**Supplemental Data**

**Supplemental Table 1.** Baseline blood phenylalanine and immunogenicity data for patients enrolled in the PRISM-1 study.

|  |  |
| --- | --- |
| **Baseline analytes** | **PRISM-1 study population (n = 261)** |
| Blood phenylalanine |  |
| n | 261 |
| Mean (SD), μmol/L | 1232∙7 (386∙36) |
| Median, μmol/L | 1221 |
| Min–max, μmol/L | 285–2330 |
| Total antibodies |  |
| n | 260 |
| Mean (SD) | 206 (949) |
| Median | 0 |
| Min–max | 0–10,700 |
| Neutralizing antibodies |  |
| n | 258 |
| Mean (SD) | 0 (1) |
| Median | 0 |
| Min–max | 0–18 |
| PEG IgG |  |
| n | 260 |
| Mean (SD) | 36 (119) |
| Median | 10 |
| Min–max | 0–810 |
| PEG IgM |  |
| n | 260 |
| Mean (SD) | 177 (1020) |
| Median | 0 |
| Min–max | 0–15,300 |
| PAL IgG |  |
| n | 260 |
| Mean (SD) | 59 (762) |
| Median | 0 |
| Min–max | 0–12,150 |
| PAL IgM |  |
| n | 260 |
| Mean (SD) | 243 (582) |
| Median | 130 |
| Min–max | 0–8201 |
| IgM-C3d CIC |  |
| n | 259 |
| Mean (SD), μg Eq/mL | 2∙1 (2∙4) |
| Median, μg Eq/mL | 1∙13 |
| Min–max, μg Eq/mL | 0∙5–16∙5 |
| IgG-C3d CIC |  |
| n | 259 |
| Mean (SD), μg Eq/mL | 10∙6 (5∙3) |
| Median, μg Eq/mL | 9∙4 |
| Min–max, μg Eq/mL | 1∙8–37∙1 |
| C3 |  |
| n | 258 |
| Mean (SD), g/L | 1∙19 (0∙234) |
| Median, g/L | 1∙2 |
| Min–max, g/L | 0∙7–2∙2 |
| C4 |  |
| n | 258 |
| Mean (SD), g/L | 0∙25 (0∙097) |
| Median, g/L | 0∙2 |
| Min–max, g/L | 0∙1–1∙3 |

CIC, circulating immune complex; IgG, immunoglobulin G; IgM, immunoglobulin M; PAL, phenylalanine ammonia lyase; PEG, polyethylene glycol.

**Supplemental Table 2.** Incidence and mean titers of antibodies in the PRISM phase 3 studies over time (n = 261).

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Baseline** | **Week 4** | **Week 8** | **Week 12** | **Week 16** | **Week 20** | **Week 24** | **Week 36** | **Week 52** | **Week 104** |
| **Incidence (%)** | | | | | | | | |  |  |
| TAb | 30∙8 | 91∙1 | 96∙3 | 98∙6 | 99∙0 | 99∙0 | 100 | 98∙9 | 100 | 98∙9 |
| NAb | 0∙4 | 0∙8 | 14∙0 | 53∙7 | 67∙5 | 73∙9 | 79∙2 | 79∙7 | 81∙3 | 72∙5 |
| PAL IgG | 6∙9 | 34∙9 | 98∙0 | 99∙5 | 100 | 100 | 100 | 100 | 100 | 100 |
| PAL IgM | 50∙0 | 74∙4 | 98∙4 | 98∙6 | 98∙5 | 95∙0 | 92∙2 | 87∙5 | 84∙0 | 83∙5 |
| PEG IgG | 52∙3 | 92∙6 | 96∙3 | 65∙0 | 59∙8 | 47∙0 | 41∙5 | 28∙6 | 14∙8 | 3∙4 |
| PEG IgM | 45∙0 | 86∙4 | 96∙3 | 91∙3 | 87∙2 | 82∙6 | 76∙6 | 67∙9 | 59∙7 | 57∙1 |
|  |  |  |  |  |  |  |  |  |  |  |
| **Mean titer** | | | | | | | | |  |  |
| TAb | 206 | 38,949 | 29,279 | 14,536 | 17,530 | 12,884 | 13,895 | 16,174 | 14,858 | 16,286 |
| NAb | 0 | 0 | 9 | 248 | 332 | 415 | 415 | 505 | 608 | 661 |
| PAL IgG | 59 | 166 | 26,104 | 584,350 | 896,429 | 884,979 | 961,296 | 1,177,665 | 1,219,788 | 1,086,602 |
| PAL IgM | 243 | 557 | 2687 | 3372 | 1675 | 1183 | 1026 | 1024 | 1355 | 2190 |
| PEG IgG | 36 | 4600 | 1556 | 316 | 122 | 89 | 69 | 38 | 22 | 0 |
| PEG IgM | 177 | 15,466 | 28,735 | 48,689 | 7958 | 6019 | 3259 | 883 | 385 | 67 |
|  |  |  |  |  |  |  |  |  |  |  |

Patients treated with pegvaliase developed sustained ADA against the PAL protein, and transient antibodies against PEG. The development of the antibody response occurred in a biphasic manner, characterized by a difference in composition of the antibodies during early versus late treatment. The early antibody response was composed of PEG IgM, PEG IgG, and PAL IgM antibodies, whereas the late antibody response was composed of PAL IgG. Anti-PEG antibody titers peaked 1−3 months after treatment initiation and then returned to baseline in most patients by 6−9 months. PAL IgM and PAL IgG titers peaked at 3 and 6 months, respectively, and remained stable through long-term treatment. The majority of patients developed a low-titer NAb response over time. ADA, antidrug antibodies; IgG, immunoglobulin G; IgM, immunoglobulin M; NAb, neutralizing antibody; PAL, phenylalanine ammonia lyase; PEG, polyethylene glycol; TAb, total antibody.

**Supplemental Table 3.** Baseline anti-PEG positivity and frequency of HAEs (n = 261).

|  |  |  |
| --- | --- | --- |
| **Anti-PEG IgG** | **Baseline positive**  **N = 136** | **Baseline negative**  **N = 123** |
| Mean number of HAEs | 5∙9 | 7∙6 |
| Number of patients with HAEs | 119 | 109 |

|  |  |  |
| --- | --- | --- |
| **Anti-PEG IgM** | **Baseline positive**  **N = 116** | **Baseline negative**  **N = 143** |
| Mean number of HAEs | 6∙7 | 6∙7 |
| Number of patients with HAEs | 105 | 123 |

HAEs, hypersensitivity adverse events; IgG, immunoglobulin G; IgM, immunoglobulin M; PEG, polyethylene glycol.

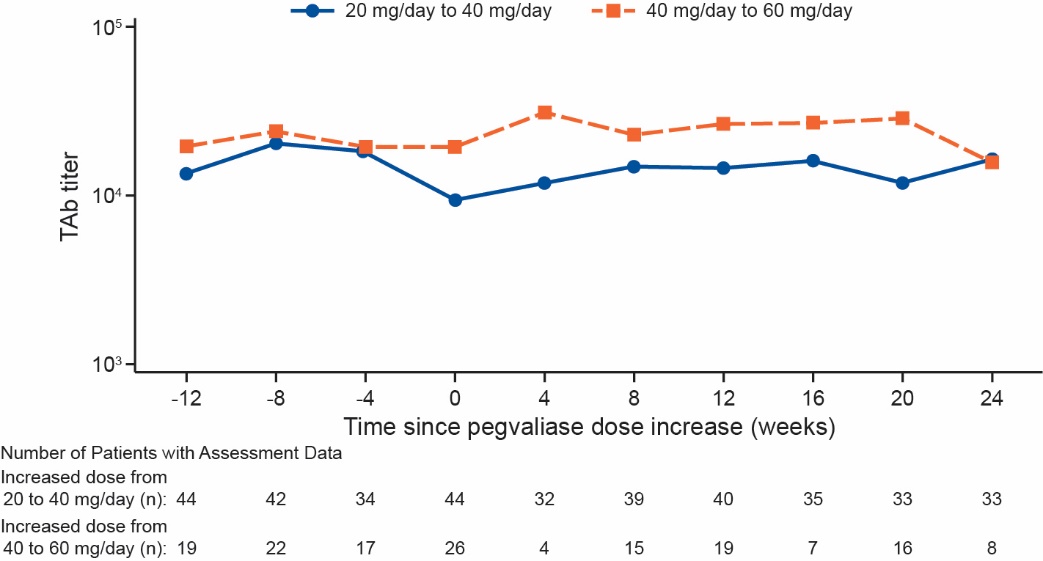
**Supplemental Table 4.** Adverse events by IgM circulating immune complex change from baseline quartiles (intent-to-treat population, N=261).

|  | **Quartile 1 (n = 65)** | **Quartile 2 (n = 65)** | **Quartile 3 (n = 65)** | **Quartile 4 (n = 64)** | **Total (n = 259)** |
| --- | --- | --- | --- | --- | --- |
| IgM CIC change from baseline quartile range (min-max) | −4∙02, 0∙79 | 0∙79, 1∙98 | 2∙01, 5∙53 | 5.59, 50.96 |  |
| Total treatment exposure, person-yearsa | 118∙0 | 120∙1 | 102∙6 | 60∙5 | 401∙2 |
| Event rate, per person-year (total number of events) | | | | | |
| Adverse events | 24∙33 (2872) | 25∙79 (3098) | 33∙54 (3443) | 47∙95 (2899) | 30∙69 (12312) |
| Serious adverse events | 0∙11 (13) | 0∙12 (15) | 0∙13 (13) | 0∙31 (19) | 0∙15 (60) |
| Hypersensitivity adverse events | 7∙24 (854) | 6∙63 (796) | 6∙62 (679) | 10∙14 (613) | 7∙33 (2942) |
| Acute systemic hypersensitivity events of anaphylaxis | 0∙03 (3) | 0∙06 (7) | (2) (0∙02) | 0∙08 (5) | 0∙04 (17) |
| Arthralgia/arthritis | 2∙14 (252) | 3∙11 (373) | (260) (2∙53) | 3∙66 (221) | 2∙76 (1106) |
| Generalized skin reaction ≥14 days’ duration | 0∙37 (44) | 0∙39 (47) | (51) (0∙50) | 0∙48 (29) | 0∙43 (171) |
| Urticaria ≥14 days’ duration | 0∙03 (3) | 0∙03 (4) | (1) (0∙01) | 0∙03 (2) | 0∙02 (10) |
| Lymphadenopathy ≥14 days’ duration | 0∙14 (16) | 0∙11 (13) | (15) (0∙15) | 0∙17 (10) | 0∙13 (54) |
| Serum sickness-like reaction | 0∙01 (1) | 0∙01 (1) | (1) (0∙01) | 0∙07 (4) | 0∙02 (7) |
| Infection and infestations ≥30 days’ duration | 0∙24 (28) | 0∙22 (27) | (18) (0∙18) | 0∙20 (12) | 0∙21 (85) |
| Infection serious adverse events | 0∙02 (2) | 0∙01 (1) | (2) (0∙02) | 0∙02 (1) | 0∙01 (6) |
| Ischemic heart disease | 0 | 0 | 0 | 0 | 0 |

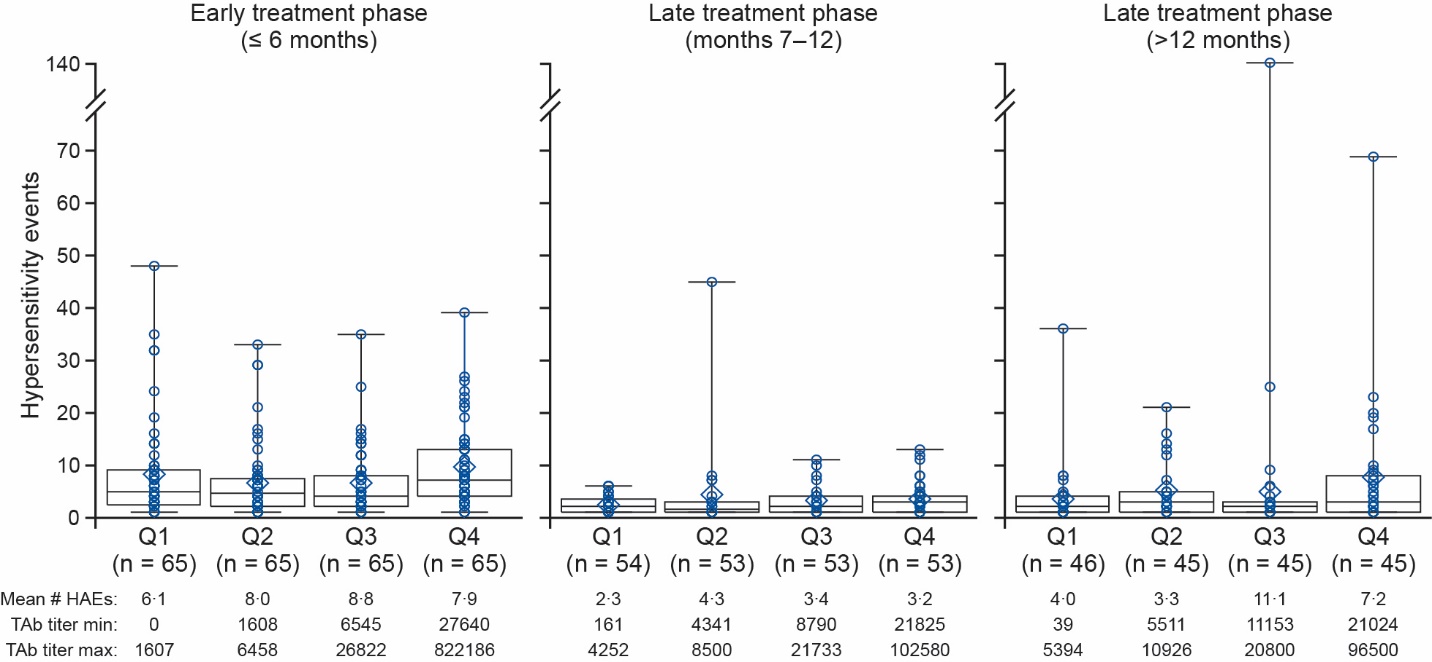
Event rate was calculated as total number of events divided by person-years of exposure.

aTotal treatment exposure was the aggregated duration of treatment across all patients (for each patient, time from the first dose to the last dose administered across all studies in which the patient was enrolled). Intervals of missing doses that were >28 consecutive days were excluded from the calculation of treatment duration.

CIC, circulating immune complex; IgM, immunoglobulin M.

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Supplemental Figure 1. Plot of mean dose increases on total anti-pegvaliase antibody (TAb) titer in patients increasing dose.Increasing pegvaliase dose was not associated with an increase in total anti-pegvaliase antibody (TAb). Patients who were originally randomized to pegvaliase 20 mg/day and had at least 4 consecutive weeks with 80% compliance on 40 mg/day dose were included in the 20 mg to 40 mg analysis. Patients who had at least 4 consecutive weeks with 80% compliance on 60 mg/day were included in the 40 mg to 60 mg analysis. TAb, total antibodies.



**Supplemental Figure 2.** Frequency of HAEs and TAb titer by treatment phase.Mean antibody titers for TAb were not associated with frequency of HAEs during any treatment phase. Additionally, there was considerable overlap within patients from all quartiles. Each dot represents one patient. Mean titer was calculated from all available antibody titers over the entire time on treatment for each patient. Antibody titers ≤1 are negative. HAE, hypersensitivity adverse event; TAb, total antibody.

**Supplemental Text**

**Overview of analytical methods**

Bioanalytical methods were developed, optimized and validated using the following documents as guidance: Bioanalytical Method Validation, FDA (CDER) Guidance for Industry, May 2001, Guideline on Bioanalytical Method Validation, EMA, February 2012; Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins, EMA April 2008; International Conference on Harmonization (ICH) Harmonized Tripartite Guideline*:* Validation of Analytical Procedures: Text and Methodology Q2 (R1), November 2005. Method validation studies were conducted to establish precision, sensitivity, specificity, selectivity, interference, and analyte stability. Pharmacokinetic assays were additionally validated for dilution linearity and accuracy.

**Quantitative measurement of Phe in human plasma**

Human plasma was processed and immediately frozen at clinical sites before shipping for analysis at a central laboratory. A quantitative ion exchange chromatography method to measure amino acids phenylalanine and tyrosine in human plasma was validated to support pegvaliase clinical studies. Amino acids in deproteinized plasma were injected into a cation exchange column (high-performance lithium column) and separated using a gradient of pH, ionic strength, and temperature. The amino acids eluting from the column were mixed with ninhydrin and passed through a high-temperature reaction coil to form colored adducts. The light absorbance of these adducts were measured with a photometer unit at 570 nm (amino acids) and integrated as a series of peaks with a specific retention time for each amino acid. The area of each peak was proportional to the concentration of the amino acid. The concentration of each amino acid, in µmol/L, was calculated using an internal standard (L-norleucine) to adjust for differences in extraction and/or injection.

**Measurement of anti-rAvPAL IgG in human serum**

A semi-quantitative direct format electrochemiluminescence assay (ECLA) method was validated to measure anti-PAL IgG antibodies in human serum samples. The method employed biotin-conjugated PAL coated on streptavidin plates to capture anti-PAL IgG from serum (1:50 minimum required sample dilution; MRD), and a ruthenium-labeled polyclonal goat antihuman IgG Fc antibody for detection. Assay plates were read on a mesoscale discovery plate reader, where the assay signal detected was proportional to the level, affinity, and avidity of the anti-PAL antibodies present in the sample. Samples that produced signal at or above the established screening cut point were considered reactive and were confirmed as PAL-specific by incubating with 204 μg/mL soluble PAL. If antibody binding was specific, the signal was lower in the presence of unlabeled PAL relative to the signal generated in the absence of PAL. A semi-quantitative titer value was determined for confirmed positive samples by serially diluting the sample until it was no longer reactive. The interpolated dilution factor at which the signal of the dilution curve crosses the titer cut point was reported as the sample titer.

**Measurement of anti-PEG IgG in human serum**

A semi-quantitative, direct-format ECLA method was validated to measure anti-PEG IgG in human serum samples. The method employed biotin-conjugated methoxy PEG coated on streptavidin plates to capture anti-PEG IgG from serum (1:10 MRD), and a ruthenium-labeled polyclonal goat anti-human IgG Fc antibody for detection. Assay plates were read on an MSD plate reader, where the assay signal detected was proportional to the level, affinity, and avidity of the anti-PEG antibodies present in the sample. Samples that produced signal at or above the established screening cut point were considered reactive and were confirmed with 2∙0 mg/mL excess PEG to compete for binding to the PEG-coated plate. A semi-quantitative titer value was determined for confirmed positive samples by serially diluting the sample until it was no longer reactive. The interpolated dilution factor at which the signal of the dilution curve crosses the titer cut point was reported as the sample titer.

**Measurement of anti-rAvPAL IgM in human serum**

A semi-quantitative, direct-format ECLA method was validated to detect anti-PAL IgM in human serum samples. Streptavidin-coated MSD plates were coated with biotin-conjugated PAL, washed, and blocked, and samples were incubated after dilution in buffer (1:10 MRD), to capture anti-PAL antibodies. Captured anti-PAL IgM was detected with a ruthenium-labeled polyclonal rabbit anti-human IgM Fc fragment-specific antibody. After washing, plates were read on an MSD Sector Imager reader. Due to a range of pre-existing anti-PAL IgM levels in normal human sera, a population of verified negative samples could not be identified, and therefore a conventional cut point delineating positive and negative could not be established. Instead a low-titer cut point was established below the lowest observed screening assay signal, in order to determine semi-quantitative titer results from all samples. Samples were serially diluted in assay diluent until the samples were no longer reactive above the established cut point. The interpolated dilution factor at which the signal of the dilution curve crossed the titer cut point was reported as the sample titer.

**Measurement of anti-PEG IgM in human serum**

A semi-quantitative, direct-format ECLA method was validated to detect anti-PEG IgM in human serum samples. Ninety-six well streptavidin-coated MSD plates were coated with biotin-conjugated methoxy PEG, washed, and blocked. Samples were diluted in buffer (1:20 MRD) and incubated on the plate to capture anti-PEG antibodies. Captured anti-PEG IgM was detected with a ruthenium-labeled polyclonal rabbit anti-human IgM Fc fragment-specific antibody. After washing, plates were read on an MSD Sector Imager reader. Samples were serially diluted in buffer until the samples were no longer reactive above the established cut point. The interpolated dilution factor at which the signal of the dilution curve crossed the titer cut point was reported as the sample titer.

**Measurement of anti-pegvaliase IgE in human serum**

Quantitative radioallergosorbent test (RAST) methods were developed and validated to measure anti-pegvaliase IgE and anti-PAL IgE in human serum samples. Biotin-conjugated pegvaliase or biotin-conjugated PAL were incubated with streptavidin-coated 6∙3 mm paper discs. Antigen-coated discs were blocked, washed, and incubated with neat serum samples in individual tubes to capture anti-pegvaliase or anti-PAL antibodies. After washing of unbound serum, discs were incubated with an I125-conjugated anti-human IgE detection reagent to detect captured anti-pegvaliase IgE and anti-PAL IgE. The discs were washed and raw assay gamma radioactivity counts were measured on a Wallac 1470 Wizard gamma counter. The gamma radioactivity adsorbed to each disc was proportional to the antigen-specific IgE concentration in each sample. The level of anti-pegvaliase or anti-PAL IgE in each sample was determined by interpolation of raw gamma counts against a human anti-rye grass IgE standard curve calibrated to the World Health Organization (WHO) international IgE‑ standard, captured on perennial rye grass-coated discs. The specificity of samples that screened positive was confirmed by pre-incubating the sample in the presence of soluble antigen to compete for binding to the antigen immobilized on the disc.

A quantitative method to measure anti-pegvaliase IgE in human serum was also developed and validated on the ImmunoCAP 1000 platform to confirm phase 3 study results. Pegvaliase-coupled ImmunoCAP cellulosic sponges were incubated with neat serum samples in the ImmunoCAP 1000 instrument to capture antigen-specific antibodies. After washing away nonspecific IgE, β-galactosidase-labeled monoclonal mouse anti-human IgE detection antibodies were added. Unbound detection reagent was washed away and the bound complex was incubated with the ImmunoCAP Development Solution containing 4-methylumbelliferyl-β-D-galactoside, a β-galactosidase fluorogenic substrate. After stopping the reaction, the fluorescence of the eluate was measured. The measured fluorescence is directly proportional to the concentration of drug-specific IgE in each patient sample. The concentration of antigen-specific IgE in each sample was determined by interpolation of raw assay signals against a human allergen-specific IgE standard curve calibrated with the WHO international IgE standard. The specificity of samples that screened positive was confirmed by signal inhibition in the presence of soluble antigen. Assay performance was monitored using quality control samples consisting of anti-pegvaliase IgE surrogate positive control (polyclonal rabbit anti-PAL IgG conjugated with human myeloma IgE) in normal human serum.

**Measurement of anti-pegvaliase total antibodies in human serum**

A semi-quantitative direct format ECLA method was validated to measure total anti-pegvaliase IgG, IgM, and IgA antibodies in human serum. Ninety-six-well MSD plates were coated with a rabbit anti-PEG monoclonal IgG capture antibody, washed, blocked, washed, coated with pegvaliase, and finally washed before addition of serum samples diluted in buffer (1:50 MRD), to capture anti-pegvaliase antibodies. Plates were incubated with a ruthenium-conjugated rabbit polyclonal as a pan-isotype detection reagent that reacts with human IgG, IgM, and IgA. MSD Read Buffer T (surfactant-free) was added to all wells, and the plates were read on the MSD Sector Imager instrument. A semi-quantitative titer value was determined for each sample by serially diluting the sample until it was no longer reactive. The interpolated dilution factor at which the signal of the dilution curve crosses the titer cut point was reported as the sample titer.

**Measurement of anti-pegvaliase activity-neutralizing antibodies in human serum**

A semi-quantitative hybrid ligand-binding: liquid chromatography/tandem mass spectrometry (LC/MS/MS) method was validated to measure anti-pegvaliase activity-neutralizing antibodies in human serum. The assay measured anti-pegvaliase antibodies in human serum that inhibit pegvaliase-mediated enzymatic conversion of the substrate L-phenylalanine (Phe) to the products *trans-*cinnamic acid (t-CA) and ammonia.

Ninety-six-well MSD plates containing immobilized rabbit monoclonal anti-PEG IgG were coated with pegvaliase. Serum samples were diluted in buffer (1:2 MRD) and acidified with glycine to dissociate antibody complexes. Acidified samples were then neutralized and added to the assay plate to capture anti-pegvaliase antibodies on the pegvaliase-coated plate. Unbound antibodies, pegvaliase, Phe, and t-CA were washed away and a Phe substrate solution was added and incubated overnight to allow enzymatic conversion of Phe to t-CA by pegvaliase. To quantify the amount of t-CA generated overnight, reaction samples were diluted in 96-deep-well plates using a solution of methanol with 0.01% acetic acid. Internal standard (trans-cinnamic-d7 acid) was added to the extraction solution for all samples except the blank matrix sample. Extracted samples were analyzed through LC/MS/MS and levels of t-CA were quantified using analyte to internal standard peak area/height ratios. Concentrations of the calibration curve standards, quality control samples, and study samples were determined by the method of 1/x2 weighted least squares linear regression. The concentration of t-CA produced after overnight incubation was inversely proportional to the concentration of NAb in each sample. Enzyme-neutralizing activity was detected by a reduction of t-CA concentration beyond the cut point established in method validation based on a panel of normal drug-naïve serum samples. The specificity of neutralizing activity in samples that screened positive was confirmed by adding 1 mg/mL of free pegvaliase to samples before the ligand-binding step. The resulting increase in t-CA corresponded to reduced neutralization. Samples that screened and confirmed positive were serially diluted in buffer and assayed to determine the relative level of NAb in each sample, reported as a semi-quantitative titer value.

**Measurement of IgG circulating immune complexes in human serum**

The Quidel MicroVue CIC-Raji Cell Replacement (also referred to as CIC-C3D EIA) assay kit was validated and used to measure circulating immune complexes (CIC) in serum samples. The assay relies on fragments of the third complement component, C3, that become covalently bound to complement-activating immune complexes. To capture immune complexes containing C3 activation fragments, standards and serum specimens in diluent (1:50 MRD) were added to microtiter plates coated with monoclonal antibodies that specifically bind the iC3b, C3d, g, and C3d fragments. After a wash cycle removed unbound serum proteins, horseradish peroxidase (HRP)-conjugated mouse anti-human IgG was added to each test well. The chromogenic substrate 2, 2’–Azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) diammonium salt was added to react with HRP, and oxalic acid was used to stop color development. The absorbance value (405 nm) was measured spectrophotometrically and was proportional to the amount of C3d containing complexes bound to the plate. A standard curve was generated by plotting the A405 values obtained with each standard versus its indicated concentration. The concentration of C3d immune complexes present in the test specimen was determined by interpolating values from a standard curve prepared from the surrogate positive control (heat-aggregated human gamma globulin; HAGG) added to pooled normal human serum. Samples with signals above the established quantitative range of the calibrator curve at 1:50 dilution factor were further diluted to generate results within the assay quantitative range. Results were expressed as micrograms of HAGG equivalents per mL (μg Eq/mL).

**Measurement of IgM circulating immune complexes in human serum**

The Quidel MicroVue C3d-CIC assay kit was modified to measure IgM-containing CIC, and was validated to support testing of human serum samples. The HRP-conjugated mouse anti-human IgG detection reagent supplied with the assay kit was replaced with a HRP-conjugated rabbit polyclonal anti-human IgM reagent to enable specific measurement of IgM-containing CIC. The kit standard calibrators and quality control (QC) samples, consisting of heat aggregated human gamma globulin, were replaced with analogous calibrators and QCs consisting of heat-aggregated human myeloma IgM. Other aspects of the assay method were unchanged from the C3d-CIC assay kit. Samples were initially tested at a dilution factor of 1:100. Samples with assay signals initially above the quantitative range of the calibrator curve were further diluted to generate results within the quantitative range. Results were expressed as micrograms of serum-treated HAGG equivalents per mL (μg Eq/mL).

**Institutional review boards by site (chairperson/director)**

Vanderbilt University Institutional Review Board (Steven L. Goudy, MD); Institutional Review Boards of UC San Diego Human Research Protections Program (Michael Caligiuri, PhD); Children’s Hospital and Research Center Oakland, Institutional Review Board (Horst Fischer, PhD); Oregon Health & Science University Research Integrity Office (Kathryn Schuff, MD, MCR); Ann and Robert H Lurie Children’s Institutional Review Board (Catherine A. Powers, RD, LDN, CCRC); Washington University in St. Louis Institutional Review Board (Amanda Unanue, BA); Boston Children’s Hospital Office of Clinical Investigation (Steven Colan, MD); University of Utah Institutional Review Board (Gerald Treiman, MD); Western Institutional Review Board (R. Bert Wilkins, JD); IU Human Subjects Office (Shelley D. Bizila, MS, CIP); Drexel University Human Research Protection (Daniel Conway, MD); Wayne State University IRB Administration Office (Niels Beck, PhD); Chesapeake IRB (Anita Tarzian, PhD, RN); Children’s Hospital and Health System Institutional Review Board (J. Paul Scott, MD); University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects (L. Maximilian Buja, MD); University of Louisville Institutional Review Board Human Subjects Protection Program Office (Laura D. Clark, MD); University of Kentucky Office of Research Integrity (Jeffrey Carrico, PharmD); University of Nebraska Medical Center Institutional Review Board (Kevin J. Epperson, CIP); University of Oklahoma Institutional Review Board for the Protection of Human Subjects (Karen Beckman, MD); Cooper Health System Institutional Review Board (David Warshal, MD); and University of Miami Medical IRB (Thomas Sick, PhD).