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The Clinical Evidence in Support of HIZENTRA for Primary Immunodeficiency (PI)

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Important Safety Information

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Hizentra: Important Safety Information

Hizentra is indicated for:

- Treatment of primary immunodeficiency (PI) in adults and pediatric patients 2 years and older.
- Maintenance therapy in adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to prevent relapse of neuromuscular disability and impairment.
    - Limitation of use: maintenance therapy in CIDP has been systematically studied for 6 months and for a further 12 months in a follow-up study. Continued maintenance beyond these periods should be individualized based on patient response and need for continued therapy.

For subcutaneous infusion only.

WARNING: Thrombosis may occur with immune globulin products, including Hizentra. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.

For patients at risk of thrombosis, administer Hizentra at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Hizentra is contraindicated in patients with a history of anaphylactic or severe systemic reaction to human immune globulin (Ig) or components of Hizentra (eg, polysorbate 80), as well as in patients with immunoglobulin A deficiency with antibodies against IgA and a history of hypersensitivity. Because Hizentra contains L-proline as stabilizer, use in patients with hyperprolinemia is contraindicated.

Hizentra: Important Safety Information

IgA-deficient patients with anti-IgA antibodies are at greater risk of severe hypersensitivity and anaphylactic reactions. Thrombosis may occur following treatment with Ig products, including Hizentra.

Monitor patients for aseptic meningitis syndrome (AMS), which may occur following treatment with Ig products, including Hizentra. In patients at risk of acute renal failure, monitor renal function, including blood urea nitrogen, serum creatinine and urine output. In addition, monitor patients for clinical signs of hemolysis or pulmonary adverse reactions (eg, transfusion-related acute lung injury [TRALI]).

Hizentra is derived from human blood. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent and its variant (vCJD), cannot be completely eliminated.

The most common adverse reactions (observed in ≥5% of study subjects) were local infusion-site reactions, as well as headache, diarrhea, fatigue, back pain, nausea, extremity pain, cough, upper respiratory tract infection, rash, pruritus, vomiting, upper abdominal pain, migraine, arthralgia, pain, fall, and nasopharyngitis.

The passive transfer of antibodies can interfere with response to live virus vaccines and lead to misinterpretation of serologic test results.

Please see full prescribing information for Hizentra accompanying this presentation and at hizentra.com/prescribinginfo.

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

About Primary Immunodeficiency

WHAT IS IT?

- A class of inherited disorders of the immune system predisposing individuals to infection and immune dysregulation with autoimmune disease and malignancy[1]

DISEASE OVERVIEW

- Severe, repetitious infections can occur in any part of the body, including the skin, sinuses, throat, ears, lungs, brain or spinal cord, urinary or intestinal tracts[2]

EPIDEMIOLOGY

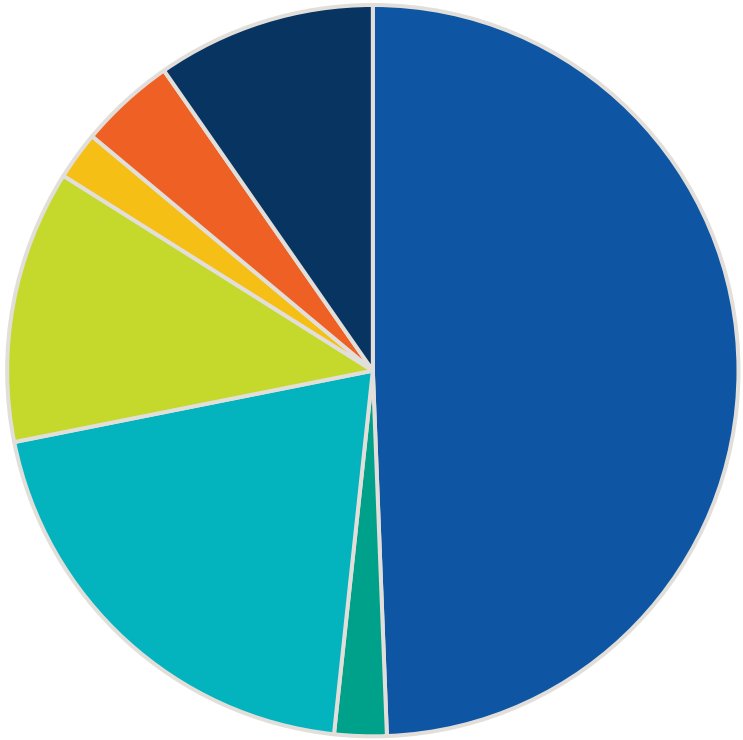
- ≈1 in 1200 people diagnosed with PI in the US[3,4]
- >400 types of PI are recognized by the International Union of Immunological Societies[5]
- National Institute of Health estimates 500,000 individuals affected in US[6]

PI, primary immunodeficiency.

1. Bonilla FA et al. *Ann Allergy Asthma Immunol.* 2005;94:S1-S63. **2.** Immune Deficiency Foundation. https://primaryimmune.org/about-primary-immunodeficiencies. Accessed February 19, 2020. **3.** Immune Deficiency Foundation. Primary immunodeficiency diseases in America: 2007. https://primaryimmune.org/wp-content/uploads/2011/04/ Primary-Immunodeficiency-Diseases-in-America-2007The-Third-National-Survey-of-Patients.pdf. Accessed September 17, 2019. **4.** McCusker et al. *Allergy Asthma Clin Immunol*. 2018; 14:61. **5**. Tangye SG et al. J Clin Immunol. 2020;40(1):24-64. **6.** National Institutes of Health. https://www.niaid.nih.gov/diseases-conditions/primary-immune-deficiency-diseases-pidds. Accessed June 22, 2020.

Major Categories of PI (US)

Distribution of PIDs registered in the USID database



Category	Examples
Predominantly Antibody Deficiencies	• CVID • Agammaglobulinemia
Combined immunodeficiencies with associated or syndromic features	• DiGeorge Syndrome • Wiskott-Aldrich Syndrome
Congenital defects of phagocyte number or function	• Chronic Granulomatous Disease
Defects in Intrinsic and Innate Immunity	• Mucocutaneous candidiasis • NK Cell Defect
Diseases of Immune Dysregulation	• HLH, including XLP and Pigmentary disorders • Autoimmune lymphoproliferative syndrome (ALPS)
Immunodeficiencies affecting cellular and humoral immunity	• Severe Combined Immune Deficiency (SCID) • Hyper IgM Syndrome
Other	• Other immune deficiency – known/unknown cause

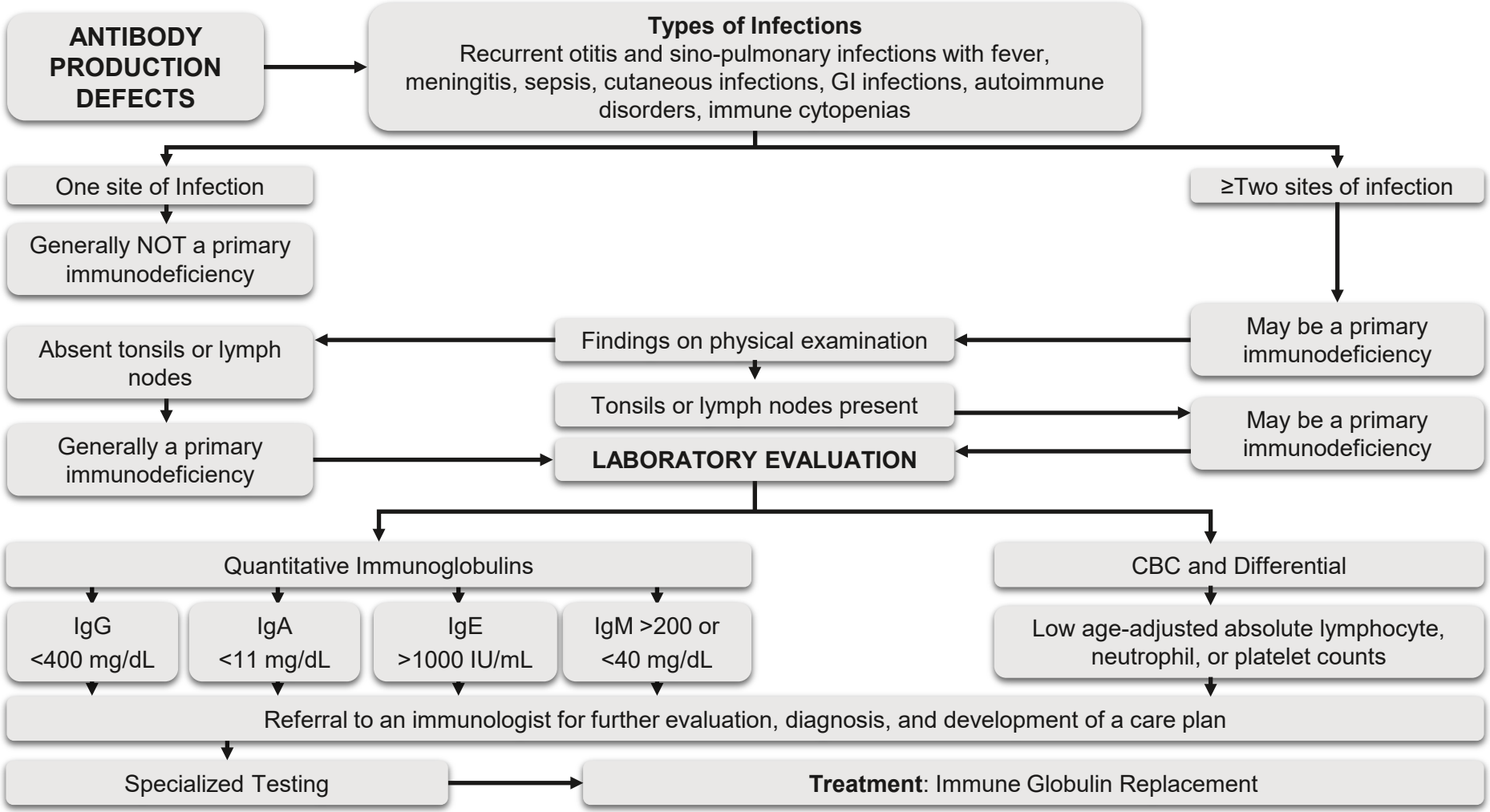
USIDNET Patient Registry. Available at: http://usidnet.org/ Accessed November 11, 2020.

Presentation of PI

- Individuals with PI are predisposed to severe and frequent infections[1]
  - Typical infections include those of the sinuses, ears, and lungs
  - Infections can lead to lung damage and shorten lifespan[2]
- PI, particularly CVID, is also associated with:
  - Immune dysregulation and autoimmune disease[4]
    - Autoimmunity complications contribute to morbidity/mortality
    - Autoimmune hematologic complications often present as immune thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA)
  - Malignancy[5]
- PIs may present as routine infections and go undetected in the primary care setting
  - PID is underdiagnosed and associated with long diagnostic delays[6]

1. McCusker C, Warrington R. *Allergy, Asthma Clin Immunol.* 2011;7(Suppl 1):S11.
2. Kobrynski L. *Biologics.* 2012;6:277–287.
3. Resnick ES, et al. *Blood.*2012;119:1650–1667.
4. Agarwal S et al. *Ann Allergy Asthma Immunol.* 2019;123(5):454-460.
5. Shapiro RS. *Am J Hematol.* 2011;86:49–55.
6. Immune Deficiency Foundation. Primary Immunodeficiency Diseases in America: 2007. The third National survey of patients. Published May 1, 2009.

Diagnosis of PI



Immune Deficiency Foundation. Diagnosis & Clinical Care Guidelines for Primary Immunodeficiency Diseases. https://primaryimmune.org/wp-content/uploads/2011/04/IDF-Diagnostic-Clinical-Care-Guidelines-for-Primary-Immunodeficiency-Diseases-2nd-Edition.pdf. Accessed May 24, 2016.

PI Diagnostic Challenges: Comorbid Conditions

- Comorbidities may confound diagnosis of PI
- For example:

Autoimmune hemolytic anemia/ thrombocytopenia	Rheumatologic complications	Malignancy	Bowel disease
• Connection with CVID may be missed[1-3]	• Chronic infection (e.g., with mycoplasma) has been identified in the synovial fluid of some patients[1,8-10]	• Similar clinical symptoms as hematological malignancy (e.g. lymphoma), and other cancers (e.g. gastric and lung)[4-6]	• Symptoms may overshadow respiratory infections[7]

1. Asia Pacific Immunoglobulins in Immunology Expert Group Inc (APIIEG). Consensus Recommendations for the Use of Immunoglobulin Replacement Therapy in Immune Deficiency. 2nd ed. Published July 2009. Accessed May 24, 2016.
2. Exley AR, et al. *Am J Respir Crit Care Med.* 2009;179:A3218.
3. Baleeiro C, Mull N. *Am J Respir Crit Care Med*. 2010;181:A3187.
4. Shapiro RS, et al. *Am J Hematol*. 2011;86(1):48-55.
5. Mayor PC, et al, *J Allergy Clin Immunol*. 2018; 141(3): 1028–1035.
6. Haas OA. *Front Immunol.* 2019 12;9:3136.
7. Kobrynski LJ, Mayer L. *Clin Immunol.* 2011;139:238–248.
8. Azizi G, et al. *Scand J Immunol.* 2018; 87(5):e12663.
9. Kitcharoensakkul M and Cooper MA. *Curr Opin Allergy Clin Immunol.* 2019;19(6):545-552.
10. Gutierrez MJ, et al. *Semin Arthritis Rheum.* 2018;48(2):318-326.

PI Diagnostic Challenges: Comorbid Conditions

Respiratory complications

- Lung disease and respiratory complications in CVID
  - Inflammatory complications, notably chronic lung disease (CLD) are a leading source of morbidity and mortality in CVID[1]
  - CLD affects as many as 30-60% of CVID patients[1,2,3]
  - CLD is characterized by bronchiectasis and/or interstitial lung disease[4]
  - A non-infectious complication of CVID is granulomatous–lymphocytic interstitial lung disease (GLILD)[5]
- Many patients with agammaglobulinaemia develop chronic lung disease and reduced lung function[6]

1. Resnick ES, et al. *Blood*. 2012;16;119(7):1650-7.
2. Chapel H, et al. *Blood.* 2008;112:277-86.
3. Quinti I, et al. *J Clin Immunol.* 2007;27:308-16.
4. Schussler E, et al. *J Allergy Clin Immunol Pract*. 2016;4(6):1039-1052.
5. Bates CA, et al. *J Allergy Clin Immunol.* 2004;114(2):415-21.
6. Stubbs, A et al. *Clin Exp Immunol*. 2018; 191(2): 212–219.

PI Diagnostic Challenges: Comorbid Conditions

Autoimmunity in PI

- Autoimmunity in CVID most commonly manifests as autoimmune cytopenia (AC), occurring in 4% to 20% of patients
- AC usually occurs with immune thrombocytopenic purpura (ITP, 14%), sometimes autoimmune hemolytic anemia (AIHA, 7%) or Evans' syndrome (4%)

Agarwal S, et al. *Ann Allergy Asthma Immunol*. 2019;123(5):454-460.

Treatment guidelines

AAAAI: Working Group Update on the use of immunoglobulin in human disease (2017)[1]

- Ig therapy (IV or SC) is required for patients with PI characterized by impaired antibody production, usually accompanied by recurrent or unusually severe infection
- Mandatory for patients with severe PIs that directly impact B-cell function and antibody production
- Increasingly seen as important in other PIs in which antibody or B-cell dysfunction is implicated by may be as apparent by conventional testing

AAAAI, ACAAI and JCAAI: Practice Parameters (2015)

- Ig therapy is indicated for all PI disorders with significantly impaired antibody production
- Patients receiving Ig therapy should have regular monitoring of IgG trough levels, blood cell counts, and serum chemistry

AAAAI: American Academy of Allery, Asthma, & Immunology. ACAAI: American College of Allergy, Asthma, and Immunology JCAAI: Joint Council of Allergy, Asthma and Immunology PID : Primary Immunodeficiency, Ig: Immunoglobulin, IV: intravenous, SC: subcutaneous

1. Perez EE, et al. *J Allergy Clin Immunol.* 2017;139(3s):S1-S46.
2. Bonilla FA, et al. *J Allergy Clin Immunol.* 2015;136(5):1186-205.e1-78.

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Features of IVIg and SCIg Therapy

Infusion	SCIg	IVIg
Administration	Infused **subcutaneously**	Infused **intravenously**
Volume*	Generally **lower** volumes	Generally **higher** volumes
Frequency	**1-2 infusions** over **1-2 consecutive days weekly**†	Typically every **3–4 weeks**
IgG Levels	**Relatively stable** IgG levels	Wider **fluctuation** in IgG levels
By Whom	Can be **self-administered** after proper training	Requires administration by a trained **HCP**
Duration	Infusion usually lasts **1–2 hours**‡	Infusion usually lasts **3–4 hours**§

No difference in the clinical benefit of SCIg and IVIg serum profiles has been demonstrated by substantial clinical evidence or experience. *Based on an equivalent dose in grams. †Dependent upon patient's clinical needs, tolerance for infusion volume and rate. ‡Based on previously approved infusion parameters. §Depending on product. HCP, health care provider.

Younger ME et al. IDF *Guide for Nurses Immunoglobulin Therapy for Primary Immunodeficiency Diseases*. 3rd ed. Towson, MD: Immune Deficiency Foundation; 2012:1-54.

Pivotal Trials in Primary Immunodeficiency

Efficacy and Safety of a New 20% Immunoglobulin Preparation for Subcutaneous Administration, IgPro20, in Patients With Primary Immunodeficiency (US Trial)

AND

Efficacy and safety of Hizentra® in patients with primary immunodeficiency after a dose-equivalent switch from intravenous or subcutaneous replacement therapy (EU Trial)

Pivotal Trials in PI: Study Design

	US Study[1]	EU Study[2]
Objective	To evaluate the efficacy and safety of Hizentra in patients with primary immunodeficiency (PI)	
Clinical Sites	12	15
Eligible PIDs	• Common variable immunodeficiency (CVID) or X-linked agammaglobulinemia (XLA) • The EU Trial also allowed patients with autosomal recessive agammaglobulinemia (ARAG)	
Patient Ages	5–72 years	2–65 years
Other Inclusion Criteria	• Regular IVIg therapy every 3 to 4 weeks for at least 3 months prior to enrollment • The EU study also allowed patients using weekly SCIg therapy for at least the preceding 6 months • Documented serum IgG trough level(s) of ≥5 g/L during this time	
Study Type	Phase III, open-label, prospective, multicenter, single-arm	
No. of Patients Enrolled	49	51
Dose Adjustment Coefficient†	1.53	1.0
Treatment Duration	15 months	10 months

1. Hagan JB, et al. *J Clin Immunol.* 2010;30:734-745.
2. Jolles S, et al. *Clin Immunol.* 2011:141:90-102.

Pivotal Trials in PI: Endpoints

	US Study[1]	EU Study[2]
Primary Endpoint	Annual rate of serious bacterial infections* (aSBI)	Serum IgG trough levels at steady state
Secondary Endpoints	Serum IgG trough levels	aSBI

*Serious bacterial infections defined as bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess

1. Hagan JB, et al. *J Clin Immunol.* 2010;30:734-745.
2. Jolles S, et al. *Clin Immunol.* 2011:141:90-102.

Pivotal Trials in PI: Efficacy

Endpoints		US Study[1] (n=38)	EU Study[2‡] (n=46)
Events per Patient-Year	Serious bacterial infection	0.00	0.00
	Any infection	2.76	5.18
Days per Patient-Year	Unable to perform usual activities or days missed from work/school	2.06	8.00
	Hospitalized due to infections	0.2	3.48
	Use of antibiotics for prophylaxis or treatment	48.5	72.75
Mean trough IgG level†, mg/dL		1253	810

†Mean of individual median levels during the study treatment period.

‡Data include 1 patient who suffered from recurrent pneumonias. Inclusion of these data affected the overall rates reported above. Annual rates per subject year excluding this subject were as follows: all infection episodes 5.16; days missed from school/work 5.25; hospitalized due to infections 0.95; use of antibiotics 66.62.

‡‡ 1 patient discontinued from the study during the wash-in/wash-out period due to relocation,

1. Hagan JB, et al. *J Clin Immunol.* 2010;30:734-745.
2. Jolles S, et al. *Clin Immunol.* 2011:141:90-102.

Hizentra (20% SCIg) PI Pivotal Trial Results for US, EU

FDA predefined success rate of <1 aSBI per subject year

	US Study[1] (n=49)	EU Study[2] (n=51)
Dose	1:1.53	1:1
Duration, weeks	64	40
Infections		
Annual rate of SBI per subject year	0	0
Annual rate for any infection per subject year	2.76	5.18
Adverse Reactions		
Any adverse events per infusion	0.773	0.288
Local reactions per infusion	0.580	0.060

aSBI: acute SBI; SBI: serious bacterial infection (defined as pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess); FDA: US Food and Drug Administration; PI: primary immunodeficiency; SCIg: subcutaneous immunoglobulin.

*At least possibly related to Hizentra

1. Hagan JB, et al. *J Clin Immunol.* 2010;30(5):734-745.
2. Jolles S, et al. *Clin Immunol.* 2011;141(1):90-102.

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Safety and Tolerability: US Trial

		% of Patients (n=49)	Rate, % of infusions† (n=2264 infusions)
Serious ARs* Considered at Least Possibly Related		0	0
Local Reactions‡		100	58.4
Systemic ARs* Observed in ≥5% of Study Patients Occurring During or Within 72h After Completion of an Infusion	Headache	24.5	1.4
	Diarrhea	10.2	0.3
	Fatigue	8.2	0.2
	Back Pain	8.2	0.2
	Nausea	8.2	0.2
	Cough	8.2	0.2
	Pain in Extremity	8.2	0.3
	Vomiting	6.1	0.1
	Upper Abdominal Pain	6.1	0.1
	Migraine	6.1	0.2
	Pain	6.1	0.2

*Excluding infections.

†Rate of ARs per infusion.

‡Includes injection-site reactions as well as bruising, scabbing, pain, irritation, cysts, eczema, and nodule at the injection site.

1. Hagan JB, et al. *J Clin Immunol.* 2010;30(5):734-745.

Safety and Tolerability: EU Trial

		% of Patients (n=51)	Rate, % of infusions† (n=1831 infusions)
Serious ARs* Considered at Least Possibly Related		0	0
Local Reactions‡		47.1	5.7
Systemic ARs* Observed in ≥5% of Study Patients Occurring During or Within 72h After Completion of an Infusion	Headache	17.6	1.1
	Rash	7.8	0.2
	Pruritus	7.8	0.7
	Fatigue	5.9	0.3

*Excluding infections.

†Rate of ARs per infusion.

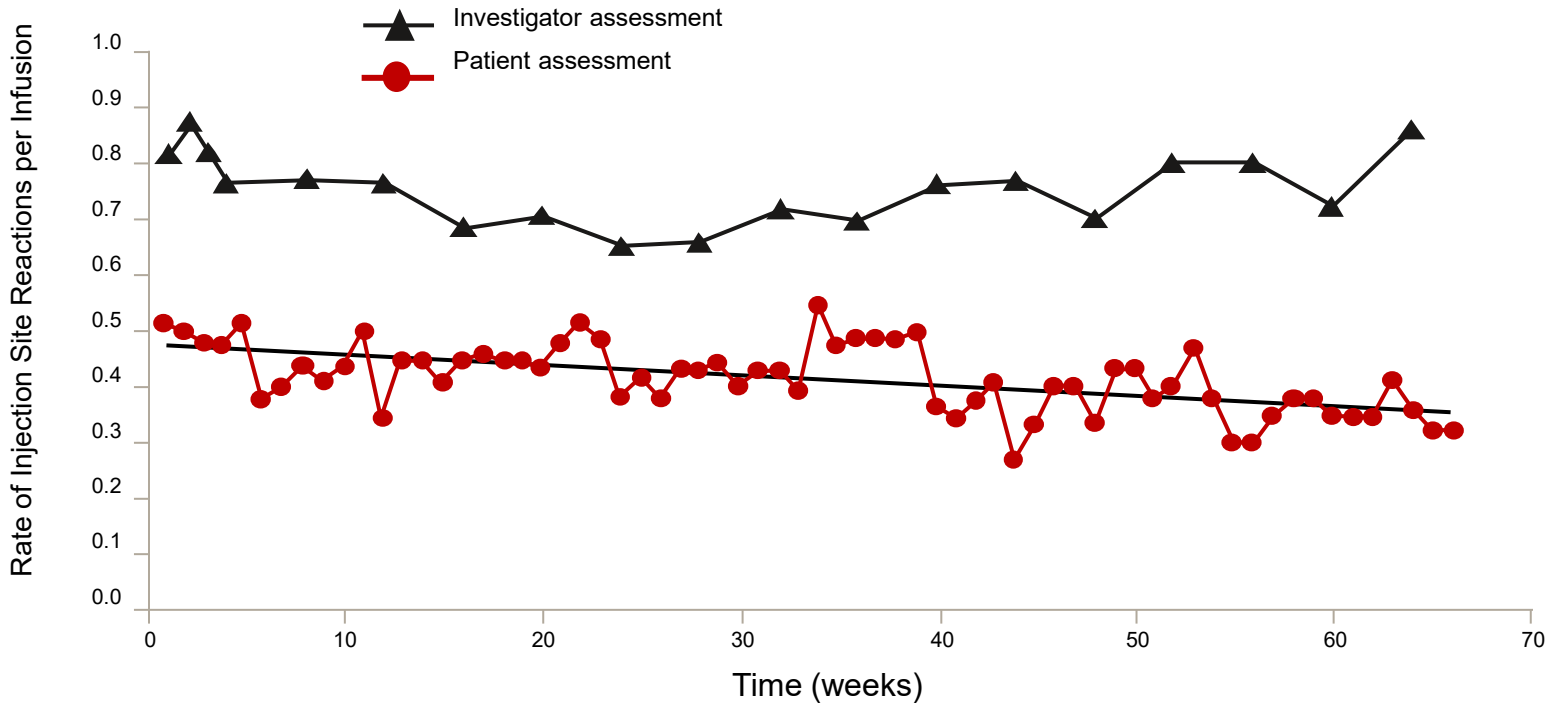
‡Includes infusion-related reaction; infusion-site mass; infusion/injection-site erythema, hematoma, induration, inflammation, edema, pain, pruritus, rash, reaction, swelling, injection-site extravasation, nodule; puncture-site reaction.

1. Jolles S, et al. *J Clin Immunol.* 2011;141:90-102.

Reports of Local Site Reactions With SCIg Infusions are Common and Usually Mild in Patients With PI

Patient Reports of Local Reactions Decreased Over Time

Occurrence of Local Reactions as Assessed by Patients and Investigators in a US study[1*]



% of local reactions reported as mild

93.4% US clinical study[1]

87.3% EU clinical study[2]

Withdrawal due to local reactions

US clinical trial: 2%

EU clinical trial: 5.9%

*Investigator assessments: performed 15 to 45 minutes post infusion at the study site, every 4 weeks; patient assessment: 24 ±3 hours post each infusion until completion of the study (completion visit, week 66). The number of infusions with available data decreased from 49 at week 1 to 28 at week 64 for both patient and investigator assessments.
Reprinted with permission from Hagan JB et al. *J Clin Immunol.* 2010;30:734-745.

1. Hagan JB et al. *J Clin Immunol*. 2010;30:734-745. **2.** Jolles S et al. *Clin Immunol*. 2011:141:90-102.

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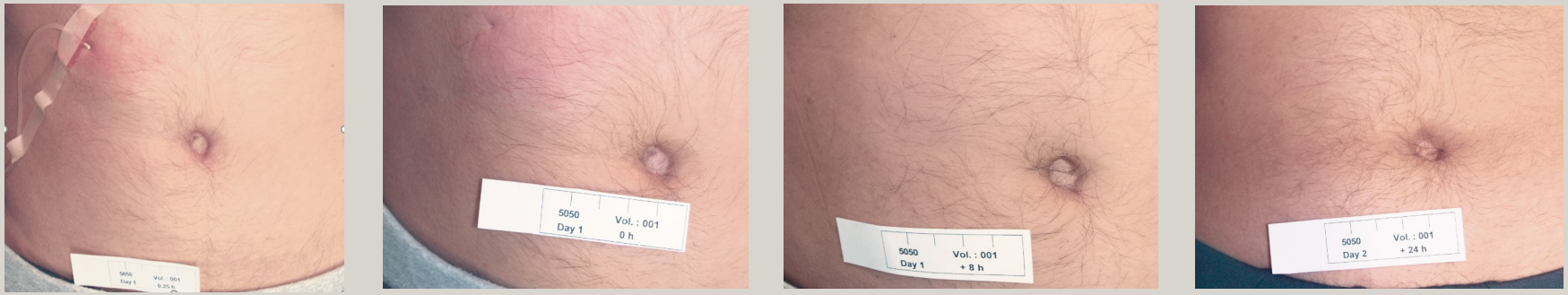
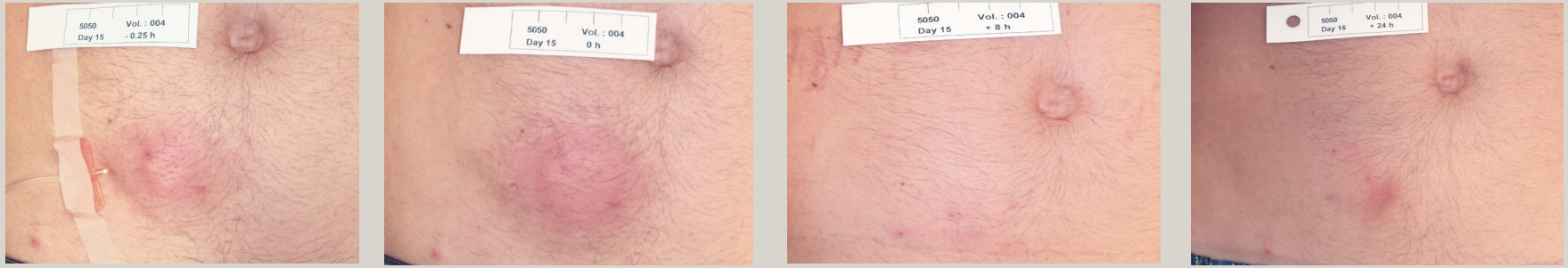
Local Reactions in PI: Mild and Moderate Local Reactions are Common and Expected*

15 min prior to end of infusion	End of infusion	8 hours post infusion	24 hours post infusion

Mild



Moderate



Mild to moderate local infusion-site reactions (eg, swelling and redness) are a common side effect of subcutaneous therapy, but patients should contact their healthcare professional if a local reaction increases in severity or persists for more than a few days.

*Mild=does not interfere with routine activities; moderate=interferes somewhat with routine activities and may have warranted intervention.
Photos are from the Hizentra Phase 1 clinical trial.

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Management of Hizentra Therapy

Hizentra Dosing in PI

PI

- Obtain patient's serum IgG trough level
- Start Hizentra 1–2 weeks after last IVIg infusion or 1 week after the last SCIg infusion
- Initial dosing calculations:
  - **Weekly dose:** $\frac{\textit{Monthly IVIg dose in g}}{\textit{Number of weeks between infusions}} \times 1.37$
  - **Every 2 weeks:** $Weekly\ dose \times 2$
  - **Frequent dosing*:** $\frac{\textit{Weekly dose in g}}{\textit{Number of days to infuse per week}}$
- Adjust the dose based on clinical response and IgG trough levels

*2–7 times per week.

Hizentra Administration in PI

Hizentra is intended for subcutaneous administration using an infusion pump

INFUSION PUMP Daily up to every 2 weeks		
Infusion parameters*	**1st infusion**	**Subsequent infusions**
Volume (mL/site)	≤15	≤25
Rate (mL/h/site)	≤15	≤25
Infusion sites	Up to 8 infusion sites allowed simultaneously, with at least 2 inches between sites	

*As tolerated.

SCIg Use in Pediatrics

- SCIg is safe and effective in children over the age of 2 with PI[1,2,3]
- Systemic adverse reactions can occur but have been shown to be infrequent[1,2,3,4]
- Local site reactions are mostly mild or moderate and decline over time[1,2,3]
- Infusions regimens can be adjusted and individualized from daily to biweekly frequency[3,5]

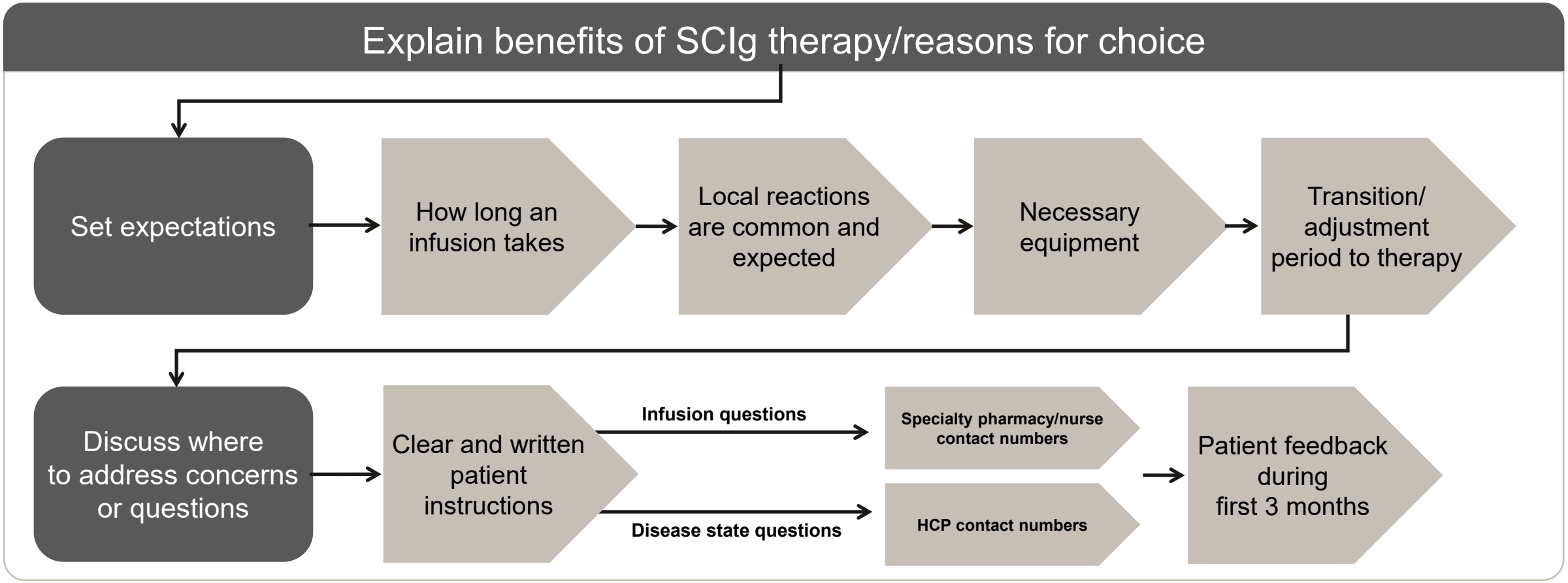
1. Gardulf A et al. J Clin Immunol. 2006;26:181-182
2. Borte M et al. J Clin Immunol. 2011;31:752-761
3. Shapiro RS et al. Pediatric Allergy and Immunology. 2013;24:49-53
4. Patel NC et al. J Clin Immunol. 2015;35:558-565
5. Canessa C et al. Pediatric Allergy, Immunology and Pulmonology. 2019;32:70-75

What Patients Need to Know

- Hizentra is now also available in prefilled syringes
- Rate adjustments, if tolerated, can decrease total infusion time
- Site volume adjustments, if tolerated, can decrease needle sticks
- Improvement in administration regimen can sometimes be achieved by changing supplies

- Dosing adjustments should be discussed with prescriber to ensure desired result is being achieved
- Specialty Pharmacy Providers should check patients' SCIg regimen regularly to adjust infusion parameters as needed
- CSL provides resources, such as Medical Information and Field Reimbursement Managers, to assist physicians as appropriate

Setting Expectations to Foster Greater Commitment to Therapy[1,2]



1. Younger ME et al. *J Infus Nursing.* 2013;36:58-68. **2.** Younger ME, et al. *IDF Guide for Nurses Immunoglobulin Therapy for Primary Immunodeficiency Diseases*. 3rd ed. Towson, MD: Immune Deficiency Foundation; 2012:1-54.