SUMMARY

[0010] In various examples, the present invention provides a dosing regimen for subcutaneous infusion of a pharmaceutical formulation of IgG incorporating a concentrated IgG formulation and methods of infusing these formulations that solve the problems of customary dosing regimens for subcutaneous infusion of IgG. In selected examples, the invention provides a kit for subcutaneous infusion of a pharmaceutical formulation of IgG at high infusion rates. An exemplary kit includes a stable 20% (w/v) IgG pharmaceutical formulation, a pharmaceutical formulation of hyaluronidase and instructions for using the formulations to infuse IgG at a high dose/volume ratio to a first infusion site at an unexpectedly high rate with excellent patient tolerability. The prior art neither discloses nor suggests methods of infusing a concentrated (e.g., 20%) IgG formulation into a first infusion site of a subject at a high rate.

[0011] Limitations with subcutaneous infusion of IgG formulations include the frequency and duration of infusion. Two approaches can be pursued (1) increasing the concentration of the IgG in the formulation or (2) increasing the volume infused per site. There are concerns remaining regarding discomfort and inconvenience related to high volume infusions per site, its potential effects on the body, local tolerability and local site reactions. Increasing the concentration of IgG in a formulation from 10% to 20% reduces the administered volume by about 50% A major challenge of increased concentration, however, is the higher viscosity of the concentrated solution, limiting the feasible infusion speed and leading to longer infusion times partly offsetting the advantage of the more concentrated formulation.

[0012] One approach to facilitating subcutaneous infusion involves administering a pharmaceutical formulation of hyaluronidase (e.g., rHuPH20) to a first infusion site prior to infusing the IgG formulation. Despite the promise of this approach studies designed to assess the feasibility of high flow rate (e.g., 3-5 mL/min) administration of the IgG formulation with rHuPH20 indicated, based on the magnitude of tissue back pressure against the IgG infusion, that rHuPH20 itself was not sufficient to support IgG flow rates of 3 mL/min or greater, which are desired for reducing infusion times of a standard dose of IgG. **FIG. 12**. Thus, until the present invention, it was not apparent how to obtain high infusion rates, e.g., 3-5 mL/min of an IgG subcutaneous infusion while maintaining the current quality and tolerability of an analogous 10% IgG formulation after administering hyaluronidase to the infusion site.

[0017] In an example, the 20% (w/v) IgG pharmaceutical formulation is formatted for subcutaneous infusion and is a component of a kit. The kit also includes a pharmaceutical formulation of hyaluronidase. The kit further includes instructions for infusing the IgG formulation at a first infusion site following infusing the hyaluronidase formulation at this site. In an example, the instructions direct the person infusing the IgG how to infuse the IgG at a high rate at a first infusion site. In an example, the 20% (w/v) IgG is infused at the first infusion site at ambient temperature (about 25 ^{o}C).

[0018] A recent clinical study involving subcutaneously infusing the 20% (w/v) IgG formulation to a first infusion site subsequent to administering hyaluronidase to this site was accompanied by surprising results. The researchers found that infusion of 80 U/g IgG of hyaluronidase to the first infusion prior to infusing the 20% (w/v) IgG formulation allowed the IgG to be infused to the first infusion site at a rate similar to that generally achieved with an analogous 10% IgG formulation facilitated with the same dosage of hyaluronidase. This result was unexpected in view of the fact that the 20% (w/v) IgG formulation is approximately 4-times as viscous as the corresponding 10% (w/v) IgG formulation. See, Example 5. The infusion of the 20% IgG formulation was surprisingly well- and broadly-tolerated across the cohort at infusion rates of up to 300 mL/hr. In pre-clinical dosing with 20% (w/v) IgG in pigs facilitated with hyaluronidase, it was found that even a 5- to 10-fold increase in administered hyaluronidase did not significantly decrease the tissue back pressure to levels equivalent to those seen when administering a 10% (w/v) IgG formulation facilitated with hyaluronidase. Given the number of subjects interrupting the 75 mL/hr/site and 100 mL/hr/site infusion in the Anderson et al. study, *supra*, the person of ordinary skill in the art, unaware of the pre-clinical studies, would have been justified in concluding that difficulties accompanying the 4-fold greater viscosity of 20% (w/v) IgG might require at least partial offsetting by infusing a correspondingly increased dosage of hyaluronidase per gram of IgG compared to that used in HyQvia® [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase],however, this did not prove to be the case. The person aware of the pre-clinical studies would have concluded that high infusion rates of 120-300 mL/hr/site when administering the viscous 20% (w/v) IgG formulation would either not be possible, would not be well-tolerated by the subjects, or both; however, surprisingly, neither of these assumptions proved true during the clinical study. It should be noted that the inventors themselves initially believed that the 20% (w/v) IgG formulation would have to be

warmed to overcome its viscosity to reach infusion rates of at least about 300 mL/hr, if that rate was even achievable in human subjects, and such high infusion rates could not be reached with 20% (w/v) IgG at room temperature.

[0019] According to various examples of the present invention, facilitated and warmed or unwarmed 20% (w/v) IgG allows for administration of a standard dose of IgG in 50% of the current standard volume for such a dose infusing a 10% IgG formulation, with reduced infusion time, the infusion rate and tolerability surprisingly unhampered by the increased viscosity of the unwarmed 20% (w/v) IgG formulation.

[0020] In some examples, the invention provides a method of subcutaneously infusing the 20% (w/v) IgG formulation in a warmed state to a first infusion site subsequent to subcutaneously infusing hyaluronidase at this site. In these examples, the 20% (w/v) IgG formulation is warmed to a temperature appropriate to reduce the formulation viscosity to a desired value prior to it being infused, during its infusion or both, leading to acceptable patient tolerability. Surprisingly, a modest increase in temperature above room temperature produced a significant decrease in viscosity. **FIG. 1**. Though it is widely understood that warming antibody and other protein solutions can degrade the proteins, and cause their aggregation, the 20% (w/v) IgG formulations of the invention were not negatively impacted by warming to as high as about 40 ^{o}C.

[0021] In various examples, the invention provides a method of rapidly infusing a warmed 20% (w/v) IgG formulation to at least a first infusion site following administration of a pharmaceutical formulation of hyaluronidase to the infusion site.

[0022] Pre-clinical studies on infusion of a 20% (w/v) IgG formulation demonstrated that infusion rates as high as 7.5 mL/min can be achieved using an in-line warming device to overcome inherent issues with infusing a highly viscous protein solution. Pharmacokinetic results from these pre-clinical studies indicate that warmed and facilitated 20% (w/v) IgG formulation infused at 5 mL/min is readily dispersed from the subcutaneous space and taken up by the systemic compartment. The invention provides a significant advantage over prior art IgG infusion formulations, methods and systems without the need for any significant redesign of the formulation other than increasing the concentration of the IgG found therein.

[0023] The kits, methods and formulations of the invention bring unexpected and significant improvements to the patient experience of those patients requiring subcutaneous infusion of an IgG formulation: the concentration of IgG in the formulation provides a subject with an

infusion experience of shorter duration than prior 10% (w/v) IgG formulations and 20% (w/v) formulations. Further, in the example in which the formulation is warmed, the infusion of the 20% (w/v) IgG formulation is accompanied by less back pressure attributable to the reduced viscosity of the antibody solution, and there is greater ease of infusion, compatibility of the infusion with a large number of infusion pump and infusion set combinations, and less discomfort to the patient. Simple, quick, and broadly tolerated infusion procedures favor patient compliance with a recommended treatment regimen, bringing advantages to the patient and the overall healthcare economy.

[0024] In an example, the invention provides a pharmaceutical formulation contained within a system for delivery of the pharmaceutical formulation by infusion to a subject in need thereof. The pharmaceutical formulation comprises at least about 20% (w/v) of an immune globulin in an aqueous pharmaceutically acceptable carrier in which the immune globulin is dissolved. The system includes a first vessel containing the pharmaceutical formulation; a first hypodermic needle comprising a first terminus configured to penetrate a first infusion site of the subject, and a terminal opening disposed therein through which the pharmaceutical formulation is delivered to the first infusion site; a first connecting member in fluidic connection with the first vessel and the hypodermic needle; and a first warming device in thermal contact with a system component selected from the first vessel, the first connecting member, and a combination thereof, the first warming device configured to heat the pharmaceutical formulation to at least about 30 ^{o}C, maintain the pharmaceutical formulation at a temperature of at least about 30 ^{o}C and a combination thereof.

[0025] In an example, the pharmaceutical formulation is at a temperature of at least about 30 ^{o}C, preferably from about 30 ^{o}C to about 40 ^{o}C, e.g., from about 35 ^{o}C to about 40 ^{o}C.

[0026] In various examples, the invention provides a pharmaceutical formulation of an immune globulin (e.g., IgG). The formulation comprises at least about 20% (w/v) of an immune globulin; and an aqueous pharmaceutically acceptable carrier dissolving the immune globulin. The pharmaceutical formulation has a viscosity allowing infusion of the pharmaceutical formulation into a first subcutaneous infusion site of a subject in need of such infusion at a rate of greater than about 3 mL/min, the pharmaceutical formulation under a first pressure from about 7000 Pa to about 47000 Pa. In an example the pressure in tissue proximate the infusion site is from about 25 to about 200 mm Hg, e.g., from about 25

to about 150 mm Hg. In an example, the pressure in the tissue proximate the first infusion site is of a magnitude at the desired infusion rate insufficient to cause the subject discomfort sufficient for the subject to discontinue the infusion.

[0027] An exemplary formulation does not include a small molecule agent incorporated expressly to reduce the viscosity of the formulation. In various examples, the formulation is not a suspension of the antibody in a mixture of a water and an organic solvent, e.g., an alcohol, e.g., ethanol.

[0028] IgG-based therapeutics are generally administered alone at monthly doses within a range of about 100 mg to about 2 g of protein agent per kg/patient/dose, e.g., about 1 g of protein agent per kg/patient/dose. In an example, the therapeutic of the invention is infused to treat a neuroimmunological indication, and the dose is from about 1 to about 2 grams of protein agent per kg/patient/ dose. In an example, the indication is selected from Primary Immunodeficiency (PID) and Secondary Immunodeficiency (SID). In an example, when used to treat PID or SID, the therapeutic of the invention is administered in an amount of from about 400 to about 800 mg/kg/patient/dose.

[0029] In various examples, in addition to a full dose being administered in a single infusion period, the dose can also be split and administered step-wise across a selected time period. Thus, for example, a dose can be split into bi-weekly doses (1/2 dose) or weekly doses (1/4 dose)

[0030] The present disclosure recognizes the source of a problem associated with highly concentrated IgG therapeutic formulations, which can present administration challenges (e.g., difficulty in administration, patient discomfort) that diminish patient compliance due to high viscosity of the therapeutic formulation and/or due to aggregation of the IgG in the formulation. Among other things, the present disclosure provides pharmaceutical formulations of IgG containing at least about 20% IgG, which are transiently of low-viscosity, i.e., of lower viscosity than such formulations are at room temperature (a “reference formulation”). Accordingly, in various examples, the formulations of the invention provide a subject being treated with the therapeutic agent with a more agreeable, more tolerable infusion experience than that experienced with current analogous products. In various examples, this experience is contrasted with current regimens by, for example, a

quicker infusion time for the required dose, and increased or similar levels of tolerability despite administration of a standard dose in reduced time.

[0031] In an example, the therapeutic formulation of the invention provides for infusion of a standard IgG dose for a given indication in a time frame that is at least about 1.2-fold, at least about 1.4-fold, at least about 1.6-fold, at least about 1.8-fold or at least about 2-fold, or higher, than the time required to administer an analogous 10% (w/v) formulation of IgG.

[0032] In some examples, despite the 20% (w/v) concentration of IgG in the formulation, the present disclosure provides low-aggregation pharmaceutical formulations of the IgG. In some examples, without being bound to a particular theory, the present disclosure encompasses the recognition that reducing surface adsorption and/or interfacial interaction can have beneficial effects for certain protein formulations. Among other things, in some examples, the present disclosure provides formulations of therapeutic protein agents with relatively low surface adsorption and/or interfacial interaction (as compared with that observed for an appropriate reference formulation, e.g., a 20% formulation of a different protein, e.g., a different antibody, or a 10% formulation of IgG). In some examples, provided formulations can be injected either subcutaneously (SC) or intramuscularly (IM). The present disclosure also provides methods of making and/or using such formulations.

[0033] In an example, the invention provides a method of infusing a pharmaceutical formulation of an immune globulin into a first infusion site of a subject in need thereof. The formulation infused according to the method comprises at least about 20% (w/v) of an immune globulin fraction in about 80% (w/v) of an aqueous pharmaceutically acceptable carrier dissolving the immune globulin fraction. The method includes delivering the pharmaceutical formulation from a first vessel through a first hypodermic needle and into the first infusion site, wherein the first vessel, and the first hypodermic needle are maintained in fluidic communication through a first connecting member, and wherein the pharmaceutical formulation is at an infusion temperature of from about 30 ^{o}C to about 40 ^{o}C as it enters into the first infusion site. In an example, the infusion temperature is about 30 ^{o}C, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39 or about 40 ^{o}C.

[0034] In an example, the invention provides a method of infusing a concentrated IgG formulation such that the infusion of the pharmaceutical formulation at the

infusion temperature is not accompanied by greater subject discomfort than that experienced by the subject upon infusion, under identical infusion parameters, of an otherwise identical pharmaceutical formulation comprising about 10% (w/v) of an immune globulin in an aqueous pharmaceutical carrier. In various examples, the infusion is accompanied by less patient discomfort than the administration of the 10% (w/w) IgG formulation, *supra*.

[0035] In an example, the invention provides a method of infusing a concentrated IgG formulation (e.g., greater than 20% (w/v)) such that the infusion of the pharmaceutical formulation at the infusion temperature is not accompanied by greater subject discomfort than that experienced by the subject upon infusion, under identical infusion parameters, of an otherwise identical pharmaceutical formulation comprising about 20% (w/v) of an immune globulin in an aqueous pharmaceutical carrier. In various examples, the infusion is accompanied by less patient discomfort that the infusion of a similar or the same 20% (w/v) IgG formulation at a temperature less than 30 ^{o}C.

[0036] In various examples, any of the formulations and methods set forth above is augmented (facilitated) by infusion into the IgG infusion site of a predetermined dosage of a pharmaceutical formulation of hyaluronidase prior to or in conjunction with the infusion at the site of the IgG formulation of the invention. The hyaluronidase is administered at the same temperature as the IgG or at a different temperature.

[0037] Additional examples, objects and advantages of the invention will be apparent from the following detailed description.

[0037a] In one aspect, the present disclosure relates to a kit comprising: (a) a first container comprising a pharmaceutical formulation of recombinant human hyaluronidase in a pharmaceutically acceptable carrier; (b) a second container comprising a pharmaceutical formulation of 20% (w/v) IgG in a pharmaceutically acceptable carrier; and (c) instructions providing guidance for sequentially subcutaneously infusing into a first infusion site, (i), a first aliquot of a pre-determined dosage of the pharmaceutical formulation of recombinant human hyaluronidase and, (ii), following (i), a first aliquot of a pre-determined dosage of the pharmaceutical formulation of 20% (w/v) IgG.

[0037b] In another aspect, the present disclosure relates to use of a pharmaceutical formulation of 20% (w/v) IgG in the manufacture of a medicament to be infused subcutaneously to a subject in need thereof, wherein (a) a first aliquot of a pre-determined dosage of hyaluronidase is to be infused to a first infusion site, by infusion of a pre-determined volume of a pharmaceutical formulation of hyaluronidase to the first infusion site; and (b) following (a), a first aliquot of a pre-determined dosage of IgG is to be infused to the first infusion site, by infusion of a first pre-determined volume of the pharmaceutical formulation of 20% (w/v) IgG to the first infusion site.

[0037c] In another aspect, the present disclosure relates to a system for subcutaneously infusing a pharmaceutical formulation of 20% (w/v) IgG, the system configured for subcutaneously infusing the pharmaceutical formulation to a first infusion site of a subject in need thereof, the pharmaceutical formulation comprising at least about 20% (w/v) of IgG and an aqueous pharmaceutically acceptable carrier in which the IgG is dissolved; the system comprising: (a) a first vessel containing the pharmaceutical formulation of 20% (w/v) IgG; (b) a second vessel containing a pharmaceutical formulation of hyaluronidase; (c) a first hypodermic needle comprising a first terminus configured to penetrate a first infusion site of the subject, and a terminal opening disposed therein through which the pharmaceutical formulation of 20% (w/v) IgG is delivered to the first infusion site; (d) an optional first connecting member configured for fluidic connection with the first vessel and the hypodermic needle; and (e) a first warming device configured for thermal contact with a system component selected from the first vessel, the first connecting member, and a combination thereof, the first warming device configured to heat the pharmaceutical formulation of 20% (w/v) IgG to at least about 30 ^{o}C, maintain the pharmaceutical formulation of 20% (w/v) IgG at a temperature of at least about 30 ^{o}C, and a combination thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] FIG. 1A and **FIG. 1B** are displays of dynamic viscosity varying with temperature of an exemplary 20% (w/v) IgG formulation of the invention.

[0039] FIG. 2 displays an exemplary experimental set up for an infusion warmer investigation directed to determining the effects of warming on 20% (w/v) IgG.

[0040] FIG. 3 depicts an *in vivo* proof of concept study in pigs, in which an experimental set up is provided with a purpose of comparing infusion pressures and local reaction of IgG 20% (w/v) versus warmed IgG 20% (w/v) versus warmed and facilitated IgG 20% (w/v), in which the experimental set up is based on experience with HyQvia® [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase] and uses pigs due to a high relevancy for humans based on a similarity in skin anatomy between pigs and humans, whereby the experimental set up utilized a first set up of 5 mL of rHuPH20 (recombinant

WHAT IS CLAIMED IS:

1. A kit comprising:

(a) a first container comprising a pharmaceutical formulation of recombinant human hyaluronidase in a pharmaceutically acceptable carrier;

(b) a second container comprising a pharmaceutical formulation of 20% (w/v) IgG in a pharmaceutically acceptable carrier; and

(c) instructions providing guidance for sequentially subcutaneously infusing into a first infusion site, (i), a first aliquot of a pre-determined dosage of the pharmaceutical formulation of recombinant human hyaluronidase and, (ii), following (i), a first aliquot of a pre-determined dosage of the pharmaceutical formulation of 20% (w/v) IgG.

2. The kit according to claim 1, wherein the pharmaceutical formulation of recombinant human hyaluronidase contains 20% (w/v) recombinant human hyaluronidase.

3. The kit according to any preceding claim, wherein the recombinant human hyaluronidase is rHuPH20.

4. The kit according to any preceding claim, further comprising an infusion apparatus for sequentially or simultaneously subcutaneously infusing (i), the pharmaceutical formulation of recombinant human hyaluronidase and, (ii), following (i), the pharmaceutical formulation of 20% (w/v) IgG.

5. The kit according to any preceding claim, further comprising a subcutaneous needle set.

6. The kit according to any preceding claim, wherein the instructions are a component of a Dosage and Administration section of Complete Prescribing Information.

7. The kit according to any preceding claim, wherein the instructions provide guidance for subcutaneously infusing the pharmaceutical formulation of rHuPH20 to the first infusion site.

8. The kit according to any preceding claim, wherein the instructions provide guidance for subcutaneously infusing from 50 U/g to 100 U/g IgG of rHuPH20 to the first infusion site.

9. The kit according to any preceding claim, wherein the instructions provide guidance for subcutaneously infusing at up to at least about 100 mL, at up to at least about 150 mL, up to at least about 200 mL, up to at least about 250 mL, or up to at least about 300 mL of the pharmaceutical formulation of 20% (w/v) IgG to the first infusion site.

10. The kit according to any preceding claim, wherein the instruction provide guidance for subcutaneously infusing the first pre-determined dosage of the pharmaceutical formulation of 20% (w/v) IgG to the first infusion site at a rate of at least about 120 mL/hr, at least about 150 mL/hr, at least about 200 mL/hr, at least about 250 mL/hr, or at least about 300 mL/hr.

11. The kit according to any preceding claim, wherein the instructions provide guidance for subcutaneously infusing at least about 120 mL of the pharmaceutical formulation of 20% (w/v) IgG to the first infusion site at a rate of at least about 120 mL/hr, at least about 150 mL/hr, at least about 200 mL/hr, at least about 250 mL/hr, or at least about 300 mL/hr.

12. The kit according to any preceding claim, wherein the instructions provide, (b) guidance for subcutaneously infusing at least about 300 mL of the pharmaceutical formulation of 20% (w/v) IgG to the first infusion site.

13. The kit according to any preceding claim, wherein the instructions provide (a) guidance for subcutaneously infusing at least about 300 mL of the pharmaceutical formulation of 20% (w/v) IgG to the first infusion site at a rate of at least about 300 mL/hr.

14. The kit according to any preceding claim, wherein the instructions provide guidance for subcutaneously infusing the pharmaceutical formulation of 20% (w/v) IgG warmed to a temperature of from 30 ^{o}C to 41 ^{o}C, said pharmaceutical formulation

warmed to the temperature prior to the infusing, during the infusing, and a combination thereof.

15. The kit according to any preceding claim, wherein the instructions further provide guidance on simultaneously or sequentially subcutaneously infusing at a second infusion site, (i), a second aliquot of the pre-determined dosage of the pharmaceutical formulation of recombinant human hyaluronidase and, (ii), following (i), subcutaneously infusing a second aliquot of the pre-determined dosage of the pharmaceutical formulation of 20% (w/v) IgG at the second infusion site.

16. The kit according to any preceding claim, wherein the instructions provide guidance on subcutaneously infusing the pharmaceutical formulation of rHuPH20 to the first infusion site, followed by infusing the pharmaceutical formulation of 20% (w/v) IgG to the first infusion site using a member selected from:

(i) a subcutaneous needle set;

(ii) a pooling bag;

(iii) a gravity fill set with vented spike;

(iv) a syringe;

(v) a pump;

(vi) a warming device;

(vii) tubing; and a combination thereof.

17. Use of a pharmaceutical formulation of 20% (w/v) IgG in the manufacture of a medicament to be infused subcutaneously to a subject in need thereof, wherein:

(a) a first aliquot of a pre-determined dosage of hyaluronidase is to be infused to a first infusion site, by infusion of a pre-determined volume of a pharmaceutical formulation of hyaluronidase to the first infusion site; and

(b) following (a), a first aliquot of a pre-determined dosage of IgG is to be infused to the first infusion site, by infusion of a first pre-determined volume of the pharmaceutical formulation of 20% (w/v) IgG to the first infusion site.

18. The use of claim 17, further comprising:

(c) a second aliquot of the pre-determined dosage of hyaluronidase to be infused to a second infusion site, by infusion of a second pre-determined volume of the pharmaceutical formulation of hyaluronidase to the second infusion site; and

(d) following (c), a second aliquot of a pre-determined dosage of IgG is to be infused to the second infusion site, by infusion of a second pre-determined volume of the pharmaceutical formulation of 20% (w/v) IgG to the second infusion site.

19. The use according to any of claims 17-18, wherein the first pre-determined volume of the pharmaceutical formulation of 20% (w/v) IgG is to be infused subcutaneously to the first infusion site at a first final pre-determined rate.

20. The use according to any of claims 17-18, wherein the first pre-determined volume of the pharmaceutical formulation of 20% (w/v) IgG is at least about 120 mL, at least about 150 mL, at least about 180 mL, at least about 200 mL, at least about 220 mL, at least about 250 mL, at least about 280 mL, or at least about 300 mL.

21. The use according to any of claims 17-20, wherein the first final pre-determined rate is at least about 120 mL/hr, at least about 150 mL/hr, at least about 180 mL/hr, at least about 200 mL/hr, at least about 220 mL/hr, at least about 250 mL/hr, at least about 280 mL/hr, or at least about 300 mL/hr.

22. The use according to any of claims 17-21, wherein the first predetermined volume of the pharmaceutical formulation of 20% (w/v) IgG is from 100 mL to 300 mL, e.g., from 150 mL to 200 mL, from 200 mL to 250 mL, from 250 mL to 300 mL, and is infused at the first infusion site at a first final rate of from 100 mL/hr to 300 mL/hr, e.g., from 150 mL/hr to 200 mL/hr, from 200 mL/hr to 250 mL/hr, or from 250 mL/hr to 300 mL/hr.

23. The use according to any of claims 17-22, wherein prior to achieving the first final rate of 300 mL/hr, a first intermediate infusing rate less than 300 mL/hr is maintained for a selected time and increased to the first final pre-determined rate.

24. The use of any of claims 17-23, wherein the first pre-determined volume of the pharmaceutical formulation of 20% (w/v) IgG is to be infused to the first infusion site

at a rate of at least about 300 mL/hr without reduction in rate or cessation of infusion due to subject discomfort, pain or a combination thereof.

25. The use of any of claims 17-24, wherein the first pre-determined volume of the pharmaceutical formulation of 20% (w/v) IgG is to be infused to the first infusion site at a rate encompassing a ramp up phase followed by a terminal phase, wherein the terminal phase rate is 200 to 300 mL/hr, e.g., about 220 mL/hr, about 240 mL/hr, about 260 mL/hr, about 280 mL/hr, the terminal phase ending upon infusion of the last of the first pre-determined volume to the first infusion site, the terminal phase proceeding without reduction in rate or cessation of infusion due to subject discomfort, pain or a combination thereof.

26. The use of claim 25, wherein at least about 60% of the first pre-determined volume of the pharmaceutical formulation of 20% (w/v) IgG is to be infused to the first infusion site during the terminal phase at the first final rate of at least 200 mL/hr to 300 mL/hr, e.g., about 220 mL/hr, about 240 mL/hr, about 260 mL/hr, about 280 mL/hr without reduction in rate or cessation of infusion due to subject discomfort, pain or a combination thereof.

27. The use of claim any of claims 17-26, wherein the first predetermined volume is from 200 mL to 300 mL, e.g., about 220 mL, about 240 mL, about 260 mL, about 280 mL and the first final rate is from 200 mL/hr to 300 mL/hr, e.g., about 220 mL/hr, about 240 mL/hr, about 260 mL/hr, about 280 mL/hr.

28. The use of claim 18, wherein the second final pre-determined rate is about 300 mL/hr, and prior to achieving the second final pre-determined rate a second intermediate infusing rate is maintained for a selected time and increased to the second final pre-determined rate.

29. The use according to any of claims 17-28, wherein the pre-determined dosage of the pharmaceutical formulation of hyaluronidase is essentially similar between infusion of the pharmaceutical formulation of 20% (w/v) IgG, and infusion of an otherwise identical pharmaceutical formulation containing 10% (w/v) IgG.

30. The use according to any of claims 17-29, wherein the first predetermined dosage of the pharmaceutical formulation of 20% (w/v) IgG is to be infused to the first infusion site at a rate of from 2-times to 3-times greater than that for infusion of a pharmaceutical formulation of 20% (w/v) IgG in the absence of the infusion to the first infusion site of the pre-determined dosage of hyaluronidase prior to infusion of the pharmaceutical formulation of 20% (w/v) IgG to the first infusion site.

31. The use according to any of claims 17-30, said use practiced with a system configured to infuse the medicament, the system comprising:

(a) a first container comprising a pharmaceutical formulation of recombinant human hyaluronidase in a pharmaceutically acceptable carrier;

(b) a second container comprising a pharmaceutical formulation of 20% w/v IgG in a pharmaceutically acceptable carrier; and

(c) means for sequentially subcutaneously infusing into a first infusion site, (i), the first aliquot of a pre-determined dosage of the pharmaceutical formulation of recombinant human hyaluronidase and, (ii), following (i), the first aliquot of a pre-determined dosage of the pharmaceutical formulation of 20% IgG.

32. The use according to claim 31, the means for sequentially subcutaneously infusing into a first infusion site, comprising:

(i) a subcutaneous needle set;

(ii) a pooling bag;

(iii) a gravity fill set with vented spike;

(iv) a syringe;

(v) a pump;

(vi) a warming device;

(vii) tubing; and a combination thereof.

33. A system for subcutaneously infusing a pharmaceutical formulation of 20% (w/v) IgG, the system configured for subcutaneously infusing the pharmaceutical

formulation to a first infusion site of a subject in need thereof, the pharmaceutical formulation comprising:

at least about 20% (w/v) of IgG and an aqueous pharmaceutically acceptable carrier in which the IgG is dissolved;

the system comprising:

a. a first vessel containing the pharmaceutical formulation of 20% (w/v) IgG;

b. a second vessel containing a pharmaceutical formulation of hyaluronidase;

c. a first hypodermic needle comprising a first terminus configured to penetrate a first infusion site of the subject, and a terminal opening disposed therein through which the pharmaceutical formulation of 20% (w/v) IgG is delivered to the first infusion site;

d. an optional first connecting member configured for fluidic connection with the first vessel and the hypodermic needle; and

e. a first warming device configured for thermal contact with a system component selected from the first vessel, the first connecting member, and a combination thereof, the first warming device configured to heat the pharmaceutical formulation of 20% (w/v) IgG to at least about 30 ^{o}C, maintain the pharmaceutical formulation of 20% (w/v) IgG at a temperature of at least about 30 ^{o}C, and a combination thereof.

34. The system of claim 33, wherein at least one component of the system is configured to heat the pharmaceutical formulation of 20% (w/v) IgG to a temperature of from 30 ^{o}C to 41 ^{o}C, to maintain the pharmaceutical formulation of 20% (w/v) IgG at a temperature of from 30 ^{o}C to 41 ^{o}C, and a combination thereof.

35. The system of any of claims 33-34, wherein the warming device is configured to maintain the pharmaceutical formulation of 20% (w/v) IgG essentially constant through the duration of the infusion to the first infusion site.

36. The system of any of claims 33-35, wherein the system further comprises a means for driving the pharmaceutical formulation of 20% (w/v) IgG from the first vessel through

the first connecting member and into the first hypodermic needle, from which the pharmaceutical formulation exits the system via the terminal opening thereof.

37. The system of any of claims 33-36, wherein the system further comprises a pump for driving the pharmaceutical formulation of 20% (w/v) IgG from the first vessel through the first connecting member and into the first hypodermic needle, from which the pharmaceutical formulation exits the system via the terminal opening thereof.

38. The system of any of claims 33-37, wherein the pharmaceutical formulation of 20% (w/v) IgG is infused into the first infusion site at a first final flow rate, which is at least about 2 mL/min, at least about 3 mL/min, or at least about 5 mL/min.

39. The system according to any of claims 33-38, wherein the pharmaceutical formulation of 20% (w/v) IgG is essentially free of a small organic molecule incorporated into the formulation expressly to reduce the viscosity thereof.

40. The system of any of claims 33-39, wherein the first vessel is selected from an infusion bag and a syringe.