IDENTIFICATION OF MEANINGFUL COGNITIVE ENDPOINTS IN STUDIES OF PHARMACOLOGICAL THERAPIES FOR COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

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BACKGROUND

- Cognitive impairment associated with schizophrenia (CIAS) is linked with poor functional outcomes, but currently approved antipsychotics do not demonstrate efficacy in the treatment of negative symptoms and cognitive deficits in schizophrenia[1]
- Specifying the primary endpoint in proof-of-concept trials assessing CIAS presents unique challenges, due to the multitude of cognitive assessments that often cover multiple domains
  - The Cambridge Neuropsychological Test Automated Battery (CANTAB) tests individual domains,[2] but it is not feasible to adequately power a study to adjust for the multiplicity of testing. Selected CANTAB domains can also be pre-specified for a study, but there is often a lack of evidence to support the selection of specific domains
  - The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) uses a composite score,[3] but there is the risk that not all domains (or even most domains) are sufficiently improved to show overall statistical significance, or that certain domains will add noise to the data
- An adaptive study design may therefore be of benefit in clinical trials investigating cognitive function

OBJECTIVE

- Here, we describe the novel 'Learn and Confirm' approach used in a Phase II clinical trial to evaluate the effects of BI 409306, a potent and selective phosphodiesterase 9 (PDE9) inhibitor, in patients with schizophrenia
- The most meaningful cognitive endpoints were identified in Stage 1 (Learn), allowing for pre-specification of the primary endpoint in Stage 2 (Confirm), which aimed to show superiority of BI 409306 over placebo in the pre-specified measure

METHODS

PATIENTS

- Eligible patients: were male or female and 18–55 years of age; had an established diagnosis of schizophrenia; were maintained on stable doses of current antipsychotics or concomitant psychotropic medications prior to randomisation; had a score of ≤4 for the hallucination and delusion items in the Positive and Negative Syndrome Scale (PANSS)–positive syndrome rating scale; and had a minimal level of extrapyramidal symptoms (Simpson-Angus Scale total score <6) and depressive symptoms (PANSS-general psychopathology syndrome Depression item score ≤4)
- Exclusion criteria included: treatment with more than two antipsychotics, long-acting hypnotics and anxiolytics, or strong or moderate CYP3A4 inhibitors; cognitive impairment severity that might compromise the validity of the cognitive outcome measures; suicidal behaviour within 2 years or suicidal ideation of type 4 or 5 in the Columbia Suicidal Severity Rating Scale (C-SSRS) within 3 months; categorical diagnosis of another current major psychiatric disorder (according to the mini-international neuropsychiatric interview); and a history of drug dependence or abuse within 2 years

STUDY DESIGN

- This was a Phase II, multicentre (55 centres, 6 countries), randomised, double-blind, placebo-controlled, parallel-group study (ClinicalTrial.gov identifier: NCT02281773)
- Post-screening, patients were randomised (2:1:1:1:1) to one of five 12-week treatments (once-daily placebo, BI 409306 10, 25, 50 or 100 mg), with a 4-week follow-up period

ENDPOINTS AND ASSESSMENTS

- The primary efficacy endpoint was to be the change from baseline in cognitive function as indicated by one or more of the CANTAB measurements, or by the composite score of MCCB, after 12 weeks of treatment
  - CANTAB or MCCB assessments were to be performed at screening (Visit 1), randomisation (Visit 2; baseline), Visit 4 and at the end of treatment visit
- The key secondary efficacy endpoint was the change from baseline in everyday functional capacity, as measured by Schizophrenia Cognition Rating Scale (SCoRS) total score
- Safety assessments included adverse event monitoring, physical examinations, vital signs, cardiac function assessments and monitoring of clinical laboratory assessment

THE 'LEARN AND CONFIRM' APPROACH

- A two-stage exploratory 'Learn and Confirm' adaptive study design was used:
  - **Stage 1: Learn**
    - A small subset of data was unblinded with respect to CANTAB measures only
    - Interim analysis of CANTAB data
    - Adaptation decisions for primary endpoint permitted
  - **Stage 2: Confirm**
    - Final analysis
    - Patients analysed in Stage 1 were not to be included in the final analysis of the same CANTAB measures in Stage 2, to reduce the risk of statistical and operational bias or Type 1 error inflation (unless the MCCB composite score was selected as the Stage 2 analysis endpoint)
- There were three potential 'Learn and Confirm' models that could be used as part of the study **(Figure 1)**
  - Model A would maximise the time for the 'Learn' stage analyses, but with the risk of differences in the 'Confirm' stage in terms of season, time period and site experience
  - Model B would allow for a homogeneous study population and site experience for patients, but with time required after database lock before the 'Confirm' stage could begin
  - Model C allowed for a near-homogeneous study population and site experience for patients, but with a shorter time period required for the 'Learn' stage before final database lock
    - Model C was selected for use in the study as it maximised the benefits of using a 'Learn and Confirm' approach

ANALYSIS

Stage 1 (Learn): Interim analysis

- The primary objective for Stage 1 analyses was to explore the CANTAB domains and identify those having a strong association with treatment effect
- Analysis of covariance (ANCOVA) was planned to assess change from baseline in 7 cognition domains as assessed by 8 CANTAB measurements **(Table 1)**, to identify any CANTAB domains strongly associated with treatment effect

Table 1: CANTAB testing domains and outcome measures

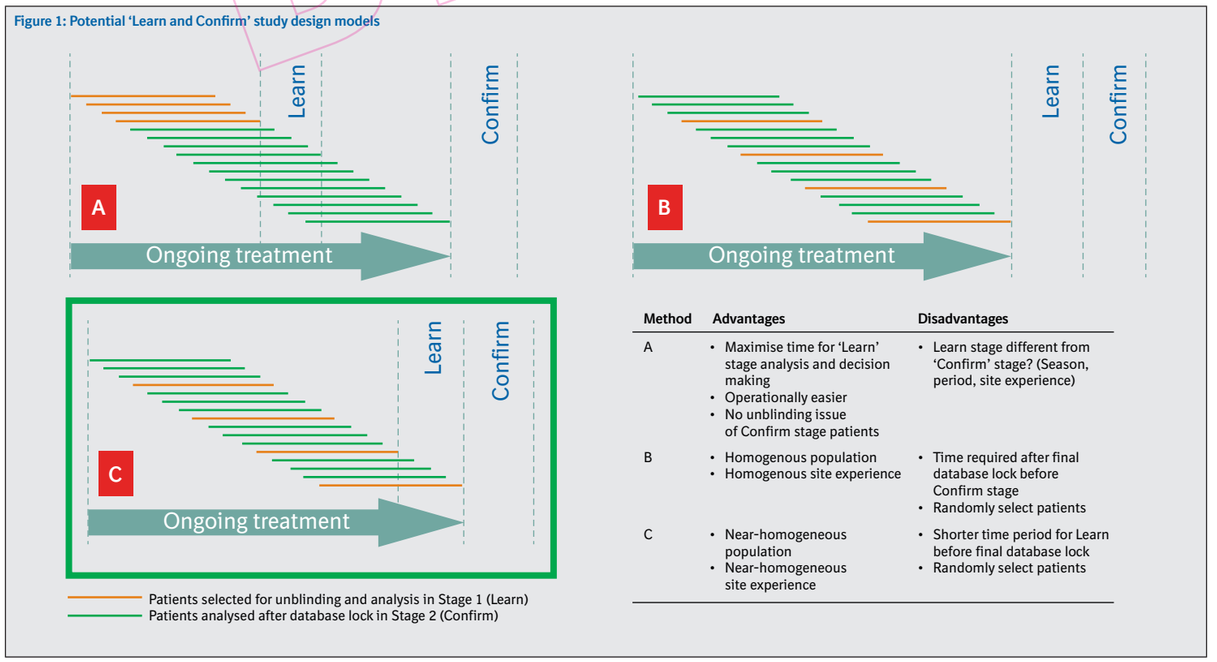
CANTAB test	Domain	Main outcome measure
Reaction time	Speed of processing	Median 5-choice reaction time
Verbal recall/recognition memory	Verbal learning	Immediate free recall total correct
Spatial working memory	Working memory	Between errors 4–8 boxes
Rapid visual information processing	Attention/vigilance	Rapid visual information processing (A-Prime)
Paired associates learning	Visual learning	Total errors (adjusted)
Emotion recognition task	Social cognition	Percent correct
One-touch stockings of Cambridge	Reasoning and problem solving	Problems solved on first choice
Attention switching task	Reasoning and problem solving	Congruency cost (median)

- 120 patients were randomly selected by an independent statistician for unblinding after 70% of patients completed the 12-week treatment period
- Sample size was based on 30% of the sample size chosen for Stage 2, and an effect size of 0.9 (double the effect size used in Stage 2 [0.45])
- A sample size of 120 (20 per active treatment and 40 for placebo), was designed to detect an effect size of 0.9 with 80% power at the two-sided alpha significance level of 5%
- If no effect size was greater than 0.5 in Stage 1, then no CANTAB domain would be selected and the composite score of MCCB would be used as the primary endpoint for Stage 2 **(Table 2)**

Stage 2: Final analysis

- Once the primary endpoint(s) were identified in Stage 1, the primary endpoint(s) and an a priori hypothesis testing order were to be pre-specified before Stage 2 database lock and unblinding
- The selected efficacy endpoints for Stage 2 were to be analysed using the restricted maximum likelihood-based mixed-model for repeated measures
- The sample size for the trial was estimated so that if a CANTAB domain was specified as the primary endpoint after Stage 1, there was a remaining sample size available in Stage 2 (66 per active treatment and 132 for placebo) to provide 84% power to detect an effect size of 0.45 in that particular CANTAB endpoint

Figure 1: Potential 'Learn and Confirm' study design models



Method	Advantages	Disadvantages
A	• Maximise time for 'Learn' stage analysis and decision making • Operationally easier • No unblinding issue of Confirm stage patients	• Learn stage different from 'Confirm' stage? (Season, period, site experience)
B	• Homogenous population • Homogenous site experience	• Time required after final database lock before Confirm stage • Randomly select patients
C	• Near-homogeneous population • Near-homogeneous site experience	• Shorter time period for Learn before final database lock • Randomly select patients

Table 2: The MCCB tests and domains contributing to the composite score

MCCB test	Domain
Category fluency, animal naming	Speed of processing
Brief assessment of cognition in schizophrenia, symbol coding	Speed of processing
Trail making, Part A	Speed of processing
Continuous performance test (identical pairs version)	Attention/vigilance
WAIS-III, letter number span	Working memory
WMS-III spatial span	Working memory
Hopkins verbal learning test-revised	Verbal learning
Brief visuospatial memory test-revised	Visual learning
Neuropsychological assessment battery mazes	Reasoning and problem solving
Mayer-Salovey-Caruso emotional intelligence test, managing emotions	Social cognition

WAIS-III Wechsler Adult Intelligence Scale, 3rd edition; WMS-III, Wechsler Memory Scale 3rd edition.

RESULTS

Stage 1

- At the end of Stage 1 the blinding of all doses was maintained. However, in each of the active treatment arms, no CANTAB endpoints were identified that differentiated between BI 409306 and placebo with an effect size of 0.5 or greater
- In the absence of pre-specified CANTAB domains for the primary endpoint, an alternative approach was to use a composite score. Change from baseline in the composite score of MCCB after 12 weeks of treatment was therefore specified as the primary endpoint for Stage 2

CONCLUSIONS

- The novel and adaptive 'Learn and Confirm' study design allows for the identification of meaningful endpoint(s) in Stage 1 of a trial, which can then be pre-specified as the primary endpoint(s) for a confirmatory analysis in Stage 2
- However, there were no appropriate CANTAB domains that could be pre-specified as the primary endpoint in the present study, and therefore the composite score of MCCB was selected as the primary endpoint for Stage 2
- When the most relevant measure for an expected drug effect cannot be pre-specified from a range of relevant tests at the start of a study (as was the case with the multitude of cognitive domains and tests in the present study), the 'Learn and Confirm' approach provides a methodologically rigorous alternative

DISCLOSURES

The authors met the criteria for authorship as recommended by the International Committee of Medical Journal Editors. Four of the authors (JM, LW, MS and SP) are employees of Boehringer Ingelheim, but received no direct compensation related to the development of this poster. DB has no disclosure details to declare. The sponsor was given the opportunity to review the poster for medical and scientific accuracy as well as intellectual property considerations.

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REFERENCES

1. Sarkar S et al. *World J Psychiatr* 2015; 5: 352–361
2. Levaux MN et al. *Eur Psychiatry* 2007; 22: 104–115
3. Nuechterlein KH et al. *Am J Psychiatry* 2008; 165: 203–213

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