CADTH

CADTH Reimbursement Review

Patient Input

IMMUNE GLOBULIN HUMAN AND RECOMBINANT HUMAN HYALURONIDASE (TBC)

(Takeda Canada Inc.)

Indication: Humoral immunodeficiency

CADTH received patient input from:
The Canadian Immunodeficiencies Patient Organization (CIPO)

July 16, 2021

CADTH

CADTH Reimbursement Review
Patient Input Template

Name of the Drug and Indication	**Immune globulin human and recombinant human hyaluronidase (HyQvia): As replacement therapy for primary humoral immunodeficiency and secondary humoral immunodeficiency in adult and pediatric patients two years of age and older**
Name of the Patient Group	**The Canadian Immunodeficiencies Patient Organization (CIPO)**
Author of the Submission	[redacted]

1. About Your Patient Group

The Canadian Immunodeficiencies Patient Organization (CIPO) is committed to creating awareness about primary immunodeficiency (PI), to advocate for new treatments, to help speed the diagnosis of patients, and to enable patients to become champions for their own quality of life. We equip patients, caregivers, family members and health care providers with the information, tools and resources they need to ensure that those affected by PI can live healthy and productive lives. **http://www.cipo.ca/**

2. Information Gathering

CIPO conducted an online survey of patients and caregivers from June 8, 2021 to June 27, 2021, to assess the challenges patients and caregivers face as a result of Primary Immunodeficiency (PI) and their experience with current treatments for PI.

A total of 246 individuals responded to the survey (n=246). 244 are from Canada, and 2 patients are from the U.S. 233 (95%) were individuals living with primary immunodeficiency, and 13 (5%) were caregivers answering the survey on behalf of patients. The survey contained the use of free-form commentary, scoring options and limited closed questions.

Additionally, semi-structured telephone interviews were conducted with eight (8) patients who are currently using either intravenous (IVIG) or subcutaneous (SCIG) immunoglobulin replacement therapy (IG) treatments for their PI.

This report reflects the results of the survey and patient interviews, as well intelligence and insights CIPO has garnered from more than two decades of experience in patient support and advocacy related to Primary Immunodeficiency.

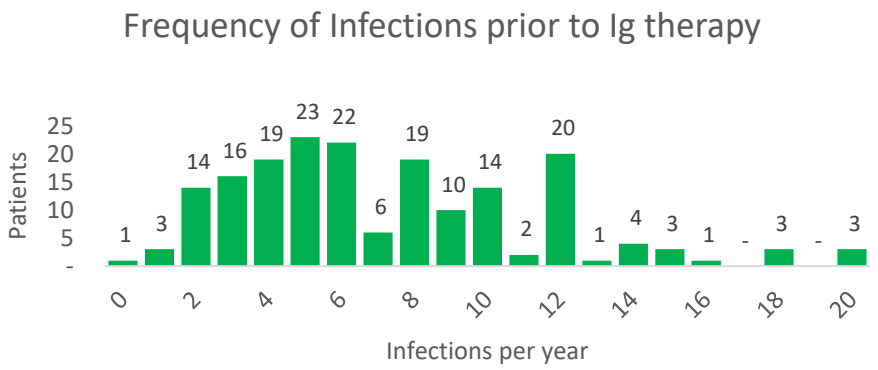
Note: CIPO had hoped to identify patients that had experience with the treatment under review but there has been no recent experience in Canada with HyQvia. And, we were unable to contact the few patients in Vancouver that participated in the Phase III trial for this treatment that ran from December 2008 to November 2010. (ClinicalTrials.gov Identifier: NCT00814320).

3. Disease Experience

Primary Immunodeficiencies (PI) are a group of inherited and genetic defects of the immune system, resulting in an immune system which is partly or totally missing or does not function properly. These deficiencies make people with PI more prone to a wide range of infections (viral, bacterial and fungal) which can include: skin infections, sinopulmonary infections, and infections of the intestines. These infections are often chronic and debilitating.

We asked patients: ***Prior to starting immunoglobulin therapy (IVIG or SCIG) to treat your PI, approximately how many infections were you experiencing per year?***

There was a wide range of reported infections (per year) **prior to starting IG therapy**, with the majority ranging from 2-12 infections per year. We plotted the infections per year of 184 patients who reported between 0 – 20 infections per year. However, 7 additional patients reported 30+ annual infections (not included in the plot below). The average # of infections per year was 8.12.



Below are excerpts from patient commentary regarding their experience with infections prior to starting IG therapy:

3 months of continuous illnesses that ended with shingles. In 6 months, every 10 days had no energy & in July had my first summer cold. Oct, had a near-death experience. Had encephalitis & pneumonia due to the severity .... Had severe coughs for years & had IBS.

"Previous to the year I was diagnosed, I had 1 or 2 (infections) per year. In the year leading up to my diagnosis I had recurrent sinus infections and extreme fatigue for 5-6 months that culminated in a severe pneumonia which I developed while on extended vacation in overseas."

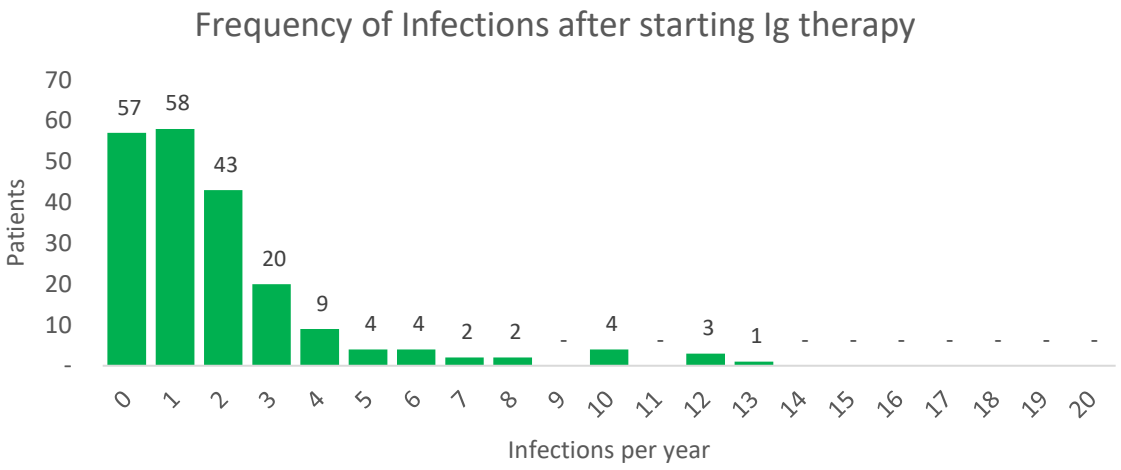
"Became ongoing mesenteric vasculitis with no relief. On top of consistent skin infections, mucous membrane ulcers."

"Too many (infections) to count. Before being diagnosed late in elementary school I would miss sometimes a month of school. I was always sick with something and had constant ear and throat infections. Most colds or flues would leave me delirious it would get so bad."

"I was experiencing sinus infections requiring antibiotics every 4-6 weeks for many years".

We also asked patients: ***After starting immunoglobulin therapy (IVIG or SCIG) to treat your PI approximately how many infections are you now experiencing per year?***

The frequency of infections changed dramatically. We plotted the infections per year of 207 patients who reported between 0 – 20 infections per year. (There were no patients reporting infection rates of over 20 per year). The average # of infections per year, for patients who had commenced immunoglobulin therapy, went down to 2.05 infections per year (from an average of 8.12 infections per year for patients prior to commencing therapy), representing almost a quartering of infections for patients who were properly diagnosed and prescribed treatment.



Because PI often presents in the form of infections, with a variety of symptoms and clinical manifestations, clinicians often treat the infections while missing the underlying cause. This frequently leads to reoccurrence of infections and persistence of the condition, leaving the patient vulnerable to health deterioration, physical disability, and possibly permanent organ damage, or even death. Patients may develop an autoimmune disorder or certain types of cancer. Left untreated, PI may result in unusually severe infections, organ damage, chronic disease and early morbidity.

Diagnostic delays are very common, and can lead to the steady deterioration of a patient's health. These delays also have a negative impact on healthcare systems due to inappropriate use of health resources caused by avoidable visits to a variety of different specialists for recurring infections.

Because many patients with PI require therapy indefinitely, the method of administration, and setting where the treatment is administered, are important factors that can significantly affect health-related quality of life (HRQOL). For this submission we will be addressing topics related to HRQOL, specifically with regards to the satisfaction of patients with specific treatment regimens, and the performance of specific treatment regimens.

4. Experiences With Currently Available Treatments

Treatment of PI includes managing current infections and preventing future infections. Antibiotics are frequently prescribed to prevent or clear bacterial infections, and antivirals can be prescribed to help patients recover from infections caused by viruses.

Immunoglobulin G (IgG) replacement is the standard of care in many of these patients and may be given intravenously (IVIG) or subcutaneously (SCIG), to replace immune system components.

In our survey, we asked patients: ***What types of treatments do you have experience with? (select all that apply):***

Answer Choices	Answered (n=215)
Intravenously administered IG (IVIG) therapy	67.44% (n=146)
Subcutaneously administered IG (SCIG) therapy	84.19% (n=181)

In our online survey and telephone interviews, we also asked patients to assess the advantages and disadvantages of IVIG and SCIG treatments:

Excerpts from Telephone Interviews:

Of the 3 patients interviewed by phone who were on SCIG treatment, two had previous experience with IVIG treatment (Patient 01 and Patient 02).

Patient 01 commented on his experience with IVIG treatment which he required every two weeks: *"After treatment I would experience muscle spasms, headaches, nausea and chills etc., and while it started to get better over time, there was always a day after the bi-monthly infusion that I needed a rest day. I needed one day for the infusion and one day for recovery. This was very disruptive. 48 days per year allocated to treatment and recovery was not sustainable. I also experienced fatigue...IG levels would be high...then down. For me the subcutaneous method is much better than IV, even though with IV there was reduced frequency of infusions."*

Patient 02 commented that: "*I am a nurse, and find the subcutaneous method much easier and much more convenient than going to the hospital. When I was going to the hospital for intravenous treatment, which was once every 4 weeks, treatment could run 5 or 6 hours, but it went faster when my body grew accustomed to treatment. Now I do subcutaneous treatment at home once a week, and it takes me about 1.5 hours, including prep time. I did not have any reaction with subcutaneous....only a small welt at injection site. I do not need to rest. I do it before going to sleep - on Monday night. No dips with subcutaneous.....but with IVIG, in the final week before my next treatment I would feel sluggish....with subcutaneous I don't feel that fatigue."*

With regards to SCIG, we asked in our online survey: ***If you are currently using a SCIG treatment at home, tell us what you think are the advantages are of this treatment. (select all that apply)***

Answer Choices	Answered (n=168)
Independence/Freedom	90.48% (n=152)
Ability to decide infusion place/time	95.24% (n=160)
Convenience	89.29% (n=150)
Avoidance of travel to infusion clinic/hospital	88.1% (n=148)
Other (please specify)	26.19% (n=44)

43 patients suggested other advantages of SCIG treatment including: 9 patients who mentioned that SCIG affords them the ability to travel, 9 patients who reported that SCIG is more tolerable with fewer side effects, 9 patients who reported that SCIG results in more stable IG levels (with no peaks and troughs). 6 patients who highlighted that SCIG enables them to avoid the risk of hospital-based infection (from attending IV clinics). 4 patients said that SCIG treatment is less disruptive or takes less time, with some patients focusing on how SCIG specifically enables them to pursue work/career with minimal disruption.

One patient (through the quantitative survey) mentioned the importance of being able to avoid hospitals in the context of COVID19 risk. Of the 8 patients interviewed by phone (of which 3 were on SCIG treatment) one patient specifically switched from IVIG treatment to SCIG due to risk of COVID19 infection (from the requirement to receive therapy in a hospital environment).

With regards to SCIG, we also asked: ***If you are currently using a SCIG treatment, tell us what you think the <u>disadvantages</u> are of this treatment. (select all that apply)***

Answer Choices	Answered (n=154)
Requires more frequent infusions (than IVIG)	67.53% (n=104)
Limited fluid volume that can be administered into a single site in a single infusion	29.22% (n=45)
Requires more infusion sites on my body (than IVIG)	51.95% (n=80)
Other (please specify)	29.87% (n=48)

35 patients provided additional comments regarding disadvantages of SCIG treatment including: 13 patients who used the opportunity to comment to expressly reiterate they thought there were **NO** disadvantages with SCIG treatment. 8 patients commented on the inconvenience of having to order, pick-up and store SCIG supplies, with one patient mentioning the risk of exposure to hospital-based infections when picking up treatment. 5 patients mentioned that self-infusing at home took a significant amount of time.
8 patients offered unique experiences or observations with regards to what they considered to be “disadvantages” with SCIG, including: risk of clots, appearance of “bulge” at injection site, the need to have a nurse present due to injection site bleeding, anaphylaxis due to the plastic and rubber components in the SCIG kit, and anxiety from self-injecting.

With regards to IVIG, we asked: ***If you are currently using an IVIG treatment, tell us what you think the <u>advantages</u> are of this treatment. (select all that apply)***

Answer Choices	Answered (n=70)
Less frequent dosing frequency (than SCIG)	42.86% (n=30)
Enables high-dose infusions	35.71% (n=25)
I have become familiar/comfortable with this method of treatment	64.29% (n=45)
Other (please specify)	37.14% (n=26)

19 patients offered comments regarding the advantages of IVIG treatment including: 5 patients who expressed how they value the monthly access to specialists (immunology residents, nurses etc) while at the infusion clinic. This theme (of valuing routine access to PI specialists) was also echoed in the qualitative interviews by patients who were receiving IVIG at a hospital infusion clinic.

One patient also commented on the "social aspect" of receiving IVIG at a clinic. She stated: "*…the social aspect of having conversations and long-standing relationships with other PI patients and nurses in the specialty clinic cannot be understated. This is a rare disease and can be very isolating. …"*

Excerpts from Telephone Interviews:

Patient 03, a 45 year-old woman in the Greater Toronto Area, employed full time, goes once a month to an infusion clinic in downtown Toronto. She reports that the option to switch to subcutaneous (at-home) treatment was discussed with her "*but, I like the social support down at the clinic, along with the routine access to (PI) disease specialists. And, I didn't like the idea of having to administer multiple times per week*." She further stated: "*the medical support and the social support you get at the clinic is very important to me. They do blood screening two times per year and abdominal ultrasounds and pulmonary function tests. And a chest X-ray once per year. And I can routinely access an expert in PI. I don't know if this would be available if I was receiving at-home treatment."*

Patient 04, a retired 59 year-old woman who also lives in the GTA goes every 4 weeks to an infusion clinic. With regards to the option of switching to SCIG, she states: "*A few of my clinic buddies are on SubQ* (SCIG). *The major thing for them was to avoid loss time at work. I stuck with IV* (IVIG). *I liked that it was 'my treatment day' ….I would have tried SubQ perhaps, but I prefer to go to a clinic because there is a healthcare team in case of complications."*

With regards to IVIG, we also asked***: If you are currently using an IVIG treatment, tell us what you think the disadvantages are of this treatment. (select all that apply)***

Answer Choices	Answered (n=63)
Invasive method of administration	34.92% (n=22)
Intolerable side effects	17.46% (n=11)
Requires travel to infusion clinic/hospital	47.62% (n=30)
Other (please specify)	52.38% (n=33)

21 patients offered comments regarding the disadvantages of IVIG treatment including: 7 patients who discussed the significant time commitment required to travel to the clinic, receive infusion, and return home and recuperate. Often these patients, when discussing this time commitment, commented on how IVIG received in a clinic was disruptive to their work or career, often requiring special dispensation from employers with regards to sick time/sick leave. One patient mentioned *"…it has prevented me from taking on more leadership positions in my employee group".* 3 patients mentioned that IVIG resulted in damage to their veins and/or scarring at the regular infusion sites.

We also asked patients: ***If you have switched from an intravenous IG (IVIG) treatment to a subcutaneous IG (SCIG) treatment, please explain why you made that switch.*** 107 patients offered comments:

58 patients highlighted the convenience, freedom and flexibility as the incentives to switch from IVIG to SCIG. There were many references to the reduced time commitment, and elimination of the need to travel, as being key motivations to switch. Two patients related experiences of long distance travel (in one case 180 kilometers each way) required to attend an infusion clinic. Many patients mentioned that switching to SCIG enabled them to pursue work and career without undue interruption.

21 patients switched to SCIG because it eliminated the *peaks and troughs* they experienced on IVIG and enabled better overall maintenance of IG levels.

24 patients informed us that severe reactions or intolerable side effects from IVIG motivated their switch to SCIG. Notably two reported getting aseptic meningitis due to treatment with IVIG.

Safety issues, with respect to the risk of infection from hospital environments, were cited by 11 patients. 5 of those patients specifically made the switch to SCIG due to the risks of contracting COVID19 in a hospital/clinic environment.

9 patients reported the switch to SCIG was needed because of problems with venous access required for IVIG, mostly due to scarring.

And, 14 patients switched to SCIG based on the recommendation of their physician.

We also asked: ***If you have switched from a subcutaneous IG (SCIG) treatment to an intravenous IG (IVIG) treatment, please explain why you made that switch.*** 19 patients offered comments:

6 patients switched to IVIG (or in many cases "switched back" to IVIG) due to adverse reactions to SCIG treatment.

7 patients did not like the frequency of infusions and the total time commitment required for at-home SCIG treatment, and preferred the once monthly schedule of IVIG treatment.

3 patients reported that SCIG treatment did not work for them, citing either treatment failure or inadequate maintenance of IG levels.

2 patients valued the access to specialist care that was available with IVIG treatment at infusion clinics.

1 patient reported lacking trust in their ability to properly self-administer treatments.

We asked: ***Please rate on a scale of 1 – 5 how important it is to you to have access to new treatments for Primary Immunodeficiency (PI)? 1 is "not important" and 5 is "very important"?***

N=219						
1 (not important)	2	3	4	5 (very important)	N/A	Weighted Average (WA)
10pts (4.57%)	7pts (3.2%)	28pts (12.79%)	41pts (18.72%)	132pts (60.27%)	1pts (0.46%)	**4.28**

Conclusions:

Experience with currently available treatments is varied with patients ascribing different values to the currently available (in Canada) treatments. Efficacy along with personal preference (with respect to lifestyle and HRQOL), along with treatment tolerability, are clearly the dominating factors that contribute to the treatment selection process. However, availability, familiarity, physician-recommendation and associated out-of-pocket costs all contribute to treatment selection decision-making. Lifestyle considerations are clearly important and consequential. Recognizing that the distribution of patients with PI have a similar distribution as the rest of the population with respect to age and employment status, the ability to work without major impedance or disruption is considered to be of high importance to many PI patients. Patients requiring IVIG therapy, either due to lack of other treatment options or due to failure on SCIG therapy, typically require one day per month to be allocated to treatment and recovery, as treatment requires travel to a designated infusion clinic, significant time for the infusion and significant time for recovery (as fatigue is a common side-effect of IVIG). Many individuals with PI have difficulty accommodating a full day per month for IVIG treatment while meeting the requirements of their employment.

Patients with the option of selecting SCIG therapy also have trade-offs. While SCIG affords a measure of independence and flexibility because the treatment can be administered at-home at a scheduled largely determined by the patient, SCIG therapy requires a higher dosing frequency, as currently available SCIG treatments do not enable high-dose infusions. This higher dosing frequency is seen by many as burdensome.

There is clearly a population of PI patients that would derive great benefit from a therapy that can be administered at home while affording the same dosing frequency as intravenous immunoglobulin (IVIG) treatments (enabling high-dose infusions every 3–4 week) along with the benefit of reducing the number of infusion sites and adverse events (compared to IVIG therapies).

Improved Outcomes

Many patients with PI are anxious for new treatment options. While many patients hope for a treatment that could be, for instance, orally administered, the demand for a treatment that minimizes disruption in areas of career and personal life would represent a significant advancement in treatment for PI and would come closer to meeting the needs of a significant subset of PI patients.

Excerpts from Telephone Interviews:

In our telephone interviews with patients, we asked: ***If HyQvia*** *(*Immune globulin human and recombinant human hyaluronidase) ***was available to you as a treatment option, would you try it?***

Patient 02 commented: "*I am glad that there are other options coming through. While I am comfortable with my (SC) treatment, I would be interested in trying HyQvia."*

Patient 01 commented: "*Having had a negative experience with a treatment change in the past, I have some concerns with switching, but I would consider it and I would discuss it with my doctor. I would ask: 'Is there an adjustment period?' If there was little risk I would consider it."*

Patient 05 commented: "I*f it gives same result...less often* (treatment administration) *is GOOD. If available I would ask Dr.* [redacted] *about it. Is this a viable option for me? Would it have the same efficacy? Should I use it?"*

Patient 06 commented: "*HyQvia sounds cool. I would ask my doctor about. I did enjoy going to the hospital to chat with people* (for her IVIG monthly treatment)*, but it is different now. I have a fear of going to the hospital because of risk of infection. If it* (HyQvia) *could reduce SubQ* (SCIG) *to once a month that would be a big reduction in personal burden. SubQ is an ever present chore. Anything to reduce the frequency would be welcome"*

Patient 07 commented: "*We need the ability to do IVIG at home. But that would require a nurse, so HyQvia might be good for some patients. I am not sure if it (HyQvia) is indicated for patients with autoimmune* (disease), *and PI patients are often autoimmune, so IVIG might be better. We are all very different. For working people, this new treatment option might be better for them. And younger people might prefer it."*

Conclusions:

Treatment for PI requires lifelong therapy for most patients and there are many who may derive great benefit from *Immune globulin human and recombinant human hyaluronidase* (HyQvia)*.* These patients include:

- Those that have difficulties accommodating the schedule of available (IVIG) infusion clinics due to career, academic pursuits etc.
- Those that do not have convenient geographic proximity to an infusion clinic, or have other encumbrances on the ability to travel
- Those that find the frequency of dosing of currently available SCIG therapies to be onerous
- Those that are seeking to avoid the risk of hospital-acquired infections (including COVID19)

Every attempt should be made to optimize treatment outcomes and QoL for patients, and *Immune globulin human and recombinant human hyaluronidase* (HyQvia) would, for many patients improve their QoL significantly.

5. Experience With Drug Under Review

CIPO had hoped to identify patients that had experience with the treatment under review but there has been no recent experience in Canada with HyQvia. And, we were unable to contact the few patients in Vancouver that participated in the Phase III trial for this treatment that ran from December 2008 to November 2010. (ClinicalTrials.gov Identifier: NCT00814320).

However, HyQvia is a facilitated SCIG treatment that affords some of the best features of both intravenous and subcutaneous treatment modalities. HyQvia offers:

- the same dosing frequency as intravenous immunoglobulin (IVIG) treatments: enabling high-dose infusions every 3–4 weeks with minimum infusion sites and fewer adverse events compared to IVIG therapies.
- the opportunity to self-administer at home like other SCIG treatments, while also requiring fewer infusions compared to conventional SCIG therapies: enabling the flexibility to manage one's own infusions, with no requirement for travel or disruption of work-week routines.

The content provided above identifies how patients in many cases prefer (and benefit from) the key features that are available through the treatment under review: HyQvia.

6. Companion Diagnostic Test

- **N/A**

7. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

Canadian Blood Services (CBS) buys IVIG from several different manufacturers. In late 2020, CBS informed stakeholders that some manufacturers could not provide their contracted volumes. Based on current demand, some IVIG brands and vial sizes are in short supply or no longer available, at least until spring 2022.[1]

CBS has been asking all clinics to switch as many patients as possible to Subcutaneous IG therapies in light of the anticipated IVIG shortages. Recognizing the anticipated shortage of IVIG products, this new treatment (Immune globulin human and recombinant human hyaluronidase/HyQvia) may offer an opportunity to reduce demand of IVIG products while offering patients a treatment that affords some of the best features of both intravenous and subcutaneous treatment modalities.

[1] FACT SHEET: Canadian Immunoglobulin (Ig) Supply and Intravenous Immunoglobulin (IVIg) Brand Switching. National Advisory Committee on Blood and Blood Products.

https://www.nacblood.ca/resources/shortages-plan/Fact%20Sheet-%20Cdn%20Ig%20SupplyIVIg%20Brand%20Switching_Feb%2023%202021_Final.pdf

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   CIPO used regular and contracted employee assistance to conduct research and complete this submission.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   The collection and analysis of data was accomplished through the use of CIPO's SurveyMonkey subscription which includes an online survey platform along with tools for data analysis, sample selection, bias elimination, and data representation. Both regular and contracted staff participated in data collection and analysis.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Takeda				x
CSL Behring Canada		x		
Grifols Canada				x
Octapharma Canada		x		

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Whitney Ayoub Goulstone
Position: Executive Director
Patient Group: CIPO
Date: July 13, 2021