Analysis of STK-001 for the Treatment of Dravet Syndrome

Stoke Therapeutics

March 25, 2024

Agenda

- **Introduction**
  Eric Rojas, Head of Investor Relations
- **Introductory Remarks**
  Edward M. Kaye, M.D., Chief Executive Officer
- **Analysis of Phase 1/2a and Open-Label Extension (OLE) Studies of STK-001**
  Barry Ticho, M.D., Ph.D., Chief Medical Officer
  Kimberly Parkerson, M.D., Ph.D., Head of Neurology Clinical Development
- **Closing Remarks**
  Edward M. Kaye, M.D., Chief Executive Officer
- **Q&A (to include additional Stoke leadership)**
  Shamim Ruff, Chief Regulatory Officer

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Introductory Remarks

Edward M. Kaye, M.D.
Chief Executive Officer

Landmark New Data Support the Potential for STK-001 to be The First Medicine to Treat the Underlying Cause of Dravet Syndrome

Reductions in seizures **and** improvements in cognition and behavior that support the potential for disease modification

Phase 1/2a Study Data: 70mg doses demonstrated **substantial & sustained** reductions in convulsive seizure frequency of:

85% at 3 months (n=10)

&

74% at 6 months (n=9)

on top of the best available anti-seizure medicines

OLE Studies (30mg, 45mg): Clinically meaningful, durable **reductions in seizures** and **improvements in multiple measures of cognition & behavior** over 12 months

Recent FDA clearance for 3 doses of 70mg and continued dosing at 45mg

Next Steps: Meet with regulatory agencies to discuss registrational study of 70mg followed by 45mg

OLE: Open-Label Extension Study

Cause of Dravet Syndrome

of Dravet cases caused by a **HAPLOINSUFFICIENCY** of the *SCN1A* gene

Resulting in

$Na_V1.1$ protein expression

Our Goal

Deliver the first disease modifying-medicine for Dravet syndrome

Our Approach

Leverage the wild-type *SCN1A* allele to boost the production of full-length, fully-functional $Na_V1.1$ protein to treat the underlying cause of Dravet syndrome

Source: Nabbout et al., Orphanet Journal of Rare Diseases, 2013

STK-001 is on Track to be the First Disease-Modifying Medicine to Treat the Underlying Cause of Dravet Syndrome

Multiple medicines available for

Seizure management

Despite these treatments, seizures are not adequately controlled in 90% of patients with Dravet syndrome

Available medicines used to control seizures:

- Acetazolamide
- Benzodiazepines
- Brivaracetam
- Cannabidiol
- Carbamazepine
- Clobazam
- Ethosuximide
- Felbamate
- Fenfluramine
- Lamotrigine
- Levetiracetam
- Mesuximide
- Oxcarbazepine
- Phenytoin
- Rufinamide
- Stiripentol
- Topiramate
- Valproate products
- Zonisamide

No medicines currently available for

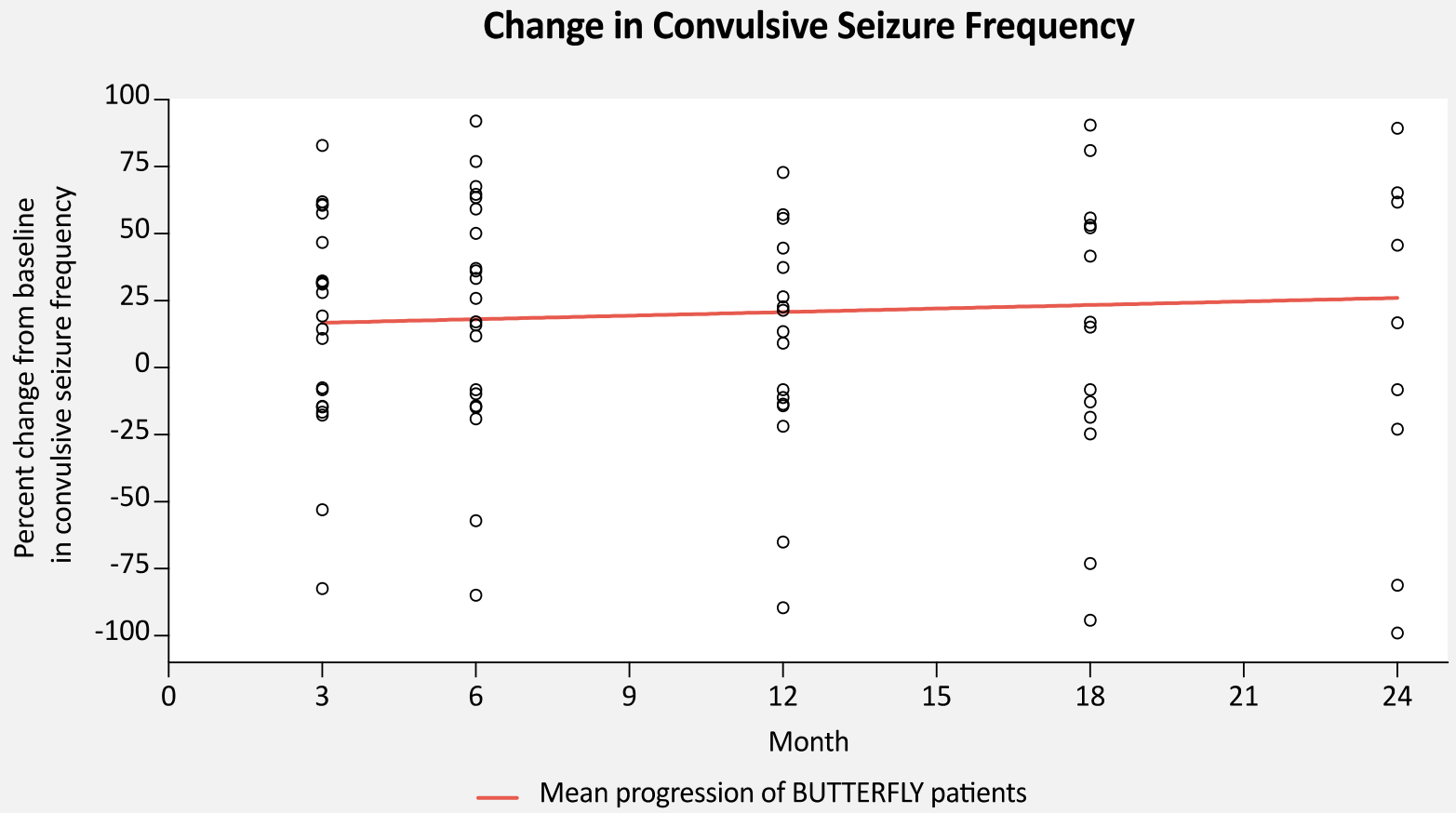
Dravet syndrome management

STK-001

The first potential disease-modifying approach to address the genetic cause of Dravet syndrome

Source: Lagae et al., Developmental Medicine & Child Neurology, 2017

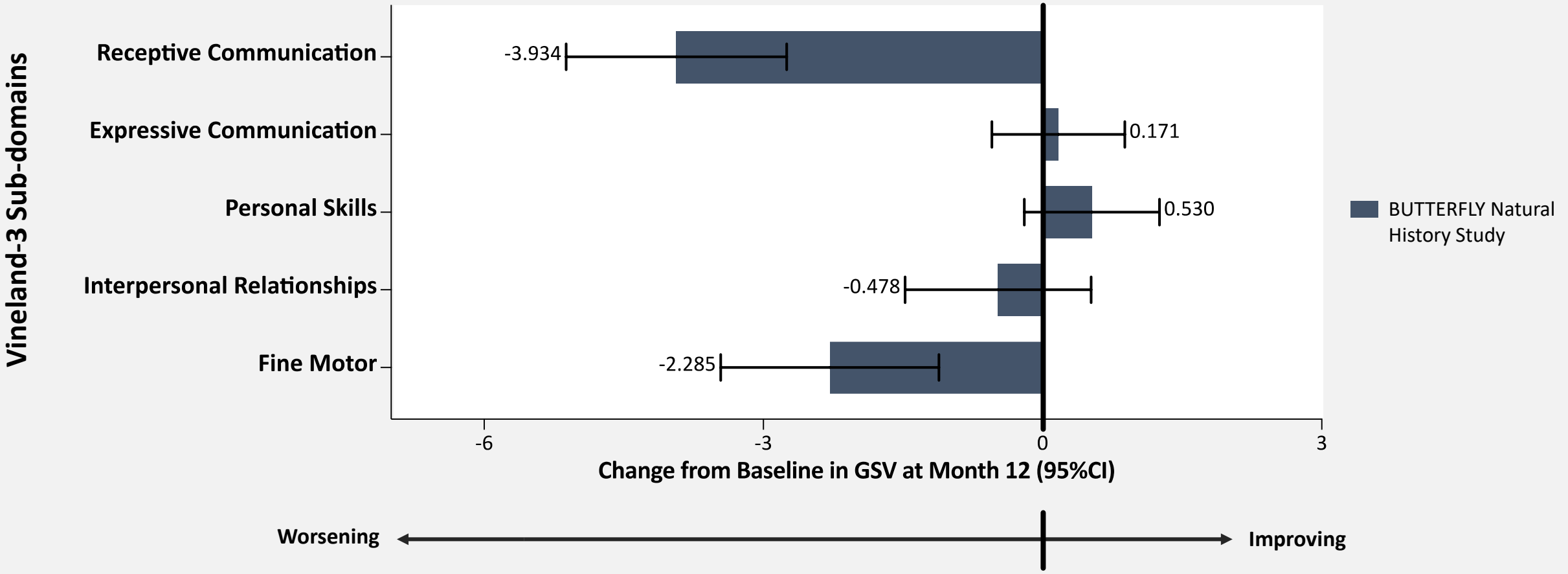
Natural History Data: Despite Standard Anti-Seizure Medicines, No Meaningful Improvement in Convulsive Seizure Frequency



Patients were treated with the best available anti-seizure medicines	
Median baseline convulsive seizure frequency per 28 days (95% CI), n=26	
10.0 (5.50, 15.5)	
Most common ongoing anti-seizure medicines, n (%)	
Clobazam	25 (69.4%)
Fenfluramine	16 (44.4%)
Stiripentol	14 (38.9%)
Valproic Acid	14 (38.9%)
Cannabidiol	12 (33.3%)
Levetiracetam	8 (22.2%)

Source: 24-Month Analysis of BUTTERFLY: A Prospective, Observational Study to Investigate Cognition and Other Non-seizure Comorbidities in Children and Adolescents with Dravet Syndrome (DS), AES 2023.

Natural History Data: Despite Best Available Anti-Seizure Medicines, No Improvement in Cognition and Behavior



Note: Analysis based on data from BUTTERFLY through Month 24 analyzed with Machine Learning.
Vineland-3: The Vineland Adaptive Behavior Scales, Third Edition. GSV = Growth Scale Value.

Analysis of Data from Studies of STK-001

Barry Ticho, M.D., Ph.D.
Chief Medical Officer

81 Patients Treated to Date with STK-001

- Ages 2-18
- Highly refractory to standard treatment
- 4 patients did not meet criteria for inclusion in seizure analysis.*

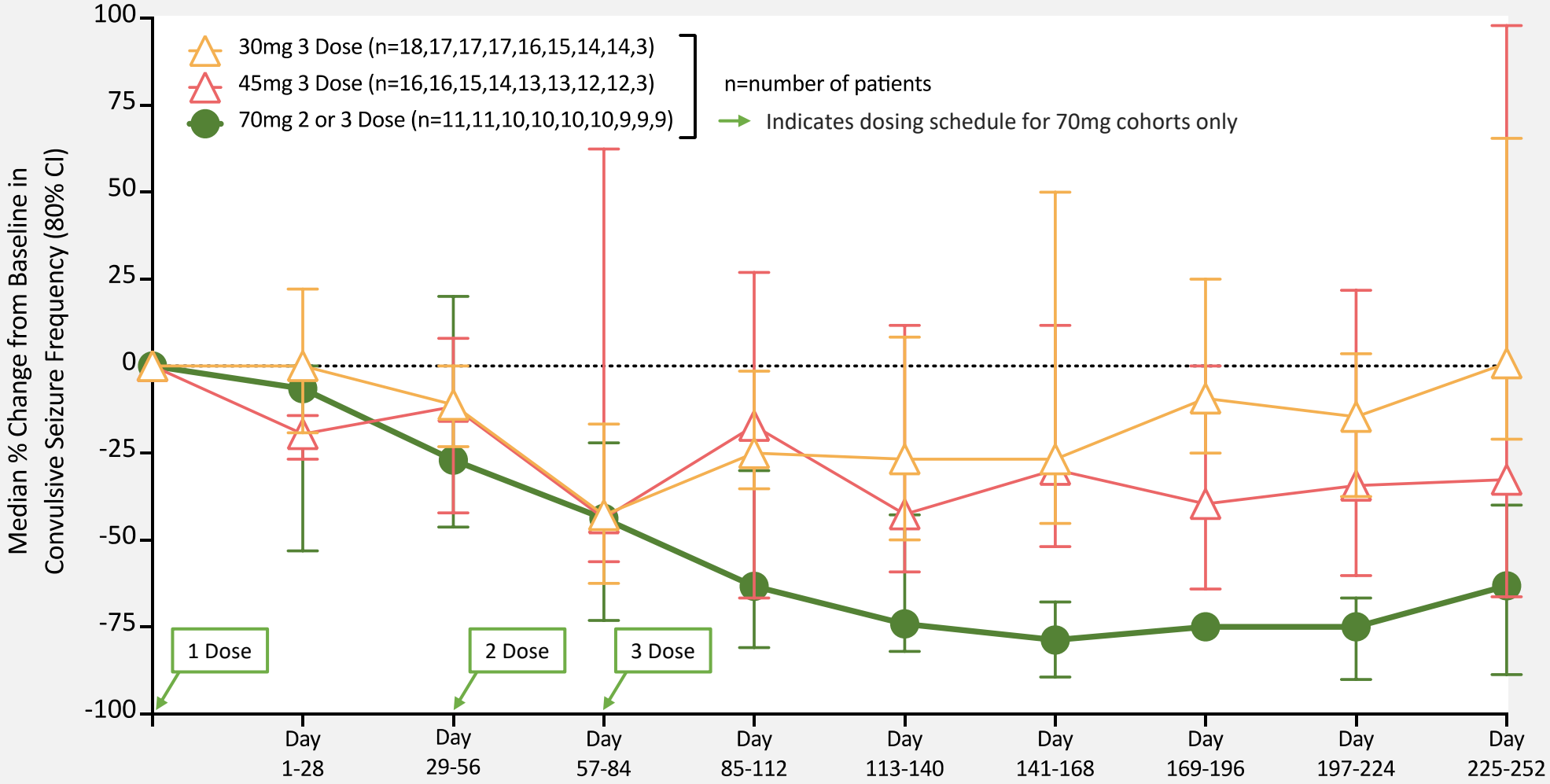
Patient Demographics at Phase 1/2a Study Initiation

	Total, n (%)
N	81
Age at Screening	
Mean (SD)	9.9 years (5.05)
Number of Concomitant Anti-Seizure Medications	
≥3	69 (85%)
≥4	44 (54%)
Concomitant Fenfluramine	
Yes	40 (49%)
Baseline Convulsive Seizure Frequency per 28 days (n = 77)	
Median (min, max)	17 (4.0, 2335)

Data cutoff dates: Phase 1/2a Studies 12DEC2023; OLE Studies 01NOV2023

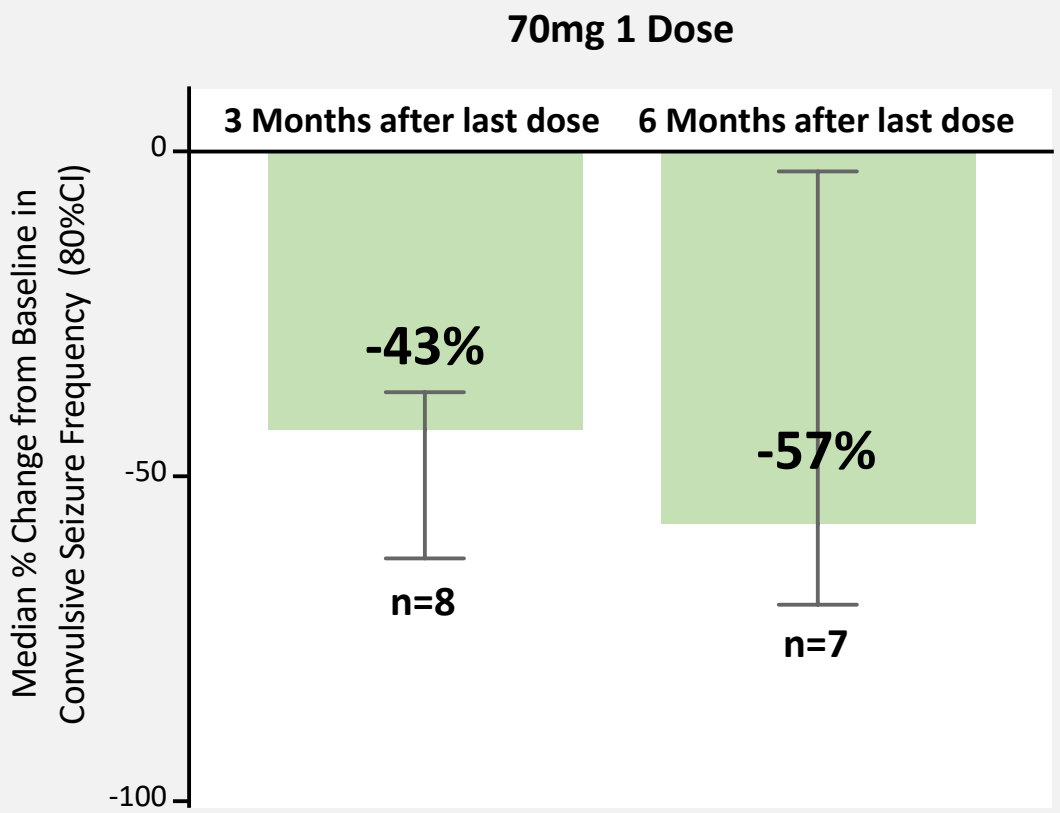
**Includes only patients that met the clinically evaluable study criteria for seizure analysis per statistical analysis plan which includes a minimum required number of seizures in the 28-day baseline period immediately prior to dosing (N=77).*

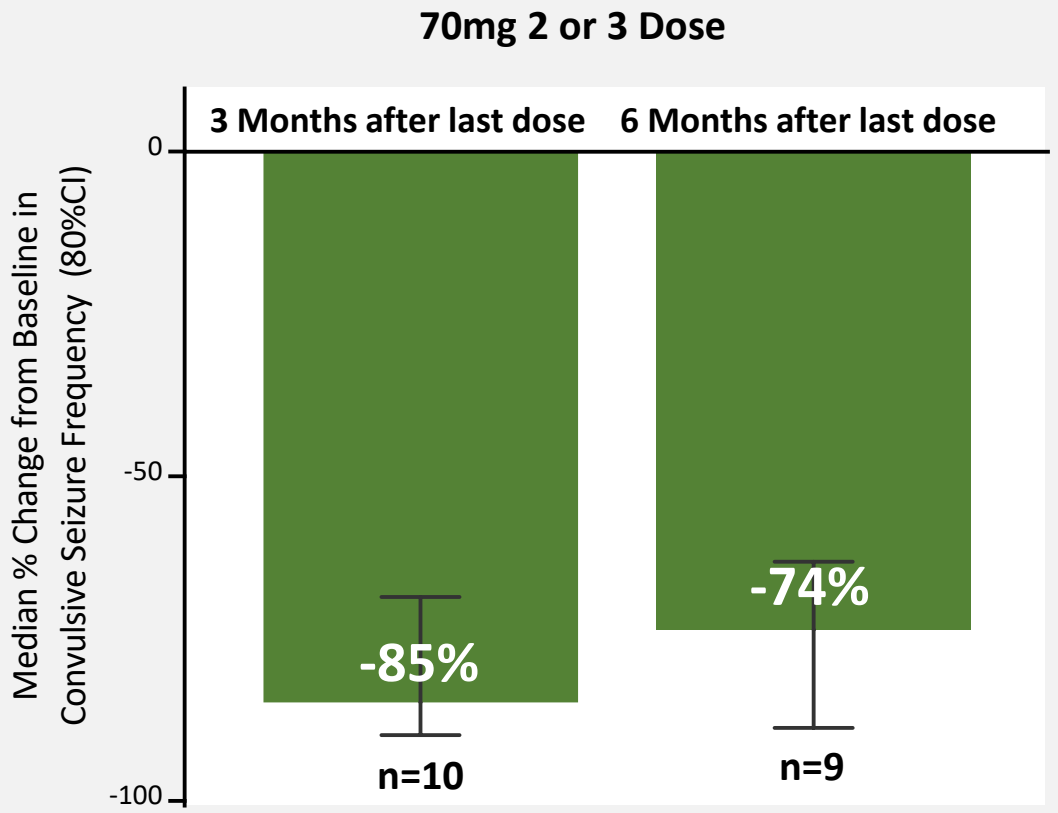
70mg Doses of STK-001 Demonstrated the Most Substantial Reductions in Seizure Frequency on Top of Standard of Care Medicines



Substantial Reductions in Seizure Frequency **at** 3 and Sustained **at** 6 Months after Last Dose with 1, 2 or 3 Doses of STK-001 (70mg)

Benefits observed across highly refractory patients already taking best available anti-seizure medicines

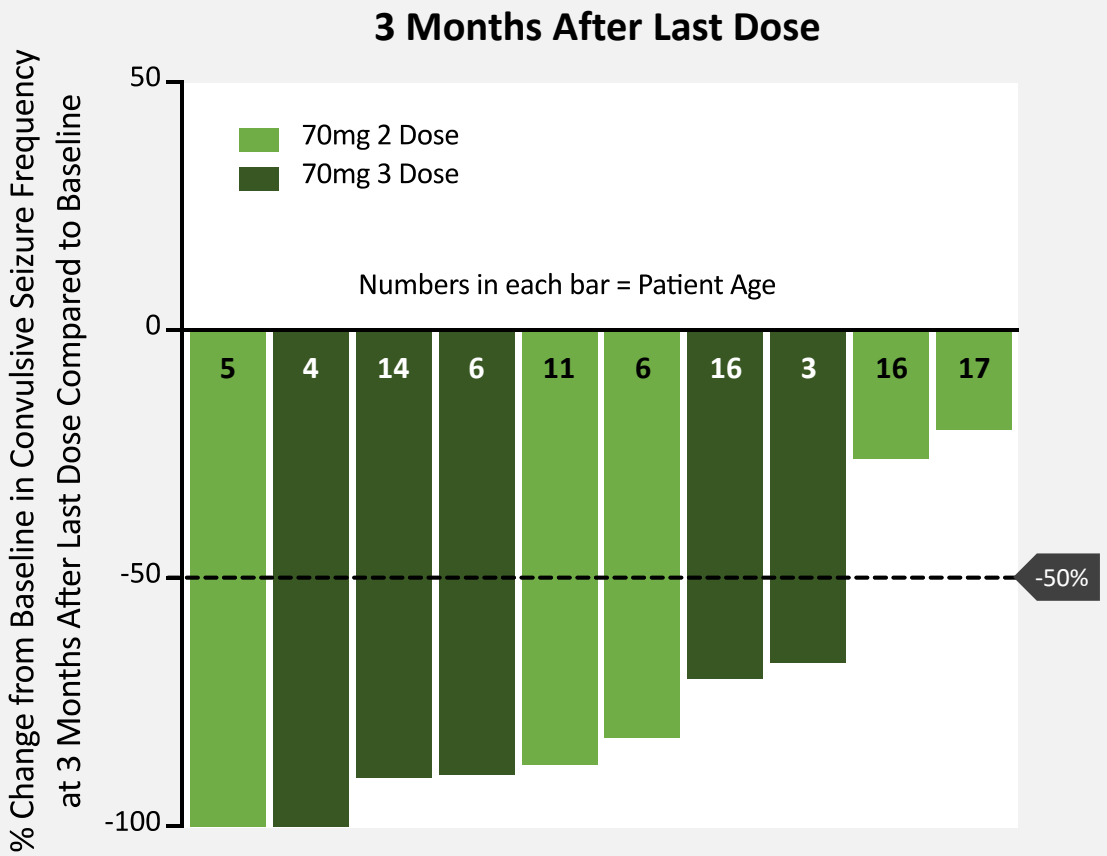


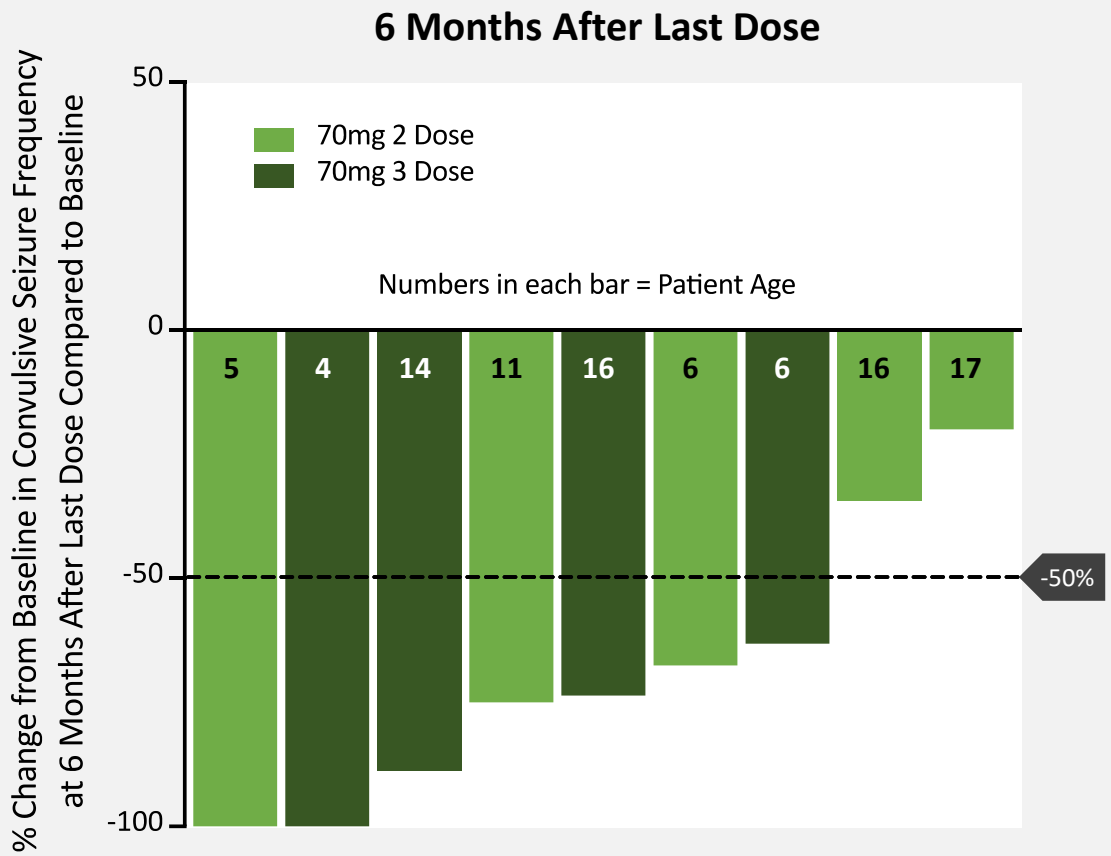


1 dose data is from the U.S. MONARCH study, 2 and 3 dose data is from UK ADMIRAL study

~80% of Patients Treated with 2 or 3 Doses of STK-001 (70mg) Experienced >50% Reduction in Seizures

A 50% responder rate is an important measure of efficacy





Note: 3 months after last dose refers to D113 to D140 (2 dose MAD) and D141 to D168 (3 dose MAD) and 6 months after last dose refers to D197 to D224 (2 dose MAD) and D225 to D252 (3 dose MAD)

2 and 3 dose data is from UK ADMIRAL study

Phase 1/2a Data Support a Potential 70mg Loading Dose Regimen in a Registrational Study

The most substantial reductions in seizures observed with 2 and 3 doses of 70mg

- 85% at 3 months and 74% at 6 months post last dose
- ~80% of patients experienced >50% reduction in convulsive seizure frequency

Patient Progression Through Studies

Ph 1/2a Studies (n=81)

Dosing	6 Month Follow Up
Single or multiple doses of STK-001 up to 70mg	ASM regimen continues
1, 2 or 3 doses of STK-001 administered on top of existing anti-seizure regimen	No STK-001 is administered
	74* patients eligible for OLE

Open Label Extension Studies (n=68)

- 92% (68/74) rolled over to OLE
- Continued treatment with STK-001 at 30mg or 45mg every 4 months
- STK-001 administered on top of anti-seizure regimen

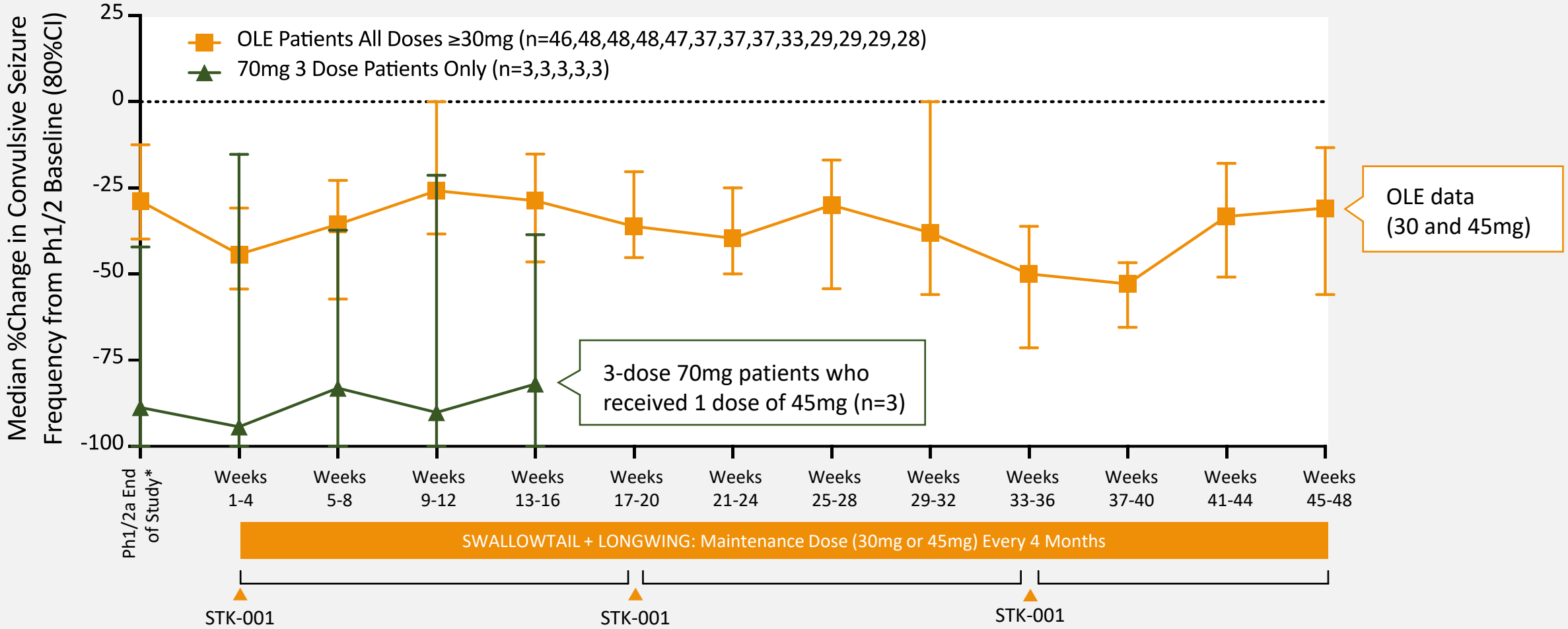
Status*

- 84% (57/68) remained on study
- 10 patients have received up to 10 doses of STK-001

Data cutoff dates: Phase 1/2a Studies 12DEC2023; OLE Studies 01NOV2023
Note: 6 additional patients had not yet completed Phase 1/2a at the time of the OLE data cut.

Durable Reductions in Seizure Frequency Observed with Continued Treatment with STK-001 in OLE Studies

OLE seizure analysis included patients that received ≥30mg in Phase 1/2a studies

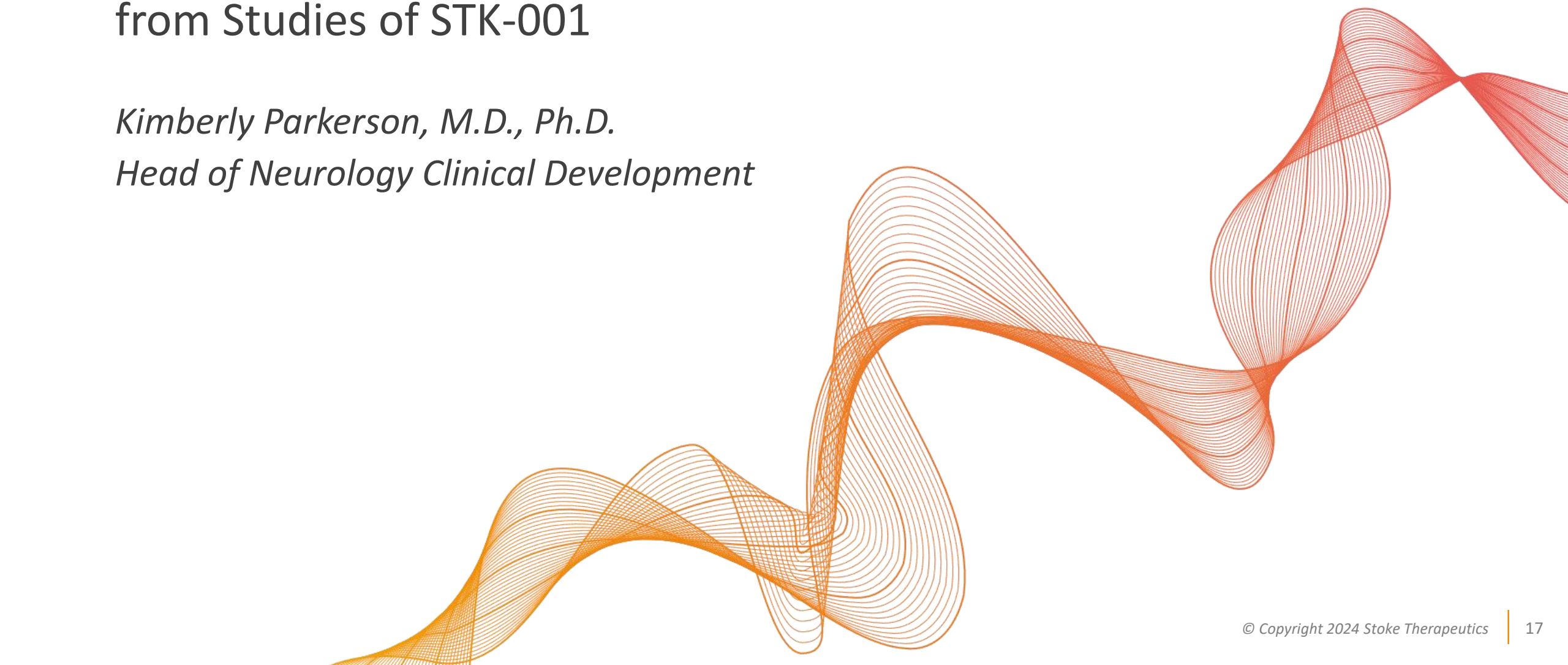


**End of Study = 24 Weeks After Last Dose in Phase 1/2 Study.*

Note: Of the 81 total patients in the Phase 1/2a studies, 15 patients from the 70mg cohort had not been evaluated in the OLE at the data cut and 18 patients received <30mg or did not roll over into the OLE, resulting in 48 patients in the OLE seizure analysis shown above.

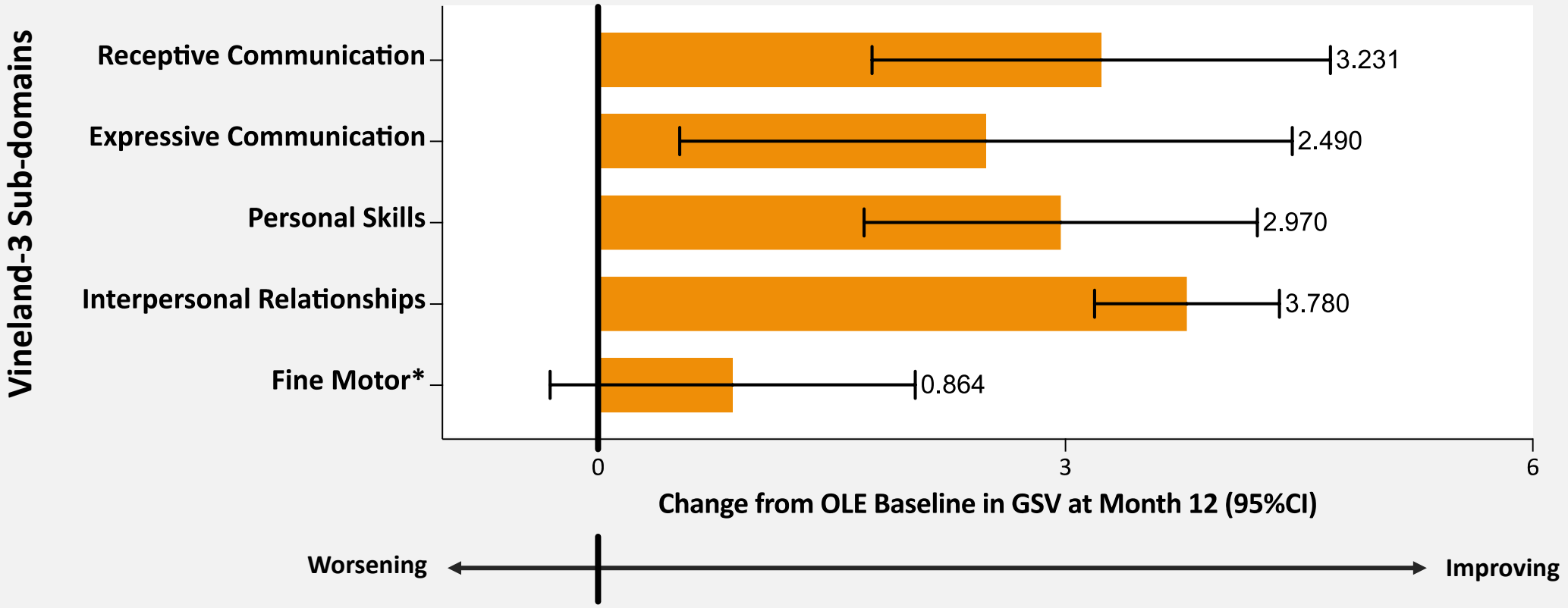
Analysis of Safety, Cognition and Behavior from Studies of STK-001

Kimberly Parkerson, M.D., Ph.D.
Head of Neurology Clinical Development



Clinically Meaningful Improvements in Cognition and Behavior Over 12 Months with Continued Treatment with STK-001 (30mg, 45mg)

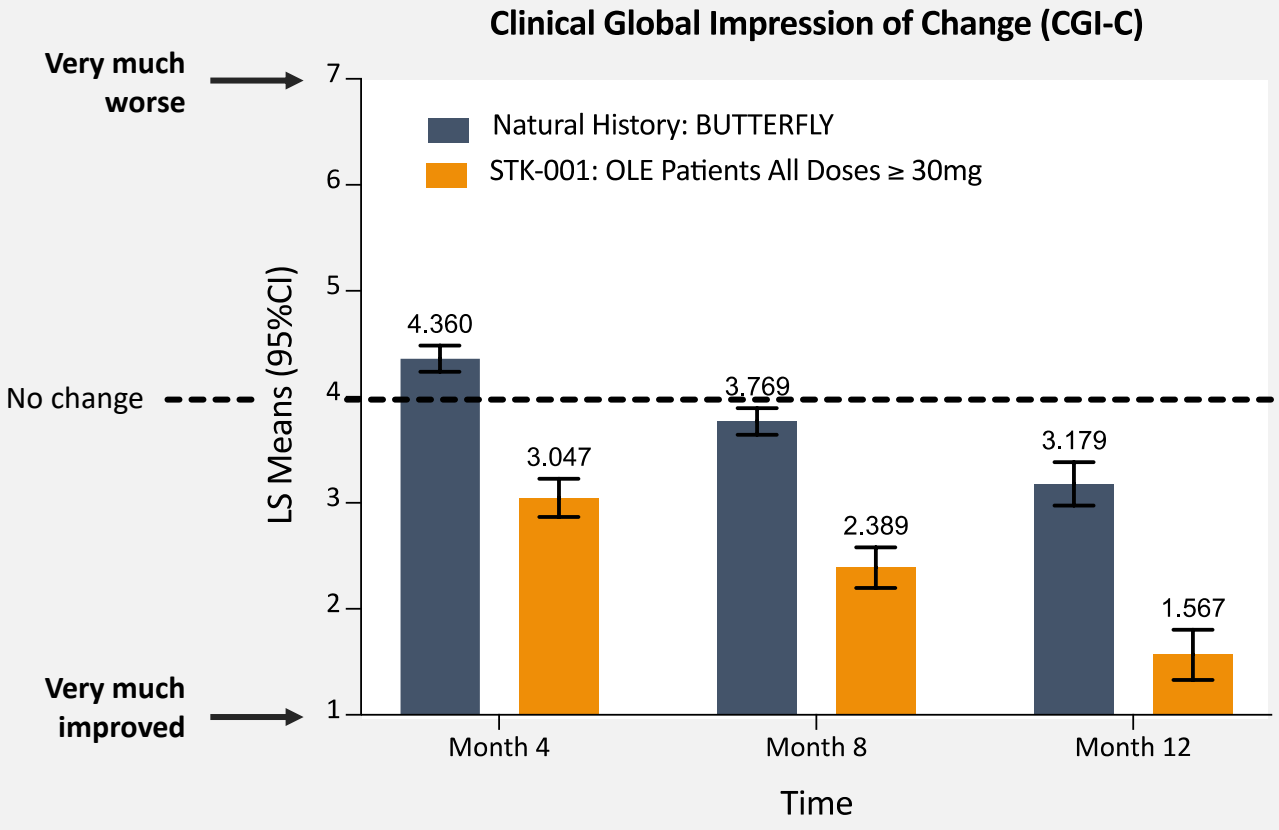
Improvements are in stark contrast to natural history study data

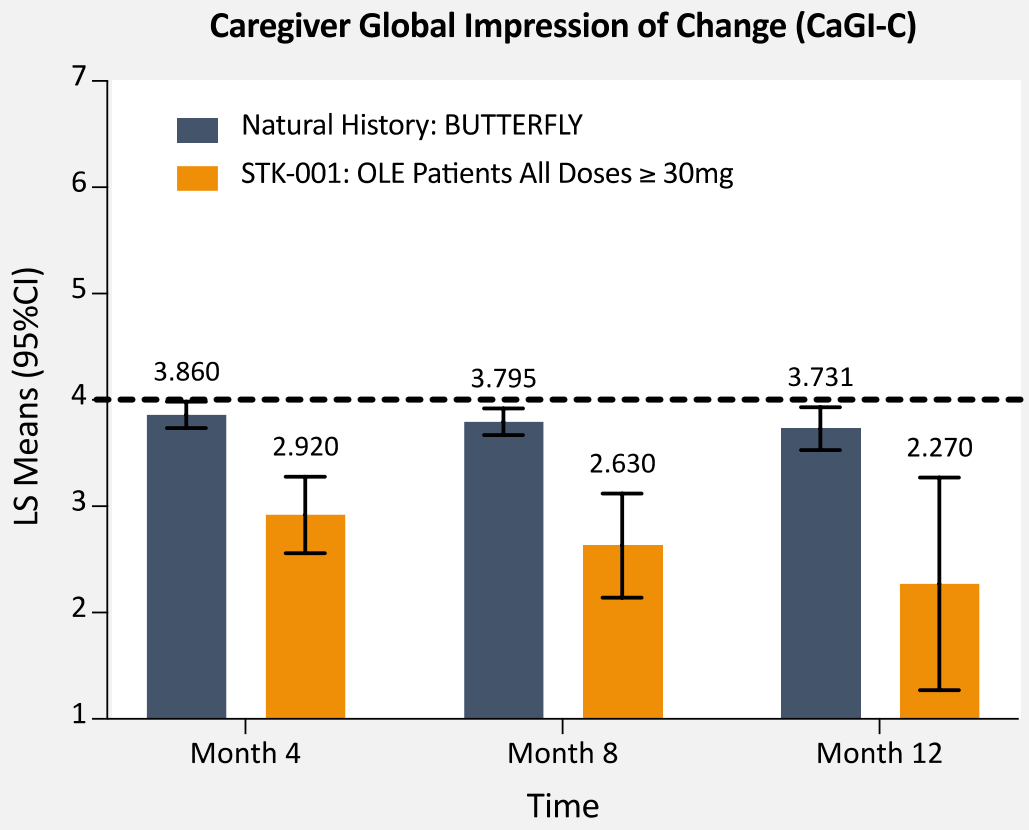


Note: Analysis based on a mixed-effects model for repeated measures (MMRM).
**Fine motor did not meet the threshold of clinically meaningful change.*
Vineland-3: The Vineland Adaptive Behavior Scales, Third Edition. GSV = Growth Scale Value.

Clinically Meaningful Improvements in Overall Condition Over 12 Months with Continued Treatment with STK-001 (30mg, 45mg)

Consistency across clinician and caregiver assessments of improvements observed in the OLEs





Note: Analysis based on a mixed-effects model for repeated measures (MMRM). Data from BUTTERFLY through Month 24 from start of study analyzed with machine learning. Due to differences between trials, cross-study comparisons may provide limited information on the efficacy or safety of a drug.

OLE Data Support a Potential 45mg Maintenance Dosing Regimen in a Registrational Study

Effects observed on cognition and behavior indicate potential for disease modification

Clinically meaningful improvements in cognition and behavior over 12 months

Improvements are in contrast to 2-year natural history study data that show widening gaps in cognition and behavior compared to neurotypical peers

Improvements in multiple measures of cognition and behavior:

- Receptive communication
- Expressive communication
- Personal skills
- Interpersonal relationships
- Fine motor skills

Consistency of improvements observed by caregivers and clinicians provide confidence in these findings

At the time of this analysis, 28 patients had reached one year of treatment in the OLE's

Single & Multiple Doses Up To 70mg Were Generally Well-Tolerated

No new safety findings related to study drug

Phase 1/2a Studies (n=81)	**30%** had a TEAE related to study drug. CSF protein elevations and procedural vomiting were the most common **22%** had a TESAE. These events were assessed as unrelated to study drug except for the previously reported case of one patient who experienced SUSARs
OLE Studies (n=68)	**74%** had CSF protein elevations*. No clinical manifestations have been observed in patients with elevated CSF protein levels. 1 patient discontinued treatment due to elevated CSF protein

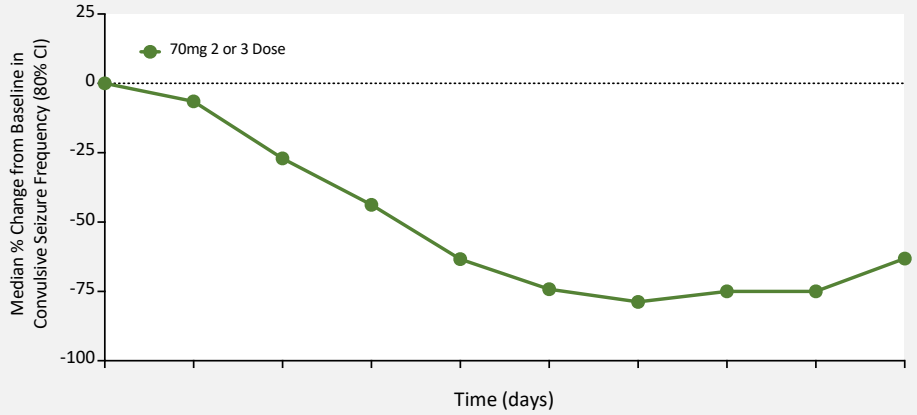
** >1 CSF protein value >50mg/dL*
TEAE: treatment-emergent adverse event.
TESAE: treatment-emergent serious adverse event
SUSARs: Suspected Unexpected Serious Adverse Reactions

Closing Remarks

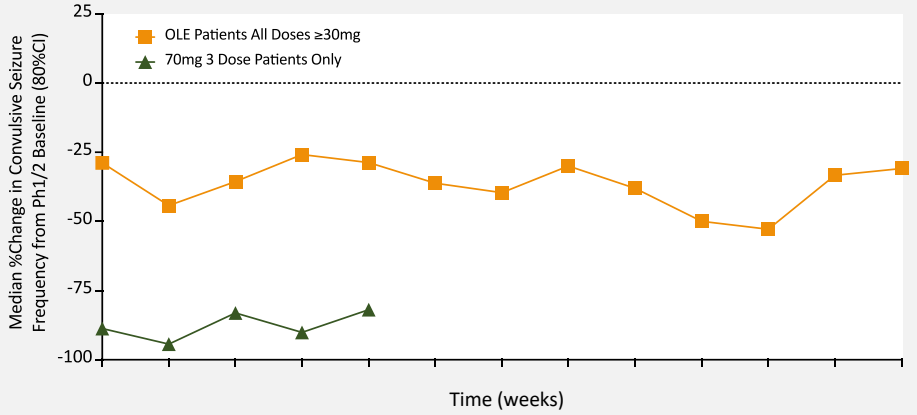
Edward M. Kaye, M.D.
Chief Executive Officer

Landmark New Data Support the Potential for STK-001 to be the First Medicine to Treat the Underlying Cause of Dravet Syndrome

Phase 1/2a (2 and 3 doses of 70mg):
Substantial & sustained reductions in seizure frequency

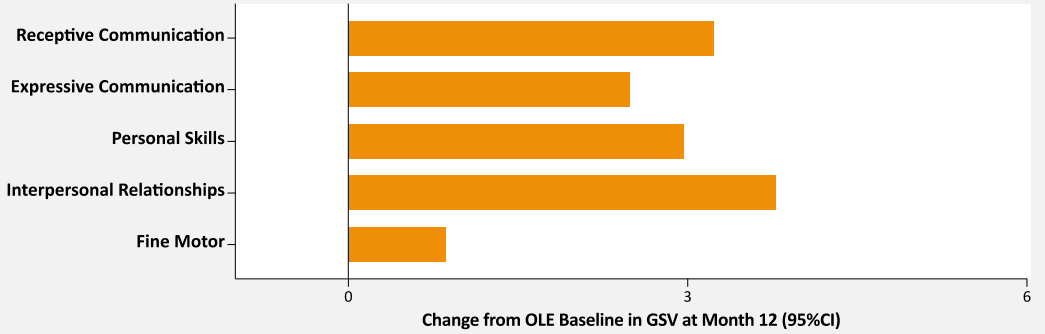


Open-Label Extensions (30mg, 45mg):
Durable reductions in seizures with dosing every 4 months

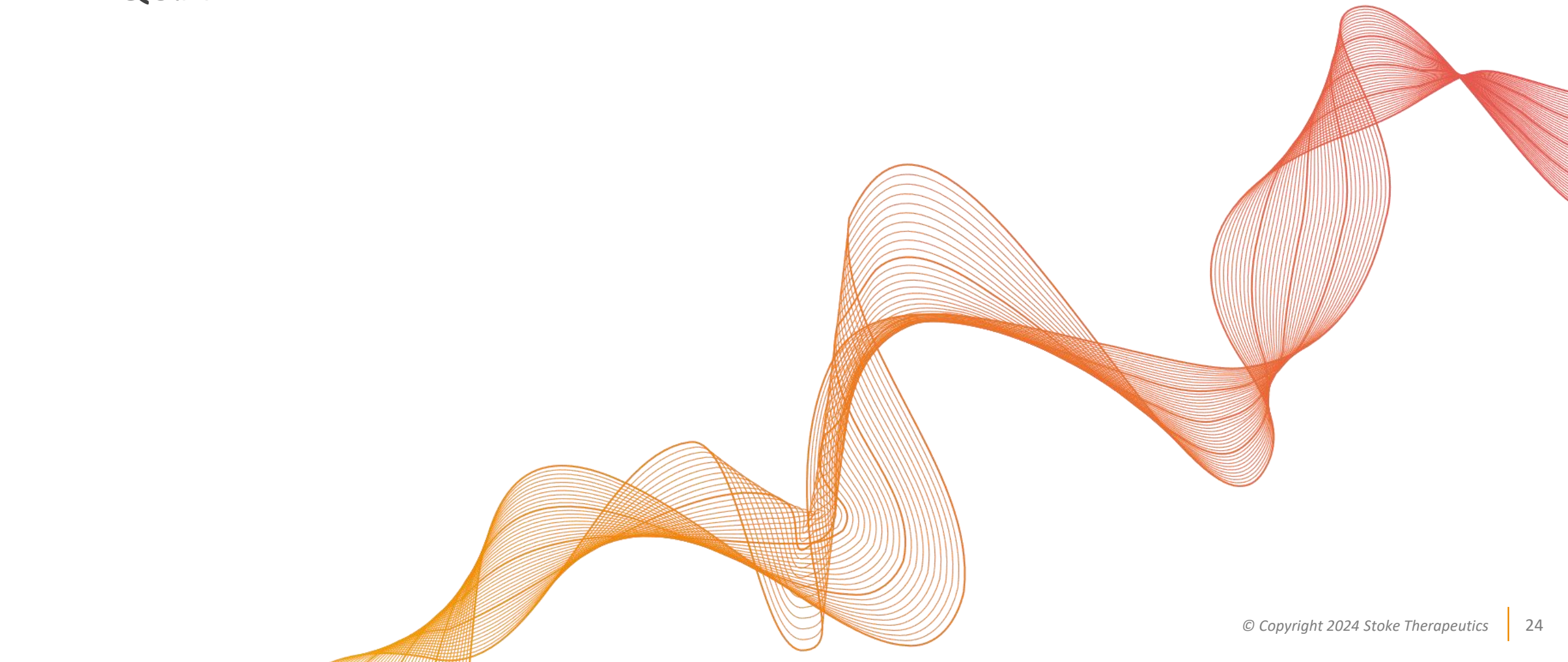


Company to meet with regulatory agencies to discuss registrational study design: 70mg loading doses followed by 45mg maintenance doses

OLE (30mg, 45mg): Clinically meaningful improvements
in multiple measures of **cognition & behavior** over 12 months



Q&A



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