Immune Globulins (IVIG and SCIG)

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Instructions for Use

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Related Policies

- N/A

Coverage Rationale

This policy refers to the following immune globulin products:

- Alyglo (immune globulin intravenous, human-stwk), 10% Liquid
- Asceniv (immune globulin intravenous, human – slra) 10% Liquid
- Bivigam- immune globulin intravenous (human) 10% injection, solution
- Cutaquig® (Immune Globulin Subcutaneous (Human) - hipp)
- Cuvitru, Immune Globulin Subcutaneous (Human)
- Flebogamma 5% DIF (immune globulin intravenous [human]), solution for intravenous administration
- Gammagard liquid, Immune Globulin Infusion (Human), 10% Solution, for intravenous and subcutaneous administration
- Gammagard S/D, Immune Globulin Intravenous (Human) IgA less than 1 microgram per mL in a 5% Solution
- Gammaked™, [Immune Globulin Injection (Human), 10% Caprylate/ Chromatography Purified]
- Gamunex -C, [Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified]
- Hizentra, Immune Globulin Subcutaneous (Human)
- HyQvia [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase] solution, for subcutaneous administration
- Octagam [Immune Globulin Intravenous (Human)] Liquid Preparation
- Panzyga, (immune globulin intravenous, human - ifas) 10% Liquid Preparation
- Privigen, Immune Globulin Intravenous (Human), 10% Liquid
- Xembify® (immune globulin subcutaneous, human- klhw)

Primary Immunodeficiency

For initial coverage of Intravenous or subcutaneous immune globulins (IVIG or SCIG) for primary immunodeficiency, the following will be required:

- For patients with a primary immunodeficiency syndrome **and**
- Clinically significant functional deficiency of humoral immunity as evidenced by one of the following:
  - Documented failure to produce antibodies to specific antigens **or**

- History of significant recurrent infections

For initial coverage of HyQvia for primary immunodeficiency, the following will be required:

- For patients with a primary immunodeficiency syndrome **and**
- Patient is 2 years of age or older **and**
- Clinically significant functional deficiency of humoral immunity as evidenced by one of the following:
  - Documented failure to produce antibodies to specific antigens **or**
  - History of significant recurrent infections

Idiopathic Thrombocytopenic Purpura (ITP)

For initial coverage of Intravenous immune globulins (IVIG) for Idiopathic Thrombocytopenic Purpura (ITP), the following will be required:

- Diagnosis of idiopathic thrombocytopenic purpura (ITP) **and**
- One of the following:
  - Patient had trial and failure, contraindication or intolerance to a corticosteroid **or**
  - A platelet count of less than 30,000 cells/mm3

Kawasaki Disease (KD)

For initial coverage of Intravenous immune globulins (IVIG) for Kawasaki Disease (KD), the following will be required:

- Diagnosis of Kawasaki Disease

B-cell Chronic Lymphocytic Leukemia (CLL)

For initial coverage of Intravenous immune globulins (IVIG) for B-cell Chronic Lymphocytic Leukemia (CLL), the following will be required:

- Diagnosis of B-cell chronic lymphocytic leukemia (CLL) **and**
- One of the following:
  - Documented hypogammaglobulinemia (IgG less than 500 mg/dL) **or**
  - History of bacterial infection(s) associated with B-cell CLL

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

For initial coverage of Alyglo, Asceniv, Hizentra, HyQvia, or Intravenous immune globulins (IVIG) for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), the following will be required:

- Diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) as confirmed by all of the following:
  - Progressive symptoms present for at least 2 months **and**
  - Symptomatic polyradiculoneuropathy as indicated by one of the following:
    - Progressive or relapsing motor impairment of more than one limb **or**
    - Progressive or relapsing sensory impairment of more than one limb **and**
  - Electrophysiologic findings when three of the following four criteria are present:
    - Partial conduction block of 1 or more motor nerve
    - Reduced conduction velocity of 2 or more motor nerves
    - Prolonged distal latency of 2 or more motor nerves
    - Prolonged F-wave latencies of 2 or more motor nerves or the absence of F waves
    - Absence of F waves of 2 or more motor nerves
    - Abnormal Temporal Dispersion of 2 or more motor nerves
    - Distal compound muscle action potential (CMAP) duration increase of 1 or more motor nerves

For reauthorization coverage of Alyglo, Asceniv, Hizentra, HyQvia, or Intravenous immune globulins (IVIG) for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), the following will be required:

- Patient demonstrates positive clinical response to therapy as measured by an objective scale (e.g., Rankin, Modified Rankin, Medical Research Council [MRC] scale) **and**
- Attestation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

Bone Marrow Transplantation (off-label) [10, 45, 66, 67, 68]

For initial coverage of Alyglo, Asceniv, or Intravenous immune globulins (IVIG) for Bone Marrow Transplantation (off-label), the following will be required:

- Confirmed allogeneic bone marrow transplant within the last 100 days **and**
- Documented severe hypogammaglobulinemia (IgG less than 400 mg/dL)

HIV (off-label) [3, 9, 45, 46, 47]

For initial coverage of Alyglo, Asceniv, or Intravenous immune globulins (IVIG) for HIV (off-label), the following will be required:

- Diagnosis of HIV disease **and**
- One of the following:
    - Documented hypogammaglobulinemia (IgG less than 400 mg/dL) **or**
    - Functional antibody deficiency as demonstrated by one of the following:
        - Poor specific antibody titers **or**
        - Recurrent bacterial infections

Multifocal Motor Neuropathy (off-label) [45, 70, 71, 74]

For initial coverage of Alyglo, Asceniv, or Intravenous immune globulins (IVIG) for Multifocal Motor Neuropathy (off-label), the following will be required:

- Diagnosis of multifocal motor neuropathy (MMN) as confirmed by all of the following:
    - Weakness with slowly progressive or stepwise progressive course over at least one month **and**
    - Asymmetric involvement of two or more nerves **and**
    - Absence of both of the following:
        - Motor neuron signs **and**
        - Bulbar signs

For reauthorization coverage of Alyglo, Asceniv , or Intravenous immune globulins (IVIG) for Multifocal Motor Neuropathy (off-label), the following will be required:

- Patient demonstrates positive clinical response to therapy as measured by an objective scale (e.g., Rankin, Modified Rankin, Medical Research Council [MRC] scale) **and**
- Attestation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

Relapsing-Remitting Multiple Sclerosis (off-label) [2, 20, 27, 45]

For initial coverage of Alyglo, Asceniv, or Intravenous immune globulins (IVIG) for Relapsing-Remitting Multiple Sclerosis (off-label), the following will be required:

- Diagnosis of relapsing remitting multiple sclerosis (RRMS) **and**
- Attestation of an MS exacerbation or progression (worsening) of the patient's clinical status from the visit prior to the one prompting the decision to initiate immune globulin therapy

For reauthorization coverage of Alyglo, Asceniv, or Intravenous immune globulins (IVIG) for Relapsing-Remitting Multiple Sclerosis (off-label), the following will be required:

- The prescriber maintains and provides chart documentation of the patient's evaluation, including both of the following:
    - Findings of interval examination including neurological deficits incurred **and**
    - Assessment of disability (e.g., Expanded Disability Status Score [EDSS], Functional Systems Score [FSS], Multiple Sclerosis Functional Composite [MSFC], Disease Steps [DS]) **and**

- Stable or improved disability score (e.g., EDSS, FSS, MSFC, DS) **and**
- Documentation of decreased number of relapses since starting immune globulin therapy **and**
- Diagnosis continues to be the relapsing-remitting form of MS (RRMS) **and**
- Attestation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

Myasthenia Gravis Exacerbation (off-label) [45, 54, 57]

For initial coverage of Alyglo, Asceniv, or Intravenous immune globulins (IVIG) for Myasthenia Gravis Exacerbation (off-label), the following will be required:

- Diagnosis of generalized myasthenia gravis **and**
- Evidence of myasthenic exacerbation, defined by one of the following symptoms in the last month:
    - Difficulty swallowing **or**
    - Acute respiratory failure **or**
    - Major functional disability responsible for the discontinuation of physical activity **and**
- Concomitant immunomodulator therapy (e.g., azathioprine, mycophenolate mofetil, cyclosporine), unless contraindicated, will be used for long-term management of myasthenia gravis **and**

Prescribed by or in consultation with a physician who has specialized expertise in managing patients on immune globulin therapy (e.g., immunologist, hematologist, neurologist)

Stiff Person Syndrome (off-label) [39, 43, 45]

For initial coverage of Alyglo, Asceniv, or Intravenous immune globulins (IVIG) for Stiff Person Syndrome (off-label), the following will be required:

- Diagnosis of stiff-person syndrome **and**
- Trial and failure, contraindication or intolerance to GABAergic medication (e.g., baclofen, benzodiazepines) **and**
- Trial and failure, contraindication or intolerance to immunosuppressive therapy (e.g., azathioprine, corticosteroids)

For reauthorization coverage of Alyglo, Asceniv, or Intravenous immune globulins (IVIG) for Stiff Person Syndrome (off-label), the following will be required:

- Attestation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

Dermatomyositis and Polymyositis (off-label) [11, 15, 16, 17, 18, 37, 45]

For initial coverage of Alyglo, Asceniv, or Intravenous immune globulins (IVIG) for Dermatomyositis and Polymyositis (off-label), the following will be required:

- One of the following diagnoses:
    - Dermatomyositis **or**
    - Polymyositis **and**
- Trial and failure, contraindication, or intolerance to immunosuppressive therapy (e.g., azathioprine, corticosteroids, cyclophosphamide, methotrexate)

For reauthorization coverage of Alyglo, Asceniv, or Intravenous immune globulins (IVIG) for Dermatomyositis and Polymyositis (off-label), the following will be required:

- Attestation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

Guillain-Barre Syndrome (off-label) [29, 45, 59, 72]

For initial coverage of Alyglo, Asceniv, or Intravenous immune globulins (IVIG) for Guillain-Barre Syndrome (off-label), the following will be required:

- Diagnosis of Guillain-Barre Syndrome **and**
- Patients with severe disease requiring aid to walk **and**
- Onset of neuropathic symptoms within the last four weeks

For reauthorization coverage of Alyglo, Asceniv, or Intravenous immune globulins (IVIG) for Guillain-Barre Syndrome (off-label), the following will be required:

- Attestation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

Lambert-Eaton Myasthenic Syndrome (off-label) [5, 45]

For initial coverage of Alyglo, Asceniv, or Intravenous immune globulins (IVIG) for Lambert-Eaton Myasthenic Syndrome (off-label), the following will be required:

- Diagnosis of Lambert-Eaton Myasthenic Syndrome (LEMS) **and**
- History of failure, contraindication, or intolerance to immunomodulator monotherapy (e.g., azathioprine, corticosteroids) **and**
- Concomitant immunomodulator therapy (eg, azathioprine, corticosteroids), unless contraindicated, will be used for long-term management of LEMS

For reauthorization coverage of Intravenous immune globulins (IVIG) for Lambert-Eaton Myasthenic Syndrome (off-label), the following will be required:

- Attestation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

Pediatric Acute-Onset Neuropsychiatric Syndrome/Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANS/PANDAS) (off-label) [22, 23, 56]

For initial coverage of Intravenous immune globulins (IVIG) for Pediatric Acute-Onset Neuropsychiatric Syndrome/Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANS/PANDAS) (off-label), the following will be required:

- Diagnosis of one of the following:
    - Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) **or**
    - Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) **and**
    - Disease is moderate to severe as defined by distressing symptoms that interfere with daily activities that occupy at least 50 percent (%) of waking hours **and**
    - Trial and failure, contraindication, or intolerance to one of the following:
        - Corticosteroids (e.g., prednisone, dexamethasone, methylprednisolone) **or**
        - NSAIDs (e.g., Ibuprofen, naproxen, celecoxib)

Antibody-mediated Transplant Rejection (off-label) [45, 78-86]

For initial coverage of Intravenous immune globulins (IVIG) for Antibody-mediated Transplant Rejection (off-label), the following will be required:

- Patient has received or will receive solid organ transplant
- One of the following:
    - Desensitization therapy prior to and/or immediately after transplantation
    - Diagnosis or suspected diagnosis of Antibody-mediated Transplant Rejection

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (eg, liquid), 500 mg
J1551	Injection, immune globulin (Cutaquig), 100 mg
J1554	Injection, immune globulin (Asceniv), 500 mg
J1555	Injection, immune globulin (Cuvitru), 100 mg
J1556	Injection, immune globulin (Bivigam), 500 mg
J1558	Injection, immune globulin (Xembify), 100 mg
J1559	Injection, immune globulin (Hizentra), 100 mg
J1561	Injection, immune globulin, (Gamunex-C/Gammaked), nonlyophilized (eg, liquid), 500 mg
J1566	Injection, immune globulin, (Gammagard S/D) intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg
J1568	Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin (Gammagard liquid), intravenous, non-lyophilized (eg, liquid), 500 mg
J1568	Injection, immune globulin, (Flebogamma/Flebogamma DIF), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1575	Injection, immune globulin/hyaluronidase, (HyQvia), 100 mg immune globulin
J1576	Injection, immune globulin (Panzyga), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1599	Injection, Immune Globulin, Intravenous, Non-lyophilized (e.g. liquid), Not Otherwise Specified

ICD-10 Code	Description
A08.0	Rotaviral enteritis
A48.3	Toxic shock syndrome
A49.9	Bacterial infection, unspecified
A87.0	Enteroviral meningitis
A87.8	Other viral meningitis
A87.9	Viral meningitis, unspecified
A88.0	Enteroviral exanthematous fever [Boston exanthem]
A88.8	Other specified viral infections of central nervous system
B20	Human immunodeficiency virus [HIV] disease
B25.0	Cytomegaloviral pneumonitis
C90.00	Multiple myeloma not having achieved remission
C90.01	Multiple myeloma in remission
C90.02	Multiple myeloma in relapse
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.11	Chronic lymphocytic leukemia of B-cell type in remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
D47.9	Neoplasm of uncertain behavior of lymphoid, hematopoietic and related tissue, unspecified
D69.3	Immune thrombocytopenic purpura
D69.51	Posttransfusion purpura
D69.59	Other secondary thrombocytopenia
D80.0	Hereditary hypogammaglobulinemia

ICD-10 Code	Description
D80.1	Nonfamilial hypogammaglobulinemia
D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.4	Selective deficiency of immunoglobulin M [IgM]
D80.5	Immunodeficiency with increased immunoglobulin M [IgM]
D80.6	Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia
D80.7	Transient hypogammaglobulinemia of infancy
D81.0	Severe combined immunodeficiency [SCID] with reticular dysgenesis
D81.1	Severe combined immunodeficiency [SCID] with low T- and B-cell numbers
D81.2	Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
D81.6	Major histocompatibility complex class I deficiency
D81.7	Major histocompatibility complex class II deficiency
D81.82	Activated Phosphoinositide 3-kinase Delta Syndrome [APDS]
D81.89	Other combined immunodeficiencies
D81.9	Combined immunodeficiency, unspecified
D82.0	Wiskott-Aldrich syndrome
D82.4	Hyperimmunoglobulin E [IgE] syndrome
D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
D83.1	Common variable immunodeficiency with predominant immunoregulatory T-cell disorders
D83.2	Common variable immunodeficiency with autoantibodies to B- or T-cells
D83.8	Other common variable immunodeficiencies
D83.9	Common variable immunodeficiency, unspecified
D84.81	Immunodeficiency due to conditions classified elsewhere
D84.821	Immunodeficiency due to drugs
D84.822	Immunodeficiency due to external causes
D84.89	Other immunodeficiencies
D89.2	Hypergammaglobulinemia, unspecified
D89.810	Acute graft-versus-host disease
D89.812	Acute on chronic graft-versus-host disease
D89.82	Autoimmune lymphoproliferative syndrome [ALPS]
D89.9	Disorder involving the immune mechanism, unspecified
G04.81	Other encephalitis and encephalomyelitis
G04.90	Encephalitis and encephalomyelitis, unspecified
G05.3	Encephalitis and encephalomyelitis in diseases classified elsewhere
G05.4	Myelitis in diseases classified elsewhere
G11.3	Cerebellar ataxia with defective DNA repair
G25.82	Stiff-man syndrome
G35	Multiple sclerosis
G40.811	Lennox-Gastaut syndrome, not intractable, with status epilepticus
G40.812	Lennox-Gastaut syndrome, not intractable, without status epilepticus

ICD-10 Code	Description
G40.813	Lennox-Gastaut syndrome, intractable, with status epilepticus
G40.814	Lennox-Gastaut syndrome, intractable, without status epilepticus
G61.0	Guillain-Barré syndrome
G61.81	Chronic inflammatory demyelinating polyneuritis
G61.89	Other inflammatory polyneuropathies
G61.9	Inflammatory polyneuropathy, unspecified
G62.89	Other specified polyneuropathies
G62.9	Polyneuropathy, unspecified
G65.0	Sequelae of Guillain-Barré syndrome
G70.00	Myasthenia gravis without (acute) exacerbation
G70.01	Myasthenia gravis with (acute) exacerbation
G70.80	Lambert-Eaton syndrome, unspecified
G70.81	Lambert-Eaton syndrome in disease classified elsewhere
G73.1	Lambert-Eaton syndrome in neoplastic disease
L10.0	Pemphigus vulgaris
L10.2	Pemphigus foliaceous
L12.0	Bullous pemphigoid
L12.1	Cicatricial pemphigoid
L12.30	Acquired epidermolysis bullosa, unspecified
L12.35	Other acquired epidermolysis bullosa
L13.8	Other specified bullous disorders
L51.1	Stevens-Johnson syndrome
L51.2	Toxic epidermal necrolysis [Lyell]
L51.3	Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome
M05.00	Felty's syndrome, unspecified site
M05.011	Felty's syndrome, right shoulder
M05.012	Felty's syndrome, left shoulder
M05.019	Felty's syndrome, unspecified shoulder
M05.021	Felty's syndrome, right elbow
M05.022	Felty's syndrome, left elbow
M05.029	Felty's syndrome, unspecified elbow
M05.031	Felty's syndrome, right wrist
M05.032	Felty's syndrome, left wrist
M05.039	Felty's syndrome, unspecified wrist
M05.041	Felty's syndrome, right hand
M05.042	Felty's syndrome, left hand
M05.049	Felty's syndrome, unspecified hand
M05.051	Felty's syndrome, right hip
M05.052	Felty's syndrome, left hip

ICD-10 Code	Description
M05.059	Felty's syndrome, unspecified hip
M05.061	Felty's syndrome, right knee
M05.062	Felty's syndrome, left knee
M05.069	Felty's syndrome, unspecified knee
M05.071	Felty's syndrome, right ankle and foot
M05.072	Felty's syndrome, left ankle and foot
M05.079	Felty's syndrome, unspecified ankle and foot
M05.09	Felty's syndrome, multiple sites
M05.20	Rheumatoid vasculitis with rheumatoid arthritis of unspecified site
M05.211	Rheumatoid vasculitis with rheumatoid arthritis of right shoulder
M05.212	Rheumatoid vasculitis with rheumatoid arthritis of left shoulder
M05.219	Rheumatoid vasculitis with rheumatoid arthritis of unspecified shoulder
M05.221	Rheumatoid vasculitis with rheumatoid arthritis of right elbow
M05.222	Rheumatoid vasculitis with rheumatoid arthritis of left elbow
M05.229	Rheumatoid vasculitis with rheumatoid arthritis of unspecified elbow
M05.231	Rheumatoid vasculitis with rheumatoid arthritis of right wrist
M05.232	Rheumatoid vasculitis with rheumatoid arthritis of left wrist
M05.239	Rheumatoid vasculitis with rheumatoid arthritis of unspecified wrist
M05.241	Rheumatoid vasculitis with rheumatoid arthritis of right hand
M05.242	Rheumatoid vasculitis with rheumatoid arthritis of left hand
M05.249	Rheumatoid vasculitis with rheumatoid arthritis of unspecified hand
M05.251	Rheumatoid vasculitis with rheumatoid arthritis of right hip
M05.252	Rheumatoid vasculitis with rheumatoid arthritis of left hip
M05.259	Rheumatoid vasculitis with rheumatoid arthritis of unspecified hip
M05.261	Rheumatoid vasculitis with rheumatoid arthritis of right knee
M05.262	Rheumatoid vasculitis with rheumatoid arthritis of left knee
M05.269	Rheumatoid vasculitis with rheumatoid arthritis of unspecified knee
M05.271	Rheumatoid vasculitis with rheumatoid arthritis of right ankle and foot
M05.272	Rheumatoid vasculitis with rheumatoid arthritis of left ankle and foot
M05.279	Rheumatoid vasculitis with rheumatoid arthritis of unspecified ankle and foot
M05.29	Rheumatoid vasculitis with rheumatoid arthritis of multiple sites
M05.30	Rheumatoid heart disease with rheumatoid arthritis of unspecified site
M05.311	Rheumatoid heart disease with rheumatoid arthritis of right shoulder
M05.312	Rheumatoid heart disease with rheumatoid arthritis of left shoulder
M05.319	Rheumatoid heart disease with rheumatoid arthritis of unspecified shoulder
M05.321	Rheumatoid heart disease with rheumatoid arthritis of right elbow
M05.322	Rheumatoid heart disease with rheumatoid arthritis of left elbow
M05.329	Rheumatoid heart disease with rheumatoid arthritis of unspecified elbow
M05.331	Rheumatoid heart disease with rheumatoid arthritis of right wrist

ICD-10 Code	Description
M05.332	Rheumatoid heart disease with rheumatoid arthritis of left wrist
M05.339	Rheumatoid heart disease with rheumatoid arthritis of unspecified wrist
M05.341	Rheumatoid heart disease with rheumatoid arthritis of right hand
M05.342	Rheumatoid heart disease with rheumatoid arthritis of left hand
M05.349	Rheumatoid heart disease with rheumatoid arthritis of unspecified hand
M05.351	Rheumatoid heart disease with rheumatoid arthritis of right hip
M05.352	Rheumatoid heart disease with rheumatoid arthritis of left hip
M05.359	Rheumatoid heart disease with rheumatoid arthritis of unspecified hip
M05.361	Rheumatoid heart disease with rheumatoid arthritis of right knee
M05.362	Rheumatoid heart disease with rheumatoid arthritis of left knee
M05.369	Rheumatoid heart disease with rheumatoid arthritis of unspecified knee
M05.371	Rheumatoid heart disease with rheumatoid arthritis of right ankle and foot
M05.372	Rheumatoid heart disease with rheumatoid arthritis of left ankle and foot
M05.379	Rheumatoid heart disease with rheumatoid arthritis of unspecified ankle and foot
M05.39	Rheumatoid heart disease with rheumatoid arthritis of multiple sites
M05.40	Rheumatoid myopathy with rheumatoid arthritis of unspecified site
M05.411	Rheumatoid myopathy with rheumatoid arthritis of right shoulder
M05.412	Rheumatoid myopathy with rheumatoid arthritis of left shoulder
M05.419	Rheumatoid myopathy with rheumatoid arthritis of unspecified shoulder
M05.421	Rheumatoid myopathy with rheumatoid arthritis of right elbow
M05.422	Rheumatoid myopathy with rheumatoid arthritis of left elbow
M05.429	Rheumatoid myopathy with rheumatoid arthritis of unspecified elbow
M05.431	Rheumatoid myopathy with rheumatoid arthritis of right wrist
M05.432	Rheumatoid myopathy with rheumatoid arthritis of left wrist
M05.439	Rheumatoid myopathy with rheumatoid arthritis of unspecified wrist
M05.441	Rheumatoid myopathy with rheumatoid arthritis of right hand
M05.442	Rheumatoid myopathy with rheumatoid arthritis of left hand
M05.449	Rheumatoid myopathy with rheumatoid arthritis of unspecified hand
M05.451	Rheumatoid myopathy with rheumatoid arthritis of right hip
M05.452	Rheumatoid myopathy with rheumatoid arthritis of left hip
M05.459	Rheumatoid myopathy with rheumatoid arthritis of unspecified hip
M05.461	Rheumatoid myopathy with rheumatoid arthritis of right knee
M05.462	Rheumatoid myopathy with rheumatoid arthritis of left knee
M05.469	Rheumatoid myopathy with rheumatoid arthritis of unspecified knee
M05.471	Rheumatoid myopathy with rheumatoid arthritis of right ankle and foot
M05.472	Rheumatoid myopathy with rheumatoid arthritis of left ankle and foot
M05.479	Rheumatoid myopathy with rheumatoid arthritis of unspecified ankle and foot
M05.49	Rheumatoid myopathy with rheumatoid arthritis of multiple sites
M05.50	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified site

ICD-10 Code	Description
M05.511	Rheumatoid polyneuropathy with rheumatoid arthritis of right shoulder
M05.512	Rheumatoid polyneuropathy with rheumatoid arthritis of left shoulder
M05.519	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified shoulder
M05.521	Rheumatoid polyneuropathy with rheumatoid arthritis of right elbow
M05.522	Rheumatoid polyneuropathy with rheumatoid arthritis of left elbow
M05.529	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified elbow
M05.531	Rheumatoid polyneuropathy with rheumatoid arthritis of right wrist
M05.532	Rheumatoid polyneuropathy with rheumatoid arthritis of left wrist
M05.539	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified wrist
M05.541	Rheumatoid polyneuropathy with rheumatoid arthritis of right hand
M05.542	Rheumatoid polyneuropathy with rheumatoid arthritis of left hand
M05.549	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hand
M05.551	Rheumatoid polyneuropathy with rheumatoid arthritis of right hip
M05.552	Rheumatoid polyneuropathy with rheumatoid arthritis of left hip
M05.559	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hip
M05.561	Rheumatoid polyneuropathy with rheumatoid arthritis of right knee
M05.562	Rheumatoid polyneuropathy with rheumatoid arthritis of left knee
M05.569	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified knee
M05.571	Rheumatoid polyneuropathy with rheumatoid arthritis of right ankle and foot
M05.572	Rheumatoid polyneuropathy with rheumatoid arthritis of left ankle and foot
M05.579	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified ankle and foot
M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis of multiple sites
M05.60	Rheumatoid arthritis of unspecified site with involvement of other organs and systems
M05.611	Rheumatoid arthritis of right shoulder with involvement of other organs and systems
M05.612	Rheumatoid arthritis of left shoulder with involvement of other organs and systems
M05.619	Rheumatoid arthritis of unspecified shoulder with involvement of other organs and systems
M05.621	Rheumatoid arthritis of right elbow with involvement of other organs and systems
M05.622	Rheumatoid arthritis of left elbow with involvement of other organs and systems
M05.629	Rheumatoid arthritis of unspecified elbow with involvement of other organs and systems
M05.631	Rheumatoid arthritis of right wrist with involvement of other organs and systems
M05.632	Rheumatoid arthritis of left wrist with involvement of other organs and systems
M05.639	Rheumatoid arthritis of unspecified wrist with involvement of other organs and systems
M05.641	Rheumatoid arthritis of right hand with involvement of other organs and systems
M05.642	Rheumatoid arthritis of left hand with involvement of other organs and systems
M05.649	Rheumatoid arthritis of unspecified hand with involvement of other organs and systems
M05.651	Rheumatoid arthritis of right hip with involvement of other organs and systems
M05.652	Rheumatoid arthritis of left hip with involvement of other organs and systems
M05.659	Rheumatoid arthritis of unspecified hip with involvement of other organs and systems
M05.661	Rheumatoid arthritis of right knee with involvement of other organs and systems

ICD-10 Code	Description
M05.662	Rheumatoid arthritis of left knee with involvement of other organs and systems
M05.669	Rheumatoid arthritis of unspecified knee with involvement of other organs and systems
M05.671	Rheumatoid arthritis of right ankle and foot with involvement of other organs and systems
M05.672	Rheumatoid arthritis of left ankle and foot with involvement of other organs and systems
M05.679	Rheumatoid arthritis of unspecified ankle and foot with involvement of other organs and systems
M05.69	Rheumatoid arthritis of multiple sites with involvement of other organs and systems
M05.70	Rheumatoid arthritis with rheumatoid factor of unspecified site without organ or systems involvement
M05.711	Rheumatoid arthritis with rheumatoid factor of right shoulder without organ or systems involvement
M05.712	Rheumatoid arthritis with rheumatoid factor of left shoulder without organ or systems involvement
M05.719	Rheumatoid arthritis with rheumatoid factor of unspecified shoulder without organ or systems involvement
M05.7A	Rheumatoid arthritis with rheumatoid factor of other specified site without organ or systems involvement
M06.1	Adult-onset Still's disease
M08.00	Unspecified juvenile rheumatoid arthritis of unspecified site
M08.011	Unspecified juvenile rheumatoid arthritis, right shoulder
M08.012	Unspecified juvenile rheumatoid arthritis, left shoulder
M08.019	Unspecified juvenile rheumatoid arthritis, unspecified shoulder
M08.021	Unspecified juvenile rheumatoid arthritis, right elbow
M08.022	Unspecified juvenile rheumatoid arthritis, left elbow
M08.029	Unspecified juvenile rheumatoid arthritis, unspecified elbow
M08.031	Unspecified juvenile rheumatoid arthritis, right wrist
M08.032	Unspecified juvenile rheumatoid arthritis, left wrist
M08.039	Unspecified juvenile rheumatoid arthritis, unspecified wrist
M08.041	Unspecified juvenile rheumatoid arthritis, right hand
M08.042	Unspecified juvenile rheumatoid arthritis, left hand
M08.049	Unspecified juvenile rheumatoid arthritis, unspecified hand
M08.051	Unspecified juvenile rheumatoid arthritis, right hip
M08.052	Unspecified juvenile rheumatoid arthritis, left hip
M08.059	Unspecified juvenile rheumatoid arthritis, unspecified hip
M08.061	Unspecified juvenile rheumatoid arthritis, right knee
M08.062	Unspecified juvenile rheumatoid arthritis, left knee
M08.069	Unspecified juvenile rheumatoid arthritis, unspecified knee
M08.071	Unspecified juvenile rheumatoid arthritis, right ankle and foot
M08.072	Unspecified juvenile rheumatoid arthritis, left ankle and foot
M08.079	Unspecified juvenile rheumatoid arthritis, unspecified ankle and foot
M08.08	Unspecified juvenile rheumatoid arthritis, vertebrae

ICD-10 Code	Description
M08.09	Unspecified juvenile rheumatoid arthritis, multiple sites
M08.0A	Unspecified juvenile rheumatoid arthritis, other specified site
M08.20	Juvenile rheumatoid arthritis with systemic onset, unspecified site
M08.211	Juvenile rheumatoid arthritis with systemic onset, right shoulder
M08.212	Juvenile rheumatoid arthritis with systemic onset, left shoulder
M08.219	Juvenile rheumatoid arthritis with systemic onset, unspecified shoulder
M08.221	Juvenile rheumatoid arthritis with systemic onset, right elbow
M08.222	Juvenile rheumatoid arthritis with systemic onset, left elbow
M08.229	Juvenile rheumatoid arthritis with systemic onset, unspecified elbow
M08.231	Juvenile rheumatoid arthritis with systemic onset, right wrist
M08.232	Juvenile rheumatoid arthritis with systemic onset, left wrist
M08.239	Juvenile rheumatoid arthritis with systemic onset, unspecified wrist
M08.241	Juvenile rheumatoid arthritis with systemic onset, right hand
M08.242	Juvenile rheumatoid arthritis with systemic onset, left hand
M08.249	Juvenile rheumatoid arthritis with systemic onset, unspecified hand
M08.251	Juvenile rheumatoid arthritis with systemic onset, right hip
M08.252	Juvenile rheumatoid arthritis with systemic onset, left hip
M08.259	Juvenile rheumatoid arthritis with systemic onset, unspecified hip
M08.261	Juvenile rheumatoid arthritis with systemic onset, right knee
M08.262	Juvenile rheumatoid arthritis with systemic onset, left knee
M08.269	Juvenile rheumatoid arthritis with systemic onset, unspecified knee
M08.271	Juvenile rheumatoid arthritis with systemic onset, right ankle and foot
M08.272	Juvenile rheumatoid arthritis with systemic onset, left ankle and foot
M08.279	Juvenile rheumatoid arthritis with systemic onset, unspecified ankle and foot
M08.28	Juvenile rheumatoid arthritis with systemic onset, vertebrae
M08.29	Juvenile rheumatoid arthritis with systemic onset, multiple sites
M08.2A	Juvenile rheumatoid arthritis with systemic onset, other specified site
M08.3	Juvenile rheumatoid polyarthritis (seronegative)
M08.40	Pauciarticular juvenile rheumatoid arthritis, unspecified site
M08.411	Pauciarticular juvenile rheumatoid arthritis, right shoulder
M08.412	Pauciarticular juvenile rheumatoid arthritis, left shoulder
M08.419	Pauciarticular juvenile rheumatoid arthritis, unspecified shoulder
M08.421	Pauciarticular juvenile rheumatoid arthritis, right elbow
M08.422	Pauciarticular juvenile rheumatoid arthritis, left elbow
M08.429	Pauciarticular juvenile rheumatoid arthritis, unspecified elbow
M08.431	Pauciarticular juvenile rheumatoid arthritis, right wrist
M08.432	Pauciarticular juvenile rheumatoid arthritis, left wrist
M08.439	Pauciarticular juvenile rheumatoid arthritis, unspecified wrist
M08.441	Pauciarticular juvenile rheumatoid arthritis, right hand

ICD-10 Code	Description
M08.442	Pauciarticular juvenile rheumatoid arthritis, left hand
M08.449	Pauciarticular juvenile rheumatoid arthritis, unspecified hand
M08.451	Pauciarticular juvenile rheumatoid arthritis, right hip
M08.452	Pauciarticular juvenile rheumatoid arthritis, left hip
M08.459	Pauciarticular juvenile rheumatoid arthritis, unspecified hip
M08.461	Pauciarticular juvenile rheumatoid arthritis, right knee
M08.462	Pauciarticular juvenile rheumatoid arthritis, left knee
M08.469	Pauciarticular juvenile rheumatoid arthritis, unspecified knee
M08.471	Pauciarticular juvenile rheumatoid arthritis, right ankle and foot
M08.472	Pauciarticular juvenile rheumatoid arthritis, left ankle and foot
M08.479	Pauciarticular juvenile rheumatoid arthritis, unspecified ankle and foot
M08.48	Pauciarticular juvenile rheumatoid arthritis, vertebrae
M08.4A	Pauciarticular juvenile rheumatoid arthritis, other specified site
M08.80	Other juvenile arthritis, unspecified site
M08.811	Other juvenile arthritis, right shoulder
M08.812	Other juvenile arthritis, left shoulder
M08.819	Other juvenile arthritis, unspecified shoulder
M08.821	Other juvenile arthritis, right elbow
M08.822	Other juvenile arthritis, left elbow
M08.829	Other juvenile arthritis, unspecified elbow
M08.831	Other juvenile arthritis, right wrist
M08.832	Other juvenile arthritis, left wrist
M08.839	Other juvenile arthritis, unspecified wrist
M08.841	Other juvenile arthritis, right hand
M08.842	Other juvenile arthritis, left hand
M08.849	Other juvenile arthritis, unspecified hand
M08.851	Other juvenile arthritis, right hip
M08.852	Other juvenile arthritis, left hip
M08.859	Other juvenile arthritis, unspecified hip
M08.861	Other juvenile arthritis, right knee
M08.862	Other juvenile arthritis, left knee
M08.869	Other juvenile arthritis, unspecified knee
M08.871	Other juvenile arthritis, right ankle and foot
M08.872	Other juvenile arthritis, left ankle and foot
M08.879	Other juvenile arthritis, unspecified ankle and foot
M08.88	Other juvenile arthritis, vertebrae
M08.89	Other juvenile arthritis, multiple sites
M08.90	Juvenile arthritis, unspecified, unspecified site
M08.911	Juvenile arthritis, unspecified, right shoulder

ICD-10 Code	Description
M08.912	Juvenile arthritis, unspecified, left shoulder
M08.919	Juvenile arthritis, unspecified, unspecified shoulder
M08.921	Juvenile arthritis, unspecified, right elbow
M08.922	Juvenile arthritis, unspecified, left elbow
M08.929	Juvenile arthritis, unspecified, unspecified elbow
M08.931	Juvenile arthritis, unspecified, right wrist
M08.932	Juvenile arthritis, unspecified, left wrist
M08.939	Juvenile arthritis, unspecified, unspecified wrist
M08.941	Juvenile arthritis, unspecified, right hand
M08.942	Juvenile arthritis, unspecified, left hand
M08.949	Juvenile arthritis, unspecified, unspecified hand
M08.951	Juvenile arthritis, unspecified, right hip
M08.952	Juvenile arthritis, unspecified, left hip
M08.959	Juvenile arthritis, unspecified, unspecified hip
M08.961	Juvenile arthritis, unspecified, right knee
M08.962	Juvenile arthritis, unspecified, left knee
M08.969	Juvenile arthritis, unspecified, unspecified knee
M08.971	Juvenile arthritis, unspecified, right ankle and foot
M08.972	Juvenile arthritis, unspecified, left ankle and foot
M08.979	Juvenile arthritis, unspecified, unspecified ankle and foot
M08.98	Juvenile arthritis, unspecified, vertebrae
M08.99	Juvenile arthritis, unspecified, multiple sites
M08.9A	Juvenile arthritis, unspecified, other specified site
M30.3	Mucocutaneous lymph node syndrome [Kawasaki]
M33.00	Juvenile dermatomyositis, organ involvement unspecified
M33.01	Juvenile dermatomyositis with respiratory involvement
M33.02	Juvenile dermatomyositis with myopathy
M33.03	Juvenile dermatomyositis without myopathy
M33.09	Juvenile dermatomyositis with other organ involvement
M33.10	Other dermatomyositis, organ involvement unspecified
M33.11	Other dermatomyositis with respiratory involvement
M33.12	Other dermatomyositis with myopathy
M33.13	Other dermatomyositis without myopathy
M33.19	Other dermatomyositis with other organ involvement
M33.20	Polymyositis, organ involvement unspecified
M33.21	Polymyositis with respiratory involvement
M33.22	Polymyositis with myopathy
M33.29	Polymyositis with other organ involvement
M33.90	Dermatopolymyositis, unspecified, organ involvement unspecified

ICD-10 Code	Description
M33.91	Dermatopolymyositis, unspecified with respiratory involvement
M33.92	Dermatopolymyositis, unspecified with myopathy
M33.93	Dermatopolymyositis, unspecified without myopathy
M33.99	Dermatopolymyositis, unspecified with other organ involvement
M36.0	Dermato(poly)myositis in neoplastic disease
O26.40	Herpes gestationis, unspecified trimester
O26.41	Herpes gestationis, first trimester
O26.42	Herpes gestationis, second trimester
O26.43	Herpes gestationis, third trimester
P61.0	Transient neonatal thrombocytopenia
T86.00	Unspecified complication of bone marrow transplant
T86.01	Bone marrow transplant rejection
T86.02	Bone marrow transplant failure
T86.03	Bone marrow transplant infection
T86.09	Other complications of bone marrow transplant
T86.10	Unspecified complication of kidney transplant
T86.11	Kidney transplant rejection
T86.12	Kidney transplant failure
T86.13	Kidney transplant infection
T86.19	Other complication of kidney transplant
Z29.89	Encounter for other specified prophylactic measures
Z29.9	Encounter for prophylactic measures, unspecified
Z48.290	Encounter for aftercare following bone marrow transplant
Z86.19	Personal history of other infectious and parasitic diseases
Z86.2	Personal history of diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
Z92.22	Personal history of monoclonal drug therapy
Z92.29	Personal history of other drug therapy
Z94.81	Bone marrow transplant status
Z94.84	Stem cells transplant status

Background

Immune globulins have been used for decades as replacement therapy in patients with primary immunodeficiencies (PIs). They are also used in a wide variety of other diseases and conditions, including autoimmune and inflammatory conditions, and provide passive immunity against infectious diseases (*Buehler et al 2015, Keller et al 2000, Leong et al 2008*). Advantages of subcutaneous immune globulins (SCIG) compared with intravenous immune globulins (IVIG) include fewer systemic reactions, more consistent serum levels of IgG, and the convenience of home administration. In addition, SC infusions may be useful in patients for whom venous access is problematic. Disadvantages of SCIG include the increased frequency of infusions with most products and the occurrence of local reactions. Furthermore, some patients may have difficulty with self-administration (*Jolles 2020*).

Primary Immunodeficiencies are inherited immune system disorders that predispose patients to an increased rate and severity of infection, immune dysregulation, and malignancy. Immune globulin is a component of standard therapy for various PI disorders (*Bonilla et al 2015*).

Clinical Evidence

Several systematic reviews and meta-analyses have been published evaluating the use of immune globulin products for their various indications. In general, meta-analyses provide results based on immune globulin products as a class, and do not draw conclusions about relative safety or efficacy of individual products.

Use of IVIG for the prevention of cardiac consequences of Kawasaki disease in children significantly decreased the number of new coronary artery abnormalities at 30 days compared to placebo (Oates-Whitehead et al 2003). A Cochrane review evaluating the effects of immunosuppressants and immunomodulatory treatments for dermatomyositis and polymyositis found that in 1 study, IVIG showed statistically significant improvement vs placebo in scores of muscle strength over 3 months (Gordon et al 2012). In addition, a double-blind (DB), randomized, placebo-controlled (PC) trial (N = 95) in adults with dermatomyositis found that a statistically significantly greater proportion of patients in the IVIG 10% group (Octagam 10%) were responders at week 16 compared to placebo (Octagam 10% Prescribing Information 2022). A Cochrane systematic review of 9 RCTs (N = 372) found that use of IVIG in CIDP was associated with significant improvement in disability for at least 2 to 6 weeks compared to placebo. During this period, IVIG had similar efficacy to oral prednisolone and IV methylprednisolone (Bus et al 2024). According to a Cochrane systematic review of 6 RCTs (N = 90) evaluating the efficacy of immune globulins for MMN, IVIG may improve disability and muscle strength compared with placebo. SCIG may be an alternative to IVIG, but more data are needed (Keddie et al 2022). A meta-analysis found similar efficacy between SCIG and IVIG in terms of muscle strength in patients with multifocal motor neuropathy (MMN) or Chronic Inflammatory Demyelinating Polyneuropathy (CIDP); however, there were many limitations to the included studies (e.g., unblinded, small sample size) (Racosta et al 2017). A systematic review and meta-analysis of 50 studies (22 studies included in meta-analysis) (N = 1400) evaluating SCIG for maintenance therapy of CIDP found that SCIG significantly improved muscle strength and sensory function, had fewer adverse events (AEs), reduced relapse rates, and was preferred by patients over alternative treatments (Ramzi et al 2024). For the treatment of children with ITP, a systematic review and meta-analysis found that IVIG was superior to anti-D immunoglobulin (anti-D) in terms of platelet count, but the benefit in bleeding outcomes remains unclear (Lioger et al 2018). Another systematic review and meta-analysis found that for newly-diagnosed children with primary ITP, the platelet count with IVIG therapy was higher than anti-D in the early and late phases, but was lower than methylprednisolone in the longer term. IVIG caused less adverse events (AEs) than anti-D and corticosteroids (Acero-Garcés & García-Perdomo 2020). A meta-analysis reviewed the use of IVIG in patients with hypogammaglobulinemia associated with CLL or multiple myeloma. Based on available data from the studies in CLL, IVIG reduced the frequency of clinically documented infections, but did not affect overall survival (Raanani et al 2009). Comparisons of IVIG to SCIG have found that SC administration is at least as effective as IV administration for the treatment of Primary Immunodeficiency (PI) and may be associated with improved health-related quality of life due to the ability to administer therapy at home instead of in a hospital setting. However, most studies were not randomized or adequately controlled (*Abolhassani et al 2012, Lingman-Framme et al 2013, Shabaninejad et al 2016*). There are few head-to-head trials among different immune globulin formulations, and the majority of published trials have compared formulations that are no longer marketed. Currently there is no evidence to support conclusions of relative safety or efficacy among products (*Buehler et al 2015*).

Alyglo

A prospective, open-label, single-arm, multi-center study was conducted in North America (the United States and Canada) to determine efficacy, safety and PK of ALYGLO (immune globulin intravenous, human-stwk) in adults and pediatric subjects with PI. Prior to enrollment, all subjects were receiving stable doses between 300 and 900 mg/kg of IGIV replacement therapy. Subjects received ALYGLO infusion administered every 21 or 28 days (both the dose and

schedule depending on their prior therapy) for 12 months. Thirty-three adults aged 17 to 70 years were enrolled and received doses ranging from 319 to 817 mg/kg. The age range was between 17 and 70 years, with a mean (SD) of 49.6 (16.41) years. Eighteen (54.5%) subjects were female, and 15 (45.5%) subjects were male; 32 (97.0%) were White and 1 (3.0%) was other. The primary efficacy analysis was annualized rate of acute serious bacterial infections (SBIs), defined as bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, and osteomyelitis/septic arthritis per subject per year. Secondary analyses were annual rate or days of other infections, antibiotic use, days out of work/school/day care or unable to perform normal activities due to infection, and days of hospitalization due to infection.

During the 12-month study period, the acute SBI rate was 0.03 (with an upper one sided 99% confidence limit: 0.31), which met the predefined success rate of less than one acute SBI per subject per year (ITT Population). One adult subject experienced an acute SBI (one episode of bacterial pneumonia).

Asceniv

A prospective, open-label, single-arm, multicenter trial assessed the efficacy, safety, and pharmacokinetics of ASCENIV in adult and pediatric subjects with PI (Asceniv Prescribing Information). Study subjects were receiving regular IGIV replacement therapy, with a stable dose between 300 and 800 mg/kg for at least 3 months prior to participation in this trial. Subjects received an ASCENIV infusion administered every 3 or 4 weeks (both the dose and schedule depending on their prior therapy) for 12 months. A total of 59 subjects were enrolled into the trial, 28 men and 31 women with a mean age of 42 years; 93% were Caucasian, 5% were Hispanic and 2% African American. Forty-eight subjects were adults (81%) between 17 and 74 years of age. There were 11 pediatric subjects, and 11 subjects (18.6%) ≥65 years of age. The oldest subject was 74 years of age. The youngest subject was 3 years of age. There were 19 subjects with a 3-week cycle and 40 subjects with a 4-week cycle. There were 45 subjects (76%) with common variable immunodeficiency (CVID) as their primary diagnosis, followed by X-linked Agammaglobulinemia (10%), Antibody Deficiencies and 'Other' (7% each). The modified intent-to-treat (mITT) population included 59 subjects and was used for efficacy analysis.

The study assessed the efficacy of ASCENIV in preventing serious bacterial infections (SBIs), defined as a rate of <1.0 cases of bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis per person-year. Secondary efficacy parameters included time to first SBI and time to first infection of any kind/seriousness, days on antibiotics (excluding prophylaxis), days off school/work due to infections, all confirmed infections of any kind or seriousness, and hospitalizations due to infection. During the 12-month study period, zero (0) serious acute bacterial infections occurred. Thus, the mean event rate of serious, acute, bacterial infections per year was 0.0 (with an upper 1-sided 99% confidence interval of <1.0 per subject year, which met the study's primary efficacy endpoint). Thirty-nine percent (39%) of subjects had days off work, school or daycare due to an infection. Of the infections reported, 1 resulted in hospitalization as a post-op local wound infection from elective surgery. The incidence and severity of infections in adolescents were similar to those in adult subjects.

Bivigam

A prospective, open-label, single-arm, multicenter trial assessed the efficacy, safety, and pharmacokinetics of BIVIGAM in adult and pediatric subjects with PI (Bivigam Prescribing Information). Study subjects were receiving regular IGIV replacement therapy, with a stable dose between 300 and 800 mg/kg for at least 3 months prior to participation. Subjects received a BIVIGAM infusion administered every 3 or 4 weeks (both the dose and schedule depending on their prior therapy) for approximately 1 year. A total of 63 subjects were enrolled in the trial, 31 men and 32 women with a mean age of 41 years. Forty-four subjects were adults (70%) between 18 and 64 years of age. There were 9 pediatric subjects, and 9 elderly subjects (14%, ≥65 years of age). The oldest subject was 75 years of age. There were 17 subjects with a 3-week cycle and 46 subjects with a 4-week cycle. There were 51 subjects (81%) with common variable immunodeficiency as their primary diagnosis, followed by X-linked agammaglobulinemia and 'Other' (9.5% each). The intent to treat (ITT) population included 58 subjects and was used for efficacy analysis.

The primary endpoint of the study was to assess the efficacy of BIVIGAM in preventing serious bacterial infections (SBIs) defined as rate of <1.0 cases of bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis per person-year. Secondary efficacy parameters included time to first SBI and time to first infection of any kind/seriousness, days on antibiotics (excluding prophylaxis), days off school/work due to infections, all confirmed infections of any kind or seriousness, and hospitalizations due to infection. During the 12-month study period, two serious acute bacterial infections occurred in two subjects with an onset date between the first infusion of BIVIGAM and the first follow-up visit, inclusive. Thus, the mean event rate of serious, acute, bacterial infections per year was 0.037 (with an upper 1-sided 99% confidence interval of 0.101, which met the study's primary efficacy endpoint). The two SBIs were cases of bacterial pneumonia. Thirty-three percent of subjects had days off work or school due to an infection. Of the 197 infections reported, 2 resulted in hospitalization. Results for the pediatric subjects were similar to those for the adult subjects.

A prospective, open-label, single-arm, multi-center study evaluating the safety, efficacy, and PK of BIVIGAM was conducted in 16 pediatric subjects; 3 subjects ≥2 to <6, 5 subjects ≥6 to <12, and 8 subjects ≥12 to ≤16 years, with confirmed and documented clinical diagnosis of PID, including hypogammaglobulinemia or agammaglobulinemia. Of the 16 subjects enrolled, all (100%) were male, and the majority (80%) were white. Subjects received a BIVIGAM infusion administrated every 3 or 4 weeks (based on the dose and schedule depending on their prior treatment regimen) for approximately 5 months. Average BIVIGAM doses administered (all infusions, both infusion regimens combined, values rounded) ranged from 368 to 1077 mg/kg in the 2 to <6 years age group, from 312 to 693 mg/kg in the 6 to <12 years age group and from 350 to 795 mg/kg in the 12 to 16 years age group. The efficacy analysis is based on the incidence of acute serious bacterial infections (SBIs). SBIs encompass bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, or visceral abscess. No acute SBIs occurred during the mean observation period of 152 days, yielding a mean number of acute SBI episodes per person-year of 0.0. No other serious infections, or hospitalizations due to infections occurred, and no subjects required IV antibiotics during the study. Trough Total IgG levels were maintained above 500 mg/dL in all subjects throughout the study. There were no apparent differences in the Total IgG or subclass concentrations before the first and last infusions.

Cutaquig

There were 2 clinical studies, one was a pivotal, prospective, open-label, single-arm, multicenter study to evaluate the pharmacokinetics (PK), efficacy, tolerability, and safety of subcutaneous human immunoglobulin (Cutaquig) in subjects with primary humoral immunodeficiency (PI) (*Cutaquig prescribing information 2021*). The other was an extension study. The pivotal study was conducted in 75 subjects (37 adult and 38 pediatric subjects < 17years of age) who received weekly SC infusions with Cutaquig during a 12-week wash-in/wash-out period followed by a 12-month efficacy period during which efficacy, pharmacokinetics, safety, tolerability, and quality of life (QoL) parameters of Cutaquig were evaluated. All patients received study treatment and 68 patients completed the study. Seven patients (4 adolescents and 3 adults) were withdrawn prematurely. Reasons for withdrawal from the study were patient's decision in 6 cases and patient's noncompliance in one adolescent patient. During the efficacy period the mean weekly dose was 174 mg/kg BW, with individual doses ranging from 60 to 390 mg/kg BW. The median duration of infusion per week was 1.5 hours. All enrolled subjects (n=75) were included in the Safety Analysis Set and the Full Analysis Set (FAS). Four subjects were excluded from the Per-Protocol (PP) Set because they terminated early before the start of the primary treatment period. Overall, 36 female subjects and 39 male subjects participated in this study. The youngest subject enrolled in the study was 2 years old and the oldest was 73 years old. The mean age in the adult group (17–75 yrs) was 47.5 years. The mean age at time of enrollment in the pediatric groups was 4.2 years, 7.9 years, and 14.1 years in the 3 pediatric age groups [young children (ages 2-5 years), older children (ages 6-11 years) and adolescents (ages 12-16 years)] respectively. Reported race was white for all but one subject, and all subjects were of not Hispanic/Latino ethnicity. The main objective of the pivotal study was to assess the efficacy of Cutaquig in preventing serious bacterial infections (SBI defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess). This endpoint was considered successful if the upper bound of the one-sided 99% confidence interval for the rate of SBIs was < 1.0 per subject-year of follow up. This criterion was met, as no SBIs were reported at any time during the study. Other endpoints of the pivotal study included but were not limited to, the number of episodes of any other infections, along with type and severity of infection and time to resolution; number of days of use and annual rate of

antibiotics; absence and number of days of absence from work/school/ kindergarten/day care; and hospitalizations due to infections and number of days and annual rate of hospitalization.

The extension study was a prospective, open-label, single-arm, multicenter phase 3 safety study that enrolled 27 patients (17 adults, 10 patients aged <17 years) with PI. Twenty-one patients were initially treated in the pivotal study and 6 patients were newly enrolled. Mean age was 39 years (range 6 to 73 years). Ten patients (37%) were male, all but 2 were White, none was Hispanic or Latino. Patients received Cutaquig on a weekly (25 patients) or an "every other week" schedule (2 patients). The primary objective of this study was to assess the medium-to-long term safety and tolerability of Cutaquig. Secondary efficacy assessments included occurrence of SBIs, the annual rate of all infections of any kind or seriousness, hospitalizations due to infections, and antibiotic use. One adult had bacteremia/sepsis. The rate of SBI per person-year was 0.03 for adults, and 0.0 for all other age groups (overall rate of 0.018).

Cuvitru

A prospective, open-label, non-controlled, multi-center clinical study was conducted in North America to determine the efficacy, tolerability, and PK of Cuvitru in 77 adult and pediatric subjects with PI (*Cuvitru prescribing information 2023*). Efficacy was determined in 53 adults aged 16 years or older, 6 adolescents aged 12 to <16 years, and 15 children aged 2 to <12 years. Cuvitru was administered to 74 subjects with a mean dose of 222 mg/kg/week ± 71 mg/kg/week for a median treatment duration of 380.5 days (range: 30 - 629 days) and a mean (± SD) of 413.1 ± 116.5 days. The median duration of treatment did not vary significantly between age groups. The total exposure to Cuvitru was 83.70 subject-years and 4327 infusions. Initially subjects received immune globulin 10% intravenously (IGIV) every 3 or 4 weeks at a monthly dose equivalent to that received prior to the study for 13 weeks. The objective of part 1 of the study was to determine AUC of total IgG following IGIV administration. In part 2 of the study, subjects received Cuvitru subcutaneously at an adjusted dose of 145% of the IGIV dose. The objective of part 2 was to determine AUC of total IgG following weekly Cuvitru administration and to calculate an adjusted dose to be used in part 3. The dose adjustment factor was assessed to be 145% of the IGIV 10% dose by comparing the AUC with the AUC, (standardized to 1 week) of part 1 for the first 15 subjects that completed part 2. Subjects who completed part 1 after this assessment was available, went directly into part 3. In part 3 of the study, subjects were treated weekly for 12 weeks at the adjusted dose. The ratio of serum IgG trough levels for part 1 and 3 were compared to the expected trough level determined in part 2 to establish the individually adapted dose for part 4 for each subject. In part 4 of the study, subjects were infused weekly with Cuvitru at the individually adapted dose for 40 weeks. During part 4, an additional pharmacokinetic assessment was performed. Follow-up with the subject either by diary system or by investigator occurred 3-5 days after every infusion in each study part to document adverse events. Adverse events were assessed using the subject's eDiary – all subjects received eDiary tablet to continuously record home treatments, adverse events, and additional information as they occurred. One acute serious bacterial infection (ASBI) of pneumonia was reported in a 78-year-old subject who had specific antibody deficiency and allergic bronchopulmonary aspergillosis while receiving Cuvitru. The point estimate of the annualized rate of ASBIs was 0.012 (upper limit of 99% CI: 0.024) during Cuvitru treatment. This annual rate of ASBIs was lower than 1.0 ASBIs /year ($p<0.0001$), the threshold specified as providing substantial evidence of efficacy.

A prospective, open-label, non-controlled, multi-center study conducted in 16 sites in Europe to evaluate the efficacy, safety, tolerability, and PK parameters of Cuvitru in subjects with PI aged 2 years and older at time of screening. The study consisted of 2 parts. In study part 1, subjects were treated with IGSC 16% for 12 weeks or with IGIV 10% for 13 weeks. Administration, dosage frequency, and dose were dependent on the pre-study treatment. However, the dose range had to be within 0.3-1.0 g/kg BW/4 weeks. During study part 2, subjects received weekly Cuvitru infusions for 51 weeks at the dose used during study part 1, adjusted to a weekly equivalent dose if necessary. PK assessments were performed before the end of study part 1 and after approximately 5 months in study part 2 in subjects aged ≥12 years. For younger subjects (aged 2 to <12 years) only IgG trough levels were assessed to avoid multiple blood draws. The geometric mean of Cuvitru trough levels was 827 mg/dL [95% CI: 748-913]. Human and population PK parameters for Cuvitru were calculated from levels of Immunoglobulin G (IgG) measured during each part of the study. Cuvitru was administered at the same weekly-equivalent dose as with the previously used IG product (mean (± SD) dose: 0.125 ± 0.042 g/kg/week). Cuvitru administered at this dose was shown to be effective in PI subjects aged ≥2 years. One acute serious bacterial infection (ASBI) of pneumonia was reported in a 12-year-old subject with a more severe form of

hypogammaglobulinemia (XLA) while receiving Cuvitru. The point estimate of the annualized rate of ASBIs was 0.022 (upper limit of 99% CI: 0.049) during Cuvitru treatment. This annual rate of ASBIs was lower than 1.0 ASBIs /year, ($p<0.0001$), the threshold specified as providing substantial evidence of efficacy.

Flebogamma DIF
A multicenter, open-label, historically controlled study was conducted in the United States to assess the efficacy, safety, and pharmacokinetics of Flebogamma 5% DIF in adult and pediatric subjects with PI (Flebogamma DIF Prescribing Information). A total of 46 subjects aged 15-75 years (63% male, 37% female) were enrolled and treated with Flebogamma 5% DIF at a dose of 300-600 mg per kg per infusion every 3-4 weeks for 12 months. Since the subjects in the clinical study were assigned to two different treatment intervals (3-week vs. 4-week infusion schedules), the dosage had to be adjusted to ensure that the subjects received approximately the same dosage on an annualized basis. Therefore, subjects in the 3-week schedule received 75% of the monthly (4-week) dosage per infusion. This resulted in a mean annualized dosage of 451 mg per kg per month for subjects in the 3-week schedule (n=13, range 288-588 mg per kg per month) and 448 mg per kg per month for subjects in the 4-week schedule (n=33, range 298-591 mg per kg per month).

During the study period, the annual rate of acute serious bacterial infection, defined as bacterial pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis per subject per year, was 0.021 (with an upper 1-sided 98% confidence interval of 0.112). One subject had one episode of bacterial pneumonia and there were no other episodes of serious bacterial infections reported. The number of days of work/school missed, hospitalizations and days of each hospitalization, the number of visits to physicians or emergency rooms, other infections documented by positive radiographic findings and fever, and days on therapeutic and prophylactic oral/parenteral antibiotic use were also evaluated. These variables were annualized by using the subject-years exposure data of those subjects experiencing the events, but not the entire study cohort. With regard to the number of other validated infections, the mean rate was less than 2 days per subject per year (this calculation used all subjects, including those who had no infections).

A multicenter, open-label, historically controlled study was conducted in the United States to assess the efficacy of Flebogamma 5% DIF in pediatric subjects with PI. A total of 24 subjects aged 2-16 years (79% male, 21% female) were enrolled and treated with Flebogamma 5% DIF at a dose of 262-625 mg per kg per infusion every 3-4 weeks for 12 months. The annual rate of acute serious bacterial infections, defined as bacterial pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis per subject per year, was 0.051 (with an upper 1-sided 99% confidence limit of 0.53). One subject had one episode of bacterial pneumonia and there were no other episodes of serious bacterial infections reported.

Gammagard Liquid
Primary Immunodeficiency (PI)
Intravenous use of GAMMAGARD LIQUID is supported by a study in subjects (N=61) who were treated with 300 to 600 mg/kg every 21 to 28 days for 12 months (Gammagard Prescribing Information). The age range of subjects was 6 to 72 years, with 54% female and 46% male, and 93% Caucasian, 5% African American, and 2% Asian. Three subjects were excluded from the per-protocol analysis due to non-study product related reasons. The annualized rate of prespecified acute serious bacterial infections, i.e., the mean number of prespecified acute serious bacterial infections per subject per year, was studied. In this study, the Mean Number of Validated Infections per Subject per Year was 0 (p-value $p < 0.0001$ 95% Confidence Interval (0.000, 0.064)) The annualized rate of other prespecified validated bacterial infections and the number of hospitalizations secondary to all validated infectious complications also were studied. In this study the Mean Number of Validated Infections per Subject per Year was 0.07 (95% Confidence Interval (0.018, 0.168)) None of the 61 treated subjects was positive for HCV, HIV-1, and HIV-2 and HBV prior to study entry and none converted from negative to positive during the 12-month period

Treatment of Primary Immunodeficiency (Subcutaneous)

A prospective, open-label, non-controlled, multicenter study was conducted in the U.S. to determine the efficacy, tolerability and PK of GAMMAGARD LIQUID subcutaneous infusion in adult and pediatric subjects (N=49) with PI. All subjects were treated for 12 weeks with GAMMAGARD LIQUID intravenous infusion every 3 or 4 weeks. Subjects who were on intravenous treatment prior to entering the study were switched to GAMMAGARD LIQUID at the same dose and frequency. Subjects who were receiving subcutaneous immune globulin were switched to GAMMAGARD LIQUID at the intravenous dose they had received prior to switching to subcutaneous treatment. A PK analysis was performed at the end of the intravenous period in all subjects aged 12 years and older. One week after the last intravenous infusion, each subject began subcutaneous treatment with GAMMAGARD LIQUID at 130% of the weekly equivalent of the intravenous dose for a minimum of 12 weeks. PK data from the first 15 adult subjects were used to determine the dose required to ensure that the IgG exposure with subcutaneous treatment was not inferior to that with intravenous treatment. The median dose determined from these subjects was 137% of the intravenous dose, and subsequently all subjects were treated for a minimum of 6 weeks at this dose. After 6 subcutaneous infusions, a trough IgG level was obtained and used to individually adapt the subcutaneous dose of GAMMAGARD LIQUID to compensate for individual variation from the mean value of 137%. All subjects received a minimum of 12 infusions at this individually adapted dose and continued to receive subcutaneous treatment with GAMMAGARD LIQUID until the last subject completed the study. Subjects (N=47) were treated with 2,294 subcutaneous infusions of GAMMAGARD LIQUID: 4 subjects treated for up to 29 weeks, 17 subjects for 30 to 52 weeks, and 26 subjects for 53 weeks or longer. Two subjects that completed the intravenous treatment part of the study did not continue to the subcutaneous treatment part of the study. The median duration of subcutaneous treatment was 379 days (range: 57 to 477 days).

Efficacy was determined throughout the entire subcutaneous phase. There were 31 adults aged 16 years or older, 4 adolescents aged 12 to <16 years, and 14 children aged 2 to <12 years. The volume of GAMMAGARD LIQUID infused was 30 mL per site for subjects weighing 40 kg and greater, and 20 mL per site for those weighing less than 40 kg. The total weekly dose was divided by those values to determine the number of sites. Mean weekly subcutaneous doses ranged from 181.9 mg/kg to 190.7 mg/kg (at 130% to 137% of the intravenous dose). In the study, the number of infusion sites per infusion was dependent on the dose of IgG and ranged from 2 to 10. In 75% of infusions, the number of infusion sites was 5 or fewer. There were 3 serious validated bacterial infections, all bacterial pneumonia. None of these subjects required hospitalization to treat their infection. The annual rate of acute serious bacterial infections while on GAMMAGARD LIQUID subcutaneous treatment was 0.067, with an upper 99% confidence limit of 0.133, which is lower than the minimal goal of achieving a rate of <1 bacterial infection per patient-year. The annual rate of any infection in this study during subcutaneous treatment, including viral and fungal infections, was 4.1 infections per subject per year.

Treatment of Multifocal Motor Neuropathy
A randomized, double-blind, placebo controlled, cross-over withdrawal study was conducted to evaluate the efficacy and safety/tolerability of GAMMAGARD LIQUID in adult subjects (N=44) with MMN. The study examined grip strength in the more affected hand (measured with dynamometer), and Guy's Neurological Disability Scale (GNDS) [upper limb part 6 subsection]. Study subjects were on a regimen of licensed immunoglobulin (existing maintenance dose ranging from 0.5 to 2.0 grams/kg/month) prior to enrollment and thus, the results cannot be generalized to naïve patients.
The study comprised of five study periods, each lasting 12 weeks: 3 stabilization phases, one randomized withdrawal phase and one cross-over phase. Open-label GAMMAGARD LIQUID was administered at the beginning (study period 1) and at the end of the study (study period 5) for clinical stabilization, and between the double-blinded periods to prevent carry-over effect (study period 3). If, during either of the double-blinded treatment periods, the subject's upper limb function involving the affected muscles deteriorated such that the subject had difficulty completing daily activities or experienced a decline in grip strength of ≥50% in the more affected hand, the subject was switched directly to the next stabilization phase of open-label GAMMAGARD LIQUID ("accelerated switch") without breaking the blind. All subjects were treated for 12 weeks with open-label GAMMAGARD LIQUID during initial stabilization (study period 1). Each subject was then randomized in a double-blind manner to continuation of GAMMAGARD LIQUID or withdrawal of GAMMAGARD LIQUID and replacement by placebo for 12 weeks (study period 2); subjects who did not tolerate treatment were immediately transitioned to open label GAMMAGARD LIQUID. After infusion of open-label GAMMAGARD LIQUID for 12 weeks (study period 3), subjects crossed-over to receive placebo or GAMMAGARD LIQUID

for 12 weeks (study period 4). No subject was allowed to experience placebo more than one time during the study. At study end, subjects were treated with open-label GAMMAGARD LIQUID for 12 weeks (study period 5).

Overall, 69% (n=29) of subjects required an accelerated switch to open-label treatment with GAMMAGARD LIQUID during the placebo period due to functional deterioration but did not switch when receiving GAMMAGARD LIQUID. The median number of treatment days using GAMMAGARD LIQUID was 84 and the median number of days using placebo was 28. One subject (2.4%) switched to open-label treatment during blinded GAMMAGARD LIQUID cross-over period 1, but did not switch during placebo administration ($p < 0.001$). Forty-four subjects were evaluated to demonstrate effectiveness of GAMMAGARD LIQUID to improve or maintain muscle strength and functional ability in patients with MMN. Statistical significance ($p<0.001$) favoring GAMMAGARD LIQUID over placebo was demonstrated by a substantially lower decline from baseline (22.30%; 95% CI: 9.92% to 34.67%) in mean grip strength in the more affected hand following treatment. The difference in relative change for GAMMAGARD LIQUID and placebo of 22.94% (95% CI: 10.69 to 35.19). Guy's Neurological Disability Scores (GNDS) for the upper limbs, reflecting both fine motor skills and proximal strength, showed a significant difference in efficacy between GAMMAGARD LIQUID and placebo at the 2.5% level in favor of GAMMAGARD LIQUID. GNDS is a patient orientated clinical disability scale designed for multiple sclerosis and is considered appropriate for other neurological disorders. As determined by GNDS scores for the upper limbs, 35.7% of subjects deteriorated while receiving placebo but not during treatment with GAMMAGARD LIQUID, whereas 11.9% of subjects deteriorated during GAMMAGARD LIQUID but not during the placebo period. This difference was statistically significant ($p=0.021$) (see Table 19). Overall, 4.8% of subjects showed deterioration with both placebo and GAMMAGARD LIQUID, while 47.6% showed no deterioration using either. When data from both treatment sequences were combined, a relative decline of ≥30% in grip strength in the more affected hand occurred in 42.9% of subjects during the placebo period, but not during treatment with GAMMAGARD LIQUID, whereas 4.8% of subjects experienced a ≥30% decline during treatment with GAMMAGARD LIQUID, but not during placebo. A relative decline of ≥30% in grip strength in the less affected hand occurred in 31.0% of subjects during the placebo period, but not during treatment with GAMMAGARD LIQUID. No subject experienced a ≥30% decline during treatment with GAMMAGARD LIQUID. The Overall Disability Sum Score (ODSS) changed by -7.14% during placebo (indicating worsening of disability) and by -1.11% (indicating minimal change in disability) during treatment with GAMMAGARD LIQUID. For this specific analysis of ODSS, lower scores represented more disability. With the dominant hand, subjects required 17% longer to complete the 9-hole peg test (a measure of dexterity) at the end of the placebo period, compared with baseline. By contrast, at the end of the GAMMAGARD LIQUID treatment period, subjects required 1.2% longer to complete the 9-hole peg test for the dominant hand compared with baseline. With the non-dominant hand, subjects required 33% longer to complete the 9- hole peg test at the end of the placebo period and 6.7% longer at the end of the GAMMAGARD LIQUID treatment period, compared with baseline. Compared with baseline, assessment by subjects of physical functioning, as measured by visual analog scale (VAS) showed a mean change of 290% during placebo compared with baseline. Assessment by subjects of physical functioning showed a mean change of 73% during GAMMAGARD LIQUID treatment. Higher visual analog scale scores represent more severe disability.

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy
In a prospective, open-label, single-arm, multicenter clinical study, a total of 18 subjects who developed a relapse in Epoch 1 and received GAMMAGARD LIQUID in Epoch 2 were included in efficacy analyses. GAMMAGARD LIQUID was administered at an induction dose of 2 g/kg body weight, followed by maintenance infusions at every 3 weeks for a period of 6 months. The dose of GAMMAGARD LIQUID treatment could be adjusted at the investigator's discretion. Adjustments to the dosing interval of every 3 weeks were not allowed. All subjects completed the study. All dosed subjects were analyzed for efficacy and safety.

Efficacy in Epoch 2 was based on responder rate, where a responder was defined as a subject who demonstrated an improvement of functional disability, indicated by at least a 1-point decrease in the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability score at the completion of the IV treatment period (6 months) or the last study visit of the IV treatment period, relative to pre-IV treatment baseline. The responder rate was 94.4% (N=18, 95% CI: 74.2% to 99.0%). The adjusted INCAT score returned back to baseline values prior to joining the study in 17 of the 18 subjects (94.4%) at 6 months. All subjects (N=18) had improvement in functional ability. Functional ability was a

composite measure based on meeting any of the following criteria: decrease of ≥1 point in the adjusted INCAT disability score, increase of ≥8 kPa in hand grip strength in the more affected hand, or increase of ≥4 points in raw summed RODs score. The mean adjusted INCAT score showed an improvement by 2.1 points. Medical Research Council (MRC) sum score improved by a mean of 5.4 points. The mean change in centile Rasch-built Overall Disability Scale (RODS) score was 15.0 points. Grip strength improved by a mean of 13.8 kPa in the more affected hand and 9.8 kPa in the less affected hand.

Gammagard S/D

Primary Immunodeficiency (PI)

Intravenous use of GAMMAGARD was initially evaluated in a study of 17 subjects with PI. Twelve (71%) were adults and 5 (29%) were children 16 years or younger (Gammagard S/D Prescribing Information). Six subjects received a series of 5 infusions at 4-week intervals, with the starting infusion dose of 100 mg/kg and then increased to 200, 300, and 400 mg/kg at rates of 0.1 to 0.2 mg/kg/hour. Five of the 6 subjects completed the 5 infusions and received another 6 monthly infusions with the following doses each administered twice: 200-400 mg/kg at 0.1 to 0.2 g/kg/hour, 400 mg/kg at 0.1 to 0.4 g/kg/hour and 400-800 mg/kg at 0.1 to 0.4 g/ kg/hour. Then all of the 17 subjects received GAMMAGARD at 400 mg/kg every 4 weeks at a rate of 0.1 to 0.4 g/kg/hour. Fifteen of the subjects were treated for 56 to 77 weeks in this study. There were no instances of pneumonia or other infections that would qualify as an acute bacterial infection. The overall rate of non-serious bacterial infections was 4.4 per subject per year. In a study of 15 subjects with PI to compare the pharmacokinetics of GAMMAGARD S/D with GAMMAGARD, the subjects received a total of 28 infusions, half with GAMMAGARD S/D and half with GAMMAGARD. Five systemic AEs were reported during the study and 2 occurred with GAMMAGARD S/D treatment. The study then enrolled an additional 38 patients with the diagnosis of PI (8), ITP (13), CVID (5), CLL (2) and other miscellaneous diseases (3) to evaluate acute tolerability and the viral safety of GAMMAGARD S/D. The mean age of the subjects was 12 years old (range 0.7 to 57.2 years); 17 were males and 21 were females. The subjects received an average of 10 (range 1-22) infusions over an average of 7.7 months (range 0.3-11 months). A total of 394 infusions were administered and all were completed. The average dose was 460 mg/kg (range: 188- 1110 mg/kg). Incidence of infections was not recorded, although one subject had a recurrence of chronic cellulitis. Adverse events and viral safety data were analyzed.

GAMMAGARD S/D was compared to Gamimune N in a double-blind, crossover study of 36 PI subjects. The mean age of subjects was 17.8 years (range 1.7 to 55.3 years); 22 subjects were male and 14 were female. Eighteen were naïve to IGIV therapy. Each subject received 6 infusions of both products. There were a total of 211 GAMMAGARD S/D infusions and 210 Gamimune N infusions. The dose of GAMMAGARD S/D administered was 300-600 mg/kg every 14 to 28 days for previously untreated subjects and the same as their pre-study dose and frequency for previously treated subjects. The infusions were started at 1.0 mL/kg/hour and increased every 30 minutes to a maximum of 4.8 mL/kg/hour as tolerated. The mean dose administered for both products was 440 mg/kg. The mean infusion rate was 2.35 ± 0.54 mL/kg/hour for GAMMAGARD S/D and 2.33 ± 0.71 for Gamimune N. Two subjects withdrew from the study. One subject was pregnant, and the other subject was withdrawn by his parents after the eighth infusion for reasons other than adverse events. The use of GAMMAGARD S/D as a 10% solution and the maximal rate of infusion were evaluated in a postmarketing study of 27 subjects with PI. Subjects were treated with GAMMAGARD S/D at 400 mg/kg every 4 weeks for up to 12 months. Each subject received an initial infusion of GAMMAGARD S/D 5% solution at 4 mL/kg/hour. Subsequently, the concentration was increased to 7.5% and then to 10% as tolerated. Thereafter, the infusion rate was gradually increased to a maximal 8 mL/kg/hour as tolerated. There were 276 infusions administered and 26 of the 27 subjects were able to reach the maximum infusion rate and concentration.

B-cell Chronic Lymphocytic Leukemia (CLL)

The efficacy of GAMMAGARD in reducing bacterial infections of B-cell CLL patients has been demonstrated in a double-blind, placebo-controlled trial of 81 subjects. Subjects were treated with 400 mg/kg/dose of GAMMAGARD or saline solution every 3 weeks for a total of 17 infusions. Forty-one subjects received GAMMAGARD and 40 subjects received saline. The infection outcomes, including the frequency of bacterial/viral/fungal infections, mean time to first bacterial infections, were compared between the two groups and are shown in the prescribing information. In this study, the frequency of bacterial infections 56.1% with Gammagard S/D, 105% vs. with placebo (0.01 p value). Patients receiving

GAMMAGARD had fewer infections with Streptococcus pneumoniae and Haemophilus influenza, but the incidence of other gram-negative infections was similar.

Idiopathic Thrombocytopenic Purpura (ITP)
The efficacy of GAMMAGARD has been demonstrated in a clinical study involving 16 patients: thirteen had chronic ITP (11 adults, 2 children), and 3 had acute ITP (one adult, 2 children). All 16 patients (100%) demonstrated a rise in platelet count to a level greater than 40,000/mm following the administration of GAMMAGARD. Ten of the 16 patients (62.5%) exhibited a platelets rise to greater than 80,000 /mm. Of these 10 patients, 7 had chronic ITP (5 adults, 2 children), and 3 had acute ITP (one adult, 2 children). Increase in platelet count to greater than 40,000/mm occurred after a single 1 g/kg infusion of GAMMAGARD in 8 patients with chronic ITP (6 adults, 2 children), and in 2 patients with acute ITP (one adult, one child). A similar response was observed after two 1 g/kg infusions in 3 adult patients with chronic ITP, and one child with acute ITP. The remaining 2 adult patients with chronic ITP received more than two 1 g/kg infusions before achieving a platelet count greater than 40,000/mm . The rise in platelet count occurred within 5 days. However, this rise was transient and not considered curative. Platelet count rises lasted 2 to 3 weeks, with a range of 12 days to 6 months. It should be noted that childhood ITP may resolve spontaneously without treatment.

Kawasaki Syndrome
The efficacy of GAMMAGARD S/D for reducing the incidence of coronary artery aneurysm in patients with Kawasaki syndrome has been demonstrated in a clinical study of 44 patients. The incidence of coronary artery aneurysm in patients with Kawasaki syndrome receiving GAMMAGARD either at a single dose of 1 g/kg (n=22) or at a dose of 400 mg/kg for four consecutive days (n=22), beginning within seven days of onset of fever, was 3/44 (6.8%). This was significantly different (p=0.008) from a comparable group of patients that received aspirin only in previous trials and of whom 42/185 (22.7%) developed coronary artery aneurysms. All patients in the GAMMAGARD trial received concomitant aspirin therapy and none experienced hypersensitivity reactions (urticaria, bronchospasm or generalized anaphylaxis).

Gammaked
Primary Immunodeficiency (PI)
In a randomized, double-blind, parallel group clinical trial with 172 subjects with primary humoral immunodeficiencies GAMMAKED was demonstrated to be at least as efficacious as GAMIMUNE N, 10% in the prevention of any infection, i.e., validated plus clinically defined, non-validated infections of any organ system, during a nine-month treatment period (Gammaked Prescribing Information). Twenty-six subjects were excluded from the Per Protocol analysis (2 due to non-compliance and 24 due to protocol violations). The analysis for efficacy was based on the annual rate of bacterial infections, pneumonia, acute sinusitis and acute exacerbations of chronic sinusitis. The annual rate of validated infections (Number of Infections/year/subject) was 0.18 in the group treated with GAMMAKED and 0.43 in the group treated with GAMIMUNE N, 10% (p=0.023). The annual rates for any infection (validated plus clinically-defined, non-validated infections of any organ system) were 2.88 and 3.38, respectively (p=0.300).

Idiopathic Thrombocytopenic Purpura (ITP)
A double-blind, randomized, parallel group clinical trial with 97 ITP subjects was carried out to test the hypothesis that GAMMAKED was at least as effective as GAMIMUNE N, 10% in raising platelet counts from less than or equal to 20 x10 /L to more than 50 x10 /L within 7 days after treatment with 2 g/kg IGIV. Twenty-four percent of the subjects were less than or equal to 16 years of age. GAMMAKED was demonstrated to be at least as effective as GAMIMUNE N, 10% in the treatment of adults and children with acute or chronic ITP. A trial was conducted to evaluate the clinical response to rapid infusion of GAMMAKED in patients with ITP. The study involved 28 chronic ITP subjects, wherein the subjects received 1 g/kg GAMMAKED on three occasions for treatment of relapses. The infusion rate was randomly assigned to 0.08, 0.11, or 0.14 mL/kg/min (8, 11 or 14 mg/kg/min). Pre-medication with corticosteroids to alleviate infusion-related intolerability was not permitted. Pre-treatment with antihistamines, anti-pyretics and analgesics was permitted. The average dose was approximately 1 g/kg body weight at all three prescribed rates of infusion (0.08, 0.11 and 0.14 mL/kg/min). All patients were administered each of the three planned infusions except seven subjects. Based on 21

patients per treatment group, the a posteriori power to detect twice as many drug related adverse events between groups was 23%. Of the seven subjects that did not complete the study, five did not require additional treatment, one withdrew because he refused to participate without concomitant medication (prednisone) and one experienced an adverse event (hives); however, this was at the lowest dose rate level (0.08 mL/kg/min).

Chronic Inflammatory Demyelinating Polyneuropathy
A multi-center, randomized, double-blind, Placebo-controlled trial (The Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified CIDP Efficacy or ICE study) was conducted with GAMMAKED.(27) This study included two separately randomized periods to assess whether GAMMAKED was more effective than Placebo for the treatment of CIDP (assessed in the Efficacy Period for up to 24 weeks) and whether long-term administration of GAMMAKED could maintain long-term benefit (assessed in the 24 week Randomized Withdrawal Period). In the Efficacy Period, there was a requirement for Rescue (crossover) to the alternate study drug if the subject did not improve and maintain this improvement until the end of the 24-week treatment period. Subjects entering the Rescue phase followed the same dosing and schedule as in the Efficacy period. Any subject who was rescued (crossed over) and did not improve and maintain this improvement was withdrawn from the study. Subjects who completed 24 weeks treatment in the Efficacy period or Rescue phase and responded to therapy were eligible for entry into a double-blind Randomized Withdrawal Period. Eligible subjects were re-randomized to GAMMAKED or Placebo. Any subject who relapsed was withdrawn from the study. The Efficacy Period and the Rescue treatment started with a loading dose of 2 g/kg body weight of GAMMAKED or equal volume of Placebo given over 2-4 consecutive days. All other infusions (including the first infusion of the Randomized Withdrawal Period) were given as maintenance doses of 1 g/kg body weight (or equivalent volume of Placebo) every three weeks. The Responder rates of the GAMMAKED and Placebo treatment groups were measured by the INCAT score. The INCAT (Inflammatory Neuropathy Cause and Treatment) scale is used to assess functional disability of both upper and lower extremities in demyelinating polyneuropathy. The INCAT scale has upper and lower extremity components (maximum of 5 points for upper (arm disability) and maximum of 5 points for lower (leg disability)) that add up to a maximum of 10-points (0 is normal and 10 is severely incapacitated).(28) At the start of the efficacy portion of the study, the INCAT scores were as follows: Upper Extremity mean was 2.2 ± 1.0, and median was 2.0 with a range of 0 to 5; Lower Extremity mean was 1.9 ± 0.9, and median was 2.0 with a range of 1 to 5; Total Overall Score mean was 4.2 ± 1.4, and median was 4.0 with a range of 2 to 9. A Responder was defined as a subject with at least 1-point improvement from baseline in the adjusted INCAT score that was maintained through 24 weeks. More subjects with CIDP responded to GAMMAKED: 28 of 59 subjects (47.5%) responded to GAMMAKED compared with 13 of 58 subjects (22.4%) administered Placebo (25% difference; 95% CI 7%-43%; p=0.006). The study included both subjects who were IGIV naïve and subjects who had previous IGIV experience. The outcome was influenced by the group of subjects who experienced prior therapy with IGIV, as shown by the outcomes table, below. Time to relapse for the subset of 57 subjects who previously responded to GAMMAKED was evaluated: 31 were randomly reassigned to continue to receive GAMMAKED and 26 subjects were randomly reassigned to Placebo in the Randomized Withdrawal Period. Subjects who continued to receive GAMMAKED experienced a longer time to relapse versus subjects treated with Placebo (p=0.011). The probability of relapse was 13% with GAMMAKED versus 45% with Placebo (hazard ratio, 0.19; 95% confidence interval, 0.05, 0.70).

Gamunex-C
Primary Immunodeficiency (PI)
In a randomized, double-blind, parallel group clinical trial with 172 subjects with primary humoral immunodeficiencies GAMUNEX-C was demonstrated to be at least as efficacious as GAMIMUNE N, 10% in the prevention of any infection, i.e., validated plus clinically defined, non-validated infections of any organ system, during a nine-month treatment period (Gamunex-C Prescribing Information). Twenty-six subjects were excluded from the Per Protocol analysis (2 due to non-compliance and 24 due to protocol violations). The analysis for efficacy was based on the annual rate of bacterial infections, pneumonia, acute sinusitis and acute exacerbations of chronic sinusitis. The annual rate of validated infections (Number of Infections/year/subject) was 0.18 in the group treated with GAMUNEX-C and 0.43 in the group treated with GAMIMUNE N, 10% (p=0.023). The annual rates for any infection (validated plus clinically-defined, non-validated infections of any organ system) were 2.88 and 3.38, respectively (p=0.300).

Idiopathic Thrombocytopenic Purpura (ITP)
A double-blind, randomized, parallel group clinical trial with 97 ITP subjects was carried out to test the hypothesis that GAMUNEX-C was at least as effective as GAMIMUNE N, 10% in raising platelet counts from less than or equal to 20 x10 /L to more than 50 x10 /L within 7 days after treatment with 2 g/kg IGIV. Twenty-four percent of the subjects were less than or equal to 16 years of age. GAMUNEX-C was demonstrated to be at least as effective as GAMIMUNE N, 10% in the treatment of adults and children with acute or chronic ITP. A trial was conducted to evaluate the clinical response to rapid infusion of GAMUNEX-C in patients with ITP. The study involved 28 chronic ITP subjects, wherein the subjects received 1 g/kg GAMUNEX-C on three occasions for treatment of relapses. The infusion rate was randomly assigned to 0.08, 0.11, or 0.14 mL/kg/min (8, 11 or 14 mg/kg/min). Pre-medication with corticosteroids to alleviate infusion-related intolerability was not permitted. Pre-treatment with antihistamines, anti-pyretics and analgesics was permitted. The average dose was approximately 1 g/kg body weight at all three prescribed rates of infusion (0.08, 0.11 and 0.14 mL/kg/min). All patients were administered each of the three planned infusions except seven subjects. Based on 21 patients per treatment group, the a posteriori power to detect twice as many drugrelated adverse events between groups was 23%. Of the seven subjects that did not complete the study, five did not require additional treatment, one withdrew because he refused to participate without concomitant medication (prednisone) and one experienced an adverse event (hives); however, this was at the lowest dose rate level (0.08 mL/kg/min).

Chronic Inflammatory Demyelinating Polyneuropathy
A multi-center, randomized, double-blind, Placebo-controlled trial (The Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified CIDP Efficacy or ICE study) was conducted with GAMUNEX-C.(27) This study included two separately randomized periods to assess whether GAMUNEX-C was more effective than Placebo for the treatment of CIDP (assessed in the Efficacy Period for up to 24 weeks) and whether long-term administration of GAMUNEX-C could maintain long-term benefit (assessed in the 24 week Randomized Withdrawal Period). In the Efficacy Period, there was a requirement for Rescue (crossover) to the alternate study drug if the subject did not improve and maintain this improvement until the end of the 24-week treatment period. Subjects entering the Rescue phase followed the same dosing and schedule as in the Efficacy period. Any subject who was rescued (crossed over) and did not improve and maintain this improvement was withdrawn from the study. Subjects who completed 24 weeks treatment in the Efficacy period or Rescue phase and responded to therapy were eligible for entry into a double-blind Randomized Withdrawal Period. Eligible subjects were re-randomized to GAMUNEX-C or Placebo. Any subject who relapsed was withdrawn from the study. The Efficacy Period and the Rescue treatment started with a loading dose of 2 g/kg body weight of GAMUNEX-C or equal volume of Placebo given over 2-4 consecutive days. All other infusions (including the first infusion of the Randomized Withdrawal Period) were given as maintenance doses of 1 g/kg body weight (or equivalent volume of Placebo) every three weeks. The Responder rates of the GAMUNEX-C and Placebo treatment groups were measured by the INCAT score. The INCAT (Inflammatory Neuropathy Cause and Treatment) scale is used to assess functional disability of both upper and lower extremities in demyelinating polyneuropathy. The INCAT scale has upper and lower extremity components (maximum of 5 points for upper (arm disability) and maximum of 5 points for lower (leg disability)) that add up to a maximum of 10-points (0 is normal and 10 is severely incapacitated).(28) At the start of the efficacy portion of the study, the INCAT scores were as follows: Upper Extremity mean was 2.2 ± 1.0, and median was 2.0 with a range of 0 to 5; Lower Extremity mean was 1.9 ± 0.9, and median was 2.0 with a range of 1 to 5; Total Overall Score mean was 4.2 ± 1.4, and median was 4.0 with a range of 2 to 9. A Responder was defined as a subject with at least 1-point improvement from baseline in the adjusted INCAT score that was maintained through 24 weeks. More subjects with CIDP responded to GAMUNEX-C: 28 of 59 subjects (47.5%) responded to GAMUNEX-C compared with 13 of 58 subjects (22.4%) administered Placebo (25% difference; 95% CI 7%-43%; p=0.006). The study included both subjects who were IGIV naïve and subjects who had previous IGIV experience. The outcome was influenced by the group of subjects who experienced prior therapy with IGIV. Time to relapse for the subset of 57 subjects who previously responded to GAMUNEX-C was evaluated: 31 were randomly reassigned to continue to receive GAMUNEX-C and 26 subjects were randomly reassigned to Placebo in the Randomized Withdrawal Period. Subjects who continued to receive GAMUNEX-C experienced a longer time to relapse versus subjects treated with Placebo (p=0.011). The probability of relapse was 13% with GAMUNEX-C versus 45% with Placebo (hazard ratio, 0.19; 95% confidence interval, 0.05, 0.70).

Hizentra

Primary Immunodeficiency (PI)
A prospective, open-label, multicenter, single-arm, clinical study conducted in the U.S. evaluated the efficacy, tolerability, and safety of Hizentra in 49 adult and pediatric subjects with PI (*Hizentra prescribing information 2023*). Subjects previously receiving monthly treatment with IGIV were switched to weekly subcutaneous administration of Hizentra for 15 months. Following
a 3-month wash-in/wash-out period, subjects received a dose adjustment to achieve an equivalent AUC to their previous IGIV dose and continued treatment for a 12-month efficacy period. The efficacy analyses included 38 subjects in the modified intention-to-treat (MITT) population. The MITT population consisted of subjects who completed the wash-in/wash-out period and received at least one infusion of Hizentra during the efficacy period. Although 5% of the administered doses could not be verified, the weekly median doses of Hizentra ranged from 72 to 379 mg/kg body weight during the efficacy period. The mean dose was 213.2 mg/kg, which was 149% of the previous IGIV dose.

In the study, the number of infusion sites per infusion ranged from 1 to 12. In 73% of infusions, the number of infusion sites was 4 or fewer. Up to 4 simultaneous infusion sites were permitted using 2 pumps; however, more than 4 sites could be used consecutively during one infusion. The infusion flow rate did not exceed 50 mL per hour for all infusion sites combined. During the efficacy period, the median duration of a weekly infusion ranged from 1.6 to 2.0 hours. The study evaluated the annual rate of serious bacterial infections (SBIs), defined as bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess. The study also evaluated the annual rate of any infections, the use of antibiotics for infection (prophylaxis or treatment), the days out of work/school/kindergarten/day care or unable to perform normal activities due to infections, hospitalizations due to infections, and serum IgG trough levels. No subjects experienced an SBI in this study. The mean IgG trough levels increased by 24.2%, from 1009 mg/dL prior to the study to 1253 mg/dL during the efficacy period.

In a prospective, open-label, multicenter, single-arm, clinical study conducted in Europe, 51 adult and pediatric subjects with PI switched from monthly IGIV (31 subjects) or weekly IGSC (20 subjects) to weekly treatment with Hizentra. For the 46 subjects in the efficacy analysis, the weekly mean dose in the efficacy period was 120.1 mg/kg (range 59 to 243 mg/kg), which was 104% of the previous weekly equivalent IGIV or weekly IGSC dose. None of the subjects had an SBI during the efficacy period, resulting in an annualized rate of 0 (upper one-sided 99% confidence limit of 0.192) SBIs per subject. The annualized rate of any infections was 5.18 infections per subject for the efficacy period.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
A multicenter, double-blind, randomized, placebo-controlled, parallel-group phase 3 study evaluated the efficacy, safety, and tolerability of 2 different weekly doses of Hizentra (0.4 g/kg body weight and 0.2 g/kg body weight) versus placebo in 172 adult subjects with CIDP and previously treated with IGIV (PATH study) (*Hizentra prescribing information 2023)*. The mean treatment duration was 129 days in the 0.4 g/kg Hizentra group and 118.9 days in the 0.2 g/kg Hizentra group (treatment duration up to 166 and 167 days in each group, respectively). Subjects generally used 4 infusion sites in parallel (maximum: 8 sites in parallel). Subjects infused an average of 20 mL per infusion site (maximum: 50 mL/site) with an infusion rate of 20 mL/h (maximum: 50 mL/h) and volumes up to 140 mL per infusion session. The infusion time was approximately 1 hour. The main endpoint was the percentage of subjects who had a CIDP relapse or were withdrawn for any other reason during the SC Treatment Period. CIDP relapse was defined as a ≥1 point increase in adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] score compared with baseline. Both Hizentra doses demonstrated superiority over placebo for the main endpoint (32.8% for 0.4 g/kg Hizentra and 38.6% for 0.2 g/kg Hizentra compared with 63.2% for placebo, $p<0.001$ or $p=0.007$, respectively), with no statistically significant difference between the doses. When only considering relapse, the CIDP relapse rates were 19.0% for 0.4 g/kg Hizentra and 33.3% for 0.2 g/kg Hizentra compared with 56.1% for placebo ($p<0.001$ or $p=0.012$, respectively), with no statistically significant difference between the doses. Eighty one percent (81%) and 67% of Hizentra-treated subjects remained relapse-free (0.4 g/kg body weight and 0.2g/kg body weight, respectively); 44% of placebo subjects remained relapse-free for up to 24 weeks. Subjects in both Hizentra dose groups remained relatively stable while subjects in the placebo group deteriorated in mean INCAT score, mean grip strength, mean Medical Research Council sum score, and mean Rasch-built Overall Disability Scale (R-ODS)

centile score.

The PATH Extension study was a multicenter, 48-week, open-label extension study that evaluated the long-term safety and efficacy of Hizentra 0.2 g/kg and 0.4 g/kg doses in the maintenance treatment of CIDP in subjects who either completed or were being successfully rescued from CIDP relapse with IGIV treatment in the PATH study. A total of 82 subjects were enrolled. In the study, subjects who started on a Hizentra 0.2 g/kg dose were up-titrated to 0.4 g/kg dose if they relapsed. In the case of no relapse, subjects remained at a dose of 0.2 g/kg. Subjects who started on a Hizentra 0.4 g/kg dose were down-titrated to 0.2 g/kg dose after 24 weeks of treatment and subjects who relapsed on a Hizentra 0.2 g/kg dose were up-titrated to a 0.4 g/kg dose. Due to the study design, the same subject could have received both doses during the study; 72 subjects received doses of 0.4 g/kg, and 73 subjects received doses of 0.2 g/kg during the efficacy evaluation period. Subjects who completed the PATH study without relapse on a 0.4 g/kg dose and initially received this dose in the PATH extension study, had a relapse rate of 5.6% (1/18 subjects). Subjects who completed the PATH study without relapse on a 0.2 g/kg dose and initially received this dose in the extension study had a relapse rate of 50% (3/6 subjects). For all subjects who received 0.4 g/kg in the PATH Extension study, 9.7% (7/72 subjects) had a relapse. For all subjects who received 0.2 g/kg in the PATH extension study, 47.9% (35/73 subjects) had a relapse. After down-titrating from Hizentra 0.4 g/kg to 0.2 g/kg, 50% (26/52) of subjects relapsed, of whom 92% (24/26) recovered after returning to Hizentra 0.4 g/kg. A total of 35 subjects relapsed on Hizentra 0.2 g/kg dose, of which 89% (31/35) subjects recovered after returning to 0.4 g/kg dose. Both the PATH and PATH Extension studies demonstrated that Hizentra 0.2 g/kg or 0.4 g/kg dose was effective in preventing CIDP relapse when administered weekly with the Hizentra 0.4 g/kg dose more likely to prevent relapse.

HyQvia

A prospective, open-label, non-controlled, multi-center trial was conducted in the US to determine the efficacy, tolerability, and pharmacokinetics (PK) of HyQvia in subjects with PI (*HyQvia prescribing information 2024*). Two cohorts of subjects were enrolled. Thirty-one subjects had been treated intravenously for three months and then subcutaneously each week at 137% of the intravenous dose for approximately one year before transitioning to the HyQvia trial. The remaining subjects also were treated intravenously for 3 months and then immediately began treatment with HyQvia in the trial. One week after the last intravenous or subcutaneous infusion, each subject began subcutaneous treatment with HyQvia. After placing the subcutaneous needle set, the Recombinant Human Hyaluronidase of HyQvia was infused through the needle set followed within 10 minutes by the immune globulin of HyQvia at 108% of the intravenous dose. Dosing began with a 1-week equivalent dose. One week later, a 2-week dose was administered, followed 2 weeks later with a 3-week dose. For those subjects who were on a 4-week dose interval prior to entering the trial, 3 weeks later the 4-week dose was administered. This ramp-up period allowed subjects to become familiar with the large volumes required for a full 3- or 4-week treatment. Subsequently, subjects continued the 3- or 4-week dosing for the remainder of the trial. After 3 doses at the full volume, a serum IgG trough level was obtained for all subjects and used to individually adapt the subcutaneous dose of HyQvia to compensate for individual variation from the mean value of 108%. All subjects who completed the trial received a minimum of 12 infusions at this individually adapted dose. The period after the ramp-up was considered the efficacy period and used for safety and efficacy analyses. Outcome measures included the rate of infections, adverse reactions, tolerability of the infusions of HyQvia, number of infusion sites per month, and infusion rate. Eighty-nine subjects were enrolled, 87 treated intravenously and 83 treated with HyQvia. The majority were Caucasian (79/87, 90.8%). Median age was 35.0 years (range 4 to 78 years). Forty-four of the subjects were naïve to subcutaneous treatment. Median serum IgG trough levels for the 6 months before enrollment were 1033.5 mg/dL (range: 405 to 3200 mg/dL) in subcutaneous-experienced subjects and 1000 mg/dL (range: 636 to 3200) in the subcutaneous-naïve subjects. The 83 subjects received a total of 1359 infusions of HyQvia during the entire trial. Of these, 1129 were administered after the ramp-up when the subjects were on a consistent interval of 3 or 4 weeks, which was predetermined to be the efficacy period for data analysis. Median duration of treatment in the IGIV period was 91 days (range 84 to 122 days). Median duration of HyQvia treatment during the dose ramp up period was 42 days (range 20 to 49), and during the efficacy period was 366 days (range 42 to 507 days). None of the subjects withdrew due to a severe or serious local or systemic adverse reaction. There were two acute serious bacterial infections (aSBI), both of which were episodes of pneumonia treated as outpatients with oral antibiotics during the 12-month efficacy period; an additional pneumonia requiring hospitalization

occurred during the ramp-up. Based on this, the annualized rate of aSBI while treated with HyQvia was 0.025, with an upper 99% confidence limit of 0.089, which is significantly less than ($p < 0.0001$) the rate of one infection per year. The secondary endpoints evaluated in the efficacy trial were the annual rate of all infections and other efficacy measures. An objective of the trial was to achieve the same number or fewer infusions with HyQvia per month as with intravenous administration and significantly fewer than with conventional subcutaneous administration. Sixteen of eighty-three subjects (19.3%) were infused every 3 weeks and 67 (80.7%) were infused every 4 weeks. Seventy-eight of 83 (94%) subjects attained the same 3- or 4-week dosing as their previous IV treatment. One decreased from 4 to 3 weeks, one from 4 to 2 weeks and one from 3 to 2 weeks. The primary reason for decreasing the interval was discomfort due to swelling. In a separate study evaluating subcutaneous treatment with Immune Globulin Infusion 10% (Human), a median of 21.43 sites were required each month with a median monthly infusion time of 5.35 hours.

A prospective, open-label, non-controlled, multi-center trial was conducted in the US to determine the efficacy, safety, immunogenicity, and pharmacokinetics (PK) of HyQvia in pediatric subjects with PI who had received IVIG or SCIG treatment before enrollment into the trial. A total of forty-four subjects were enrolled, and the median age of pediatric subjects was 9.5 years (range: 3 to 15 years). Of the enrolled subjects, twenty-six subjects (59.1%) were male, eighteen subjects (40.9%) were female, and 40 subjects (90.9%) were White. Most subjects were not Hispanic or Latino (39 subjects [88.6%]). Pediatric subjects switched to HyQvia SC immunoglobulin treatment schedule administered at doses (volumes and treatment intervals) typical for IVIG administration. Treatment intervals and doses gradually increased in a ramp-up phase to an interval of 3 or 4 weeks. Data were analyzed when all subjects completed 12 months of participation (one year of observation) in the trial. Overall, the median number of infusions per month was 1.1 (range: 1.0 to 1.5) and was comparable across the age groups. The median number of infusion sites per month was 2.2 (range: 1.1 to 2.9), with a similar median number for all age categories. There were no clinically meaningful differences in trough IgG levels across age groups. The primary analysis for efficacy was based on the rate of aSBIs, defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess, per subject per year. Secondary analyses included the annual rate of other infections and health resource utilization outcome measures (e.g., days out of work/school/daycare). During the 12-month trial period, the mean aSBI rate per year was 0.04 (with an upper 1-sided 99% confidence interval of 0.21, $p<0.001$), which met the predefined success rate of less than one aSBI per subject per year. One subject experienced two aSBIs of bacterial pneumonia, and there were no other episodes of serious bacterial infections reported in this trial. The mean rate of all infections per subject-year was 3.20, with an upper limit of the 95% CI of 4.05. The overall rate of infections per subject is consistent with results obtained in the pivotal clinical study. Pediatric subjects missed a mean (95% CI) of 5.0 (2.2 to 7.9) days of work/school/daycare.

Octagam

In an open-label, multicenter study, 46 patients (including 10 patients between the ages of 6 and 12, and one 15 years old) with primary humoral immunodeficiency (PI) received Octagam 5% liquid in individualized doses of 300 - 600 mg/kg every 3 or 4 weeks for 12 months (Octagam Prescribing Information). More than half of the patients (n=27; 59%) were on a 4-week treatment schedule, the remainder received the study drug every 3 weeks. Six patients discontinued the study prematurely. The study examined the number of episodes of serious infections (pneumonia, bacteremia, sepsis, osteomyelitis, septic arthritis, visceral abscesses, bacterial or viral meningitis) per patient in a year, as well as the number of other infections, number of school or work days missed, the number and length of hospitalizations, and the number of visits to a physician or the emergency department for acute problems. The rate of serious infections per patient per year was 0.1 (5 infections over 43.5 patient-years). There were no other infections documented by positive radiograph or fever during the study period.

Panzyga

Primary Immunodeficiency (PI)

Study 1: In a prospective, open-label, single-arm, multicenter study in 51 children and adults with PI, subjects received PANZYGA at a dose between 200 to 800 mg/kg body weight every 3 or 4 weeks (Panzyga Prescribing Information). Subjects participated in the study for a mean of 360 days. Infusions were initiated at a rate of 1 mg/kg/min for the first 30 minutes, and, if tolerated, could be advanced to a maximum tolerated rate not exceeding 8 mg/kg/min. The mean

age of subjects was 26.8 years (range: 2 to 65 years). The primary efficacy endpoint was the number of episodes of serious bacterial infections per patient per year. Serious infection included pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscesses, or bacterial meningitis. Secondary efficacy variables included: occurrence of any infection of any kind or seriousness; time to resolution of infections; use of antibiotics; the number of days of work/school missed; the number and days of hospitalizations; and the number of episodes of fever. For the primary endpoint, the observed rate was 0.08 serious bacterial infections per patient per year (4 infections over 50.2 patient-years). Only 1 adult patient was hospitalized due to an infection for 4 days (overall rate of days in hospital per person-year: 0.080). Episodes of fever were observed for less than 25% of all patients. The mean resolution time was 14 days for serious bacterial infections and 18 days for other infections. Approximately 50% of all patients missed at least 1 day of work or school due to infections, with an annual rate of less than 4 days/person-year.

Idiopathic Thrombocytopenic Purpura (ITP)
A prospective, open-label, single-arm, multicenter study assessed the efficacy, safety, and tolerability of PANZYGA in 40 subjects with chronic ITP and a platelet count of 20 x 10 /L or less. Subjects ranged in age from 18 to 72 years (median: 32 years); 43% were female and 57% were male. Ninety percent of the subjects were Caucasian and 10% were Asian. Subjects received a 2 g/kg dose of PANZYGA administered as two daily 1 g/kg intravenous doses, given on 2 consecutive days. All but one patient received the maximum infusion rate of 8 mg/kg/minute, starting at 1 mg/kg/minute. Platelet counts were measured on Days 1 to 8, 15, and 22. The study was designed to determine the response rate, defined as the percentage of subjects with an increase in platelet count to at least 50 x 10 /L within 7 days after the first infusion (responders). Additionally, maximum platelet count, the time to reach a platelet count of at least 50 x 10 /L within the first 7 days, the duration of that response (i.e., the number of days the platelet count remained in excess of 50 x 10 /L), and the regression of hemorrhages in subjects who had bleeding at baseline were observed. Of the 36 subjects in the full analysis set, 29 (81%: 95% CI: 64%- 92%).) responded to PANZYGA with a rise in platelet count to at least 50 x 10 /L within 7 days after the first infusion. The lower bound of the overall 95% confidence interval for the response rate in all 36 subjects (64%) is above the predefined response rate of 60%. Of the 36 subjects, 23 (64%) subjects had bleeding at baseline. Bleeding was minor in 14 subjects (39%), mild in 2 subjects (6%) and moderate in 7 subjects (19%). On Day 7, only 14% of subjects were bleeding (5/36). Persistent bleeding was mild in 1 and minor in 2 subjects. Information regarding bleeding resolution was missing in 2 subjects with moderate bleeding.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
The efficacy of PANZYGA in adults with CIDP was evaluated in a prospective, doubleblind, randomized, multicenter study that enrolled 142 adult subjects (between 18 and 83 years of age) with CIDP who deteriorated in the Wash-out Phase, during which the current medication (immunoglobulins or corticosteroids) was reduced gradually. Subjects were randomized 1:2:1 to receive first a loading dose of 2 g/kg, and then 0.5 g/kg, 1.0 g/kg or 2.0 g/kg PANZYGA according to their respective dose arm for 7 maintenance infusions at 3-week intervals during the 24-week Dose-evaluation Phase. Subjects in the 0.5 g/kg and 1.0 g/kg arms had the option of rescue treatment with two consecutive infusions of 2.0 g/kg Panzyga at 3-week intervals if criteria were met. Efficacy was based on the proportion of responders in the 1.0 g/kg PANZYGA arm at Week 24 relative to Baseline (Week 0). A responder was defined as a subject with a decrease of at least 1 point in the adjusted 10-point Inflammatory Neuropathy Cause and Treatment (INCAT) disability score at Week 24 relative to Baseline. The proportion of responders in the 1.0 g/kg arm was 79.71% (95% CI: 68.8, 87.5), with 55 out of 69 subjects classified as responders. Efficacy was supported by the proportion of responders in the 2.0 g/kg dose arm in the adjusted INCAT disability score, and the proportion of responders in the 1.0 g/kg and 2.0 g/kg dose arms in the grip strength, inflammatory Rasch-built Overall Disability Scale (I-RODS) and Medical Research Council (MRC) sum scores.

Privigen
Treatment of Primary Humoral Immunodeficiency
A prospective, open-label, single-arm, multicenter study assessed the efficacy, safety, and pharmacokinetics of PRIVIGEN in adult and pediatric subjects with PI, who were treated for 12 months at a 3-week or 4-week dosing interval (Privigen Prescribing Information). Subjects ranged in age from 3 to 69; 46 (57.5%) were male and 34 (42.5%) were female; 77.5% were Caucasian, 15% were Hispanic, and 7.5% were African-American. All subjects had been on regular IGIV replacement therapy for at least 6 months prior to participating in the study. The efficacy analysis included 80 subjects,

16 (20%) on the 3-week dosing interval and 64 (80%) on the 4-week dosing interval. Doses ranged from 200 mg/kg to 888 mg/kg per infusion. The median dose for the 3-week interval was 428.3 mg/kg per infusion; the median dose for the 4-week interval was 440.6 mg/kg per infusion. Subjects received a total of 1038 infusions of PRIVIGEN, 272 for the 3-week dosing regimen and 766 for the 4-week dosing regimen. The maximum infusion rate allowed during this study was 8 mg/kg/min with 715 (69%) of the infusions administered at a rate of 7 mg/kg/min or greater. The primary analysis for efficacy was based on the annual rate of acute serious bacterial infections (aSBIs), defined as pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess, per subject per year. Secondary analyses were based on the annual rate of other infections, antibiotic use, days out of work/school/day care or unable to perform normal activities due to illness, and days of hospitalization.

During the 12-month study period, the aSBI rate was 0.08 (with an upper 1-sided 99% confidence interval of 0.203), which met the predefined success rate of less than one aSBI per subject per year. Six subjects experienced an aSBI, including three cases of pneumonia and one case each of septic arthritis, osteomyelitis, and visceral abscess. All six subjects completed the study. The rate of other infections was 3.55 infections per subject per year. The infections that occurred most frequently were sinusitis (31.3%), nasopharyngitis (22.5%), upper respiratory tract infection (18.8%), bronchitis (13.8%), and rhinitis (13.8%). Among the 255 infections, 16 (6.3%) occurring in 10 subjects were considered severe.

Treatment of Chronic Immune Thrombocytopenic Purpura
A prospective, open-label, single-arm, multicenter study assessed the efficacy, safety, and tolerability of PRIVIGEN in 57 subjects with chronic ITP and a platelet count of 20 × 10 /L or less. Subjects ranged in age from 15 to 69; 23 (40.4%) were male and 34 (59.6%) were female; all were Caucasian. Subjects received a 2 g/kg dosage of PRIVIGEN administered as 1 g/kg (10 mL/kg) intravenous infusion daily for 2 consecutive days and were observed for 29 days. Fifty-three (93%) subjects received PRIVIGEN at the maximum infusion rate allowed (4 mg/kg/min [0.04 mL/kg/min]). The primary analysis was based on the response rate defined as the percentage of subjects with an increase in platelet counts to at least 50 × 10 /L within 7 days after the first infusion (responders). Secondary analyses were based on the increase in platelet counts and the time to reach a platelet count of at least 50 × 10 /L at any point within the study period, the duration of that response, and the regression (decrease in the severity) of hemorrhage in subjects who had bleeding at baseline. Platelet counts were measured on Days 1, 2, 4, 6, 8, 15, 22, and 29. Additional measurements on Days 57 and 85 occurred in subjects with a platelet count of at least 50 × 10 /L at the previous visit.

Of the 57 subjects in the efficacy analysis, 46 (80.7%) responded to PRIVIGEN with a rise in platelet counts to at least 50 × 10 /L within 7 days after the first infusion. The lower bound of the 95% confidence interval for the response rate (69.2%) is above the predefined response rate of 50%. The highest median increase in platelet counts was seen 7 days after the first infusion (123 × 10 /L). The median maximum platelet count achieved was 154 × 10 /L. The median time to reach a platelet response of more than 50 × 10 /L was 2.5 days after the first infusion. Twenty-five (43%) of the 57 subjects reached this response by Day 2 prior to the second infusion and 43 (75%) subjects reached this response by Day 6. The duration of platelet response was analyzed for the 48 subjects who achieved a response any time after the first infusion. The median duration of platelet response in these subjects was 15.4 days (range: 1 to >82 days). Thirty-six (75%) of the 48 subjects maintained the response for at least 8.8 days and 12 (25%) of them for at least 21.9 days. Five (9%) subjects maintained a response up to Day 29 and two (4%) up to Day 85. A decrease in the severity of hemorrhage from baseline was observed in the following bleeding locations: skin (31 of 36 subjects), oral cavity (11 of 11 subjects), and genitourinary tract (7 of 9 subjects). This decrease was not sustained in all subjects up to the end of the 29-day study period.

Postmarketing Commitment Study in Chronic Immune Thrombocytopenic Purpura
A prospective, open-label, single-arm, multicenter study assessed efficacy and safety parameters in 57 IGIV-treated subjects with chronic ITP with a platelet count of $<30 \times 10^9$/L at screening. Fifty-three subjects had a history of chronic ITP with a duration of greater than 6 months and 4 subjects, all of whom had received prior treatment for ITP with subsequent elevation followed by falls in platelet counts, had a duration of ITP less than 6 months. The study examined the incidence of subjects who met laboratory and clinical criteria for hemolysis and was intended to identify antibodies

most frequently bound to erythrocytes in subjects who experienced clinically significant intravascular hemolysis. Subjects ranged in age from 18 to 65; 20 (35.1%) were male and 37 (64.9%) were female; all were Caucasian. Twenty-one (21) subjects (37%) received 1 infusion of 1 g/kg on Day 1 and 36 subjects (63%) received 2 infusions of 1 g/kg (Day 1 and Day 3). The second infusion was administered based on the subject's platelet response to the Day 1 dose (<50 × 10^9/L) and investigator's discretion.

The efficacy endpoint platelet response (increase in platelet count at least once to at least 50 × 10^9/L within 6 days after the first infusion) was achieved in 42 subjects (74%; 95% confidence interval [CI]: 61% to 83%). Fifteen subjects with a suspicion of hemolysis based on laboratory data were referred for independent expert adjudication during the study. The adjudication committee selected from 3 options for their determination: no hemolysis, hemolysis, or clinically significant intravascular hemolysis. The set of antibodies most frequently bound to erythrocytes in subjects with clinically significant intravascular hemolysis could not be analyzed, because no subject experienced clinically significant intravascular hemolysis. No irregular antibodies were detected in any subject; therefore, no association between such antibodies and hemolytic laboratory changes could be established. Hemolytic laboratory changes were most often found in non-O blood group (especially the A blood group) subjects and those receiving 2 infusions. These laboratory parameters improved or normalized by the end of the study in the majority of subjects. Seven subjects (12% of the study population) with a normal hemoglobin at baseline had an abnormal hemoglobin at Day 29 (end of study) with a hemoglobin range from 11.2 to 13.6 g/dL. Post-hoc analyses were performed using a set of defined criteria for hemolysis. The hemolysis group (18 subjects, 32%) met the criterion for greater than 1 g/dL drop in hemoglobin within a 21-day interval since the last IGIV administration not explained by blood loss or repeated phlebotomy, were treatment-emergent DAT positive, and met at least one other minor criterion (eg, fall in serum haptoglobin level to below the lower limit of normal, rise in lactate dehydrogenase level above the upper limit of normal, rise in indirect or total bilirubin to above the upper limit of normal, or rise in plasma-free hemoglobin above the upper limit of normal). Fourteen of 15 previously adjudicated presumptive hemolysis cases during the study were included in this post-hoc hemolysis group.

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy
In a prospective, open-label, single-arm, multicenter clinical study (PRIVIGEN Impact on Mobility and Autonomy [PRIMA]), 28 subjects with CIDP (13 IGIV-pretreated and 15 IGIV-untreated) received a PRIVIGEN loading dose of 2 g/kg followed by PRIVIGEN maintenance doses of 1 g/kg for up to 21 weeks with a 3 week follow up. Efficacy in the PRIMA study was based on the responder rate of PRIVIGEN in comparison to an historical control in the adjusted 10-point Inflammatory Neuropathy Cause and Treatment (INCAT) score. The responder rate was defined as the proportion of subjects who demonstrated clinically meaningful improvement (at least 1 point decrease on adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] score) between baseline and Week 25, with a pre-specified threshold of 35% in the lower limit of the 2-sided 95% Wilson-Score confidence interval (CI). The overall percentage of responders in PRIMA was 61% (95% CI: 42.4% to 76.4%). Response rates were 47% in IGIV-untreated and 77% in IGIV-pretreated subject subgroups. In a post-hoc analysis, the overall percentage of subjects in PRIMA who responded by week 10 and maintained the response through week 25 and lacked confounding changes in glucocorticoid/immunosuppressant dosage was 53.6% (95% CI: 35.8% to 70.5%).

In a second study (PATH) with the same PRIVIGEN dosing regimen, all 207 subjects were IGIV-pretreated and had relapsed following withdrawal of IGIV prior to being administered PRIVIGEN. The response rate was 73%. Among the subset of 151 subjects in the PATH study who had deteriorated by one or more points in adjusted INCAT score following withdrawal of IGIV, 137 subjects (90.7%) responded during the PRIVIGEN "restabilization" period with an increase of one or more adjusted INCAT score points. The overall median time to first adjusted INCAT response in PRIMA was 7.5 weeks (18 weeks in IGIV-untreated and 3 weeks in IGIV-pretreated). The median time to first adjusted INCAT response in PATH (all IGIV-pretreated) was 3.7 weeks (95% CI: 3.4 to 5.9 weeks). Mean INCAT score in PRIMA showed a clinically meaningful improvement by 1.4 points (1.1 points for IGIV-untreated, and 1.8 points for IGIV-pretreated [1.2 points in PATH]).

Medical Research Council (MRC) sum score in PRIMA improved by a mean of 6.9 points (7.7 points for IGIV-untreated and 6.1 points for IGIV-pretreated). MRC sum score in PATH improved by a mean of 3.6 points. Grip strength of the dominant hand improved in PRIMA by a mean of 14.1 kPa (17.0 kPa for IGIV-untreated and 10.8 kPa for IGIV-pretreated subgroups). Grip strength of the dominant hand improved in PATH by a mean of 12.2 kPa. Similar results were observed for the non-dominant hand in both studies.

Xembify
Study 1 was a prospective, open-label single-arm, multi-center clinical trial designed to evaluate pharmacokinetics and safety of Xembify as compared to Gamunex-C (Xembify prescribing information 2024). Efficacy was based on annualized serious bacterial infection (SBI) rate during the 6 months on Xembify. The Gamunex-C run-in phase prior to Xembify (subcutaneous phase) lasted 3 or 4 months to achieve steady state prior to pharmacokinetic profiling. The definition of SBI was either bacteremia/sepsis, bacterial meningitis, bacterial pneumonia, osteomyelitis/septic arthritis, or visceral abscess. This clinical trial determined the safety and pharmacokinetics of Xembify in 53 adult and pediatric subjects with PI (9.4% Hispanic or Latino; 90.6% White, 3.8% Black or African American, 5.7% American Indian or Alaskan Native). During the run-in and IV Gamunex-C phases 4 subjects discontinued (1 lost to follow-up, 2 withdrawals by subject, 1 adverse event). Xembify was administered to a total of 49 subjects (14 children aged 2 to ≤ 16 years and 35 adults) with a mean ± SD dose of 179 ± 45 mg/kg/week for a median treatment duration of 24 weeks and mean ± SD of 21.6 ± 6.5 weeks. The median dose was 171 mg/kg/week, and the range of doses was 71 mg/kg/week to 276 mg/kg/week. The total exposure of Xembify was 20.28 subject-years and 1053 infusions.

Study 2 is an ongoing study in which Xembify is being administered for 1 year and is being conducted in the European Union and Australia. A total of 61 subjects including 29 children were enrolled. The interim safety data in adult and pediatric study subjects appear consistent with the safety results of the clinical trial in Study 1. The rate of serious bacterial infections (SBIs) which was an exploratory endpoint in Study 1, was 0.05 events per subject-year (1 event in 20 subject-years) (upper 99% confidence limit: 0.11) during Xembify treatment. This annual rate was lower than 1.0 SBI/subject-year, the threshold specified as effective.

Place in Therapy

According to guidelines, immune globulin is a component of standard therapy for various PI disorders (Bonilla et al 2015, Perez 2017). Guidelines also support the use of immune globulins for the treatment of appropriately selected patients with ITP, Kawasaki disease, CLL, CIDP, DM, MMN, hepatitis A prophylaxis, and measles prophylaxis (Centers for Disease Control and Prevention [CDC] 2013, Gorelik et al 2022, McCrindle et al 2017, National Comprehensive Cancer Network [NCCN] v2.2025, Nelson et al 2020, Neunert et al 2019, Patwa et al 2012, Provan et al 2019).

Immune globulin has not been shown to prevent rubella or mumps infection after exposure and is not recommended for that purpose (CDC 2013).

In general, guidelines do not specify or recommend one immune globulin product over another for treatment of specific indications.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Alyglo (immune globulin intravenous, human-stwk) is a 10% immune globulin liquid for intravenous injection, indicated for the treatment of primary humoral immunodeficiency (PI) in adults.

Asceniv (immune globulin intravenous, human – slra) is a 10% immune globulin liquid for intravenous injection, indicated for the treatment of primary humoral immunodeficiency (PI) in adults and adolescents

(12 to 17 years of age).

Bivigam is an Immune Globulin Intravenous (Human), 10% Liquid, indicated for the treatment of adults and pediatric patients 2 years of age and older with primary humoral immunodeficiency (PI).

Cutaquig (Immune Globulin Subcutaneous (Human) - hipp) is a 16.5% immune globulin solution for subcutaneous infusion indicated for treatment of primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older.

Cuvitru is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Solution indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age and older.

Flebogamma DIF is an immune globulin intravenous (human), indicated for treatment of primary (inherited) immunodeficiency (PI) in adults and pediatric patients 2 years of age and older.

Gammagard Liquid is an immune globulin infusion (human) indicated as a:

- Replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age or older.
- Maintenance therapy to improve muscle strength and disability in adult patients with Multifocal Motor Neuropathy (MMN).
- Therapy to improve neuromuscular disability and impairment in adult patients with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).

Gammagard S/D is an Immune Globulin Intravenous (Human) indicated for:

- Treatment of primary immunodeficiency (PI) in adults and pediatric patients two years of age or older.
- Prevention of bacterial infections in hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell chronic lymphocytic leukemia (CLL).
- Prevention and/or control of bleeding in adult chronic idiopathic thrombocytopenic purpura (ITP) patients.
- Prevention of coronary artery aneurysms associated with Kawasaki syndrome in pediatric patients.

Gammaked is an immune globulin injection (human), 10% liquid indicated for treatment of:

- Primary Humoral Immunodeficiency (PI) in patients 2 years of age and older
- Idiopathic Thrombocytopenic Purpura (ITP) in adults and children
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in adults

Gamunex-C is an immune globulin injection (human), 10% liquid indicated for treatment of:

- Primary Humoral Immunodeficiency (PI) in patients 2 years of age and older
- Idiopathic Thrombocytopenic Purpura (ITP) in adults and children
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in adults

Hizentra is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated for the treatment of:

- Primary immunodeficiency (PI) in adults and pediatric patients 2 years of age and older.
- Maintenance therapy in adults with chronic inflammatory demyelinating polyneuropathy (CIDP).

HyQvia is an immune globulin with a Recombinant Human Hyaluronidase indicated for the treatment of:

- Primary Immunodeficiency (PI) in adults and pediatric patients two years of age and older.
- Maintenance therapy in adults with chronic inflammatory demyelinating polyneuropathy (CIDP).

Octagam is an immune globulin intravenous (human), 5% liquid, indicated for treatment of primary humoral immunodeficiency (PI).

Panzyga is an immune globulin intravenous (human) - ifas 10% liquid preparation indicated for the treatment of:

- Primary humoral immunodeficiency (PI) in patients 2 years of age and older
- Chronic immune thrombocytopenia (ITP) in adults
- Chronic inflammatory demyelinating polyneuropathy (CIDP) in adults

Privigen is an Immune Globulin Intravenous (Human), 10% Liquid indicated for the treatment of:

- Primary humoral immunodeficiency (PI)
- Chronic immune thrombocytopenic purpura (ITP) in patients age 15 years and older
- Chronic inflammatory demyelinating polyneuropathy (CIDP) in adults

Xembify (immune globulin subcutaneous, human- klhw) is a 20% immune globulin solution for subcutaneous injection indicated for treatment of Primary Humoral Immunodeficiency (PI) in patients 2 years of age and older.

References

1. Abolhassani H, Sadaghiani MS, Aghamohammadi A, et al. Home-based subcutaneous immunoglobulin versus hospital-based intravenous immunoglobulin in treatment of primary antibody deficiencies: systematic review and meta-analysis. J Clin Immunol. 2012;32:1180-1192.
2. Achiron A, Gabbay U, Gilad R, et al. Intravenous immunoglobulin treatment in multiple sclerosis. Effect on relapses. Neurology. 1998;50:398-402.
3. AHFS Drug Information/Lexi-Comp Online [internet database]. Hudson, OH. Lexi-Comp, Inc. Updated periodically. Available by subscription at: http://online.lexi.com/. Accessed March 27, 2025.
4. Apostolski, ES, Doorn PV, Gilhus NE, et al. EFNS Task Force. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases. European Journal of Neurology 2008; 15:893-908.
5. Bain PG, Motomura M, Newsom-Davis J, et al. Effects of intravenous immunoglobulin on muscle weakness and calcium-channel autoantibodies in the Lambert-Eaton myasthenic syndrome. Neurology. 1996;47:678-83.
6. Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2015;136(5):1186-1205.e78.
7. Buehler AM, Flato UP, Ferri CP, Fernandes JG. Is there evidence for recommending specific intravenous immunoglobulin formulations? A systematic review of head-to-head randomized controlled trials. Eur J Pharmacol. 2015;747:96-104.
8. Centers for Disease Control and Prevention. Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children. MMWR 2009;58(No. RR-11):11-12.
9. Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-oi/guidelines-adult-adolescent-oi.pdf. Accessed March 27, 2025.
10. Centers for Disease Control and Prevention; Infectious Disease Society of America; American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep. 2000;49(RR-10):1-125.
11. Cherin P, Herson S, Wechsler B, et al. Efficacy of intravenous gammaglobulin therapy in chronic refractory polymyositis and dermatomyositis: an open study with 20 adult patients. Am J Med. 1991;91:162-8.

12. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia: Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia: a randomized, controlled trial. N Engl J Med. 1988;319:902-907.
13. Cutaquig Prescribing Information. Octapharma USA, Inc. Paramus, NJ. November 2021.
14. Cuvitru Prescribing Information. Baxalta US Inc. Lexington, MA. February 2025.
15. Dalakas MC, Fujii M, Li M, et al. High-dose intravenous immune globulin for stiff-person syndrome. N Engl J Med. 2001;345:1870-6.
16. Dalakas MC, Illa I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. N Engl J Med. 1993;329:1993-2000.
17. Danieli M, Malcangi G, Palmieri C, et al. Cyclosporin A and Intravenous Immunoglobulin Treatment in Polymyositis/Dermatomyositis. Ann Rheum Dis. 2002;61;37-41.
18. Drake LA, Dinehart SM, Farmer ER, et al. Guidelines of care for dermatomyositis. American Academy of Dermatology. J Am Acad Dermatol. 1996;34:824-9.
19. Dyck PJ, Litchy WJ, Kratz KM, et al. A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol. 1994;36:838-45.
20. Fazekas F, Deisenhammer F, Strasser-Fuchs S, et al. Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis. Austrian Immunoglobulin in Multiple Sclerosis Study Group. Lancet. 1997;349:589-93.
21. Federico P, Zochodne DW, Hahn AF, et al. Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study. Neurology. 2000;55:1256-62.
22. Frankovich J, Swedo S, Murphy T, et al. Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part II—Use of Immunomodulatory Therapies. Journal of Child and Adolescent Psychopharmacology. 2017;27(7):574-593.
23. Gagliano A, Carta A, Tanca MG, Stefano Sotgiu. Pediatric Acute-Onset Neuropsychiatric Syndrome: Current Perspectives. 2023;Volume 19:1221-1250.
24. Gajdos P, Chevret S, Clair B, et al. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Myasthenia Gravis Clinical Study Group. Ann Neurol. 1997;41:789-96.
25. Gajdos P, Chevret S, Toyka K. Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD002277.
26. Gamm H, Huber C, Chapel H, et al. Intravenous immune globulin in chronic lymphocytic leukaemia. Clin Exp Immunol. 1994;97 Suppl 1:17-20.
27. Goodin DS, Frohman EM, Garmany GP Jr, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology 2002;58:169-78.
28. Hughes RA, Bouche P, Cornblath DR, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the EFNS and PNS. Eur J Neurol 2006 Apr;13(4):326-32.
29. Hughes RA, Wijdicks EF, Barohn R, et al. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: immunotherapy for Guillain-Barre syndrome: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2003;61:736-40.
30. Hughes R, Bensa S, Willison H, et al. Inflammatory Neuropathy Cause and Treatment (INCAT) Group. Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol. 2001;50:195-201.
31. HyQvia Prescribing Information. Baxalta US Inc. Lexington, MA. September 2024.

32. Hizentra Prescribing Information. CSL Behring LLC. Kankakee, IL. April 2023.
33. Jolles S. Subcutaneous and intramuscular immune globulin therapy. UpToDate Web site. Updated July 27, 2024. http://www.uptodate.com. Accessed March 27, 2024.
34. Jongen JL, van Doorn PA, van der Meche FG. High-dose intravenous immunoglobulin therapy for myasthenia gravis. J Neurol. 1998;245:26-31.
35. Keller MA, Stiehm ER. Passive immunity in prevention and treatment of infectious diseases. Clin Microbiol Rev. 2000;13(4):602-614
36. Koller H, Kieseier BC, Jander S, et al. Chronic inflammatory demyelinating polyneuropathy. N Engl J Med. 2005;352(13):1343-56.
37. Lang BA, Laxer RM, Murphy G, et al. Treatment of dermatomyositis with intravenous gammaglobulin. Am J Med. 1991;91:169–72.
38. Leger JM, Chassande B, Musset L, et al. Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. Brain. 2001;124:145-53.
39. Levy LM, Dalakas MC, Floeter MK. The stiff-person syndrome: an autoimmune disorder affecting neurotransmission of gamma-aminobutyric acid. Ann Intern Med. 1999 Oct 5;131(7):522-30.
40. Leong H, Stachnik J, Bonk ME, Matuszewski KA. Unlabeled uses of intravenous immune globulin. Am J Health-Syst Pharm. 2008;65:1815-1824.
41. Lingman-Framme J, Fasth A. Subcutaneous immunoglobulin for primary and secondary immunodeficiencies: an evidence-based review. Drugs. 2013;73:1307-1319.
42. Maddison P. Treatment in Lambert-Eaton myasthenic syndrome. Ann N Y Acad Sci. 2012 Dec;1275:78-84. doi: 10.1111/j.1749-6632.2012.06769.x.
43. McKeon A, Robinson MT, McEvoy KM, et al. Stiff-man syndrome and variants: clinical course, treatments, and outcomes. Arch Neurol. 2012 Feb;69(2):230-8. doi: 10.1001/archneurol.2011.991.
44. Mendell JR, Barohn RJ, Freimer ML, et al. Working Group on Peripheral Neuropathy. Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculoneuropathy. Neurology. 2001;56:445-9.
45. Micromedex Healthcare Series [database on the internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically. Available by subscription at: http://www.thomsonhc.com/. Accessed March 27, 2025.
46. Mofenson LM, Moye J Jr, Bethel J, et al. Prophylactic intravenous immunoglobulin in HIV-infected children with CD4+ counts of 0.20 x 10(9)/L or more. Effect on viral, opportunistic, and bacterial infections. The National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. JAMA. 1992;268:483-8.
47. Mofenson LM, Moye J Jr, Korelitz J, et al. Crossover of placebo patients to intravenous immunoglobulin confirms efficacy for prophylaxis of bacterial infections and reduction of hospitalizations in human immunodeficiency virus-infected children. The National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. Pediatr Infect Dis J. 1994;13:477-84.
48. Molica S, Musto P, Chiurazzi F, et al. Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIG) in chronic lymphocytic leukemia. Results of a cross-over study. Haematologica. 1996;81:121-126.
49. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma v2.2025. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed March 27, 2025.
50. National Institute of Neurological Disorders and Stroke. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). Available at: https://www.ninds.nih.gov/health-information/disorders/chronic-inflammatory-demyelinating-polyneuropathy-cidp. Accessed March 27, 2025.

51. Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med. 1991;324:1633-9.
52. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med. 1986;315:341-7.
53. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation. 2004;110:2747-71.
54. Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2006;117:S525-S553.
55. Oscier D, Fegan C, Hillmen P, et al. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. Br J Haematol. 2004;125:294-317.
56. PANS/PANDAS Flowcharts | PPN. PPN. Published December 15, 2020. Accessed July 27, 2024.
57. Patwa HS, Chaudhry V, Katzberg H, et al. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2012 Mar 27;78(13):1009-15.
58. Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. J Allergy Clin Immunol. 2017;139(3S):S1-S46.
59. Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barre syndrome. Lancet. 1997;349:225-30.
60. Privigen Prescribing Information. CSL Behring LLC. Kankakee, IL. March 2022.
61. Racosta JM, Sposato LA, Kimpinski K. Subcutaneous versus intravenous immunoglobulin for chronic autoimmune neuropathies: A meta-analysis. Muscle Nerve. 2017;55(6):802-809.
62. Sanders DB. Lambert-Eaton myasthenic syndrome: diagnosis and treatment. Ann N Y Acad Sci. 2003 Sep;998:500-8.
63. Saperstein DS, Katz JS, Amato AA, et al. Clinical spectrum of chronic acquired demyelinating polyneuropathies. Muscle Nerve. 2001;24:311-24.
64. Shabaninejad H, Asgharzadeh A, Rezaei N, Rezapoor A. A comparative study of intravenous immunoglobulin and subcutaneous immunoglobulin in adult patients with primary immunodeficiency diseases: A systematic review and meta-analysis. Expert Rev Clin Immunol. 2016;12(5):595-602.
65. Sharshar T, Chevret S, Mazighi M, et al. Validity and reliability of two muscle strength scores commonly used as endpoints in assessing treatment of myasthenia gravis. J Neurol. 2000;247:286-90.
66. Sokos DR, Berger M, Lazarus HM. Intravenous immunoglobulin: appropriate indications and uses in hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2002;8:117-30.
67. Sullivan KM, Kopecky KJ, Jocom J, et al. Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. N Engl J Med. 1990;323:705-12.
68. Sullivan KM, Storek J, Kopecky K, et al. A controlled trial of long-term administration of intravenous immunoglobulin to prevent late infection and chronic graft-vs.-host disease after marrow transplantation: clinical outcome and effect on subsequent immune recovery. Biol Blood Marrow Transplant. 1996;2:44-53.
69. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. J Pediatr 1997;131:888–93.
70. Van den Berg LH, Franssen H, Wokke JH. The long-term effect of intravenous immunoglobulin treatment in multifocal motor neuropathy. Brain. 1998;121:421-8.

71. Van den Berg LH, Kerkhoff H, Oey PL, et al. Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. J Neurol Neurosurg Psychiatry. 1995;59:248-52.
72. van der Meche FG, Schmitz PI. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barre syndrome. Dutch Guillain-Barre Study Group. N Engl J Med. 1992;326:1123-9
73. van Schaik IN, Winer JB, de Haan R, et al. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review. Lancet Neurol. 2002;1:491-8.
74. van Schaik IN, van den Berg LH, de Haan R, et al. Intravenous immunoglobulin for multifocal motor neuropathy. Cochrane Database Syst Rev. 2005;(2):CD004429.
75. Wegner B, Ahmed I. Intravenous immunoglobulin monotherapy in long-term treatment of myasthenia gravis. Clin Neurol Neurosurg. 2002;105:3-8.
76. Xembify Prescribing Information. Grifols Therapeutic LLC. Research Triangle Park, NC. July 2024.
77. Yap PL. Does intravenous immune globulin have a role in HIV-infected patients? Clin Exp Immunol. 1994 Jul;97 Suppl 1:59-67.
78. Parajuli S. Kidney transplantation in adults: Prevention and treatment of antibody-mediated rejection. UpToDate Web site. Updated September 3, 2024. http://www.uptodate.com. Accessed March 27, 2025.
79. Djamali A, Kaufman DB, Ellis TM, et al. Diagnosis and management of antibody-mediated rejection: current status and novel approaches. Am J Transplant 2014; 14:255.
80. Haas M, Loupy A, Lefaucheur C, et al. The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. Am J Transplant 2018; 18:293.
81. Chih S, McDonald M, Dipchand A, et al: Canadian Cardiovascular Society/Canadian Cardiac Transplant Network position statement on heart transplantation: patient eligibility, selection, and post-transplantation care. Can J Cardiol 2020; 36(3):335-356.
82. Costanzo MR, Dipchand A, Starling R, et al: The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2010; 29(8):914-956.
83. Baradaran H, Dashti-Khavidaki S, Taher M, et al: Antibody-mediated rejection in adult liver transplant recipients: a case series and literature review. J Clin Pharmacol 2022; 62(2):254-271.
84. Kim PT, Demetris AJ, & O'Leary JG: Prevention and treatment of liver allograft antibody-mediated rejection and the role of the 'two-hit hypothesis'. Curr Opin Organ Transplant 2016; 21(2):209-218.
85. Witt CA, Gaut JP, Yusen RD, et al: Acute antibody-mediated rejection after lung transplantation. J Heart Lung Transplant 2013; 32(10):1034-1040.
86. Neuhaus K , Hohlfelder B , Bollinger J , et al: Antibody-mediated rejection management following lung transplantation. Ann Pharmacother 2022; 56(1):60-64.
87. Asceniv (immune globulin intravenous, human – slra) 10% Liquid. ADMA Biologics, Inc. Boca Raton, FL. April 2019.
88. Bivigam (immune globulin intravenous, human) 10% injection, solution. ADMA Biologics, Inc. Boca Raton, FL. March 2024.
89. Flebogamma 5% DIF (immune globulin intravenous [human]), solution for intravenous administration] Prescribing Information. Grifols USA LLC. Research Triangle Park, NC. September 2019.
90. Gammagard Liquid (Immune Globulin Infusion, Human), 10% Solution, for intravenous and subcutaneous administration Prescribing Information. Takeda Pharmaceuticals America, Inc. Lexington, MA. September 2024.
91. Gammagard S/D (Immune Globulin Intravenous, Human) IgA less than 1 microgram per mL in a 5% Solution Prescribing Information. Takeda Pharmaceuticals America, Inc. Lexington, MA. March 2023.

92. Gammaked, [Immune Globulin Injection (Human), 10% Caprylate/ Chromatography Purified]. Kedrion Biopharma, Inc. Fort Lee, NJ. January 2020.

93. Gamunex -C, [Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified] Prescribing Information. Grifols USA LLC. Research Triangle Park, NC. January 2020.

94. Octagam [Immune Globulin Intravenous (Human)] Liquid Preparation Prescribing Information. Octapharma USA Inc. Paramus, NJ. April 2022.

95. Panzyga, (immune globulin intravenous, human - ifas) 10% Liquid Preparation Prescribing Information. Octapharma USA Inc. Paramus, NJ. February 2021.

96. Belmokhtar C, Lozeron P, Adams D, et al. Efficacy and safety of Octagam in patients with chronic inflammatory demyelinating polyneuropathy. *Neurol Ther*. 2019;8(1):69-78.

97. Eftimov F, Winer JB, Vermeulen M, et al. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev*. 2013;(12): Art. No.: CD001797. DOI: 10.1002/14651858.CD001797.pub3.

98. Acero-Garcés DO, García-Perdomo HA. First line treatments for newly diagnosed primary immune thrombocytopenia in children: A systematic review and network meta-analysis. *Curr Pediatr Rev*. 2020;16(1):61-70.

99. Gordon PA, Winer JB, Hoogendijk JE, Choy EH. Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis. *Cochrane Database Syst Rev*. 2012;2012(8):CD003643.

100. Lioger B, Maillot F, Ternant D, Passot C, Paintaud G, Bejan-Angoulvant T. Efficacy and safety of anti-D immunoglobulins versus intravenous immunoglobulins for immune thrombocytopenia in children: Systematic review and meta-analysis of randomized controlled trials. *J Pediatr*. 2018. pii: S0022-3476(18)30974-0.

101. Merkies ISJ, van Schaik IN, Leger JM, et al. Efficacy and Safety of IVIG in CIDP: Combined data of the PRIMA and PATH studies. *J Peripher Nerv Syst.* 2019; 24(1):48-55.

102. Oates-Whitehead RM, Baumer JH, Haines L, et al. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev*. 2003;(4):CD004000.

103. Raanani P, Gafter-Gvili A, Paul M, et al. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis. *Leuk Lymphoma*. 2009;50(5):764-772.

104. McCrindle BW, Rowley AH, Newburger JW, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135(17):e927-e999.

105. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv*. 2019;3(23):3829-3866.

106. Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of hepatitis A virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, 2020. *MMWR Recomm Rep*. 2020;69(5):1-38. doi:10.15585/mmwr.rr6905a1

107. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. *Blood Adv*. 2019;3(22):3780-3817.

108. Alyglo (immune globulin intravenous, human-stwk), 10% Liquid [package insert], Teaneck, NJ: GC Biopharma Corp.; December 2023.

109. Broderick C, Kobayashi S, Suto M, Ito S, Kobayashi T. Intravenous immunoglobulin for the treatment of Kawasaki disease. *Cochrane Database Syst Rev*. 2023;1(1):CD014884. doi:10.1002/14651858.CD014884.pub2

110. Bus SR, de Haan RJ, Vermeulen M, van Schaik IN, Eftimov F. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev*. 2024;2(2):CD001797. doi:10.1002/14651858.CD001797.pub4

111. Centers for Disease Control and Prevention (CDC). Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: Summary recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report. June 14, 2013;62(RR04):1-34.

112. Keddie S, Eftimov F, van den Berg LH, Brassington R, de Haan RJ, van Schaik IN. Immunoglobulin for multifocal motor neuropathy. *Cochrane Database Syst Rev*. 2022;1(1):CD004429. doi:10.1002/14651858.CD004429.pub3

113. Ramzi A, Maya S, Balousha N, et al. Subcutaneous immunoglobulins (SCIG) for chronic inflammatory demyelinating polyneuropathy (CIDP): A comprehensive systematic review of clinical studies and meta-analysis. *Neurol Sci*. Published online June 28, 2024. doi:10.1007/s10072-024-07640-3

Policy History/Revision Information

Date	Summary of Changes
12/13/2023	Approved by OptumRx P&T Committee
5/16/2024	Annual Review. Updated references. Updated background section. Added Asceniv, Bivigam, Flebogamma, Gammagard, Gammaked, Gamunex -C, Octagam, Panzyga, Privigen, and Xembify to list of medications. The addition of these IVIG products led to the addition of the following indications to the policy: Idiopathic Thrombocytopenic Purpura (ITP), Kawasaki Disease (KD), B-cell Chronic Lymphocytic Leukemia (CLL), Bone Marrow Transplantation (off-label), HIV (off-label), Multifocal Motor Neuropathy (off-label), Relapsing-Remitting Multiple Sclerosis (off-label), Myasthenia Gravis Exacerbation (off-label), Stiff Person Syndrome (off-label), Dermatomyositis and Polymyositis (off-label), Guillain-Barre Syndrome (off-label), Lambert-Eaton Myasthenic Syndrome (off-label), Pediatric Acute-Onset Neuropsychiatric Syndrome/Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANS/PANDAS) (off-label), Antibody-mediated Transplant Rejection (off-label)
9/18/2024	Added Alyglo to list of medication. Addition of temporary HCPCS code of J1599 for Alyglo to applicable codes section. Updated background section and references.
10/16/2024	For HIV off label criteria, age requirement removed.
4/16/2025	Annual Review. Updated background section. Updated references. Added coverage to Alyglo, Asceniv, and HyQvia for CIDP, Added coverage to Alyglo and Asceniv for bone marrow transplantation, HIV, MMN, RRMS, Myasthenia Gravis, Stiff Person Syndrome, Dermatomyositis and Polymyositis, Guillain-Barre Syndrome, Lambert-Eaton Myasthenic Syndrome.

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. The insurance reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

OptumRx may also use tools developed by third parties to assist us in administering health benefits. OptumRx Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Archived Policy Versions (Internal Only)

Effective Date	Policy Number	Policy Title
mm/dd/yyyy – mm/dd/yyyy	######	Title of Policy Hyperlinked to KL or Other Internal Location

Nondiscrimination & Language Access Policy

Discrimination is Against the Law. Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex, (including sex characteristics, including intersex traits; pregnancy or related conditions; sexual orientation, gender identity and sex stereotypes), consistent with the scope of sex discrimination described at 45 CFR § 92.101(a)(2). Aspirus Health Plan, Inc. does not exclude people or treat them less favorably because of race, color, national origin, age, disability, or sex.

Aspirus Health Plan, Inc.:
Provides people with disabilities reasonable modifications and free appropriate auxiliary aids and services to communicate effectively with us, such as:

- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If *you* need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

If *you* believe that Aspirus Health Plan, Inc. has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, *you* can file a *grievance* with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

You can file a *grievance* in person or by mail, fax, or email. If *you* need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html. This notice is available at Aspirus Health Plan, Inc.'s website: https://aspirushealthplan.com/webdocs/70021-AHP-NonDiscrim_Lang-Assist-Notice.pdf.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1-800-332-6501 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف1-800-332-6501(رقم هاتف الصم والبك : 711)

French: ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-332-6501 (ATS: 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zurVerfügung. Rufnummer: 1-800-332-6501 (TTY: 711).

Hindi: _यान द_: य_द आप ि हंदी बोलते ह_ तो आपके ि लए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_।1-800-332-6501 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1-800-332-6501 (TTY: 711).

Korean: 주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다.1-800-332-6501 (TTY: 711)번으로 전화해 주십시오.

Polish: UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer1-800-332-6501 (TTY: 711).

Russian: ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода.Звоните 1-800-332-6501 (телетайп: 711).

Spanish: ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al1-800-332-6501 (TTY: 711).

Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1-800-332-6501 (TTY: 711).

Traditional Chinese: 注意：如果您使用繁體中文， 您可以免費獲得語言援助服務。請 致電 1-800-332-6501 (TTY: 711)

Vietnamese: CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1-800-332-6501 (TTY: 711).

Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzscht, kannscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1-800-332-6501 (TTY: 711).

Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1-800-332-6501 (TTY: 711).

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