

2016 ISCTM – Washington DC

Lessons Learned:

*Development of a GABA Receptor Agonist
for Autism and for Fragile X*

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Disclosures

- Financial conflicts of interest: none
- Other: formerly at Seaside Therapeutics

Arbaclofen (STX209):

Rationale for development in ASD & FXS

- Clinical anecdote with racemic baclofen (n=1)
- Neurobiological theories of ASD
 - mGluR theory of FXS: decrease glutamate release
 - E:I imbalance: augment cortical inhibition; decrease glutamate release
 - Oscillopathy: modulate MEG/EEG coherence
- Preclinical effects: FMR1 KO mouse
 - Rescues audiogenic seizure susceptibility
 - Normalizes synaptic protein synthesis, AMPAR turnover
 - Corrects synaptic morphology
- Preclinical effects in BTBR and C58/J mice (Silverman et al., 2015)
- Known pediatric safety & tolerability of racemic baclofen

STX209: Clinical Program Overview

Population	Phase	Study	N	age	Design
NHV	1	22004	8	adult	Single-dose XO
	1	209NV103	8	adult	Single-dose XO
Fragile X	2	22001	63	6-40 y	RCT, XO, 4 wks
	3	209FX301	125	12-50 y	RCT, parallel, 8 wks
	3	209FX302	172	5-11 y	RCT, parallel (4 arms), 8 wks
	OLE	22002	–	–	–
	OLE	209FX303	–	–	–
Autism	2	22003	32	6-17 y	Open-label, 8 wks
	2	209AS208	150	5-21 y	RCT, parallel, 12 wks
	OLE	22007	–	–	–
	OLE	209AS209	–	–	–

Regulatory precedents in ASD: Risperidone & aripiprazole

- Indication
 - “Treatment of irritability associated with autistic disorder”
- Pivotal trials
 - Short term efficacy: 8-week RCT
 - Long-term efficacy (risperidone): Randomized withdrawal study
 - Age 5-16 years; 6-17 yrs (large majority <12, 13 y.o.)
- Key endpoints
 - ABC-Irritability scale: Tantrums, aggression, self-injury
 - CGI-Improvement/Change (short-term studies only)

RUPP 2022 trial of risperidone

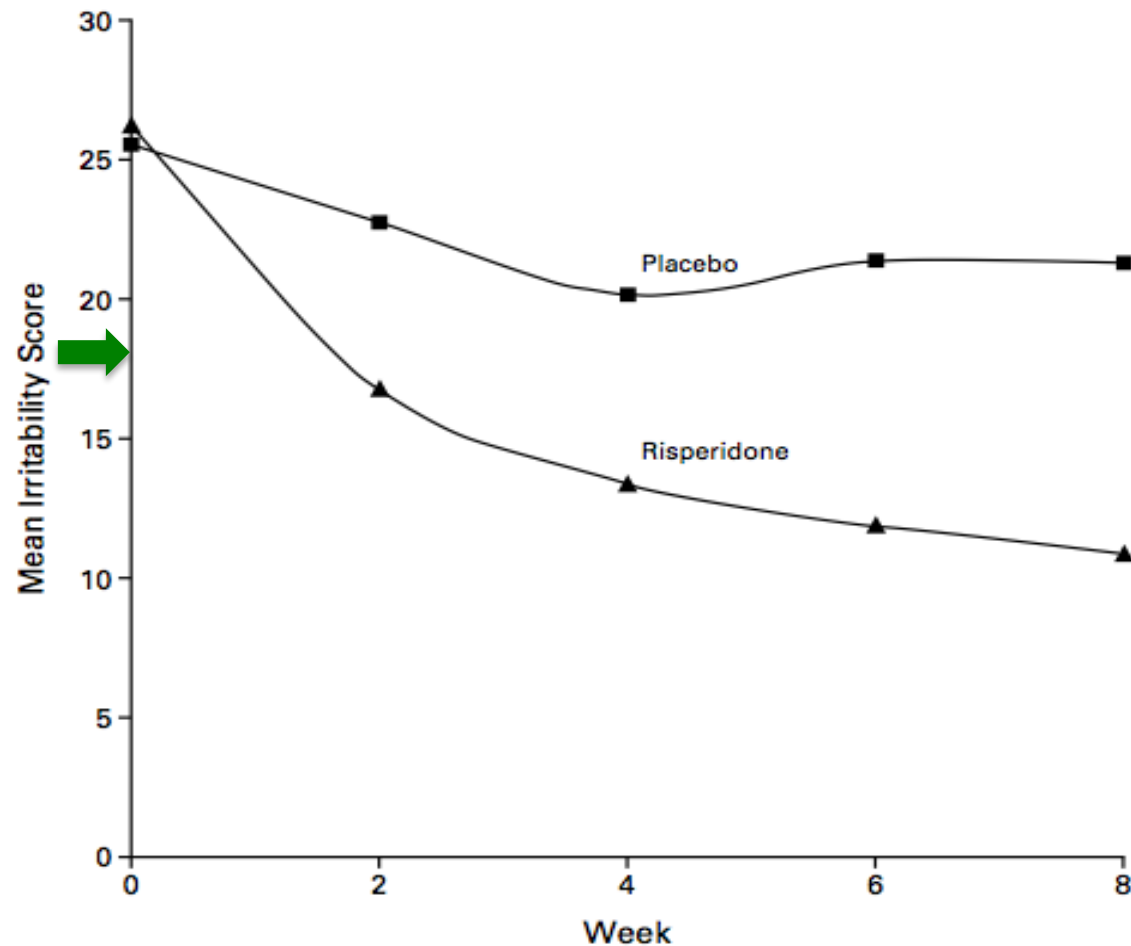


Figure 1. Mean Scores for Irritability in the Risperidone and Placebo Groups during the Eight-Week Trial. Data are for all 101 children (49 assigned to the risperidone group and 52 assigned to the placebo group). Higher scores indicate greater irritability.

Aberrant Behavior Checklist (Aman et al., 1985)

Irritability (& agitation & crying)	Lethargy (& Social Withdrawal)	Stereotypic Behavior	Hyperactivity (& noncompliance)	Inappropriate Speech
Aggressive to others	Listless sluggish inactive	Recurring body movements	Excessively active	Talks excessively
Screams inappropriately	Seeks isolation	Stereotyped repetitive behavior	Boisterous, noisy/rough	Repetitive speech
Temper tantrums/outbursts	Preoccupied stares into space	Odd, bizarre in behavior	Impulsive	Talks to self loudly
Irritable and whiny	Prefers solitary activities	Move/rolls head repetitively	Restless	Repeats word / phrase
Yells at inappropriate times	Fixed expression, lacks response	Repetitive hand body head	Disobedient	
Depressed mood	Just sits and watches others	Waves/shakes extremities repeatedly	Disturbs others	
Demands must be met	Resists physical contact	Rocks back and forth	Uncooperative	
Cries over minor annoyances	Isolates self from others		No pay attention instructions	
Mood changes quickly	Sits/stands in one position		Disrupts group activities	
Cries and screams inappro	Unresponsive to activities		Doesn't stay seated.	
Stamps,, bangs, slams	Difficult to reach contact		Not sit still for time	
Outbursts/ doesn't get way	Prefers to be alone		Distractible	
Deliberately hurts self	Doesn't communicate		Constantly runs or jumps	
Physical violence to self	Inactive		No attention when spoken to	
Injures self on purpose	Negative to affection		Excessively active	
	Shows few social reactions		Ignores directions	

ABC scale: Validation

- Original validation in adult inpatients with MR/ID
 - Designed to be a measure of change
- ASD validation
 - Kaat, Lecavalier, Aman, 2014
 - Original factor structure remains valid in ASD
- Fragile X syndrome validation
 - Sansone, et al., 2012; n=630; 6 centers
 - Newly identified factor score: ABC-FXS Social Avoidance
- Seaside study 22001 results (ITT)
 - Original factor scale: STX209 -2.0 ± 6.86 PBO -1.3 ± 6.79 $p > 0.50$
 - New factor scale: STX209 -1.2 ± 2.37 PBO -0.1 ± 2.53 $p < 0.01$

P2 study design: 209AS208

- Endpoint
 - Symptom domain Many (irritability, social, hyperactivity, stereotypy, other)
 - Assessment tool Many – Primary endpoint: ABC-Lethargy/Soc Withdrawal
- Effect size; sample size 4 points (SD 7.5); n=150; 80% power
- Subject selection
 - Age 5 – 21 years
 - Symptom severity ABC-LSW ≥ 8
 - Co-morbidity Any (no known genetic disorder)
 - Concomitant medications ≤ 2 psychoactives (no antipsychotics, anxiolytics, GABAergics)
- Posology
 - Dose Flexible, 5 mg BID – 15 mg TID
 - Dosing schedule
- Duration of treatment
 - Duration x Dose x Age 12 weeks x dose described x “child”

Outcome measures: 209AS208

Primary endpoint	Aberrant Behavior Checklist – Lethargy/Social Withdrawal (ABC-LSW)
Key secondary	Clinical Global Impression – Improvement (CGI-I)
Secondary	Vineland Adaptive Behavior Scale – Socialization (VABS-Soc)
Secondary	Clinical Global Impression – Severity (CGI-S)
Secondary	Visual Analog Scale of Disruptive and Anxiety-driven behaviors
Secondary	ADHD-IV Rating Scale
Exploratory	Parenting Stress Index
Exploratory	VABS – Maladaptive Behavior Index
Exploratory	VABS – Communication (VABS-Comm)
Exploratory	ABC – Irritability (and other subscales)
Exploratory	Children’s Sleep Habits Questionnaire
Exploratory	Short Sensory Profile (SSP)

Vineland Adaptive Behavior Scales – II (VABS)

- Gold standard for functional evaluation
 - Cornerstone of psychoeducational evaluation; co-equal of IQ
 - Endorsed by Autism Speaks workgroup on outcome measures
 - Key endpoint in Early Start Denver behavioral/educational trial
- Multiple domains
 - Communication
 - Socialization
 - Interpersonal
 - Play & Leisure
 - Coping Skills
 - Daily Living Skills
 - Motor
 - Maladaptive Behavior

VABS-Socialization-Interpersonal items

1	Looks at face of parent or caregiver.
2	Watches (that is, follows with eyes) someone moving by crib or bed for 5 seconds or more.
3	Shows two or more emotions (for example, laughs, cries, screams, etc.).
4	Smiles or makes sounds when approached by a familiar person.
5	Makes or tries to make social contact (for example, smiles, makes noises, etc.).
6	Reaches for familiar person when person holds out arms to him or her.
7	Shows preference for certain people and objects (for example, smiles, reaches for or moves toward person or object, etc.).
8	Shows affection to familiar persons (for example, touches, hugs, kisses, cuddles, etc.).
9	Imitates or tries to imitate parent's or caregiver's facial expressions (for example, smiles, frowns, etc.).
10	Moves about looking for parent or caregiver or other familiar person nearby.
11	Shows interest in children the same age, other than brothers or sisters (for example, watches them, smiles at them, etc.).
12	Imitates simple movements (for example, claps hands, waves good-bye, etc.).
13	Uses actions to show happiness or concern for others (for example, hugs, pats arm, holds hands, etc.).
14	Shows desire to please others (for example, shares a snack or toy, tries to help even if not capable, etc.).
15	Demonstrates friendship-seeking behavior with others the same age (for example, says, "Do you want to play?" or takes another child by the hand, etc.).
16	Imitates relatively complex actions as they are being performed by another person (for example, shaving, putting on makeup, hammering nails, etc.).
17	Answers when familiar adults make small talk (for example, if asked, "How are you?" says, "I'm fine"; if told, "You look nice," says, "Thank you"; etc.).
18	Repeats phrases heard spoken before by an adult (for example, "Honey, I'm home"; "No dessert until you clean your plate"; etc.).
19	Uses words to express own emotions (for example, "I'm happy"; "I'm scared"; etc.).
20	Has best friend or shows preference for certain friends (of either sex) over others.

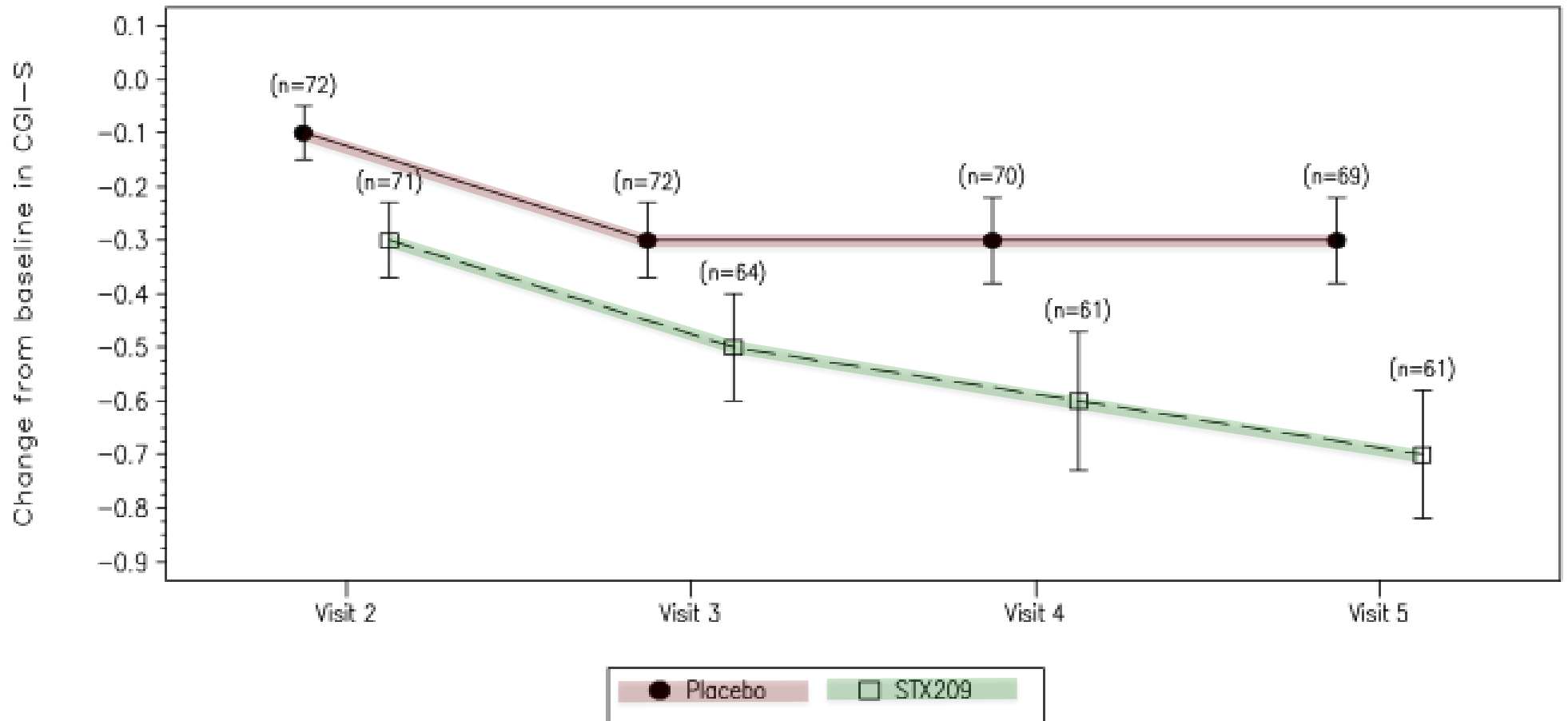
21	Imitates relatively complex actions several hours after watching someone else perform them (for example, shaving, putting on makeup, hammering nails, etc.).
22	Uses words to express happiness or concern for others (for example, says, "Yeah! You won"; "Are you all right?"; etc.).
23	Acts when another person needs a helping hand (for example, holds door open, picks up dropped items, etc.).
24	Recognizes the likes and dislikes of others (for example, says, "Chow likes soccer"; "Susie doesn't eat pizza"; etc.).
25	Shows same level of emotion as others around him or her (for example, does not downplay or overdramatize a situation, etc.).
26	Keeps comfortable distance between self and others in social situations (for example, does not get too close to another person when talking, etc.).
27	Talks with others about shared interests (for example, sports, TV shows, summer plans, etc.).
28	Starts small talk when meets people he or she knows (for example, says, "How are you?"; "What's up?"; etc.).
29	Meets with friends regularly.
30	Chooses not to say embarrassing or mean things or ask rude questions in public.
31	Places reasonable demands on friendship (for example, does not expect to be a person's only friend or to have the friend always available, etc.).
32	Understands that others do not know his or her thoughts unless he or she says them.
33	Is careful when talking about personal things.
34	Cooperates with others to plan or be part of an activity (for example, a birthday party, sports event, etc.).
35	Demonstrates understanding of hints or indirect cues in conversation (for example, knows that yawns may mean, "I'm bored," or a quick change of subject may mean, "I don't want to talk about that"; etc.).
36	Starts conversations by talking about things that interest others (for example, says, "Tyrone tells me you like computers"; etc.).
37	Goes on group dates.
38	Goes on single dates.

Topline: 209AS208

ITT population (n=148)				
		Change from baseline, except CGI-I (mean ± SEM)		
		STX209	Placebo	P-value
ABC-LSW	(lower score better)	-5.3 ± 0.87	-6.1 ± 0.83	0.477
CGI-I		3.1 ± 0.12	3.3 ± 0.12	0.305
CGI-S		-0.7 ± 0.10	-0.3 ± 0.10	0.009
ABC-Irritability		-3.6 ± 0.91	-3.3 ± 0.86	0.805
Sensory Profile	(higher score better)	10.9 ± 2.12	7.5 ± 2.01	0.250
VABS-Communication		2.6 ± 0.91	1.4 ± 0.88	0.365
VABS-Socialization		4.4 ± 1.19	2.0 ± 1.15	0.152

CGI-S by visit

209AS208



VABS-Social:

Post-hoc exclusion of “rater change” subjects

- Inter-interviewer reliability = 0.64
 - Protocol required same raters throughout study
 - Sites violated protocol for about 1/4 of completers
- Post-hoc ANCOVA
 - Same model as planned analysis (covariates: age, baseline)
 - Excluding subjects with change in raters (i.e., protocol violation)

VABS-Social	STX209 (n=44)	Placebo (n=53)	Difference	<i>p</i>
LSMean ± SEM	7.1 ± 1.38	1.8 ± 1.26	5.3 ± 1.87	0.006
(95% CI)	(4.36, 9.85)	(-0.68, 4.32)	(1.56, 9.01)	

IQ Subgroups: Pre-planned analyses

209AS208

	IQ ≥ 70			IQ < 70		
		Change from baseline, except CGI-I (mean ± SD)			Change from baseline, except CGI-I (mean ± SD)	
	Baseline STX209; PBO	STX209 n=35	PBO n=40	Baseline STX209; PBO	STX209 n=36	PBO n=33
ABC-LSW	19.2; 19.1	-7.6 ± 8.61	-6.6 ± 7.36	21.0; 19.8	-3.5 ± 7.84	-4.7 ± 5.72
CGI-I	–	2.9 ± 1.10	3.2 ± 1.02	–	3.5 ± 0.86	3.4 ± 0.82
CGI-S	4.7; 4.5	-0.8 ± 1.05	-0.2 ± 0.61	5.1; 5.2	-0.6 ± 0.80	-0.4 ± 0.77
ABC-Irritability	15.9; 14.1	-5.5 ± 7.34	-2.8 ± 6.73	17.6; 17.6	-2.2 ± 9.62	-2.0 ± 5.73
VABS-Comm	73.4; 76.3	4.0 ± 11.23	0.8 ± 6.82	55.3; 58.2	0.0 ± 6.00	1.9 ± 4.42
VABS-Social	66.0; 68.3	5.9 ± 14.19	2.6 ± 9.19	51.6; 55.5	1.5 ± 7.91	1.3 ± 5.16
Sensory	117.8; 126.5	16.3 ± 19.04	6.3 ± 20.21	116.1; 123.0	8.0 ± 13.93	4.4 ± 11.09
VABS-Social (no rater chg)	65.0; 67.4	9.1 ± 12.09 (n=27)	2.9 ± 9.56 (n=28)	50.9; 55.1	4.2 ± 6.98 (n=15)	0.5 ± 4.22 (n=24)

ADOS module subgroups

209AS208 post-hoc

	Module 1		Module 2		Module 3		Module 4	
	Change from baseline (mean ± SD) – except CGI-I							
	STX209	PBO	STX209	PBO	STX209	PBO	STX209	PBO
CGI-I	3.4 ± 1.04 (n=20)	3.5 ± 0.67 (n=22)	3.5 ± 1.13 (n=11)	3.5 ± 1.18 (n=10)	2.9 ± 0.91 (n=19)	3.2 ± 1.15 (n=22)	2.7 ± 0.95 (n=10)	3.0 ± 0.78 (n=14)
CGI-S	-0.6 ± 0.88 (n=20)	-0.3 ± 0.84 (n=22)	-0.7 ± 1.01 (n=11)	-0.4 ± 0.70 (n=10)	-0.6 ± 0.83 (n=19)	-0.3 ± 0.55 (n=22)	-0.9 ± 1.29 (n=10)	-0.2 ± 0.70 (n=14)
ABC-Irritability	-2.7 ± 10.37 (n=20)	-1.8 ± 6.65 (n=22)	-5.4 ± 11.72 (n=11)	-4.5 ± 5.04 (n=10)	-5.2 ± 6.19 (n=19)	-1.6 ± 5.44 (n=21)	-5.1 ± 5.45 (n=10)	-3.9 ± 7.54 (n=14)
Vineland-Social	0.5 ± 7.21 (n=20)	1.5 ± 5.47 (n=22)	1.5 ± 5.78 (n=10)	-0.6 ± 7.62 (n=10)	6.6 ± 12.69 (n=19)	2.9 ± 9.88 (n=22)	11.0 ± 13.44 (n=10)	3.9 ± 6.70 (n=14)
VABS-Soc (no rater chg)	2.5 ± 5.41 (n=13)	0.8 ± 3.57 (n=18)	5.2 ± 3.11 (n=5)	-0.2 ± 7.98 (n=9)	7.6 ± 12.99 (n=17)	2.8 ± 10.66 (n=15)	14.5 ± 12.56 (n=8)	4.2 ± 7.52 (n=10)

Age subgroups

209AS208

	Children (5-11 years)			Adolescents (12-21 years)		
		Change from baseline (mean ± SD)			Change from baseline (mean ± SD)	
	Baseline STX209; PBO	STX209 n=37	PBO n=38	Baseline STX209; PBO	STX209 n=37	PBO n=36
ABC-LSW	19.9; 17.8	-6.7 ± 8.00	-4.3 ± 6.44	20.3; 20.9	-4.9 ± 8.55	-7.4 ± 6.59
CGI-I	–	3.0 ± 1.09	3.4 ± 0.95	–	3.2 ± 0.97	3.3 ± 0.95
CGI-S	5.1; 5.0	-0.9 ± 0.99	-0.3 ± 0.81	4.8; 4.6	-0.5 ± 0.88	-0.3 ± 0.56
ABC-Irritabil	22.6; 18.4	-7.1 ± 10.29	-2.5 ± 6.62	11.9; 12.6	-2.2 ± 6.23	-2.6 ± 5.93
VABS-Social	58.2, 61.1	2.5 ± 9.92	2.0 ± 6.97	58.8, 63.1	5.1 ± 13.23	2.0 ± 8.10
Sensory	115.3; 121.0	10.9 ± 14.37	1.6 ± 14.13	117.7; 129.6	13.5 ± 19.15	9.8 ± 18.58

STX209: Efficacy results in FXS studies

Study 301	ABC-FX Soc Avd	Vineland- Social	CGI-I	CGI-S	ABC-FX Irritability	ABC-FX Hyperactiv
Baseline	~7.7	~54.3	–	~4.6	~16.3	~12.1
Arbaclofen (flexible)	-2.3 ± 0.33	0.1 ± 1.17	3.2 ± 0.12	-0.5 ± 0.08	-4.2 ± 0.89	-3.6 ± 0.58
Placebo	-2.4 ± 0.32	2.5 ± 1.17	3.1 ± 0.12	-0.3 ± 0.08	-5.3 ± 0.88	-3.4 ± 0.57
p-value	0.974	0.151	0.587	0.063	0.421	0.811

Study 302	ABC-FX Soc Avd	Vineland- Social	CGI-I	CGI-S	ABC-FX Irritability	ABC-FX Hyperactiv
Baseline	~6.8	~65.1	–	~4.9	~29.0	~20.6
Arbaclofen 10mg TID	-3.7 ± 0.38	7.5 ± 2.73	3.0 ± 0.16	-0.5 ± 0.11	-9.7 ± 1.40	-6.0 ± 0.81
Placebo	-2.8 ± 0.36	5.1 ± 2.46	3.3 ± 0.15	-0.4 ± 0.10	-5.5 ± 1.31	-4.0 ± 0.75
p-value	0.085	0.510	0.119	0.909	0.031	0.081

Treatment values: LS Mean ± SEM

Study 209AS208: STX209 for ASD

- Endpoint
 - Symptom domain ~~Many (irritability, social, hyperactivity, stereotypy, other)~~ *???* *Sensory?*
 - Assessment tool ~~Many – Primary endpoint: ABC Lethargy/Social~~ *Vineland-Socialization*
 - Withdrawal
- Effect size; sample size *5 pts?* 4 points (SD 7.5); n=150; 80% power *SD 15?*
- Subject selection
 - Age *???* 5 – 21 years
 - Symptom severity ~~ABC LSW ≥ 8~~ *IQ ≥ 70*
 - Co-morbidity Any (no known genetic disorder) *Biomarker analyses pending*
 - Concomitant medications Up to 2 psychoactives (no antipsychotics or anxiolytics)
- Posology
 - Dose Flexible, 5 mg BID – 15 mg TID *Higher?*
 - Dosing schedule
- Duration of treatment
 - Duration x Dose x Age *???* 12 weeks x dose described x “child”

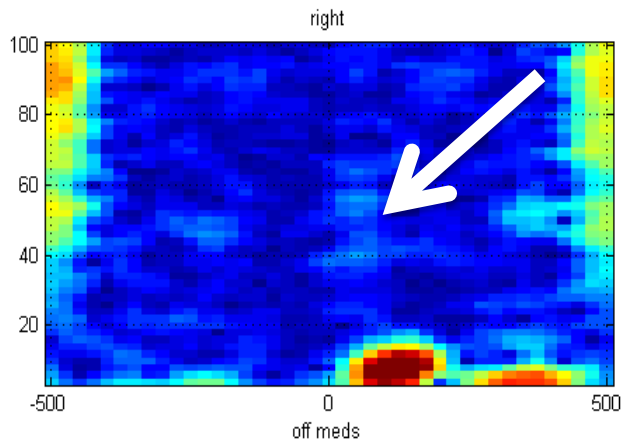
Outcome measures for ASD: Expert reviews

- Anagnostou et al., *Autism* 2015; 19:622-36
“Measuring social communication behaviors as a treatment endpoint in individuals with autism spectrum disorder”
 - Hanratty et al., *PLoS One* 2015;10:e0144649
“Systematic review of the measurement properties of tools used to measure behavior problems in young children with autism”
- No existing measure is (known to be) fully satisfactory

MEG Measures of Inter Trial Coherence in Autism: Response to STX209 (Initial Results)

(slide courtesy of Tim Roberts, CHOP/U-Penn)

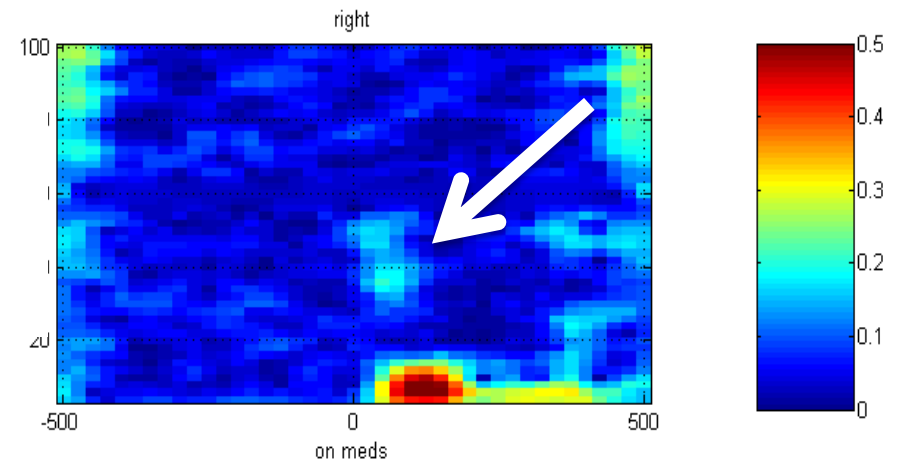
Baseline



Time (ms)

Baseline:
No significant gamma ITC

Post STX209



Time (ms)

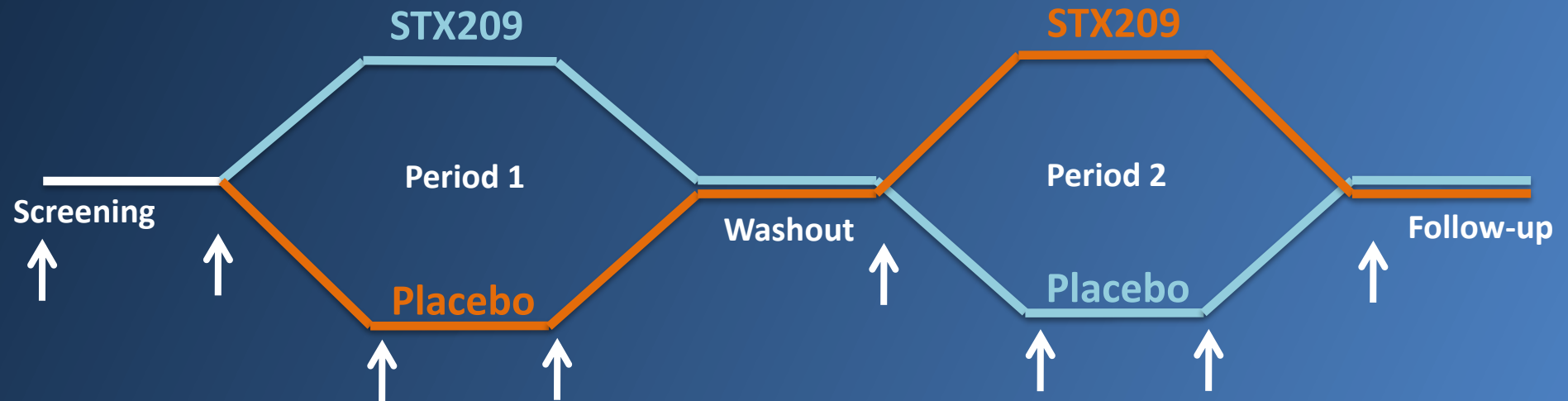
Post-treatment:
Gamma ITC restored (normalized?)

Considerations in ASD trial design & execution

- Observer effects
 - Placebo effects (parent, clinician)
 - Inter-rater variability
- Baseline severity
- Potential stratification factors
 - Age
 - IQ
 - Verbal ability

BACKUPS

Study 22001 design

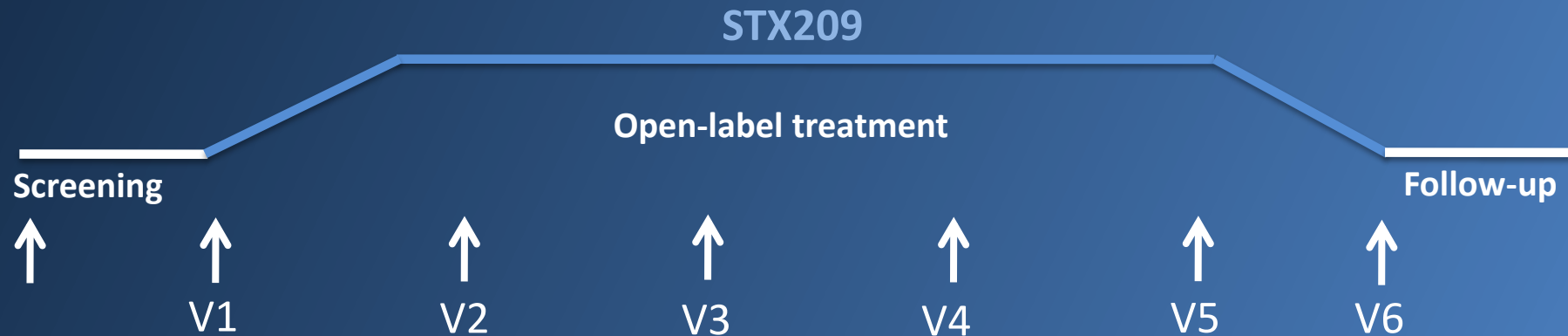


- Age 6-40 years; N=63 (24 aged 6-11yrs, 22 aged 12-17, 17 aged 18-40)
- Baseline ABC-Irrit ≥ 9 (age 6-11), 12 (age 12-40); mean ~ 21
- Comorbid Autistic disorder (DSM-IV, ADOS): n=37
- Mean IQ ~ 46

Efficacy endpoints: Per protocol

	STX209 (mean ± SE)	Placebo (mean ± SE)	p-value
ABC-Irritability	-4.2 ± 0.85	-4.5 ± 0.85	ns
CGI-I	3.3 ± 0.13	3.5 ± 0.13	0.181
CGI-S, change from baseline	-0.6 ± 0.12	-0.3 ± 0.12	< 0.10
Treatment preference (clinician)	57%	28%	< 0.10
Treatment preference (parent)	59%	33%	< 0.10
Visual analog scales (top 3 problems)	-2.2 ± 0.32	-1.2 ± 0.33	< 0.05

Open-label study of STX209 in ASD: Study 22003



- n = 32, age 6-17 years
- Autistic Disorder or PDD-NOS
- ABC-Irritability ≥ 16 at baseline
- Concomitant medications: up to 2 psychoactives; no antipsychotics
- Treatment period: 8 weeks, flexible titration

22003 (Autism): Efficacy analyses

	Baseline (mean \pm SD)	Week 8 (mean \pm SD)	p-value
ABC-Irritability	27.0 \pm 7.6	17.7 \pm 10.4	< 0.001
ABC-Social Withdrawal	17.3 \pm 8.2	12.6 \pm 9.3	= 0.001
ABC-Total	90.3 \pm 29.4	64.0 \pm 35.0	< 0.001
CGI-I	–	2.5 \pm 0.9	< 0.05
CGI-S	5.1 \pm 0.9	4.4 \pm 1.2	< 0.001
ADHD-IV Rating Scale	34.2 \pm 11.4	26.1 \pm 13.0	< 0.001
CY-BOCS	14.8 \pm 4.1	11.6 \pm 5.0	< 0.001
CASI-Anxiety	20.4 \pm 10.6	16.5 \pm 13.8	< 0.001
Social Responsiveness	117.0 \pm 33.8	103.0 \pm 29.6	< 0.05
Vineland-Communication	61.4 \pm 10.5	65.4 \pm 9.5	< 0.01