 0.2 |
| Pancreatitis | | | 1 | | 1 | 0.2 |
| Prolonged QTc interval | | 1 | | | 1 | 0.2 |
| Psychosis | 1 | | | | 1 | 0.2 |
| Rash/desquamation | 1 | | | | 1 | 0.2 |
| Weight loss | 1 | | | | 1 | 0.2 |

1.1.4 TOLERABILITY OF VORINOSTAT IN PEDIATRIC EPILEPSY PATIENTS

AS VOR has not been tested in a population with epilepsy, it is not possible to give the tolerability of VOR within this population. Further, findings from the reviewed VOR studies cannot be extrapolated to a population with epilepsy, due to the severity of illness and heavy pre-treatment of the populations of patients enrolled. However, as indicated previously, VPA – a widely utilized AED - has been shown to be in the same class of drug as VOR. VPA is a broad-spectrum AED used as a first-line agent for both generalized and partial seizures. A wealth of data exists for VPA as a result of length of time on the market and widespread utilization. It was first used in Europe in 1968 and in the United States in 1978⁵⁵. VPA is one of the most widely-used AEDs in different regions of the world, being the most frequently prescribed AED in children in several European countries^{56, 57}, and the second most frequently prescribed AED for children in the United States in the 1990's⁵⁸. VPA can be administered as monotherapy, however it is commonly administered as part of polytherapy regimens comprising several AEDs⁵⁹. Therefore, although safety of VOR in a pediatric population is not known since the data is not available; the safety/tolerability of VOR can be taken in context of the safety data of VPA - a commonly utilized AED with HDAC inhibitor activity in pediatric populations of children with seizures/epilepsy, combined with that of commonly utilized AEDs, to infer the safety of VOR in a currently untested pediatric population with seizures.

1.1.4.1 TOLERABILITY OF VPA IN POPULATIONS WITH EPILEPSY

The safety/tolerability profile of VPA is generally positive in relation to efficacy, however there are several AEs, some potentially serious, reported with the use of VPA. For instance, the product monograph lists pancreatitis and hepatotoxicity, as known SAEs. Fatal hepatotoxicity has an estimated occurrence of 1:10,000 exposed patients and young children on polytherapy are a special group at risk⁶⁰. Other potential SAEs listed in the product monograph include hyperammonemia and thrombocytopenia. Other less serious AEs, commonly associated with treatment discontinuation are also reported. However, reported rates vary greatly and prevalence and associated risk are difficult to assess. For example, thrombocytopenia, the most commonly reported AE for VPA is reported to occur in 5-60%⁶¹ of treated patients. Weight gain, one of the most commonly reported reasons for drug discontinuation is reported to occur between 4-44% of patients⁶²⁻⁶⁵. Reasons for wide margins of reported prevalence of AEs include: variability in study design; number of participants; dosage; rate of titration; monotherapy vs polytherapy; and duration of follow up. Therefore a review of several large, multi-centered studies utilizing VPA for the treatment of epilepsy was conducted to gain context regarding the wide incidence rates of AEs, severity, and relationship to drug discontinuation with VPA.

A total of 17 studies were reviewed, however one study was the 12-month follow up of the original study, and another study was an analysis of the pediatric sub-population of the original study. The studies comprised of large multi-national studies within the last 25 years. The range of participants treated with VPA in these studies was 78 – 1192 in each study, for a total of 3,777 participants. Participants were followed between 4 weeks – 6.6 years. 3 studies included adult participants only; 9 studies included adult and pediatric participants, and 5 studies included pediatric patients only. 3 studies allowed for polytherapy. Patient populations included newly diagnosed patients; therapy-resistant patients; and those who attained remission but had relapsed. All studies with the exception of one were multi-centered. 12 studies were AED comparative studies, of these - 10 were randomized; 7 were double-blind; and 5 were open-label. 2 studies were dose concentration studies, where patients were randomized to a low or high concentration dose. 3

studies investigated various formulations of VPA only. Dosage ranged from 987 mg/day – 4114 mg/day for adult studies and combined adult/pediatric studies, and 17 mg/kg/day – 68.86 mg/kg/day for pediatric studies.

In general, most treatment emergent AEs considered related were generally rated as mild to moderate in severity; occurred early in therapy, were transient, and rarely required discontinuation; most SAEs were not considered related to study medication⁶⁶⁻⁶⁹. Rates of overall AEs with VPA ranged from 23% to 88% in the 6 studies that reported overall rates of AEs⁷⁰⁻⁷⁵ the other 11 studies did not report overall rates^{66-69, 76-81}. 13 studies reported 25 AE types that demonstrated a prevalence of $\geq 10\%$ ^{66, 69-74, 76, 77, 79-82}; 4 studies had no specific AE types that presented with a prevalence of $\geq 10\%$ ^{67, 68, 75, 78}.

Adverse Events

The most commonly reported AEs are shown in Table 2 below, only AEs with greater than $\geq 10\%$ prevalence within each study have been included.

TABLE 2: MOST COMMONLY REPORTED ADVERSE EVENTS (GREATER THAN 10% INCIDENCE) FOR VALPROIC ACID IN REVIEWED STUDIES (n=16)

| Reported Adverse Event | % of studies reporting AE (n/16) | Reported incidence rate |
|---------------------------|----------------------------------|-------------------------|
| Weight Gain | 56% (9/16) | 10-43% |
| Asthenia/Fatigue/Sedation | 44% (7/16) | 11-42% |
| Tremor | 38% (6/16) | 11-45% |
| Headache | 38% (6/16) | 12-18% |
| Alopecia | 31% (5/16) | 11-18% |
| Appetite increase | 25% (4/16) | 10-18% |
| Personality Changes | 19% (3/16) | 11-25% |
| Vomiting | 19% (3/16) | 11-14% |
| Dizziness | 19% (3/16) | 10-23% |
| Nausea | 19% (3/16) | 11-14% |
| Behavioural/psychiatric | 13% (2/16) | 18-59% |
| Cold Symptoms, | 13% (2/16) | 12-53% |
| Somnolence | 13% (2/16) | 20-32% |
| Thrombocytopenia | 13% (2/16) | 18-21% |

Serious Adverse Events

Overall reported SAE rates ranged from 0.8% - 10% in the 6 studies reporting an SAE rate or where the rate could be calculated^{67, 69, 74, 76, 80, 81}. The SAEs presented in Table 3 were reported in studies reviewed; since the actual number of participants who had experienced an SAE was often not clear, it was elected to summarize the number of studies where specific SAEs were reported.

TABLE 3: SERIOUS ADVERSE EVENTS REPORTED FOR VALPROIC ACID IN REVIEWED STUDIES (n=16)

| Reported Serious Adverse Event | % of studies reporting AE (n/16) |
|----------------------------------|----------------------------------|
| Studies not giving an SAE report | 50% (8/16) |
| Pancreatitis | 19% (3/16) |
| specified | 13% (2/16) |
| Pneumonia/Pneumonitis | 13% (2/16) |
| Atelectasis | 6% (1/16) |
| Accidental overdose | 6% (1/16) |
| Aggravation of epilepsy | 6% (1/16) |
| Chronic Bronchitis | 6% (1/16) |
| Empyema | 6% (1/16) |
| Encopresis | 6% (1/16) |
| Gastroenteritis | 6% (1/16) |
| Headache | 6% (1/16) |
| Hyperammonemia | 6% (1/16) |
| Myocardial Infarction | 6% (1/16) |
| Neoplasm/Malignant neoplasm | 6% (1/16) |
| Peripheral Ischemia | 6% (1/16) |
| Pyrexia | 6% (1/16) |
| Shunt Occlusion | 6% (1/16) |
| Single cluster focal seizure | 6% (1/16) |
| Thrombocytopenia | 6% (1/16) |
| Other Single AEs | 6% (1/16) |

Therapy discontinuations due to intolerable AEs

All studies reviewed reported a rate of therapy discontinuation due to intolerable AEs. The range of rates of discontinuation due to intolerable AEs was 0%-33%. AEs presented in Table 4 were reported as the reason for treatment discontinuation. Rates of prevalence for individual AEs resulting in discontinuation were mostly not given, therefore it was elected to report number of studies where a specific AE was given as the reason for discontinuation.

TABLE 4: EVENTS LEADING TO THERAPY DISCONTINUATION DUE TO INTOLERABLE ADVERSE EVENTS FOR VALPROIC ACID IN REVIEWED STUDIES (n=16)

| Reported Intolerable AE | % of studies reporting AE (n/16) |
|---------------------------------|----------------------------------|
| Weight gain | 56% (9/16) |
| Alopecia | 50% (8/16) |
| Fatigue | 44% (7/16) |
| Psychiatric/behavioural | 25% (4/16) |
| Rash | 25% (4/16) |
| Somnolence | 25% (4/16) |
| Tremor | 25% (4/16) |
| Digestive disorders | 19% (3/16) |
| Nausea/Vomiting | 19% (3/16) |
| Thrombocytopenia | 19% (3/16) |
| Pancreatitis | 13% (2/16) |
| Headache | 13% (2/16) |
| Abdominal pain | 13% (2/16) |
| Abnormal Gait | 6% (1/16) |
| Appetite increase | 6% (1/16) |
| Appetite decrease | 6% (1/16) |
| Arterial Embolism | 6% (1/16) |
| AST elevation | 6% (1/16) |
| Ataxia | 6% (1/16) |
| Bleeding Complications | 6% (1/16) |
| Dizziness | 6% (1/16) |
| Granulocytopenia | 6% (1/16) |
| Hematuria | 6% (1/16) |
| Hyperammonemia | 6% (1/16) |
| Lab Abnormality (not specified) | 6% (1/16) |
| Liver Function Abnormalities | 6% (1/16) |
| Menstrual disorder | 6% (1/16) |

1.1.4.2 TOLERABILITY OF AEDs IN POPULATIONS WITH EPILEPSY

There are over 20 AEDs that have been approved in North America and Europe. AEDs are considered to be of “3 generations”, based on the timeframe of their development - 1st generation includes: carbamazepine (CBZ); clobazam; clonazepam; ethosuximide (ETX); phenobarbital; phenytoin; sulthiame; and VPA; 2nd generation includes: felbamate (FBM); gabapentin(GBP); lamotrigine (LTG); levetiracetam (LEV); oxcarbazepine (OXC); pregabalin; tigabine; topiramate (TPM); vigabatrin; zonisamide (ZNS); and 3rd generation includes: brivaracetam (BVC) , eslicarbazepine acetate, lacosamide (LCM); perampanel (PMP); retigabine; rufinamide; and stiripentol⁸³. Modern AEDs (2nd and 3rd generation) are generally considered less enzyme-inducing, or are not metabolized by the oxidative cytochrome p450 system, and are therefore less likely to be involved in drug interaction based on enzyme induction⁸⁴. However in various studies comparing 1st generation to subsequent generations of AED, the efficacy/tolerability profile was comparable or better. Additionally, most 2nd/3rd generation AEDs are listed as adjunctive treatment of epilepsy in adults, and therefore used off-label in pediatric populations⁸³. In general, the safety/tolerability of VPA is comparable to other AEDs, based on AEs, SAEs, and discontinuation rates.

CBZ and VPA are both 1st generation AEDs and have been compared substantially since they were approved over 40 years ago. The overall prevalence of AEs is similar for the two AEDs [52% VPA vs 55% CBZ⁷¹; 49.4 % VPA vs 48.4% CBZ⁷⁰; 52% VPA vs 55% CBZ⁷⁶]. Treatment failure due to SAEs is also comparable, with treatment failing in 5% of

patients on VPA vs. 3% of patients on CBZ over a period of 6 months – 3 years⁷⁰. Lastly, 90% of patients on VPA remained on treatment at 6 months, as compared to 75% of CBZ patients⁷⁰

OXC is a 2nd generation AED. Safety profiles are also similar between the drugs, where the proportion of patients in the OXC group and VPA groups experiencing at least one AE, regardless of relationship to the trial drug, is similar (89.8 % VPA vs. 87.6% OXC)⁷². Further, there were no statistically significant differences between VPA and OXC with respect to the total number of premature discontinuations or those due to AEs⁷².

TPM is also a 2nd generation AED, and like VPA is a broad-spectrum AED. In one study, the time to exit study for any reason did not differ between VPA, TPM, or CBZ⁶⁶. However in the pediatric substudy, discontinuation due to AEs was 32% for VPA, 14% for TPM, and 4% for CBZ⁷⁷. However in another study, which included an adult and pediatric population, there was no significant difference in overall clinically important AEs (22.7% VPA vs 24.9% TPM)⁷⁵. There was also no significant differences for treatment failure due to intolerable AEs⁷⁵.

LTG is also a 2nd generation AED. LTG has been suggested as an alternative to VPA, particularly for women of childbearing age, because of concerns about higher rates of teratogenicity and delayed cognitive development in children exposed to VPA in utero⁷³. However for time to treatment failure, there were significant differences between drugs, where VPA was the best option, as compared to LTG and TPM⁷³. Further, cumulative incidence analysis of treatment failure for intolerable AEs indicated that TPM is significantly inferior to both VPA and LTG⁷³. Similarly, another study also indicated that there was no significant difference in AEs leading to withdrawals between VPA and LTG⁷⁸. Another study compared VPA with LTG and ETX (another 1st generation AED). There were no significant differences among the treatment groups at 20 weeks in the frequency of treatment failures due to either intolerable AEs or withdrawal from the study⁸⁰. Although certain side-effects occurred more frequently among children treated with ETX or VPA, as opposed to LTG, these side effects were transient and did not require discontinuation of treatment⁸⁰. However by 12 months, the largest percentage of subjects discontinuing due to AEs were in the VPA group 9% vs 3% for LTG, and 1% for ETX⁸¹. Although VPA discontinuations were mostly due to weight increase after 20 weeks of therapy⁸¹. Another study also did not show statistical differences for treatment failure due to intolerable AEs between VPA, LTG and ETX⁶⁷

Other 2nd generation AEDs are GBP, LEV, ZNS, and FBM. Overall treatment emergent AEs was reported at 77.9% for patients treated with ZNS⁸⁵ and 63%⁸⁶ for FBM. Report of incidence of drug-related AEs was 39-55%⁸⁷ for LEV, and 77.9% with ZNS⁸⁵. Report of intolerable AEs was 15.2%⁸⁸, and 19.3%⁸⁷ for GBP and ZNS respectively. For LEV, incidence of drug-related SAEs were reported between 0-4.7%⁸⁷, while for ZNS it was reported to be 16.4%⁸⁵. Reported life-threatening SAEs, namely – aplastic anemia and hepatotoxicity have severely limited the widespread use of FBM. The risk of hepatic failure with FBM has been estimated to be 1:18,500-25,000⁸⁹ and some cases have resulted in liver transplant or death. Aplastic anemia is estimated to be 1:3000⁸⁹. As a result of these SAEs, the manufacturer recommends that written consent be obtained before therapy is initiated.

The most recent AEDs are termed 3rd generation AEDs; included in this grouping are LCM, BVC, and PMP. Reported AEs incidence was reported at 42%⁹⁰ for LCM, 37%⁹¹ for BVC, and between 64.5-89%⁹² for PMP, depending on dose. Discontinuations due to AEs were reported at 11%⁹³ for LCM, and 3% for BVC⁹¹. SAEs were reported at 3.5-8.2% for PMP, depending on dose⁹².

1.1.4.3 COMPARISON OF SAFETY/TOLERABILITY PROFILES OF VOR, VPA, and AEDs

As VOR has only been trialed in populations with malignancies, a population with a serious illness burden that is heavily pretreated, safety and tolerability findings from these studies are potentially not applicable to an epilepsy population. Therefore it was decided to compare the safety and tolerability findings of VOR to those of VPA, a widely utilized HDAC inhibitor for the treatment of seizures and epilepsy. In turn, these findings were compared to the general tolerability of commonly used AEDs. As VOR is not approved for use in children, the tolerability in a pediatric population was examined by reviewing five Phase 1 trials, which included only pediatric participants or a combination of adult/pediatric participants testing VOR for the treatment of various malignancies. As the reported margins of safety and tolerability for VPA were quite large, a review of sixteen large (~100 pediatric/adult patients or more on VPA per study), international, multi-centered trials, utilizing VPA for the treatment of seizures/epilepsy was conducted to determine context for the wide reporting margins.

Adverse Events

The rate of overall AEs reported in the adult studies of VOR were 324 AEs (all grades) in 86 patients; in the reviewed pediatric studies for VOR, there were a total of 378 AEs reported (Grade 2-5) in 110 patients. In the adult VOR studies, the most common AEs were diarrhea, nausea and thrombocytopenia; most Grade 3-4 AEs consisted of thrombocytopenia and nausea. In the reviewed pediatric studies, the most common AEs were hematologic type, and included leukocytopenia, lymphopenia, thrombocytopenia, neutropenia, and anemia; and the most common non-hematologic AE was nausea; this profile of AEs was the case regardless of grade. There was a higher prevalence of Grade 3-4 AEs in the reviewed pediatric studies than the adult studies.

For VPA, incidence of reported AEs ranged from 23-88% in reviewed studies; for AEDs (all generations), this ranged from 14 -89%. The most commonly reported AEs for VPA are weight gain, fatigue, tremor, headache, alopecia, nausea, thrombocytopenia, dizziness and vomiting. Overall it appears that the incidence of AEs is higher in VOR than in VPA or AEDs.

Serious AEs:

In the adult studies for VOR, the reported incidence rate of SAEs was 7%, which included pulmonary embolism and anemia. However SAEs are defined as “any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization”. According to this definition, Grade 4 events would qualify as SAEs, however in the adult VOR studies, Grade 3-4 AEs were grouped together. The incidence rate of Grade 3-4 events in these studies was 24%. In the reviewed pediatric studies for VOR, the rate of incidence of reported serious events (serious DLTs and death) was 5%, and included thromboembolic events, bleeding/hemorrhage, neuropathy, and hypoxic/acute respiratory distress, however none of these events were considered to be related to VOR therapy. The incidence of Grade 4 events (considered SAEs as per the standard SAE definition) in these pediatric studies was 65%, the majority of which included: lymphopenia, thrombocytopenia, leukopenia, and nausea.

The rates of SAEs for VPA and AEDs were comparable with 0.8 -10% for VPA, and 4.7-8.2% for AEDs. The most commonly reported SAEs for VPA were pancreatitis, hospitalization (unspecified) and pneumonia. Overall the rates of SAEs appears to be comparable for VOR, VPA and AEDs. However, when considering Grade 4 events as SAEs, as

per the standard definition of SAE, it appears that children on VOR therapy exhibit a much higher prevalence of serious events, comprised mostly of hematologic events.

AEs resulting in death

In the adult VOR studies, there was a total of 5 deaths, each of which were considered unrelated. In the reviewed pediatric VOR studies there were a total of 3 events leading to death all of which were also considered unrelated. Several deaths were reported in the VPA studies reviewed, however none were deemed related to therapy.

Discontinuation of therapy due to Intolerable Adverse Events or Dose-Limiting Toxicities

In the adult VOR studies, rate of discontinuation due to AEs was 10.5% and included anemia, angioneurotic edema, asthenia, chest pain, death, DVT, ischemic stroke, lethargy, pulmonary embolism and skin lesions. In the reviewed pediatric VOR studies, the prevalence of AEs meeting the criteria for DLT was 33 %, one-third of these discontinuations were due to thrombocytopenia. For VPA, reported incidence of discontinuation due to intolerable AEs was between 0 - 33%, but the majority of studies reported rates of up to 15%. For AEDs, rates of discontinuation due to intolerable AEs was between 3-19%. In the VPA reviewed studies, the most common reasons for discontinuation reported was weight gain, alopecia, fatigue, psychiatric/behavioral type AEs, tremor, and nausea/vomiting. The rates of discontinuation due to AEs is comparable for the adult studies of VOR, and reviewed studies of VPA and AEDs (when the median of the ranges are taken). However three of the reviewed VPA studies^{69, 77, 80, 81} reported discontinuation rates similar to the pediatric VOR studies; all of these studies were either exclusively pediatric or included pediatric patients.

Anticipated safety and tolerability of VOR in pediatric patients with medically refractory epilepsy

Overall, VOR is considered to be tolerable in populations of patients with various malignancies, however VOR has not been trialed in a pediatric population with seizures, and the safety and tolerability are unknown in this population. The pivotal studies for approval of VOR were reviewed, however this patient population only included adult patients with CTCL. In order to gain a better understanding of safety and tolerability of VOR in a pediatric population, Phase 1 studies utilizing VOR in pediatric populations were reviewed. However the patient populations in these studies included various refractory and recurrent malignancies that were heavily pretreated, and nearly all treatment arms included combination therapy. Given these conditions, it is unlikely that these findings can be translated to the population in this proposed study. Therefore, it was elected to also review and compare the safety and tolerability profile of VPA, another HDAC inhibitor that has been commonly used as a broad spectrum AED for over 30 years; to better set the context for the use of an HDAC inhibitor in the proposed population. Additionally, this was compared to the overall tolerability of AEDs in general. Three metrics were examined: overall AEs, SAEs, and discontinuations due to intolerable AEs. Following this analysis, a reasonable assumption of the safety and tolerability of VOR in a pediatric population with seizures can be made.

When comparing overall AEs for VOR, it appears that there is higher prevalence of Grade 3-4 AEs in the pediatric population than in the adult population, and the majority of these events in the pediatric population are hematologic events, as opposed to constitutional events found in the adult studies. This is most likely due to several factors including: the inclusion of various other refractory/recurrent malignancies (solid tumors, CNS tumors, leukemia) in the pediatric population in addition to CTCL patients; patients in the pediatric population were heavily pre-treated prior to

commencing in the studies; study treatment included combination therapy in addition to VOR in nearly all treatment arms. Further, in the pediatric studies, patients were only required to demonstrate moderate hematologic function (platelet count $\geq 100,000/\mu\text{L}$; and absolute neutrophil count $\geq 1000/\mu\text{L}$) and not be transfusion dependent, whereas in the adult studies, eligibility criteria required patients to demonstrate adequate hematologic function. It is likely that the pediatric population in the Phase 1 VOR studies were particularly susceptible to the adverse hematologic effects of VOR. Indeed, thrombocytopenia is also a known AE associated with VPA, which has been shown to be dosage dependent⁷⁹. There is also a possibility that the immature systems of children are more susceptible to these effects, however in large dose-dependent study, it was found that female gender and increased dose were correlated with greater likelihood of thrombocytopenia, however age was not⁷⁹. Aside from the noted hematologic events, which made up approximately two-thirds of all AEs, the most commonly reported AE in the VOR pediatric studies was nausea; similarly the most commonly reported AEs in the adult VOR studies were diarrhea, nausea, and thrombocytopenia, albeit at less prevalent rates. It also appears that overall, there is a greater prevalence of AEs reported with VOR than with VPA or other AEDs. Although, the interpretation of this comparison is limited since the margins of the reported incidence rates for VPA and AEDs are quite large. Given the generally stable health status of patients in the proposed population, incidence of overall AEs is anticipated within the range of that typically found for AEDs, although there is a possibility that there may be a higher prevalence of hematologic type AEs.

The second metric reviewed was SAEs. The incidence of SAEs as reported for the adult VOR studies was 7%; 5% for the pediatric VOR studies, 0.8-10% for VPA studies, and 4.7-8.2% for AEDs. Given the differences in study designs and populations, the rates of SAEs are comparable. The most common SAEs reported in the adult VOR studies were thromboembolic events and anemia; in the pediatric VOR studies, SAEs consisted of thromboembolic events, bleeding/hemorrhage, neuropathy, and hypoxic/acute respiratory distress. Indeed the product monograph indicates that thromboembolic events maybe associated with VOR therapy with an overall incidence rate of 6.8%. However in the pediatric VOR studies, all SAEs were not considered to be related to VOR. Typically however, severity of events in cancer trials are graded using the National Institutes of Health CTCAE Grading system, whereas clinical trials typically utilize the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/ Good Clinical Practice Guidelines (GCP) for rating severity of events. Utilizing the ICH-GCP definitions, a "serious" AE includes events that are life-threatening. Events rated as Grade 4 using the CTCAE system are considered to be life-threatening. Given this, Grade 4 events using the CTCAE reporting could be considered to be "SAEs". An analysis could not be carried out on the adult VOR studies because Grade 3 and 4 events were grouped together for reporting, however in the pediatric VOR studies, inclusion of the Grade 4 as SAEs caused the incidence rate of SAEs to jump to 65%, with again the most commonly reported events comprising hematologic events and nausea. Although this is an important consideration, it is also important to note that the term 'life-threatening' in the ICH/GCP definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. It is not absolutely clear whether these Grade 4 events meet the ICH/GCP criteria for a serious event. However, the fact remains that Grade 4 hematologic events, which according to the CTCAE are platelets $< 25 \times 10^9/\text{L}$; absolute neutrophil count $< 0.5 \times 10^9/\text{L}$; and lymphocyte count $< 0.2 \times 10^9/\text{L}$; are medically quite serious, regardless of whether they meet a pre-set definition. As discussed in the above section, it is unlikely that the rates of incidence found in the Phase 1 VOR pediatric studies are expected in an overall medically stable population; it is anticipated that incidence of SAEs in the proposed population will be that typically seen with VPA/AEDs. However potentially serious hematologic events cannot be ruled out and hematologic testing, in addition to other lab safety testing will be conducted every 2 weeks to monitor study patients. Patients will also be advised of signs of symptoms associated with these hematologic events and to contact the study team in the event of these signs and symptoms. Regarding the other events cautioned to require special monitoring in

the product monograph, the incidences in the VOR pediatric studies were quite low, with only 1 event of prolonged QT/QTc (Grade 3); 3 events of hyperglycemia (2 – Grade 3; 1 – Grade 4); and 3 events of dehydration (1 – Grade 2; 2 – Grade 3); incidence of these AE types are anticipated to be quite low. Deaths are not expected to occur in this study.

The final metric investigated was rate of discontinuation due to intolerable AE/DLTs. The rate of discontinuation in the adult VOR studies was 10.5%; in the pediatric VOR studies the prevalence of patients meeting the criteria for a DLT was 33%; for VPA, rate of discontinuation was 0-33%, and for AEDs, this was reported as 3-19%. On first impression, the rate of discontinuation due to intolerable AEs appear similar for the VOR pediatric studies and VPA reviewed studies. However, the VPA discontinuation rate may be somewhat inflated since the majority of the VPA reviewed studies reported rates of up to 15% (11/15 studies); and the studies with the higher reported rates did not allow for dose de-escalation in their study designs, which is not typical in clinical practice. It is of interest to note however that three of the studies reporting higher discontinuation rates due to AEs were pediatric only studies or included pediatric patients. The rate of discontinuation for the pediatric VOR studies may also be somewhat inflated, because in fact this rate actually represents DLTs. In our analysis, DLT events were counted as “discontinuations due to intolerable AEs” in order to allow for comparison. Furthermore, all DLT events regardless of dosage of VOR and dosage of the other combined therapies was included in our analysis for discontinuation. In reality however, the majority of DLTs occurred at doses higher than 230 mg/m², which is why this was recommended as the MTD for pediatric patients with malignancies. It is of note however that over one-third of discontinuations was due thrombocytopenia, once again suggesting that adverse hematologic events are common, potentially serious and often are the cause for discontinuation. This is in contrast to VPA, in which the most common reasons for discontinuation are weight gain, fatigue, alopecia, and behavioral changes in children. Although it has been indicated that, in general, findings of the VOR pediatric studies are most likely not applicable, nor expected in a pediatric population with seizures, it is possible that rate of discontinuation may actually be similar given that rates of discontinuations for VPA are seen in the range of 33% particularly in pediatric studies. Therefore it can be expected that rate of discontinuations may be in the range of that seen in the Phase 1 VOR pediatric studies, and that seen in the pediatric VPA studies.

Following a careful review of adult studies of VOR, pediatric studies with VOR and comparing the safety and tolerability to VPA and AEDs, it is anticipated that VOR in a population of pediatric patients with epilepsy will be well-tolerated. Given the stable health status of patients to be recruited in this study and treating with VOR at a dosage of 230 mg/m², it is anticipated that the rates will not be more remarkable than at seen for normally prescribed AEDs and VPA in all three metrics reviewed. It is anticipated however that there may be a higher proportion of events that are hematological in nature, as compared to other AEDs. However, this is not a surprising event for the HDAC inhibitor class of drugs, since VPA is known to be associated with greater incidences of thrombocytopenia. Safety measures are in place to carefully monitor and identify such events, as well as other possible AEs.

1.2 RATIONALE FOR THE STUDY

A single centre, open-label, phase 2A/B pediatric epilepsy pilot study, evaluating safety, tolerability, and efficacy of VOR in a pediatric population with medically intractable epilepsy is proposed. Currently the incidence of medically refractory epilepsy remains unacceptably high and an unmet medical need exists for these patients. Newly identified treatment targets to control seizures are clearly required, however typically drug development takes greater than a decade to become available as a treatment option. Therefore, a strategy which rapidly identifies potential therapies

that can be rapidly tested in the clinical setting is paramount. The metabolism based discovery platform, initiated by our group is such a platform in which potential targets can be rapidly escalated to clinical trials in an accelerated knowledge translation manner. Via this platform, Dr. Kurrasch *et al*³⁰ identified VOR as a potential viable therapy for the treatment of seizures in epilepsy. The pre-clinical work described above indicates outstanding efficacy and supports the potential benefit for VOR in potentially reducing refractory seizures in children with medically intractable epilepsy. VOR is currently approved by Health Canada for the treatment of CTCL malignancies. VOR demonstrated good tolerability in pediatric patients with various malignancies. When reviewing the safety and tolerability of VOR in the context of that of VPA and other AEDs, it is anticipated that tolerability of VOR will not be worse than that normally seen with currently approved AEDs in pediatric patients with medically refractory epilepsy.

To our knowledge – this proposed study is the first trial investigating VOR within a pediatric population with medically intractable epilepsy. In this proposed pilot trial, pediatric patients, aged 4 to 17 (inclusive) with medically intractable epilepsy will be given VOR, at a dose of 230 mg/m²/day for a duration of 6 weeks to determine safety, tolerability and efficacy at this dose in combination with standard of care anti-seizure medications.

SECTION 2.0: OBJECTIVES

2.1 PRIMARY OBJECTIVES

Characterize the safety and tolerability of 230 mg/m²/day VOR, administered orally, in a pediatric population with medically intractable epilepsy in combination with standard of care anti-seizure drugs.

2.2 SECONDARY OBJECTIVES

Evaluate the efficacy of 230 mg/m²/day of VOR, administered orally, in reducing seizures in a pediatric population with medically intractable epilepsy in combination with standard of care anti-seizure drugs.

SECTION 3: STUDY DESIGN

3.1 OVERVIEW OF STUDY DESIGN AND DOSING REGIMEN

The study will consist of a single centre, open-label Phase 2A/B pilot study evaluating the safety, tolerability, and efficacy, of VOR in a pediatric population with medically intractable epilepsy. Participants will be administered 230 mg/m²/day of VOR in addition to standard of care anti-seizure medication for a duration of 6 weeks.

3.1.1 DOSAGE

Participants will be administered 230 mg/m²/day of VOR in addition to standard of care anti-seizure medication for a duration of 6 weeks. The dosage was chosen based on the MTD of five Phase 1 trials, which included pediatric patients or were exclusively pediatric trials⁵⁰⁻⁵⁴.

Briefly, in a Phase 1 study, Fouladi et al⁵⁰, investigated VOR alone and in combination with 13cRA in children with recurrent or refractory malignancies (Part A – solid tumors; Part B – leukemia). Three dose levels were utilized: 180 mg/m² VOR; 180 mg/m² VOR + 13cRA; 230 mg/m² VOR; 300 mg/m² VOR). In the solid tumors group at a dose of 180 mg/m² VOR, one patient suffered an SAE, however this was deemed to not related to treatment. At the 230 mg/m²/d VOR dose level, there were no DLT in the first three patients enrolled. At 300 mg/m²/d DLT occurred in 2 of 6 patients but since the AEs were of different classes, the cohort was expanded to six additional evaluable patients. At this dose, 2 patients had DLT thereby exceeding the MTD, therefore three additional patients were subsequently enrolled at the 230 mg/m². In this cohort, only one experienced a DLT, defining 230 mg/m²/d as the MTD and recommended phase II dose for children with solid tumors. The recommended phase II dose was then trialed in the refractory leukemia group. Two of the first five patients experienced DLT, therefore this dose did not appear tolerable in children with refractory leukemia; no other dose finding was attempted in this population.

In a Phase 1 study, Hummel et al⁵¹ investigated VOR in combination with TEM in children with recurrent or refractory brain or spinal cord tumors. Three dose levels were tested: 230 mg/m² VOR + 150 mg/m² TEM; 300 mg/m² VOR + 150 mg/m² TEM; 300 mg/m² VOR + 200 mg/m² TEM. There were no DLTs at Dose level 1 or 2. At dose 3, 4 patients had DLTs, therefore the recommended phase 2 dose for the combination of VOR and TEM as 300 mg/m² VOR + 150 mg/m² TEM.

In a Phase 1 study, Muscal et al⁵² investigated VOR in combination with BOR in children with recurrent or refractory solid tumors, including CNS tumors. Three dose levels were tested: 180 mg/m² VOR + 1.3 mg/m²/d BOR; 230 mg/m² VOR + 1.3 mg/m²/d BOR; 300 mg/m² VOR + 1.3 mg/m²/d BOR. At the third dose level, 2 patients experienced DLTs, thus dose level 2 (230 mg/m² + 1.3 mg/m²/d BOR) is the recommended phase 2 dose.

Burke et al⁵³ performed a pilot study investigating the combination of DEC and VOR followed by standard re-induction chemotherapy in patients with relapse or refractory acute lymphoblastic leukemia. The only dosage tested was 230 mg/m² VOR + 15 mg/m² DEC. The choice of this dosage was based on prior Phase 1 studies identifying the MTD for these agents. 12 patients completed the full 4 days of treatment and were evaluable for toxicity assessment; 8 patients completed full protocol therapy and end of course evaluation; the one patient who did not complete the 4 days died of progressive disease on Day 4; the other 4 patients did not complete protocol therapy due to progressive disease , toxic

death; family decision to stop due to toxicity; patient found to have leukemic involvement and physician elected to change treatment .

Dubois et al⁵⁴ conducted a phase I multicenter clinical trial conducted through the New Approaches to Neuroblastoma Therapy (NANT) consortium with the primary objective to determine the MTD of vorinostat and MIBG when used in combination. Five dosage levels were assessed: 8 mCi/kg ¹³¹I-MIBG + 180 mg/m² VOR; 12 mCi/kg ¹³¹I-MIBG + 180 mg/m² VOR; 12 mCi/kg ¹³¹I-MIBG + 230 mg/m² VOR; 15 mCi/kg ¹³¹I-MIBG + 230 mg/m² VOR; 18 mCi/kg ¹³¹I-MIBG + 230 mg/m² VOR. There was no DLT at dose levels 1-3; at dose level 4, there was 1 DLT; and at dose level 5 – 2 patients had DLT. Due to 2/2 patients with DLT at Dose 5, the dose was de-escalated to 18 mCi/kg ¹³¹I-MIBG + 180 mg/m² VOR because there were no DLT at that dose level. Therefore the MTD is 18 mCi/kg ¹³¹I-MIBG + 180 mg/m²VOR; this is because MIBG is the main active agent in this combination and VOR acts a radiation sensitizer; the usual maximum feasible dose is 18 mCi/kg

3.1.2 PHASES OF STUDY

There are three phases to the study.

Phase 1: Screening period

During this phase, participants will be screened for study eligibility, which will last a total of 4 weeks. This will include several baseline investigations including full review of medical history and current medications, seizure frequency, physical examination, vital signs, laboratory safety testing, pregnancy testing for eligible patients, and electrocardiogram (ECG) (see Section 5 Schedule of Assessments and Procedures for complete list of screening procedures). In addition, baseline seizure frequency will be determined during this period. Clinically stable participants, fulfilling all eligibility criteria (see sections 4.2 and 4.3) will be enrolled in the treatment period of the study.

Phase 2: Treatment period

The duration of the treatment period will be 6 weeks. VOR will be given as fixed doses of 230 mg/m²/day. Following the enrollment visit, participants will visit the clinic for 2 more visits every 2 weeks, plus an end of treatment (EOT) visit (see Section 5.1 for detailed schedule). Participants may be seen more frequently for unscheduled visits for follow up of AEs, etc. as per the investigator's discretion. Study visits will include a physical examination, height and weight measurement, vital signs, pregnancy testing (required patients only). Safety monitoring during the treatment period will include laboratory safety testing and ECG. Investigators will review current medications, AEs, seizure diary/frequency at each visit. Investigators will assess study medication adherence at all visits; unused study medication will be returned to site at each visit and new study medication will be dispensed by local pharmacy, as recommended by the investigator. Unused study medication will be destroyed as per local standard operating procedures. All assessments and visit procedures will occur as stipulated in Section 5: Schedule of Assessments and Procedures.

Phase 3: Follow-up period

A safety follow-visit (SFU) will take place 6 weeks after the EOT Visit. The SFU visit will include a physical examination, height and weight measurement, vital signs. Safety monitoring for this visit will include laboratory safety testing and ECG. Investigators will review AEs since last visit and seizure diary/frequency. Any ongoing AEs will be followed by the investigator until resolution or stability.

3.1.2 END OF STUDY

The end of the study is defined as the date of the last patient's last visit, or the date at which the last data point, required for analysis, is completed, whichever date is later.

3.2 RATIONALE FOR STUDY DESIGN

The pre-clinical data for VOR is highly suggestive of a potential novel therapy for the treatment of medically intractable epilepsy. However, VOR is currently approved only for the treatment of cutaneous manifestations in patients with advanced CTCL who have progressive, persistent or recurrent disease subsequent to prior systemic therapies. A safety/efficacy trial of VOR in a population with medically intractable epilepsy is largely warranted, given the existing need for additional therapeutic strategies. The target population will consist of pediatric patients with medically intractable epilepsy, recruited from the Alberta Children's Hospital (ACH) Neurology Outpatient Clinic, with medically intractable epilepsy despite exhaustive treatment with current standard therapies, who would be anticipated to benefit from a novel intervention strategy.

The primary endpoints of this study are the safety & tolerability of VOR in pediatric patients with medically intractable epilepsy. The secondary endpoints of this study is the efficacy of VOR in reducing seizure frequency in this population pool. Participants will receive 230 mg/m²/day of VOR in addition to standard of care anti-seizure medication for a duration of 6 weeks, to evaluate the risk/benefit of VOR at this dosage on top of standard of care anti-seizure treatment.

The proposed study design will allow for the study objectives to be met within the context of a typical Canadian clinical epilepsy treatment centre. Completion of this pilot study in this population will begin to indicate the safety & efficacy profile of VOR at a dosage of 230 mg/m²/day as a potential therapy for the treatment of seizures, and based on findings may justify a larger randomized study to further investigate this potential avenue in children with medically intractable epilepsy in a rapidly translational manner.

3.3 NUMBER OF SUBJECTS

12 pediatric patients meeting the criteria of medically intractable epilepsy in addition to the other eligibility criteria, recruited from the ACH Neurology Outpatient Clinic will be enrolled in study.

SECTION 4: STUDY POPULATION

4.1 OVERVIEW

The target population will consist of pediatric patients with medically intractable epilepsy, recruited from the ACH Neurology Outpatient Clinic, who continue to experience seizures despite exhaustive treatment with current standard therapies, and anticipated to possibly benefit from a novel intervention strategy.

4.2 INCLUSION CRITERIA

Patients must meet **ALL** of the following criteria in order to be eligible for this study:

1. Males or females aged 2 – 17 years (inclusive)
2. Medically intractable epilepsy, defined as having failed at least 2 standard anti-seizures therapies and experiencing at least 3 motor seizures per week, separated by at least 24 hours that are quantifiable by observation (e.g. discrete episodes of motor activity). Participants experiencing other seizure types in addition to motor seizures may also be enrolled but must meet the minimal requirement for motor seizures.
3. Ability and willingness of family and/or caregiver (when appropriate) to give written informed consent and to comply with requirement of the study
4. Adequate bone marrow function (defined as an absolute neutrophil count (ANC) of $\geq 2 \times 10^9/L$; platelet count of $\geq 150 \times 10^9/L$; hemoglobin of ≥ 110 g/L [3-11 years], ≥ 120 g/L [females 12 years or over], ≥ 125 g/L [males 12-14 years], ≥ 137 g/L [males 15 years or older])
5. Adequate renal function (defined as serum creatinine $< 1.5X$ age-adjusted upper limit of normal [ULN], or glomerular filtration rate ≥ 70 mL/min/1.73 m²)
6. Adequate hepatic function (defined as total bilirubin < 1.5 times ULN, and alanine aminotransferase [ALT] and aspartate transaminase [AST] < 3 times ULN, and albumin > 33 g/L)
7. Corrected QT (QTc) interval of < 450 msec
8. Prothrombin time (PTT) < 1.5 ULN/International Normalized Ratio (INR) < 1.5 ULN
9. Participants on corticosteroids must be taking a stable or decreasing dose for at least 7 days prior to enrollment

4.3 EXCLUSION CRITERIA

Patients meeting any of the following criteria by the day of enrollment are **NOT** eligible for this study

1. Treatment with valproic acid or other HDACi class drugs within at least the last 3 months at time of screening
2. Enzyme-inducing AEDs (including oxcarbazepine (Trileptal), phenobarbital, phenytoin (Dilantin), topiramate (Topamax))
3. Coumarin-derivative anti-coagulants
4. Participants being considered for surgery for management of seizures during screening or who will be receiving surgery during for management of seizures during study period (includes all neurosurgery for the management of seizures or device implantation for the management of seizures)
5. Neurosurgery within the past 12 months
6. Use of Vagus Nerve Stimulator (VNS) where settings have not been stable for at least 6 months

7. Planned surgery or other invasive medical treatment during screening or during treatment period
8. Hypokalemia or hypomagnesemia
9. Participants starting or currently on any neurometabolic diet (including but not limited to ketogenic diet; medium-chain triglyceride diet; modified Atkins diet; low glycemic index diet) during study
10. History of non-catheter related deep venous thrombosis
11. Pleural effusion
12. Malignancy within the past 5 years.
13. Any serious medical condition that according to the investigator could interfere with the conduct of the study
14. Serious comorbid disease in which the life expectancy of the patient is shorter than the duration of the trial
15. Unwillingness or inability to comply with study requirements
16. Positive pregnancy test, lactating females or heterosexually active participants not willing to use highly effective methods of contraception (See [Section 4.6](#))
17. Participation in any clinical trial with an investigational drug, or therapy not approved by Health Canada, within one month prior to screening

4.4 DIAGNOSTIC CRITERIA FOR MEDICALLY INTRACTABLE EPILEPSY

Medically intractable epilepsy as defined by the ILAE 2010 task force as experiencing at least 3 motor seizures per week, separated by at least 24 hours that are quantifiable by observation (e.g. discrete episodes of motor activity), despite treatment with standard clinical therapies. Participants experiencing other seizure types in addition to motor seizures may also be enrolled but must meet the minimal requirement for motor seizures.

4.5 CONCOMITANT MEDICATIONS AND TREATMENTS

4.5.1 PROHIBITED CONCOMITANT MEDICATIONS AND TREATMENTS

Participants may not be initiated on the following treatments or therapies during the study:

- neurometabolic diets including but not limited to ketogenic diet; medium-chain triglyceride diet; modified Atkins diet; low glycemic index diet
- surgery for the management of seizures; patients who have previously had surgery for the treatment of seizures may participate as long as surgery was completed a minimum of 12 months at time of enrolment
- device implantation or use of other devices for the management of seizures; patients may be entered if device was implanted a minimum of 12 months prior to enrolment and settings have remained stable for a minimum of 6 months at time of enrollment
- Valproic acid/valproate/divalproex sodium or other Histone Deacetylase (HDAC) Inhibitors
- Enzyme inducing AEDs, including oxcarbazepine (Trileptal), phenobarbital, phenytoin (Dilantin), topiramate (Topamax)
- Coumarin-derivative Anticoagulants
- Any other therapy that is experimental or not approved by Health Canada (e.g. cannabidiol oil)

4.5.2 PERMITTED CONCOMITTANT MEDICATIONS

The use of any concomitant medication will be recorded in the study record.

Treatment for Epilepsy

Patients will continue on their evidence-based medical care for epilepsy as described in regional guidelines and institutional care pathways. All contemporary evidence-based medical care for ACH should be initiated as early as possible during the screening period to allow time for stabilization of the treatment effects before enrollment.

Investigators will monitor patients/treat patients as per normal clinical practice with regard to these medications for the duration of the study. Therapy dose adjustments for the treatment of epilepsy will be left to the investigators' discretion, however it is highly recommended that adjustments be minimized throughout the period of the study.

Patients who have a VNS device implanted for the management of seizures, and whose device treatment parameters are optimized and stable for the last 6 months may participate in study. Changes to the device treatment parameters should be avoided during the study.

Permitted medications with special precautions

Other QT/QTc Prolonging Drugs:

As per the product insert, concomitant use of VOR with another QTc prolonging drug may have an additive effect on QTc interval, and the concomitant use of VOR with another QT/QTc-prolonging drug should be avoided. This includes: Class IA antiarrhythmics; Class III antiarrhythmics; Class IC antiarrhythmics; anthracyclines; tyrosine kinase inhibitors antipsychotics; antidepressants; opioids; macrolide antibiotics and analogues; quinolone antibiotics; pentamidine; antimalarials; azole antifungals; domperidone; 5-HT₃ receptor antagonists; tacrolimus; beta-2 adrenoceptor agonists. In the case where a participant is taking a QT/QTc prolonging drug during treatment phase, it is recommended that an ECG be conducted within one week of starting VOR and the QT/QTc prolonging drug if the next protocol ECG is longer than one week. Additional ECGs should be conducted as per the investigator's discretion if the participant is exhibiting signs of QT/QTc prolongation.

Drugs that Disrupt Electrolyte Levels:

Electrolyte imbalance such as hypokalemia increases the risk of QTc interval prolongation, therefore the use of VOR with drugs disrupting electrolyte level is discouraged. Drugs that can disrupt electrolyte levels include, but is not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; and high dose corticosteroids. Additional laboratory testing may be conducted as per the investigator's discretion if the participant is exhibiting signs of disruption of electrolyte levels.

4.6 CONTRACEPTION PROTECTION

Heterosexually active females and males (partners of male participants, as appropriate) must use an acceptable method of contraception to prevent pregnancy. Acceptable methods of contraception include the following:

- Abstinence
- Barrier type devices (e.g. female condom, diaphragm and contraceptive sponge) used ONLY in combination with a spermicide
- Intra-uterine devices
- Oral contraceptive agents started at least 90 days before start of study
- Depo-Provera (medroxyprogesterone acetate)
- Levonorgestrel implants
- Naturally or surgically sterile females (amenorrheic for at least 1 year and no record of conception for naturally sterile persons)
- Male partner is sterile and is the only sexual partner.

4.7 CRITERIA FOR PREMATURE WITHDRAWAL

Participants have the right to refuse treatment or completely withdraw from the study at any time for any reason. The investigator also has the right to discontinue treatment and withdraw participants from the study treatment in the event of intercurrent illness, AE, treatment failure, protocol violations, administrative reasons, or other reasons deemed necessary by the investigator.

Participants with significant drug compliance issues or safety monitoring compliance issues, not related to AEs will be withdrawn from the treatment phase of the study by the investigator and an EOT visit as well as an SFU visit will be attempted to be performed in all cases.

If the participant withdraws from study treatment only, they will undergo an EOT visit and SFU visit. If the reason for removal of a participant from the study is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded in the study record. If the participant explicitly withdraws consent for additional follow-up, the participant will be asked to undergo a phone SFU visit at the absolute minimum. In addition, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible. A complete final evaluation at the time of the participant's withdrawal should be made with an explanation of why the participant is withdrawing from the study. In the event that a participant is lost to follow up, the last assumed day of medication will be the last day for which number of doses was provided. An attempt will be made to contact participants, via provided phone, email, and registered letter to the address provided. All attempts to contact will be recorded in the study record. In the event that all attempts for contact fail, a chart review and review of NetCare will done at 6 weeks following the last assumed day of medication.

4.8 REPLACEMENT POLICY

PROTOCOL: VOR-17-2471
Version 2: 2018-07-18

Participants who withdraw/are withdrawn or discontinue study medication will not be replaced. Participants who discontinue medication/withdraw from study for non-safety issues within 14 days of commencing study medication will not be included in the final analysis.

SECTION 5: SCHEDULE OF ASSESSMENTS AND PROCEDURES

5.1 PROCEDURES

A detailed schedule of assessments by visit is shown in Table 5 below.

Table 5: Schedule of events

| Study Period | Screening | Enrollment | Treatment Period | | | Follow Up |
|-----------------------------------|-----------|------------|------------------|----------------|------------------|------------------|
| | | | Visit | V3 | V4 | |
| Visit | V1 | V2 | V3 | V4 | EOT ⁶ | SFU ⁷ |
| Total duration (weeks) | - 4 weeks | 0 | 2 | 4 | 6 | 12 |
| Visit windows (weeks) | | | ± 2 days | ± 2 days | ± 2 days | ± 5 days |
| Written informed consent | X | | | | | |
| Eligibility criteria | X | X | | | | |
| Medical history ¹ | X | X | | | | |
| Physical examination | X | | X | X ² | X | X |
| Complete Neurological examination | X | X | X | X | X | X |
| Anthropometrics | X | X | X | X | X | X |
| Vital signs ³ | X | X | X | X | X | X |
| Laboratory testing | X | | X | X | X | X |
| Serum Pregnancy test ⁴ | X | | | X | | X |
| Urine pregnancy test | | X | | | | |
| Study medication dispense | | X | X | X | | |

| | | | | | | |
|-------------------------------|----------------|---|---|---|---|---|
| Medication compliance audit | | | X | X | X | |
| Concomitant medication review | X | X | X | X | X | X |
| Seizure Frequency review | X | X | X | X | X | X |
| Adverse Events | | | X | X | X | X |
| ECG | X ⁵ | | X | | | X |

1. Medical history and Epilepsy history, including other relevant baseline disease characteristics. All available epilepsy history will be collected. Other Medical history will be collected for the past 12 months.
2. Abbreviated physical exam
3. Blood pressure, heart rate, breathing rate, and temperature.
4. Only for female patients of childbearing potential.
5. For screening, the results of a clinically indicated ECG, found to be non-clinically significant within the last 4 weeks can be utilized.
6. EOT may occur prior to 6 weeks if participant is discontinued or withdrawn before completing entire study as per protocol. In the case of withdrawal, the EOT visit should be completed within 2 weeks of the date of withdrawal.
7. SFU visit may occur prior to 12 weeks if participant is discontinued or withdrawn before completing entire study as per protocol. In the case of withdrawal, an SFU visit (or at minimum telephone contact) should be completed within 6 weeks of the EOT visit.

5.1.1 SCREENING EXAMINATION AND ELIGIBILITY SCREENING FORM – VISIT 1

All participants must sign and date the most current Institutional Review Board (IRB)-approved written informed consent before any study-specific assessments or procedures are performed. A screening number will be allocated to each participant. An Eligibility Screening Form (ESF) documenting the investigator’s assessment of each screened participant with regard to the protocol’s inclusion and exclusion criteria will be completed by the investigator. A screen failure log will be maintained by the investigator.

The following study-specific activities will be completed at the screening examination:

- Medical history: Medical history for the past 12 months and all Epilepsy history will be abstracted from participant’s hospital medical record and patient interview.
- Physical examination: the investigator will conduct a complete physical and neurological examination
- Anthropometrics: height and weight will be taken
- Vital signs: blood pressure and heart rate, breathing rate, and temperature will be taken

- Baseline laboratory testing (see [Section 5.3.2.4](#) for description of laboratory testing): This will be done through a service contract via Calgary Lab Services. The Calgary Lab Services reference range will be utilized to assess the clinical relevance of results.
- Pregnancy test: a serum pregnancy test will be administered to all sexually active females of post-menarche status. All heterosexually active males and females will be counseled on the use of appropriate contraceptives during study participation.
- Concomitant medications: will be collected to ensure that the patient is not on any prohibited medications
- Seizure frequency: current seizure types and frequency will be reviewed. Proper seizure tracking will be reviewed with the participant/patient and family; participants will be encouraged to download and use the Seizure Tracker app on their smart phone. Participants will be asked to track their seizures for the duration of the screening period.
- ECG: An ECG will be collected through a service contract via the Cardiology department at the ACH. Participants who have had a clinically indicated ECG, found to be non-clinically significant, within 1 month prior to screening will not require another ECG, provided the investigator deems the participant stable. The ECG may be collected at any point following the screening visit until enrollment visit (Visit 2), as long as results are available and may be reviewed by the investigator prior to enrollment

5.1.2 ENROLLMENT VISIT – VISIT 2

Participants meeting all inclusion and no exclusion criteria will be enrolled. Participants will receive study medication at this visit.

The following study specific activities will be completed at the enrolment visit (Visit 2):

- Medical history: Medical history and Epilepsy history will be reviewed once again to ensure that any new history since screening is captured.
- Anthropometrics: height and weight will be captured to establish baseline growth and to calculate body surface area (BSA) for proper medication dosing
- Vital signs: blood pressure and heart rate
- Pregnancy test: a urine pregnancy test will be done for all applicable participants
- Study medication dispensed: Study medication will be prepared and dispensed by the ACH research pharmacy, with dosage based on participant BSA ([see Section 6.1](#)). Participants will be counseled by the investigator on: how to take the medication, including to consume enough fluids to maintain adequate daily hydration, as adjusted for age; to contact the investigator promptly if excessive vomiting/diarrhea; or dizziness, palpitations, syncope, or increased seizures develop; or to contact the investigator immediately or present to the emergency room if leg swelling, chest pain, or shortness of breath develop. Participants will take VOR, 230 mg/m² once daily, preferably at the same time of the day throughout the treatment portion of the study, in addition to their prescribed evidence-based medical care for seizure management.
- Participants will be given enough study medication to last until the next study visit plus 2 days in the event that the participant cannot make this visit. In this case, the study coordinator will ensure, via phone communication, that participant is not missing a visit due to AEs. In the event of an AE, the investigator will speak to participants/caregivers to give further instruction. If patient is hospitalized, appropriate SAE measures will be undertaken. If participants need to reschedule beyond the 2-day window, additional study

medication may be prescribed by the investigator and dispensed by the ACH research pharmacy on a case by case basis. Participants will not be given medication if the following visit is also missed, without explicit permission by the investigator.

- Concomitant medications: will be reviewed again to ensure that information has not changed since screening visit
- Seizure frequency: current seizure types and frequency will be reviewed. Proper seizure tracking will be reviewed again with the participant/patient and family.

5.1.3 ASSESSMENTS AND PROCEDURES DURING THE TREATMENT PERIOD

Participants will be required to undergo regular visits during the treatment period for the assessments of safety/tolerability and efficacy as outlined in [Table 5: Schedule of events](#)

. They will visit the study center at 2-, and 4 weeks, at 6 weeks for the EOT visit, and 6-weeks after the EOT for the SFU visit. If a participant is discontinued from study medication and/or withdrawn prior to completing the study as per protocol, the EOT visit may occur prior to 6 weeks following enrollment. The SFU visit should be completed within 6 weeks of medication discontinuation.

In addition, the following evaluations will be performed at each visit at the clinic throughout the treatment period:

- Physical examination: standardized physical examinations will be performed at all study visits; an abbreviated physical exam will be conducted at Visit 4 (week 4 visit)
- Complete neurological examination: a complete neurological examination will be completed at all study visits.
- Anthropometrics: height and weight will be captured at all study visits to assess for appropriate growth and for proper medication dosing
- Vital signs: will be captured at all study visits
- Laboratory monitoring: participants will visit the lab for testing at all study visits during this period. Investigators will contact participants if results warrant intervention prior to the next scheduled visit.
- Pregnancy test: Serum pregnancy test will be taken at Visit 4.
- Study medication dispensing and medication compliance: Following investigator recommendation, participants will receive new drug supply at each defined visit. Participants will be required to bring in old unused drug for assessment of compliance. The importance of compliance will be emphasized at each visit. Participants will also be reminded to strive to consume enough fluids to maintain adequate daily hydration, as adjusted for age. Medication will not be dispensed at the EOT visit.
- Concomitant medications: will be reviewed at each study visit.
- Review of AE: Participant's AEs will be reviewed at each study visit. However participants are encouraged to inform investigators about occurrence of AEs as soon as possible; i.e. not wait until their next scheduled visit.
- Seizure Frequency: Participants will be asked to provide their seizure tracker information since the last study visit. Participants' seizure types and how to accurately record seizure frequency will be reviewed by the investigator at each study visit. If participants commence to exhibit new seizure types, they will be asked to collect the seizure frequency of the new seizure type.
- ECG: an ECG will be conducted on Visit 3. The ECG may be collected within 1 week prior to study visit depending on appointment availability at the ECG lab.

5.1.4 SAFETY FOLLOWUP

An SFU for all participants, including patients prematurely withdrawn from treatment, will be conducted 6 weeks after the EOT visit. This visit will include:

- Physical examination
- Complete neurological examination
- Anthropometrics
- Vital signs
- Laboratory monitoring. Participants will be contacted with results requiring intervention
- Pregnancy test: a serum pregnancy test will be taken for applicable participants.
- Concomitant medications
- Seizure Frequency
- Review of Adverse Events
- Review of seizure frequency
- ECG: may be collected within 1 week prior to study visit.

5.2 OUTCOMES ASSESSMENTS

5.2.1 SAFETY AND TOLERABILITY ASSESSMENT

The safety and tolerability of VOR at a dose of 230 mg/m²/day in a pediatric population with medically intractable epilepsy will be assessed via incidence of AEs and SAEs, as well as discontinuations due to intolerable AEs, identified through Safety Monitoring Activities (See [Section 5.3](#)).

It is anticipated that the tolerability of VOR in a medically resistant population of pediatric patients with epilepsy will be similar to that seen with currently prescribed AED therapies. Namely, the incidence rate for overall AEs is anticipated to be up to 55%; incidence of SAEs to be no more than 10%; no deaths are expected in the course of the trial; and discontinuation rate due to intolerable AEs is expected to be up to 30%.

5.2.2 EFFICACY ASSESSMENTS

5.2.2.1 PRIMARY EFFICACY ASSESSMENTS

Treatment response will be determined by the proportion of participants who have at least at 50% reduction rate of seizures.

5.3 SAFETY MONITORING

5.3.1 ADVERSE EVENTS

AEs (serious and non-serious) reported by the participant or observed by the investigator will be collected throughout the study. At each visit, the investigator will ask the participant if any untoward medical event occurred since the last visit. For each event, the date of onset and date of resolution, intensity, relationship to study medication, outcome and treatments administered for the event will be recorded in the study record.

AEs will include any symptom, sign, illness or experience, or clinically relevant lab abnormality, regardless of causality, which develops or worsens in severity during the course of the study. An SAE will comprise of any AE, occurring at any dose, regardless of causality that was either life-threatening, requires inpatient hospitalization or prolonging an existing hospitalization, or is determined as an important medical event by the treating physician, or results in death.

All AEs will be reported as stipulated in [Section 7.1](#). SAEs will be reported to the research ethics board (REB) and to Health Canada.

5.3.2 SAFETY MONITORING

All safety monitoring will be performed as summarized in [Table 5: Schedule of events](#).

5.3.2.1 VITAL SIGNS

Seated blood pressure and pulse will be recorded after at least a 5-minute rest. Two measurements should be made for each blood pressure measurement and the average derived.

5.3.2.2 ANTHROPOMETRICS

Body weight and height will be measured at each study visit.

5.3.2.3 DIRECTED PHYSICAL EXAM

The directed physical examination will include a general physical examination and neurological examination. Special attention will be paid to the signs and symptoms reported with VOR. Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until achievement of a clinically stable endpoint.

5.3.2.4 LABORATORY BLOOD SAMPLES

All blood samples will be taken and processed by the Calgary Lab Services.

Hematology

Blood samples will be obtained to conduct a complete blood count, according to the schedule summarized in [Table 5: Schedule of events](#).

Coagulation

Blood samples will be obtained to assess coagulation (PTT/INR)

Serum Chemistry

Blood samples will be obtained to assess the following, according to the schedule summarized in [Table 5: Schedule of events](#):

- renal function (serum creatinine and blood urea nitrogen)
- hepatic function (bilirubin, ALT, AST, and albumin)
- electrolyte monitoring, including: sodium, potassium, chloride, magnesium, and calcium
- blood glucose
- lactate dehydrogenase

5.3.2.5 PREGNANCY TEST

Serum β -HCG levels test will be obtained for heterosexually active women of childbearing potential, according to the schedule summarized in [Table 5: Schedule of events](#).

A urine pregnancy test will be done in office at the enrollment visit for applicable participants.

5.3.2.6 ECG

ECG will be recorded a total of 3 times, according to the schedule summarized in [Table 5: Schedule of events](#).

SECTION 6: INVESTIGATIONAL MEDICINAL PRODUCT

6.1 FORMULATION, PACKAGING AND LABELING

6.1.1 FORMULATION

The oral formulation of VOR is available as a 100-mg capsule.

6.1.2 PACKAGING & LABELING

VOR will be packaged by the ACH research pharmacy in an open-label fashion in high-density polyethylene bottles. Labeling will be labeled as per Health Canada requirements, which includes the drug name, pill count, dosing instructions and storage instructions.

6.1.3 STORAGE

The study medication must be stored in a secure place at room temperature (not above 25°C).

6.2 DOSE AND SCHEDULE OF STUDY MEDICATION

6.2.1 DOSAGE RATIONALE

Several studies have investigated the MTD, and DLT, when administered as a single agent and in combination of other cancer treatment in pediatric populations with various malignancies⁵⁰⁻⁵⁴. VOR administered orally to these populations at a dosage of 230 mg/m²/day was found to be efficacious, and was overall considered to be well-tolerated in these populations.

6.2.2 DOSAGE

Participants will take 100 mg VOR capsules orally to meet dose of 230 mg/m² once per day as closely as possible. The following dose rounding table will be used as a reference for drug dosing dispensed based on BSA, where

$$BSA(m^2) = \text{SQRT}([\text{height}(cm) \times \text{weight}(kg)]/3600)$$

| VOR dosage (mg/m ²) | BSA | | | | | | | |
|---------------------------------|------------|-------------|----------|-------------|------------|-------------|----------|-------------|
| | 0.5 – 0.74 | 0.75 – 0.99 | 1 – 1.24 | 1.25 – 1.49 | 1.5 – 1.74 | 1.75 – 1.99 | 2 – 2.24 | 2.25 – 2.49 |
| 230 | 100 | 200 | 200 | 300 | 300 | 400 | 400 | 500 |

6.2.3 DOSE INTERRUPTIONS

If a dose is missed, it should be taken as soon as possible. If the participant does not remember until it is nearly time for the next dose, the participant should skip the missed dose and go back to the regular schedule. A double dose of should not be taken.

There will be no temporary interruptions of study medication due to safety reasons. If study medication is stopped due to safety reason, there will be no re-challenge.

6.3 ASSESSMENT OF COMPLIANCE

Assessment Accountability and subject compliance will be assessed by maintaining adequate drug dispensing and return records. Participants will be asked to return all used and unused drug supply containers at each visit as a measure of compliance. An investigator may decide to withdraw a participant within the first 14 days, if the participant is found to be non-compliant. Compliance will be defined as having taking study medication as directed 80% of the time. Participants will be encouraged to discuss issues affecting compliance with the investigator.

A Drug Dispensing Log will be kept current with the following information:

- Identification of the participant to whom the study medication was dispensed
- Date[s], quantity of the study medication dispensed to the participant
- Date[s] and quantity of the study medication returned by the participant

6.4 DESTRUCTION OF STUDY MEDICATION

Following reconciliation against the documentation of quantity dispensed and returned, destruction of drug will be done as per the ACH Research pharmacy's standard operating procedures.

This includes:

- Identity [batch numbers or subject numbers] of study medication destroyed
- Quantity of study medication destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person looking after study medication destruction

SECTION 7: SAFETY INSTRUCTION AND GUIDANCE

7.1 ADVERSE EVENTS AND LABORATORY ABNORMALITIES

7.1.1 CLINICAL ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient or clinical investigation participant, administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign including an abnormal laboratory finding, symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal investigational product. Pre-existing conditions which worsen during a study are also to be reported as AEs.

7.1.1.1 INTENSITY

All clinical AEs encountered during the clinical study will be reported in the study record. The intensity of AEs will be graded by the investigator on a three-point scale (mild, moderate, severe) and reported in detail on the CRF.

| | |
|----------|---|
| Mild | discomfort noticed but no disruption of normal daily activity |
| Moderate | discomfort sufficient to reduce or affect daily activity |
| Severe | inability to work or perform normal daily activity |

7.1.1.2. DRUG – ADVERSE EVENT RELATIONSHIP

Relationship of the AE to the treatment will be assessed by the investigator as either: **Yes or No**

If there is a reasonable suspected causal relationship to the study medication, i.e., there are facts (evidence) or arguments to suggest a causal relationship, drug-event relationship should be assessed as **Yes**. The following criteria should be considered in order to assess the relationship as **Yes**:

- Reasonable temporal association with drug administration.
- May or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- Known response pattern to suspected drug
- Disappears or decreases on cessation

The following criteria should be considered in order to assess the relationship as **No**:

- It does not follow a reasonable temporal sequence from the administration of the drug.
- It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

- It does not follow a known pattern of response to the suspected drug.

7.1.1.3 SERIOUS ADVERSE EVENTS

An SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills at least one of the seriousness criteria following criteria:

- is fatal/results in death (**NOTE:** death is an outcome, not an event)
- is life-threatening (i.e. refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe).
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is medically significant or requires intervention to prevent one or other of the outcomes listed above.

SAE reporting procedures are described in [Section 7.2](#). Death is the outcome of an event and will not be reported as the SAE term, rather the event causing the death will be reported as the SAE. The only exception is when the cause of death is not known; these cases will be reported as “Death Unknown”.

7.1.2 LABORATORY TEST ABNORMALITIES

Any laboratory result abnormality fulfilling the criteria for a SAE will be reported as such, in addition to being recorded as an AE in the study record.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, will be recorded as a single diagnosis in the study record:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g., interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

This will apply to any protocol and non-protocol specified safety and efficacy laboratory result from tests performed after the first dose of study medication, which falls outside the laboratory reference range and meets the clinical significance criteria.

This will not apply to any abnormal laboratory result which falls outside the laboratory reference range but which does not meet the clinical significance criteria, or those which are a result of an AE which has already been reported.

7.1.3 TREATMENT AND FOLLOW UP OF AEs

AEs will be followed up until they have returned to baseline status or stabilized. Details of follow up will be recorded in the study record including if return to baseline status or stabilization cannot be achieved.

In the event of medically significant unexplained abnormal laboratory test values, the tests will be repeated and followed up until they have returned to the normal range or the baseline value and/or an adequate explanation of the abnormality is found. All details will be included in the study record.

If the study drug is discontinued due to an AE or a laboratory abnormality, the study medication will not be reinstated. If the investigator decides to discontinue study drug treatment, the rationale for their decision will be provided in the AE comment/SAE narrative field of the study record.

Study drug will be discontinued in the presence of an SAE that is deemed to be related or possibly related. Thromboembolic events or any event which a participant finds intolerable, which cannot be mitigated with therapy, will be cause for VOR discontinuation. Participants experiencing a $\geq 50\%$ increase in seizure frequency, as compared to baseline at any time during the treatment period will be discontinued from study medication. Additionally, participants presenting with status epilepticus at any time during the treatment period will be discontinued from study medication.

7.1.3.1 Project Specific Adverse Events

The following AEs are noted in the VOR product monograph as warning and precautions, based on CTCL clinical trials in adults.

Thromboembolism

Pulmonary embolism and DVT have been reported as drug-related AEs in clinical trials with VOR. In greater than 1000 patients with hematologic malignancies and solid tumors who have been treated with VOR as monotherapy, or in combination with other chemotherapy agents, in completed and ongoing clinical studies, the proportion of patients that experienced a venous thromboembolic event was approximately 5.0%⁴⁰. An increase in the incidence of venous thromboembolic events was also found in patients with advanced non-small cell lung cancer who received VOR (400 mg once daily) in combination with chemotherapy (carboplatin and paclitaxel) as compared to patients who received chemotherapy alone. In this study, deep venous thrombosis and/or pulmonary embolism was reported in 6.5% (8/124) of patients in the VOR chemotherapy treatment arm compared to 2.4% (3/124) of patients in the placebo/chemotherapy treatment arm⁴⁰.

Investigators will closely monitor patients for signs and symptoms of these events, particularly in patients with a prior history of thromboembolic events. In the instance of a thromboembolic event, study drug will be discontinued.

Hyperglycemia

Hyperglycemia has been observed in patients receiving VOR⁴⁰. Serum glucose will be monitored as part of the biochemistry laboratory safety panel as summarized in [Table 5: Schedule of events](#).

. In the event of hyperglycemia, adjustment of diet or anti-hyperglycemic therapy may be trialed in the event of intolerable hyperglycemia.

Gastrointestinal Disturbances

Gastrointestinal disturbances, including nausea, vomiting and diarrhea have been reported very commonly in patients treated with VOR⁴⁰. Antiemetic and/or antidiarrheal medications may be trialed in the event of moderate to severe nausea, vomiting, diarrhea. Additional potassium and magnesium monitoring should be considered in symptomatic patients.

Dehydration

Dehydration has been reported as a common serious drug-related adverse experience in clinical trials⁴⁰. Participants will be instructed to consume enough fluids to maintain adequate daily hydration, as adjusted for age.

Hematologic Disturbances

Treatment with VOR is associated with dose-related hematologic adverse effects⁴⁰. Participants will be monitored as per laboratory testing schedule to identify such disturbances. Additionally participants will be advised to contact the investigator if presenting with frequent bruising, nose bleeds or gum bleeding, blood in urine or stools, or petechiae.

QT/QTc Prolongation

Treatment with VOR is associated with QT/QTc interval prolongation⁴⁰, which is suspected to increase the risk of Torsade de pointes. Torsade de pointes may be asymptomatic or may be experienced as dizziness, palpitations, syncope, or increased seizures. Participants will be instructed to contact the investigator if presenting with these symptoms. Additional ECG monitoring may be conducted.

7.2 HANDLING OF SAFETY PARAMETERS

7.2.1 REPORTING OF SERIOUS ADVERSE EVENTS

All new AEs occurring during the study should be recorded in the study record. AEs that occur intermittently will be recorded as a single AE. AEs will be collected and reported for up to 6 weeks after the last dose of study medication.

7.2.2 EXEMPTION OF PROJECT SPECIFIC SERIOUS AEs FROM IMMEDIATE REPORTING TO HEALTH AUTHORITIES AND IRBs

For any clinical AE or abnormal laboratory test value that is serious [as defined in Section 7.1.1.3], the investigator will complete SAE reporting in the study record within 24 hours of the study team becoming aware of the event. The REB and Health Canada will be notified as per reporting requirements.

SAEs monitoring and reporting will commence at the time following administration of the first dose of study medication until 6 weeks following administration of the last dose of study medication. At any time after the 6-week period following the last dose of study drug, only SAEs considered by the investigator to be related to study drug or protocol procedures will continue to be reported as stipulated.

7.2.3. PREGNANCY

Pregnancies occurring in female participants exposed to the study medication, or partners of male participants exposed to the study medication, will be reported to the REB. Female participants, or partners of male participants will be instructed to notify the investigator as soon as possible. Female participants will be instructed to discontinue taking the study medication immediately. Study medication will be permanently discontinued in female participants and an EOT and SFU visit will be conducted as per protocol. Participants or partners of male participants will be followed until the conclusion of pregnancy. Pregnancies occurring up to 90 days after the completion of the study medication will be followed in the same manner.

The investigator will counsel and discuss with the participant/partner of participant the risks of continuing with the pregnancy and the possible effects of early exposure to study medication on the fetus.

Where a SAE occurs in the pregnant female participant, the SAE must be collected separately, regardless of whether it is pregnancy related or not.

SECTION 8: STATISTICAL CONSIDERATION AND ANALYTICAL PLAN

8.1 PRIMARY AND SECONDARY STUDY ENDPOINTS

8.1.1 PRIMARY ENDPOINTS

The primary endpoint for this study will be the incidence of related AEs and SAEs, and discontinuation of therapy due to intolerable AEs.

8.1.2 SECONDARY ENDPOINT

The secondary endpoint for this study will be efficacy. Treatment response will be evaluated by:

- Proportion of patients who have at least a 50% reduction in seizures
- Change in seizure remission status

8.2 STATISTICAL AND ANALYTICAL METHODS

8.2.1 SAMPLE SIZE

The rationale for selection of sample size to investigate safety in a pilot study in this population was based on feasibility in regards to recruitment potential, according to prior knowledge of our referred/existing clinical base, and cost of conducting this study. Further, as this medication has not been tested in this population and rate of AEs in this population is not known, a power based/effect size calculation of sample size cannot be determined.

8.2.2 ANALYSIS

8.2.2.1. SAFETY & TOLERABILITY ANALYSIS

Safety and tolerability will be assessed by calculating the incidence rate of AEs per number of drug days from the time medication is started through to the completion of the SFU (or 42 days following the last dose of study medication). This will be done for the following time points: 14 days following drug initiation; 30 days following drug initiation; 42 days following drug initiation; and 42 days following drug discontinuation. AEs will be further stratified by mild/moderate AEs, severe AEs, and SAEs, as well as project specific AEs (thromboembolism, hyperglycemia, gastrointestinal disturbances, dehydration, hematologic disturbances, QT/QTc prolongation).

8.2.2.2 EFFICACY ANALYSIS

Primary efficacy assessment:

- Treatment response will be evaluated by calculating the proportion of response of participants who demonstrate a 50% reduction rate or greater at 6 weeks as compared to baseline.

Secondary efficacy assessments:

- Seizure status will be tabulated 14 days following drug initiation; 30 days following drug initiation; 42 days following drug initiation; and 42 days following drug discontinuation. Seizure status will be defined as: **significant response** (at least 50% reduction in seizure frequency as compared to baseline, or no seizures while on medication); **partial response** (25% - 49% reduction in seizure frequency as compared to baseline); **no change**, (0 – 24% reduction in seizure frequency as compared to baseline); and **worsening** (increase in seizure frequency as compared to baseline).

SECTION 9: DATA COLLECTION & MANAGEMENT

Source visit data will be captured via the electronic clinic note during clinic visits. This will then be transcribed on the electronic data collection form which will be developed, maintained and managed via RedCap software. RedCap is a browser-based electronic data capture (EDC) software, in which electronic data collection form (eDCFs) can be custom-built by the user. RedCap is managed and supported by the Clinical Research Unit at the University of Calgary, in collaboration with Cumming School of Medicine. RedCap also maintains an audit trail which tracks a record of initial entries and changes made; time and date of entry; and username of person who made the change.

SECTION 10: ETHICAL ASPECTS

INFORMED CONSENT

The investigator, or designate will obtain signed informed consent/assent from each participant/legal guardian prior to participating in this study as per our departmental SOPs (SOP002: Obtaining Informed Consent V1_2017-08-04; and SOP003: Obtaining Assent, Consent & Decision making Capacity in Minors V1_2017-08-14). Briefly, the investigator or designate will explain the aims, methods, anticipated benefits, and potential hazards of the study. The investigator/designee will also explain that the participant is completely free to refuse to enter the study or to withdraw at any time without any consequence to their future care, for any reason. If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary. All participants (including those already being treated) will be notified of the new information, and the revised consent form will be given for review for participants to give consent to continue in the study for the revised study.

INSTITUTIONAL REVIEW BOARD

This protocol (and future modifications) along with all other study conduct procedures, and study documentation, will be submitted for review by the Conjoint Health Research Ethics Board (CHREB) at the University of Calgary. The study will not commence until it is approved by the CHREB.

SECTION 11: STUDY DOCUMENTATION, RECORDKEEPING, AND CONFIDENTIALITY OF TRIAL DOCUMENTS AND PARTICIPANT RECORDS

11.1 INVESTIGATOR'S FILES/RETENTION OF DOCUMENTS

Adequate and accurate records will be maintained to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be kept via the Investigator's Study File and participant clinical source documents.

As per Good Clinical Practice Guidelines, the Investigator's Study File will contain the protocol/amendments, Institutional Review Board documentation, governmental approvals with correspondence, sample informed consent, drug records, staff curriculum vitae, authorization forms and other appropriate documents/correspondence related to study conduct, etc.

Participant clinical source documents include completed data collection forms, participant hospital/clinic records, physicians' and nurses' notes, appointment book, original laboratory reports, ECG reports, and signed informed consent forms. Data collection forms will also include all changes to data and reasons for changes.

All study documents will be kept on site for 2 years following study publication. Following the on-site archiving period, study records will be moved to a secure storage facility to be stored for a total of 25 years, as per Health Canada requirements. Following the required archiving period, study documents will be securely destroyed as per the facility's standard operating procedure for secure document destruction.

11.2 CONFIDENTIALITY OF TRIAL DOCUMENTS AND PARTICIPANT RECORDS

Participants' anonymity will be maintained and their identities protected from unauthorized parties. Master identification lists will be updated and maintained by research personnel. The master list will be managed and stored via an Excel sheet, will be kept separate from the main data set and stored on a research drive on a firewall-protected AHS server, which is password protected and available only to the Investigators and research personnel.

Investigators and/or research personnel will review the medical records of patients meeting eligibility criteria. Study data collected will be anonymized, entered, stored and managed using RedCap. The RedCap database will be maintained by a member of the research team assigned as the database manager for this data set. The data base manager will oversee programming the collections form; issuing/removing access for participating research team members; data locks and pulling data for analysis. All research team members will have access to view and enter data.

At the time of data disposal, the data set will be purged as per the University of Calgary Clinical Research Unit standard protocols. The master list will be purged from the AHS server at the same time point. All data analysis will take place on anonymized data.

PROTOCOL: VOR-17-2471
Version 2: 2018-07-18

All staff involved in research activities are aware of and adhere to, the privacy standards set out by AHS and the requirements set forth by the Alberta Health Information Act. All study activities occurring at the ACH will be conducted as per the terms of agreement set forth by the Alberta Health Services Provincial Research Administration, Innovation & Research Management.

SECTION 12: REFERENCES

1. Major P, Thiele EA. Seizures in children: Determining the variation. *Pediatrics in review*. 2007;28:363-371
2. Theodore WH, Spencer SS, Wiebe S, Langfitt JT, Ali A, Shafer PO, Berg AT, Vickrey BG. Epilepsy in north america: A report prepared under the auspices of the global campaign against epilepsy, the international bureau for epilepsy, the international league against epilepsy, and the world health organization. *Epilepsia*. 2006;47:1700-1722
3. Arya R, Glauser TA. Pharmacotherapy of focal epilepsy in children: A systematic review of approved agents. *CNS drugs*. 2013;27:273-286
4. Glauser TA, Loddenkemper T. Management of childhood epilepsy. *Continuum (Minneapolis, Minn.)*. 2013;19:656-681
5. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. *N Engl J Med*. 2011;365:919-926
6. Chaves J, Sander JW. Seizure aggravation in idiopathic generalized epilepsies. *Epilepsia*. 2005;46 Suppl 9:133-139
7. Perucca E, Meador KJ. Adverse effects of antiepileptic drugs. *Acta neurologica Scandinavica. Supplementum*. 2005;181:30-35
8. Sillanpaa M, Schmidt D. Natural history of treated childhood-onset epilepsy: Prospective, long-term population-based study. *Brain : a journal of neurology*. 2006;129:617-624
9. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshe SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc task force of the ilae commission on therapeutic strategies. *Epilepsia*. 2010;51:1069-1077
10. Bell B, Lin JJ, Seidenberg M, Hermann B. The neurobiology of cognitive disorders in temporal lobe epilepsy. *Nat Rev Neurol*. 2011;7:154-164
11. Bernhardt BC, Bernasconi N, Concha L, Bernasconi A. Cortical thickness analysis in temporal lobe epilepsy: Reproducibility and relation to outcome. *Neurology*. 2010;74:1776-1784
12. Pavlou E, Gkampeta A. Learning disorders in children with epilepsy. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery*. 2011;27:373-379
13. Thompson PJ, Duncan JS. Cognitive decline in severe intractable epilepsy. *Epilepsia*. 2005;46:1780-1787
14. Souza-Oliveira C, Escosi-Rosset S, Funayama SS, Terra VC, Machado HR, Sakamoto AC. Intellectual functioning in pediatric patients with epilepsy: A comparison of medically controlled, medically uncontrolled and surgically controlled children. *Jornal de pediatria*. 2010;86:377-383
15. Moreira H, Carona C, Silva N, Frontini R, Bullinger M, Canavarro MC. Psychological and quality of life outcomes in pediatric populations: A parent-child perspective. *The Journal of pediatrics*. 2013;163:1471-1478
16. Austin JK, Caplan R. Behavioral and psychiatric comorbidities in pediatric epilepsy: Toward an integrative model. *Epilepsia*. 2007;48:1639-1651
17. Camfield P, Camfield C, Arts WF, Brouwer OF, Arzimanoglou A. The outcome of childhood epilepsy: What improvements are needed? *Epileptic disorders : international epilepsy journal with videotape*. 2013;15:101-104
18. Sperling MR. The consequences of uncontrolled epilepsy. *CNS spectrums*. 2004;9:98-101, 106-109
19. England MJ, Liverman CT, Schultz AM, Strawbridge LM. Epilepsy across the spectrum: Promoting health and understanding. A summary of the institute of medicine report. *Epilepsy & behavior : E&B*. 2012;25:266-276
20. Yoon D, Frick KD, Carr DA, Austin JK. Economic impact of epilepsy in the united states. *Epilepsia*. 2009;50:2186-2191
21. Begley CE, Famulari M, Annegers JF, Lairson DR, Reynolds TF, Coan S, Dubinsky S, Newmark ME, Leibson C, So EL, Rocca WA. The cost of epilepsy in the united states: An estimate from population-based clinical and survey data. *Epilepsia*. 2000;41:342-351
22. Cramer JA, Wang ZJ, Chang E, Powers A, Copher R, Cherepanov D, Broder MS. Healthcare utilization and costs in adults with stable and uncontrolled epilepsy. *Epilepsy & behavior : E&B*. 2014;31:356-362

23. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, Whitney A, Cross JH. The ketogenic diet for the treatment of childhood epilepsy: A randomised controlled trial. *The Lancet. Neurology*. 2008;7:500-506
24. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, Whitney A, Cross JH. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. *Epilepsia*. 2009;50:1109-1117
25. Kossoff EH, Rho JM. Ketogenic diets: Evidence for short- and long-term efficacy. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics*. 2009;6:406-414
26. Rogawski MA, Loscher W, Rho JM. Mechanisms of action of antiseizure drugs and the ketogenic diet. *Cold Spring Harbor perspectives in medicine*. 2016;6
27. Kang HC, Lee YM, Kim HD, Lee JS, Slama A. Safe and effective use of the ketogenic diet in children with epilepsy and mitochondrial respiratory chain complex defects. *Epilepsia*. 2007;48:82-88
28. Greco T, Glenn TC, Hovda DA, Prins ML. Ketogenic diet decreases oxidative stress and improves mitochondrial respiratory complex activity. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2016;36:1603-1613
29. Pathak D, Berthet A, Nakamura K. Energy failure: Does it contribute to neurodegeneration? *Annals of neurology*. 2013;74:506-516
30. Ibhazehiebo K, Gavrilovici C, de la Hoz CL, Ma SC, Rehak R, Kaushik G, Meza Santoscoy PL, Scott L, Nath N, Kim DY, Rho JM, Kurrasch DM. A novel metabolism-based phenotypic drug discovery platform in zebrafish uncovers hdacs 1 and 3 as a potential combined anti-seizure drug target. *Brain : a journal of neurology*. 2018
31. Howe K, Clark MD, Torroja CF, Torrance J, Berthelot C, Muffato M, Collins JE, Humphray S, McLaren K, Matthews L, McLaren S, Sealy I, Caccamo M, Churcher C, Scott C, Barrett JC, Koch R, Rauch GJ, White S, Chow W, Kilian B, Quintais LT, Guerra-Assuncao JA, Zhou Y, Gu Y, Yen J, Vogel JH, Eyre T, Redmond S, Banerjee R, Chi J, Fu B, Langley E, Maguire SF, Laird GK, Lloyd D, Kenyon E, Donaldson S, Sehra H, Almeida-King J, Loveland J, Trevanion S, Jones M, Quail M, Willey D, Hunt A, Burton J, Sims S, McLay K, Plumb B, Davis J, Clee C, Oliver K, Clark R, Riddle C, Elliot D, Threadgold G, Harden G, Ware D, Begum S, Mortimore B, Kerry G, Heath P, Phillimore B, Tracey A, Corby N, Dunn M, Johnson C, Wood J, Clark S, Pelan S, Griffiths G, Smith M, Glithero R, Howden P, Barker N, Lloyd C, Stevens C, Harley J, Holt K, Panagiotidis G, Lovell J, Beasley H, Henderson C, Gordon D, Auger K, Wright D, Collins J, Raisen C, Dyer L, Leung K, Robertson L, Ambridge K, Leongamornlert D, McGuire S, Gilderthorp R, Griffiths C, Manthravadi D, Nichol S, Barker G, Whitehead S, Kay M, Brown J, Murnane C, Gray E, Humphries M, Sycamore N, Barker D, Saunders D, Wallis J, Babbage A, Hammond S, Mashreghi-Mohammadi M, Barr L, Martin S, Wray P, Ellington A, Matthews N, Ellwood M, Woodmansey R, Clark G, Cooper J, Tromans A, Grafham D, Skuce C, Pandian R, Andrews R, Harrison E, Kimberley A, Garnett J, Fosker N, Hall R, Garner P, Kelly D, Bird C, Palmer S, Gehring I, Berger A, Dooley CM, Ersan-Urun Z, Eser C, Geiger H, Geisler M, Karotki L, Kim A, Konantz J, Konantz M, Oberlander M, Rudolph-Geiger S, Teucke M, Lanz C, Raddatz G, Osoegawa K, Zhu B, Rapp A, Widaa S, Langford C, Yang F, Schuster SC, Carter NP, Harrow J, Ning Z, Herrero J, Searle SM, Enright A, Geisler R, Plasterk RH, Lee C, Westerfield M, de Jong PJ, Zon LI, Postlethwait JH, Nusslein-Volhard C, Hubbard TJ, Roest Crollius H, Rogers J, Stemple DL. The zebrafish reference genome sequence and its relationship to the human genome. *Nature*. 2013;496:498-503
32. Schier AF. Genomics: Zebrafish earns its stripes. *Nature*. 2013;496:443-444
33. Kettleborough RN, Busch-Nentwich EM, Harvey SA, Dooley CM, de Bruijn E, van Eeden F, Sealy I, White RJ, Herd C, Nijman IJ, Fenyes F, Mehroke S, Scahill C, Gibbons R, Wali N, Carruthers S, Hall A, Yen J, Cuppen E, Stemple DL. A systematic genome-wide analysis of zebrafish protein-coding gene function. *Nature*. 2013;496:494-497
34. Baraban SC, Taylor MR, Castro PA, Baier H. Pentylene tetrazole induced changes in zebrafish behavior, neural activity and c-fos expression. *Neuroscience*. 2005;131:759-768
35. Baraban SC, Dinday MT, Castro PA, Chege S, Guyenet S, Taylor MR. A large-scale mutagenesis screen to identify seizure-resistant zebrafish. *Epilepsia*. 2007;48:1151-1157

36. Baxendale S, Holdsworth CJ, Meza Santoscoy PL, Harrison MR, Fox J, Parkin CA, Ingham PW, Cunliffe VT. Identification of compounds with anti-convulsant properties in a zebrafish model of epileptic seizures. *Disease models & mechanisms*. 2012;5:773-784
37. Zdebik AA, Mahmood F, Stanescu HC, Kleta R, Bockenbauer D, Russell C. Epilepsy in *kcj10* morphant zebrafish assessed with a novel method for long-term eeg recordings. *PLoS one*. 2013;8:e79765
38. White HS, Johnson M, Wolf HH, Kupferberg HJ. The early identification of anticonvulsant activity: Role of the maximal electroshock and subcutaneous pentylenetetrazol seizure models. *Italian journal of neurological sciences*. 1995;16:73-77
39. Barton ME, Peters SC, Shannon HE. Comparison of the effect of glutamate receptor modulators in the 6 hz and maximal electroshock seizure models. *Epilepsy research*. 2003;56:17-26
40. MerckCanadaInc. Product monograph zolinza® vorinostat capsules 100mg histone deacetylase inhibitor, anti-neoplastic agent. 2013
41. Gottlicher M, Minucci S, Zhu P, Kramer OH, Schimpf A, Giavara S, Sleeman JP, Lo Coco F, Nervi C, Pelicci PG, Heinzel T. Valproic acid defines a novel class of hdac inhibitors inducing differentiation of transformed cells. *The EMBO journal*. 2001;20:6969-6978
42. Marks PA, Richon VM, Breslow R, Rifkind RA. Histone deacetylase inhibitors as new cancer drugs. *Current opinion in oncology*. 2001;13:477-483
43. Marks PA, Dokmanovic M. Histone deacetylase inhibitors: Discovery and development as anticancer agents. *Expert opinion on investigational drugs*. 2005;14:1497-1511
44. Kelly WK, O'Connor OA, Krug LM, Chiao JH, Heaney M, Curley T, MacGregore-Cortelli B, Tong W, Secrist JP, Schwartz L, Richardson S, Chu E, Olgac S, Marks PA, Scher H, Richon VM. Phase i study of an oral histone deacetylase inhibitor, suberoylanilide hydroxamic acid, in patients with advanced cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2005;23:3923-3931
45. Garcia-Manero G, Yang H, Bueso-Ramos C, Ferrajoli A, Cortes J, Wierda WG, Faderl S, Koller C, Morris G, Rosner G, Loboda A, Fantin VR, Randolph SS, Hardwick JS, Reilly JF, Chen C, Ricker JL, Secrist JP, Richon VM, Frankel SR, Kantarjian HM. Phase 1 study of the histone deacetylase inhibitor vorinostat (suberoylanilide hydroxamic acid [saha]) in patients with advanced leukemias and myelodysplastic syndromes. *Blood*. 2008;111:1060-1066
46. Kelly WK, Richon VM, O'Connor O, Curley T, MacGregor-Curtelli B, Tong W, Klang M, Schwartz L, Richardson S, Rosa E, Drobnjak M, Cordon-Cordo C, Chiao JH, Rifkind R, Marks PA, Scher H. Phase i clinical trial of histone deacetylase inhibitor: Suberoylanilide hydroxamic acid administered intravenously. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2003;9:3578-3588
47. O'Connor OA, Heaney ML, Schwartz L, Richardson S, Willim R, MacGregor-Cortelli B, Curly T, Moskowitz C, Portlock C, Horwitz S, Zelenetz AD, Frankel S, Richon V, Marks P, Kelly WK. Clinical experience with intravenous and oral formulations of the novel histone deacetylase inhibitor suberoylanilide hydroxamic acid in patients with advanced hematologic malignancies. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2006;24:166-173
48. Mann BS, Johnson JR, Cohen MH, Justice R, Pazdur R. Fda approval summary: Vorinostat for treatment of advanced primary cutaneous t-cell lymphoma. *The oncologist*. 2007;12:1247-1252
49. Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, Frankel SR, Chen C, Ricker JL, Arduino JM, Duvic M. Phase iib multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous t-cell lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007;25:3109-3115
50. Fouladi M, Park JR, Stewart CF, Gilbertson RJ, Schaiquevich P, Sun J, Reid JM, Ames MM, Speights R, Ingle AM, Zwiebel J, Blaney SM, Adamson PC. Pediatric phase i trial and pharmacokinetic study of vorinostat: A children's oncology group phase i consortium report. *J Clin Oncol*. 2010;28:3623-3629
51. Hummel TR, Wagner L, Ahern C, Fouladi M, Reid JM, McGovern RM, Ames MM, Gilbertson RJ, Horton T, Ingle AM, Weigel B, Blaney SM. A pediatric phase 1 trial of vorinostat and temozolomide in relapsed or refractory primary brain or spinal cord tumors: A children's oncology group phase 1 consortium study. *Pediatr Blood Cancer*. 2013;60:1452-1457

52. Muscal JA, Thompson PA, Horton TM, Ingle AM, Ahern CH, McGovern RM, Reid JM, Ames MM, Espinoza-Delgado I, Weigel BJ, Blaney SM. A phase i trial of vorinostat and bortezomib in children with refractory or recurrent solid tumors: A children's oncology group phase i consortium study (advl0916). *Pediatr Blood Cancer*. 2013;60:390-395
53. Burke MJ, Lamba JK, Pounds S, Cao X, Ghodke-Puranik Y, Lindgren BR, Weigel BJ, Verneris MR, Miller JS. A therapeutic trial of decitabine and vorinostat in combination with chemotherapy for relapsed/refractory acute lymphoblastic leukemia. *Am J Hematol*. 2014;89:889-895
54. DuBois SG, Groshen S, Park JR, Haas-Kogan DA, Yang X, Geier E, Chen E, Giacomini K, Weiss B, Cohn SL, Granger MM, Yanik GA, Hawkins R, Courtier J, Jackson H, Goodarzian F, Shimada H, Czarnecki S, Tsao-Wei D, Villablanca JG, Marachelian A, Matthay KK. Phase i study of vorinostat as a radiation sensitizer with ¹³¹i-metaiodobenzylguanidine (¹³¹i-mibg) for patients with relapsed or refractory neuroblastoma. *Clin Cancer Res*. 2015;21:2715-2721
55. Colletti RB, Trainer TD, Krawisz BR. Reversible valproate fulminant hepatic failure. *Journal of pediatric gastroenterology and nutrition*. 1986;5:990-994
56. Hsia Y, Neubert A, Sturkenboom MC, Murray ML, Verhamme KM, Sen F, Giaquinto C, Ceci A, Wong IC. Comparison of antiepileptic drug prescribing in children in three european countries. *Epilepsia*. 2010;51:789-796
57. Cvitanovic-Sojat L, Bielen I, Sruk A, Kosicek M, Planjar-Prvan M, Baraba R, Bergman-Markovic B, Butkovic-Soldo S. Social and medical care of preschool children with epilepsy in croatia: Population-based survey. *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society*. 2010;14:73-77
58. Berg AT, Levy SR, Testa FM, Shinnar S. Treatment of newly diagnosed pediatric epilepsy: A community-based study. *Archives of pediatrics & adolescent medicine*. 1999;153:1267-1271
59. Nanau RM, Neuman MG. Adverse drug reactions induced by valproic acid. *Clinical biochemistry*. 2013;46:1323-1338
60. Brodie MJ. Established anticonvulsants and treatment of refractory epilepsy. *Lancet (London, England)*. 1990;336:350-354
61. Verrotti A, Scaparrotta A, Grosso S, Chiarelli F, Coppola G. Anticonvulsant drugs and hematological disease. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2014;35:983-993
62. Egger J, Brett EM. Effects of sodium valproate in 100 children with special reference to weight. *British medical journal (Clinical research ed.)*. 1981;283:577-581
63. Easter D, O'Bryan-Tear CG, Verity C. Weight gain with valproate or carbamazepine--a reappraisal. *Seizure*. 1997;6:121-125
64. Novak GP, Maytal J, Alshansky A, Eviatar L, Sy-Kho R, Siddique Q. Risk of excessive weight gain in epileptic children treated with valproate. *Journal of child neurology*. 1999;14:490-495
65. Jallon P, Picard F. Bodyweight gain and anticonvulsants: A comparative review. *Drug safety*. 2001;24:969-978
66. Privitera MD, Brodie MJ, Mattson RH, Chadwick DW, Neto W, Wang S. Topiramate, carbamazepine and valproate monotherapy: Double-blind comparison in newly diagnosed epilepsy. *Acta neurologica Scandinavica*. 2003;107:165-175
67. Cnaan A, Shinnar S, Arya R, Adamson PC, Clark PO, Dlugos D, Hirtz DG, Masur D, Glauser TA. Second monotherapy in childhood absence epilepsy. *Neurology*. 2017;88:182-190
68. Jedrzejczak J, Kuncikova M, Magureanu S. An observational study of first-line valproate monotherapy in focal epilepsy. *European journal of neurology*. 2008;15:66-72
69. Beydoun A, Sackellares JC, Shu V. Safety and efficacy of divalproex sodium monotherapy in partial epilepsy: A double-blind, concentration-response design clinical trial. Depakote monotherapy for partial seizures study group. *Neurology*. 1997;48:182-188
70. Richens A, Davidson DL, Carlidge NE, Easter DJ. A multicentre comparative trial of sodium valproate and carbamazepine in adult onset epilepsy. Adult epileptology collaborative group. *Journal of neurology, neurosurgery, and psychiatry*. 1994;57:682-687

71. Verity CM, Hosking G, Easter DJ. A multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy. The paediatric epileptology collaborative group. *Developmental medicine and child neurology*. 1995;37:97-108
72. Christie W, Kramer G, Vigonius U, Pohlmann H, Steinhoff BJ, Brodie MJ, Moore A. A double-blind controlled clinical trial: Oxcarbazepine versus sodium valproate in adults with newly diagnosed epilepsy. *Epilepsy research*. 1997;26:451-460
73. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B, Gamble C, Goulding PJ, Howell SJ, Hughes A, Jackson M, Jacoby A, Kellett M, Lawson GR, Leach JP, Nicolaides P, Roberts R, Shackley P, Shen J, Smith DF, Smith PE, Smith CT, Vanoli A, Williamson PR. The sanad study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: An unblinded randomised controlled trial. *Lancet (London, England)*. 2007;369:1016-1026
74. Lenz RA, Elterman RD, Robieson WZ, Vigna NV, Saltarelli MD. Divalproex sodium in children with partial seizures: 12-month safety study. *Pediatric neurology*. 2009;41:101-110
75. Hu Y, Huang X, Shen D, Ding M, Sun H, Peng B, Hu X, Li H, Zeng K, Xi Z, Zhang Y, Cao Q, Liu J, Zhou Y, Wu M, Lu Y, Chen G, Wang X. Outcomes of sustained-release formulation of valproate and topiramate monotherapy in patients with epilepsy: A multi-centre, cohort study. *PLoS one*. 2012;7:e47982
76. Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The department of veterans affairs epilepsy cooperative study no. 264 group. *The New England journal of medicine*. 1992;327:765-771
77. Wheless JW, Neto W, Wang S. Topiramate, carbamazepine, and valproate monotherapy: Double-blind comparison in children with newly diagnosed epilepsy. *Journal of child neurology*. 2004;19:135-141
78. Mohanraj R, Brodie MJ. Pharmacological outcomes in newly diagnosed epilepsy. *Epilepsy & behavior : E&B*. 2005;6:382-387
79. Nasreddine W, Beydoun A. Valproate-induced thrombocytopenia: A prospective monotherapy study. *Epilepsia*. 2008;49:438-445
80. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, Clark PO, Capparelli EV, Adamson PC. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *The New England journal of medicine*. 2010;362:790-799
81. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, Clark PO, Adamson PC. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: Initial monotherapy outcomes at 12 months. *Epilepsia*. 2013;54:141-155
82. Verrotti A, Nanni G, Agostinelli S, Alleva ET, Aloisi P, Franzoni E, Spalice A, Chiarelli F, Coppola G. Effects of the abrupt switch from solution to modified-release granule formulation of valproate. *Acta neurologica Scandinavica*. 2012;125:e14-18
83. Rosati A, De Masi S, Guerrini R. Antiepileptic drug treatment in children with epilepsy. *CNS drugs*. 2015;29:847-863
84. Schmidt D. Drug treatment of epilepsy: Options and limitations. *Epilepsy & behavior : E&B*. 2009;15:56-65
85. Brodie MJ, Ben-Menachem E, Chouette I, Giorgi L. Zonisamide: Its pharmacology, efficacy and safety in clinical trials. *Acta neurologica Scandinavica. Supplementum*. 2012:19-28
86. Cilio MR, Kartashov AI, Vigevano F. The long-term use of felbamate in children with severe refractory epilepsy. *Epilepsy research*. 2001;47:1-7
87. Lyseng-Williamson KA. Levetiracetam: A review of its use in epilepsy. *Drugs*. 2011;71:489-514
88. Kennedy GM, Lhatoo SD. Cns adverse events associated with antiepileptic drugs. *CNS drugs*. 2008;22:739-760
89. Chung AM, Eiland LS. Use of second-generation antiepileptic drugs in the pediatric population. *Paediatric drugs*. 2008;10:217-254
90. McGinnis E, Kessler SK. Lacosamide use in children with epilepsy: Retention rate and effect of concomitant sodium channel blockers in a large cohort. *Epilepsia*. 2016;57:1416-1425

91. Steinhoff BJ, Bacher M, Bucurenciu I, Hillenbrand B, Intravooth T, Kornmeier R, Kurth C, Stockinger J, Staack AM. Real-life experience with brivaracetam in 101 patients with difficult-to-treat epilepsy-a monocenter survey. *Seizure*. 2017;48:11-14
92. Frampton JE. Perampanel: A review in drug-resistant epilepsy. *Drugs*. 2015;75:1657-1668
93. Bottcher S, Lutz MT, Mayer T. Lacosamide in the treatment of patients with epilepsy and intellectual disabilities: A long-term study of 136 patients. *Epilepsia*. 2017;58:1749-1754