Title of Project: The efficacy of efgartigimod PH20 SC (VYVGART Hytrulo) in patients with Stiff Person Syndrome (SPS): A double-blind, placebo-controlled, cross-over trial

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Abstract

SPS is a rare autoimmune disorder, characterized by: a) incapacitating diffuse muscle stiffness prominent in the axial, abdominal and thoracolumbar paraspinal muscles leading to hyperlordosis, difficulty turning and bending; b) painful muscle spasms precipitated by external stimuli with difficulty performing routine daily activities; and c) slow freezing gait with frequent falls and need for walking aids leading to disability. SPS is due to impaired inhibitory GABAergic neurotransmission associated with high-titer IgG antibodies against Glutamic Acid Decarboxylase (GAD), the rate-limiting enzyme for the synthesis of the inhibitory gamma-aminobutyric acid (GABA). Although SPS patients respond to IVIg based on the PI's controlled study (NEJM 2001), several patients do not improve, or their response is modest and declines over time, as documented in a longitudinal study of 36 patients followed in our Jefferson clinic; because another controlled study we performed with Rituximab was negative and SPS is a progressive disease, new therapies are needed. *Efgartigimod* is an FcRn inhibitor that enhances the catabolism of circulating IgG; its subcutaneous, self-administered form, *HYTRULO,* has been effective and FDA-approved in patients with myasthenia gravis or CIDP poorly responding to IVIg. There is evidence that patients with myasthenia who also had SPS, Hytrulo not only helped their myasthenia but the SPS also impressively improved.

The present study is an investigator- initiated, double-blind, placebo controlled, cross-over, trial in 26 GAD-positive SPS patients poorly responding to available therapies. Patients will be recruited from the large number of patients seen and referred to the PI who is known for his work in SPS and has conducted the 2 previous controlled trials. Although Hytrulo is approved as self-administered subcutaneous drug with pre-refilled syringes, in this study will be given by a contracted home infusion company once a week to ensure convenience, safety and validity. Patients will be randomized by the Jefferson Pharmacy to receiving Hytrulo or identical hyaluronidase-containing placebo for 3 months; then they will be crossed-over to placebo/Hytrulo for another 3 months. Efficacy will be based on one primary endpoint, the stiffness index, previously validated by the PI, and on two also validated secondary endpoints of time to walk and excitability index. This design provides the statistical power to objectively assess a 25-50% or greater change and objectively determine if Hytrulo offers meaningful benefits in reducing stiffness and spasms, improving gait and increasing quality of life in SPS patients poorly responding to current therapies.

A. Specific aims

Investigate in a 6-month, placebo-controlled cross-over study, the efficacy of Hytrulo (a subcutaneous FcRn inhibitor) in patients with **Stiff-Person Syndrome (SPS)** poorly or insufficiently responding to current immunotherapies.

B. Background and Significance

SPS is a rare autoimmune disorder, characterized by a) incapacitating diffuse muscle stiffness prominent in the axial, abdominal and thoracolumbar paraspinal muscles leading to hyperlordosis, difficulty turning and bending; b) painful muscle spasms precipitated by external stimuli with difficulty performing routine daily activities; and c) slow freezing gait with frequent falls and the need for walking aids leading to disability (1-4). SPS is due to impaired inhibitory GABAergic neurotransmission associated with high-titer IgG antibodies against Glutamic Acid Decarboxylase (GAD), the rate-limiting enzyme for the synthesis of the inhibitory gamma-aminobutyric acid (GABA) (1-4). Although SPS patients respond to intravenous immunoglobulin based on a controlled study we performed in 2001 and published in NEJM (Dalakas et al) (5), several patients do not improve, or their response is modest and declines over time based on a longitudinal study in 36 patients we followed in our Jefferson Neurology Clinic (Yi and Dalakas) (6); additionally, Rituximab is partially helpful in only 35% of patients based on another controlled study we have conducted [Dalakas et al (7)]. Collectively, SPS remains a steadily progressive disease (8). Because based on our studies, the GAD-specific IgG from SPS patients inhibits GAD activity or GABA synthesis and decreases GABA release from presynaptic nerve terminals (1, 2,9), targeting the IgG antibodies is a reasonable therapy for SPS patients poorly responding to IVIg to prevent permanent disability (10).

Efgartigimod (VYVGART), is an FcRn inhibitor that enhances the catabolism of circulating IgG; it has been effective and FDA- approved for myasthenia gravis by reducing the circulating AChR -antibodies (11); its subcutaneous self-administered *HYTRULO* has been also impressively effective and FDA-approved not only for myasthenia gravis but also for the autoimmune neuropathy, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), in patients poorly responding to IVIg (12). On this basis, the efficacy of Hytrulo is now being explored in several antibody-mediated autoimmune neurological disorders like inflammatory myopathies, Neuromyelitis and others.

C. Preliminary studies/Progress Report

Efgartigimod, given to 3 patients with Myasthenia Gravis who also had SPS, showed impressive improvement not only in their myasthenia but also in SPS with excellent safety profile and tolerance (13). These results prompted the present study to explore the efficacy of Hytrulo in SPS patients poorly responding to IVIg.

The PI is an internationally recognized expert in SPS with pioneering research that started first while Chief of Neuromuscular Diseases Section at the NIH and then at Jefferson Neurology. His

work-published in more than 50 original papers and reviews- has among others: a) established the diagnostic criteria of SPS (called the Dalakas criteria) (2,3); b) explored the effect of GAD antibodies in inhibiting GABAergic inhibitory pathways, highlighting the significance of high-GAD antibody- titers in diagnosis and pathogenesis (9); c) established disease biomarkers and validated scales to assess disease severity and progression based on "stiffness index" and "heightened sensitivity" (2,3,8); and, d) most importantly, performed two placebo-controlled clinical trials, and the only ones in SPS, one with IVIg (5) and the other with rituximab (7), on which the present therapeutic schemes are based (10). The present protocol is his third placebo-controlled trial in SPS and will be performed based on the large number of patients seen in Jefferson Neurology from around the country.

D. Research Design and Methods:

1. Patient selection, and criteria for inclusion

26 symptomatic patients (based on inclusion/exclusion criteria highlighted on section G) poorly or partially responding to IVIg but with declining benefits, and significant symptomatology of stiffness, painful muscle spasms, and impaired walking ability will be selected. All will have typical SPS, as per Dalakas's diagnostic criteria (1-3), and will be GAD or Glycin-receptor-antibody positive. Enrolled patients will continue receiving the non-immunosuppressive symptomatic drugs, such as diazepam, gabapentin, or baclofen at stable doses throughout the study. If still on IVIg, despite no benefit, they should be willing to stop it one month prior to enrollment. Baseline data using validated scales of stiffness index, Rankin scale, and timed 25-foot walk (T25-FW) will be obtained prior to randomization; routine blood work and IgG levels should be normal.

2. *Randomization and treatment plan.* Patients will be blindly randomized to two groups (A,B)

-Group A: These patients will receive 1000 mg efgartigimod PH20 SC **(VYVGART Hytrulo),** every week for 12 weeks (as per Hytrulo's therapeutic guidelines)

-Group B: Subcutaneous **Hytrulo-placebo (consisting of Hyaluronidase**), in identical syringes (as used in other Hytrulo trials) (12), every week for 12 weeks.

-Cross-over Phase: After the first 12-weeks, all patients, will be blindly crossed-over to the other arm **(Group A to placebo and Group B to Hytrulo)** for 12 more weeks**.** This cross-over design is an important incentive because all patients will receive the real drug during the study period and will allow objective assessment of efficacy response. There is no need for wash-out based on the same design used for the approved CIDP trial (12).

4. *Blinding Preparation, infusion schedules and study visits.* Hytrulo and Hytrulo-placebo will be provided in ready syringes by ARGENX (the company that has marketed the drug) to Thomas Jefferson University central Pharmacy who will arrange the blindly randomized vials and deliver them for each patient to the home-infusion company INFUCARE which has been contracted specifically for the study and their experienced nursing staff will perform each weekly injection

at the patients' home. Injection schedules will be coordinated for detailed record keeping with the research nurse recruited for the study, the PI or Associate PI's and the research coordinators to ensure accurate and safe weekly administrations. Every patient will be seen in the Outpatient Clinic by the PI or one of the AP's every month for the total of 9-month duration of study to assess clinical efficacy and safety as follows:
*a) visit #1***:** screening visit and enrollment;
b) visits #2,3,4, every month, for 3 consecutive months (12 weeks), while on *Hytrulo/Placebo*;
c) visits # 5,6,7, after cross-over, every month for 3 consecutive months (12 weeks), while on *Placebo/Hytrulo***;** and
d) visit # 8,9 every month for 2 more months at the end of the study, to assess long-lasting effects**.**

5. *Assessment of response at monthly clinic visits**:*** Efficacy endpoints will be based on:
a) change in *the stiffness index,* which is the primary endpoint, and has been validated in SPS and used in two previous Dalakas's controlled trials (5,7)]; and
b) two *secondary end-points*, the T25-FW (time to walk 25 feet) and Modified Rankin Scale.
Assessments will be based on the monthly Clinic exams from baseline to Week 12 (monthly visits #1-4,) and after the cross-over from Week 12 to 24 (visits# 5-7).
Other exploratory endpoints, concurrently assessed, will be changes in the heightened sensitivity scales and SF-36, as used in our previous controlled trials (5,7). Changes in mobility will be also explored using the wearable device, *Syde®,* for the lower-limb/ambulatory patterns that assess stride velocity, walking perimeter, stair-climbing velocity and number of falls.

6. Tolerability and Rescue therapy. Safety and tolerance of Hytrulo are known from other studies (as stated below), hence the reason the drug is self-administered; for convenience, extra safety and objectivity however, we have chosen trained nurses to give the injections at the patients' home. If rescue therapy is needed because of worsening stiffness, it will be handled by increasing the anti-spasmodic medications (Diazepam, Gabapentin or Baclofen); if severe worsening in mobility occurs that substantially impacts daily activities, their previous IVIg, 2 gram/kg will be resumed. Such worsening is however highly unlikely based on the selected patients because SPS does not severely worsen in such a short study period; severe episodic spasms can occur but they respond to anti-spasmodics.

7. Laboratory Studies. CMP, routine chemistry, hepatic and autoantibody panel, total immunoglobulins (IgG, IgA, IgM) will be obtained. In women of child-bearing age, pregnancy test will be done. For research studies on GAD-antibodies and related autoimmune factors that require specialized assays, serum will be collected at enrollment, and every month thereafter till month 8; part of these blinded sera will be for antibody research and will be stored at -80 at the clinic. At the end of the study, and per patients' consent, these anonymized research specimens will be sent to the University of Athens Medical School at Dr Dalakas's Neuroimmunology laboratory which has long-standing experience with antibody assays in SPS.

8. Drug Accountability and records. Hytrulo and placebo will be provided free of charge by ARGENX to Thomas Jefferson University pharmacy who, along with the PI, the AP's and study coordinator, will ensure blinding, drug delivery to the infusion company INFUCARE, and maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with Federal Regulations. The study site will maintain accurate records demonstrating dates and amount of drug/placebo received, to whom was dispensed (subject-by-subject accounting), and accounts of any amount of drug or placebo accidentally or deliberately destroyed. Unless otherwise notified, all vials, both used and unused, and to when and which patient were given, will be saved for drug accountability until the end of the study.

9. Syde® Wearable Device:

Patients will be provided with a wearable device to collect mobility data to accurately measure time to walk, gait velocity or falls during normal daily activities, outside of investigational site visits. The Syde® device -similar to an i-watch for the feet- consists of 2 sensors (and a docking station). It is a Digital Health Technology manufactured by Sysnav. Subjects will wear one sensor on each ankle. Because the wearable device battery requires recharging daily after use, it will not be worn at night and should be removed when subjects take part in activities that may expose the sensors to repeated impacts or potential damage (e.g., contact sports) or where the device could be in contact with water. Subjects must return the wearable device in the event of early termination, or after study completion. There are minimal inconveniences to the subjects who will wear the Syde and patients will be instructed to stop wearing it if not mobile or they experience discomfort.

Patients will be asked to wear the Syde® device during the following 4-week recording periods, based on the study visit schedule:

- Between Visit 1 and Visit 2
- Between Visit 3 and Visit 4
- Between Visit 4 and Visit 5
- Between Visit 6 and Visit 7

Subjects will be instructed on how and when to wear the device daily throughout each recording period. Site staff will train patients (and their caregivers) on the correct use of the system and will follow up on their compliance. The Syde team will provide all training materials and evidence of training for any staff trained on the device including instructions detailed in the device manual and quick start guide.

E. Statistics: Sample Size Determination and Power Analysis

Based on our published data of stiffness index scores for untreated patients and a variance of 0.83, using a repeated measures analysis of variance with Greenhouse-Geisser correlation, a

total sample size of 26 patients (13 in each group) will provide the basis for detecting a change of 25-50% or greater. Based on our 2 previous control trials (5,7), a decrease stiffness index by 1.5-2.5 points with power greater than 0.80 and probability of Type-I error no more than 0.05, the size of 26 patients (13 in each phase) is expected to achieve 90% power. A linear mixed model will be followed with 25-50% assumption of the endpoints; each patient has 2 values with no carry over effects (carry-over effects will be tested separately).

F. Gender/Minority/Pediatric Inclusion for Research

SPS is more common in women than men and 25% of our large number of patients we have studied or being referred to us are African Americans (1); it is anticipated that more women and several African Americans will be enrolled. No patient below the age of 20 will be enrolled.

G. Human Subjects

Inclusion criteria. 26 patients age 25-80 with typical SPS as per Dalakas's diagnostic criteria (1,2) poorly or partially responding to IVIg or rituximab with declining benefits, exhibiting significant symptomatology of stiffness, painful muscle spasms, and impaired walking ability will be selected. All enrolled patients will be GAD-ab or Glycin-receptor-antibody-positive and will continue receiving the non-immunosuppressive symptomatic drugs, such as diazepam, gabapentin, or baclofen. All selected patients will be among the large number we currently follow in our outpatient clinic or among those being continuously referred for a second opinion or better therapies when unresponsive to current drugs. All patients should be able to provide informed consent and willing to travel for scheduled protocol visits.
Exclusion criteria. Patients will be excluded if: a) have minimal disease, and less than 1 stiffness index; b) have very severe disease unresponsive to all therapies or non-ambulatory; and c) have paraneoplastic SPS.

H. Data and Safety Monitoring Plan

Because Hytrulo has been approved for several antibody-mediated autoimmune neuromuscular diseases and is very well-tolerated with minimal adverse events, even as self-administration, there is no need for DSMB. Among 322 patients with CIDP who received Hytrulo for 12 weeks, Treatment-emergent adverse events (TEAE's) were similar to placebo consisting of injection site erythema in 10% and headache in 5%; in those receiving the drug for 48 weeks, low rate of non-serious infections were also noted but these were similar to placebo without opportunistic infections because efgartigimod, reduces circulating IgG but does not impair IgG production, maintaining the patient's ability to mount a normal IgG immune response . Overall, Hytrulo was well tolerated for 60 weeks with similar TEAE rates to the placebo group (12). Patients will be informed from the outset about the known and expected mild TEAE's; any unexpected or serious AE will be handled as per standard of care and reported to the IRB; if any serious or life-threatening

event occurs, the study will be on hold till permission to restart is given by the IRB.

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