Efgartigimod for the Treatment of Long-COVID Postural Orthostatic Tachycardia Syndrome (POTS): A Phase 2 Study

Tae Chung, MD
Neuromuscular Medicine
Associate Professor
Director, Johns Hopkins POTS Program
Johns Hopkins School of Medicine

Background

- This was a randomized, double-blind, placebo-controlled, 36-week, phase 2 study on post-COVID-onset POTS.

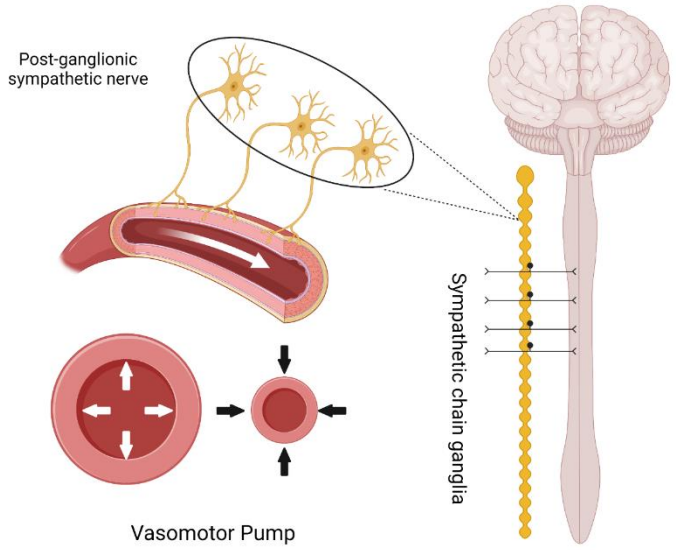
- The first FDA-regulated trial on POTS
- Started in September 2022

- Open-label extension (OLE) study started in June 2023

- Completed in April 2024, OLE was terminated in the middle.

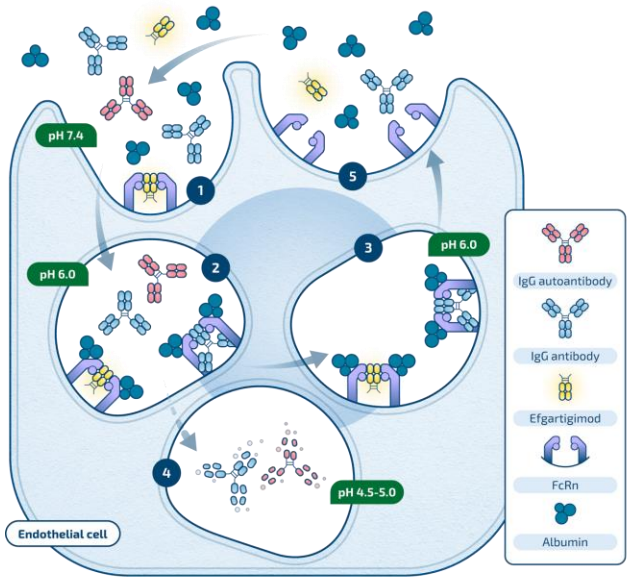
Rationale

- Evidence of autonomic and small fiber denervation in POTS
- Post-COVID-onset POTS is likely immune-mediated.
- Immune-modulation may provide disease-modifying benefits.
- Anecdotal evidence of IVIG or subcutaneous IVIG on post-COVID POTS



Efgartigimod – FcRn receptor antagonist

- Selectively lowers serum IgG level by facilitating lysosomal degradation
- Intact IgA and IgM levels
- Likely works similarly to IVIG
- Many functional autoantibodies are IgG-based



Study Design

- A randomized, double-blind, placebo-controlled, parallel-group, 36-week, phase 2 study, conducted at 11 sites in the United States
- Randomized 2:1 to receive efgartigimod or matching placebo
- Efgartigimod (10 mg/kg) or placebo were administered by IV infusion once weekly for 24 weeks
- 4-week screening period, a 24-week treatment period, and an 8-week follow-up period

Eligibility

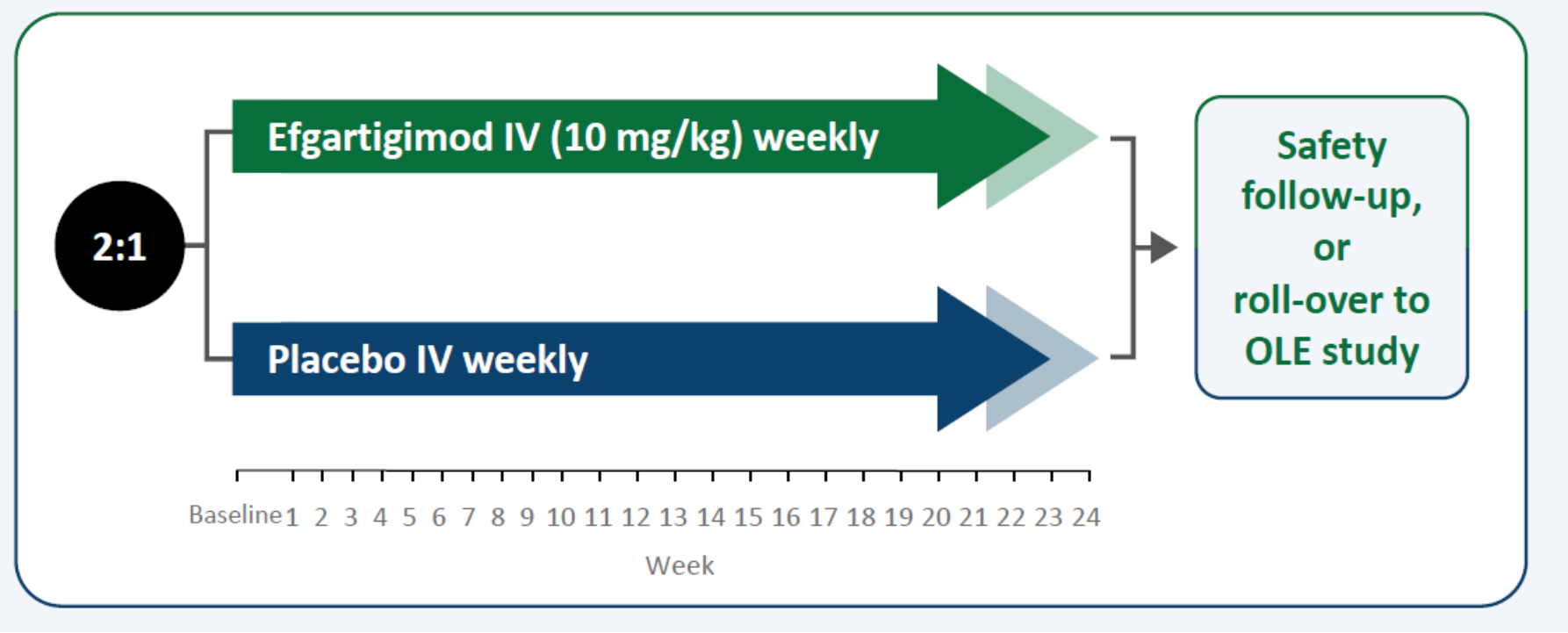
Inclusion

- A history of COVID-19 confirmed by PCR or documentation
- Evidence of POTS with tilt table or active standing test
- Ongoing symptoms of POTS lasting >12 weeks after either diagnosis of COVID-19
- COMPASS-31 score ≥35

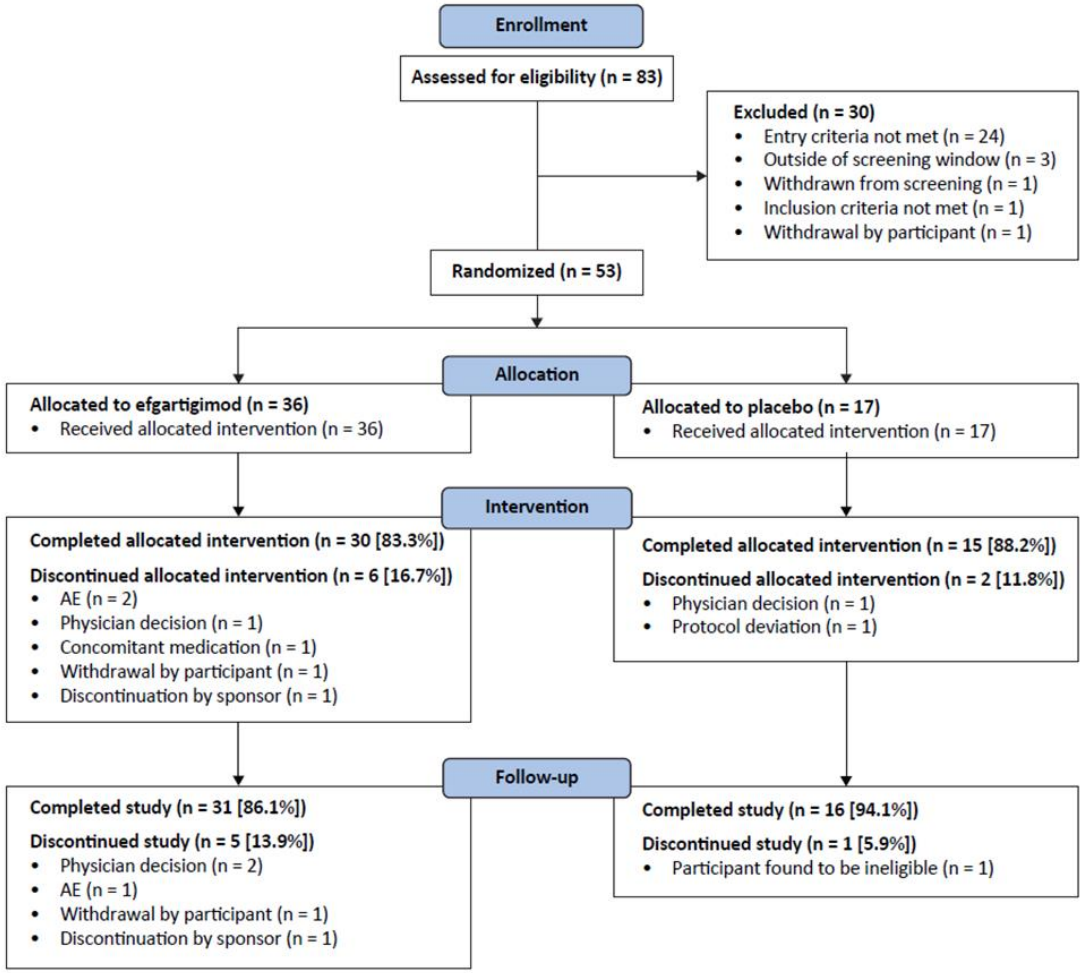
Exclusion

- Any known autoimmune disease or confounding medical conditions
- A history of malignancy, or hypersensitivity to treatment
- A diagnosis or treatment received pre–COVID-19 for peripheral neuropathy, POTS, ME/CFS, Ehlers Danlos syndrome, uncontrolled active or chronic infections or diseases

Study Overview



Results

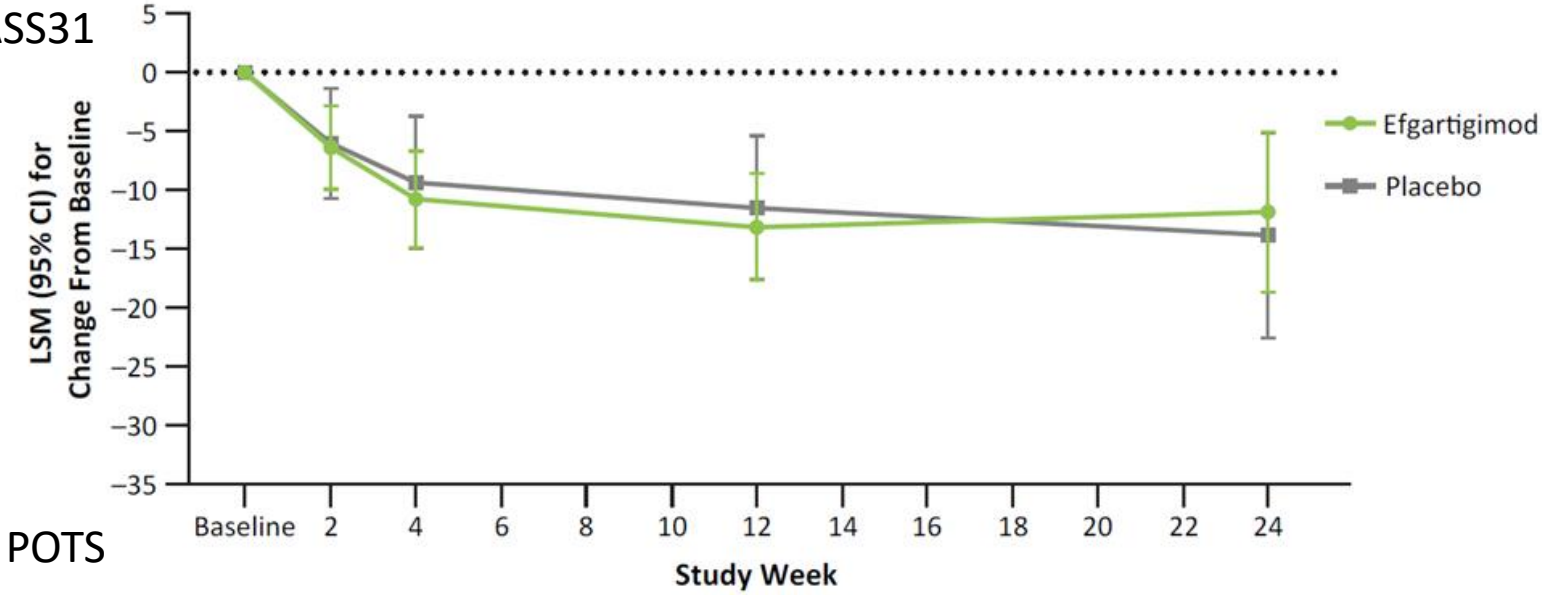

Enrollment
Assessed for eligibility (n = 83)
Excluded (n = 30)
• Entry criteria not met (n = 24)
• Outside of screening window (n = 3)
• Withdrawn from screening (n = 1)
• Inclusion criteria not met (n = 1)
• Withdrawal by participant (n = 1)
Randomized (n = 53)
Allocation
Allocated to efgartigimod (n = 36)
• Received allocated intervention (n = 36)
Allocated to placebo (n = 17)
• Received allocated intervention (n = 17)
Intervention
Completed allocated intervention (n = 30 [83.3%])
Discontinued allocated intervention (n = 6 [16.7%])
• AE (n = 2)
• Physician decision (n = 1)
• Concomitant medication (n = 1)
• Withdrawal by participant (n = 1)
• Discontinuation by sponsor (n = 1)
Completed allocated intervention (n = 15 [88.2%])
Discontinued allocated intervention (n = 2 [11.8%])
• Physician decision (n = 1)
• Protocol deviation (n = 1)
Follow-up
Completed study (n = 31 [86.1%])
Discontinued study (n = 5 [13.9%])
• Physician decision (n = 2)
• AE (n = 1)
• Withdrawal by participant (n = 1)
• Discontinuation by sponsor (n = 1)
Completed study (n = 16 [94.1%])
Discontinued study (n = 1 [5.9%])
• Participant found to be ineligible (n = 1)

Results – Primary Outcomes

- The reductions from baseline to week 24 in the mean COMPASS-31 and MaPS were similar in the efgartigimod and placebo.

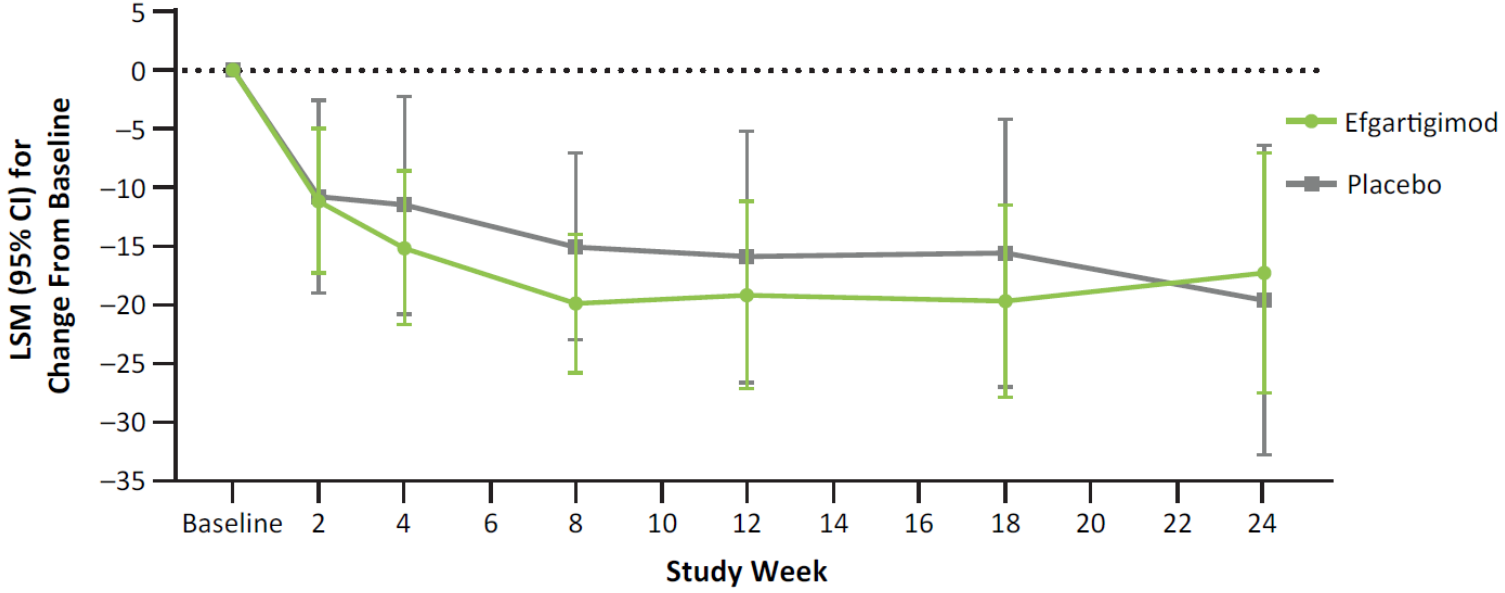
- Both groups showed significant improvements in the symptoms.

COMPASS31



Malmo POTS

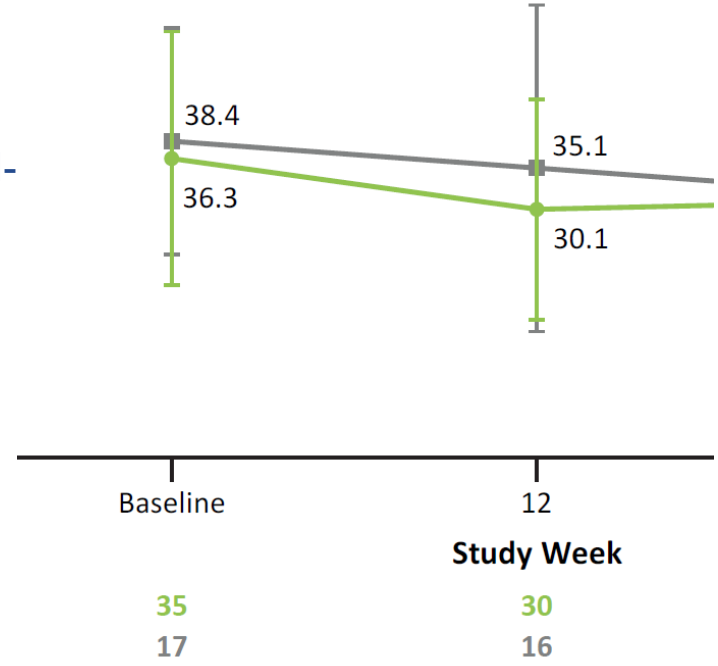
Efgartigimod (n)	30	27	28		27		22
Placebo (n)	17	16	14		15		15



Efgartigimod (n)	30	27	28		26		26		26			22
Placebo (n)	17	16	13		15		15		13			15

Results – Secondary Outcomes

- Changes in HR on tilt table test were larger in the baseline, but no difference between efgartigimod and placebo.
- Other secondary outcomes showed similar results – PGI-C, PROMIS fatigue scale, and 6MWT.
- No changes in inflammatory biomarkers
- Reduction in vWF and VCAM was larger in efgartigimod than placebo



Results – Secondary Outcomes

- No changes in inflammatory biomarkers
- Reduction in vWF and VCAM was larger in efgartigimod than placebo.
- The total IgG mean baseline levels were similar between the two groups but reduced in the efgartigimod arm by week 4 (68.1%) and was maintained until week 24.
- The mean IgG levels in the placebo arm remained stable over time

Safety

- Similar proportions of participants in the efgartigimod and placebo arms experienced adverse events.
- Proportionally fewer participants in the efgartigimod arm than the placebo arm experienced treatment-related AEs, events leading to treatment interruption.
- No SAEs or fatal TEAEs were reported during the study.
- Common AE includes fatigue, headache, nausea, oropharyngeal pain, and UTIs.

Conclusion

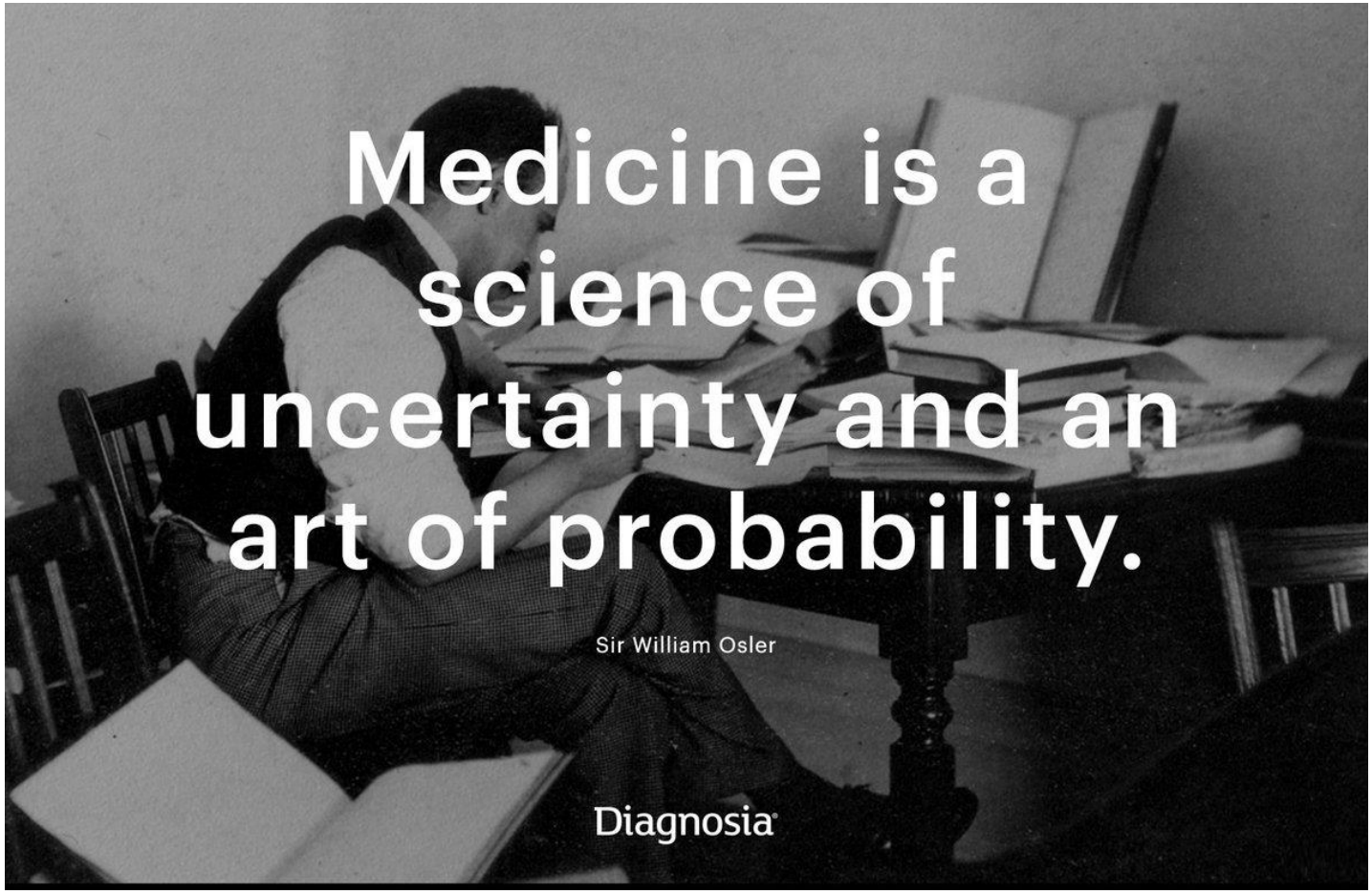
- Both efgartigimod and placebo treatment arms improved over 24 weeks in symptom scores, HR changes on head-up tilt test, 6MWT and patient-reported outcomes, suggesting partial natural recovery or nonspecific treatment effects.

- No safety signals were observed.

Take-home Messages

- Huge placebo effects in this population
- Need for better biomarkers
- Need for better outcome measures specific for POTS
- Longer trial?
- Others?

Questions?


Medicine is a science of uncertainty and an art of probability.
Sir William Osler
Diagnosia