Developmental & Epileptic Encephalopathy (DEEs): Choosing Medical Therapy

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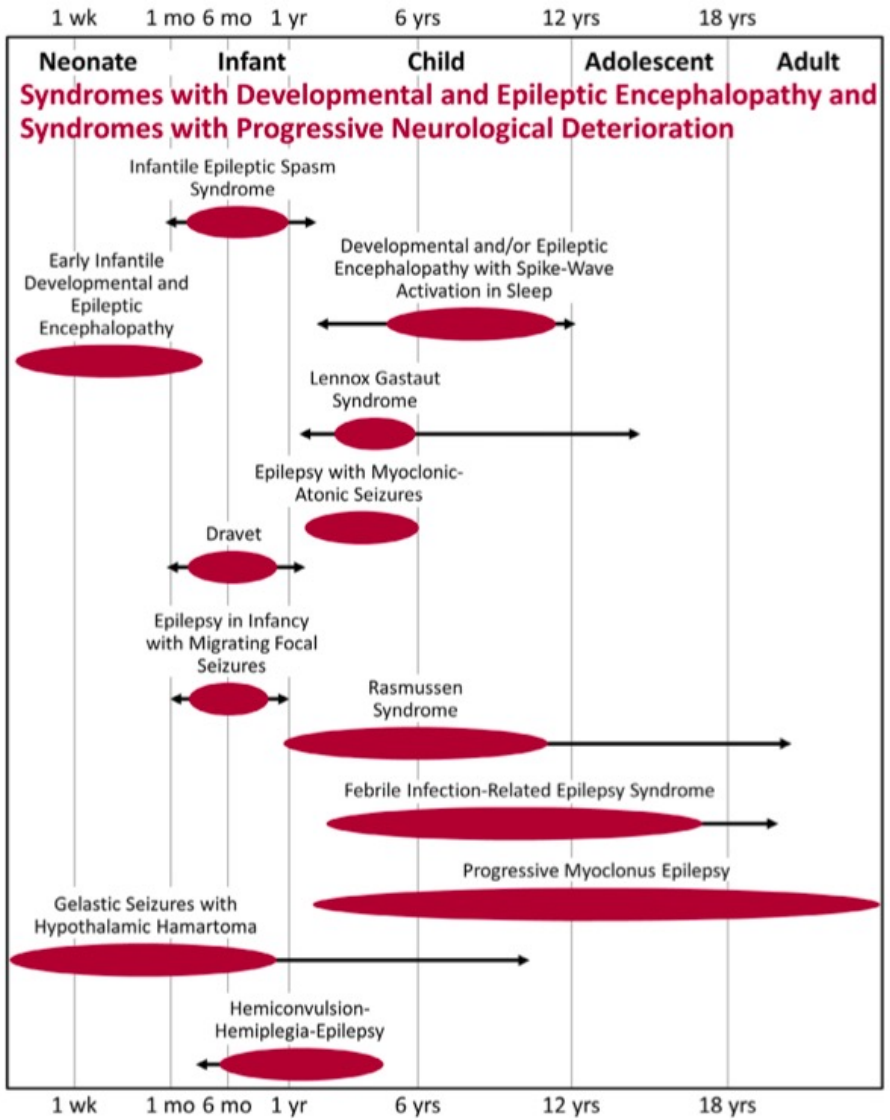
Developmental & Epileptic Encephalopathy (DEE): What Matters to Families

1. Seizure control
2. Adverse events
3. Developmental outcome
4. Sleep
5. Behavior
6. Quality-of-life (QOL) outcomes

These apply to the patient; however, many also apply to the caregiver.

Syndromes with Developmental & Epileptic Encephalopathy



Wirrell EC et al. Epilepsia, 2022; 63 (6): 1333 – 1348.

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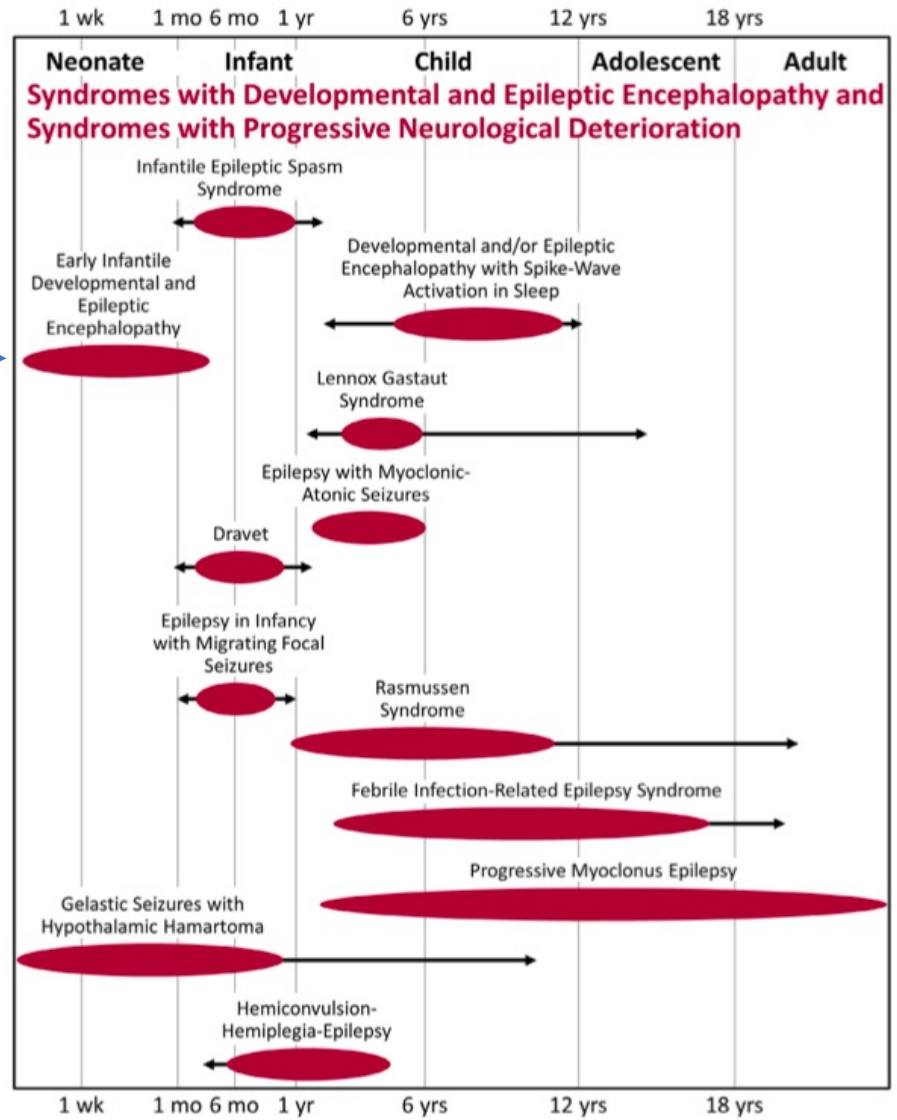
Syndromes with Developmental & Epileptic Encephalopathy

***CDKL5* Deficiency Disorder (CDD)**



Wirrell EC et al. Epilepsia, 2022; 63 (6): 1333 – 1348.

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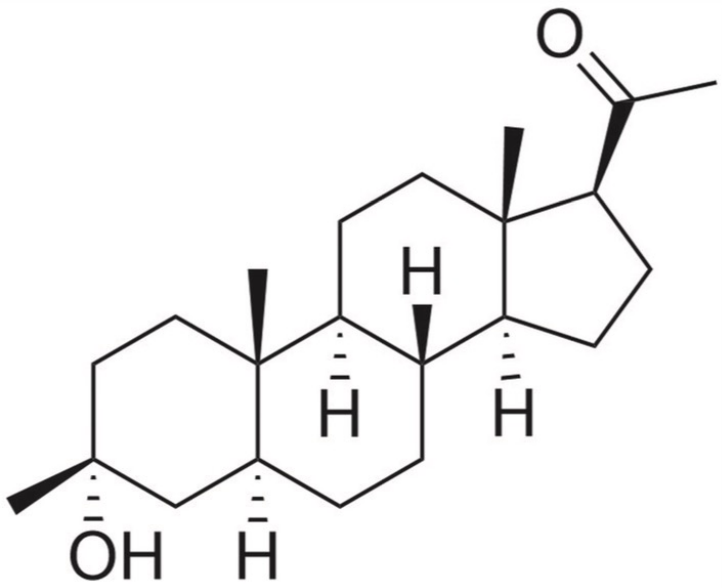
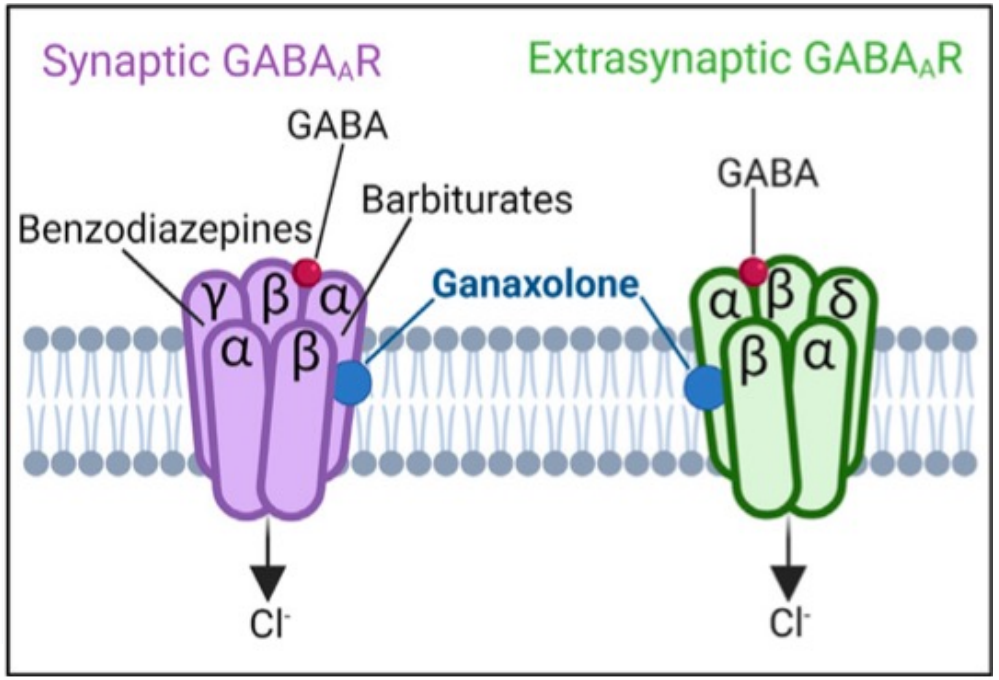
Ganaxolone (Ztalmy^{R})

Marinus Pharmaceuticals





Key Pharmacokinetic Points:

1. Administer with food TID
2. 99% protein bound
3. Terminal $t_{1/2}$ ~ 34 hrs.
4. CYP3A4/5 strong inducers will lower levels
5. GNX does NOT affect other ASM levels.
6. Suspension 50 mg/ml

Mechanism of Action:
Allosteric modulator that targets both synaptic and extrasynaptic $GABA_A$ receptor.

Indication: Treatment of seizures associated with *CDKL5* Deficiency Disorder (CDD) in patients 2 years of age and older.

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FDA Approved MARCH 2022

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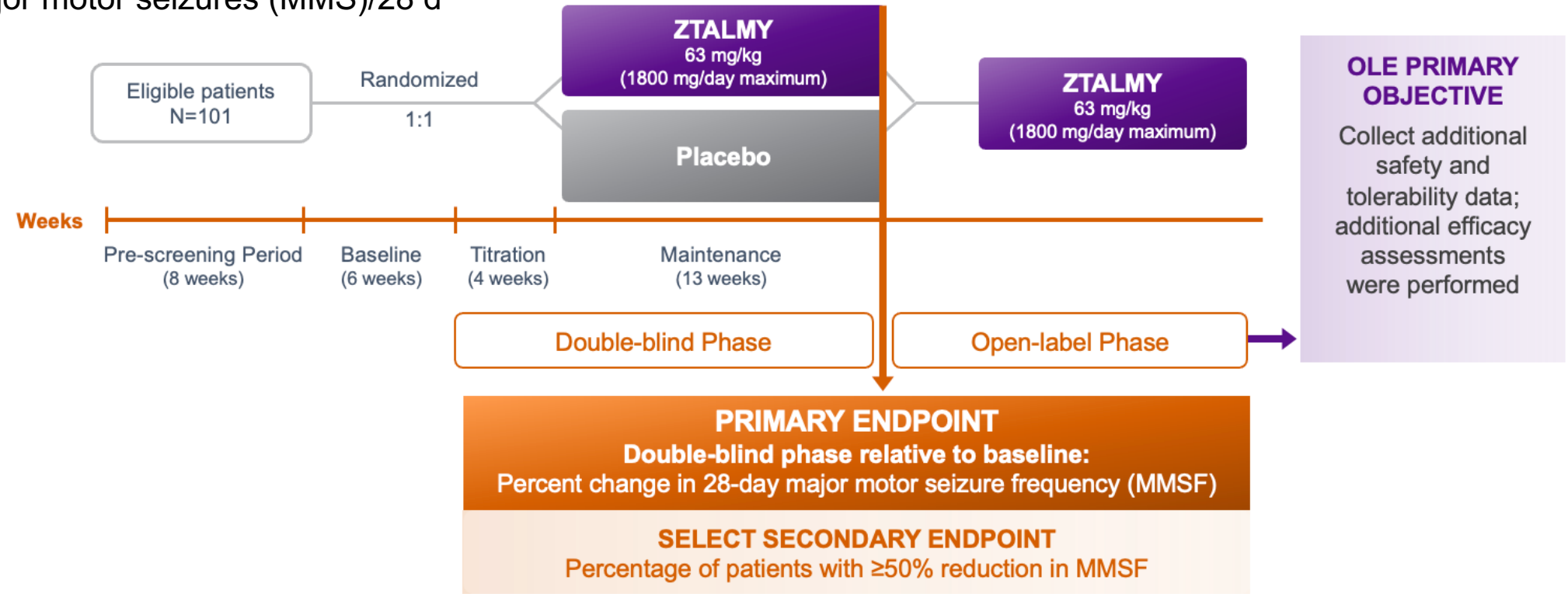
Ganaxolone: Phase 3 RCT

Eligible Patients:

CDKL5 +
2 – 21 years of age
≥ 16 major motor seizures (MMS)/28 d



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Pestana Knight EM et al. Lancet Neurol, 2022; 21 (5): 417 – 427.

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Ganaxolone: Dosing

Days	Patients ≤28 kg		Patients >28 kg	
	Dosage	Total daily dosage	Dosage	Total daily dosage
Titration Week 1 Days 1-7	6 mg/kg TID	18 mg/kg/day	150 mg TID	450 mg/day
Titration Week 2 Days 8-14	11 mg/kg TID	33 mg/kg/day	300 mg TID	900 mg/day
Titration Week 3 Days 15-21	16 mg/kg TID	48 mg/kg/day	450 mg TID	1350 mg/day
Maintenance Day 22 + ongoing	21 mg/kg TID	63 mg/kg/day	600 mg TID	1800 mg/day

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Ganaxolone: Dosing

110 ml
Cherry Flavor

Days	Patients ≤28 kg		Patients >28 kg	
	Dosage	Total daily dosage	Dosage	Total daily dosage
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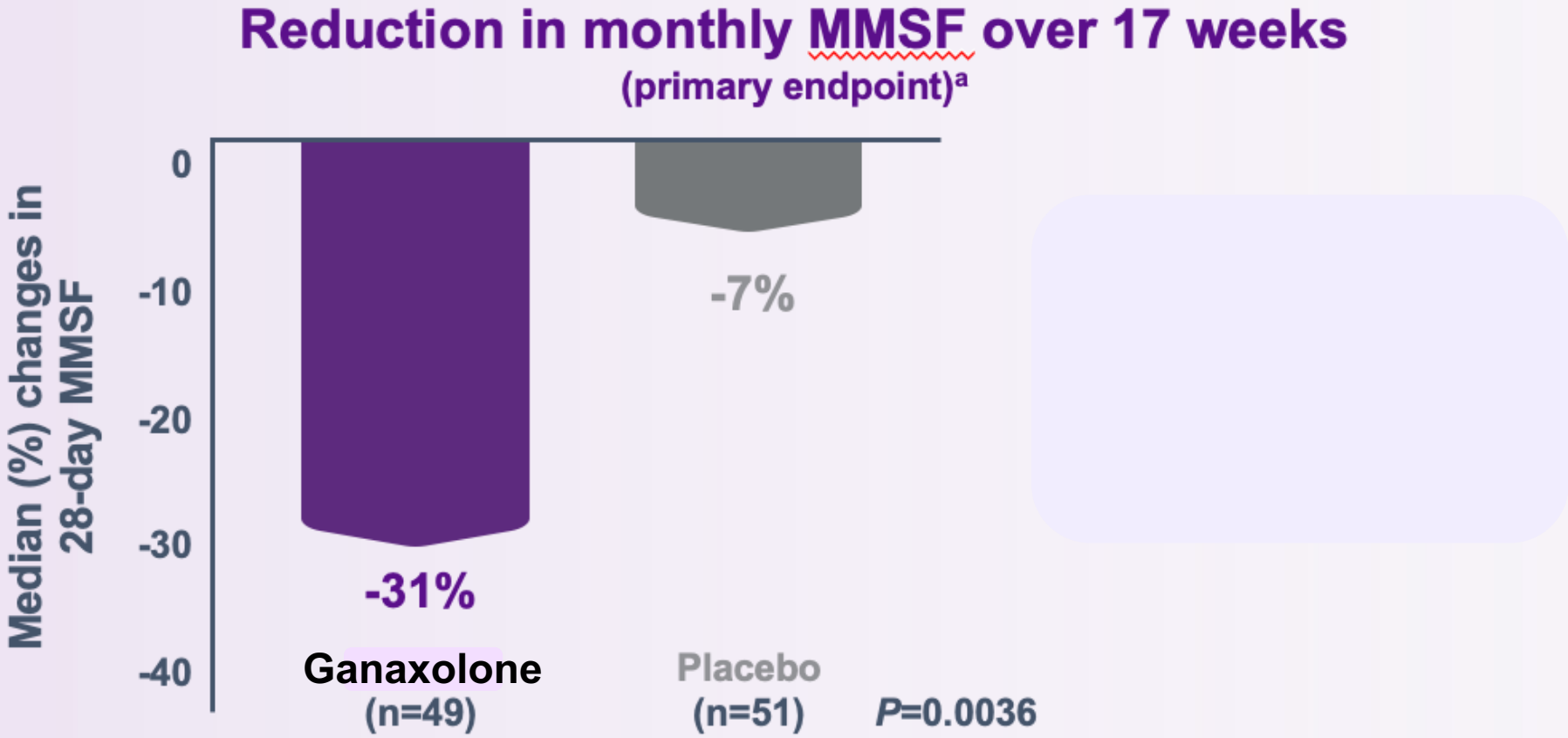
Ganaxolone: Efficacy



[a]Change from baseline. Baseline frequency of major motor seizures per 28 days was a median of 54 for the Ganaxolone group (n=49) and the median of 49 for the placebo group (n=51).

Ganaxolone: Adverse Events

Adverse reactions that occurred over 17 weeks (incidence ≥3% and greater than placebo)

Adverse Event	Ganaxolone (n=50) %	Placebo (n=51) %
Somnolence	38	20
Pyrexia	18	8
Upper respiratory tract infection	10	6
Sedation	6	4
Salivary hypersecretion	6	2
Seasonal allergy	6	0
Bronchitis	4	0
Influenza	4	2
Gait disturbance	4	2
Nasal congestion	4	2

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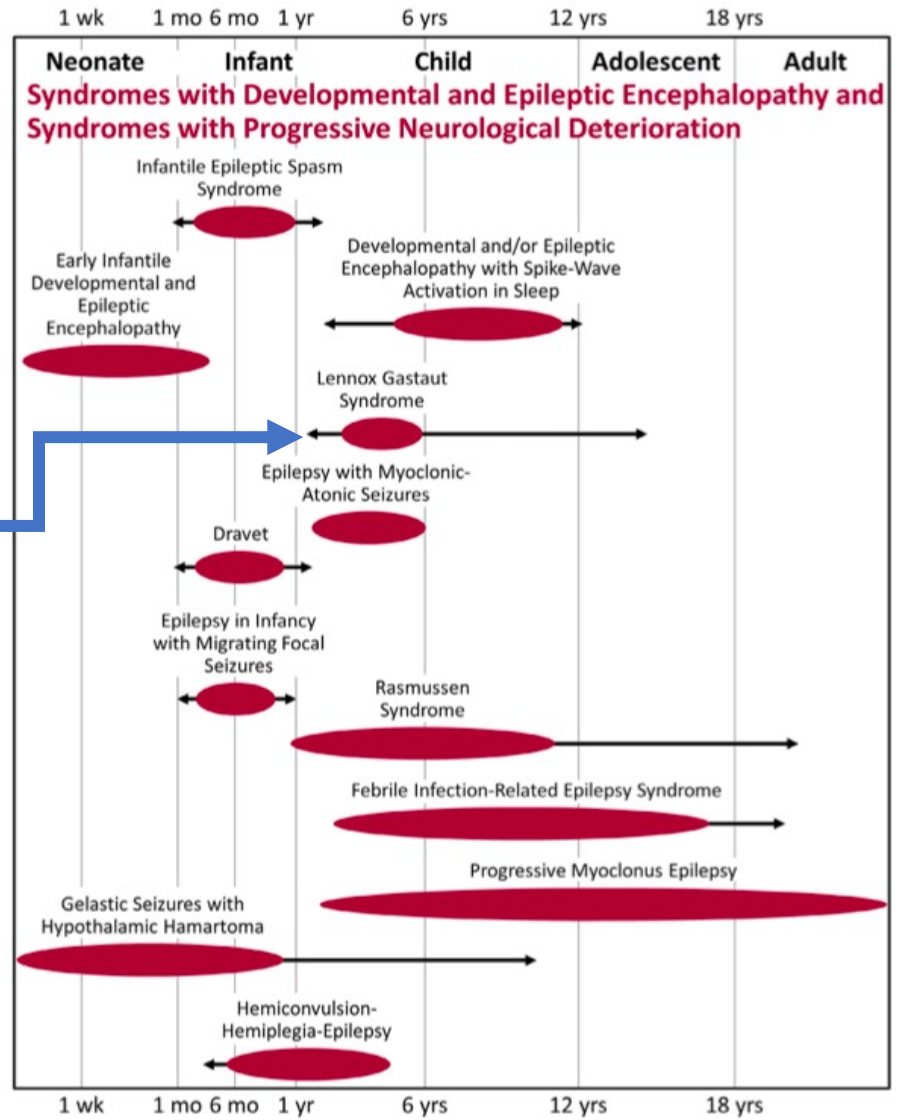
Syndromes with Developmental & Epileptic Encephalopathy

***Lennox- Gastaut Syndrome* (LGS)**



Wirrell EC et al. Epilepsia, 2022; 63 (6): 1333 – 1348.

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LGS Treatment

Start with medications approved to treat seizures associated with LGS !

- Clonazepam (Klonopin^{R})
- Felbamate (Felbatol$^{R)}$
- Topiramate (Topamax^{R}, Eprontia^{R} , Trokendi XR^{R} or Qudexy XR^{R})
- Lamotrigine (Lamictal^{R}, Lamictal XR^{R})
- Rufinamide (Banzel^{R})
- Clobazam (Onfi^{R})
- Cannabidiol (Epidiolex^{R})
- Fenfluramine (Fintepla^{R})
- Valproate (Depakene^{R}, Depakote^{R}, Depakote ER^{R}) historically used the most, no “official” approval.

Brigo F et al. Cochrane Database Syst Rev, 2021; 4 (4): CD003277.

Medical Therapy in Lennox-Gastaut Syndrome

Evidence base for one therapy vs. another is limited; each patient needs to be considered individually, taking into account potential benefit of each therapy vs. risk of adverse events.

Newest Medical Treatments In Lennox-Gastaut Syndrome

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Fenfluramine (Fintepla®)

Seizure Types Assessed in the Study

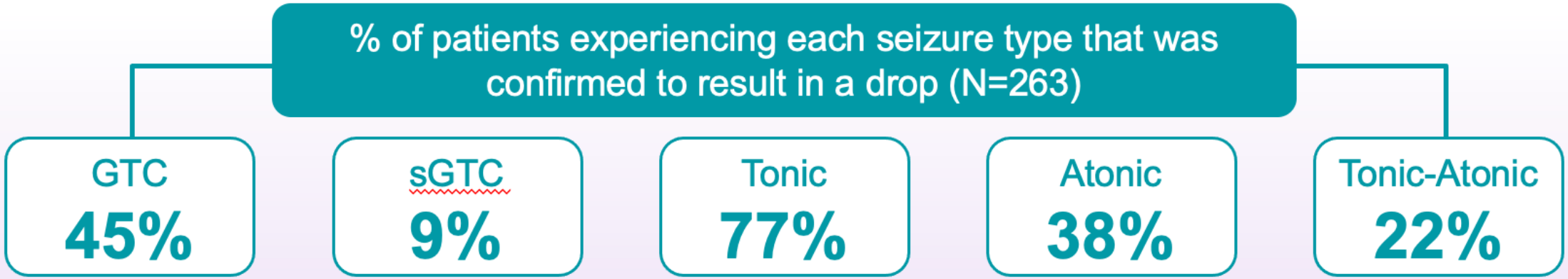
All Countable Motor Seizures
GTC, sGTC, Tonic, Atonic, Tonic-Atonic, Clonic, Hemiclonic, Focal seizures with clear observable motor signs

→

Seizure subtypes typically associated with a drop
GTC, sGTC, Tonic, Atonic, Tonic-Atonic

→

Primary Endpoint: Reviewed and confirmed as drop seizures by the Epilepsy Study Consortium



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Knupp KG et al. JAMA Neurol, 2022; 79 (6): 554 – 564.
Knupp KG et al. Epilepsia, 2022. DOI: 10.1111/epi.17431

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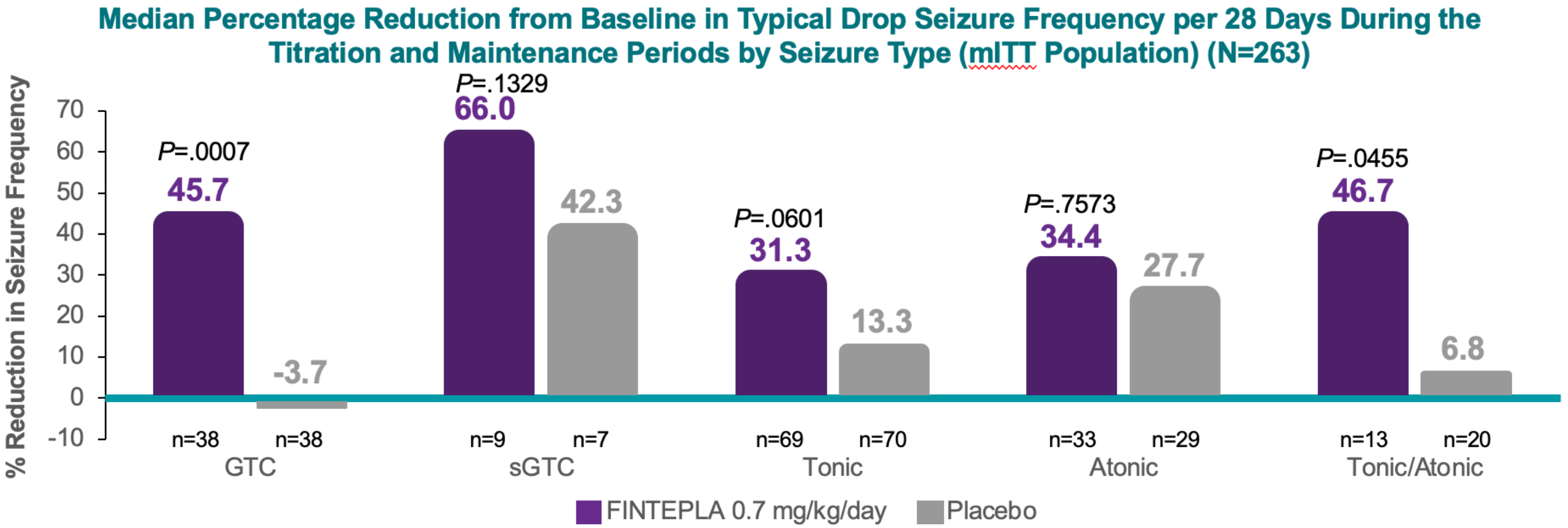
Fenfluramine Associated Reduction in Seizure Subtypes Typically Associated With a Drop



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Knupp KG et al. JAMA Neurol, 2022; 79 (6): 554 – 564.

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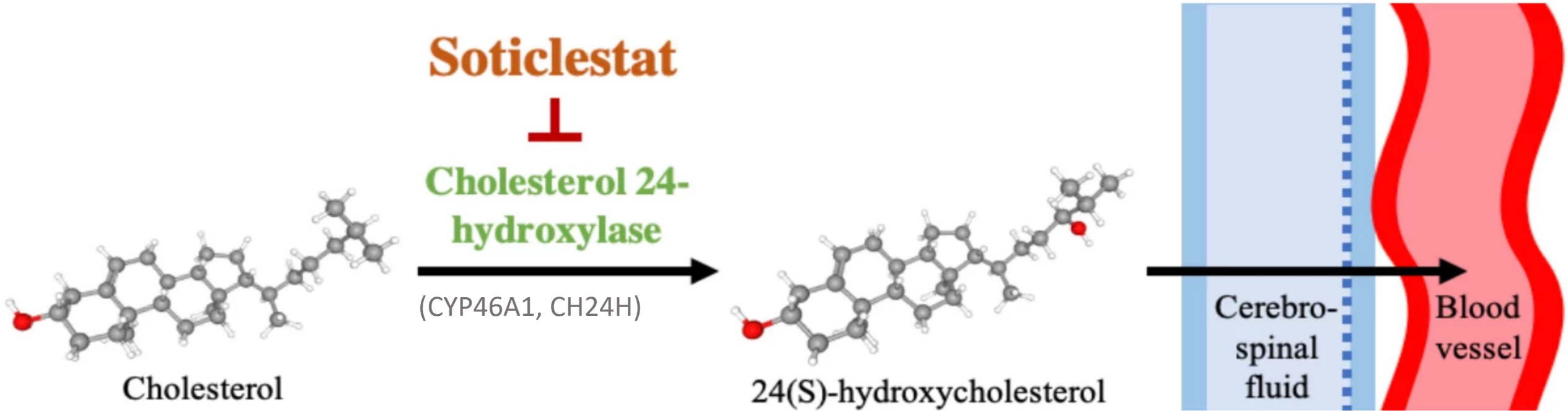
Soticlestat (TAK-935/OV935)
Takeda/Ovid Pharm

- **Mechanism of Action**: Inhibitor of cholesterol 24-hydroxylase(24(S)-hydroxycholesterol is a positive allosteric modulator of the NMDA receptor & modulates glutamatergic signaling associated with epilepsy).

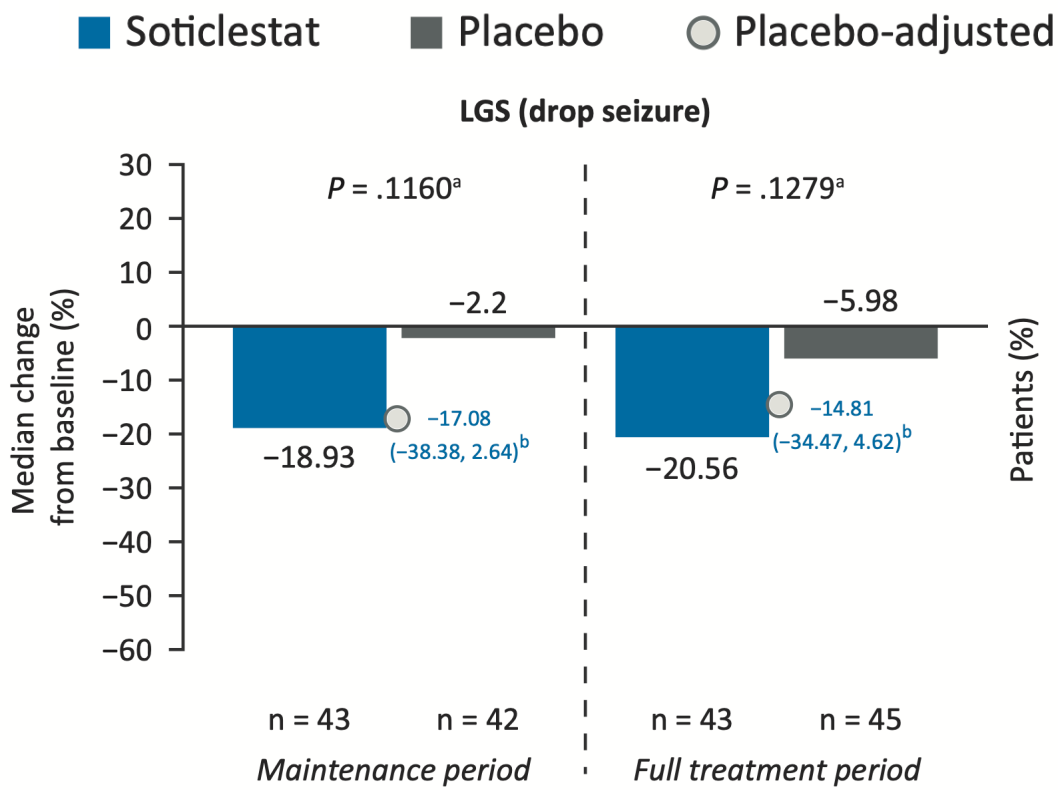


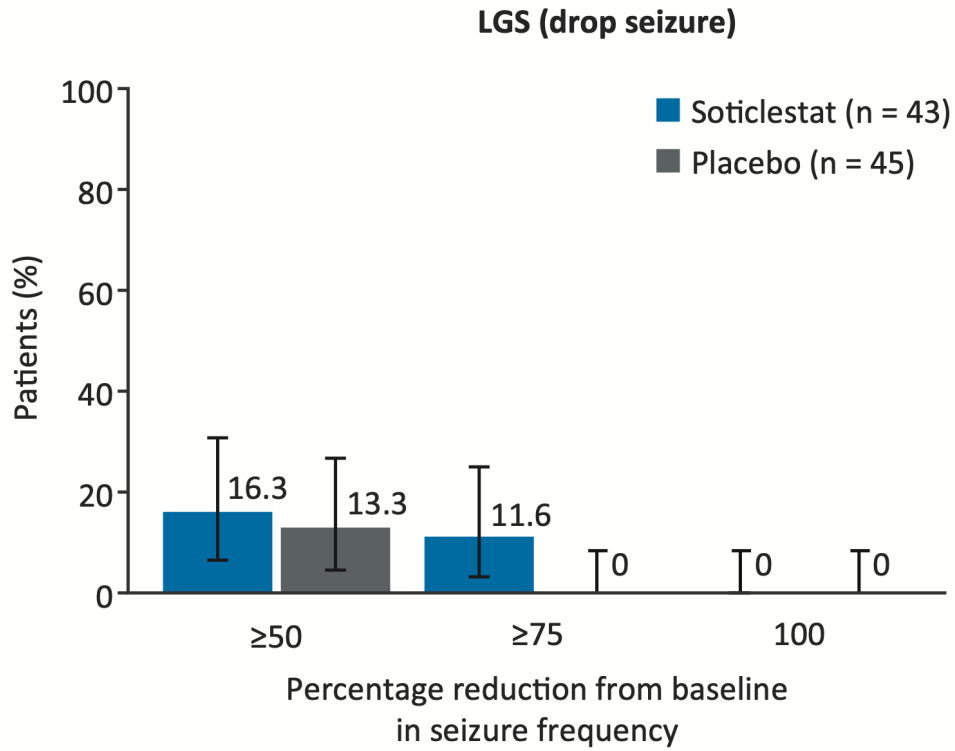
Sun JS. Neurology Live, 2020; 3 (5): 40-41.
Nishi T et al. Sci Rep, 2020; 10 (1): 7081.
Nishi T et al. Epilepsia, 2022; 63 (6): 1580 – 1590
Salamone A et al. Neurobiol of Dis, 2022; 173: 105835

Soticlestat Adjunctive Treatment in Lennox-Gastaut Syndrome

- Phase II Study (ELEKTRA Study)
- 2 – 17 Yrs. Old
- N = 88
- ≤ 300 mg BID
- No Perampanel

Side Effects *
- Lethargy
- Constipation





* >5% more common than placebo

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Hahn C et al. Epilepsia, 2022: 63 (10): 2671 – 2683.
Halford JJ et al. Epilepsy Res, 2021; 174 : 106646.

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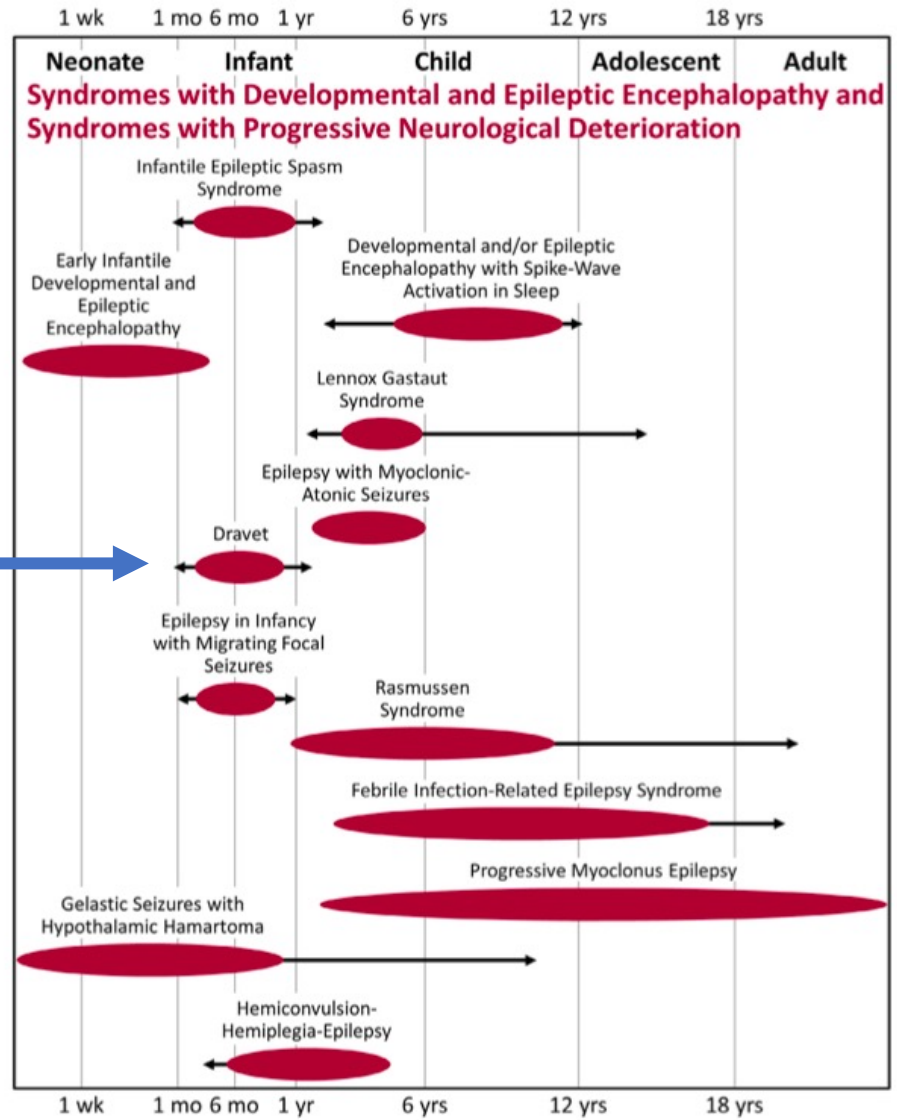
Syndromes with Developmental & Epileptic Encephalopathy

Dravet Syndrome



Wirrell EC et al. Epilepsia, 2022; 63 (6): 1333 – 1348.

Dravet Syndrome: Monogenetic Epilepsy (*SCN1A*)

Dravet Syndrome (DS) is a Severe and Progressive Genetic Epilepsy

1 out of 16,000 babies are born with DS

Up to 20% of children and adolescents with DS die before adulthood, due to SUDEP[1], prolonged seizures, seizure-related accidents or infections

Seizures are not adequately controlled in **90%** of people with DS

No approved disease-modifying therapies for DS

Non-seizure comorbidities of DS are not addressed by current therapies

- Intellectual disability
- Developmental delays
- Movement and balance issues
- Sleep abnormalities
- Language and speech disturbances
- Mood disorders

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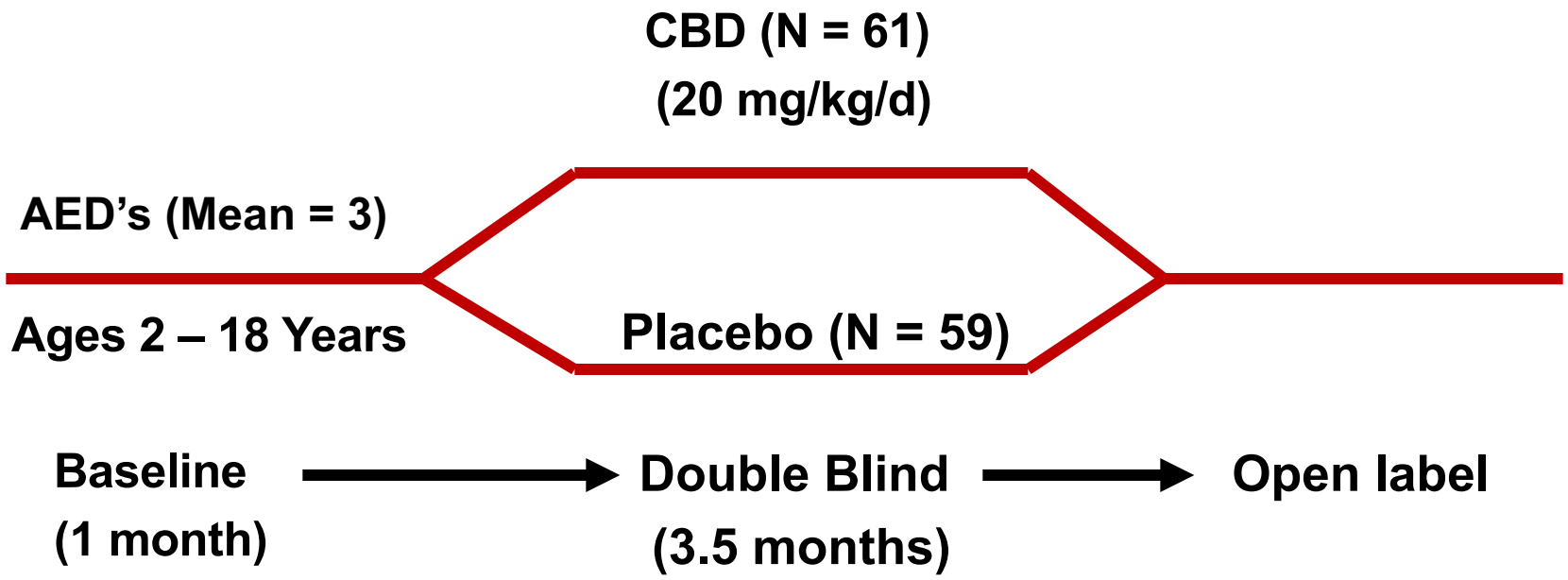
Cannabidiol (Epidiolex ®)
Jazz (Greenwich Biosciences / GW Pharmaceuticals)

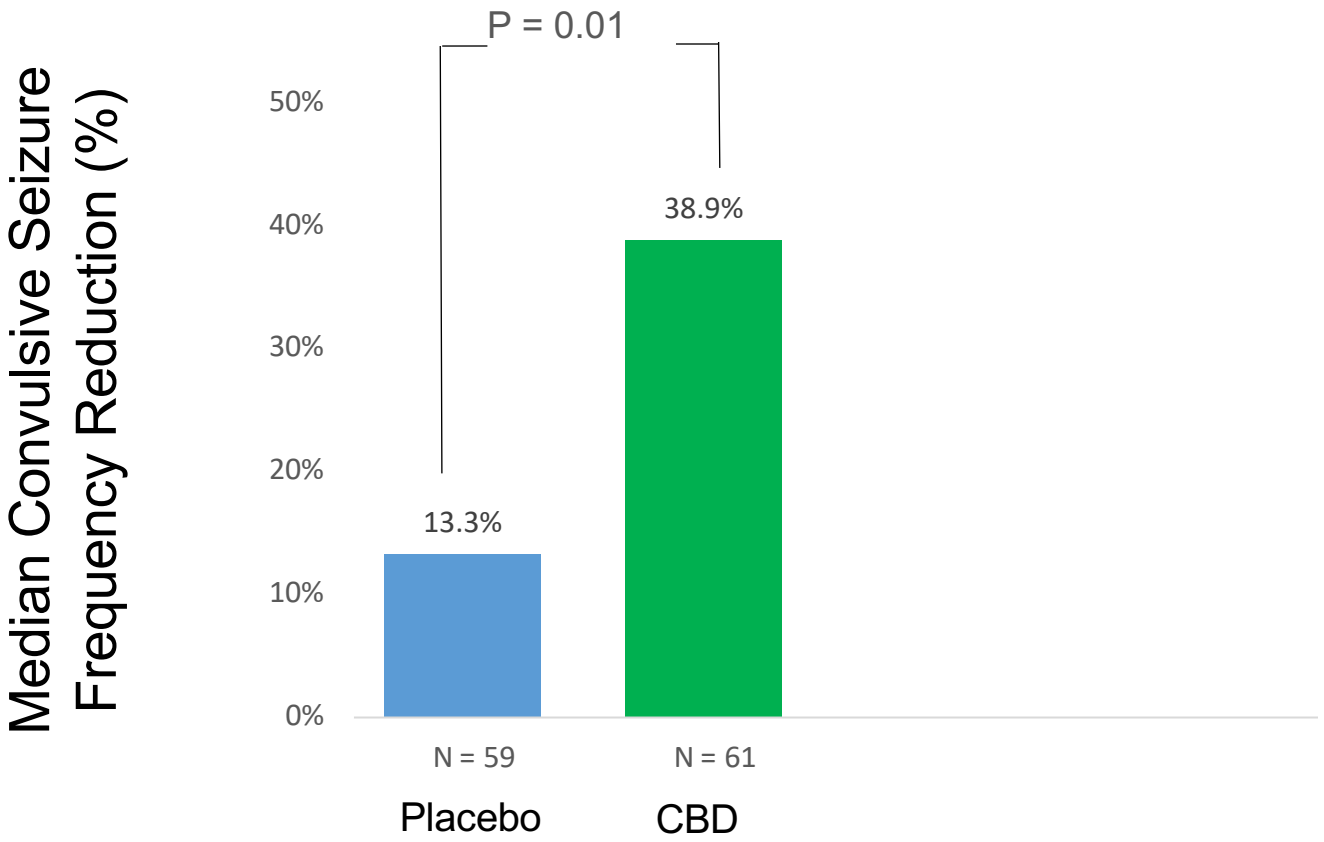
- 2007 Pre-clinical research begins with cannabidiol (CBD).
- 2018 FDA approval.
  - Treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) or Dravet Syndrome in patients 2 years of age and older (7/31/2020 TSC added, and age lowered to 1 year).
- Novel AED: Cannabinoid.
- Mechanism of action: ? (unknown).

Dravet Syndrome: Adjunctive Treatment With Cannabidiol



Devinsky O et al. NEJM, 2017; 376 (21): 2011 - 2020

Cannabidiol: Efficacy in Dravet Syndrome



Devinsky O et al. NEJM, 2017; 376 (21): 2011-2020

Cannabidiol: Adverse Events & Dosing

- Vomiting (15%)
- Decreased Appetite (28%)
- Diarrhea (31%)
- Fatigue (20%)
- Pyrexia (15%), URI's (11%)
- Lethargy (13%), Somnolence (36%)
- Abnormal Liver Function Tests (ALT) (20%)
  (all on valproate)
  - Need for periodic assessment of LFT's

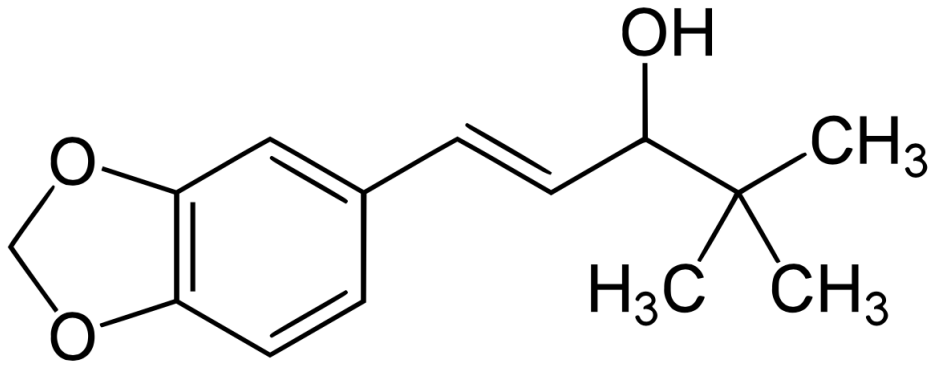
Dosing

- Take with food (prefer fatty meal), BID
- Liquid (sesame oil): 100 mg/ml
- Increase over 4 weeks to 20 mg /kg/d

Devinsky O et al. NEJM, 2017; 376 (21): 2011-2020

Stiripentol (Diacomit^{R}) Biscodex

- **1978 Discovered by Bisocodex**
- **2000 European Medicines Agency (EMA)**
  - Orphan drug status (France) – Dravet syndrome (combined with valproate, clobazam) (Approved 2007)
- **2018 FDA approval**
  - Treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam (9/21/2022 age lowered to 6 months).



- **Novel AED: aromatic allyl alcohol**
- **Mechanism of action:**
  - Inhibition of several CYP450 enzymes (3A4, 2C19)
  - Enhancement of GABAnergic transmission.
    1. inhibiting synaptosomal uptake of GABA (Result: ↑GABA levels in brain)
    2. positive allosteric modulation of $GABA_A$ receptors (with alpha-3 sub-unit).

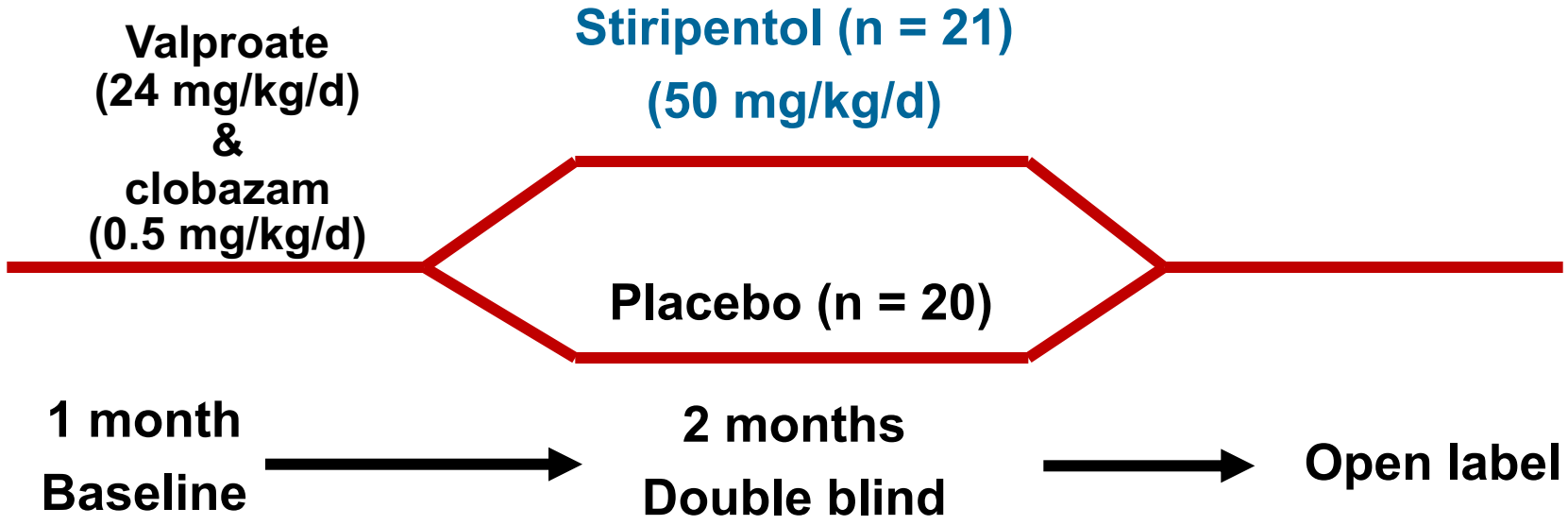
Mudigoudar B, Weatherspoon S, Wheless JW. Semin Pediatr Neurol, 2016; 23 (2): 167-179.

Stiripentol (STP): Drug Interactions

- **STP inhibits**: CYP2C19 (N-desmethylclobazam)
  CYP3A4 (valproate, clobazam, cannabidiol)
  CYP2D6 (beta-blockers, fluoxetine, paroxetine, sertraline, codeine, haloperidol, fenfluramine)
- No significant effect on cannabidiol or vice-versa.
- STP increases fenfluramine levels.

Mudigoudar B et al. Semin Pediatr Neurol, 2016, 23 (2); 167-179

Dravet Syndrome: Adjunctive Treatment With Stiripentol

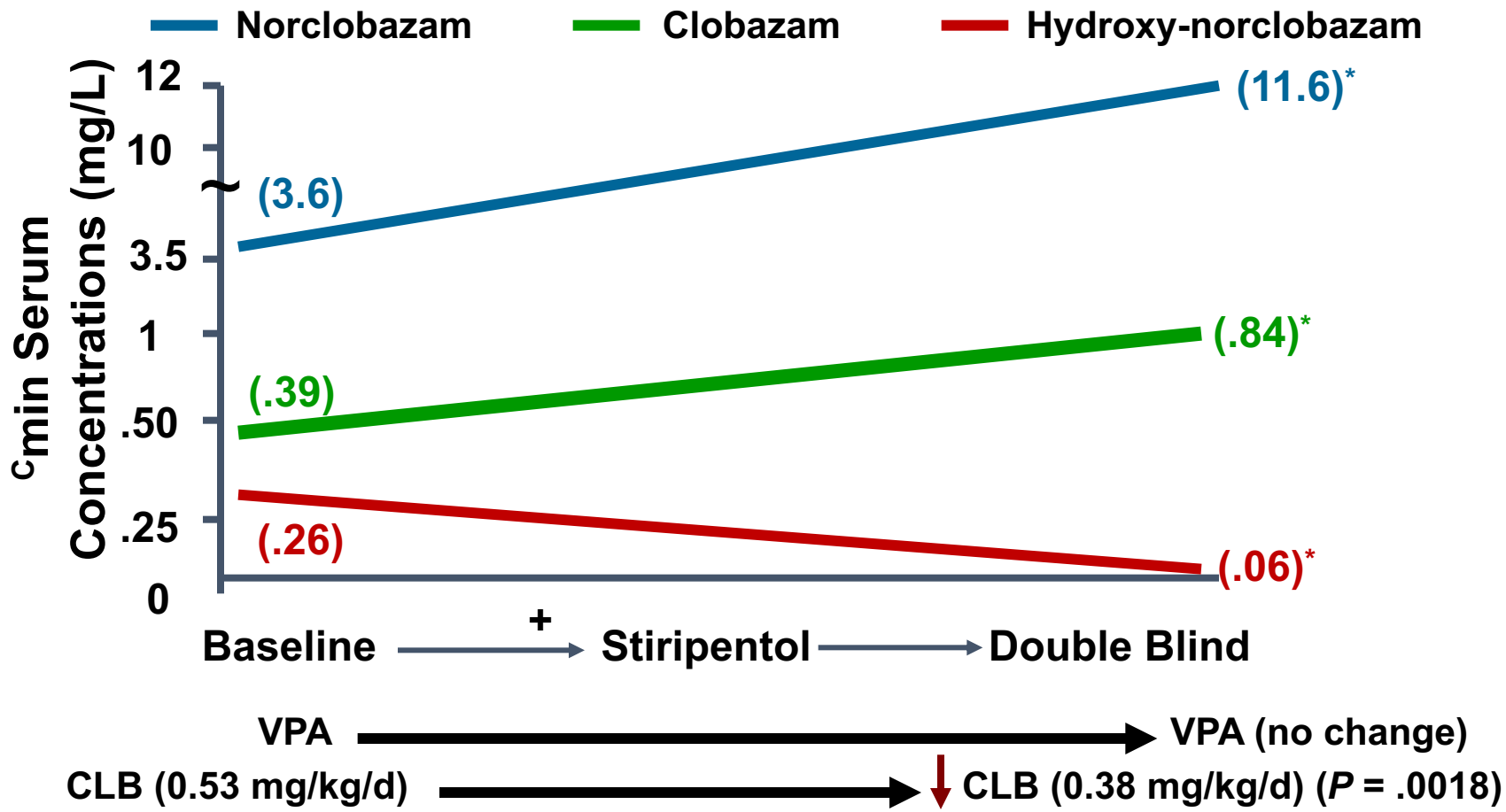


Stiripentol: 71% responders vs 5% placebo (*P* <.0001)

43% seizure-free (*P* <.0013)

Chiron C et al. Lancet. 2000; 356 (9242): 1683-1642.

Dravet Syndrome: Adjunctive Treatment With Stiripentol



CLB = clobazam; VPA = valproate.

Chiron C et al. Lancet. 2000; 356 (9242): 1683-1642.

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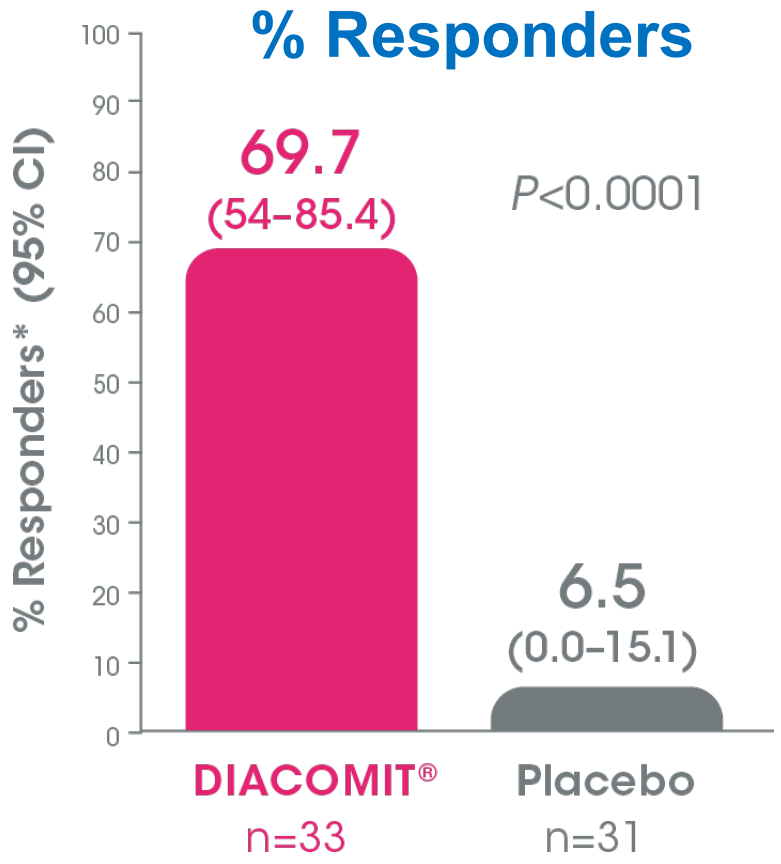
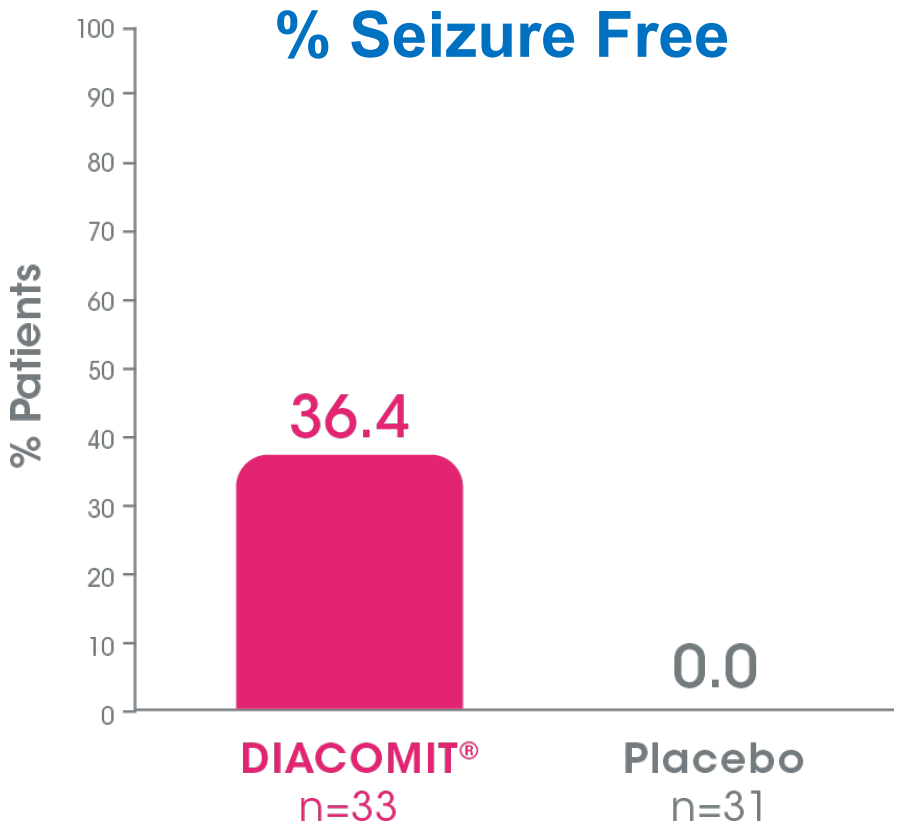
Stiripentol Phase III Pooled Results: STICLO France[1] & STICLO Italy[2]





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[1]Chiron C et al. Lancet, 2000; 356 (9242): 1638-1642.
[2]Guerrini R et al. Epilepsia, 2002; 43 (Suppl.8); S155.

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Stiripentol: Adverse Events & Dosing

Adverse Events

- Anorexia, weight loss.
- Drowsiness, ataxia, hypotonia, insomnia, agitation (most due to interactions with other AEDs)
- Rare thrombocytopenia, neutropenia, altered LFTS

Dosing

- Take with meals
- Capsules: 250, 500mg
- Powder for oral suspension: 250, 500 mg
- Given bid or tid
- Increase over 3-4 weeks to 50 mg/kg/d if <10 years old (<30kg); to 25 mg/kg/d if >10 years old (> 30 kg) (Maximum dose 3000 mg/d)

Mudigoudar B et al. Sem Pediatr Neurol, 2016; 23(2): 167-179.
Peigne S et al. Clin Pharmacokinet, 2018; 57 (6): 739-748.

Fenfluramine (Fintepla ®)
UCB (Zogenix Pharmaceuticals)

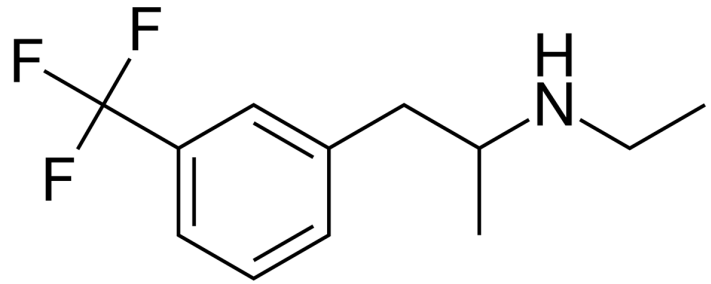
- 1973 – USA approval as an anorectic agent (Pondimin ®)

↓ Cardiac Valvulopathy

- 1997 – Removed from USA market

↓

- Spring 2019 – New Drug Application submitted – Dravet Syndrome



- Mechanism of Action: serotoninergic activity (induces serotonin release from vesicular storage sites and inhibits serotonin reuptake)

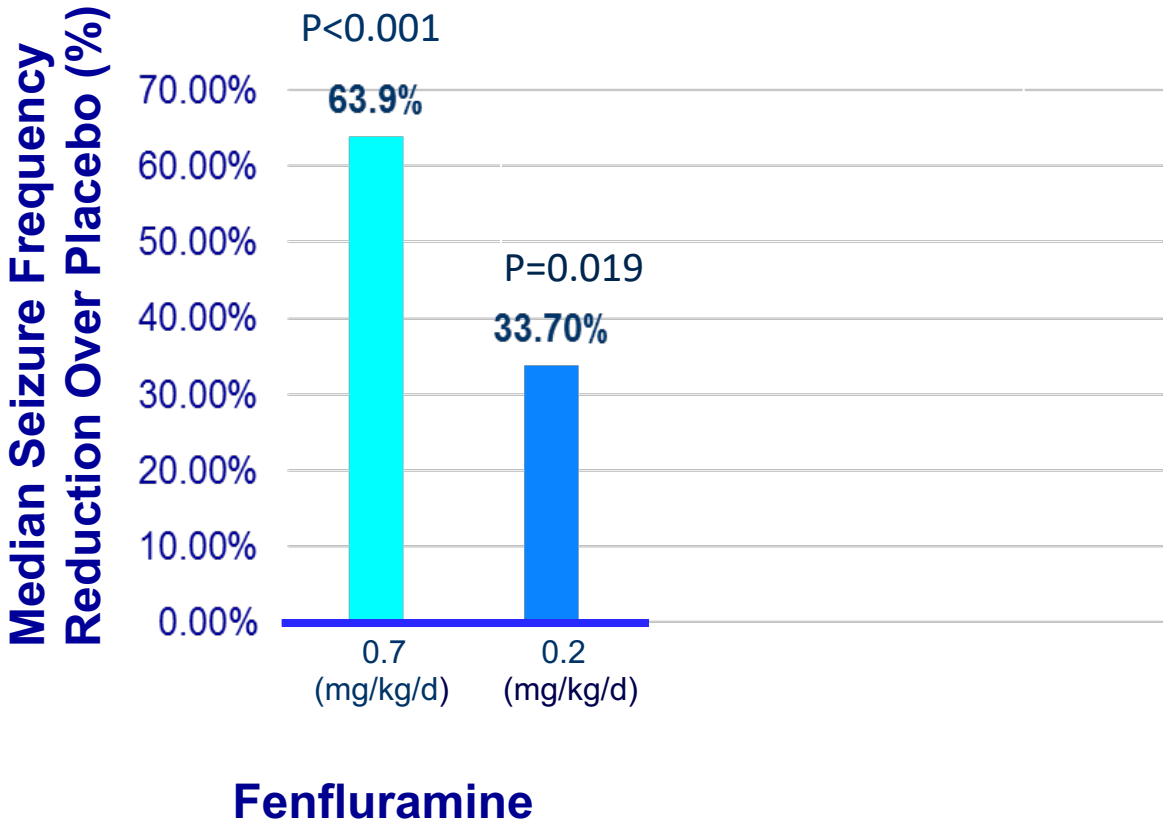
Polster T. Epilepsy & Behav, 2019; 91: 99 - 102.

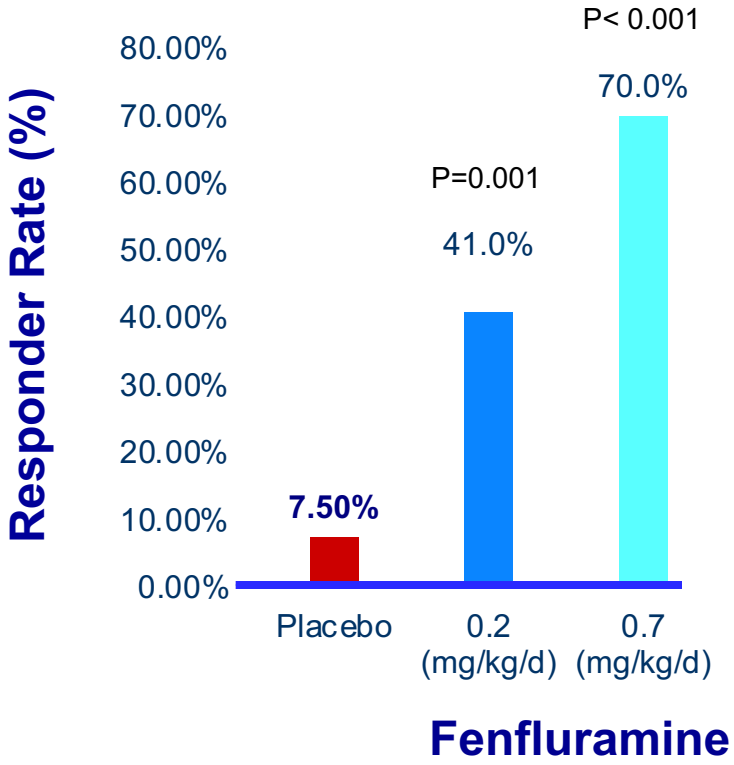
Fenfluramine: Pharmacokinetics

- Bioavailability ~ 100% (first-pass effect lowers to 6—70%). No food effect.
- Tmax: 1-2 hr
- t½ : 20hr. (30 hr. for 5-HT_{2C} receptor binding is responsible for anorexic effect)
- Protein binding : low (<40%)
- Hepatic metabolism (CYP2D6) to norfenfluramine (~ equal amounts to fenfluramine)
- Drug interactions: Stiripentol increases fenfluramine serum levels

Boyd B et al. Int J Clin Pharmacol Ther, 2019; 57 (1): 11-19
Mudigoudar B et al. Semin Pediatr Neurol, 2016; 23 (2): 167-179

Fenfluramine: Efficacy in Dravet Syndrome





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Bailer M et al. Epilepsia, 2018; 59 (10): 1842-1866.

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Fenfluramine: Adverse Events

- Most common: somnolence, fatigue and anorexia
- No cardiac valvulopathy

Bailer M et al. Epilepsia, 2018; 59 (10): 1842 - 1866

Fenfluramine: Dosing

0.15 mg/kg/d divided BID

↓

Increase every 1-2 weeks by 0.15 mg/kg/d

↓

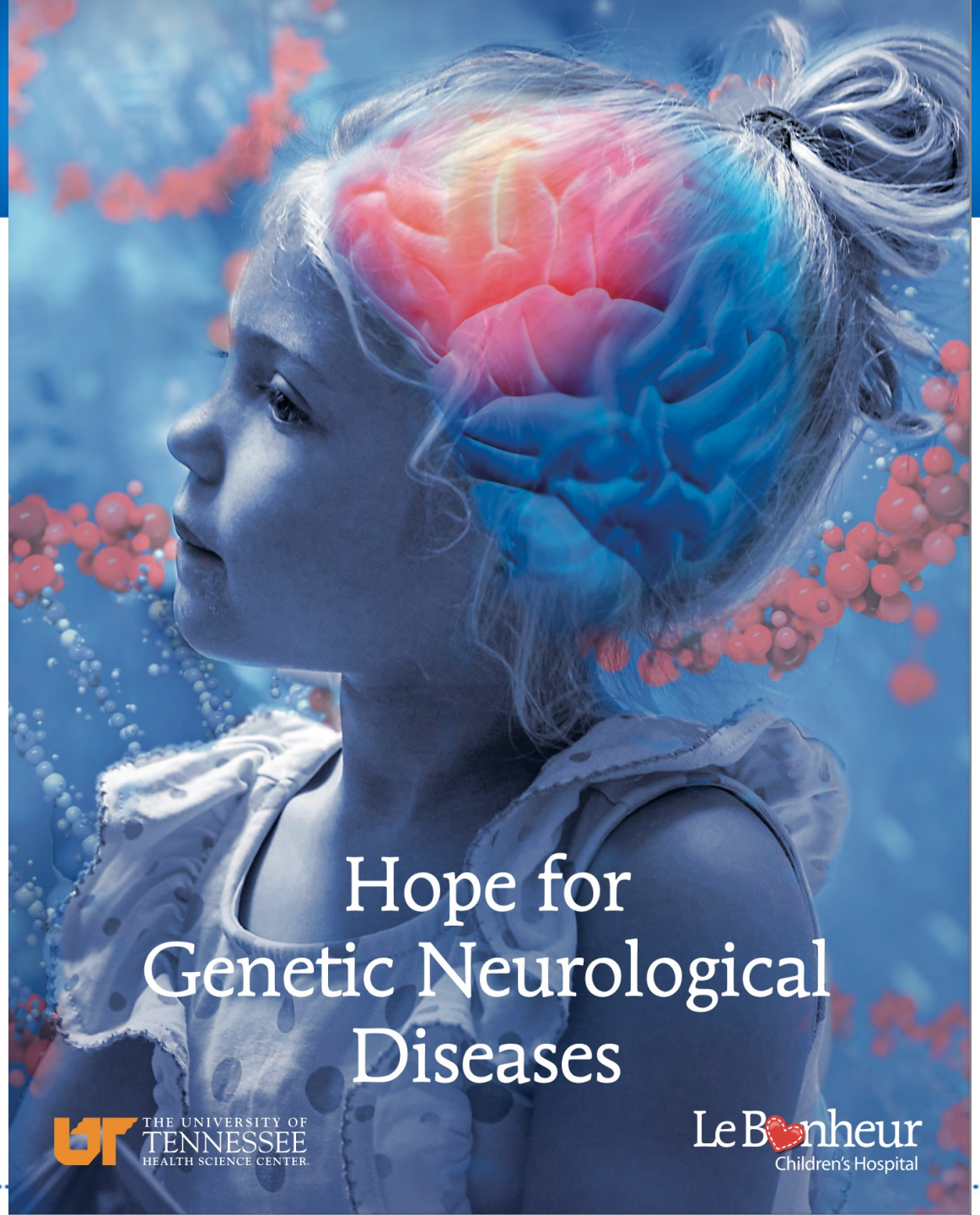
Maximum: 26 mg/d or 0.7 mg/kg/d

(If on Stiripentol: 0.4 mg/kg/d or 17 mg/d)

Solution (2.2 mg/ml)

Serum levels 20 – 140 ng/ml

Dravet Syndrome



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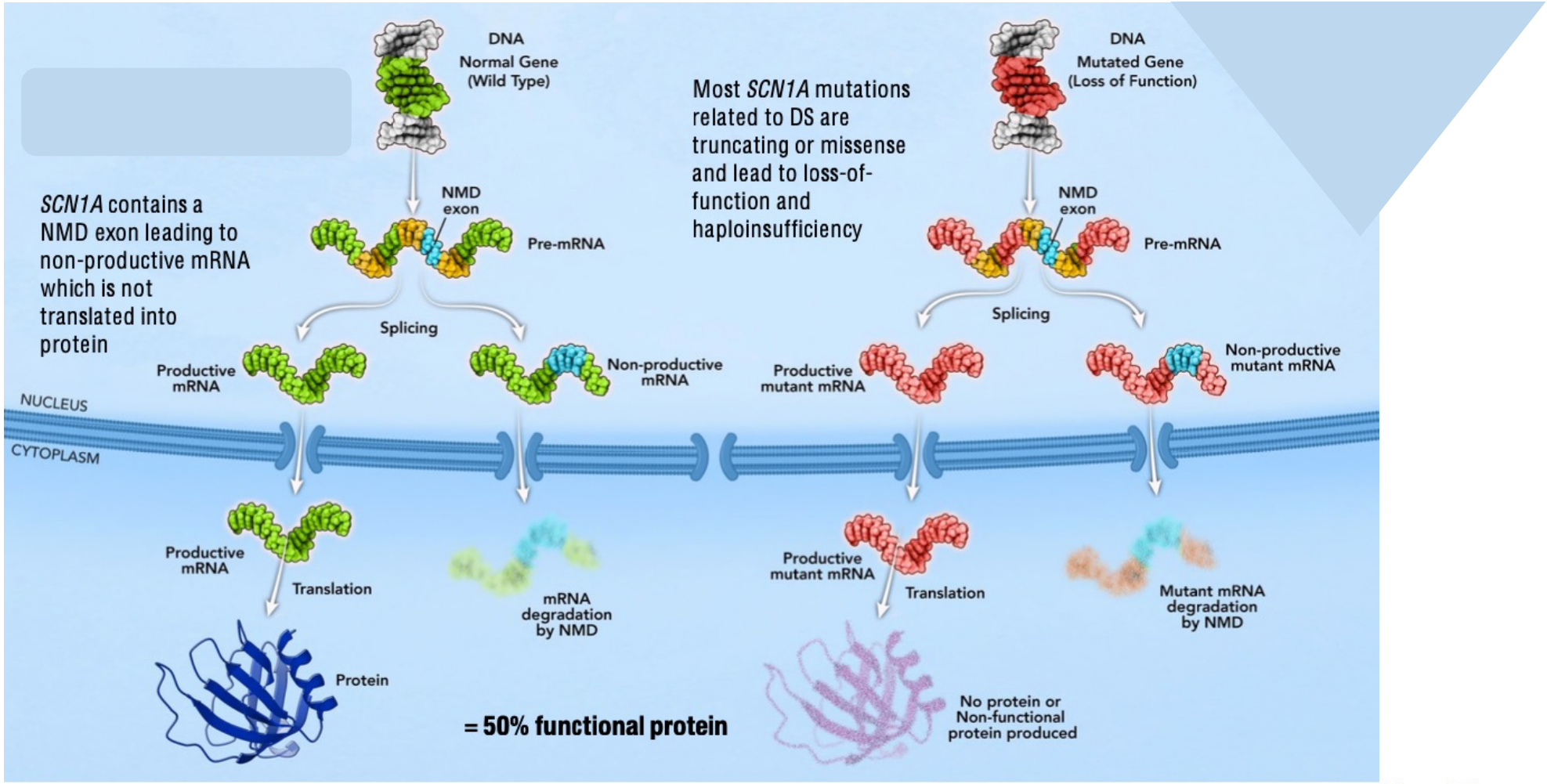
Dravet Syndrome



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Targeted Augmentation of Nuclear Gene Output (TANGO)

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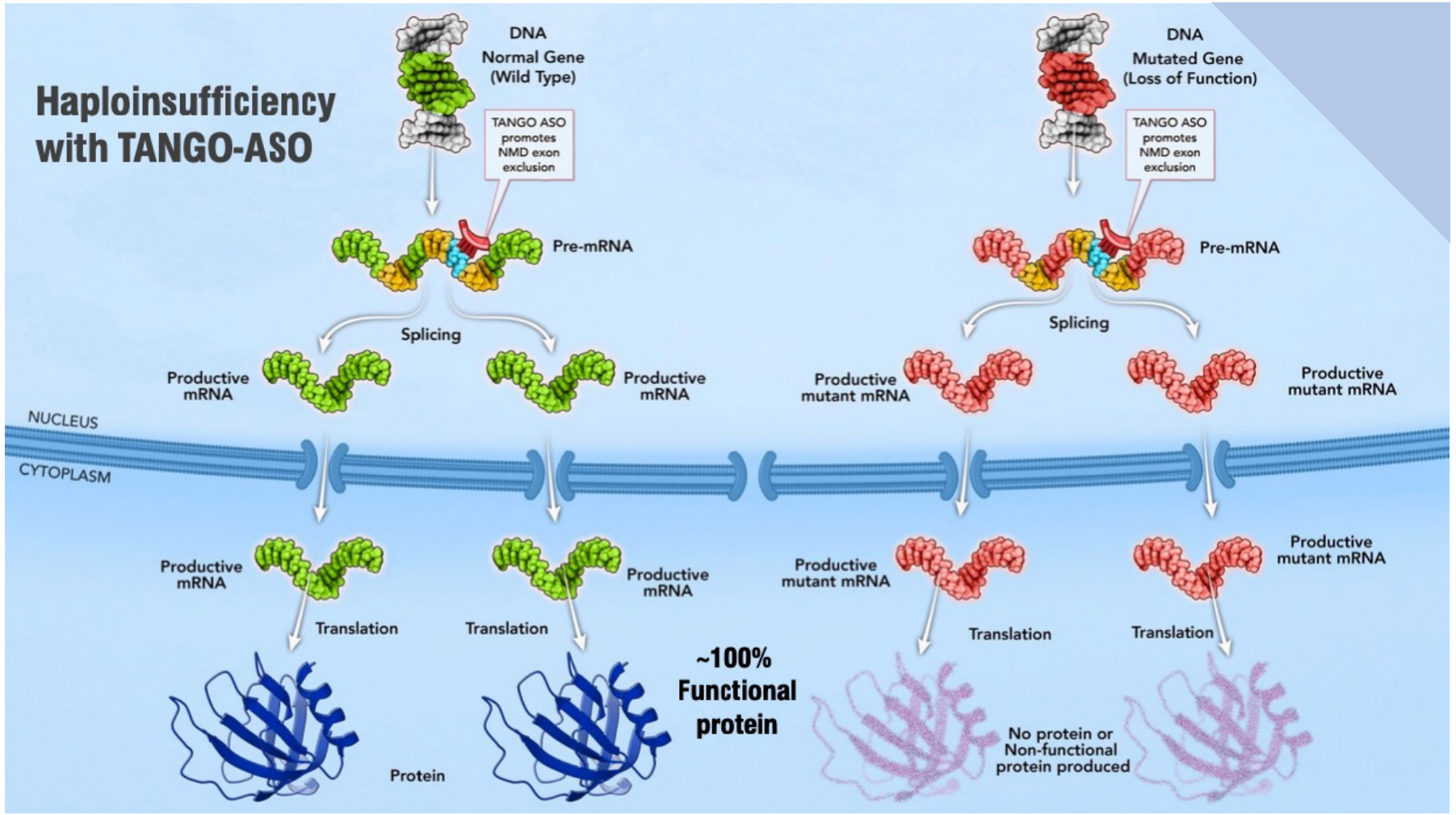
Dravet Syndrome



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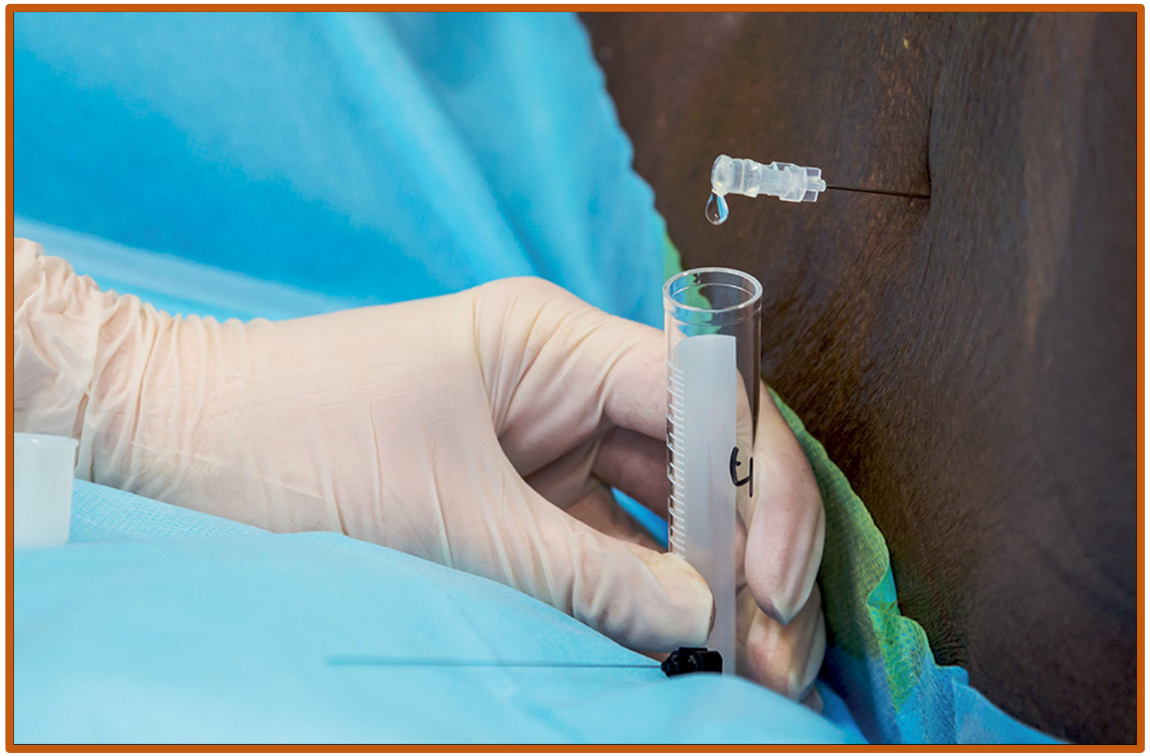
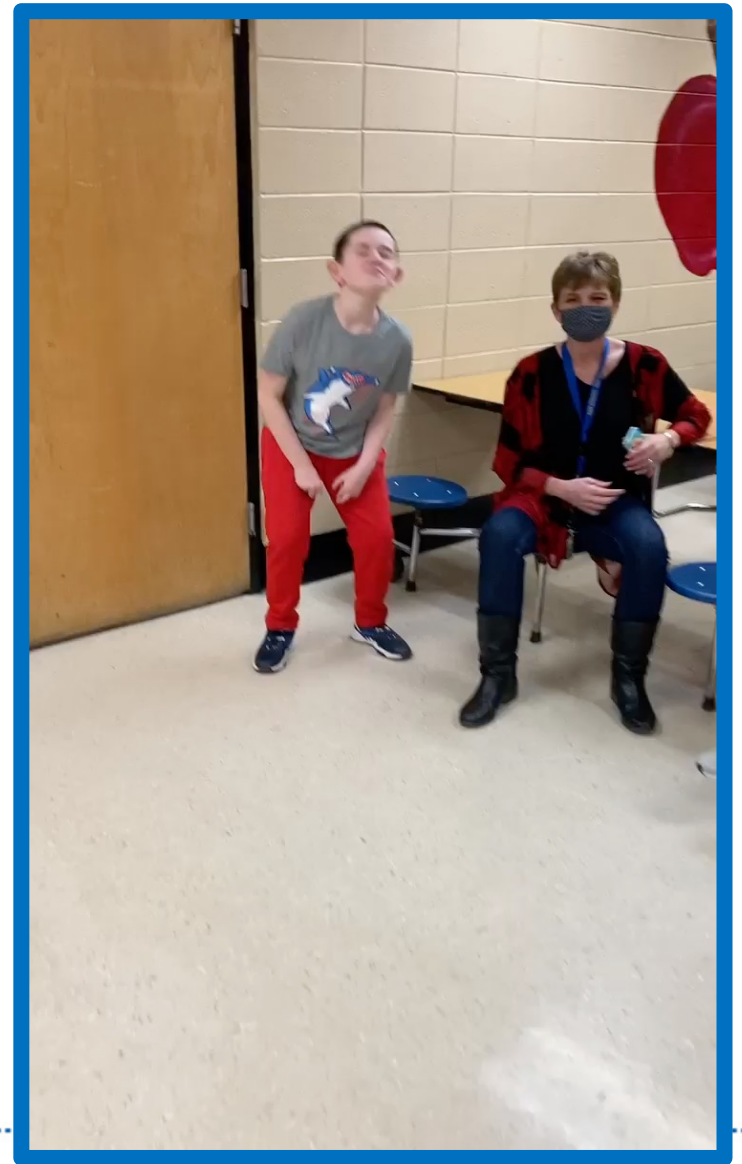
Intrathecal ASO Therapy



Dravet Syndrome:
5 Days After Intrathecal ASO Therapy



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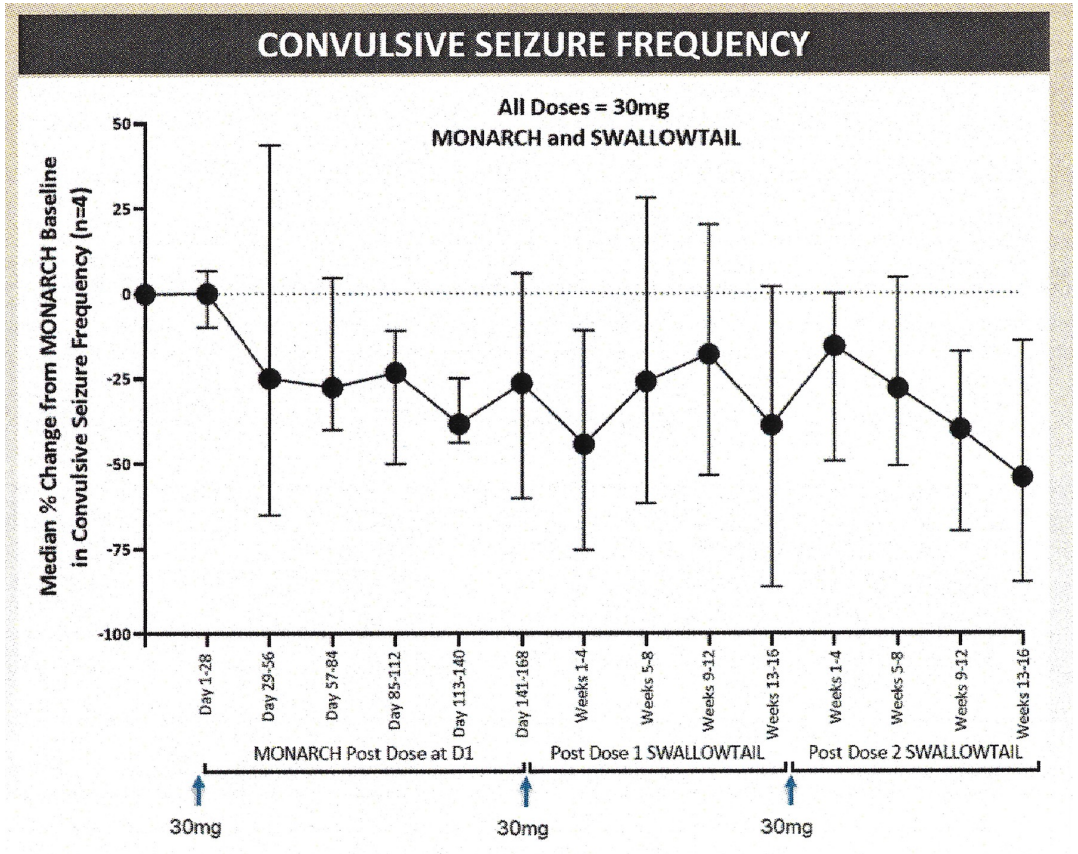
Dravet Syndrome: Efficacy of ASO Therapy (STK-001)

Open-Label Study, N = 17



www.aesnet.org

Assessed 1.16.2023 (Abstract 1.216, Presented at 2022 AES in Nashville, TN on 12/3/2022).

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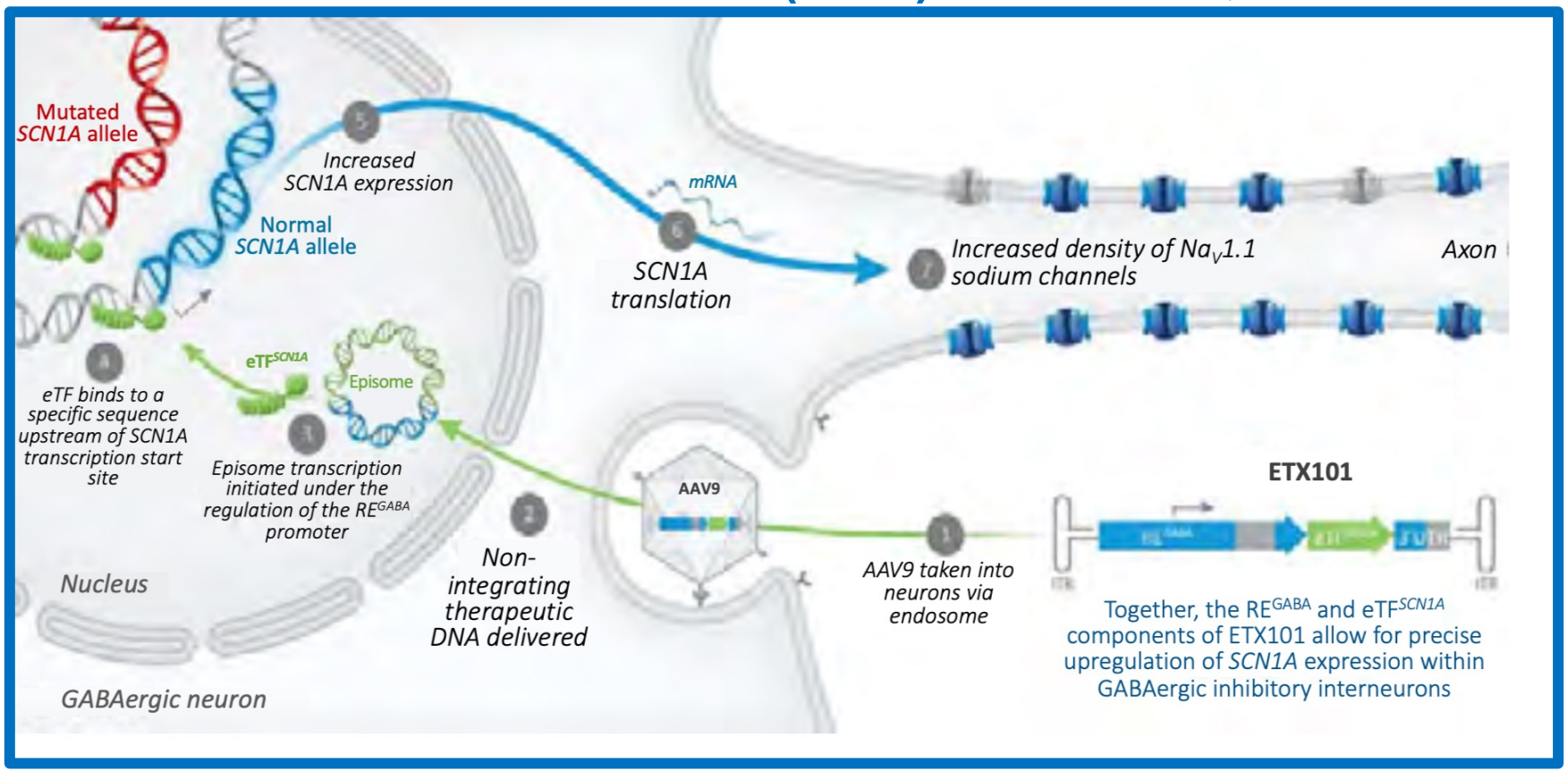
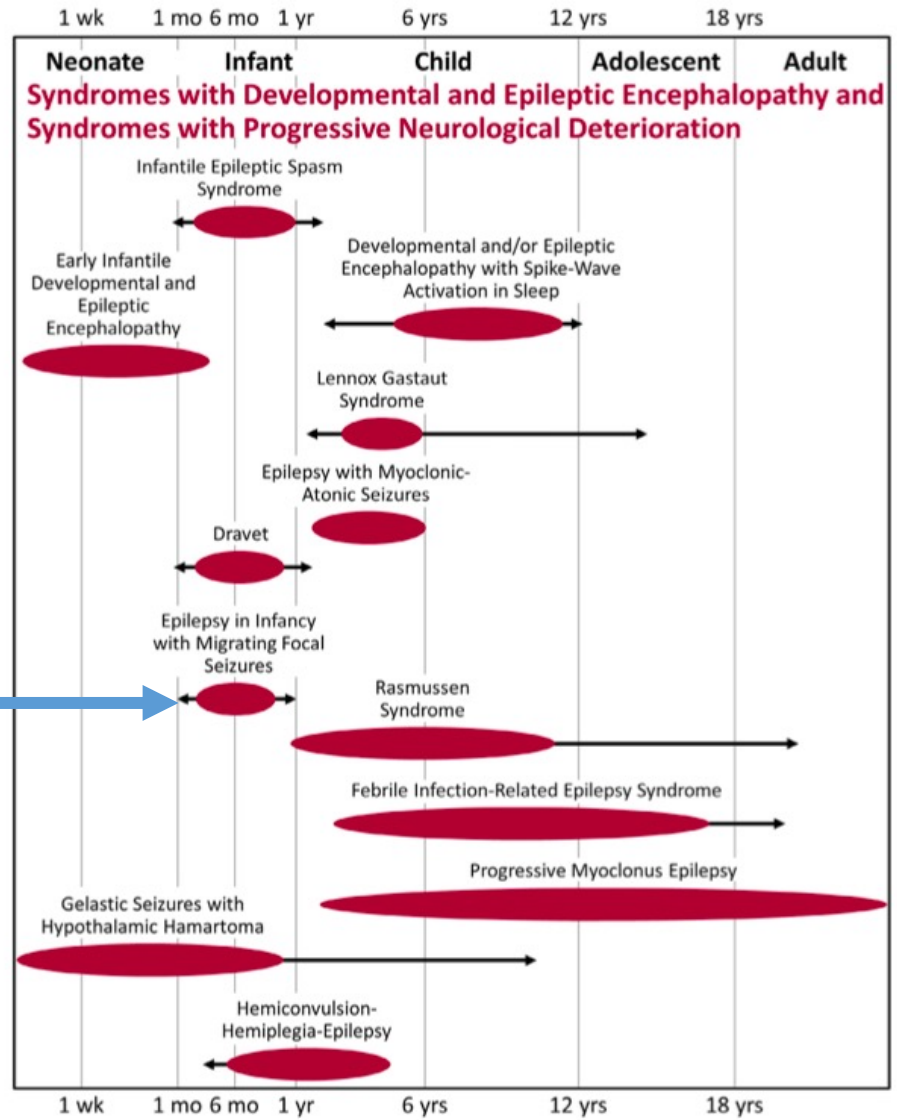
Dravet Syndrome: AAV Treatment

Encoded Therapeutics:
Adeno- Associated Virus (AAV) Treatment; ETX101



Syndromes with Developmental & Epileptic Encephalopathy

Epilepsy in Infancy with Migrating Focal Seizures *(KCNT1)*



Wirrell EC et al. Epilepsia, 2022; 63 (6): 1333 – 1348.

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Epilepsy in infancy with migrating focal seizures (EIMFS)(*KCNT1*): ASO Therapy

Hopes for Antisense Oligonucleotides Remain Strong Despite Severe Adverse Events in Trials

ARTICLE IN BRIEF: Two children who were administered an antisense oligonucleotide (ASO) for a severe genetic epilepsy disorder developed hydrocephalus, and one of them died. Experts suggest that while the therapies have potential for these otherwise fatal disorders, they remain highly experimental, and greater efforts should be made to share data from other research and outcomes involving ASOs.

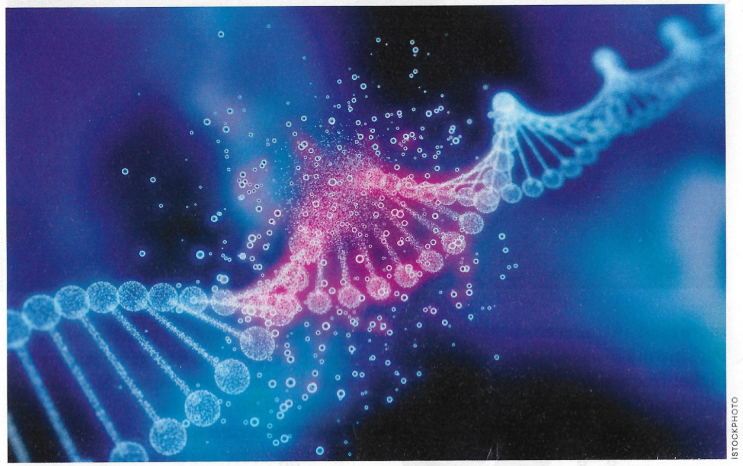
BY DAN HURLEY

A 3-year-old girl treated with an antisense oligonucleotide (ASO) for a devastating form of genetically caused epileptic encephalopathy died last year after developing hydrocephalus, the principal investigator of the trial reported in October at the annual meeting of the American Neurological Association.

Another child treated with the same ASO also developed hydrocephalus but underwent a successful shunt placement, reported Timothy Yu, MD, PhD, a neurologist, associate professor of pediatrics at Harvard Medical School, and an attending physician in the division of genetics and genomics at Boston Children's Hospital.

Both children had a severe form of KCNT1 epileptic encephalopathy.

"Patients with KCNT1 epileptic



ISTOCKPHOTO

both cases. The intervention has the capability of producing transformative change. We just need more studies. I don't think we will begin to know how successful this approach will be, or not, until we get the numbers up."

How do we work cooperatively with people doing similar work? I do worry that this field needs to move forward carefully or we're going to repeat the errors of the gene therapy world."

The Development of ASOs

"We were shocked to see the seizures respond as well as they did, especially in patient No. 2 [the one who survived]. And yet we know that we also incurred this serious adverse event in both cases. The intervention has the capability of producing transformative change. We just need more studies. I don't think we will begin to know how successful this approach will be, or not, until we get the numbers up."

—DR. TIMOTHY YU

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Neurology Today, 2022; 22 (24): 8 - 9.

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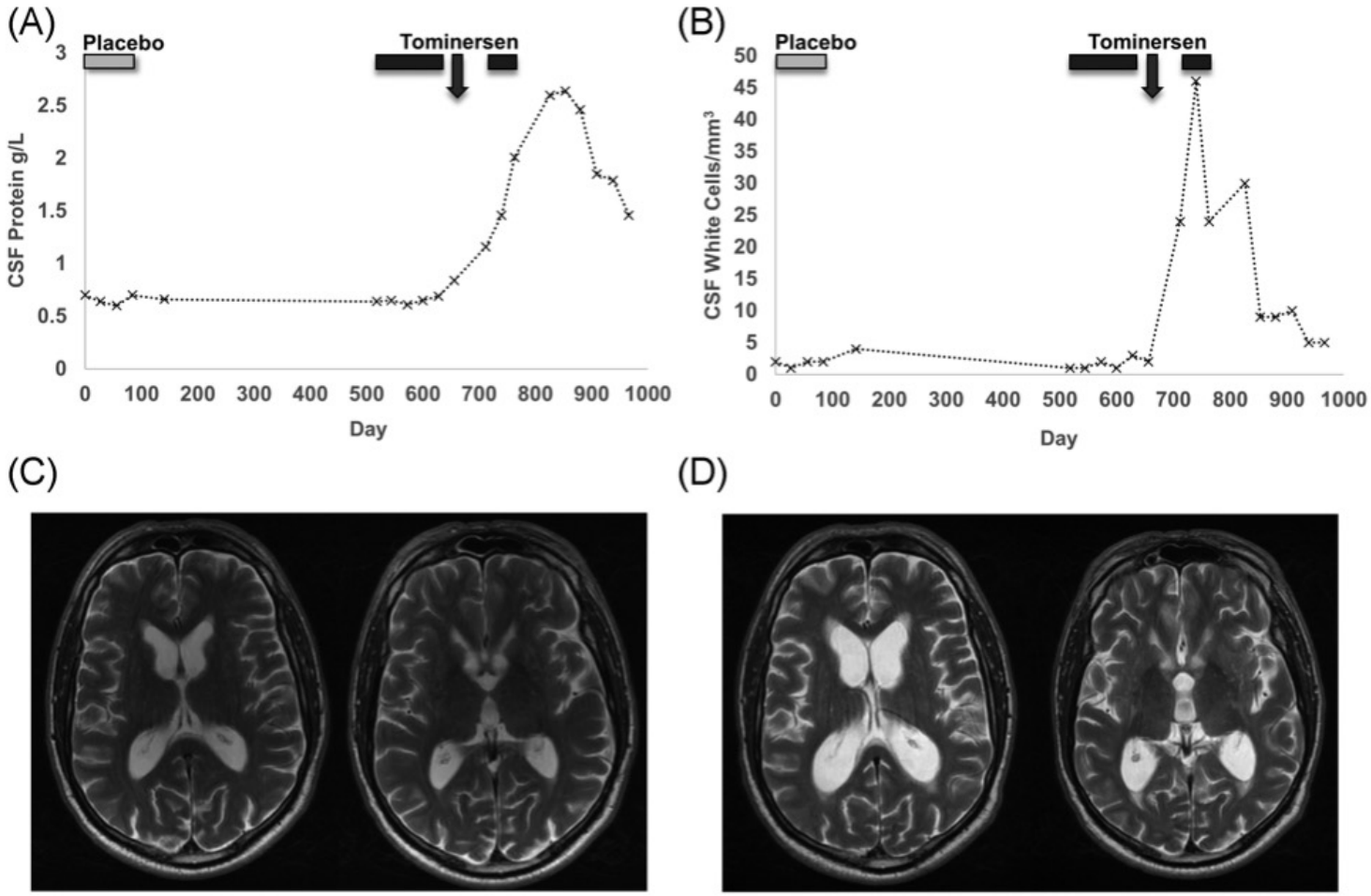
Hydrocephalus Complicating ASO Therapy for Huntington's Disease



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Stoker TB et al. Movement Dis, 2021; 36 (1): 263 – 264.

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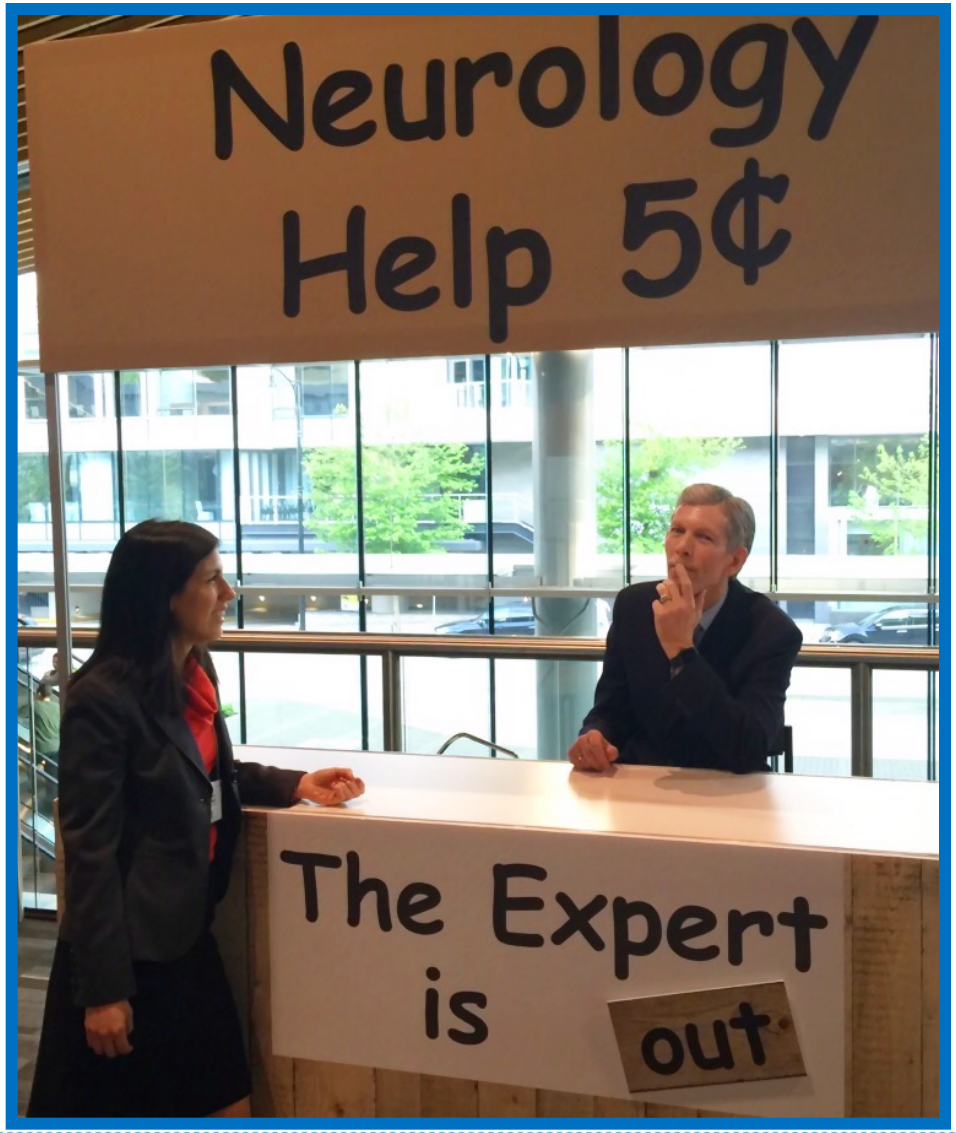
Developmental & Epileptic Encephalopathy (DEE): What Matters to Families

1. Seizure control
2. Adverse events
3. Developmental outcome
4. Sleep
5. Behavior
6. Quality-of-life (QOL) outcomes

These apply to the patient; however, many also apply to the caregiver.

Questions ?



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Thank You For Your Attention!

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