

October 24, 2023

Report of the Scientific Advisory Committee to the 2023 Annual Meeting of Soft Bones Canada (SBC)

The Scientific Advisory Committee (SAC) of Soft Bones Canada (SBC) met one time early in 2023. However, there were many informal discussions between various Board members. The HPP SAC consists of Dr. Cheryl Rockman-Greenberg (Chair), Dr. Sandra Sirrs, Dr. Marc McKee, Dr. Bob Schroth, Dr. Leanne Ward, Dr. Frank Rauch, Mark DeBrincat, Jessica Hartley, Amy Yakimoski and Alie Johnston (Dr. Rockman-Greenberg's research coordinators) and President of SBC. We mourn the loss of our esteemed SAC colleague and friend Dr. Philippe Crine who passed away in June 2023.

- Dr. Rockman-Greenberg is a member of the Medical Advisory Board of the Alexion-sponsored Global Patient HPP Registry. Amy Yakimoski is the HPP Registry coordinator for the Canada site. The Registry enrolls HPP individuals who are on enzyme replacement therapy (ERT) or who are ERT naïve. The goal of the Registry is to provide Real World Data on HPP. Globally there are 1308 patients enrolled in 12 countries with 68 sites. With respect to Canadian stats, 31 patients (adults and children, both on and not on ERT) have been enrolled and 20 patients are currently active. No new patients have been enrolled in the past year. HPP Registry Scientific Advisory Board met in person in Boston on May 26 2023 and has an upcoming virtual Investigator meeting in Nov 2023. Since 2015, the HPP Registry has published 6 manuscripts- 3 in the past year- and presented 12 abstracts at scientific conferences. The recent publications on HPP from the HPP Global Registry are on clinical profiles of HPP, burden of illness of patients and the spectrum of variants found in the *ALPL* gene. For further information on the Registry, please see website www.hppregistry.com or contact Amy Yakimoski at ayakimoski@chrom.ca.
- Discussions continue how to expand reimbursement strategies to include Canadian adults with HPP who may meet eligibility criteria. Last year Dr. Rockman-Greenberg had approached CADTH regarding reviewing reimbursement criteria. She had learned that new data must first be formally presented to CADTH, which then must undergo appropriate and rigorous review by CADTH but there are other options as well. Alexion Canada has held two meetings of Canadian HPP expert physicians this past year to discuss increasing access to ERT in adults with pediatric-onset HPP. The latest meeting in Oct 2023 discussed the newly approved UK NICE criteria that now reimburses ERT for adults with pediatric-onset HPP if 2 of the 3 following criteria are met. The

Canadian medical experts at this October 2023 meeting discussed and endorsed the UK NICE criteria with a few modifications and next steps to try to expand the current reimbursement criteria in Canada for adults with pediatric-onset HPP are being discussed, including seeking formal input from SBC and from adult patients with HPP. The UK NICE criteria for the treatment of adults with pediatric-onset HPP include **AT LEAST TWO OF THE FOLLOWING:**

- Limited mobility assessed by a specialist using the modified Bleck Ambulation Efficiency Score (mobility score) and a Bleck score between 1 and 6 **OR**
 - Current fractures with a history of non-traumatic, recurring or non- or poorly healing fractures **OR**
 - Continuing or recurring musculoskeletal pain that affects daily activities which: affects quality of life and has not gotten better with 2 different types of painkillers that have been recommended by a national pain specialist.
- Dr. Wolfgang Hogler, from Johannes Kepler University in Linz, Austria is the lead principal investigator of the global research consortium to study genetic variants found in the *ALPL* gene. Dr. Hogler’s study is called “Functional Testing of Variants of Unclear Significance in the *ALPL* gene as a cause of Hypophosphatasia” and Dr. Cheryl Rockman-Greenberg is a member of Dr. Hogler’s global research consortium. Variants are documented in this continuously expanding, publicly available *ALPL* gene variant database. The database greatly enhances our ability to understand which and how gene variants actually cause disease. We have recently learned that ongoing funding for this international consortium beyond April 2024, which evaluates the significance of variants identified in *ALPL*, is in jeopardy. The importance of DNA testing and of this Consortium to help establish the diagnosis of HPP and to inform clinical management is unequivocal. Please note if a patient with a DNA variant of “unknown significance” consents and wishes to enroll in this study, no DNA sample is sent (such as a cheek swab or blood sample)—only the specific DNA lettering of the *ALPL* variant found on the initial DNA testing by the Canadian physician involved will be sent to the Consortium molecular laboratory in Linz, Austria for its specialized molecular testing to allow for precise classification of a variant into pathogenic or benign. As DNA testing is critical to the diagnosis of HPP and ultimately to patient care this study will be of great importance. SBC has kindly written a letter to Alexion AstraZeneca

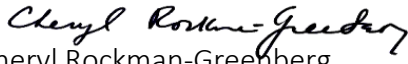
Rare Disease strongly advocating for continued funding on this Consortium.
This has been greatly appreciated.

- Dr. Aliya Khan from McMaster University and colleagues Dr. Eric Rush (Kansas City) and Dr. Maria Luisa Brandi (Florence, Italy) are leading an International Working Group that has done a systematic review of the literature and is developing diagnostic criteria for pediatric and adult HPP based on scientific evidence. Two publications regarding diagnostic criteria are now **In Press!**
- BEYOND ERT: There are new research initiatives being led by two pharmaceutical companies exploring gene therapy in HPP. These are very exciting times as results of gene therapy in animal models have been very promising and applications are being made to the FDA to explore Phase 1 and 2 trials in humans! Several members of SBC SAB are involved in these ventures. No new recent information is available.
- The Canadian HPP Clinical Expert Committee is active and receives requests from the provinces to consider applications for beginning ERT and renewals. Its terms of reference, eligibility criteria for ERT, and details of both the application process and the renewal process can be found on the Garrod website www.garrod.ca. This Canadian HPP Clinical Expert Committee is encouraging physicians to provide complete medical information so that the committee can truly make an informed decision.

Dr. Rockman-Greenberg wishes to remind SBC Board that at the Children's Hospital Foundation of Manitoba there is a fund designated specifically for HPP patient care, education, research and related initiatives. Any request or queries regarding this fund can be sent to her.

Lastly, the last almost 4 years have been very challenging for everyone and on behalf of the SAB, I extend our hopes that everyone has felt supported and safe during these very difficult times. Be safe and be well,

Respectfully submitted


Cheryl Rockman-Greenberg
Chair SBC, SAC