

**A multi-site, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of vigabatrin (VGB) for treating cocaine dependence**

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## Collaborators

### Study Design

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### Statistics and Analysis

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### Funding

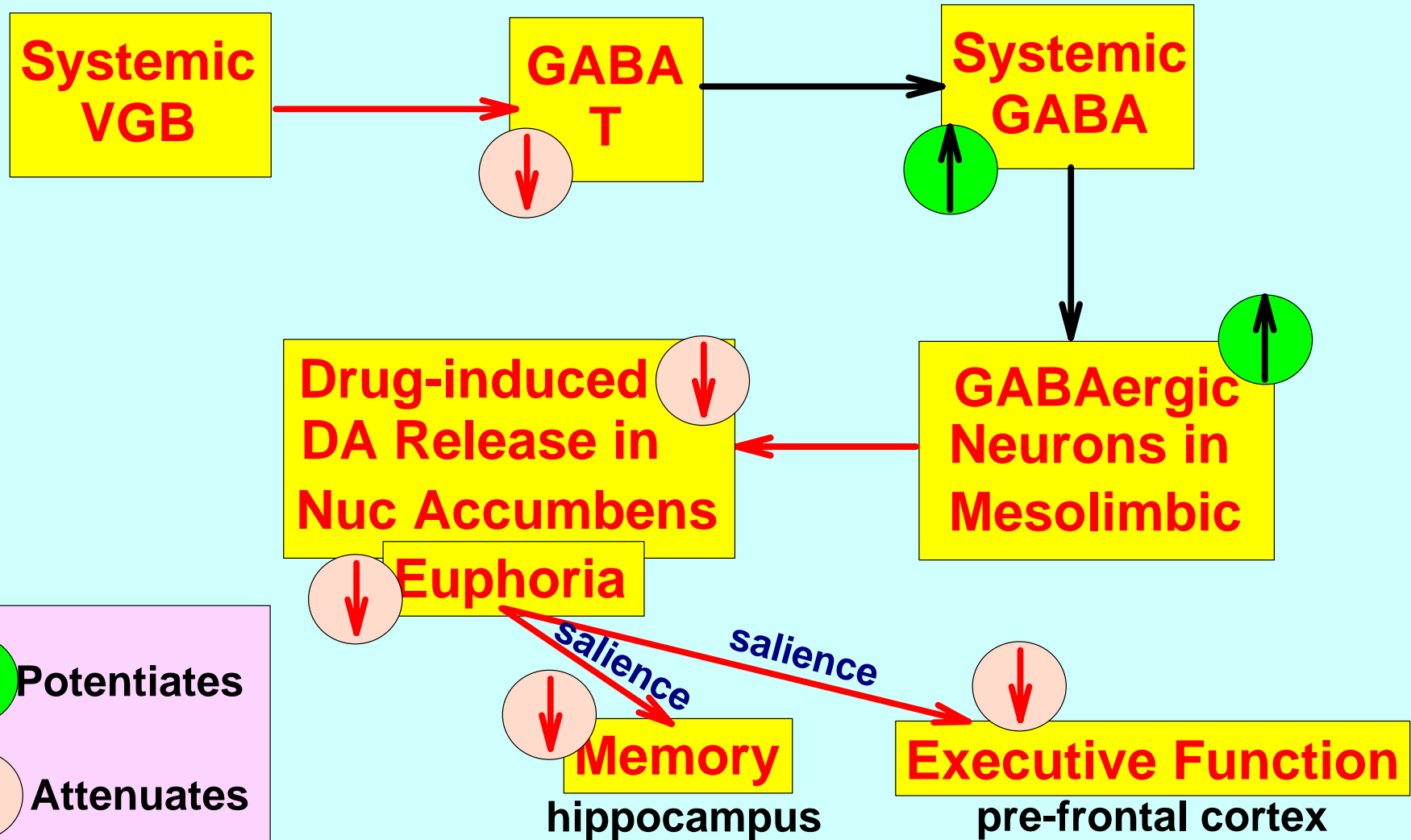
**Catalyst Pharmaceutical Partners**

## ● **Principal Investigators of Clinical Sites**

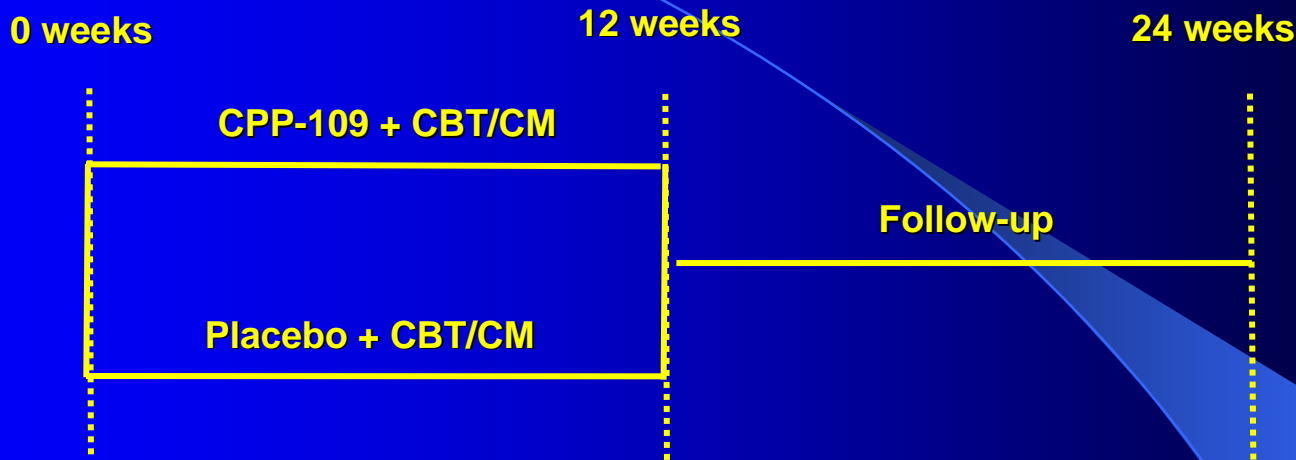
- **Warren Bickel, PhD**, University of Arkansas for Medical Sciences
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- **Gantt Galloway, PharmD**, California Pacific Medical Center
- **Donald Jasinski, MD**, Johns Hopkins University
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- **Scott Segal, MD**, Segal Institute for Clinical Research
- **Michael Sheehan, MD**, Operation PAR
- **Eugene Somoza, MD, PhD**, Cincinnati VA Medical Center and Dayton VA Medical Center
- **Donnie Watson, PhD**, CCRC Friends Research Institute

**Where does vigabatrin (GVG) fit in, & why might it be effective in treating cocaine dependence?**

# Pharmacologically Potentiating GABAergic neurons in the NAcc attenuates cocaine-induced increases in synaptic dopamine (DA)

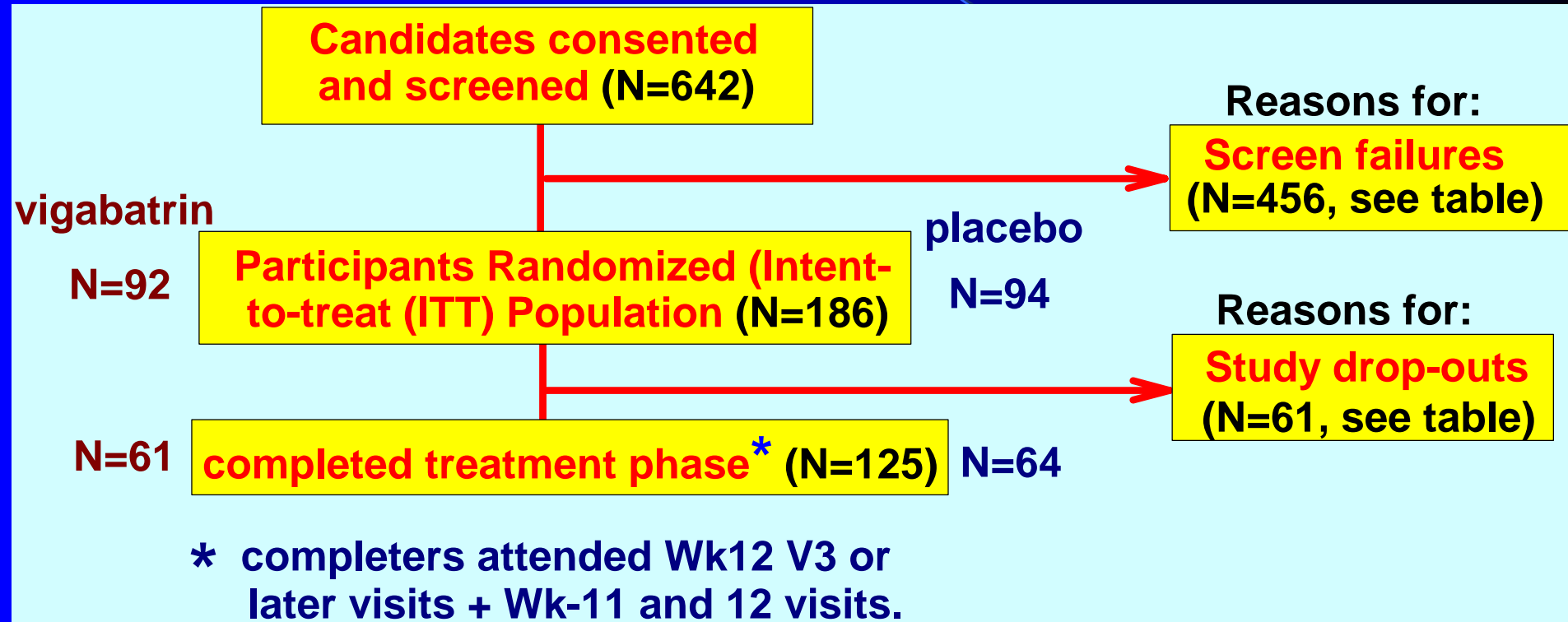


# CPP-01004 Phase II Cocaine Trial



- Primary endpoint: Proportion of each treatment group achieving drug abstinence during the final two weeks of the active phase (trial weeks 11 and 12)
- Secondary endpoints: Reduction in craving, drug use & drug use days
- 11 centers, mostly academic
- Trial design similar to other NIDA-sponsored studies (CTO & MDS)
- Urine specimens collected 3x/week sent to central lab to maintain site blinding
- Computerized cognitive behavioral therapy & counseling (1/week) + contingency management

# Participant flow through study phases



<b>Reason for Failing Screening (N=456)</b>	<b>%</b>
<b>Withdrawed Consent or Left Study</b>	<b>48</b>
<b>Serious Medical or Psych problems or abnormal labs</b>	<b>15</b>
<b>Abnormal visual fields</b>	<b>9</b>
<b>Could not attend regularly</b>	<b>8</b>
<b>Did not produce 4 urines with at least one being positive for cocaine</b>	<b>4</b>
<b>Not cocaine dependent (SCID)</b>	<b>2</b>
<b>Current dependence on other substances (SCID)</b>	<b>2</b>
<b>Ophthalmologic Disease</b>	<b>1</b>
<b>Other</b>	<b>11</b>
<b>Total:</b>	<b>100</b>

## Reasons for dropping out of the study.

<b>Study Drop-Outs (N=61)</b>	<b>%</b>
<b>Lost to follow-up</b>	<b>56</b>
<b>Non-compliance with protocol</b>	<b>15</b>
<b>Consent Withdrawn</b>	<b>11</b>
<b>Incarceration</b>	<b>5</b>
<b>Administrative</b>	<b>1</b>
<b>Adverse Event</b>	<b>1</b>
<b>Death</b>	<b>1</b>
<b>Other</b>	<b>10</b>
<b>TOTAL</b>	<b>100</b>

# Demographics

# Patient Demographics

<b>Gender</b>	<b>Male</b>	<b>124</b>
	<b>Female</b>	<b>62</b>
<b>Race</b>	<b>Black</b>	<b>112</b>
	<b>White</b>	<b>58</b>
	<b>Other</b>	<b>16</b>
<b>Age</b>	<b>45 (Range 21-69)</b>	
<b>Randomization</b>	<b>Vigabatrin</b>	<b>92</b>
	<b>Placebo</b>	<b>94</b>
<b>Frequency of Cocaine Use</b>	<b>≤ 18 day/month</b>	<b>126</b>
	<b>&gt; 18 day/month</b>	<b>60</b>
<b>Cocaine Use Method</b>	<b>IV/smoke</b>	<b>159</b>
	<b>Snorting</b>	<b>27</b>

# Results

# **Primary Outcome Variable:** **Abstinence during last two weeks of study**

## **Algorithm for urine and self-report requirements for weeks in which abstinence is to be determined.**

**Provide at least 4 urines/week during weeks 11 and 12**

**Last urine of wk-12 collected  $\geq 9$  days after 1st urine of wk-11**

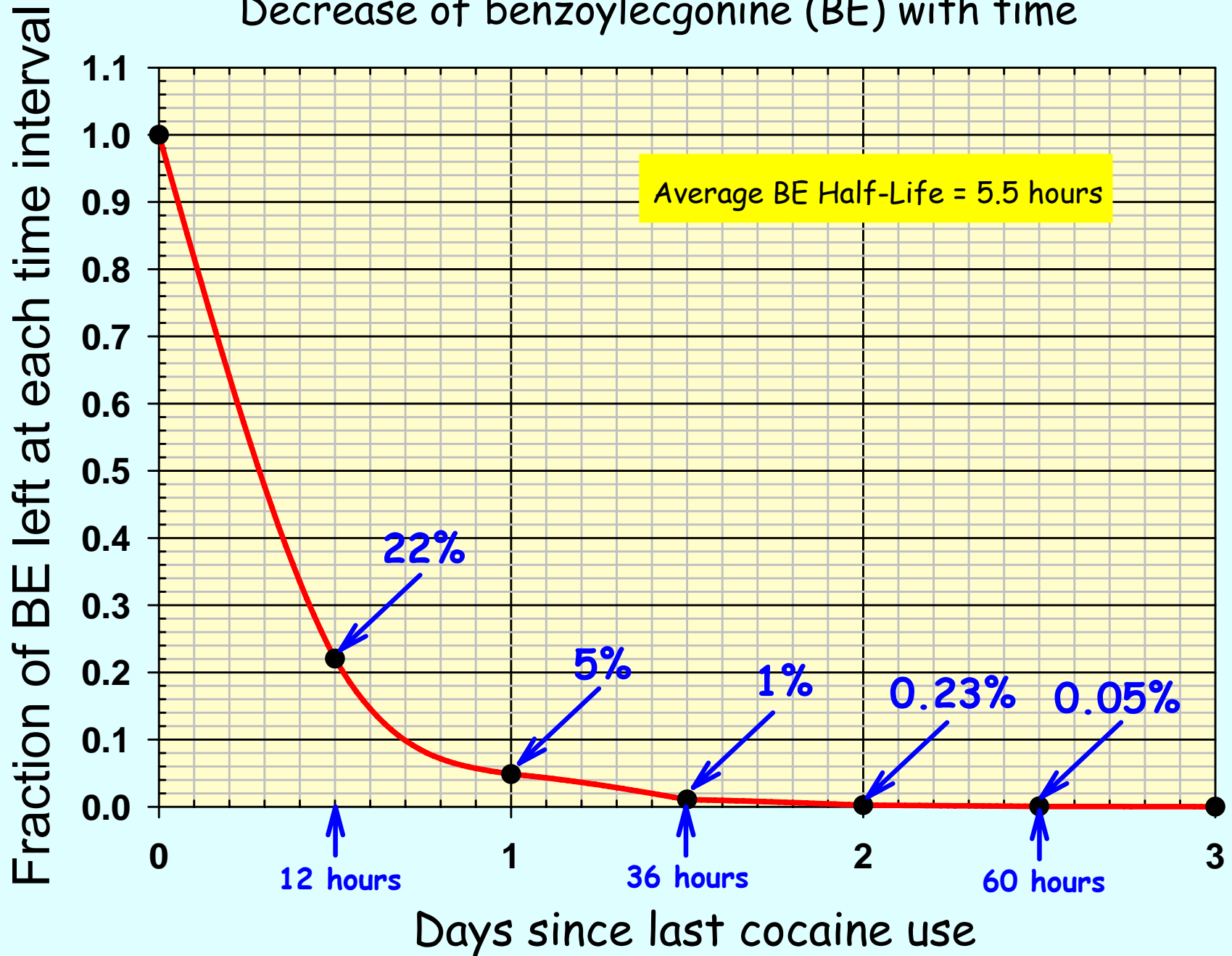
**$\leq 4$  clinic days (or 5 calendar days) between any 2 successive urines.**

**All urines collected have a BE level  $\leq 300$  ng/ml & creatinine  $\geq 20$  mg/dL**

**There is a self-report for all 14 days of this 2-week period,  
and all must be "NO USE".**

**(Note that there must be a urine & a self-report  
at the start of wk-13 to be sure that no use has  
occurred between the final visit of wk-12 and  
the last day of the 14-day period).**

# Decrease of benzoylecgonine (BE) with time



**Results of Primary Outcome Variable  
(Abstinence during last 2 weeks of study)**

<b>Route</b>	<b>Vigabatrin</b>	<b>Placebo</b>	<b>Ratio</b>	<b>P</b>
<b>Snorting</b>	<b>3 of 14 (21.4%)</b>	<b>0 of 13</b>	<b>17,810<sup>1</sup></b>	<b>0.038</b>
<b>Smoking/IV</b>	<b>4 of 78 (5.1%)</b>	<b>5 of 81 (6.2%)</b>	<b>0.83</b>	<b>0.77</b>
<b>Totals</b>	<b>7 of 92 (7.6%)</b>	<b>5 of 94 (5.3%)</b>	<b>1.3</b>	<b>0.67</b>
<b>Coc Usage</b>				
<b>&gt;18x /30 days</b>	<b>0 of 28 (0.0%)</b>	<b>1 of 32 (3.1%)</b>	<b>0</b>	<b>0.25</b>
<b>≤18x/30 days</b>	<b>7 of 64 (10.9%)</b>	<b>4 of 62 (6.7%)</b>	<b>1.70</b>	<b>0.43</b>

(<sup>1</sup>)Fitted odds ratio from logistic regression

# Key Secondary Outcome Variable

## Weekly fraction of cocaine use days.

Uses an algorithm combining **quantitative** urine BE levels with self-report of use for each day in the study (via TLFB).

Somoza et al., 2008

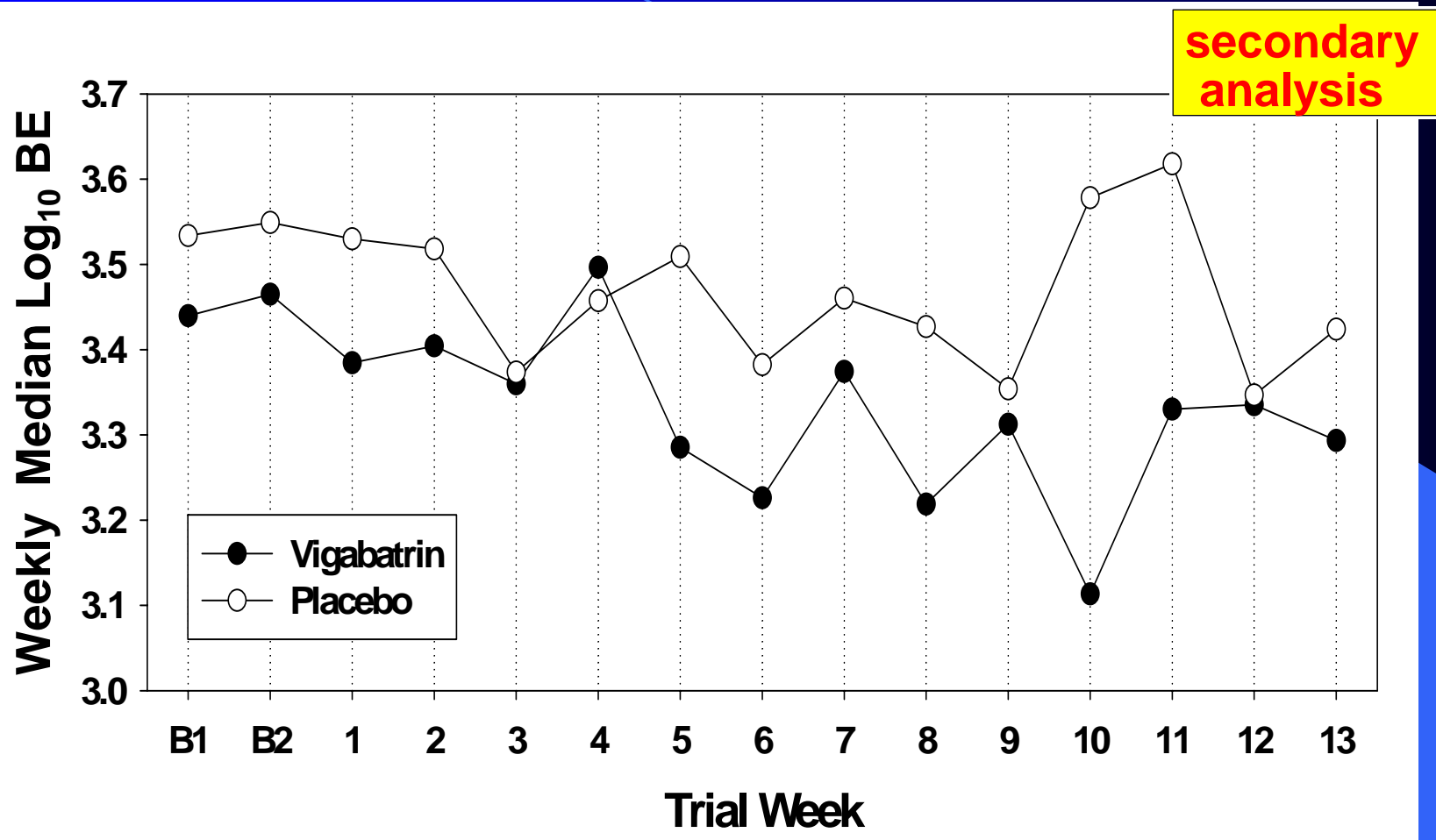
# Results

**Failed primary endpoint (Abstinence throughout weeks 11 and 12.)**

**Failed key secondary endpoint  
SRPhK1 (Self-Report Pharmacokinetics)**

# Planned secondary analyses

# BE Concentration in Urine (Log[ng/ml]) ITT Population

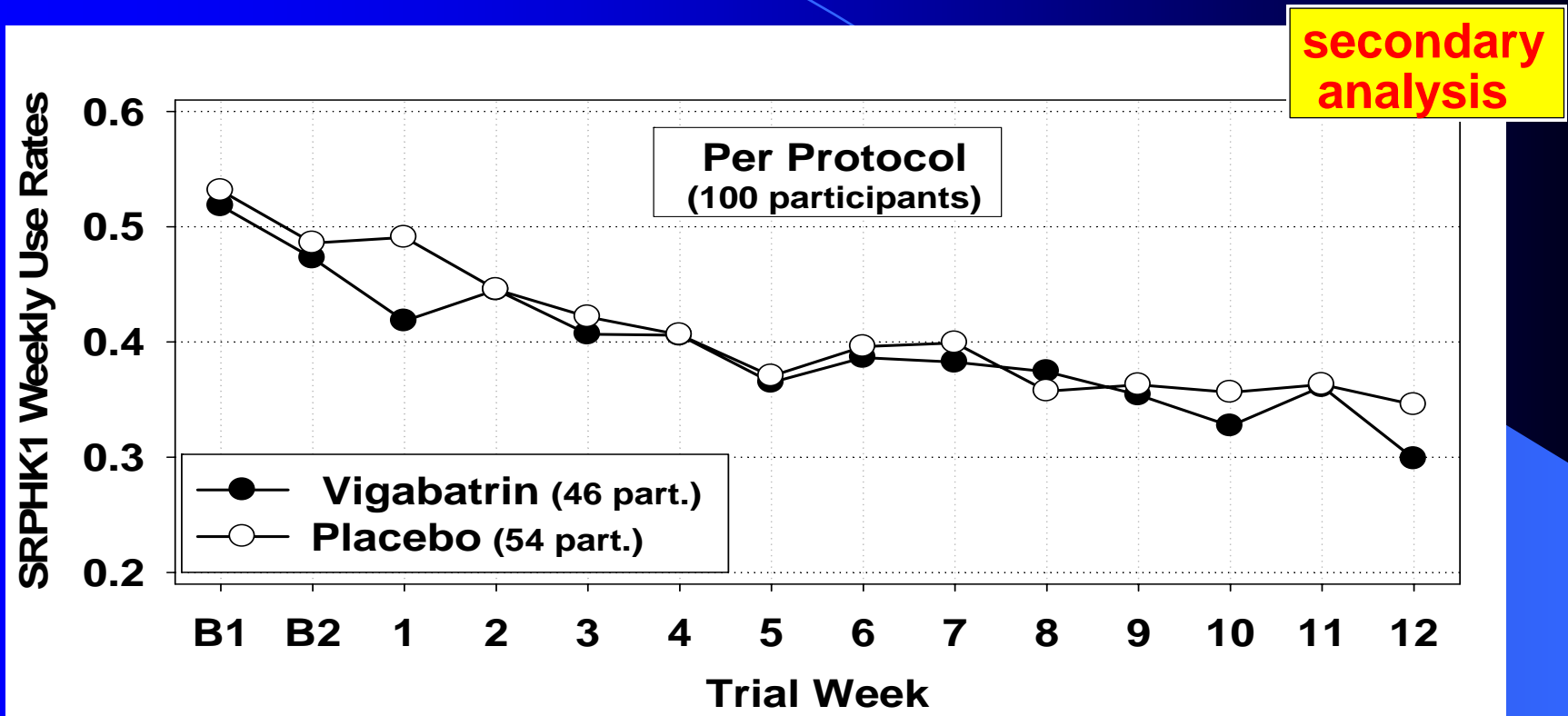


Test	Interpretation
Binomial Sign Test	Vigabatrin subjects used consistently less cocaine than placebo subjects during the 12-week treatment phase (P = 0.006).

# Per protocol population

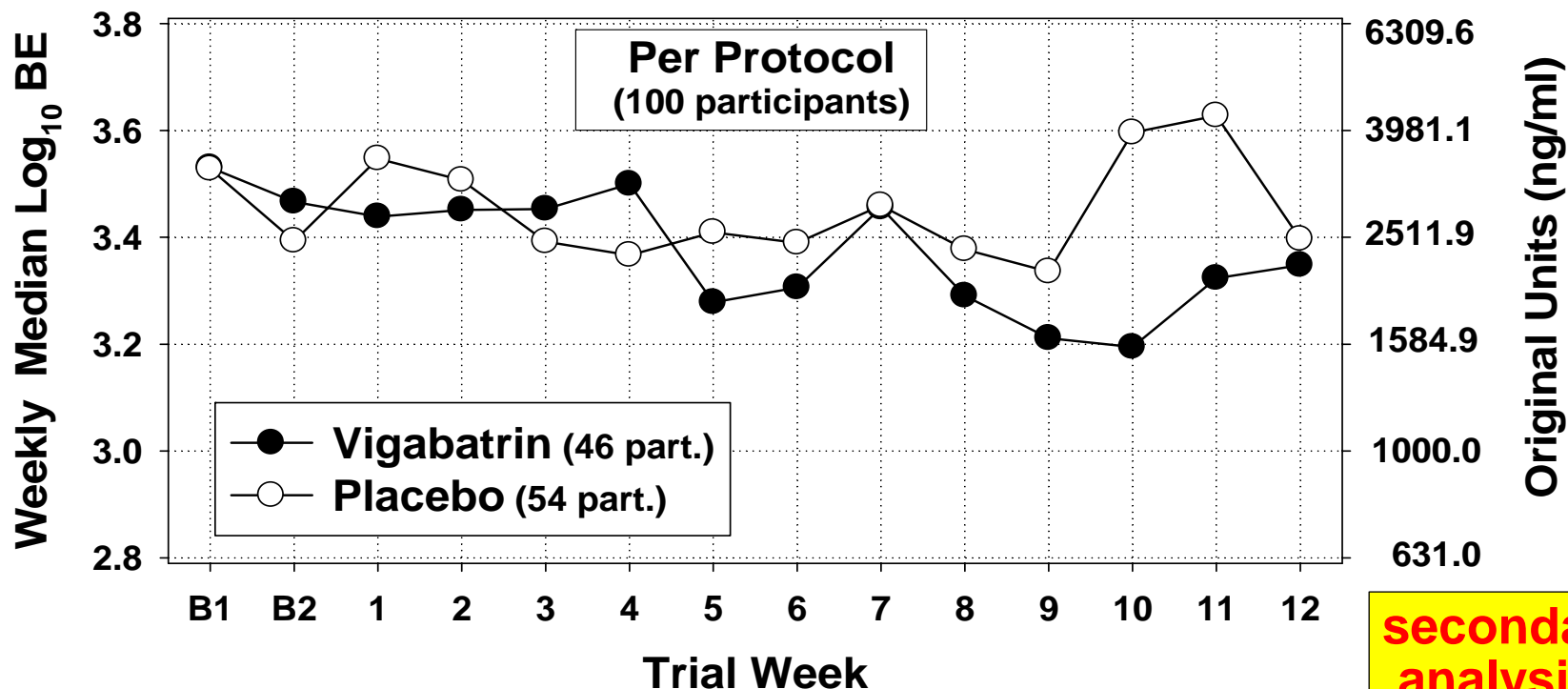
**Per Protocol = attendance at  $\geq 70\%$  of both visits and CBT sessions during the thirteen weeks of treatment**

# Results of Principal Secondary Outcome Variable (SelfReport-Pharmacokinetics (SRPhK1))



<b>Test</b>	<b>P</b>
<b>GEE for difference in rates of change</b>	<b>0.89</b>
<b>GEE for difference in values</b>	<b>0.79</b>
<b>Binomial Sign Test for consistently different averages</b>	<b>0.0063</b>

# BE Concentration in Urine (Log[ng/ml]) Per Protocol Population



Test	P
GEE for difference in rates of change	0.1538
GEE for difference in values	0.0635
Binomial Sign Test for consistently different averages	0.0386

# CPP-01004 Adverse Events >10% By Treatment Group

	Placebo	Vigabatrin
Subjects with $\geq 1$ Adverse Event	81 (86.2)	73 (79.3)
Headache	26 (27.7)	10 (10.9)
Nasopharyngitis	17 (18.1)	17 (18.5)
Diarrhea	15 (16.0)	14 (15.2)
Nausea	17 (18.1)	9 (9.8)
Back pain	10 (10.6)	8 (8.7)

# CPP-01004 Overall Results Summary

- Study did not meet protocol specified primary and secondary endpoint analyses, but:
  - BE levels were consistently lower in the vigabatrin group vs. placebo ( $p = 0.006$ )
- Vigabatrin safe
  - No visual field defects observed
  - Changes in blood pressure observed did not appear to differ between vigabatrin and placebo groups
  - No unexpected SAE's or AE's so no safety concerns going forward

**So,..... Why are we so surprised  
with these negative results?**

## Comparison: US vs. Mexican Vigabatrin Study

Study Element	U.S: CPP-01004	Mexico
# of centers	11	1
# of patients (ITT)	N=186 92/186(59.5%) VGB 94/186 (50.5%) PBO	N=103 50/103 (48.5%) VGB 53/103 (51.5%) PBO
Completers	125/186 (68.1%) 61/92 (66.3%) 64/94 (68.1%) PBO	53/103 ( 52.5%) 31/50 (62%) VGN 22/53 (42%) PBO
Dosage	1.5 g (2 tabs) BID	3g drink QD
Checks on Med compliance	pill count + self report (85% compl.)	Observation of 28.6%
Treatment Duration	12 weeks	9 weeks
"Motivation"	seeking treatment (radio & TV ads.)	parolees seeking Tx
Treatment Platform	Computerized CBT/ Contingency	Group therapy + lottery
Urine collection	3x/wk quantitative	2x/wk qual
Primary Outcome	Abstinence (weeks 11 & 12)	Abstinence (weeks 7 through 9)
Success in primary outcome variable (ITT population)	12/186 (6.5%) 7/92 (7.6%)VGB 5/94 (5.3%) PBO P=0.67	18/103 (17.5%) 14/50 (28%) VGB 4/53 (7.5%) PBO p< 0.009

# Hypotheses after comparing the U.S. study with the Mexican study.

1

It seemed very likely that in the U.S. study participants were not taking their medication. In the Mexican study, ingestion was observed on 2/7 th of the days.

2

Since vigabatrin is excreted in the urine unchanged and in sufficient quantity to analyze, medication compliance could be verified.

3

It seemed very likely that in the U.S study participants were not as motivated to stop using as they were in the Mexican study.

# Medication Compliance Verification Methodology

- **Still blinded to individual group assignments, urine specimens collected from all subjects randomized were reviewed**
- **“Compliant” & “Partially Compliant” vigabatrin concentration thresholds developed**
- **Subjects with urine vigabatrin concentrations at or above the thresholds at least 70% of the time were considered “Compliers” or “Partial Compliers”**

# Medication Adherence Results

- Adherence results determined from urine vigabatrin threshold levels

Medication Compliance Status	Vigabatrin Completer & Per Protocol Populations			
	Compliers ( $\geq 630$ $\mu\text{g/ml}$ )	Partial Compliers ( $\geq 158$ $\mu\text{g/ml}$ )	Non- Compliers	All Completers
Completer Population <sup>1</sup>	24 (39.3%)	8 (13.1%)	29 (47.6%)	61
Per Protocol Population <sup>2</sup>	20 (43.5%)	7 (14.3%)	19 (41.3%)	46

(1)Completers-Attendance at W12V3 or a later visit plus W11 and 12 visits

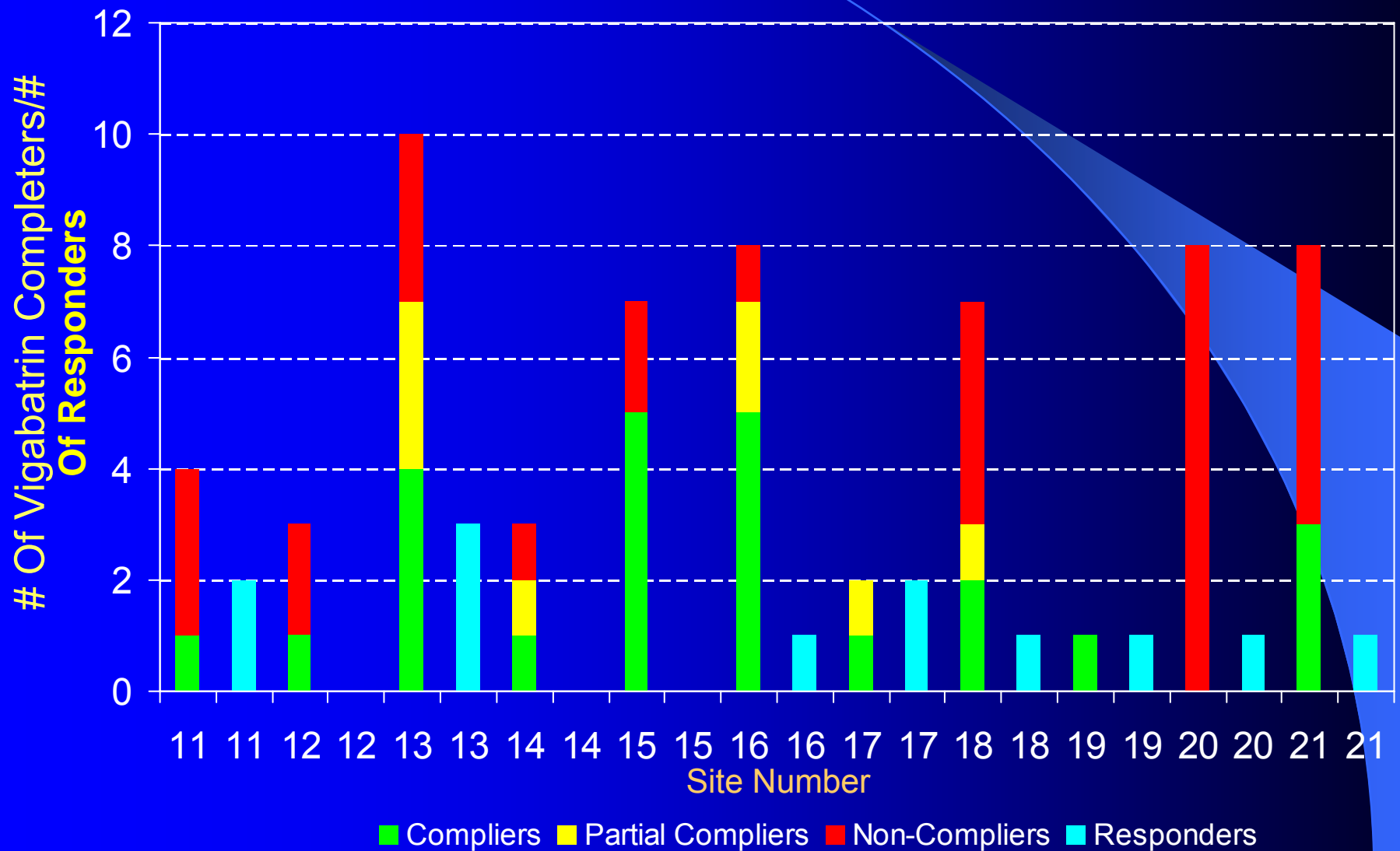
(2)Per Protocol-Attendance at  $\geq 70\%$  of both visits and CBT sessions through W13

# CPP-01004 Primary Endpoint/Vigabatrin Responder Compliance

Medication Compliance Status	Vigabatrin Responders			
	Compliers	Partial Compliers	Non-Compliers	All Responders
Completer Population	3/24 (12.5%)	1/8 (12.5%)	3*/29 (10.3%)	7/61 (11.5)
Per Protocol Population	3/20 (15%)	1/7 (14.3%)	3*/19 (15.8%)	7/46 (15.2%)

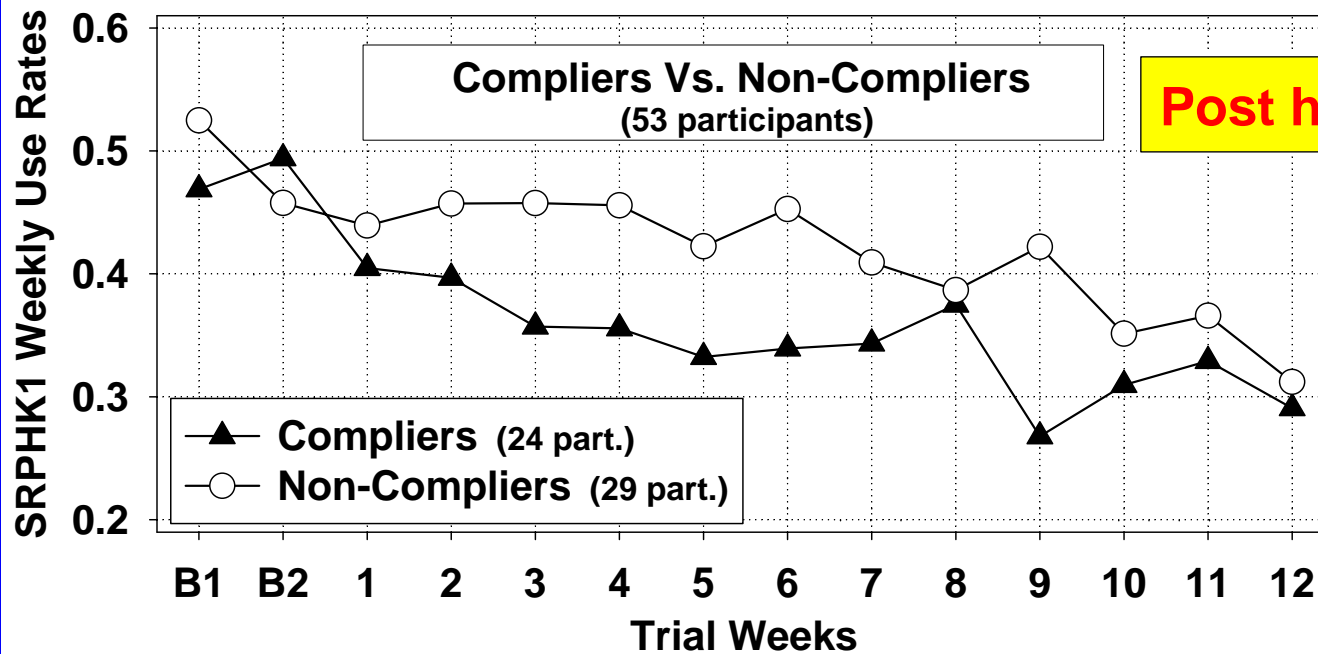
\* One subject appeared to be complying with medication through Week 9 Visit 2

# Vigabatrin Compliance & Responses by Site



# Results of Principal Secondary Outcome Variable (SelfReport-Pharmacokinetics (SRPhK1))

Participants randomized to vigabatrin arm



Test	Interpretation
Regression	Data suggest that compliers had fewer cocaine use days than non-compliers (P = 0.084)
Binomial Sign Test	Compliers had consistently fewer cocaine use days than non-compliers (P < 0.001) .

# U.S Phase II Cocaine Trial Results

- **Why do we believe trial failed and not the drug:**
  - BE levels consistently lower in Per-Protocol vigabatrin group vs. placebo ( $p = 0.064$ )
  - Cocaine use days also consistently lower in Complier vigabatrin group vs. Non-complier group ( $p=0.084$ )
  - Compliers ( $p = 0.001$ ) had consistently fewer cocaine use days than non-compliers.
  - Vigabatrin group ( $p = 0.006$ ) consistently used less cocaine than placebo group (ITT).
  - **Mexican trial results!!**
- **Safety analyses**
  - No visual field defects or abnormalities
  - No drug related SAEs
  - Generally the drug was very safe
- **Medication compliance significant problem**
  - <40% of subjects took medication as prescribed vs. >85% by pill count
- **Difficulty to attract treatment motivated subjects**
  - At 5/11 sites, <50% of subjects took medication as prescribed

# CPP-109 Next Steps

- **Lessons From Phase 2a Trial**
  - Address issue of medication adherence of subjects
    - More observed doses and/or
    - Add marker substance to vigabatrin and placebo formulations (e.g. riboflavin)
  - Address issue of attracting subjects motivated to seek treatment (subjects with a real desire to change their lives)
    - Better screening out of non-treatment seeking candidates
    - Advertising directed at demographic more likely to be seeking treatment
  - Try to find a clinical setting which more replicates Mexico III; i.e. treatment centers
  - Address perceived issues related to Contingency Management
- **Conduct new trial with help from NIDA (CTA executed)**