Call – Pilot-Trial for Direct Drug Repurposing in HSP/SPG11

European Federation of HSP Associations – Euro-HSP – in cooperation with Life4HSP

Motivation: Decades of basic research provided significant insight in the field of hereditary spastic paraplegias (HSPs). In particular for HSP subtype SPG11 (and SPG15) animals models demonstrated potential beneficiary disease modification by using compounds which are either already approved for other kinds of progressing neurological disease (e.g., Fingolimod) or which are neuroprotective dietary supplements (e.g., Naringenin). Such findings shall allow for a direct repurposing (i.e., the molecule is useable in its commercially available formulation), thereby allowing for finally making steps towards stopping or delaying neurodegeneration in affected individuals by now.

Challenge: Randomized controlled trials (RCTs) are the well-established gold standard for demonstrating superiority of novel treatments over established clinical management. However, beyond a sound scientific medical basis, RCTs require significant resources (budgets of some millions of Euros) and long-term investigations (some years might be required for demonstrating a meaningful improvement in HSPs). Thus, prospective planning of such RCTs in the field of HSPs involves an inherent risk of failure. This restricts industries willingness for directly investing in such studies. Raising public funds appears difficult due to the unavoidable commercial interest in superiority trials. Patient associations typically can provide funding only at lower scales.

Proposed Two-Step Approach: For overcoming the above-mentioned difficulties a stepwise test design is proposed.

a) Pilot Trials may provide a systematic and quantitative **first-step experience** for direct drug repurposing in HSPs. They can be performed at a budget which can be raised by patient organizations. In the case of encouraging results, pilots shall provide a valuable basis for convincing industry to invest into further investigations. In the case of disappointing outcome, they might justify the termination of further developments. Most importantly, pilot trails must investigate safety (adverse events or adverse response) and confirm or modify dose recommendations when repurposing an already available compound to HSPs (redo some phase I and phase II investigations for a novel HSP indication, see Appendix A). Secondly, they should provide *reasonable grounds* for a potentially observed treatment effect. Here surrogate markers and descriptive statistics of clinically relevant read-outs in combination with confidence intervals may allow for generating a meaningful quantitative first step experience (see Appendix B). Thus, Euro-HSP in cooperation with Life4HSP is calling for proposals for such Pilot-Trials.

We intend to support such a Pilot-trial by a minimum of 350.000 Euro.

b) RCTs will of course be needed for confirming superiority of a re-purposed compound over current clinical management. First step pilot-trials allow clinical research to focus on promising compounds. Such promising findings will significantly increase the willingness of industry to invest in advanced trials which provide the required **scientific evidence in a second step**.

Our offer: We are reaching out for a **lead-partner** who is interested and willing to translate our first-step pilot trial concept into the design and lead of a clinical pilot-trial (principal investigator) including dissemination of findings. We kindly ask interested potential partners to propose the tested compound. First contact applications should be made in written and English language with a maximum

length of two pages. We propose to follow-up each application by online meetings which shall clarify the approach.

We provide two Appendices A & B to this call. They summarize Euro-HSPs considerations when planning the call. We feel that it might be helpful for potential applicants making our preliminary considerations on trial design public. However, since we are looking for a medical lead-partner the Appendices reflect only our brainstorming. We are of course flexible in supporting the for sure necessary modifications for finally converting basic research into highly demanded first step interventional trials.

We are happy to receive applications by e-mail.

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Download Appendices A & B here.