

# Adaptive Design in CIAS

or

“If you don’t know where you’re going, any road will get you there...”

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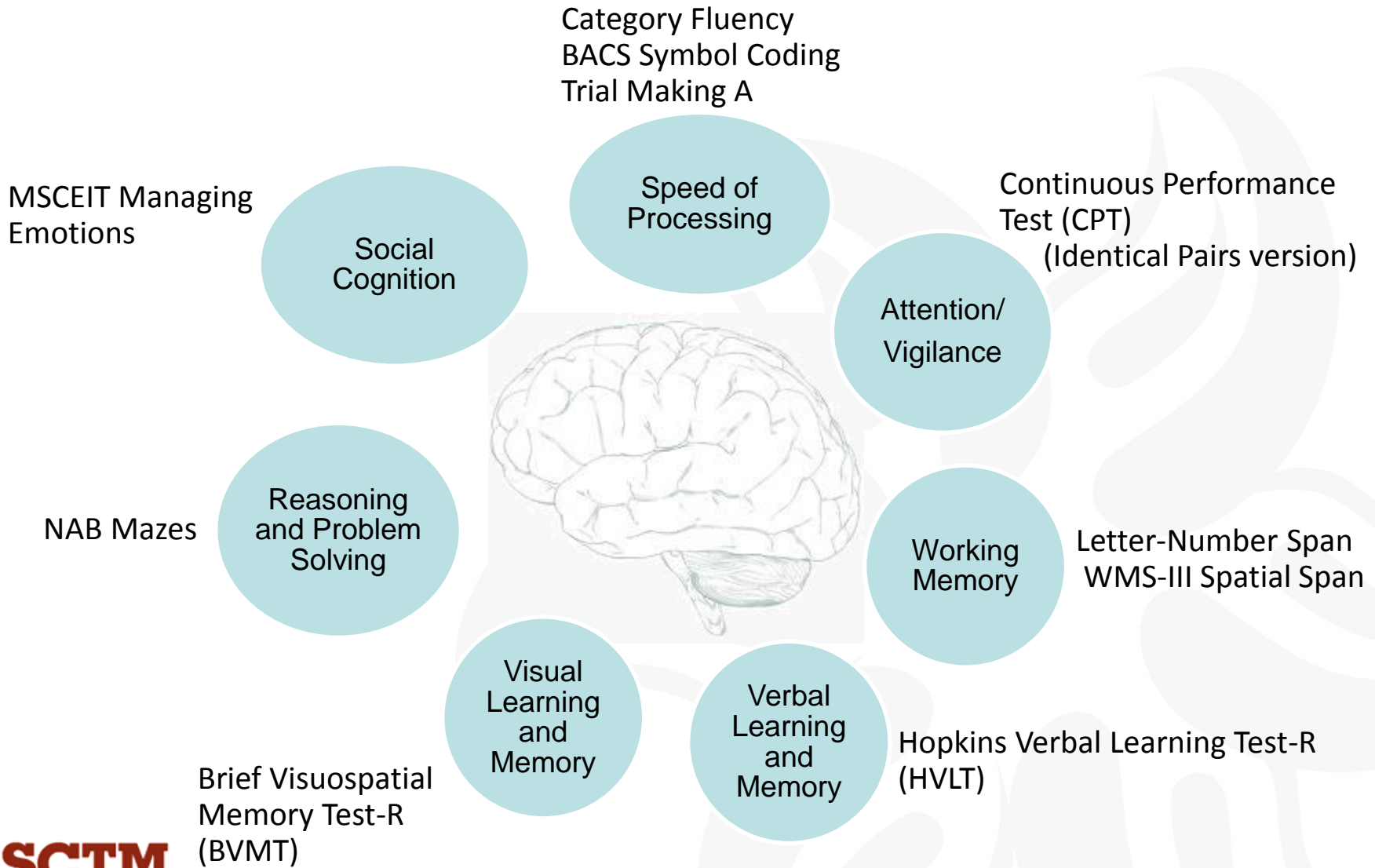
# Disclosures

- I'm an employee of Boehringer-Ingelheim
- The opinions presented are mostly plagiarized from smarter people; the dumb ones are my own.
- Nothing I will discuss today represents the views or policies of the company I work for, the Institute I'm affiliated with, and my own family will probably deny knowing me.

# The Background.....

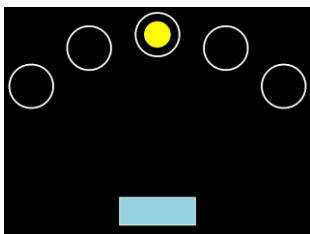
- Tasked with designing a Phase II, PoC Trial
  - Objective: Explore and characterize the effect of BI 409306 on the **cognitive function of patients with schizophrenia**
- Measurements for cognitive efficacy endpoints
  - CANTAB?
  - MCCB (composite score)?
  - CogState?
  - All contain multiple assessments.
  - Composite score may not directly reflect the improvement of cognitive impairment.

# Separable Cognitive Domains in Schizophrenia Assessed in the MCCB



# CANTAB Schizophrenia Battery

## *Processing Speed*



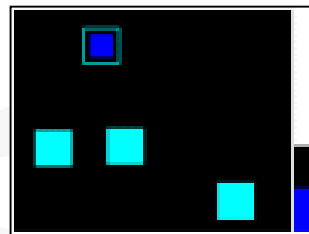
5-Choice Serial Reaction Time (RTI)

## *Verbal Learning*



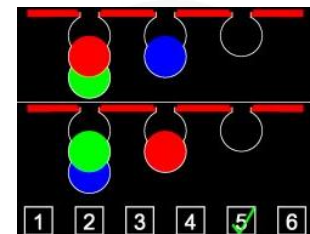
Verbal Recognition Memory (VRM)

## *Working Memory*



Spatial Working Memory (SWM)

## *Reasoning / Problem Solving*



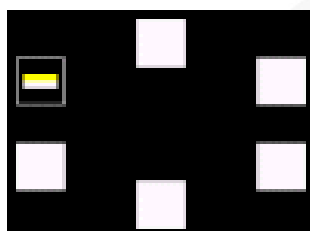
One-touch Stockings of Cambridge (OTS)

## *Attention/Vigilance*



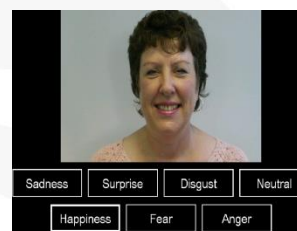
Rapid Visual Information Processing (RVP)

## *Visual Learning*

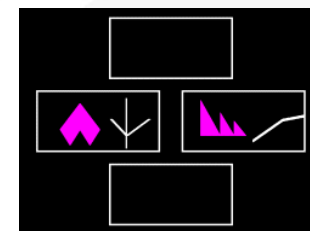


Paired Associates Learning (PAL)

## *Social Cognition*



Emotion Recognition Task (ERT)



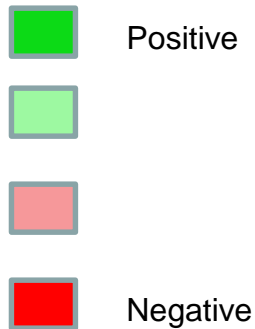
Intra/ Extra-dimensional Shifting (IED)

# Conundrum # 1

- If you prespecify a composite score (MCCB) , you are relying on either a moderate effect on multiple domains of cognition OR a massive effect in one or two tests to “float all boats”.
- Seems reasonable, but to date, no compounds have successfully made it....and at the timing of this design, not even past phase II.....
- What is the likelihood of improving cognition in multiple domains? What if you only have preclinical data for one or two?

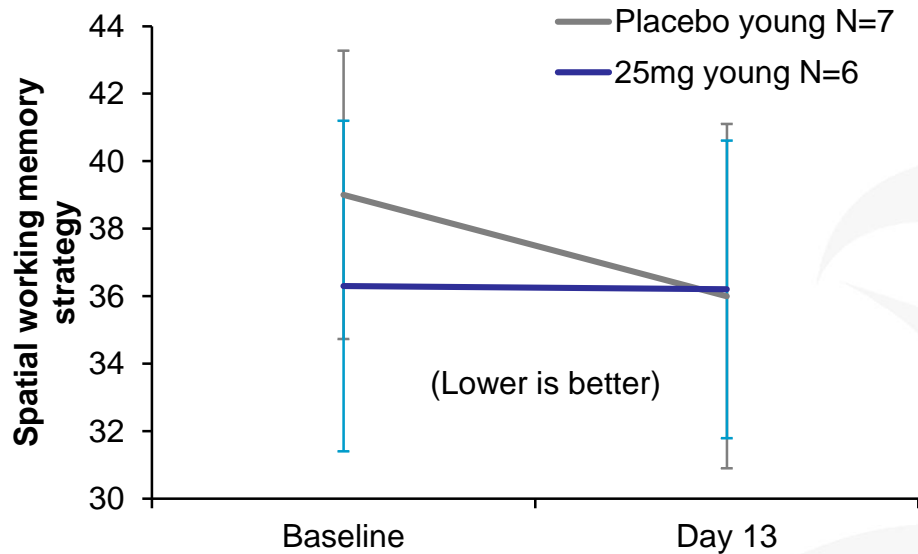
# Conundrum #2

Summary table depicting significant and trend significant effects of BI 409306 in healthy volunteers at Day 7, Day 13, and overall (Day 7 + Day 13)



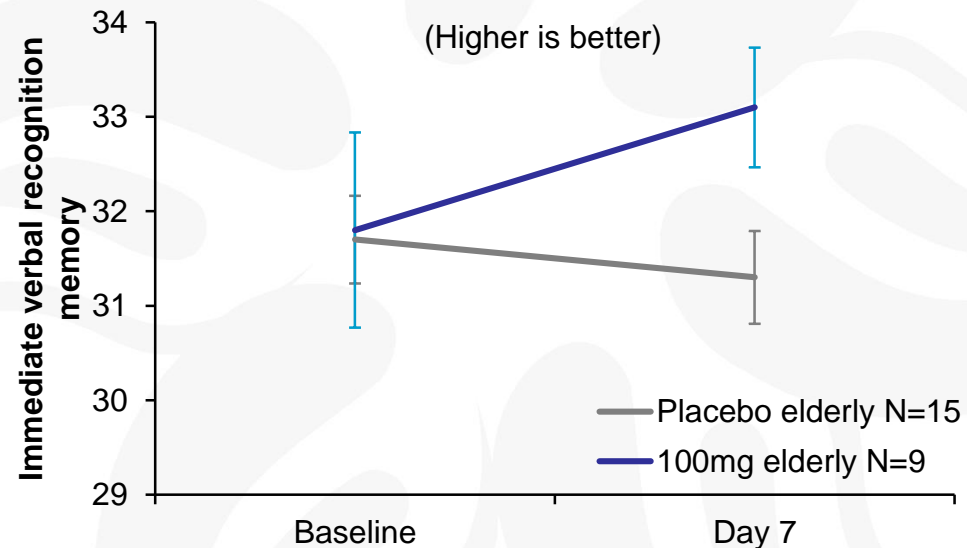
	Day 7			Day 13			Day 7 + Day 13		
	25 mg vs placebo	50 mg vs placebo	100 mg vs placebo	25 mg vs placebo	50 mg vs placebo	100 mg vs placebo	25 mg vs placebo	50 mg vs placebo	100 mg vs placebo
R T I	Median 5-CRT								
	SD 5-CRT								
	Median SRT								
P A L	Total errors adjusted								
	N solved 1st choice								
	Median latency to correct								
D M S	Percent correct								
	Median correct latency								
V R M	I-Recall Total correct								
	I-Recog Total correct								
	D-Recog Total correct								
A S T	Congruency cost								
	Switch cost								
S W M	Between errors, 4-8								
	Strategy, 6-8								
R V P	A prime								
	Median response latency								
S S T	Stop signal reaction time								
	Median Go RT								

# More confusing.....



- 25mg: trend towards impairment at Day 13
- Apparent DETRIMENTAL effect driven by improvement (lower strategy score) in placebo

- 100mg: trend improvement at Day 7
- Apparent BENEFICIAL effect driven by improvement in 100mg group



# So What Could We Say?

1. **Given the large number of statistical tests (171 comparisons), NO FIRM CONCLUSIONS can be made regarding BI409306 and cognition from Phase I data**
2. Possible explanations for lack of clear signal detection include:
  - a. BI409306 is ineffective
  - b. N was too small, study too short to capture signal
  - c. HV's baseline cognitive function is such that improvement is unlikely (ceiling effect)
3. Challenging to select, a priori, a domain of cognition to base go / no-go criteria on

# The Dilemma.....

- We can use MCCB with a composite score....but it is very unlikely that we will improve all domains (or perhaps even most domains) of cognition. Risk of failure via “blunting” good effect on subdomains.
- Similar dilemma has been demonstrated in Alzheimer’s Disease using ADAS-Cog. The basic ADAS-Cog with 11 items and was designed to measure cognitive areas commonly seen to decline in Alzheimer’s disease (AD), specifically learning (word list), naming (objects), following commands (1 to 5 elements), ideational praxis (mail a letter), constructional praxis (copy 4 figures), orientation (person, time and place), recognition memory (from a second word list), and remembering test instructions (from the recognition subtest)
- Most AD trials show movement in only a few of these domains (language), leading to “failure”

# The Dilemma, con't....

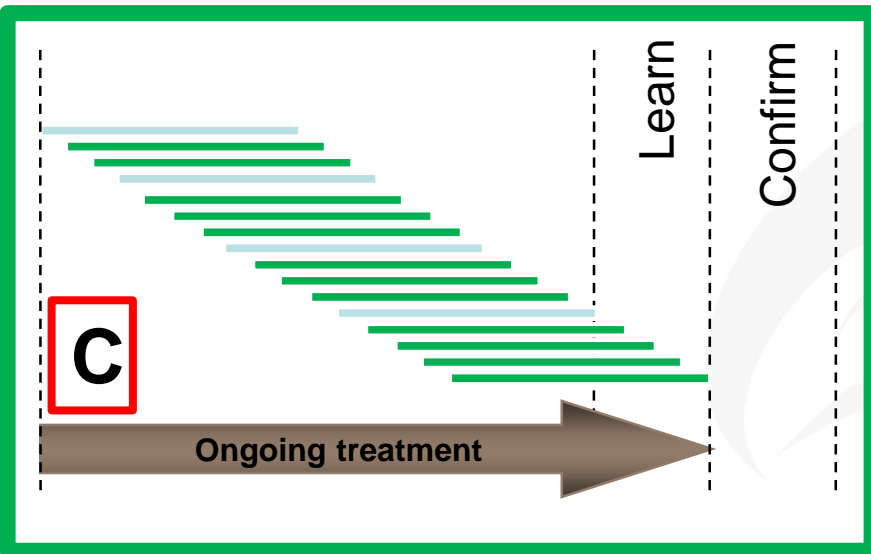
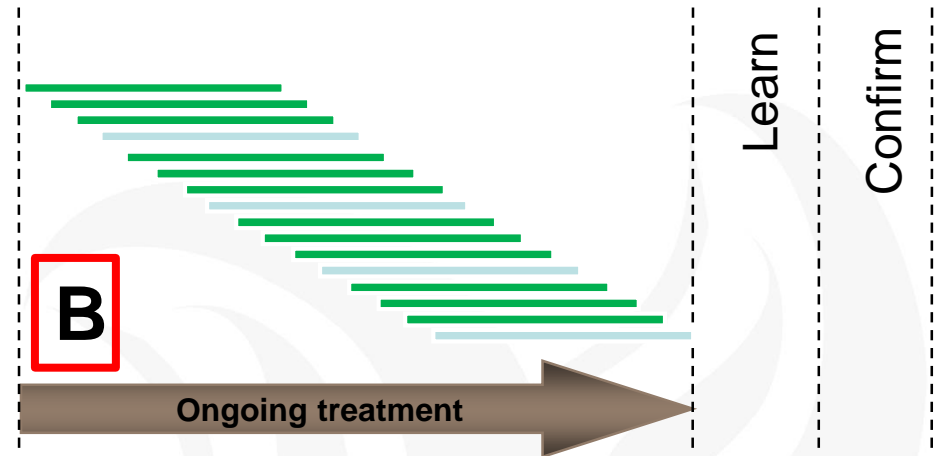
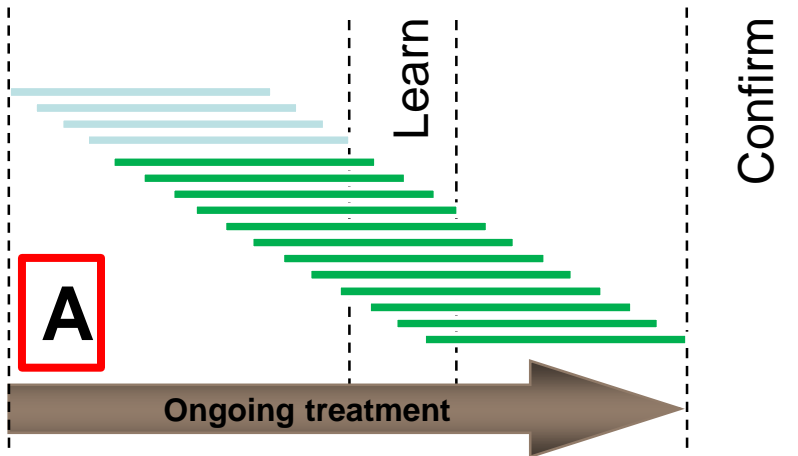
- We can use CANTAB, and look at individual domains....but as we have already seen, we may have effects by chance alone. Not feasible to power adequately to adjust for multiplicity
- We can use CANTAB and prespecify specific domains.....but in doing so a priori we are guessing, with no solid evidence, which domains to choose.

# Learn-Confirm Adaptive Design

- **Two –Stage Exploratory Learn-Confirm Adaptive Design**
- **Stage I: Learn**
  - Interim Analysis, used to finalize TSAP (without disclosure to trial team)
  - Unblinded subset of data with access granted to a small, decision-making team
  - Adaptation Decisions
  - Limited sample size to base decisions carries risk
- **Stage II: Confirm**
  - Final Analysis
  - Analysis does not use data from Stage I ... in return, full alpha can be used
- **NOTE**
  - Patients analyzed in Stage I are not used in the final analysis in Stage 2
  - Complete separation of the 2 stages allows for cleaner analysis of Stage 2 without concerns regarding statistical and operational bias or type I error inflation

# Learn-Confirm

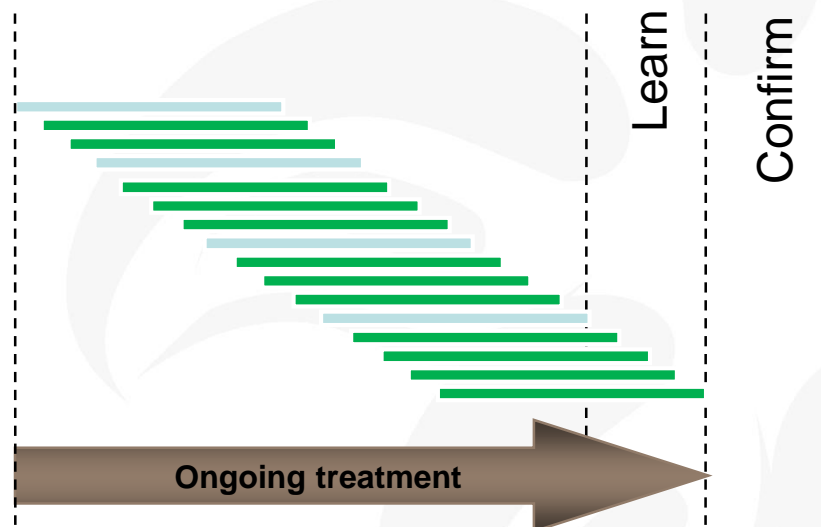
## Selection of patients to use for learn analysis



	PROs	CONs
<b>A</b>	<ul style="list-style-type: none"> <li>+ Maximize time for learn stage analysis and decision making</li> <li>+ Operationally easier</li> <li>+ No unblinding issue of confirm stage patients</li> </ul>	<ul style="list-style-type: none"> <li>- Learn stage different from confirm stage? (season, period, site experience)</li> </ul>
<b>B</b>	<ul style="list-style-type: none"> <li>+ Homogenous population</li> <li>+ Homogenous site experience</li> </ul>	<ul style="list-style-type: none"> <li>- Time required after final DBL before confirm stage</li> <li>- Randomly select patients</li> </ul>
<b>C</b>	<ul style="list-style-type: none"> <li>+ Homogenous population (almost)</li> <li>+ Homogenous site experience (almost)</li> </ul>	<ul style="list-style-type: none"> <li>- Shorter time period for Learn before final DBL</li> <li>- Randomly select patients</li> </ul>

# Stage 1: Learn

- Stage 1 (learn) is an **interim analysis** in order to identify meaningful cognition endpoint(s) that clearly differentiates between treatment effects of BI409306 and placebo.
- The selected patients will be unblinded and analyzed as part of the Stage 1 interim analysis. The analysis of covariance (ANCOVA) will be used to explore the change from baseline to week 12 on the 8 cognition domains assessed by CANTAB.
- **The endpoint(s) that differentiate the treatment effects of BI 409306 and placebo will then be pre-specified as the primary endpoint(s) for the Stage 2 (Confirm) analysis.**

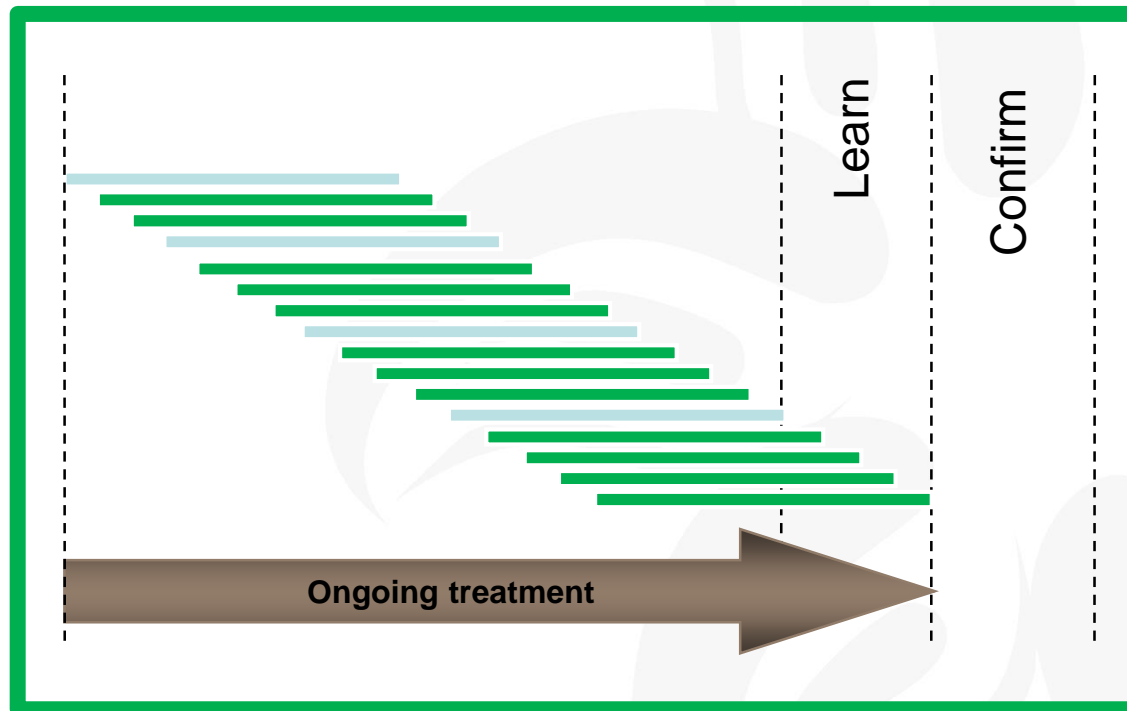


# Learn Phase Decision Rules

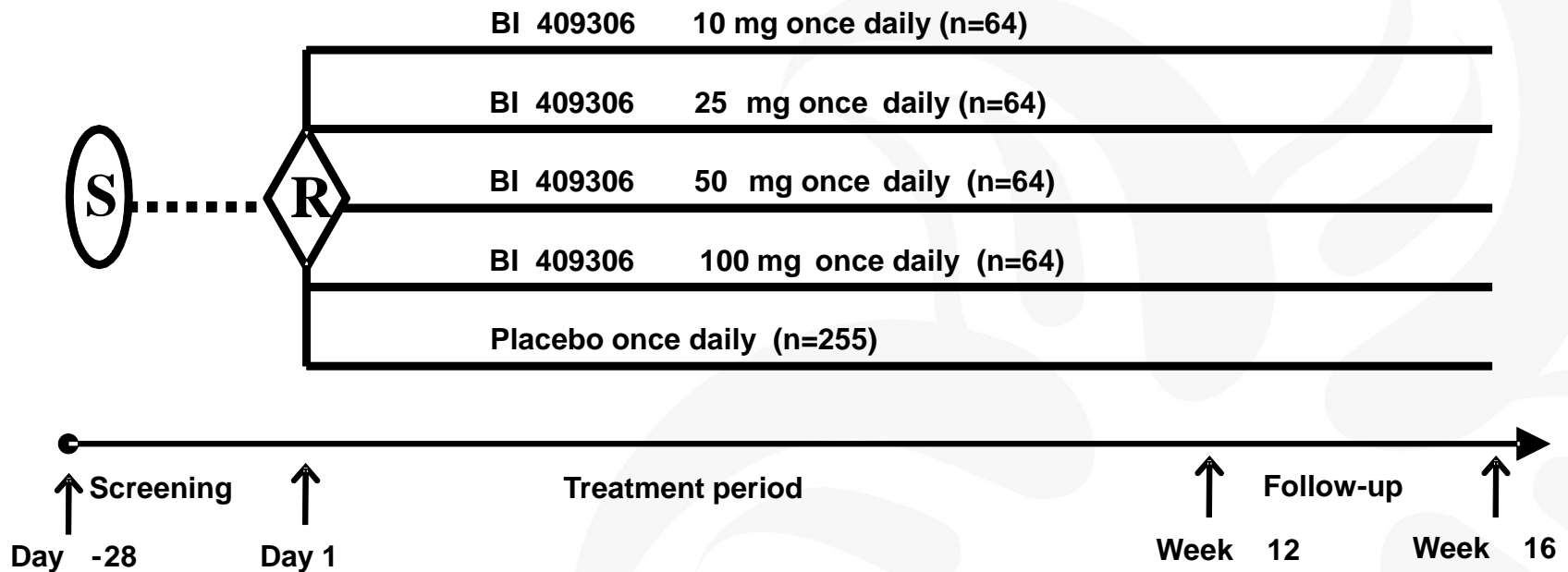
- 4 doses of BI 409306 were analysed for each of the 8 potential CANTAB primary endpoints
- If no effect size was larger than 0.5, then no CANTAB endpoint would be selected and the MCCB composite score would be used as the primary endpoint
- If at least one effect size was larger than 0.5 for any dose and any CANTAB endpoint then:
  - If exactly 1 or 2 endpoints showed an effect size larger than 0.5, these endpoints would be selected as the primary endpoint(s)
  - If more than 2 endpoints showed an effect size larger than 0.5, the correlation between endpoints and the magnitude of the corresponding effect sizes would be considered in primary endpoint selection.

# Stage 2: Confirm

- Once the primary endpoint(s) are identified in Stage 1, the primary endpoint(s) and an **a priori hypothesis testing order will be pre-specified before Stage 2 database lock and unblinding.**
- **IF** a CANTAB endpoint is selected in Stage 1, then Stage 2 will be performed on the remainder of patients who were not analyzed as part of the Stage 1 interim analysis.
- The restricted maximum likelihood based mixed model repeated measurement (MMRM) will be performed on the selected endpoint(s).



# 1289.6 Trial Design



# Analytical Strategy

- Stage 1 is the exploratory stage of the trial in order to identify one or more meaningful cognition endpoints that clearly differentiate between treatment effects of BI 409306 and placebo.
- A total of 120 patients (20 patients per active BI 409306 treatment arm and 40 patients on placebo) will be randomly selected after 70% of patients complete the 12 week treatment period (i.e. randomly select a total of 120 patients when about 361 patients complete).
- These selected patients will be unblinded and analysed in the Stage 1 analysis.

# Stage 1: Learn phase CANTAB results

## Test

RTI: **negative** change indicates improvement; motor and mental response speeds, as well as impulsivity.

VRM: **positive** change indicates improvement; verbal memory and new learning, and measures the ability to encode and subsequently retrieve verbal information

SWM: **negative** change indicates improvement; retention and manipulation of visuospatial information. This self-ordered test has notable executive function demands

RVP: **positive** change indicates improvement; measure of sustained attention

PAL: **negative** change indicates improvement; assesses episodic memory and new learning

ERT: **positive** change indicates improvement; ability to identify emotions in facial expressions

OTS: **positive** change indicates improvement; executive function, spatial planning and working memory

AST: interpretation is complex; measure top-down cognitive control processes involving the prefrontal cortex

Dose (blinded)	W	X	Y	Z
RTI	Light Green	Light Green	Light Orange	Light Orange
VRM	Light Orange	Light Orange	Light Orange	Light Green
SWM	Dark Green	Light Green	Light Orange	Light Orange
RVP	Dark Green	Light Green	Light Green	Light Orange
PAL	Dark Green	Light Green	Light Green	Light Orange
ERT	Dark Red	Dark Red	Light Orange	Dark Red
OTS	Dark Red	Dark Red	Light Green	Dark Red
AST	Light Green	Light Green	Light Green	Light Green

# My 2 cents' worth at the time

- There is a consistent pattern of benefit in dose W and X (4 tests indicating positive effects)
- There is a consistent pattern of benefit in several tests, with largest benefits seen in SWM, RVP, and PAL. These are tests of:
  - SWM: retention and manipulation of visuospatial information - prefrontal cortex, hippocampus
  - RVP: sustained attention - parietal and frontal lobes
  - PAL: episodic memory and new learning - medial temporal lobe
- NO test demonstrated an effect size of improvement of 0.5 or greater, therefore in accordance with our pre-specified TSAP, MCCB was declared the primary endpoint for the confirm phase

# Did it work?

- Congratulations! Your abstract, “Evaluation of the Efficacy, Safety, and Tolerability of BI 409306, a Novel Phosphodiesterase 9 Inhibitor, in Cognitive Impairment in Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Phase II Study,” has been accepted for oral presentation at the 16<sup>th</sup> International Congress on Schizophrenia Research.
- Come to San Diego in a few weeks and find out.....

# Acknowledgments

- Boehringer-Ingelheim
  - Jennifer McGinniss, PhD
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  - Kiri Granger, PhD
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