



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research**

MEMORANDUM

Date: 21 April 2014

From: Wambui Chege, MD
Medical Officer, Pharmacovigilance Branch

Re: 125402/0

Through: Craig Zinderman, MD, MPH
Acting Branch Chief, Pharmacovigilance Branch
Associate Director for Product Safety, Division of Epidemiology

Manette Niu, MD
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Product: HyQvia – Immune Globulin Infusion (Human), 10% with Recombinant Human Hyaluronidase

Subject: Addendum to Review of Baxter Response to FDA Complete Response letter
Initial ADD 13Jun2014, extended due to major amendment to 12Sep2014

Sponsor: Baxter

1. INTRODUCTION

1.1 Product description

HyQvia is a combination product, composed of a currently licensed intravenous immunoglobulin (IgIV), Gammagard Liquid (STN 125105), and recombinant hyaluronidase (rHuPH20). HyQvia is designed to be given as two sequential subcutaneous infusions of recombinant human hyaluronidase followed by infusion of 10% Ig. The sponsor notes that the purpose of the hyaluronidase is to facilitate “dispersion and absorption of the Immune Globulin Infusion ... thereby improving bioavailability.”¹ A limitation of current subcutaneous immunoglobulin (IgSC) therapy is that a limited amount of fluid can be administered at a given injection site. This necessitates the use of multiple injection sites and weekly therapy. The rHuPH20 component of HyQvia enzymatically dissolves the hyaluron component of the extracellular matrix, allowing greater dispersion of fluid and larger volumes to be injected at a single site. The advantage to the patient is the administration of the product via fewer injection sites and less frequently – every 3 to 4 weeks instead of weekly. The proposed indication for HyQvia is “for the treatment of adult patients (≥ 16 years) with primary immunodeficiency (PI) associated with defects in humoral immunity.”¹

1.2 Regulatory History

The regulatory history of HyQvia is summarized in Table 1 below.

Table 1. Regulatory History ^{2,3}

Date	Action
20Jun2011	Baxter submits an original Biologics License Application (BLA) for HyQvia to FDA with ADD of 27Apr2012
19Mar2012	FDA notifies Baxter that due to a major amendment, the review clock is extended by 3 months resulting in a new ADD of 29Jul2012
08Aug2012	OBE/DE completes a comprehensive review of Baxter’s proposed Pharmacovigilance Plan (PVP) including assessment of potential postmarketing safety issues
27Jul2012	FDA issues a complete response (CR) letter, informing Baxter that the BLA cannot be approved due primarily to concerns about possible effects of anti-rHuPH20 antibodies on neuronal (particularly enteric neuronal plexus) and male reproductive tissues and potential toxicity in pediatric patients and the developing fetus.
16May2013	HyQvia is licensed in the European Union and is first launched in Germany on 21Jul2013
12Dec2013	Baxter resubmits the BLA to FDA with a second version of the PVP and an ADD of 13Jun2014
11Feb2014	HyQvia is presented at the CBER Blood Meeting. The discussion includes a review of additional non-clinical data from animal studies submitted by Baxter, which does not adequately address the potential long term effects of anti-rHuPH20 antibodies on neuronal tissues, fertility or fetal development. It was therefore decided that two experts on hyaluronidase research would be appointed Special Government Employees (SGE) and consulted for review of this potential safety concern.
18Apr2014	OBE/DE completes a review of the available safety data including the updated PVP in the resubmitted BLA. Three outstanding data sources yet to be reviewed include the response from one of the two hyaluronidase experts, and postmarketing data from both Baxter and the European Medicines Agency (EMA).
23Apr2014	Additional CMC and safety-related data requested respectively by OBRR and OBE is received and results in a major amendment. The ADD is therefore changed from 13Jun2014 to 12Sep2014

2. OBJECTIVES

To date, OBE/DE has completed two comprehensive safety reviews for HyQvia – the first, evaluating the proposed PVP submitted with the original BLA is dated 08Aug2012, and the second, dated 18Apr2014, reviewed the available safety data in the resubmitted BLA.

The purpose of this memorandum is to review data from three sources which were not available at the time of the most recent review by OBE/DE. Two additional documents from the sponsor containing new data submitted in support of the current BLA have also been reviewed in this memorandum. The five data sources reviewed in this memorandum include:

1. Information provided by the second SGE (Private communication)
2. Postmarketing data provided by EMA (Private communication)
3. Postmarketing adverse event (AE) data provided by Baxter in response to OBE/DE's information request (125402/0/34)
4. New safety related clinical data and regulatory analyses submitted by Baxter (125402/0/35)
5. Amendment 041 from Baxter, Follow-Up to July 31, 2014 BPAC recommendations (125402/0/42)

This memorandum will therefore serve as an addendum to OBE/DE's two prior reviews dated 08Aug2012 and 18Apr2014.

3. REVIEW OF ADDITIONAL SAFETY-RELATED INFORMATION

3.1 Response from Special Government Employee #2

On 19Apr2014, the second SGE retained by FDA to help evaluate potential safety concerns resulting from the development of anti-rHuPH20 antibodies, responded to FDA's request. The SGE reports that several studies contradict the findings of Halozyme, the manufacturer of rHuPH20. While Halozyme's data indicates that only testes express PH20, other studies suggest that PH20 may be expressed in brain tissue, murine stem cells, female reproductive tissues, and a variety of neoplasms. In addition, while there is no conclusive proof that PH20 is involved in the remyelination, demyelination or regulation of neuronal tissue, there is some data to suggest that PH20 has an important role in regulating oligodendrocyte precursor cell maturation in development.

It is not clear why some studies detect PH20 expression in tissues other than testicular tissue, while other studies do not. Differences in the stringency of laboratory techniques or choice of reagents may result in false positives and may therefore account for the contradictory results. The SGE notes however, that there is insufficient data to evaluate the contradictory results or resolve any discrepancies.

The SGE further notes that several potential AEs are foreseeable from anti-PH20 antibodies including reduced fertility in males due to decreased ability to fertilize oocytes and cytotoxic destruction of testicular tissue. According to the SGE, AEs may occur in other organ systems as well, depending on the presence and level of expression of PH20 in extra-testicular tissues. Treatment of these AEs would likely require chronic treatment with IgIV, plasmapheresis or anti-B-cell treatments to counteract the effects of persistent production of anti-PH20 antibodies. Given the likelihood that PH20 is expressed in multiple tissues, the SGE suggests that AE monitoring associated with anti-PH20 antibodies in a trial should therefore involve monitoring for a wide variety of AEs including changes in both male and female reproductive function as well as any dysfunction of the gut, joint, bone or skin.

With regard to preclinical studies that might be useful in evaluating potential AEs associated with anti-PH20 antibodies, the SGE suggests that animals could be injected with anti-PH20 antibodies then monitored for AEs of interest, tested for relevant laboratory parameters and eventually sacrificed for pathologic examination of tissues of interest. The SGE notes however that circulating anti-PH20 antibodies are blocked from reaching testicular and neuronal tissues by the blood-testes and blood-brain

1 Page Determined to be Not Releasable: (b)(3) and (b)(4)

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3.2.3 Postmarketing Clinical Studies Listed in the EU PVP

Two studies are listed in the EU PVP – a pregnancy registry and a study to evaluate long-term local and systemic effects of HyQvia. The sponsor is proposing two additional studies in the US that are similar, but not identical, to the EU studies. The similarities between the planned postmarketing studies “will allow Baxter to combine the results from the US and European studies to increase the size of the database and improve the ability to detect any safety signal.”⁵ The EMA provided protocols for both European studies to FDA and Baxter provided protocols for both US studies to FDA. Pertinent information from these studies is summarized in Tables 3 and 4 below

Table 3. Summary of Pregnancy Registry planned for HyQvia ^{5, 6, 7}

Study Title:	Registry Study to collect Long-Term Safety Data from Female Subjects who become pregnant during treatment with HyQvia; Protocol Number --(b)(3)-- 161404 (US)
Study Design:	Non-interventional, prospective, uncontrolled, open-label, multicenter, post-authorization registry.
Inclusion criteria:	<ul style="list-style-type: none"> • Subjects who become pregnant during treatment with HyQvia, defined in the US protocol as exposure to HyQvia while pregnant or in the 30 days prior to conception • In the US, women who become pregnant while being treated with HyQvia are encouraged to call a toll-free number listed on the label and educational information
Exclusion criteria:	<ul style="list-style-type: none"> • None
Study Duration:	<ul style="list-style-type: none"> • 6 years from study initiation to end of data collection. • Subject participation is from enrollment to 2 years after delivery to permit assessment of infant development, unless prematurely discontinued.
1° Objectives:	<ul style="list-style-type: none"> • Assess clinical safety data regarding possible effects of HyQvia on the course and outcome of the pregnancy, and on growth and development of the fetus exposed to HyQvia <i>in utero</i>
2° Objectives:	<ul style="list-style-type: none"> • Collect any laboratory safety data and additional safety assessments obtained during the clinical management of pregnancy and in evaluation of the fetus <i>in utero</i> and the infant post-partum
Safety related endpoints:	<ul style="list-style-type: none"> • Incidence of all serious and non-serious AEs • Incidence of local/immunologic AEs including skin changes • Mandated measurement of anti-rHuPH20 antibodies in the mother but not the infant. Measurements occur for the mother at the screening visit, every 3 months during pregnancy and at study termination. • Complications and outcomes of pregnancy • Fetal growth/development, Neonatal assessment according to clinical practice, Status of the infant at birth, Growth measurement and charts for the infant, if available and Development milestones, if available
Data Collection and Analysis:	<ul style="list-style-type: none"> • Safety related data on both the pregnancy and infant development will be collected during study visits at prespecified intervals – at screening, q3mo while pregnant, at delivery and upon study completion for the mother; and at birth,

	6,12 and 18 mo of age and upon study completion for the infant <ul style="list-style-type: none"> • Each AE from enrollment until study completion or discontinuation will be described on the AE Case Report Form (CRF) by the study investigator and assessed for seriousness, severity and causality. • The study site will maintain patient identifier information including telephone number and dates of follow-up contacts. Patients will be defined as lost to follow-up following 3 documented unsuccessful attempts to contact the subject • Outcome measures regarding pregnancy loss, stillbirth, and congenital abnormalities, will be compared to published data for the region and, if known, for the specific patient population. Growth and development of the infant will be compared to growth parameters for the specific region, if available, or else to standard published charts. 	
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US Estimated Milestones:	Final Protocol Submission	3 months after licensure
	Trial initiation	6 months after agreement of protocol with FDA
	End of Patient Accrual	3 years
	Study completion	6 years from study initiation to study completion
	Interim Study Reports	Annually
	Final Study Report	6 months after last subject out

Reviewer Comment:

Given the rarity of PID and the need to include only pregnant women in the registry, the pool of potential study subjects is likely to be limited, resulting in a relatively small sample size. -----

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With regard to a comparison population, as there is currently no ongoing pregnancy registry for Gammagard Liquid⁹ (the Ig component of HyQvia), a true comparator group may be difficult to establish. The proposed option to use known historical data or standard published charts for comparison, is therefore probably a reasonable alternative. Of note however, the sponsor plans simple descriptive analyses of safety related endpoints with no specific statistical methodology planned to compare study results with the historical comparator group. This approach to data analysis may further limit the interpretation of study results.

Finally, biases associated with registry enrollment may also affect study results. For instance, if patients with multiple comorbidities or complicated pregnancies seek greater medical oversight during the pregnancy, they may be more likely to self-select for registry enrollment as a means of acquiring additional medical care during the pregnancy. However, since these patients may be at greater risk for poor outcomes due to their underlying medical conditions, adverse events identified in the study may be a reflection of this selection bias rather than an indication of a true causative finding.

Table 4. Summary of Long-term Safety Study planned for HyQvia^{5,10,11}

Study Title:	Non-Interventional Post-Authorization Safety Study on the Long-Term Safety of HyQvia in Subjects treated with HyQvia; Protocol Number --(b)(3)--	
Study Design:	Non-interventional, prospective, uncontrolled, open-label, multicenter, post-authorization safety study	
Inclusion criteria:	<ul style="list-style-type: none"> • -----(b)(3)----- • Adult patients (≥ 16 years) who have been prescribed treatment with HyQvia at one of 20 participating sites in the US will be offered the opportunity to enroll in this study 	
Exclusion criteria:	<ul style="list-style-type: none"> • Subject with known hypersensitivity to any of the components of HyQvia, has participated in an interventional clinical study involving a medicinal product or device within 30 days prior to enrollment, or is scheduled to participate in an interventional clinical study involving a medicinal product or device during the course of this study. • Subject is pregnant or breastfeeding at the time of enrollment. 	
Study Duration:	----- (b)(3) ----- ----- In US study duration of 8 years with enrollment period of 5 years and minimum 3 year follow-up	
Goal enrollment:	----- (b)(3) ----- and 550 subjects in US	
1° Objectives:	<ul style="list-style-type: none"> • Long-term safety of HyQvia treatment in subjects receiving treatment with HyQvia 	
2° Objectives:	<ul style="list-style-type: none"> • Treatment regimen, anti-rHuPH20 antibodies and, as available, other laboratory safety assessments, total IgG, further safety assessments, product administration, and health-related quality of life and health resource use assessments. 	
Safety related endpoints:	<ul style="list-style-type: none"> • Incidence of all serious and non-serious AEs • Incidence of local/immunologic AEs including skin changes • Incidence of temporally and/or causally associated systemic allergic AEs • Incidence of new onset AEs that are potentially immunologically mediated, such as arthritis, nephritis, or pneumonitis • Incidence of gastrointestinal symptoms • Incidence and titer of binding and neutralizing antibodies to rHuPH20, and, if available, lab tests such as clinical chemistry, total IgG, etc. 	
Data Collection and Analysis	<ul style="list-style-type: none"> • Data will be collected by the investigator via CRFs at prespecified visits – at screening, every 3 months and at the end of follow-up (60 months or early discontinuation) • Each AE from first product exposure until study completion will be described on the AE Case Report Form (CRF) by the study investigator and assessed for seriousness, severity and causality. • Additional data will be collected via patient diaries where AE, medications, non-drug therapies and product administration details can be recorded • Subjects will be requested (but not mandated) to have blood draws for assessment of antibodies to rHuPH20 at the time of routine laboratory assessments approximately q 3mo but not more than four times a year 	
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US Estimated Milestones:	Final Protocol Submission	3 months after licensure
	Trial initiation	6 months after agreement of protocol with FDA
	End of Patient Accrual	2 years
	Study completion	6 years from first subject in to last subject out
	Interim Study Reports	After 50 patients enrolled, then 6 months after enrollment is complete then 2 years after enrollment is complete
	Final Study Report	6 months after last subject out

Reviewer Comment:

While the proposed long-term safety study includes general evaluation of multiple AEs, the specific safety concern of potential long-term impact on fertility may not adequately be addressed by the proposed protocol. Additional information regarding the risk window for exposure to antibodies, the effect of dose frequency or total dose on fertility and the latency of the effect of these antibodies on fertility would be needed in order to design a study capable of addressing this specific safety concern. Since, this information is not currently available, the proposed observational study may provide general safety information but is unlikely to fully elucidate the role of anti-rHuPH20 antibodies, if any, on fertility. Similarly, while assessment of gastrointestinal AEs may provide insight into neuronal injury to the enteric plexus, the frequency of GI symptoms in the general population and the absence of a symptom pathognomonic for enteric plexus dysfunction may make it difficult to assess causality. For similar reasons, the potential impact of anti-rHUP20 antibodies on myelination at other sites of neuronal injury may not adequately be captured by the proposed study. In addition, if testing of anti-rHuP20 antibodies is not readily available in clinical practice, the prespecified endpoint to assess the incidence and titer of these antibodies is unlikely to be met-----

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3.3 Postmarketing Adverse Event Data from Baxter

On 01Apr2014, as part of the review of the resubmitted HyQvia BLA, OBE/DE requested the following information from Baxter:

1. A copy of all post-marketing adverse event reports received for HyQvia (from any source or country, including spontaneous reporting and solicited sources, such as observational or other postmarketing studies) from initial licensure (16May2013) through the present date.
2. Any additional review or analysis of these post-marketing adverse events, if applicable.

The sponsor responded to FDA’s information request on 15Apr2014 and provided the results of a search of Baxter’s pharmacovigilance database conducted for all post-marketing adverse event reports after HyQvia (including spontaneous reporting, solicited case reports, and case reports from observational and/or postmarketing studies) received between 16May2013 and 8Apr2014.¹³ The search resulted in a total of 11 reports of which 8 were assessed as possibly associated by Baxter, and 3 as unlikely or not associated. Of these 11 reports, 3 were categorized as serious and 2 refer to the same patient (reports 2013BAX043839 and 2013BAX051799). These 11 reports include a total of 59 adverse events, of which 53 were assessed as related by Baxter, and 6 as unrelated. Baxter’s analysis of all 11 reports is summarized in Table 2 below.

Table 5. Baxter’s Analysis of all Adverse Event Reports received for HyQvia between 16May2013 and 8Apr2014.

MedDRA PT	Event Level Labeling (per CCDS)	Baxter Event Level Causality	Total (n)
Nausea	Labeled	Possibly	4
Headache	Labeled	Possibly	3
Local swelling	Labeled	Possibly	3
Abdominal pain	Labeled	Possibly	2
Arthralgia	Labeled	Possibly	2
Back pain	Unlabeled	Possibly	2
Erythema	Labeled	Possibly	2
Genital swelling	Labeled	Possibly	2
Influenza like illness	Unlabeled	Possibly	2
Injection site pain	Labeled	Possibly	2
Injection site swelling	Labeled	Possibly	2
Vomiting	Labeled	Possibly	2
Allergy to metals	Unlabeled	Not associated	1
Chills	Labeled	Possibly	1
Device occlusion	Unlabeled	Unlikely	1
Discomfort	Labeled	Possibly	1
Dry mouth	Unlabeled	Possibly	1
Dyspnoea	Labeled	Unlikely	1
Excessive skin	Unlabeled	Possibly	1
Gastrointestinal viral infection	Unlabeled	Unlikely	1
Hypersensitivity	Labeled	Possibly	1
Hypotonia	Unlabeled	Possibly	1
Impaired self-care	Unlabeled	Not associated	1
Induration	Labeled	Possibly	1
Infection	Unlabeled	Unlikely	1
Injection site erythema	Labeled	Possibly	1
Injection site irritation	Labeled	Possibly	1
Injection site paraesthesia	Unlabeled	Possibly	1
Injection site pruritus	Labeled	Possibly	1
Insomnia	Unlabeled	Possibly	1
Migraine	Labeled	Possibly	1
Muscle tightness	Unlabeled	Possibly	1
Myalgia	Labeled	Possibly	1
Pruritus	Labeled	Possibly	1
Pyrexia	Labeled	Possibly	1
Rash	Labeled	Possibly	1
Rash macular	Labeled	Possibly	1
Rash pruritic	Labeled	Possibly	1
Renal pain	Unlabeled	Possibly	1
Skin warm	Unlabeled	Possibly	1
Sticky skin	Unlabeled	Possibly	1
Tension headache	Labeled	Possibly	1
Vulvovaginal swelling	Labeled	Possibly	1

Reviewer's Comment:

Baxter has provided all 11 adverse event reports and these have been reviewed in detail. All reports were analyzed for demographic information, product information and additional adverse event information. The results of this additional analysis are listed in Table 6 below. All reports are foreign, as can be expected since the product is currently licensed only in the EU. As noted in Baxter's analysis, one potential duplicate was identified - 2013BAX043839 and 2013BAX051799, shaded gray in Table 6 for ease of reference. These two cases appear to be reports of AEs occurring in the same patient on different dates. Of the 11 reports received, 3 were coded as serious (highlighted in bold in Table 6). Of note, all 3 reports were coded serious due to important medical events and none of the serious reports resulted in death, life-threatening illness, hospitalization or disability. Although 2 of the 3 serious reports share a common lot (LE16N066AE, shaded blue in Table 6), no single lot is shared by all 11 reports, or by all 3 serious reports. A second lot (LE16N077AG, shaded orange in Table 6), is shared by two patients however, these patients do not report similar AEs or share a common clinical syndrome. Of note, the two shared lots in this analysis may be a reflection of a shared geographic location where similar lots are distributed rather than an indication of a problem with a specific lot. In addition, no particular pattern was noted for AE reports following administration of either high or low doses of Ig. However given the relatively small sample size the possibility of a dose dependent AE cannot be excluded.

Table 6. Summary of FDA Analysis of all Adverse Event Reports received for HyQvia between 16May2013 and 8Apr2014.

AE Report #	Age (y)	Sex	Location	Indication	Date of AE	rHu Dose (g)	Ig Dose (g)	Ig Dose (ml)	Lot Number
2013BAX041440	76	F	Germany	CVID	?/?/2013	U	20	200	LE16N066AE
2013BAX043839	50	F	Netherlands	PID	11/01/2013	U	5-20	U	LE16N073AD
2013BAX045157	35	F	Netherlands	MG	11/08/2013	U	5-20	U	LE15N001AD LE16N077AG
2013BAX046321	43	M	Germany	CVID	09/18/2013	U	20	200	LE16N066AE
2013BAX049687	U	U	Netherlands	U	U	U	U	U	U
2013BAX051799	50	F	Netherlands	PID	11/22/2013	U	20	200	LE16N066AD
2013BAX052616	43	F	Germany	HIgE	12/10/2013 12/19/2013	U	5-10	50-100	LE16NA55AB
2014BAX000800	64	F	Netherlands	CVID	?/?/2014	2.5-5	15-30	U	LE16N055AD LE16N077AG LE16N194AF LE16N100AD
2014BAX005424	32	F	Netherlands	CVID	U	U	50	U	U
2014BAX005425	32	F	Netherlands	HypoIG	U	U	60	U	U
2014BAX005812	71	M	Germany	IgGDef	U	U	30	300	U

CVID=Common Variable Immunodeficiency, PID=Primary Immunodeficiency, MG=Myasthenia Gravis, HIgE=Hyper IgE Syndrome, HypoIG=Hypogammaglobulinemia, IgGDef = Selective IgG subclass deficiency, U=Unreported

3.3.1 Adverse events of interest – Potential effect of anti-rHuP20 antibodies on reproductive tissue

2014BAX000800 – 64 yo F with CVID administered a third dose of HyQvia (15g) in the abdomen to the right of the umbilicus and experienced swelling in the groin which resolved after 2days. The patient administered the fourth dose of HyQvia (30g) and experienced swelling of the vulvar labium which resolved after 2-3days but was followed by development of skin changes above the pubis which also eventually resolved.

Reviewer's Comment:

The potential safety concern with HyQvia results from the observation that anti-rHuP20 antibodies bind to hyaluronidase expressed in male reproductive tissues. However, available data suggests that PH20 may also be expressed in female reproductive tissues (Section 3.1 above). This adverse event report concerns the development of labial swelling in a female patient following administration of HyQvia. The report of similar symptoms with repeated administration of the product, is suggestive of a positive rechallenge. However, no laboratory analyses were conducted to evaluate the possibility of anti-rHuPH20 antibodies. In addition, while PH20 expression is described in murine vaginal and oviduct tissues¹⁴, it is unclear that PH20 is expressed in human vulvar tissues. Thus although the adverse event appears to be temporally associated to administration of HyQvia with a suggestion of positive rechallenge, there is insufficient evidence to determine the role, if any, of anti-rHuPH20 antibodies in this report of labial swelling.

3.4 Additional safety related clinical data and regulatory analyses submitted by Baxter

On 28Apr2014 Baxter submitted an amendment to the BLA (125402/0/35) which includes new non-clinical, clinical and regulatory information. Clinical data submitted includes long-term safety data from study subjects treated with HyQvia in two clinical trials as well as epidemiological data regarding the prevalence of anti-rHuPH20 antibodies in the general population. Regulatory information submitted by Baxter includes an overall benefit-risk assessment including updated risk mitigation measures and revisions to the package insert. Safety related clinical and regulatory information has been reviewed and are summarized in sections 3.4.1 and 3.4.2 below respectively.

3.4.1 Additional safety-related clinical data

3.4.1.1 Clinical Trial Data - Study 160902 and 160603

Baxter has provided safety related data from two clinical trials Study 160902 and 160603, both of which were conducted prior to licensure. Study 160603 is a prospective, open-label, non-controlled Phase III study of PID patients designed to study the efficacy, tolerability, and pharmacokinetic properties of HyQvia. Study 160902 is an extension of Study 160603 and is a prospective, open-label, non-controlled study in PID patients, designed to evaluate long term tolerability and safety of HyQvia. Of the 68 patients who completed Study 160603, 66 elected to continue in the extension study 160902. Both studies have previously been reviewed in detail as documented in OBE/DE's two previous memoranda dated 08Aug2012 and 18Apr2014. On 25Apr2014, Baxter submitted additional data from these two studies in an attempt to address concerns that anti-rHuPH20 antibodies could have an effect on the adverse event profile of HyQvia. Baxter performed analyses evaluating potential differences in safety by comparing subjects with one or more positive antibody titers to patients with no detectable antibodies. Of the 66 subjects enrolled in the extension study 160902, 63 received HyQvia for a median treatment duration of 669 days and a mean treatment duration of (\pm standard deviation) of 565.9 (\pm) 211.8 days. A total of 15 of the 63 subjects withdrew or were discontinued from the study but no subject withdrew due to a HyQvia related adverse event. A total of 15 serious AEs (SAE) occurred in 1600 infusions (SAE rate per infusion 0.009) and no SAEs were assessed as causally or temporally associated events by the sponsor.

Of the 68 subjects in study 160603, a total of 13 subjects tested positive for anti-rHuPH20 antibodies and 11 of these 13 subjects elected to enroll in the extension study 160902. Two additional subjects developed anti-rHuPH20 antibodies in study 160902 for a total of 15 unique subjects across both studies who tested positive for the antibodies. Antibody titers ranged from 1:160 to 1:81,920 with most elevated levels transient, except for 6 subjects who had persistently elevated antibody levels. No subjects developed neutralizing antibodies. In all but one of the subjects, antibody levels declined to nearly baseline despite continued exposure to rHuPH20. Titers continued to drop after use of the product was discontinued and returned to the level observed in treatment-naïve individuals by the end of the study

With regard to comparing subjects who tested positive for anti-rHuPH20 antibodies to those who test negative, Baxter previously reported that “[p]atients with detectable treatment-emergent antibodies had no

statistical or clinically meaningful differences in patient outcomes such as days missed from school or work, days hospitalized, days on antibiotics and out-patient visits, compared to those who were antibody negative”. From additional analyses comparing subjects with one or more positive antibody titers to patients with no detectable antibodies, Baxter makes the following conclusions:

1. The rates of gastrointestinal (GI) AEs by percent of subjects or percent of infusions were lower in the antibody positive subjects. Events of dysphagia, constipation and distension, which are most strongly associated with a decrease in GI motility, were the same or lower in the antibody positive subjects. Other events, such as nausea, vomiting, diarrhea and abdominal pain are more indicative of GI infections and inflammatory bowel disease and were essentially the same in both groups.
2. The rates of two neurologic AEs - headache and migraine, were similar in the antibody positive group, with a rate of headaches of 2.14% of infusions compared to 2.04% for the antibody negative group. Many neurological AEs present in the antibody negative group, such as lethargy, dizziness, syncope, and confusional state did not occur in the positive group. The data do not support the hypothesis that development of antibody to rHuPH20 is associated with adverse neurologic reactions.

Baxter also evaluated AEs in subjects with *de novo* seroconversion from negative to positive for anti-rHuPH20 during the study. The sponsor compared the rate of AEs prior to and after the first positive test for anti-rHuPH20 antibodies. Since it could not be determined precisely when the subject seroconverted between the last negative test and the first positive, a conservative approach was taken and all AEs that occurred after the last negative test were counted as AEs occurring after seroconversion. Baxter concludes that compared to the period prior to seroconversion, “[t]here was no increase in the rate of any of the AEs of interest after the subject developed the first positive anti-rHuPH20 antibody titer”.

Reviewer’s Comment:

Baxter’s additional sub-group analysis of subjects who tested positive for anti-rHuPH20 antibodies is based on a total of 15 subjects. All but one of these subjects remained persistently positive for anti-rHuPH20 antibodies while on HyQvia although Baxter reports that titers dropped to “nearly baseline”. It is unclear however, what effect persistent low level antibodies might have on individuals who are continually exposed to HyQvia over many years, as is likely to happen with chronic use of this product for the proposed indication. In addition, Baxter’s analysis of GI and neurologic AEs in this subset of patients is limited by the fact that the AEs of interest are not specific to dysfunction of the enteric plexus or other neuronal injury. For instance, Baxter’s contention that abdominal distension is “strongly associated” with decreased GI motility (and therefore presumably with enteric plexus dysfunction) while abdominal pain is not, seems to be an arbitrary distinction. Baxter has presented no evidence that abdominal distension is a strong proxy for enteric plexus dysfunction, and given the multiple symptoms that might occur due to enteric plexus dysfunction it is unlikely that any such proxy can be identified, making surveillance for this specific AE challenging, if not impossible.

3.4.1.2 Epidemiological Data – Halozyme Report 12222 r2: Prevalence of Pre-Existing rHuPH20 Antibodies in the Normal Adult Population

Baxter reports that this “study was designed to determine prevalence, persistence and demographics of rHuPH20 antibody positivity in the general population and to elucidate whether there is any relationship between rHuPH20 antibodies and selected medical conditions as reported in a questionnaire of medical and reproductive history. An interim analysis of 692 adults, recently presented at the Clinical Immunology Society (Rosengren Poster, April 2014), demonstrated an overall rHuPH20 antibody prevalence of 5.1%. Prevalence of rHuPH20 antibody was higher in men (27/311; 8%) than women (8/346; 2.3%) (p=0.0007). In the 5 subjects where a second sample was available, antibodies persisted for at least 5 months. None of the antibody positive subjects reported any autoimmune or inflammatory

conditions, or any history of injury or inflammation in reproductive organs. There were no differences in the reported rates of parenthood between antibody positive and antibody negative men or women.

Reviewer’s comment:

It is not clear from the information provided by Baxter how patients were selected in this study. It is also unclear if any of the patients included in the study had prior exposure to rHuPH20 or products containing hyaluronidase, in which case the study would not meet the prespecified objective to determine the “prevalence of pre-existing rHuPH20 antibodies in the normal adult population”. In addition, depending on the sensitivity of the assay by which anti-rHuPH20 antibodies are detected, antibodies to other isoforms of hyaluronidase may also be detected. It is important to note that the AE profile of anti-rHuPH20 antibodies may not be the same as that of other isoforms of hyaluronidase. Thus any AEs reported by subjects in the study who test positive for anti-rHuPH20 antibodies but were in fact exposed to other isoforms of hyaluronidase may confound the study results. Finally the time course with regard to antibody positivity may also be important. For instance, Baxter reports that no antibody positive subjects reported autoimmune or inflammatory conditions and that antibodies in a subset of these patients persisted for at least 5 months. If the medical conditions of interest only occur following prolonged exposure to anti-rHuPH20 antibodies, they may not have been detected in these study subjects given the relatively short time frame that antibodies were found to persist in this particular population. Similarly, if for instance, fertility is affected only in subjects who are exposed to anti-rHuPH20 antibodies pre-puberty, the date of initial seroconversion may be a contributing factor to Baxter’s finding that there was no difference in rates of parenthood between subjects who were antibody positive and those who were antibody negative.

3.4.2 Additional regulatory information

Based on information submitted in support of this BLA, Baxter concludes that the risk-benefit profile for HyQvia is favorable and that HyQvia “has been demonstrated to be safe and effective for use in adult (≥16 years) PIDD patients.”

Baxter proposes the following Risk Mitigation Measures. In addition to the long-term postmarketing surveillance study, pregnancy registry and postmarketing animal study planned post-licensure, the sponsor also proposes an educational communication plan to inform physicians and patients of potential safety concerns as well as targeted follow-up of events of special interest for spontaneous AEs. Baxter proposes the educational communication plan be distributed to all potential HyQvia prescribers. The educational package will consist of a folder containing hard copies of the package insert, the informational material, and instructions for the physician to verbally educate patients and provide a take-home copy to each patient. The package will also contain information on enrollment in the Pregnancy Registry. A patient sample group will be used to assess general readability and comprehensibility of the informational material.

Baxter also proposes to develop a list of events of special interest (EOSI) based upon the risk (to be determined in collaboration with FDA). Spontaneous reporting of an EOSI will initiate targeted follow-up by Baxter including a questionnaire to evaluate the relationship of event to HyQvia and expedited reporting of prioritized events. If a confirmed signal associated with these EOSIs is identified, the FDA will be notified immediately and further risk mitigation activities will be evaluated.

Reviewer’s comment:

While the education plan may be useful in informing physicians and patients about potential safety concerns, any AEs reported as a result of this risk mitigation activity are unlikely to be pathognomonic for the effect of anti-rHuPH20 antibodies on neuronal tissues, fertility or fetal development and may therefore be of limited use in evaluating these specific safety concerns. In other words, a comprehensive list of EOSI is likely to be too broad and nonspecific to effectively identify cases of AEs specific to anti-

rHuPH20 antibodies. Finally, should a safety concern arise, it should be reported to FDA even if the signal has yet to be confirmed.

3.5 Amendment 041 from Baxter, Follow-Up to July 31, 2014 BPAC recommendations

On 31 Jul 2014, OBRR presented HyQvia to the Blood Products Advisory Committee (BPAC) and asked the Committee to consider whether “the available data indicate a favorable benefit/risk ratio for HyQvia taking into consideration the antibodies detected against PH20 which bind human tissues.”¹⁵ The BPAC voted 15 to 1 in favor of the overall benefit of HyQvia and 16 to 0 in favor of risk communication for patients and physicians, but had mixed opinions with regard to restricted labeling for certain sub-populations (9 to 5 against, with 2 abstentions) and monitoring for emergence and/or increasing levels of anti-rHuPH20 antibodies (10 to 6 against).¹⁶

On 8 Aug 2014, following the BPAC meeting, Baxter submitted an amendment to FDA in support of the HyQvia BLA and taking into account the BPAC recommendations (125402/0/42). The amendment includes three documents - an updated package insert, updates regarding the postmarketing and a copy of the brochure planned for use in the education of physicians and patients on the use of HyQvia. Updates of note included in the amendment include changes in the package insert where the age indication is changed from adults ≥ 16 years of age to adults and children ≥ 2 years of age. The updated package insert also removes the restriction on use in nursing women and recommends use in pregnant women only if clearly indicated. The sponsor notes that these changes are made to reflect the guidance of the BPAC. Additional updates include clarification with regard to milestones for the 2 planned clinical postmarketing US studies and an increase in the proposed sample size of the Long-Term Observational postmarketing study to 550 subjects as noted in Tables 3 and 4 above.

4. SUMMARY AND RECOMMENDATIONS

This memorandum documents a comprehensive evaluation of five data sources as part of the review of Baxter’s BLA for HyQvia. First, the second SGE’s response was reviewed and was notable for comments regarding the difficulty in assessing causality to anti-PH20 antibodies if many widespread, potentially non-specific AEs are detected in a clinical trial (section 3.1). Additionally, the SGE notes there may also be scientific and technical challenges in evaluating the effect of these antibodies in animal models. Second, EU postmarketing data and the EU RMP provided to FDA by EMA are notable for a paucity of AE reports as might be expected so soon after licensure (section 3.2). Two postmarketing studies are planned to be conducted in the US and are similar to the 2 studies being conducted in the EU and listed in the EU RMP. But these studies may be of limited value due to several limitations noted on review of the study protocols. Third, postmarketing data provided by Baxter was also reviewed and was once again notable for a paucity of data given the recent date of licensure in the EU (section 3.3). Fourth, additional data submitted by Baxter in support of this BLA was notable for a subgroup analysis of a cohort of 15 patients positive for anti-rHuPH20 antibodies. The significance of the data submitted is difficult to interpret given the nonspecific AEs reported and the small sample size (section 3.4). Epidemiological data provided by Baxter regarding the prevalence of these antibodies in the general population, must be interpreted with care given the limitations of the study. The proposed risk mitigation measures submitted by Baxter may be useful for patient and physician education but are unlikely to result in an improved ability to assess causality for any AEs reported due to this risk mitigation activity. Finally, following the BPAC’s recommendations, the sponsor has proposed changes to the PI, which remove prior restrictions on use in certain sub-populations including children, pregnant women and nursing mothers (section 3.5).

The safety concerns identified on review of this BLA are unlikely to be fully evaluated in the postmarketing phase due to the challenges described above. While the proposed postmarketing studies and risk mitigation activities may provide additional information, it is unclear how much they can contribute to causality assessment or signal detection for risks resulting from effects of anti-rHuPH20 antibodies. The protocol for the Long-Term Safety study may be improved by requiring mandatory

assessments of anti-rHuPH20 antibodies at pre-specified intervals, similar to the mandatory antibody assessments required in the Pregnancy Registry. For instance, mandatory assessments of anti-rHuPH20 antibodies can occur, at minimum twice a year. In this way, the study results may lead to a better understanding of the natural history of anti-rHuPH20 antibody formation and persistence in this study population. (Note that the BPAC recommendation against monitoring for emergence and/or increasing levels of anti-PH 20 antibodies was related to routine testing of antibody levels in all or some patients treated with HyQvia in the post-market setting, not testing in the context of an active clinical study.)¹⁷ While differences in AE incidence potentially related to anti-rHuPH20 antibodies will not likely be quantifiable from these studies due to the small sample size, the long-term nature of the outcomes and other limitations discussed above, the study can provide a means to qualitatively compare the rate of AE occurrence between patients with and without elevated antibodies. This study will also provide a mechanism for additional surveillance for clusters or trends involving certain types of AEs and examination of the results for possible associated risk factors (e.g., anti-rHuPH20 antibodies, sub-group population, indication, etc.) Finally, given the BPAC recommendation against restricting use in certain subpopulations, including male children, if the product is approved for use in children, it may be useful to broaden inclusion criteria in the Long-Term Safety study to include pediatric patients. In this way, the AE profile of this product in the pediatric population can be better understood. The planned Pregnancy Registry protocol proposes following children from birth to the age of 2, to monitor infant development and collect safety information on children exposed to the product *in utero*. Should the Long-Term Safety study protocol be amended to include children who either require periodic treatment with HyQvia or have been exposed to HyQvia *in utero*, parents of infants who complete the Pregnancy protocol study may be offered recruitment in the Long-Term Safety study thus providing additional information on any potential long term effects of these antibodies in the pediatric population.

At this time, the reviewed safety data do not substantiate a need for a post-marketing requirement (PMR) study or a Risk Evaluation and Mitigation Strategy (REMS). Interim study reports of the planned post-marketing (PMC) studies should be submitted periodically to FDA for review, in accordance with the proposed study milestones.

¹ Baxter. Pharmacovigilance Plan for USA. HyQvia. Version 2.0 21Nov2013, page 6, eCTD 125402/0/32

² Baxter. eCTD 125402/0 HyQvia Submissions

³ FDA. eCTD 125402/0 CBER Documents

⁴ Winiecki S, FDA. Personal communication 08Apr2014

⁵ Baxter. Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase. Follow-Up to July 31, 2014 BPAC Recommendations – Amendment 041 8Aug2014, page 3. eCTD125402/0/042

⁶ Baxter. Clinical Study Protocol 161404. Registry Study to collect Long-Term Safety Data from Female Subjects who become pregnant during treatment with HyQvia (Immune Globulin (Human) 10% with rHuPH20). 17Jun2014 eCTD 125402/0/36

⁷ Baxter. Clinical Study Protocol --(b)(3)--. Registry Study to collect Long-Term Safety Data from Female Subjects who become pregnant during treatment with HyQvia (Immune Globulin (Human) 10% with rHuPH20) 27Jun2013. Private communication from EMA

⁸ European Medicines Agency. 29 August 2013. EMA/PRAC/530800/2013. Pharmacovigilance Risk Assessment Committee (PRAC), -----(b)(3)-----

⁹ Baxter. Gammagard Liquid. Package Insert. June 2012. Available at <http://www.fda.gov/biologicsbloodvaccines/bloodbloodproducts/approvedproducts/licensedproductsblas/fractionatedplasma/products/ucm089392.htm>

¹⁰ Baxter. Protocol/Study Number TBD. Post-Marketing, Observational Study to Examine the Long-Term Safety for Patients treated with HyQvia in Routine Clinical Care. Version 1.0 16Jun2014. eCTD 125402/0/36

¹¹ Baxter. Clinical Study Protocol --(b)(3)--. Non-Interventional Post-Authorization Safety Study on the Long-Term Safety of HyQvia in Subjects treated with HyQvia. 26Jul2013. Private communication from EMA

¹² European Medicines Agency. 10Oct2013. PRAC advice and Overview assessment on PASS protocol (HyQvia). --
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¹³ Baxter. eCTD 125402/0/34 HyQvia Submission. Response to FDA Information Request.

¹⁴ Martin-DeLeon PA. Germ-cell hyaluronidases: their roles in sperm function. *Int J Androl* 2011, 34(5 Pt 2):e306-18

¹⁵ FDA. BLOOD PRODUCTS ADVISORY COMMITTEE. 110th Meeting, July 31, 2014. ISSUE SUMMARY. Topic I. Recombinant Human Hyaluronidase (rHuPH20) combined with Immune Globulin (Human) (IG10%), for treatment of subjects with Primary Immune Deficiency (PI) administered subcutaneously (SC): Benefit/Risk Considerations with particular focus on immunogenicity of recombinant human hyaluronidase. Available at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm386681.htm>

¹⁶ The Pink Sheet. 11Aug2014. HyQvia Needs Provider, Patient Education, Not Population Restrictions, Panel Says. Available at <http://www.pharmamedtechbi.com/publications/the-pink-sheet/76/32/emhyqviaem-needs-provider-patient-education-not-population-restrictions-panel-says>

¹⁷ FDA. CBER. 110th Meeting of The Blood Products Advisory Committee July 31, 2014. Transcript p.160-3 Available at

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm386681.htm>