



# **SEQUEL (COG0202)**

## **Topline Results**

*A Pilot Electroencephalography (EEG) Study to Evaluate the Effect of CT1812 Treatment on Synaptic Activity in Subjects with Mild to Moderate Alzheimer's Disease*

# Forward-looking Statements

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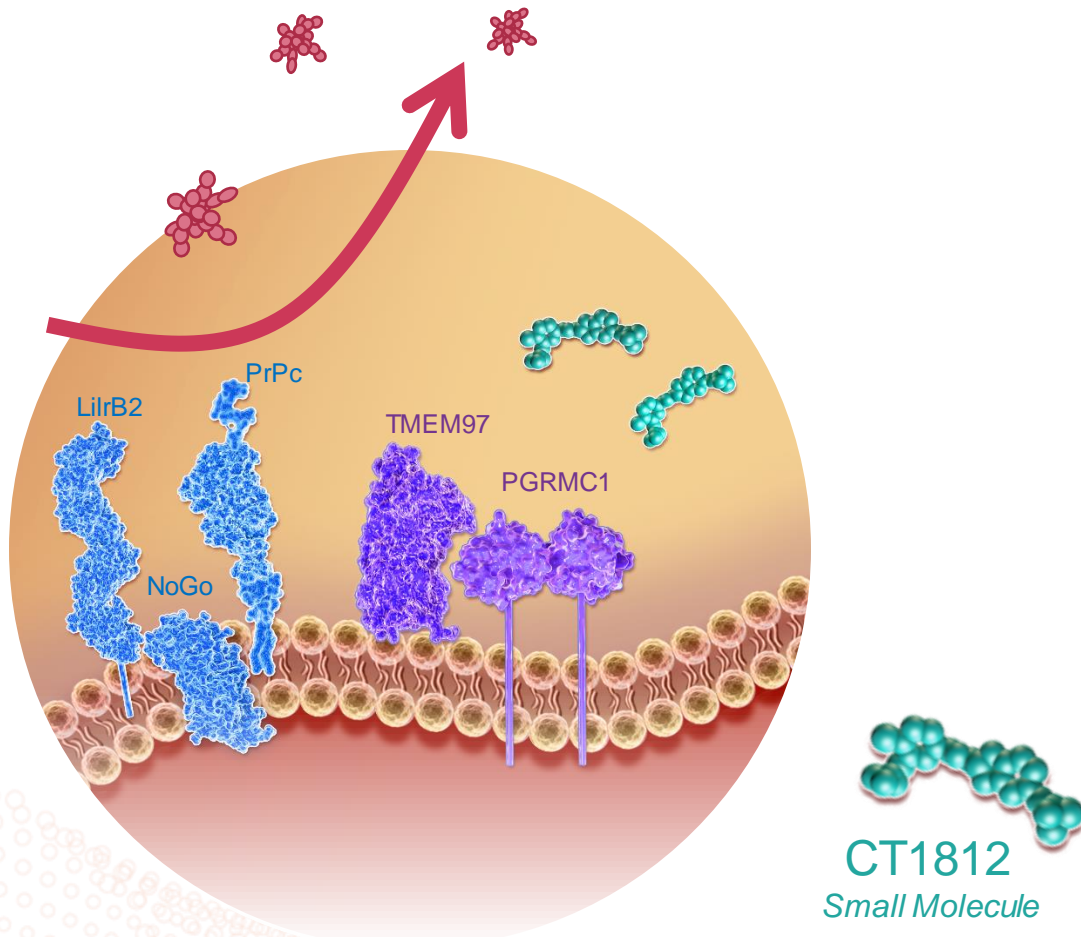
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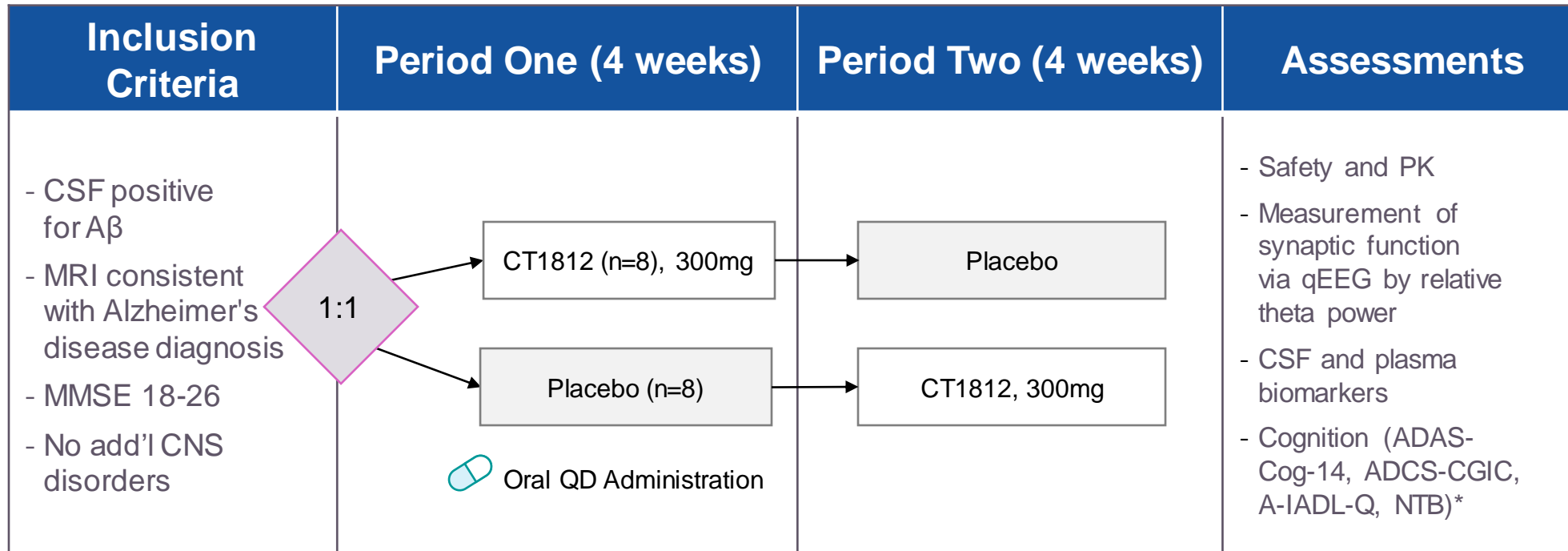
# SEQUEL Hypothesis



- Aβ oligomers impair synaptic and neuronal activity
- Will displacement of Aβ oligomers from synapses after treatment with CT1812 lead to a detectable change in EEG patterns?

# SEQUEL (COG0202): Single-site qEEG Study in 16 Adults with Mild-to-moderate Alzheimer's Disease

*Two-group cross-over design*



<https://clinicaltrials.gov/ct2/show/NCT04735536>

# Study Design

**Design:** Two-group cross-over study in 16 adults with mild-to-moderate AD

**Single site:** VUmc Alzheimer's Center, Amsterdam

## **Primary objectives:**

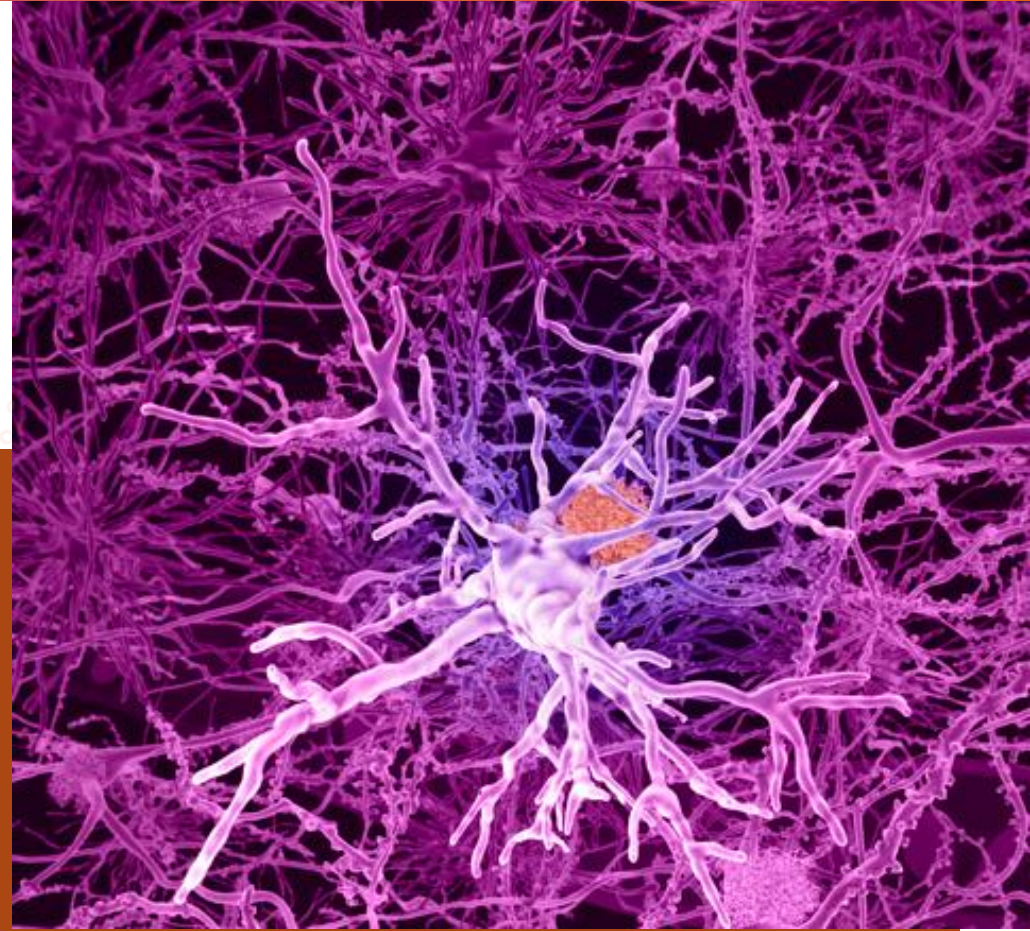
- Assess safety, tolerability, PK of CT1812 following repeated dosing for 28 days
- Evaluate efficacy of CT1812 in restoring synaptic function through quantitative EEG as measured by:
  - Global relative theta power (primary endpoint)
  - Global alpha AECC, global relative alpha power, global relative beta power – key pre-specified exploratory endpoints
  - Additional pre-specified EEG exploratory endpoints

## **Exploratory objectives:**

- Cognitive measures: impact of CT1812 on cognitive and global functioning, as measured by the following:
  - ADAS-Cog-14, ADCS-CGIC, A-IADL-Q
  - Neuropsychological test battery (NTB), Controlled Word Association Test (COWAT), Trail Making Test (TMT) Parts A & B, and Wechsler Memory Digit Span (VMDS)
  - Exploratory – biomarkers – pending

# Topline Data Overview

- Disposition and demographics
- Safety and tolerability
- Topline EEG findings



# COG0202 Disposition and Demographics

## Disposition

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- 34 subjects screened; 16 randomized
- 15 completed the study
  - No subjects discontinued due to AEs
  - One patient discontinued after treatment period 1 due to withdrawal of consent (death in the family)
- n=14 for placebo period (one participant missed visit 7); n=16 for CT1812 period

## Demographics

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- Mean Age: 66.4 years
- 50% Female
- 100% White, non-Hispanic
- Baseline cognitive measures:
  - Mean MMSE: 21.1
  - ADAS-Cog14: 30.2
  - Amsterdam IADL: 52.6
- ApoE genotypes:
  - 31.3% ApoE e3/e3
  - 37.5% ApoE e3/e4
  - 31.3% ApoE e4/e4
- Time since diagnosis: 1.14 years

# COG0202 SEQUEL: Safety and Tolerability

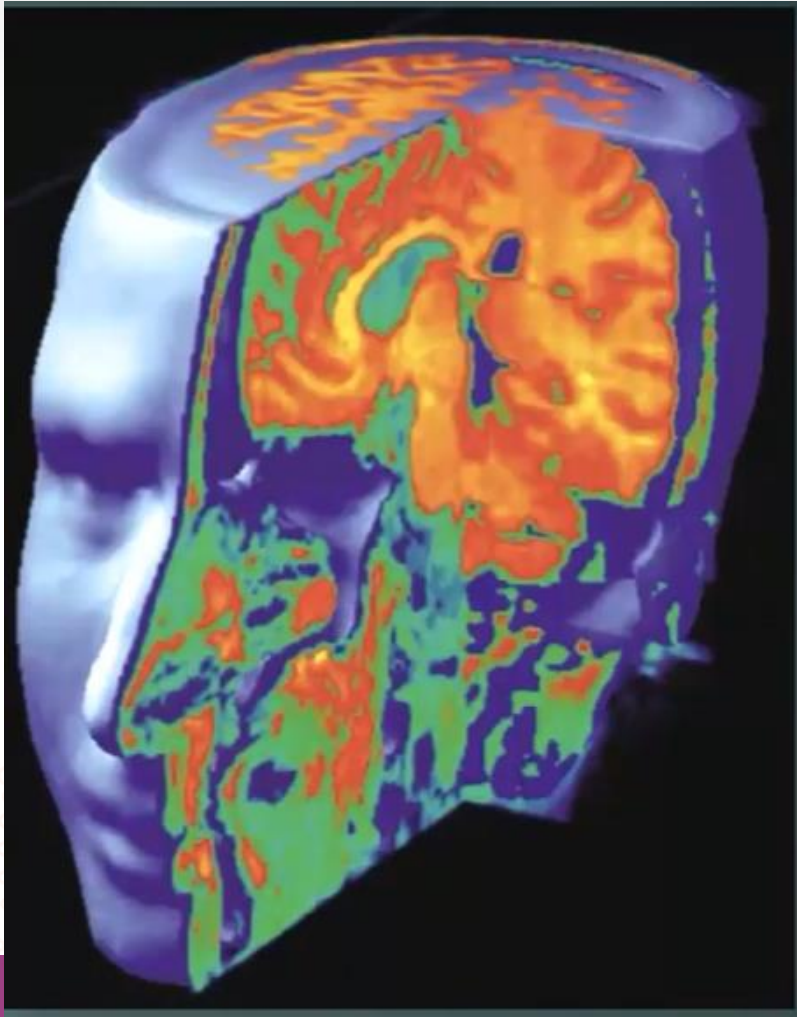
*Safety and tolerability profile consistent with previous studies*

- CT1812 was well-tolerated
  - All AEs were mild and moderate
  - No Severe AEs, No SAEs, No AEs leading to death or discontinuation
- TEAEs:
  - Occurred in 11 participants in the CT1812 period and 6 participants in the placebo period
  - 6 TEAEs were categorized as related to study drug (3 in CT1812 period and 3 in placebo period)
- Most common AEs by MedDRA system organ class:
  - GI: nausea, diarrhea
  - Injury & procedural complications: procedural headache
- Consistent with previous studies – 1 participant with mild (2X ULN) elevated liver enzymes



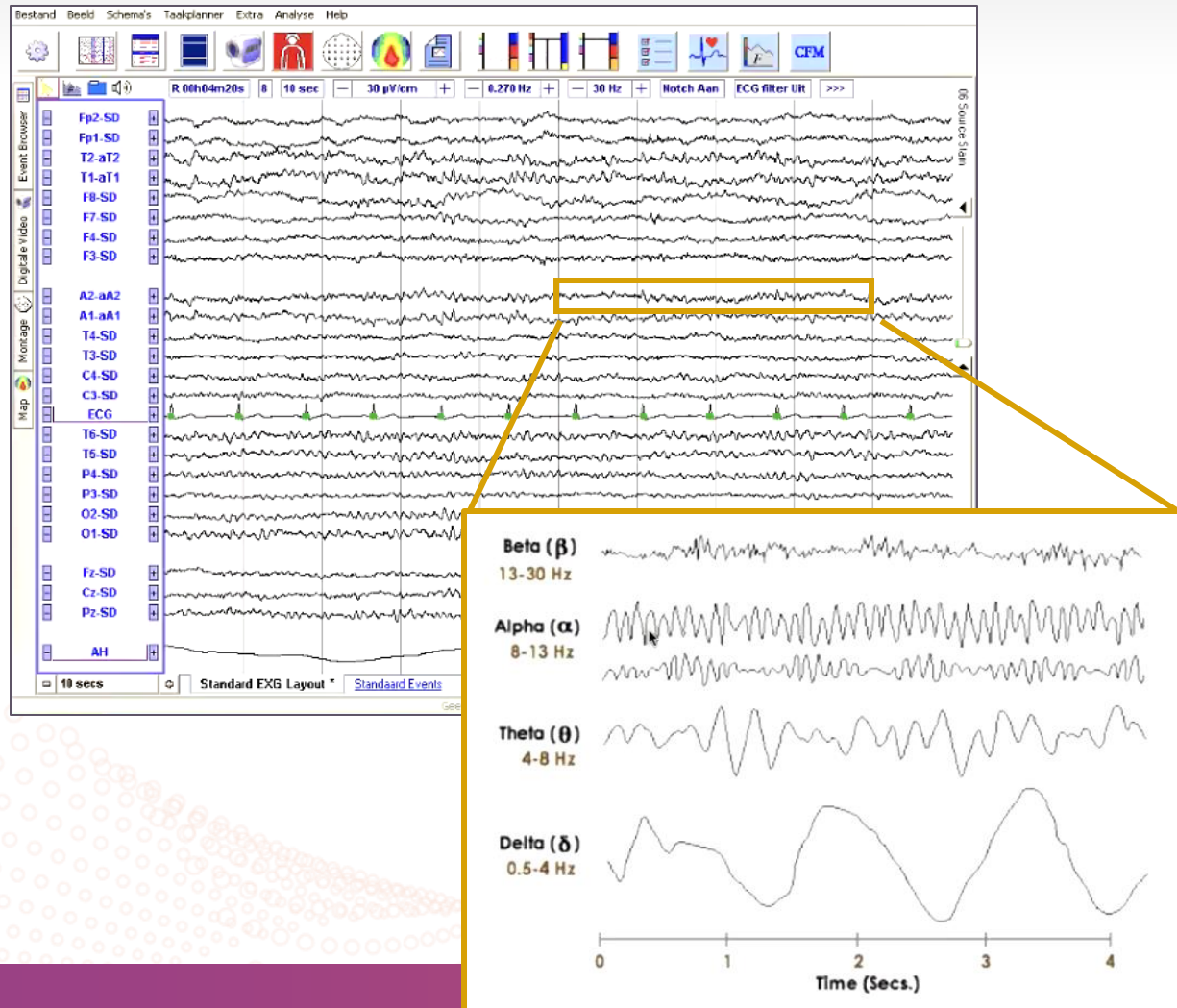
# Biomarkers of Disease

## *Introducing quantitative EEG*



- Amyloid burden can be measured by PET
- Canonical biomarkers assessed via serum and blood
- Anatomic changes can be measured by vMRI
- Cognition and executive function can be measured with ADAS-Cog and other scales
- Neurophysiology / quantitative EEG:
  - Global and regional brain activity
  - Regional connectivity

# Brain Waves – a Brief Primer



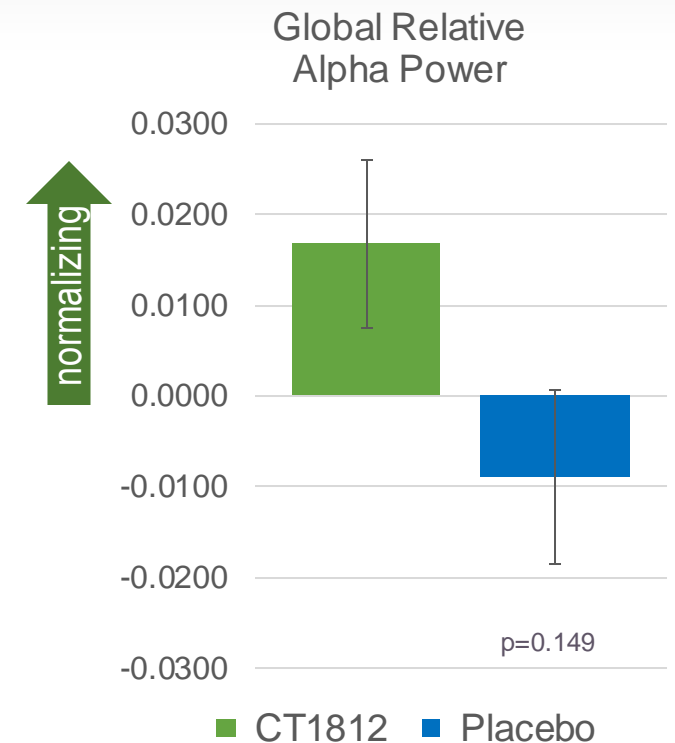
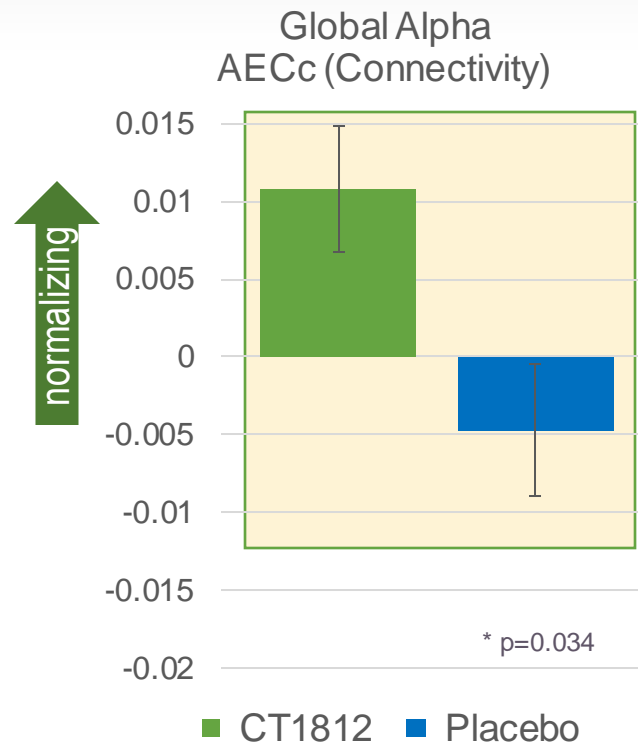
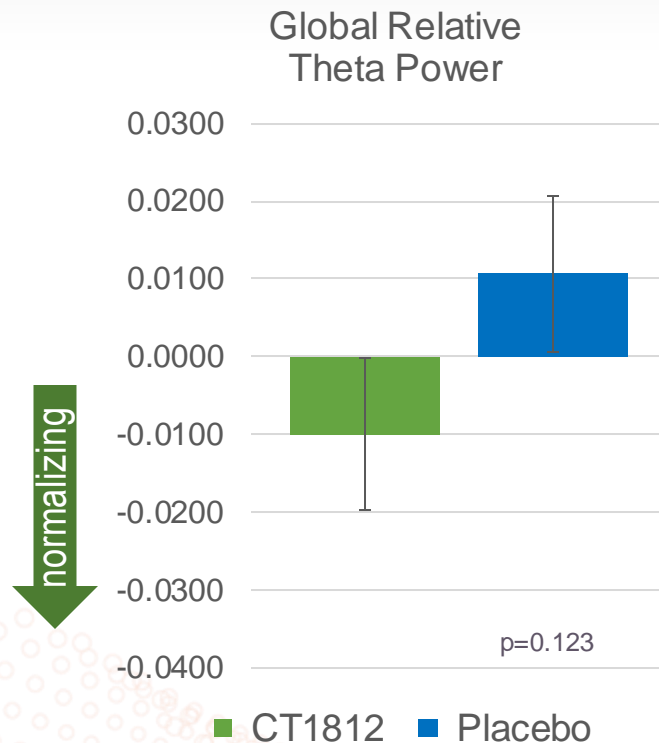
- An EEG reading compares electrical activity between electrodes on the scalp
- Fast waves in the alpha and beta frequencies dominate healthy EEG patterns
- Alzheimer's disease is associated with slower waves – a theta or delta pattern
- The dominance of one wave pattern over another is referred to as "relative power"

# SEQUEL: Topline EEG Data

- ✓ Assess safety, tolerability, PK of CT1812 following repeated dosing for 28 days
  - Evaluate efficacy of CT1812 in restoring synaptic function through quantitative EEG as measured in rank order:
    - Global relative theta power (primary endpoint)
    - Global alpha AECC, global relative alpha power, global relative beta power – key pre-specified exploratory endpoints
    - Additional pre-specified EEG exploratory endpoints

# SEQUEL Topline Results

Positive trends in first three ranked outcomes measures

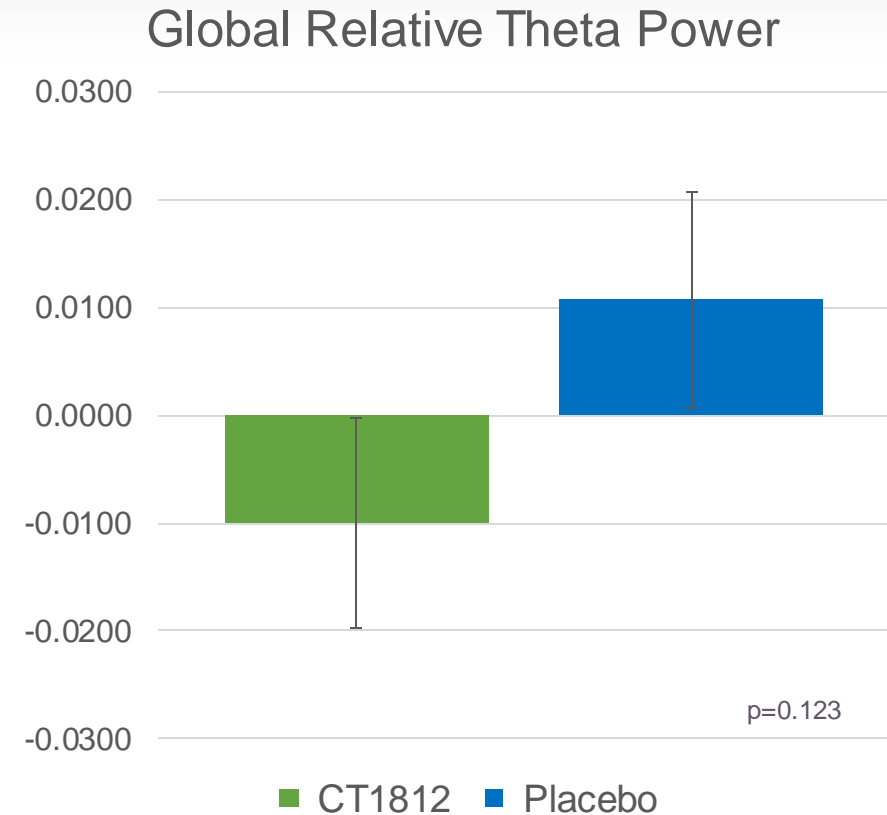


\* Nominally significant

# SEQUEL Topline Results

*Positive trends in brain activity - reduced global & regional theta power - following 4 wks of treatment*

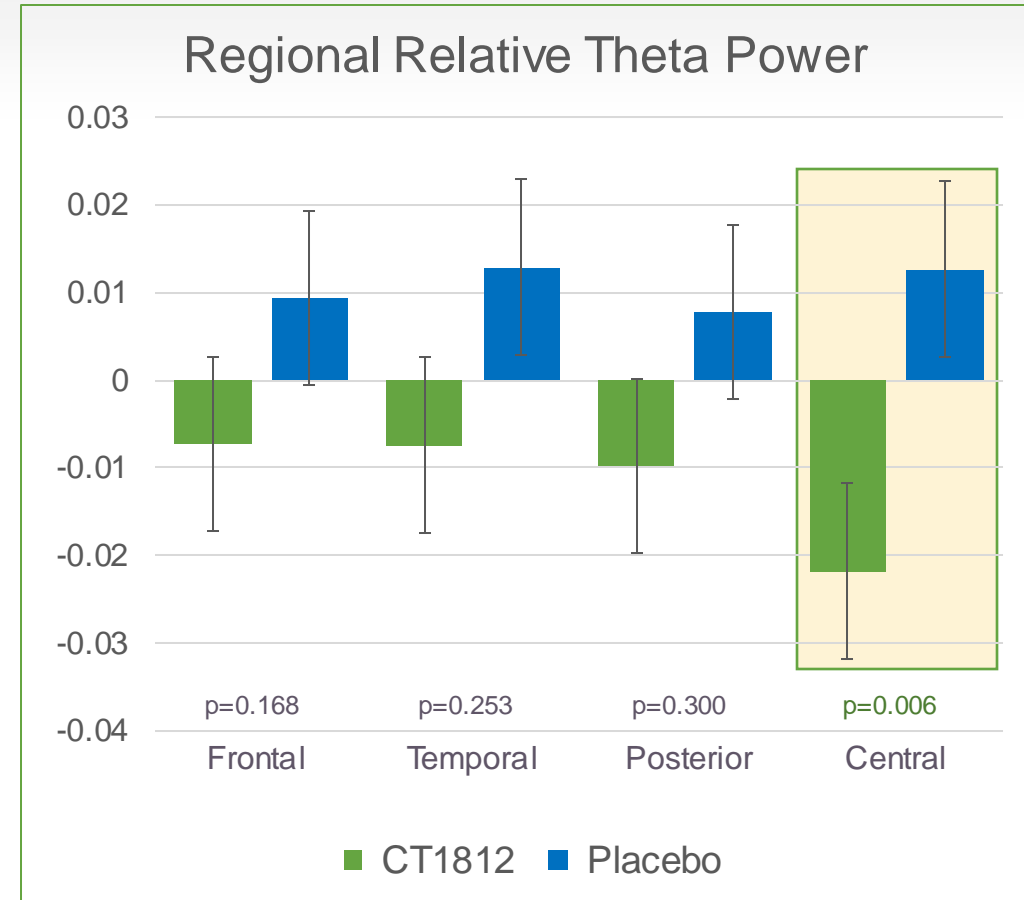
- CT1812 treatment was associated with a reduction in global relative theta power



# SEQUEL Topline Results

*Positive trends in brain activity - reduced regional theta power - following 4 wks of treatment*

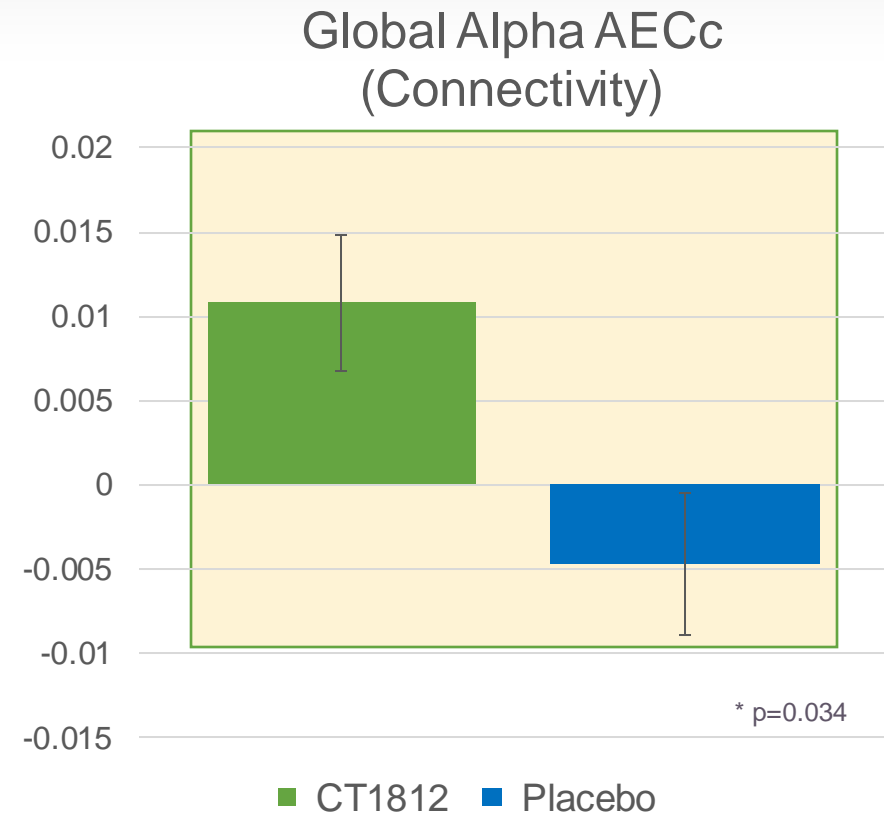
- Decreases in relative theta power were also observed in specific brain regions: frontal, temporal, posterior (parietal and occipital), and central
  - Statistical significance was only achieved in the central region ( $p < 0.006$ )



# SEQUEL Topline Results

*Positive trends in brain activity - increased connectivity - observed following 4 wks of treatment*

- In addition, an analysis of the qEEG results showed that CT1812 treatment was associated with greater connectivity between brain regions
  - This suggests that the brain's ability to communicate and exchange information between regions can be rescued by CT1812

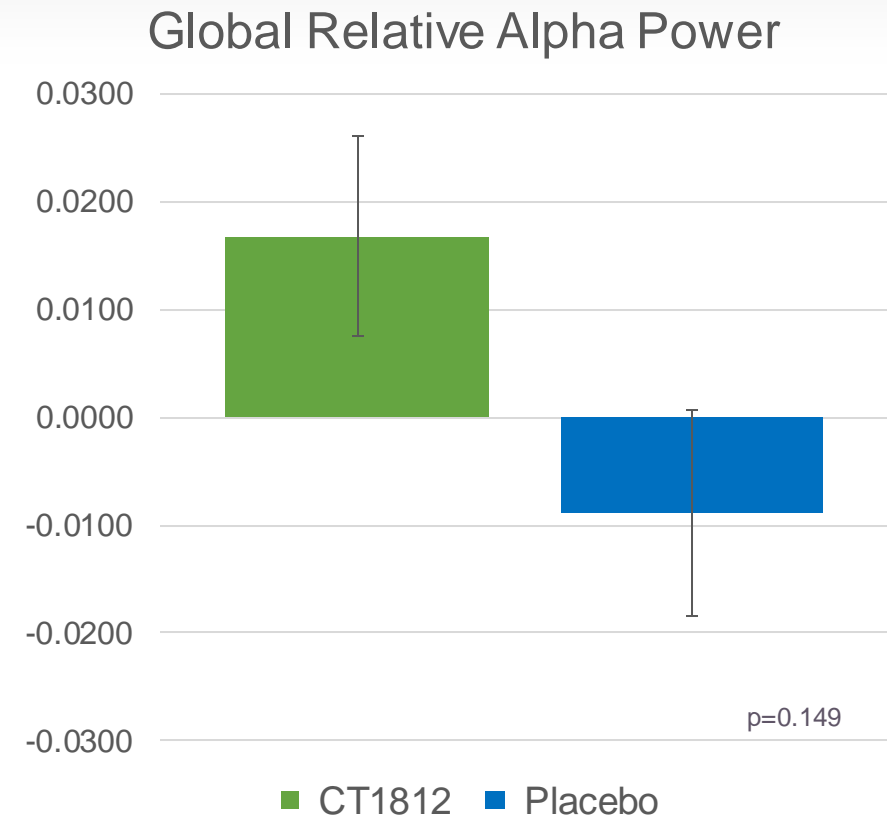


\* Nominally significant

# SEQUEL Topline Results

*Positive trends in brain activity - increased alpha power - observed following 4 wks of treatment*

- Increases in relative power in the alpha band were observed globally
  - Fast alpha waves are considered to be part of the normal background rhythm of a healthy brain
  - In Alzheimer's, alpha waves lose their dominance and are gradually replaced by slower-oscillating, lower-amplitude theta and delta waves





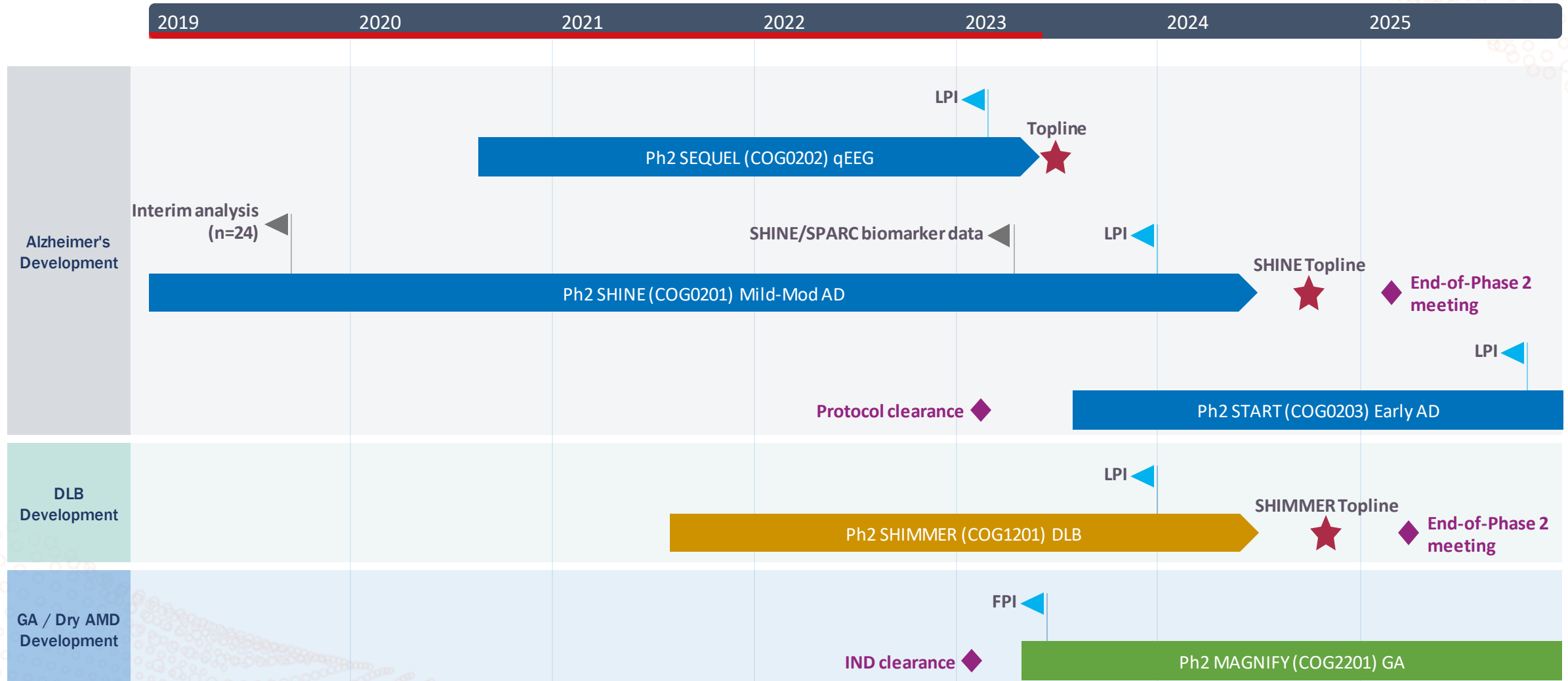
# Conclusions

- CT1812 was well tolerated in this 28-day study
  - All AEs were mild to moderate
  - There were no serious or severe AEs
  - No AEs led to study discontinuation or death
- Strong trends on pre-specified qEEG measures
  - Consistent trend across all qEEG measures
  - Nominally significant treatment differences including global alpha AECc and central relative theta power
- In conclusion, CT1812 has demonstrated an impact on brain activity in mild-to-moderate Alzheimer's patients

# Evidence of CT1812 Impact on Alzheimer's Disease

- Studies to date provide evidence of:
  - Target engagement (SNAP)
  - Anatomical effect (SPARC)
  - Preliminary cognitive improvement (SHINE cohort A)
  - Neurophysiology (SEQUEL)
- Supportive biomarker evidence of biological effect
- Fully funded proof-of-concept studies ongoing:
  - Early Alzheimer's disease
  - Mild-to-moderate Alzheimer's disease
  - Dementia with Lewy bodies

# Multiple Near-term Catalysts Expected





# Thank You

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