

TITLE

Prefilled Autoinfusion Device

TECHNICAL FIELD

[0001] The present disclosure generally relates to a prefilled autoinfusion device for delivery of
5 a medicament.

BACKGROUND

[0002] Current autoinfusion devices like syringe pumps are limited to extremely low flow rates, limiting their usefulness for delivery of high volumes. Current biologics typically can have dose
10 volumes of 5-50 mL. Higher flow rates are required to make use of an autoinfusion device practical for doses of larger volumes.

SUMMARY OF THE DISCLOSURE

[0003] In one embodiment, the present disclosure provides a method of treating a disease or
15 disorder in a subject in need thereof, the method comprising administering to the subject via subcutaneous administration about 3 mL to about 50 mL of a formulation comprising a therapeutically effective amount of an active ingredient selected from a small molecule, a peptide fragment, a biologic, a nanoparticle, an antibody, an antibody fragment, and a small molecule antiviral, wherein the subcutaneous administration occurs via a high-volume autoinfusion device
20 with a starting delivery force of about 5 lbf to about 50 lbf, an ending delivery force of about 3 lbf to about 20 lbf, a starting pressure of about 50 psi to about 200 psi, and/or an ending pressure of about 20 psi to about 75 psi. In one embodiment, the formulation further comprises a hyaluronidase enzyme. In one embodiment, the hyaluronidase enzyme is a recombinant human hyaluronidase enzyme. In one embodiment, the hyaluronidase enzyme is a recombinant human hyaluronidase
25 PH20 enzyme. In one embodiment, the hyaluronidase enzyme has an activity of about 150 U/mL to about 150 kU/mL. In one embodiment, the hyaluronidase enzyme has an activity of about 500 U/mL to about 5,000 U/mL. In one embodiment, the hyaluronidase enzyme has an activity of about 1,500 U/mL to about 10,000 U/mL. In one embodiment, the active ingredient is a small molecule, a peptide fragment, a biologic, or a nanoparticle. In one embodiment, the active ingredient is an
30 antibody, an antibody fragment, or a small molecule antiviral. In one embodiment, the method comprises administering to the subject about 10 mL to about 20 mL of the formulation. In one

embodiment, the method comprises administering to the subject about 3 mL to about 15 mL of the formulation. In one embodiment, the method comprises administering to the subject about 3 mL, about 3.1 mL, about 3.2 mL, about 3.4 mL, about 3.5 mL, about 3.6 mL, about 3.7 mL, about 3.8 mL, about 3.9 mL, about 4 mL, about 4.1 mL, about 4.2 mL, about 4.3 mL, about 4.4 mL, about 4.5 mL, about 5 mL, about 5.1 mL, about 5.2 mL, about 5.3 mL, about 5.4 mL, about 5.5 mL, about 5.6 mL, about 5.7 mL, about 5.8 mL, about 5.9 mL, about 6 mL, about 6.1 mL, about 6.2 mL, about 6.3 mL, about 6.4 mL, about 6.5 mL, about 6.6 mL, about 6.7 mL, about 6.8 mL, about 6.9 mL, about 7 mL, about 7.1 mL, about 7.2 mL, about 7.3 mL, about 7.4 mL, about 7.5 mL, about 7.6 mL, about 7.7 mL, about 7.8 mL, about 7.9 mL, about 8 mL, about 8.1 mL, about 8.2 mL, about 8.3 mL, about 8.4 mL, about 8.5 mL, about 8.6 mL, about 8.7 mL, about 8.8 mL, about 8.9 mL, about 9 mL, about 9.1 mL, about 9.2 mL, about 9.3 mL, about 9.4 mL, about 9.5 mL, about 9.6 mL, about 9.7 mL, about 9.8 mL, about 9.9 mL, about 10 mL, about 10.1 mL, about 10.2 mL, about 10.3 mL, about 10.4 mL, about 10.5 mL, about 10.6 mL, about 10.7 mL, about 10.8 mL, about 10.9 mL, about 11 mL, about 11.1 mL, about 11.2 mL, about 11.3 mL, about 11.4 mL, about 11.5 mL, about 11.6 mL, about 11.7 mL, about 11.8 mL, about 11.9 mL, about 12 mL, about 12.1 mL, about 12.2 mL, about 12.3 mL, about 12.4 mL, about 12.5 mL, about 12.6 mL, about 12.7 mL, about 12.8 mL, about 12.9 mL, about 13 mL, about 13.1 mL, about 13.2 mL, about 13.3 mL, about 13.4 mL, about 13.5 mL, about 13.6 mL, about 13.7 mL, about 13.8 mL, about 13.9 mL, about 14 mL, about 14.1 mL, about 14.2 mL, about 14.3 mL, about 14.4 mL, about 14.5 mL, about 14.6 mL, about 14.7 mL, about 14.8 mL, about 14.9 mL, about 15 mL, about 15.1 mL, about 15.2 mL, about 15.3 mL, about 15.4 mL, about 15.5 mL, about 15.6 mL, about 15.7 mL, about 15.8 mL, about 15.9 mL, about 16 mL, about 16.1 mL, about 16.2 mL, about 16.3 mL, about 16.4 mL, about 16.5 mL, about 16.6 mL, about 16.7 mL, about 16.8 mL, about 16.9 mL, about 17 mL, about 17.1 mL, about 17.2 mL, about 17.3 mL, about 17.4 mL, about 17.5 mL, about 17.6 mL, about 17.7 mL, about 17.8 mL, about 17.9 mL, about 18 mL, about 18.1 mL, about 18.2 mL, about 18.3 mL, about 18.4 mL, about 18.5 mL, about 18.6 mL, about 18.7 mL, about 18.8 mL, about 18.9 mL, about 19 mL, about 19.1 mL, about 19.2 mL, about 19.3 mL, about 19.4 mL, about 19.5 mL, about 19.6 mL, about 19.7 mL, about 19.8 mL, about 19.9 mL, about 20 mL, about 20.1 mL, about 20.2 mL, about 20.3 mL, about 20.4 mL, about 20.5 mL, about 20.6 mL, about 20.7 mL, about 20.8 mL, about 20.9 mL, about 21 mL, about 21.1 mL, about 21.2 mL, about 21.3 mL, about 21.4 mL, about 21.5 mL, about 21.6 mL, about 21.7 mL, about 21.8 mL, about 21.9 mL, about 22 mL, about 22.1 mL, about 22.2 mL, about 22.3 mL, about 22.4 mL, about 22.5 mL, about 22.6 mL, about 22.7 mL, about 22.8 mL, about 22.9 mL, about 23 mL, about 23.1 mL, about 23.2 mL, about 23.3 mL, about 23.4 mL, about 23.5 mL, about 23.6 mL,

about 23.7 mL, about 23.8 mL, about 23.9 mL, about 24 mL, about 24.1 mL, about 24.2 mL, about 24.3 mL, about 24.4 mL, about 24.5 mL, about 24.6 mL, about 24.7 mL, about 24.8 mL, about 24.9 mL, or about 25 mL. In another embodiment, the method comprises administering to the subject, about 26 mL, about 27 mL, about 28 mL, about 29 mL, about 30 mL, about 31 mL, about 32 mL, 5 about 33 mL, about 34 mL, about 35 mL, about 36 mL, about 37 mL, about 38 mL, about 39 mL, about 40 mL, about 41 mL, about 42 mL, about 43 mL, about 44 mL, about 45 mL, about 46 mL, about 47 mL, about 48 mL, about 49 mL, or about 50 mL. In one embodiment, the method comprises administering the formulation using a high-volume autoinfusion device. In one embodiment, the method comprises administering the formulation with a starting delivery force of 10 about 3 lbf to about 50 lbf using a high-volume autoinfusion device. In one embodiment, the method comprises administering the formulation with an ending delivery force of about 5 lbf to about 20 lbf using a high-volume autoinfusion device. In one embodiment, the method comprises administering the formulation with a starting pressure of about 50 psi to about 200 psi using a high-volume autoinfusion device. In one embodiment, the method comprises administering the 15 formulation with an ending pressure of about 20 psi to about 75 psi using a high-volume autoinfusion device. In one embodiment, the formulation is in a prefilled syringe. In one embodiment, the prefilled syringe contains about 3 mL, about 3.1 mL, about 3.2 mL, about 3.4 mL, about 3.5 mL, about 3.6 mL, about 3.7 mL, about 3.8 mL, about 3.9 mL, about 4 mL, about 4.1 mL, about 4.2 mL, about 4.3 mL, about 4.4 mL, about 4.5 mL, about 5 mL, about 5.1 mL, about 5.2 mL, 20 about 5.3 mL, about 5.4 mL, about 5.5 mL, about 5.6 mL, about 5.7 mL, about 5.8 mL, about 5.9 mL, about 6 mL, about 6.1 mL, about 6.2 mL, about 6.3 mL, about 6.4 mL, about 6.5 mL, about 6.6 mL, about 6.7 mL, about 6.8 mL, about 6.9 mL, about 7 mL, about 7.1 mL, about 7.2 mL, about 7.3 mL, about 7.4 mL, about 7.5 mL, about 7.6 mL, about 7.7 mL, about 7.8 mL, about 7.9 mL, about 8 mL, about 8.1 mL, about 8.2 mL, about 8.3 mL, about 8.4 mL, about 8.5 mL, about 8.6 mL, about 25 8.7 mL, about 8.8 mL, about 8.9 mL, about 9 mL, about 9.1 mL, about 9.2 mL, about 9.3 mL, about 9.4 mL, about 9.5 mL, about 9.6 mL, about 9.7 mL, about 9.8 mL, about 9.9 mL, about 10 mL, about 10.1 mL, about 10.2 mL, about 10.3 mL, about 10.4 mL, about 10.5 mL, about 10.6 mL, about 10.7 mL, about 10.8 mL, about 10.9 mL, about 11 mL, about 11.1 mL, about 11.2 mL, about 11.3 mL, about 11.4 mL, about 11.5 mL, about 11.6 mL, about 11.7 mL, about 11.8 mL, about 11.9 30 mL, about 12 mL, about 12.1 mL, about 12.2 mL, about 12.3 mL, about 12.4 mL, about 12.5 mL, about 12.6 mL, about 12.7 mL, about 12.8 mL, about 12.9 mL, about 13 mL, about 13.1 mL, about 13.2 mL, about 13.3 mL, about 13.4 mL, about 13.5 mL, about 13.6 mL, about 13.7 mL, about 13.8 mL, about 13.9 mL, about 14 mL, about 14.1 mL, about 14.2 mL, about 14.3 mL, about 14.4 mL,

about 14.5 mL, about 14.6 mL, about 14.7 mL, about 14.8 mL, about 14.9 mL, about 15 mL, about 15.1 mL, about 15.2 mL, about 15.3 mL, about 15.4 mL, about 15.5 mL, about 15.6 mL, about 15.7 mL, about 15.8 mL, about 15.9 mL, about 16 mL, about 16.1 mL, about 16.2 mL, about 16.3 mL, about 16.4 mL, about 16.5 mL, about 16.6 mL, about 16.7 mL, about 16.8 mL, about 16.9 mL, about 17 mL, about 17.1 mL, about 17.2 mL, about 17.3 mL, about 17.4 mL, about 17.5 mL, about 17.6 mL, about 17.7 mL, about 17.8 mL, about 17.9 mL, about 18 mL, about 18.1 mL, about 18.2 mL, about 18.3 mL, about 18.4 mL, about 18.5 mL, about 18.6 mL, about 18.7 mL, about 18.8 mL, about 18.9 mL, about 19 mL, about 19.1 mL, about 19.2 mL, about 19.3 mL, about 19.4 mL, about 19.5 mL, about 19.6 mL, about 19.7 mL, about 19.8 mL, about 19.9 mL, about 20 mL, about 20.1 mL, about 20.2 mL, about 20.3 mL, about 20.4 mL, about 20.5 mL, about 20.6 mL, about 20.7 mL, about 20.8 mL, about 20.9 mL, about 21 mL, about 21.1 mL, about 21.2 mL, about 21.3 mL, about 21.4 mL, about 21.5 mL, about 21.6 mL, about 21.7 mL, about 21.8 mL, about 21.9 mL, about 22 mL, about 22.1 mL, about 22.2 mL, about 22.3 mL, about 22.4 mL, about 22.5 mL, about 22.6 mL, about 22.7 mL, about 22.8 mL, about 22.9 mL, about 23 mL, about 23.1 mL, about 23.2 mL, about 23.3 mL, about 23.4 mL, about 23.5 mL, about 23.6 mL, about 23.7 mL, about 23.8 mL, about 23.9 mL, about 24 mL, about 24.1 mL, about 24.2 mL, about 24.3 mL, about 24.4 mL, about 24.5 mL, about 24.6 mL, about 24.7 mL, about 24.8 mL, about 24.9 mL, or about 25 mL of the formulation. In another embodiment, the prefilled syringe contains about 26 mL, about 27 mL, about 28 mL, about 29 mL, about 30 mL, about 31 mL, about 32 mL, about 33 mL, about 34 mL, about 35 mL, about 36 mL, about 37 mL, about 38 mL, about 39 mL, about 40 mL, about 41 mL, about 42 mL, about 43 mL, about 44 mL, about 45 mL, about 46 mL, about 47 mL, about 48 mL, about 49 mL, or about 50 mL of the formulation. In one embodiment, the prefilled syringe comprises a needle having a gauge of about 20 to about 33. In one embodiment, the prefilled syringe comprises a 20-gauge needle, a 21-gauge needle, a 22-gauge needle, a 23-gauge needle, a 24-gauge needle, a 25-gauge needle, a 26-gauge needle, a 27-gauge needle, a 28-gauge needle, a 29-gauge needle, a 30-gauge needle, a 31-gauge needle, a 32-gauge needle, or a 33-gauge needle. In one embodiment, the method comprises administering the formulation at a rate of about 4 to about 21 mL/min. In one embodiment, the method comprises administering the formulation at a rate of at least about 5 to about 20 mL/min. In one embodiment, the method comprises administering the formulation at a rate of at least or faster than about 10 to about 15 mL/min. In one embodiment, the administration takes about 30 seconds to about 360 seconds. In one embodiment, the administration takes at least about 60 seconds to about 300 seconds. In one embodiment, the administration takes at least or less than about 120 seconds to about 240 seconds. In one embodiment, the administration takes about 15

seconds to about 30 seconds. In one embodiment, the administration takes at least about 60 seconds to about 180 seconds. In one embodiment, the administration takes at least or less than about 120 seconds to about 240 seconds. In one embodiment, the method comprises administering about 5 mL of the formulation at a rate of about 4 mL/min to about 21 mL/min. In one embodiment, the method
5 comprises administering about 10 mL of the formulation at a rate of about 4 mL/min to about 21 mL/min. In one embodiment, the formulation has a viscosity of about 1 cP to about 50 cP. In one embodiment, administration of the formulation requires less applied force when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In one embodiment, the method comprises administering about 5 mL of the formulation at a rate of about 4 mL/min to about
10 21 mL/min with an applied force of about 10 N to about 45 N. In one embodiment, the method comprises administering the formulation to the subject using a prefilled syringe comprising a 25-gauge needle. In one embodiment, the method comprises administering about 10 mL of the formulation to the subject at a rate of about 4 mL/min to about 21 mL/min with an applied force of about 25 N to about 50 N. In one embodiment, the method comprises administering the formulation
15 to the subject using a prefilled syringe comprising a 25-gauge needle. In one embodiment, administration of the formulation is faster when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In one embodiment, administration of the formulation causes fewer side effects in the subject when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In one embodiment, administration of the formulation causes less pain and
20 discomfort in the subject when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In one embodiment, administration of the formulation causes less back leakage at the injection site when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In one embodiment, the back leakage at the injection site is about 100% to about 30% less when compared to a similar formulation that does not comprise a hyaluronidase
25 enzyme. In one embodiment, administration of the formulation causes less swelling volume and/or swelling height at the injection site when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In one embodiment, the formulation causes about 35% to about 1% less swelling and/or swelling height at the injection site when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In one embodiment, administration of the formulation
30 yields a lower bleb swelling size, less bleb induration, and/or quicker bleb resolution when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In one embodiment, the subject is human. In one embodiment, the administering comprises the subject self-administering the formulation. In one embodiment, the administering comprises a healthcare

provider or a caregiver administering the formulation to the subject. In one embodiment, the subcutaneous administration comprises a single injection. In one embodiment, the subcutaneous administration comprises two or more injections. In one embodiment, the subcutaneous administration is delivered via an on-body device.

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BRIEF DESCRIPTION OF THE DRAWINGS

[0004] The following detailed description of embodiments of the prefilled autoinfusion device will be better understood when read in conjunction with the appended drawings of exemplary embodiments. It should be understood, however, that the invention is not limited to the precise
10 arrangements and instrumentalities shown.

[0005] Fig. 1 is a side perspective view of a prefilled autoinfusion device in accordance with an exemplary embodiment of the present invention.

[0006] Fig. 2 is a side cross-section view of a delivery apparatus in accordance with a second exemplary embodiment of the present invention.

15 [0007] Fig. 3 is a top view of a conduit and port of the prefilled autoinfusion device of Fig. 1.

[0008] Fig. 4 is a partial magnified view of a first end of the conduit and a distal end of the delivery apparatus of the prefilled autoinfusion device of Fig. 1.

[0009] Fig. 5 is a side perspective view of the delivery apparatus of Fig. 2 with a conduit connected thereto.

20 [0010] Fig. 6 is a graph of HVAI injection times (mean $\pm$ SEM).

[0011] Fig. 7 shows mean (mg $\pm$ SEM) and individual weights of back-leakage.

[0012] Fig. 8 shows individual swelling volumes (mL) after SC injection of Ig-120 and Ig-120 + rHuPH20 taken by caliper measurement at T0.

25 [0013] Fig. 9 shows individual swelling area (cm²) after SC injection of Ig-120 and Ig-120 + rHuPH20 taken by caliper measurement at T0.

[0014] Fig. 10 shows individual swelling height (mm) after SC injection of Ig-120 and Ig-120 + rHuPH20 taken by caliper measurement at T0.

[0015] Fig. 11 is a graph of swelling volume (mL $\pm$ SEM) taken by caliper measurement over time (T0-T15-T30).

30 [0016] Fig. 12 is a graph of swelling area (cm² $\pm$ SEM) taken by caliper measurement over time (T0-T15-T30).

- [0017] Fig. 13 is a graph swelling height (mm $\pm$ SEM) taken by caliper measurement over time (T0-T15-T30).
- [0018] Fig. 14A shows a colorimetric assessment taken by 3D imaging of bleb shape and size after injection with Ig120. Fig. 14B shows a colorimetric assessment taken by 3D imaging of bleb shape and size after injection with Ig120 + rHuPH20.
- [0019] Fig. 15 is a graph of individual bleb volume (mL) after SC injection of Ig-120 and Ig-120 + rHuPH20 taken by 3D imaging.
- [0020] Fig. 16 is a graph of individual bleb area (cm²) after SC injection of Ig-120 and Ig-120 + rHuPH20 taken by 3D imaging.
- [0021] Fig. 17 is a graph of individual bleb height (mm) after SC injection of Ig-120 and Ig-120 + rHuPH20 taken by 3D imaging.
- [0022] Fig. 18 shows a qualitative assessment of post-injection erythema over time (T0-T15-T30-T2h).
- [0023] Fig. 19 shows a qualitative assessment of post-injection swelling size at T0.
- [0024] Fig. 20 shows a qualitative assessment of post-injection swelling size over time (T0-T15-T30-T2h).
- [0025] Fig. 21 shows a qualitative assessment of post-injection induration at T0.
- [0026] Fig. 22 shows a qualitative assessment of post-injection induration over time (T0-T15-T30-T2h).
- [0027] Fig. 23 shows injection sites of AID #6053L before and immediately post-injection with Ig-120 and then at T15, T30, T2h and T24h.
- [0028] Fig. 24 shows injection sites of AID #6053R before and immediately post-injection with Ig-120 + rHuPH20 and then at T15, T30, T2h and T24h.
- [0029] Fig. 25 shows injection sites of AID #6054R before and immediately post-injection with Ig-120 and then at T15, T30, T2h and T24h.
- [0030] Fig. 26 shows injection sites of AID #6054L before and immediately post-injection with Ig-120 + rHuPH20 and then at T15, T30, T2h and T24h.
- [0031] Fig. 27 shows injection sites of AID #6055L before and immediately post-injection with Ig-120 and then at T15, T30, T2h and T24h.
- [0032] Fig. 28 shows injection sites of AID #6055R before and immediately post-injection with Ig-120 + rHuPH20 and then at T15, T30, T2h and T24h.
- [0033] Fig. 29 shows injection sites of AID #6060R before and immediately post-injection with Ig-120 and then at T15, T30, T2h and T24h.

- [0034] Fig. 30 shows injection sites of AID #6060L before and immediately post-injection with Ig-120 + rHuPH20 and then at T15, T30, T2h and T24h.
- [0035] Fig. 31 shows injection sites of AID #6061L before and immediately post-injection with Ig-120 and then at T15, T30, T2h and T24h.
- 5 [0036] Fig. 32 shows injection sites of AID #6061R before and immediately post-injection with Ig-120 + rHuPH20 and then at T15, T30, T2h and T24h.
- [0037] Fig. 33 shows injection sites of AID #6062R before and immediately post-injection with Ig-120 and then at T15, T30, T2h and T24h.
- [0038] Fig. 34 shows injection sites of AID #6062L before and immediately post-injection with
10 Ig-120 + rHuPH20 and then at T15, T30, T2h and T24h.
- [0039] Fig. 35 is a graph of HVAI Injection Times (Mean $\pm$ SEM)c.
- [0040] Fig. 36 displays mean (mg $\pm$ SEM) and individual weights of back-leakage.
- [0041] Fig. 37 shows individual swelling volumes (mL) after SC injection of Ig-120 and Ig-120 + rHuPH20 taken by caliper measurement at T0.
- 15 [0042] Fig. 38 shows individual swelling area (cm²) after SC injection of Ig-120 and Ig-120 + rHuPH20 taken by caliper measurement at T0.
- [0043] Fig. 39 shows individual swelling height (mm) after SC injection of Ig-120 and Ig-120 + rHuPH20 taken by caliper measurement at T0.
- [0044] Fig. 40 shows an assessment of swelling volume over time (T0-T15-T30) taken by
20 caliper measurement (mL $\pm$ SEM).
- [0045] Fig. 41 displays an assessment of swelling area over time (T0-T15-T30) taken by caliper measurement (cm² $\pm$ SEM).
- [0046] Fig. 42 displays an assessment of swelling height over time (T0-T15-T30) taken by caliper measurement (mm $\pm$ SEM).
- 25 [0047] Fig. 43A shows a colorimetric assessment taken by 3D imaging of bleb shape and size after injection with Ig120. Fig. 43B shows a colorimetric assessment taken by 3D imaging of bleb shape and size after injection with Ig120 + rHuPH20.
- [0048] Fig. 44 shows individual bleb volume (mL) after SC injection of Ig-120 and Ig-120 + rHuPH20 taken by 3D imaging.
- 30 [0049] Fig. 45 shows individual bleb area (cm²) after SC injection of Ig-120 and Ig-120 + rHuPH20 taken by 3D imaging.
- [0050] Fig. 46 shows individual bleb height (mm) after SC injection of Ig-120 and Ig-120 + rHuPH20 taken by 3D imaging.

- [0051] Fig. 47 displays a qualitative assessment of post-injection swelling size at T0.
- [0052] Fig. 48 displays a qualitative assessment of post-injection swelling size over time (T0-T15-T30-T2h).
- [0053] Fig. 49 displays a qualitative assessment of post-injection induration at T0.
- 5 [0054] Fig. 50 displays a qualitative assessment of post-injection induration taken over time (T0-T15-T30-T2h).
- [0055] Fig. 51 shows injection sites of AID #6256L before and immediately post-injection with Ig-120 and then at T15, T30, T2h and T24h.
- [0056] Fig. 52 shows injection sites of AID #6256R before and immediately post-injection with
10 Ig-120 + rHuPH20 and then at T15, T30, T2h and T24h.
- [0057] Fig. 53 shows injection sites of AID #6259R before and immediately post-injection with Ig-120 and then at T15, T30, T2h and T24h.
- [0058] Fig. 54 shows injection sites of AID #6259L before and immediately post-injection with Ig-120 + rHuPH20 and then at T15, T30, T2h and T24h.
- 15 [0059] Fig. 55 shows injection sites of AID #6367L before and immediately post-injection with Ig-120 and then at T15, T30, T2h and T24h.
- [0060] Fig. 56 shows injection sites of AID #6367R before and immediately post-injection with Ig-120 + rHuPH20 and then at T15, T30, T2h and T24h.
- [0061] Fig. 57 shows injection sites of AID #6397R before and immediately post-injection with
20 Ig-120 and then at T15, T30, T2h and T24h.
- [0062] Fig. 58 shows injection sites of AID #6397L before and immediately post-injection with Ig-120 + rHuPH20 and then at T15, T30, T2h and T24h.
- [0063] Fig. 59 shows injection sites of AID #6400L before and immediately post-injection with Ig-120 and then at T15, T30, T2h and T24h.
- 25 [0064] Fig. 60 shows injection sites of AID #6400R before and immediately post-injection with Ig-120 + rHuPH20 and then at T15, T30, T2h and T24h.
- [0065] Fig. 61 shows injection sites of AID #6407R before and immediately post-injection with Ig-120 and then at T15, T30, T2h and T24h.
- [0066] Fig. 62 shows injection sites of AID #407L before and immediately post-injection with
30 Ig-120 + rHuPH20 and then at T15, T30, T2h and T24h.

DETAILED DESCRIPTION

[0067] Several indications require long-term and sometimes lifetime subcutaneous drug delivery (e.g., polyclonal IgG for primary and secondary immunodeficiency) where patients deliver 10-100+ mL per injection site as often as multiple times per week. These injections are often given at a rate of 1 mL/min or less and therefore require delivery times from at least 10-60 min and are often delivered by a syringe with attached tubing using an external off-body mechanical syringe driver.

[0068] Syringe drivers, also referred to as syringe pumps, are precision instruments commonly used in medical, scientific, and industrial settings to deliver precise and controlled amounts of fluids. They consist of a syringe holder that receives and securely holds a syringe and a motor-driven mechanism that pushes or pulls the plunger to control the flow rate of the fluid. Their ability to provide a constant and controlled flow rate over an extended period makes them valuable in situations where accuracy and repeatability are critical.

[0069] Despite their many advantages, syringe pumps do have certain limitations. One significant limitation is their flow rate range. While they excel at delivering very low flow rates with exceptional precision, they may not be suitable for high-flow applications. The maximum flow rate is limited by the syringe size and the design of the pump, making them unsuitable for high-volume fluid transfer tasks.

[0070] Syringe pumps integrated with wearable ports represent an innovative approach to long-term drug delivery, particularly in the context of oncology and home healthcare. Wearable ports are often subcutaneous or intravenous access devices that allow for the continuous infusion of medications or fluids without the need for repeated needle sticks. Wearable ports, infusion pumps, and syringe pumps in tandem offer patients a higher degree of mobility and comfort, as they can go about their daily activities while receiving their prescribed treatments.

[0071] Nonetheless, there are limitations to the use of syringe pumps in conjunction with wearable ports. One notable challenge is the size and weight of the syringe pump. This may affect the overall comfort and convenience of the wearable port system, particularly for patients who require long-term use. Further, cost and access to these pumps is limited and can prevent a patient from receiving the treatment they need due to a doctor or healthcare facility not having the proper pump or equipment.

[0072] Accordingly, there is a need for a highly portable and accessible device that can deliver high volumes of medicament at sufficient delivery rates. Devices disclosed herein may allow for 10-100+ mL deliveries. Using an autoinjector-like device in place of a pump can also remove the

need for high-cost equipment, thereby reducing the burden on the subjects to require access to an external pump to deliver their therapy.

[0073] Referring to the drawings in detail, wherein like reference numerals indicate like elements throughout, there is shown in Figs. 1-4 a prefilled autoinfusion device, generally designated 100, in accordance with an exemplary embodiment of the present invention.

[0074] As shown in Fig. 1, the prefilled autoinfusion device 100 may include a delivery apparatus 102, a flexible tube or conduit 104, and a port 106 that attaches to the patient. The prefilled autoinfusion device 100 may allow for extended delivery of a medicament without the use of a pump, which can increase access to therapies for patients. The prefilled autoinfusion device 100 is modular and can accommodate variations of ports 106 with various needle gauges, conduit 104 of varying lengths and thicknesses, and delivery apparatuses with varying volumes of medicament.

[0075] The delivery apparatus 102 may include a housing 108 configured to receive components therein. The housing 108 may be sized and shaped to allow a user to comfortably hold the delivery apparatus 102 in one hand. The housing 108 may include one or more flat sides to allow the delivery apparatus 102 to be placed on a flat surface (e.g., table or desk) during use, preventing the delivery apparatus 102 from rolling side to side.

[0076] The housing 108 may have a proximal end 108a and a distal end 108b opposite the proximal end 108a. As shown in Fig. 2, the housing 108 may contain a plurality of components therein. Such components may include, for example, a medicament container 110, an energy source 112, and a trigger mechanism 114. As shown in Fig. 1, the medicament container 110 may be disposed entirely within the housing 108. In some embodiments, as shown in Fig. 2, the medicament container 110 is partially disposed within the housing 108. The medicament container 110 may extend distally from the distal end 108b of the housing 108. The medicament container 110 may be fixed relative to the housing 108 or may not be intended to be removable from the housing 108. The housing 108 may have a window 109 defined thereon. The user may be able to view the level or volume of the medicament within the medicament container 110 through the window 109 before and during delivery of the medicament.

[0077] The medicament container 110 may contain a volume of a medicament. The medicament container 110 may be a prefilled syringe. A prefilled syringe is a medical device that contains a premeasured and preloaded dose of a medicament and does not require loading or filling the device at the point of care. In some embodiments, the volume of the medicament is at least 10 mL. The volume of the medicament may be at least 10 mL, at least 15 mL, at least 20 mL, at least 25 mL, at

least 30 mL, at least 35 mL, at least 40 mL, at least 45 mL, at least 50 mL, at least 60 mL, at least 70 mL, at least 80 mL, at least 90 mL, or at least 100 mL. The volume of the medicament may be between 10 mL and 100 mL, between 15 mL and 90 mL, between 20 mL and 80 mL, between 25 mL and 70 mL, between 30 mL and 60 mL, between 35 mL and 50 mL, or between 40 mL and 45 mL.

[0078] As shown in Fig. 1, the housing 108 may include an outlet 116 on the distal end 108b thereof. The outlet 116 may be a secure attachment point for various medical devices, allowing for quick and leak-free connections between different components, ensuring aseptic and precise fluid transfer in medical procedures. The outlet 116 may be in fluid communication with the medicament container 110. In a case where the medicament container 110 is only partially disposed within the housing 108, the outlet 116 may be integral to the medicament container 110 or may be directly attached to the medicament container 110. As shown in Fig. 4, the outlet 116 may be a luer port. The outlet 116 may be a generally cylindrical member and may comprise threads protruding radially outward from an exterior wall thereof. As shown in Figs. 2 and 4, the outlet 116 may be a luer port comprising threads protruding radially inward from an exterior wall thereof. The outlet 116 may have a removeable cap 117 disposed therein. The removeable cap 117 may prevent the medicament from escaping from the outlet 116. The removeable cap 117 may be a luer plug. The outlet 116 may be sized and shaped to receive a first end of the conduit 104. The removeable cap 117 may be removed to allow a separate component to be coupled to the outlet 116. In some embodiments, the removeable cap 117 is removed for the conduit 104 to be received in the outlet 116. The conduit 104 may have threads 118 extending radially outward on the first end thereof configured to secure the conduit 104 to the outlet 116 by threaded engagement, as shown in Fig. 4. The outlet 116 may be a standardized and threaded medical connector commonly used in healthcare settings. In some embodiments, the outlet 116 may be a twist-lock connector, a snap-fit connector, a slip connector, or may be fixed with an adhesive. In other embodiments, the outlet 116 may be a or a custom interface to specifically prevent interfacing with incompatible line sets, so as to provide optimal performance for priming, delivery rate and delivered volume.

[0079] In order to eject the medicament from the medicament container 110, an energy source is utilized to facilitate the controlled delivery of medicament. As discussed above, the energy source 112 may be disposed within the housing 108. The energy source 112 may be configured to interact with the medicament container 110 to expel the medicament from the outlet 116. The energy source 112 may include at least one component capable of storing energy, such as one or more springs. The energy source 112 may have a proximal end and a distal end opposite the proximal end. Non-

spring configurations could be considered for example gas-powered or electrical motor-powered devices where flow rate can be more directly controlled and lead to improved flow rates. In an exemplary embodiment, energy source 112 includes a compression spring; however, an electric pump, an elastomer or compressed-gas spring, or a gas generator, or other suitable energy storage members may be used. In some embodiments, the energy source 112 includes two springs. The force exerted by the two springs may be combined to produce a force greater than that produced by either one spring alone, or may be used in a two-stage configuration where a first spring and a second spring act on the medicament container 110 in succession. There may be two or more stages of delivery. For example, there may be a separate energy source 112 or other biasing member to prime the conduit 104, as discussed in more detail below.

[0080] To initiate ejection of the medicament from the medicament container 110 by the energy source 112, a user must initiate the ejection by manipulating the trigger mechanism 114. The trigger mechanism 114 may be coupled to the housing 108 and may be engageable with the energy source 112. The trigger mechanism 114 may be configured to activate the energy source 112 in response to a user input. As shown in Fig. 2, the trigger mechanism may include a button 120 and a ram 122 located at the proximal end 108a of the housing 108. The ram 122 may be disposed between the distal end of the energy source 112 and the medicament container 110. The ram 122 may be generally cylindrical and sized and shaped to prevent the medicament from passing thereby. When the ram 122 is urged proximally by the energy source 112, pressure in the medicament container 110 may build such that the medicament is ejected through the outlet 116.

[0081] The autoinfusion device 100 may have one or more states during use. The autoinfusion device 100 may transition between states during use. The autoinfusion device 100 may have at least one or more of the following states: locked (e.g., out of the box), priming, primed and triggered. The transition between states of the autoinfusion device 100 may be initiated by a user manipulating the button 120.

[0082] As shown in Fig. 5, the button 120 may include one or more status indicators 121 disposed thereon. The housing 108 may have a recess 123 (e.g., a window or cutout) through which the status indicator 121 may be visible to the user. In the locked state, the status indicator 121 may show a first icon (e.g., red marking) that signifies that the autoinfusion device 100 is in the locked state. In the locked state, the user may be unable to move the button 120 relative to the housing 108 along the longitudinal axis.

[0083] As shown in Fig. 5, the user may rotate the button 120 in a first direction (e.g., clockwise) about the longitudinal axis relative to the housing 108 to move the autoinfusion device

100 from the locked state to the priming state. In the priming state, the status indicator 121 may show a second icon (e.g., a yellow marking) to indicate that the autoinfusion device 100 is in the priming state. In the priming state, the autoinfusion device 100 may force a volume of the medicament through the conduit 104 to remove any air, as described in more detail below. In the priming state, the user may be unable to move the button 120 relative to the housing 108 along the longitudinal axis and may be temporarily restricted from rotating the button 120 about the longitudinal axis past the position indicating the priming state until the autoinfusion device 100 is primed. In some embodiments, priming may occur by means of rotating the button to manually advance the ram via a threaded mechanism. In other embodiments, priming may be automatically activated by pressing a button, rotating a button or sliding of a button. In some embodiments, priming may be achieved as part of a 2-stage triggering mechanism where the ram is initially advanced a fixed distance to facilitate priming and then a second triggering to deliver the dose. The priming button may be the same as the triggering button or different.

[0084] Upon completion of priming, the user may be able to rotate the button 120 in the first direction about the longitudinal axis relative to the housing 108 to move the autoinfusion device 100 from the priming state to the primed state. In some embodiments, the button 120 may automatically move to show the status indicator showing the primed state upon completion of priming. In the primed state, the status indicator 121 may show a third icon (e.g., a green marking) to indicate that the autoinfusion device 100 is in the primed state. As shown in Fig. 5, in the primed state, the user may be able to move the button 120 relative to the housing 108 along the longitudinal axis to initiate triggering and delivery of the medicament. In the primed state, the user may be prevented from rotating the button 120 about the longitudinal axis relative to the housing 108.

[0085] When the button 120 is moved along the longitudinal axis relative to the housing 108, the status indicator 121 may show a fourth icon (e.g., a check mark) to indicate that the autoinfusion device 100 is in the triggered state. In the fired state, the button 120 may be fixed relative to the housing 108 to avoid any attempts to trigger the device multiple times. The autoinfusion device 100 may be locked out when the button 120 indicates the autoinfusion device 100 being in the fired state. In some embodiments, the button 120 may produce an audible indication (e.g., a click or a ring) upon completion of delivery of a dose. This may be achieved by the button 120 extending to an original position along the longitudinal axis, or the ram 122 extending to an original position along the longitudinal axis and engaging the button 120, for example. The autoinfusion device 100 may be a single-use injector and may be disposed of after being transitioned into the fired state. In some

embodiments, the injector is configured to receive a new medicament container and can be reset for subsequent delivery of medicament.

[0086] The volume of the medicament may be expelled from the outlet in at least 30 seconds. In some embodiments, the volume of the medicament is expelled from the outlet in at least 30 seconds, at least 60 seconds, at least 90 seconds, at least 120 seconds, at least 150 seconds, at least 180 seconds, at least 210 seconds, at least 240 seconds, at least 270 seconds, at least 300 seconds, at least 330 seconds, and at least 360 seconds. In some embodiments, the volume of the medicament is expelled from the outlet in between 30 seconds and 60 seconds, between 60 seconds and 120 seconds, between 120 seconds and 180 seconds, between 180 seconds and 240 seconds, between 240 seconds and 300 seconds, or between 300 seconds and 360 seconds. In some embodiments, the volume of the medicament is expelled from the outlet between 30 seconds and 60 seconds, between 60 seconds and 90 seconds, between 90 seconds and 120 seconds, between 120 seconds and 150 seconds, between 150 seconds and 180 seconds, between 180 seconds and 210 seconds, between 210 seconds and 240 seconds, between 240 seconds and 270 seconds, between 270 seconds and 300 seconds, between 300 seconds and 330 seconds, or between 330 seconds and 360 seconds.

[0087] The volume of the medicament may be expelled from the outlet at a rate of at least 4 mL/min. In some embodiments, the volume of the medicament may be expelled from the outlet at least 4 mL/min, at least 5 mL/min., at least 6 mL/min., at least 7 mL/min., at least 8 mL/min., at least 9 mL/min., at least 10 mL/min., at least 11 mL/min., at least 12 mL/min., at least 13 mL/min., at least 14 mL/min., at least 15 mL/min., at least 16 mL/min., at least 17 mL/min., at least 18 mL/min., at least 19 mL/min., at least 20 mL/min., or at least 21 mL/min. The volume of the medicament may be expelled from the outlet at a rate of between 4 mL/min. and 5 mL/min., between 5 mL/min. and 6 mL/min, between 6 mL/min. and 7 mL/min., between 7 mL/min. and 8 mL/min, between 8 mL/min. and 9 mL/min, between 9 mL/min. and 10 mL/min, between 10 mL/min. and 11 mL/min, between 11 mL/min. and 12 mL/min, between 12 mL/min. and 13 mL/min., between 13 mL/min. and 14 mL/min., between 14 mL/min. and 15 mL/min., between 15 mL/min. and 16 mL/min., between 16 mL/min. and 17 mL/min., between 17 mL/min. and 18 mL/min., between 18 mL/min. and 19 mL/min., between 19 mL/min. and 20 mL/min., and between 20 mL/min. and 21 mL/min. In other embodiments, the volume of the medicament may be expelled from the outlet at a rate of between 5 mL/min. and 10 mL/min., between 10 mL/min. and 15 mL/min., and between 15 mL/min. and 20 mL/min.

[0088] The port 106 may be wearable by a user or may be inserted for a set amount of time, for example, 1 hour, 1 day, 1 week, etc. As shown in Figs. 1 and 3, the port 106 may comprise a user

engagement surface 124, an injection apparatus 126, and an inlet 128. The injection apparatus 126 may be a needle. In some embodiments, the injection apparatus 126 may be a cannula. The port 106 may be removably coupled to the injection site of a user during use. The user engagement surface 124 may have an adhesive disposed thereon to prevent or at least reduce movement of the port 106 relative to the injection site.

[0089] The user engagement surface 124 may be generally flat or may be slightly concave to match the curvature of the area of the patient it is configured to adhere to (e.g., chest, shoulder, stomach). The user engagement surface 124 may include an aperture extending therethrough. The aperture may be a generally central portion of the user engagement surface 124. The injection apparatus 126 may extend through the aperture on a plane generally perpendicular to a plane extending along the generally flat surface of the user engagement surface 124.

[0090] As shown in Fig. 3, the conduit 104 may be removably coupled to the outlet 116 and the port 106 and may extend therebetween. The conduit 104 may fluidly connect the delivery apparatus 102 and the port 106 when coupled therebetween. The conduit may be a specialized tubing or channel made from biocompatible materials, such as silicone or polyurethane, and may be designed to transport fluids or medical instruments. The conduit 104 may be a flexible or pliable tubing. The conduit 104 may be at least 6 inches in length. In some embodiments, the conduit 104 is at least 6 inches, at least 8 inches, at least 10 inches, at least 12 inches, at least 14 inches, at least 16 inches, at least 18 inches, at least 24 inches, at least 30 inches, at least 36 inches, or at least 48 inches.

[0091] The conduit 104 must be “primed” to expel most of the air located therein to ensure proper and safe administration of the medicament. The delivery apparatus 102 may purge the conduit 104 of air before the injection apparatus 126 is inserted into the injection site of a patient. In some embodiments, the energy source 112 is prevented from expelling the medicament from the outlet 116 until the conduit 104 is purged of air. For example, when the autoinfusion device 100 is in the locked state and the priming state. The button 120 or ram 122 may be used to prime the conduit 104. During priming, the ram 122 is advanced a fixed distance distally to expel a volume of the medicament into the conduit 104. In some embodiments, the autoinfusion device 100 includes a second button 220 to initiate priming in the case of, for example, a two-stage triggering mechanism. In that case, the second button 220 may be engaged by the user to initiate priming, and then the button 120 may be engaged to initiate a triggering event. In some embodiments, the button 120 may initiate priming and the second button 220 may initiate a triggering event.

[0092] The priming volume may be at least 0.05 mL. In some embodiments, the priming volume is at least 0.05 mL, at least 0.1 mL, at least 0.15 mL, at least 0.2 mL, at least 0.25 mL, at

least 0.3 mL, at least 0.35 mL, at least 0.4 mL, at least 0.45 mL, at least 0.5 mL, at least 0.75 mL, or at least 1 mL. In some embodiments, the priming volume is between 0.05 mL and 1 mL, between 0.1 mL and 0.75 mL, between 0.15 mL and 0.5 mL, between 0.2 mL and 0.45 mL, between 0.25 mL and 0.4 mL, or between 0.3 mL and 0.35 mL. In some embodiments, the priming volume is less than 0.05 mL, at least 0.1 mL, at least 0.15 mL, at least 0.2 mL, at least 0.25 mL, at least 0.3 mL, at least 0.35 mL, at least 0.4 mL, at least 0.45 mL, at least 0.5 mL, at least 0.75 mL, or at least 1 mL.

[0093] This priming movement of the ram 122 can be performed by the energy source 112 or by a separate biasing member. Once the ram 122 is advanced into a primed position and all air has been removed from the conduit 104, the delivery apparatus 102 may eject the medicament through the conduit 104 and through the injection apparatus 126. During delivery of the medicament, the ram 122 may occlude the window 109 of the housing 108. The occlusion of the window 109 by the ram 122 may enable the user to monitor the volume of the medicament and the status of the delivery. The window 109 may be entirely occluded by the ram 122 upon completion of the delivery. In some embodiments, the window 109 is partially occluded by the ram 122 upon completion of the delivery. The delivery apparatus 102 may automatically purge the conduit 104 of air when the conduit 104 is coupled to the outlet 116. The outlet 116 may have a septum that is forced open when the conduit 104 is coupled to the outlet 116. The outlet 116 may include one or more sensors to detect the presence of the conduit 104. In some embodiments, the delivery apparatus 102 purges the conduit 104 of air after the injection apparatus 126 is inserted into the injection site of a patient.

[0094] In some embodiments, the delivery apparatus 102 does not purge the conduit 104 before ejecting the medicament into the injection site. In some embodiments, the port 106 may include an air release valve 130 (not shown). The air release valve 130 may prime the prefilled autoinfusion device 100 by removing any air located in the conduit 104 after the injection apparatus 126 is inserted into the injection site.

[0095] The energy source 112 urges the volume of the medicament through the injection apparatus 126 when the volume of the medicament is expelled from the outlet 116. The conduit 104 may be decoupled from the port 106 after the volume of the medicament is expelled from the outlet 116. The delivery apparatus 102 is not resettable after the volume of the medicament is expelled from the outlet 116. For example, the delivery apparatus 102 may be disposed after use.

[0096] A method of delivering a medicament into a patient using a delivery apparatus 102 comprising a prefilled medicament container 110 containing a volume of a medicament, an energy source 112 configured to interact with the medicament container 110 to expel the medicament, and a

trigger mechanism 114 configured to activate the energy source 112 in response to a user input is disclosed herein.

[0097] The method may include coupling the delivery apparatus 102 to a first end of a conduit 104, the conduit 104 in fluid communication with the prefilled medicament container 110. The method may include transitioning the autoinfusion device 100 into a priming state, for example by rotating the button 120 in a first direction about the longitudinal axis. The autoinfusion device 100 may be configured to advance the ram 122 a predetermined distance to eject a volume of the medicament through the conduit 104 to prepare the conduit for delivery of the medicament therethrough. The method may include transitioning the injector into a primed state, for example by rotating the button 120 in the first direction about the longitudinal axis.

[0098] The method may include coupling a second end of the conduit 104 to a port 106 including an injection apparatus 126 extending therefrom. The injection apparatus 126 may be in fluid communication with the prefilled medicament container 110 when the conduit 104 is coupled to the delivery apparatus 102 and the port 106. In some embodiments, more than one delivery apparatus 102 is in fluid communication with the port 106. Each delivery apparatus 102 may be coupled to a distinct inlet 128. Each delivery apparatus 102 may be coupled to the same inlet 128.

[0099] The method may include inserting the injection apparatus 126 into an injection site on a patient and manipulating the trigger mechanism 114 (e.g., button 120) to allow the energy source 112 to expel the medicament from the prefilled medicament container 110. The energy source 112 may urge the volume of the medicament through the injection apparatus 126 during the injection.

[00100] It would be appreciated by one having ordinary skill in the art that the steps above may be performed in a different order than presented. For example, the method may include inserting the injection apparatus 126 into an injection site on a patient prior to coupling a second end of the conduit 104 to the port 106.

[00101] The volume of the medicament may be expelled at a rate of at least 5 mL/min. In some embodiments, the volume of the medicament may be expelled at a rate of at least 5 mL/min., at least 7.5 mL/min., at least 10 mL/min., at least 12.5 mL/min., at least 15 mL/min., at least 17.5 mL/min., or at least 20 mL/min.

[00102] The method may include purging the conduit 104 of air prior to the injection. In some embodiments, the delivery apparatus purges the conduit 104 of air before the needle is inserted into an injection site of a patient. In some embodiments, the delivery apparatus purges the conduit 104 of air while the needle is inserted into an injection site of a patient. In some embodiments, the

delivery apparatus purges the conduit 104 of air after the needle is inserted into an injection site of a patient. In some embodiments, the delivery apparatus 102 is not resettable.

[00103] It will be appreciated by those skilled in the art that changes could be made to the exemplary embodiments shown and described above without departing from the broad inventive concepts thereof. It is to be understood that the embodiments and claims disclosed herein are not limited in their application to the details of construction and arrangement of the components set forth in the description and illustrated in the drawings. Rather, the description and the drawings provide examples of the embodiments envisioned. The embodiments and claims disclosed herein are further capable of other embodiments and of being practiced and carried out in various ways.

10 Definitions

[00104] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference in their entireties.

15 [00105] As used herein, the terms “administer,” “administration,” or “administering” refer to (1) providing, giving, dosing, and/or prescribing by either a health practitioner or his or her authorized agent or under his or her direction according to the disclosure, and/or (2) putting into, taking, or consuming by a subject, for example a mammal, including a human, according to the disclosure.

[00106] The terms “co-administration,” “co-administering,” “administered in combination with,” “administering in combination with,” “simultaneous,” and “concurrent,” as used herein, encompass administration of two or more active pharmaceutical ingredients to a subject so that both active pharmaceutical ingredients and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which two or more active pharmaceutical ingredients are present. In some embodiments, simultaneous administration in separate compositions and administration in a composition in which both agents are present are preferred.

25 [00107] The term “effective amount” or “therapeutically effective amount” refers to that amount of a compound or combination of compounds as described herein that is sufficient to effect the intended application including, but not limited to, disease treatment. A therapeutically effective amount may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated (*e.g.*, the weight, age and gender of the subject), the severity of the disease condition, the manner of administration, *etc.*, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in

target cells (*e.g.*, the reduction of platelet adhesion and/or cell migration). The specific dose will vary depending on the subject to whom the dose is to be administered, the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

[00108] A “therapeutic effect” as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition; delaying or eliminating the onset of symptoms of a disease or condition; slowing, halting, or reversing the progression of a disease or condition; or any combination thereof.

[00109] As used herein, the terms “treat,” “treatment,” and/or “treating” may refer to the management of a disease, disorder, or pathological condition, or symptom thereof, with the intent to cure, ameliorate, stabilize, and/or control the disease, disorder, pathological condition, or symptom thereof. Regarding control of the disease, disorder, or pathological condition more specifically, “control” may include the absence of condition progression, as assessed by the response to the methods recited herein, where such response may be complete (*e.g.*, placing the disease in remission) or partial (*e.g.*, lessening or ameliorating any symptoms associated with the condition). As used herein, the terms “prevent,” “preventing,” and/or “prevention” may refer to reducing the risk of developing a disease, disorder, or pathological condition.

[00110] As used herein, a soluble hyaluronidase is a hyaluronidase of form thereof that is not GPI anchored, and that is soluble under physiological conditions and is secreted upon expression. Soluble hyaluronidases include any that, upon expression, are secreted from a cell and exist in soluble form. Human PH20 hyaluronidase does not occur as a soluble hyaluronidase. It is known in the art that removal of all or a part of the GPI anchor results in soluble forms. Such soluble hyaluronidases include, but are not limited to, bacterial soluble hyaluronidases, non-human soluble hyaluronidases such as bovine PH20 and ovine PH20, human soluble PH20, and variants thereof. Generally soluble forms of PH20 are produced using protein expression systems that facilitate correct N-glycosylation to ensure that the polypeptide retains activity, since glycosylation is important for the catalytic activity and stability of hyaluronidases. Such cells include, for example, Chinese Hamster Ovary (CHO) cells (*e.g.*, DG44 CHO cells).

[00111] As used herein the term “rHuPH20” refers to the soluble hyaluronidase composition produced upon expression in a mammalian cell, such as a CHO cell, or other cell that effects glycosylation, of nucleic acid encoding residues 36-482 of SEQ ID NO: 1. For expression in cells the encoding nucleic acid is linked to the native (residues 1-35 of SEQ ID NO: 1) or a heterologous

signal sequence for trafficking and secretion of the encoded polypeptides. The resulting secreted soluble glycoprotein is a heterogeneous mixture of polypeptides, including polypeptides that terminate at residues 479, 480, 481, and 482, and are composed of residues 36-479, 36-480, 36-481, and 36-482 with reference to SEQ ID NO: 1. Shorter C-terminally truncated forms also may be included, in various abundance. Typically, rHuPH20 is produced in cells that facilitate correct N-glycosylation to retain activity, such as CHO cells (e.g., DG44 CHO cells). In some embodiments, one of the most abundant species is the 446 amino acid polypeptide corresponding to residues 36-481 of SEQ ID NO: 1. Also included are polypeptides that are soluble or secreted upon expression in a mammalian cell and have at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more sequence identity with residues 36-482 of SEQ ID NO: 1.

[00112] As used herein, “combination therapy” refers to a treatment in which a subject is given two or more therapeutic agents, such as at least two or at least three therapeutic agents, for treating a single disease.

[00113] As used herein, “hyaluronidase activity” refers to the ability to enzymatically catalyze the cleavage of hyaluronic acid. The United States Pharmacopeia (USP) XXII assay for hyaluronidase determines hyaluronidase activity indirectly by measuring the amount of higher molecular weight hyaluronic acid, or hyaluronan, (HA) substrate remaining after the enzyme is allowed to react with the HA for 30 minutes at 37 °C (USP XXII-NF XVII (1990) 644-645 United States Pharmacopeia Convention, Inc, Rockville, MD). A Reference Standard solution can be used in an assay to ascertain the relative activity, in units, of any hyaluronidase. In vitro assays to determine the hyaluronidase activity of hyaluronidases, such as PH20, including soluble PH20 and esPH20, are known in the art and described herein. Exemplary assays include the microturbidity assay that measures cleavage of hyaluronic acid by hyaluronidase indirectly by detecting the insoluble precipitate formed when the uncleaved hyaluronic acid binds with serum albumin and the biotinylated-hyaluronic acid assay that measures the cleavage of hyaluronic acid indirectly by detecting the remaining biotinylated-hyaluronic acid non-covalently bound to microtiter plate wells with a streptavidin-horseradish peroxidase conjugate and a chromogenic substrate. Reference Standards can be used, for example, to generate a standard curve to determine the activity in Units of the hyaluronidase being tested.

[00114] “Pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” or “physiologically compatible” carrier or carrier medium is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and inert ingredients. The use of such pharmaceutically acceptable carriers or

pharmaceutically acceptable excipients for active pharmaceutical ingredients is well known in the art. Except insofar as any conventional pharmaceutically acceptable carrier or pharmaceutically acceptable excipient is incompatible with the active pharmaceutical ingredient, its use in the therapeutic compositions of the invention is contemplated. Additional active pharmaceutical ingredients, such as other drugs, can also be incorporated into the described compositions and methods.

[00115] As used herein, “specific activity” refers to Units of activity per mg protein. The milligrams of hyaluronidase is defined by the absorption of a solution at 280 nm assuming a molar extinction coefficient of approximately 1.7, in units of $M^{-1} cm^{-1}$.

[00116] As used herein, “neutral active” refers to the ability of a PH20 polypeptide to enzymatically catalyse the cleavage of hyaluronic acid at neutral pH (e.g., at or about pH 7.0).

[00117] As used herein, a “GPI-anchor attachment signal sequence” is a C-terminal sequence of amino acids that directs addition of a preformed GPI-anchor to the polypeptide within the lumen of the ER. GPI-anchor attachment signal sequences are present in the precursor polypeptides of GPI-anchored polypeptides, such as GPI-anchored PH20 polypeptides. The C-terminal GPI-anchor attachment signal sequence typically contains a predominantly hydrophobic region of 8-20 amino acids, preceded by a hydrophilic spacer region of 8-12 amino acids, immediately downstream of the ω -site, or site of GPI-anchor attachment. GPI-anchor attachment signal sequences can be identified using methods well known in the art, such as, but not limited to, in silico methods and algorithms (see, e.g., Udenfriend et al. (1995) *Methods Enzymol.* 250:571-582, Eisenhaber et al., (1999) *J. Biol. Chem.* 272: 741-758, Fankhauser et al., (2005) *Bioinformatics* 21:1846-1852, Omaetxebarria et al., (2007) *Proteomics* 7:1951-1960, Pierleoni et al., (2008) *BMC Bioinformatics* 9:392), including those that are readily available on bioinformatic websites, such as the ExPASy Proteomics tools site (e.g., the World Wide Web site expasy.ch/tools/).

[00118] As used herein, “sequence identity” refers to the relatedness between or among polypeptides among nucleic acid molecules. Sequence identity can be assessed by aligning two sequences and counting the number of differences between the aligned portion and the sequence to which it is compared. Whether any two molecules have nucleotide sequences or amino acid sequences that are at least 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% “identical” or “homologous” can be determined using known computer algorithms such as the “FASTA” program, using, for example, the default parameters as in Pearson et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:2444 (other programs include the GCG program package (Devereux, J., et al., *Nucleic Acids Research* 12(I):387 (1984)), BLASTP, BLASTN, FASTA (Altschul, S.F., et al., *J Mol Biol* 215:403

(1990)); Guide to Huge Computers, Martin J. Bishop, ed., Academic Press, San Diego, 1994, and Carrillo et al. (1988) SIAM J Applied Math 48:1073). For example, the BLAST function of the National Center for Biotechnology Information database can be used to determine identity. Other commercially or publicly available programs include, the DNASTar “MegAlign” program (Madison, WI) and the University of Wisconsin Genetics Computer Group (UWG) “Gap” program (Madison, WI). Percent homology or identity of proteins and/or nucleic acid molecules can be determined, for example, by comparing sequence information using a GAP computer program (e.g., Needleman et al. (1970) J. Mol. Biol. 48:443, as revised by Smith and Waterman ((1981) Adv. Appl. Math. 2:482)). Briefly, the GAP program defines similarity as the number of aligned symbols (i.e., nucleotides or amino acids), which are similar, divided by the total number of symbols in the shorter of the two sequences. Default parameters for the GAP program can include: (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-identities) and the weighted comparison matrix of Gribskov et al. (1986) Nucl. Acids Res. 14:6745, as described by Schwartz and Dayhoff, eds., ATLAS OF PROTEIN SEQUENCE AND STRUCTURE, National Biomedical Research Foundation, pp. 353 358 (1979); (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps.

[00119] Therefore, as used herein, the term “identity” or “homology” represents a comparison between a test and a reference polypeptide or polynucleotide.

[00120] As used herein, the term “at least 90% identical to” refers to percent identities from 90 to 99.99 relative to the reference nucleic acid or amino acid sequence of the polypeptide. Identity at a level of 90% or more is indicative of the fact that, assuming for exemplification purposes a test and reference polypeptide length of 100 amino acids are compared, no more than 10% (i.e., 10 out of 100) of the amino acids in the test polypeptide differs from that of the reference polypeptide. Similar comparisons can be made between test and reference polynucleotides. Such differences can be represented as point mutations randomly distributed over the entire length of a polypeptide or they can be clustered in one or more locations of varying length up to the maximum allowable, e.g., 10/100 amino acid difference (approximately 90% identity). Differences are defined as nucleic acid or amino acid substitutions, insertions or deletions. At the level of homologies or identities above about 85-90%, the result should be independent of the program and gap parameters set; such high levels of identity can be assessed readily, often by manual alignment without relying on software.

[00121] As used herein, an “aligned sequence” refers to the use of homology (similarity and/or identity) to align corresponding positions in a sequence of nucleotides or amino acids. Typically, two or more sequences that are related by 50% or more identity are aligned. An aligned set of

sequences refers to 2 or more sequences that are aligned at corresponding positions and can include aligning sequences derived from RNAs, such as ESTs and other cDNAs, aligned with genomic DNA sequence.

[00122] As used herein, “denaturing condition” or “denaturation condition” refers to any condition or agent that, when exposed to a protein, affects or influences the degradation or denaturation of the protein, generally as a result of a loss or partial loss of the tertiary or secondary structure of the protein. Denaturing conditions can result in effects such as loss or reduction in activity, or loss or reduction of solubility, aggregation and/or crystallization.

[00123] As used herein, “resistance to a denaturation condition” refers to any amount of decreased reduction or elimination of a property or activity of the protein associated with or caused by denaturation. For example, denaturation is associated with or causes increased crystallization or aggregation, reduced solubility, or decreased activity. Hence, resistance to denaturation means that the protein exhibits decreased aggregation or crystallization, increased solubility or increased or greater activity (e.g., hyaluronidase activity) when exposed to a denaturing condition compared to a reference protein (e.g., unmodified enzyme).

[00124] As used herein, “stability of a modified PH20 hyaluronidase” means that it exhibits resistance to denaturation caused by a denaturation condition or denaturing agent.

[00125] When ranges are used herein to describe, for example, physical or chemical properties such as molecular weight or chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. Use of the term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary. The variation is typically from 0% to 15%, from 0% to 10%, from 0% to 5%, or the like, of the stated number or numerical range.

[00126] The term “about” or “approximately” is used herein to provide literal support for the exact number that it precedes, as well as a number that is near to or approximately the number that the term precedes. As used herein, the term “about” means that amounts, sizes, formulations, parameters, shapes and other quantities and characteristics are not, and need not be, exact, but may be approximate and/or larger or smaller, as desired, reflecting tolerances, conversion factors, rounding off, measurement error and the like, and other factors known to those of skill in the art. In general, an amount, size, formulation, parameter, shape or other quantity or characteristic is “about” or “approximate” whether or not expressly stated to be such. The term “about” generally refers to a particular numeric value that is within an acceptable error range as determined by one of ordinary

skill in the art, which will depend in part on how the numeric value is measured or determined, i.e., the limitations of the measurement system. For example, “about” can mean a range of $\pm 20\%$ (inclusive), $\pm 10\%$ (inclusive), $\pm 5\%$ (inclusive), $\pm 3\%$ (inclusive), $\pm 2\%$ (inclusive), $\pm 1\%$ (inclusive), $\pm 0.5\%$ (inclusive), $\pm 0.1\%$ (inclusive), or $\pm 0.01\%$ (inclusive) of a given numeric value.

5 **[00127]** The transitional terms “comprising,” “consisting essentially of,” and “consisting of,” when used in the appended claims, in original and amended form, define the claim scope with respect to what unrecited additional claim elements or steps, if any, are excluded from the scope of the claim(s). The term “comprising” is intended to be inclusive or open-ended and does not exclude any additional, unrecited element, method, step, or material. The term “consisting of” excludes any
10 element, step or material other than those specified in the claim and, in the latter instance, impurities ordinarily associated with the specified material(s). The term “consisting essentially of” limits the scope of a claim to the specified elements, steps, or material(s) and those that do not materially affect the basic and novel characteristic(s) of the claimed invention. All compounds, compositions, formulations, and methods described herein that embody the present invention can, in alternate
15 embodiments, be more specifically defined by any of the transitional terms “comprising,” “consisting essentially of,” and “consisting of.” The term “comprising” (and related terms such as “comprise” or “comprises” or “having” or “including”) includes those embodiments such as, for example, an embodiment of any composition of matter, method, or process that “consist of” or “consist essentially of” the described features.

20 **[00128]** Specific features of the exemplary embodiments may or may not be part of the claimed invention and various features of the disclosed embodiments may be combined. Unless specifically set forth herein, the terms “a,” “an,” and “the” are not limited to one element but instead should be read as meaning “at least one.” Finally, unless specifically set forth herein, a disclosed or claimed method should not be limited to the performance of their steps in the order written, and one skilled
25 in the art can readily appreciate that the steps may be performed in any practical order.

[00129] The present disclosure generally relates to automatic or manual triggering devices that are used in the delivery of high volumes of injectable fluid, such as medicament, (e.g., 2 ml, 3 ml, 5 ml, 10 ml or higher doses) for sub skin surface penetration (e.g., subcutaneous and intramuscular injections). Devices that deliver high volumes of medicament are prone to configuration restrictions
30 as the delivery volume of the medicament increases, such as spring force limitations and syringe container breakage. Due to the current configurations of overall device design, and the limitations of the biological uptake factors that limit injection speed and volume, injection devices would be

held for long durations, and often result in other delivery methods being used such as on-body delivery systems that are attached to the patient during delivery.

[00130] Increasingly, more biologics are allowing for at-home administration for patients. However, for many biologics, high doses and the resulting high volume of medicament that must be delivered often precludes self-administration because of the length of time required to hold the delivery device in place. Protein hyper-concentration can be used to reduce injection volume, but the resulting medicament often has a much higher viscosity than the traditional biologics. High-powered injectors may allow delivery of these hyper-concentrated proteins. However, typical handheld injector designs only allow for up to 2.25 mL of a viscous medicament to be injected in 30 seconds.

[00131] With the development of enzymes that locally degrade hyaluronan (HA) in the subcutaneous (SC) space, thereby temporarily removing a barrier to fluid flow, the traditional limitations of biological uptake factors that limit injection speed and volume may be reduced. As such, higher volumes of viscous medicaments may be delivered. Accordingly, there is a need to provide a handheld device capable of delivering a high dose (e.g., 3 mL, 5 mL, 10 mL, 20 mL and up to 50 mL) of a viscous medicament in a delivery time appropriate for a handheld device.

[00132] Drug delivery technology of high doses of a viscous medicament is currently based on the proprietary recombinant human hyaluronidase PH20 enzyme (e.g., rHuPH20; Halozyme, Inc.) that facilitates SC delivery of co-administered therapeutics. rHuPH20 works by degrading the HA, thus decreasing the resistance to bulk fluid flow in the SC space, and permitting high-volume SC drug delivery, dispersion, and absorption. Co-administration of rHuPH20 with injectable therapies can overcome administration time and volume barriers associated with existing SC therapeutic formulations and has been shown to reduce the burden on patients and healthcare providers compared with intravenous formulations. rHuPH20 has countless applications in the current field of injectable therapies by increasing the dispersion and absorption of other injected drugs, such as anticancer therapies (e.g., trastuzumab and rituximab), immunodeficiency treatment, in subcutaneous urography for improving resorption of radiopaque agents, and fluid delivery for rehydration.

Formulation for High-Dose Injection

[00133] The present disclosure provides a formulation for a high-dose injection comprising a hyaluronidase enzyme. In one embodiment, the formulation is an aqueous formulation. In one embodiment, the formulation comprises one or more pharmaceutically acceptable carriers.

Forms of Soluble Hyaluronidases

[00134] Soluble hyaluronidases include any that, upon expression, are secreted from a cell and exist in soluble form. Such soluble hyaluronidases include, for example, but are not limited to, bacterial soluble hyaluronidases, non-human soluble hyaluronidases, such as bovine PH20 and ovine PH20, human soluble PH20, and variants thereof. Generally soluble forms of PH20 are produced using protein expression systems that facilitate correct N-glycosylation to ensure that the polypeptide retains activity, since glycosylation is important for the catalytic activity and stability of hyaluronidases. Such cells include, for example Chinese Hamster Ovary (CHO) cells (e.g., DG44 CHO cells).

[00135] Vorhyaluronidase alfa is a recombinant human hyaluronidase PH-20 analog corresponding to the amino acid sequence of human hyaluronidase PH-20 at positions 36-482. Vorhyaluronidase alfa is produced in Chinese hamster ovary cells. Vorhyaluronidase alfa is a glycoprotein (molecular weight: 60,000 – 65,000) consisting of 447 amino acid residues. In one embodiment, the soluble PH20 product is the composition produced by expression of nucleic acid encoding residues 36-482 in CHO cells resulting in a mixture of polypeptides with C-termini at residues 477, 478, 479, 480, 481, and 482.

[00136] Soluble PH20 hyaluronidase is available and sold, for example, under the trademark ENHANZE® (CAS name of 36-482-Hyaluronoglucosaminidase PH20 (human)). ENHANZE® is the mixture of polypeptides produced by expression of nucleic acid encoding amino acids 36-482 (SEQ ID NO: 2). The product is a mixture of polypeptides, produced by expression of nucleic acid encoding amino acids 36-477 (SEQ ID NO: 3), 36-478 (SEQ ID NO: 4), 36-479 (SEQ ID NO: 5), 36-480 (SEQ ID NO: 6), 36-481 (SEQ ID NO: 7), and 36-482 (SEQ ID NO: 2). ENHANZE® technology provides to a drug delivery technology, employing the soluble hyaluronidases to facilitate the delivery of injected drugs and fluids. When co-formulated with other drugs or administered with other drugs, the ENHANZE® technology reduces treatment burden for patients. It can allow for large volume subcutaneous injection with increased dispersion and absorption of co-administered therapies.

[00137] In one embodiment, one or more of N47, N131, N200, N219, N333, N358, or T440 in SEQ ID NOs: 2-7 are glycosylation sites. In one embodiment, one or more of Q444, I445, F446, or Y447 in SEQ ID NOs: 2-7 are partial processing sites. In one embodiment, one or more of C25-C316, C189-C203, C341-C352, C346-C400, C402-C408, or C423-C429 in SEQ ID NOs: 2-7 are disulfides.

[00138] rHuPH20 refers to the composition produced upon expression in a cell, such as a CHO cell, of nucleic acid encoding residues 36-482 of SEQ ID NO: 8, generally linked to the native or a

heterologous signal sequence (residues 1-35 of SEQ ID NO: 8). rHuPH20 is produced by expression of a nucleic acid molecule, such as encoding amino acids 1-482 (set forth in SEQ ID NO: 8) in a mammalian cell. Translational processing removes the 35 amino acid signal sequence. As produced in the culture medium there is heterogeneity at the C-terminus such that the product, designated rHuPH20, includes a mixture of species that can include any one or more of the polypeptides 36-480, 36-481, and 36-482 of SEQ ID NO: 8, and some shorter polypeptides, in various abundance. rHuPH20 and forms of soluble hyaluronidase are produced in cells, such as CHO cells, for example DG44 CHO cells, that facilitate N-glycosylation. PH20 is a glycoprotein, and as known in the art, requires glycosylation retain activity. See, *e.g.*, U.S. Patent Nos. 8,927,249 and 9,284,543 (and PCT Publication No. WO 2010/077297), which describe the effects of glycosylation and partial glycosylation and elimination of glycosylation on the activity of soluble forms of PH20. These patents and publications also describe and exemplify soluble C-terminally truncated forms of PH20.

Forms of Soluble Human PH20

[00139] Soluble hyaluronidases include bovine and ovine PH20, and recombinant and humanized forms thereof. Human PH20 in nature includes a GPI anchor and exists linked to sperm cells; it is not soluble. C-terminally-truncated forms thereof are soluble. Soluble forms of recombinant human PH20 have been produced and can be used in the compositions, combinations and methods described herein. Descriptions of and production of such soluble forms of PH20 are described, for example, in U.S. Patent Nos. 7,767,429, 8,202,517, 8,431,380, 8,431,124, 8,450,470, 8,765,685, 8,772,246, 7,871,607, 7,846,431, 7,829,081, 8,105,586, 8,187,855, 8,257,699, 8,580,252, 9,677,061, and 9,677,062, each incorporated by reference herein. The soluble hyaluronidases thus include forms of human PH20, which are neutral active hyaluronidases and which require glycosylation for activity.

[00140] SEQ ID NO: 1 sets forth the sequence of the precursor polypeptides; the mature PH20 polypeptide (residues 36-509); soluble forms also include those with amino acid truncations at the N-terminal, such as deletions of the first one, two, three, or four residues, such that the resulting polypeptides have an N-terminus, for example, at residue 36, 37, 38, 39, or 40, and a C-terminus at a residue from 465 to 500, and variants thereof, including, but not limited to, variants discussed below, variants known in the art, and allelic variants.

[00141] Hyaluronidases for use in the compositions, combinations and methods herein are soluble neutral active hyaluronidases. Exemplary thereof are the soluble C-terminally truncated forms of mature human PH20. Soluble forms that have hyaluronidase activity include, but are not

limited to, those that are truncated at residues from 465 to 500 of SEQ ID NO: 1, and that are, upon expression, secreted. Exemplary thereof are polypeptides that have sequence 36-465, 36-466, 36-467, 36-468, 36-469, 35-470, 36-471, 36-472, 36-474, 36-475, 36-476, 35-477, 36-478, 36-479, 36-480, 36-481, 36-482, 36-483, 35-484, 36-485, 36-486, 36-487, 36-488, 36-489, 36-490, 35-491, 36-492, 36-493, 36-494, 36-495, 36-496, 36-497, 35-498, 36-499, and 36-500 of SEQ ID NO: 1, as well as N-terminally truncated forms of each of the preceding that lack two to five residues at the N-terminus, such as for example 37-368, 38-468, and any others that exhibit hyaluronidase activity at neutral pH, such as pH in the range of 7.0-7.4.

[00142] Thus, such soluble forms include truncated forms of the mature form of human PH20 lacking all or a portion of the C-terminal GPI anchor, so long as the hyaluronidase is soluble and retains hyaluronidase activity. Soluble forms are secreted upon expression in mammalian cells, and are encoded with a signal sequence, such as residues 1-35 of SEQ ID NO. 1 or a heterologous signal sequence that is cleaved by the cell to effect secretion. Soluble forms are forms that, when expressed in a cell, lack the signal peptide. Also included among soluble hyaluronidases are variants of the soluble PH20 polypeptides that exhibit hyaluronidase activity. Variants include polypeptides having at least 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to any of the PH20 polypeptides 36-465, 36-466, 36-467, 36-468, 36-469, 35-470, 36-471, 36-472, 36-474, 36-475, 36-476, 35-477, 36-478, 36-479, 36-480, 36-481, 36-482, 36-483, 35-484, 36-485, 36-486, 36-487, 36-488, 36-489, 36-490, 35-491, 36-492, 36-493, 36-494, 36-495, 36-496, 36-497, 35-498, 36-499, and 36-500 of SEQ ID NO: 1. Amino acid variants include conservative and non-conservative insertions, or deletions, or replacements, and include the modifications, singly or combinations of the modifications detailed, for example, in U.S. Patent No. 11,041,149 and International PCT publication No. WO 2013/102144. U.S. Patent No. 11,041,149 and International PCT publication No. WO 2013/102144 describe a systematic analysis and results identifying the effects of amino acid modifications at each residue in PH20 to thereby provide a structure/function map of PH20; a skilled person can identify replacement residues and consequent alterations in properties and activities, such as for effecting increases in enzymatic activity, stability in denaturing conditions, and also residues whose replacement or deletion decreases or eliminates enzymatic activity.

[00143] It is understood that residues that are important or otherwise required for the activity of a hyaluronidase, such as any described above or known to those of skill in the art, are generally invariant and, except for possible conservative amino acid substitutions, cannot be changed. These include, for example, active site residues. For example, amino acid residues 111, 113 and 176

(corresponding to residues in the mature PH20 polypeptide) of a human PH20 polypeptide, or soluble form thereof, are generally invariant and are not altered. Other residues that confer glycosylation and formation of disulfide bonds required for proper folding also can be invariant.

[00144] The soluble human PH20 hyaluronidase is GPI-anchored and is rendered soluble by truncation at the C-terminus by removal of all or a part of the GPI anchor. Such truncation can remove all of the GPI anchor attachment sequence or can remove only some of the GPI anchor attachment sequence. The resulting polypeptide, however, is soluble. In instances where the soluble hyaluronidase retains a portion of the GPI anchor attachment signal sequence, 1, 2, 3, 4, 5, 6, 7 or more amino acid residues in the GPI anchor attachment signal sequence can be retained, provided that the polypeptide is soluble. Polypeptides containing one or more amino acids of the GPI anchor are termed extended soluble hyaluronidases. One of skill in the art can determine whether a polypeptide is GPI-anchored using methods well known in the art. Such methods include, but are not limited to, using known algorithms to predict the presence and location of the GPI anchor attachment signal sequence and ω -site, and performing solubility analyses before and after digestion with phosphatidylinositol-specific phospholipase C (PI-PLC) or D (PI-PLD).

[00145] Extended soluble hyaluronidases, that terminate for example, at residues 495, 496, 497, 498, 499, and 500, with reference to SEQ ID NO: 1, such as those set forth in SEQ ID NO: 9 (residues 1-495), SEQ ID NO: 10 (residues 1-496), SEQ ID NO: 11 (residues 1-497), SEQ ID NO: 12 (residues 1-498), SEQ ID NO: 13 (residues 1-499), and SEQ ID NO: 14 (residues 1-500), can be produced by making C-terminal truncations to any naturally GPI-anchored hyaluronidase such that the resulting polypeptide is soluble and contains one or more amino acid residues from the GPI anchor attachment signal sequence (see, e.g., U.S. Patent No. 8,927,249). These include hyaluronidases that are neutral active, soluble, contain amino acid substitutions, and have at least 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95% or more sequence identity to any of SEQ ID NOs: 9-14.

[00146] Typically, for use in the compositions, combinations, and methods herein, a soluble human hyaluronidase, such as a soluble human PH20, is used, such as a PH20 and variants having, for example, at least 91% or 95% or 98% sequence identity thereto, including those with 1 to 5 N-terminal residues deleted. Hyaluronidases used in the regimens, combinations, compositions, and methods herein can be recombinantly produced or can be purified or partially purified from natural sources, such as, for example, from testes extracts. Methods for production of recombinant proteins, including recombinant hyaluronidases, are well known in the art.

[00147] Recombinant soluble forms of human PH20 have been generated and can be used in the compositions, combinations and methods provided herein. For example, with reference to SEQ ID NO: 1, which sets forth the sequence of full length precursor PH20, which includes a signal sequence (residues 1-35), soluble forms include, but are not limited to, C-terminal truncated polypeptides of human PH20 set forth in SEQ ID NO: 1 having a C-terminal amino acid residue 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499 or 500 of the sequence of amino acids set forth in SEQ ID NO: 1, or polypeptides that exhibit at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more sequence identity thereto, when aligned with the unmodified sequence of the soluble PH20, have activity at neutral pH, and are soluble (secreted into the medium when expressed in a mammalian cell). Soluble forms of human PH20 generally include those that contain amino acids 36-464 set forth in SEQ ID NO: 1 and terminate at any of residues, 465-500, and optionally include a 1-3 amino acid deletion at the N-terminus (i.e. lack residues 36, 36-37, or 36-38 of SEQ ID NO: 1). For example, when expressed in mammalian cells, the 35 amino acid N-terminal signal sequence (residues 1-35 of SEQ ID NO: 1) is cleaved during processing, and a soluble form of the protein is secreted. Thus, the mature soluble polypeptides include those that contain amino acids 36 to 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, and up to and including 500 of SEQ ID NO: 1. Exemplary of soluble hyaluronidases are soluble human PH20 polypeptides that are 442, 443, 444, 445, 446 or 447 amino acids in length, such as those set forth above, and variants thereof that have, for example, at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity thereto and retains hyaluronidase activity. The generation of such soluble forms of recombinant human PH20 are described, for example, in U.S. Patent Nos. 7,767,429, 8,202,517, 8,431,380, 8,431,124, 8,450,470, 8,765,685, 8,772,246, 7,871,607, 7,846,431, 7,829,081, 8,105,586, 8,187,855, 8,257,699, 8,580,252, 9,677,061, and 9,677,062.

[00148] Generally soluble forms of PH20 are produced using protein expression systems that facilitate correct N-glycosylation to ensure the polypeptide retains activity, since glycosylation is important for the catalytic activity and stability of hyaluronidases. Such cells include, for example Chinese Hamster Ovary (CHO) cells (e.g., DG44 CHO cells).

[00149] The composition that is recombinantly produced from mammalian cells, such as CHO cells, has been referred to rHuPH20. It refers to the composition produced upon expression in a cell, such as a CHO cell, of nucleic acid encoding residues 36-482 of SEQ ID NO: 1, generally linked to the native (residues 1-35 of SEQ ID NO: 1) or a heterologous signal sequence. rHuPH20 is

produced by expression of a nucleic acid molecule, such as encoding amino acids 1-482 (set forth in SEQ ID NO: 1) or 36 to 482 with a heterologous signal sequence. Post-translational processing removes the 35 amino acid signal sequence, resulting in polypeptide or a mixture of polypeptides, including those set forth in SEQ ID NO: 2 (residues 36-482), SEQ ID NO: 3 (residues 36-477), SEQ ID NO: 4 (residues 36-478), SEQ ID NO: 5 (residues 36-479), SEQ ID NO: 6 (residues 36-480), and SEQ ID NO: 7 (residues 36-481). As produced in the culture medium there is heterogeneity at the C-terminus such that the product, designated rHuPH20, includes a mixture of species that can include any one or more of SEQ ID NOs: 3 and 44-49 in various abundance. Generally, the soluble hyaluronidase rHuPH20 is produced in cells that facilitate correct N-glycosylation to retain activity, such as CHO cells (e.g. DG44 CHO cells). Human soluble PH20 hyaluronidase requires glycosylation for activity. When produced recombinantly from a vector encoding residues 36-582, the most abundant species is the 446 amino acid polypeptides corresponding to residues 36-481 of SEQ ID NO: 1. The particular distribution of resulting polypeptides can depend upon the particular method of production. An exemplary method for production of high levels of PH20 is detailed, for example in U.S. Patent Nos. 8,187,855 and 8,343,487.

Glycosylation of Hyaluronidases

[00150] Glycosylation, including N- and O-linked glycosylation, of some hyaluronidases, including the soluble PH20 hyaluronidases, can be important for their catalytic activity and stability. For some hyaluronidases, removal of N-linked glycosylation can result in near complete inactivation of the hyaluronidase activity. For such hyaluronidases, the presence of N-linked glycans can be important for generating an active enzyme.

[00151] N-linked oligosaccharides fall into several primary types (oligomannose, complex, hybrid, sulfated), all of which have (Man)₃-GlcNAc-GlcNAc- cores attached via the amide nitrogen of Asn residues that fall within -Asn-Xaa-Thr/Ser-sequences (where Xaa is not Pro). Glycosylation at an -Asn-Xaa-Cys-site has been reported for coagulation protein C. In some instances, a hyaluronidase, such as a PH20 hyaluronidase, can contain N-glycosidic and O-glycosidic linkages. For example, PH20 has O-linked oligosaccharides as well as N-linked oligosaccharides. There are six potential N-linked glycosylation sites at N82, N166, N235, N254, N368, N393 of human PH20 exemplified in SEQ ID NO: 1.

Variants of PH20

[00152] As discussed above, variants of PH20 are known to those of skill in the art, or readily can be prepared in view of the skill and knowledge in the art. Variants include those with amino acid replacements, insertions, and deletions. Variants of the soluble PH20 polypeptides that have altered

properties, such as increased stability and/or activity, have been produced. U.S. Patent No. 9,447,401 and family members U.S. Patent Nos. 10,865,400, 11,041,149 and 11,066,656 describe and provide a structure/function map of human PH20 detailing the effects of amino acid replacements at every residue in the catalytic domain of PH20. These patents provide about 7000
5 examples in which the effects of replacing each amino acid with 15 other amino acids on activity and stability were identified and described. By virtue of those patents, and earlier publications/patents, describing virtually all variants of soluble PH20 polypeptides are known in the art. A skilled person readily can prepare soluble hyaluronidases and variants thereof and know the properties of the resulting hyaluronidase.

10 **[00153]** Other variants also are known to those of skill in the art, and can be used in the combinations, regimens, and methods described herein. For example, see International PCT Publication Nos. WO2020/022791 and WO2020/197230, which are incorporated by reference, and which describe modified PH20 polypeptides. These polypeptides, which include variants of the PH20 polypeptides that generally span residues 38-468, and include replacements, insertions, and
15 deletions. The variants include for example one or more amino acid residues changes S343E, I344N, M345T, M348K, K349E, L353A, L354I, N356E, and I361T (with reference to SEQ ID NO: 1), and others, including about 15 amino acid variations, and truncations at the N-terminus and C-terminus. Variants that contain such modifications and others are set forth in SEQ ID NOs: 60-115 of International PCT publication No. WO2020/022791. Exemplary of these polypeptides is the
20 polypeptide of SEQ ID NO: 99, therein, and reproduced herein as SEQ ID NO: 15. International PCT Publication No. WO2021/150079 provides variant PH20 polypeptides described as having increased stability relative to unmodified PH20, such as those in rHuPH20. These variant polypeptides have been shown to have PH20 activity and are described as having use for subcutaneous co-administration with other agents.

25 **[00154]** In one embodiment, the variant of PH20 is a variant of human PH20 or rHuPH20 selected from any one of SEQ ID NOs: 16-47.

[00155] In one embodiment, the hyaluronidase enzyme is a human hyaluronidase enzyme. Exemplary human hyaluronidase enzymes include HYAL1, HYAL2, HYAL3, HYAL4, HYAL5 (also known as SPAM1 or PH20), and HYAL6 (also known as HYALP1). In one embodiment, the
30 hyaluronidase enzyme is a recombinant hyaluronidase enzyme. In one embodiment, the hyaluronidase enzyme is a recombinant human hyaluronidase enzyme. In one embodiment, the hyaluronidase enzyme is a recombinant human hyaluronidase PH20 enzyme. Exemplary hyaluronidase enzymes that can be used in the disclosure can be found in the following patents and

patent applications which are incorporated by reference herein in their entirety: U.S. 2022/0289864 (Alteogen), U.S. 9,084,743 (Baxter), U.S. 9,993,529 (Halozyme), U.S. 8,795,654, U.S. 2009/0311237 (Greg Frost), U.S. 9,284,543 (Halozyme), U.S. 10,265,410 (Halozyme), U.S. 10,137,104 (Halozyme), U.S. 2013/0022592, U.S. 2019/0284263 (Greg Frost), U.S. 11,0653,09, 5 WO 2017/185383, U.S. 11,041,149 (Halozyme), U.S. 2010/0003238 (Greg Frost), U.S. 8,343,487 (Halozyme), U.S. 10,301,376 (Baxalta), U.S. 2013/0344048, U.S. 2021/0363270 (Alteogen), U.S. 2021/0155913 (Alteogen), WO 2021/150079 (Dassault Systems SolidWorks), and WO 2022/031093 (Toshiba TEC Kabushiki Kaisha).

[00156] In one embodiment, the hyaluronidase enzyme has an activity of between about 150 10 U/mL to about 1,000 kU/mL, about 150 U/mL to about 900 kU/mL, about 150 U/mL to about 800 kU/mL, about 150 U/mL to about 700 kU/mL, about 150 U/mL to about 600 kU/mL, about 150 U/mL to about 500 kU/mL, about 150 U/mL to about 400 kU/mL, about 150 U/mL to about 300 kU/mL, about 150 U/mL to about 200 kU/mL, about 500 U/mL to about 200 kU/mL, about 1 kU/mL to about 200 kU/mL, about 10 kU/mL to about 200 kU/mL, about 25 kU/mL to about 200 15 kU/mL, about 50 kU/mL to about 200 kU/mL, about 100 kU/mL to about 200 kU/mL, about 100 kU/mL to about 150 kU/mL, or about 120 kU/mL. In one embodiment, the hyaluronidase enzyme has an activity of about 10 kU/mL for a 5 mL formulation or about 5 kU/mL for a 10 mL formulation. In one embodiment, the hyaluronidase enzyme has a minimum activity of about 150 U/mL and a maximum activity of about 110,000 U/mL (110 kU/mL). In one embodiment, the 20 hyaluronidase enzyme is recombinant human hyaluronidase PH20 enzyme with an activity of about 120 kU/mL. In another embodiment, the hyaluronidase enzyme is recombinant human hyaluronidase PH20 enzyme with a minimum activity of about 150 U/mL and a maximum activity of about 110,000 U/mL.

[00157] In one embodiment, the concentration of hyaluronidase enzyme in the formulation is 25 between about 10 U/mL to about 50,000 U/mL, about 10 U/mL to about 45,000 U/mL, about 10 U/mL to about 40,000 U/mL, about 10 U/mL to about 35,000 U/mL, about 10 U/mL to about 30,000 U/mL, about 10 U/mL to about 25,000 U/mL, about 10 U/mL to about 20,000 U/mL, about 10 U/mL to about 15,000 U/mL, about 10 U/mL to about 10,000 U/mL, about 100 U/mL to about 9,000 U/mL, about 100 U/mL to about 8,000 U/mL, about 100 U/mL to about 7,000 U/mL, about 30 100 U/mL to about 6,000 U/mL, about 100 U/mL to about 5,000 U/mL, about 500 U/mL to about 5,000 U/mL, about 500 U/mL to about 4,000 U/mL, about 500 U/mL to about 3,000 U/mL, about 1,000 U/mL to about 3,000 U/mL, about 1,500 U/mL to about 3,000 U/mL, about 1,500 U/mL to about 2,500 U/mL, or about 2,000 U/mL. In one embodiment, the formulation comprises about

1,500 U/mL to about 10,000 U/mL of hyaluronidase enzyme. In one embodiment, the formulation comprises about 1,500 U/mL to about 10,000 U/mL of recombinant human hyaluronidase PH20 enzyme. In one embodiment, the formulation comprises about 2,000 U/mL of recombinant human hyaluronidase PH20 enzyme. In one embodiment, the formulation comprises about 5,000 U/mL of recombinant human hyaluronidase PH20 enzyme. In another embodiment, the formulation comprises at least 4,000 U/mL of recombinant human hyaluronidase PH20 enzyme. In another embodiment, the formulation comprises at least 7,500 U/mL of recombinant human hyaluronidase PH20 enzyme. In another embodiment, the formulation comprises at least 10,000 U/mL of recombinant human hyaluronidase PH20 enzyme. In one embodiment, the formulation comprises about 4,000 U/mL of recombinant human hyaluronidase PH20 enzyme.

[00158] In one embodiment, the formulation comprises a hyaluronidase enzyme that permits a high volume of the formulation to be injected into a subject in need thereof at a high flow rate. In one embodiment, the formulation comprises a hyaluronidase enzyme at a concentration and/or activity that permits a high volume of the formulation to be injected into a subject in need thereof at a high flow rate.

[00159] In one embodiment, the formulation comprises one or more pharmaceutically acceptable additives including, but not limited to, carriers, excipients, fillers, preservatives, stabilizers, and antioxidants. The pharmaceutically acceptable additive can be any pharmaceutically acceptable additive known to a person of skill in the art for an injectable formulation. In one embodiment, the formulation comprises histidine. In one embodiment, the formulation comprises sodium chloride. In one embodiment, the formulation comprises polysorbate. In one embodiment, the polysorbate comprises polysorbate 80. In one embodiment, the formulation comprises between about 0.001% to about 5%, about 0.001% to about 4.5%, about 0.001% to about 4.0%, about 0.001% to about 3.5%, about 0.001% to about 3.0%, about 0.001% to about 2.5%, about 0.001% to about 2.0%, about 0.001% to about 1.5%, about 0.001% to about 1.0%, about 0.001% to about 0.5%, about 0.005% to about 0.5%, about 0.005% to about 0.1%, about 0.005% to about 0.05%, about 0.01% to about 0.05%, or about 0.02% polysorbate 80. In one embodiment, the formulation comprises an antioxidant. In one embodiment, the antioxidant comprises methionine. In one embodiment, the formulation comprises between about 0.5 mM to about 50 mM, about 0.5 mM to about 45 mM, about 0.5 mM to about 40 mM, about 0.5 mM to about 35 mM, about 0.5 mM to about 30 mM, about 0.5 mM to about 25 mM, about 0.5 mM to about 20 mM, about 5 mM to about 20 mM, about 5 mM to about 15 mM, or about 10 mM antioxidant. In one embodiment, the formulation comprises about 10 mM methionine. In one embodiment, the formulation comprises a carrier protein.

[00160] In one embodiment, the formulation has a pH of between about 4.0 to about 8.0, about 4.2 to about 8.0, about 4.4 to about 7.8, about 4.6 to about 7.8, about 4.6 to about 7.6, about 4.8 to about 7.8, about 5.0 to about 7.8, about 5.2 to about 7.8, about 5.4 to about 7.6, about 5.6 to about 7.4, about 5.8 to about 7.2, about 6.0 to about 7.0, about 6.2 to about 6.8, about 6.4 to about 6.6, or about 6.5. In one embodiment, the formulation has a pH of between about 4.6 to about 7.6. In one embodiment, the formulation has a pH of between about 4.0 to about 8.0.

[00161] In one embodiment, the formulation comprises an active ingredient. The active ingredient can be any active ingredient to treat a disease or disorder in a subject in need thereof provided that the active ingredient can be administered via injection to the subject in need thereof.

In one embodiment, the active ingredient is selected from a small molecule, a peptide fragment, a biologic, a nanoparticle, an antibody, an antibody fragment, or a small molecule antiviral.

Methods of Treatment

[00162] In one aspect, the present disclosure provides a method of treating a disease or disorder in a subject in need thereof, the method comprising administering to the subject via injection a formulation comprising a hyaluronidase enzyme and a therapeutically effective amount of an active ingredient. The formulation is described elsewhere herein. In one embodiment, the hyaluronidase enzyme is a recombinant human hyaluronidase PH20 enzyme. In one embodiment, the subject is a mammal. In one embodiment, the subject is a human. In one embodiment, the formulation is administered to the subject via a subcutaneous injection. In one embodiment, the formulation is self-administered. In another embodiment, the formulation is administered to the subject by a healthcare professional. In yet another embodiment, the formulation is administered to the subject by a layperson, such as a caregiver. In one embodiment, the formulation is administered using an autoinfusion device. In one embodiment, the formulation is administered using an HVAI. In one embodiment, the formulation is administered from a prefilled syringe using an HVAI. In another embodiment, the formulation is administered manually using a manually triggered injection device. In another embodiment, the formulation is administered from an on-body device.

[00163] In one embodiment, the formulation is administered to the abdomen or thigh of the subject. In one embodiment, the formulation is subcutaneously administered to the abdomen or thigh of the subject.

[00164] In one embodiment, the amount of the disclosed formulation administered to the subject is dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compounds, and/or the discretion of the prescribing physician. In one embodiment, an effective dosage of the active ingredient in the disclosed formulation is in the

range of about 0.001 to about 100 mg per kg body weight per day, such as about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, such as about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, for example by dividing such larger doses into several small doses for administration throughout the day.

[00165] In one embodiment, the disclosed formulation is administered to the subject in multiple doses. Dosing may be about once, twice, three times, four times, five times, six times, or more than six times per day. Dosing may be about once a month, once every two weeks, once a week, or once every other day. In one embodiment, the disclosed formulation is administered about once per day to about 6 times per day. In one embodiment, the administration of the disclosed formulation continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

[00166] In one embodiment, an effective dosage of the active ingredient in the disclosed formulation is in the range of about 1 mg/mL to about 500 mg/mL, about 10 mg/mL to about 450 mg/mL, about 20 mg/mL to about 400 mg/mL, about 30 mg/mL to about 350 mg/mL, about 50 mg/mL to about 300 mg/mL, about 75 mg/mL to about 250 mg/mL, about 100 mg/mL to about 200 mg/mL, or about 150 mg/mL.

[00167] In one embodiment, the formulation is administered using an HVAI fitted with a needle. In one embodiment, the needle is a 20-gauge needle, a 21-gauge needle, a 22-gauge needle, a 23-gauge needle, a 24-gauge needle, a 25-gauge needle, a 26-gauge needle, a 27-gauge needle, a 28-gauge needle, a 29-gauge needle, a 30-gauge needle, or a 31-gauge needle. In one embodiment, the needle is a 27-gauge regular wall needle x ½", a 27-gauge regular wall x 5/8" needle, a 27-gauge regular wall x 3/4" needle, a 27-gauge regular wall x 1" needle, a 27-gauge thin wall x ½" needle, a 27-gauge thin wall x 5/8" needle, a 27-gauge thin wall x 3/4" needle, a 27-gauge thin wall x 1" needle, a 25-gauge regular wall x ½" needle, a 25-gauge regular wall x 5/8" needle, a 25-gauge regular wall x 3/4" needle, a 25-gauge regular wall x 1" needle, a 25-gauge thin wall x ½" needle, a 25-gauge thin wall x 5/8" needle, a 25-gauge thin wall x 3/4" needle, a 25-gauge thin wall x 1" needle, a 23-gauge regular wall x ½" needle, a 23-gauge regular wall x 5/8" needle, a 23-gauge regular wall x 3/4" needle, or a 23-gauge regular wall x 1" needle. In one embodiment, the needle is a 25-gauge thin wall x ½" needle. In one embodiment, the needle is a 25-gauge thin wall x 5/8" needle.

[00168] In one embodiment, a high volume of the formulation is administered to the subject. In one embodiment, a “high volume” is greater than 2.25 mL in a single administration. In one embodiment, 3 mL to 5 mL, 3 mL to 10 mL, 3 mL to 15 mL, 3 mL to 20 mL, 3 mL to 25 mL, 3 mL to 30 mL, 3 mL to 35 mL, 3 mL to 40 mL, 3 mL to 45 mL, 3 mL to 50 mL, 5 mL to 10 mL, 5 mL to 15 mL, 5 mL to 20 mL, 5 mL to 25 mL, 5 mL to 30 mL, 5 mL to 35 mL, 5 mL to 40 mL; 5 mL to 45 mL, 5 mL to 50 mL, 10 mL to 15 mL; 10 mL to 20 mL; 10 mL to 25 mL; 10 mL to 30 mL; 10 mL to 35 mL; 10 mL to 40 mL, or 10 mL to 50 mL are administered to the subject in a single administration. In one embodiment, about 3 mL to about 5 mL, about 3 mL to about 10 mL, about 3 mL to about 15 mL, about 3 mL to about 20 mL, about 3 mL to about 25 mL, about 3 mL to about 30 mL, about 3 mL to about 35 mL, about 3 mL to about 40 mL, about 3 mL to about 45 mL, about 3 mL to about 50 mL, about 5 mL to about 10 mL, about 5 mL to about 15 mL, about 5 mL to about 20 mL, about 5 mL to about 25 mL, about 5 mL to about 30 mL, about 5 mL to about 35 mL, about 5 mL to about 40 mL; about 5 mL to about 45 mL, about 5 mL to about 50 mL, about 10 mL to about 15 mL; about 10 mL to about 20 mL; about 10 mL to about 25 mL; about 10 mL to about 30 mL; about 10 mL to about 35 mL; about 10 mL to about 40 mL, or about 10 mL to about 50 mL are administered to the subject in a single administration. In one embodiment, at least about 3 mL, at least about 3.5 mL, at least about 4 mL, at least about 4.5 mL, at least about 5.5 mL, at least about 6 mL, at least about 6.5 mL, at least about 7 mL, at least about 7.5 mL, at least about 8 mL, at least about 8.5 mL, at least about 9 mL, at least about 9.5 mL, at least about 10 mL, at least about 10.5 mL, at least about 11 mL, at least about 11.5 mL, at least about 12 mL, at least about 12.5 mL, at least about 13 mL, at least about 13.5 mL, at least about 14 mL, at least about 14.5 mL, at least about 15 mL, at least about 15.5 mL, at least about 16 mL, at least about 16.5 mL, at least about 17 mL, at least about 17.5 mL, at least about 18 mL, at least about 18.5 mL, at least about 19 mL, at least about 19.5 mL, at least about 20 mL, at least about 25 mL, at least about 30 mL, at least about 35 mL, at least about 40 mL, at least about 45 mL, or at least about 50 mL are administered to the subject in a single administration. In one embodiment, at least 3 mL, at least 3.5 mL, at least 4 mL, at least 4.5 mL, at least 5.5 mL, at least 6 mL, at least 6.5 mL, at least 7 mL, at least 7.5 mL, at least 8 mL, at least 8.5 mL, at least 9 mL, at least 9.5 mL, at least 10 mL, at least 10.5 mL, at least 11 mL, at least 11.5 mL, at least 12 mL, at least 12.5 mL, at least 13 mL, at least 13.5 mL, at least 14 mL, at least 14.5 mL, at least 15 mL, at least 15.5 mL, at least 16 mL, at least 16.5 mL, at least 17 mL, at least 17.5 mL, at least 18 mL, at least 18.5 mL, at least 19 mL, at least 19.5 mL, at least 20 mL, at least 25 mL, at least 30 mL, at least 35 mL, at least 40 mL, at least 45 mL, or at least 50 mL are administered to the subject in a single administration.

[00169] In one embodiment, greater than about 2.25 mL, about 2.5 mL, about 3.0 mL, about 3.5 mL, about 4.0 mL, about 4.5 mL, about 5.0 mL, about 5.5 mL, about 6.0 mL, about 6.5 mL, about 7.0 mL, about 7.5 mL, about 8.0 mL, about 8.5 mL, about 9.5 mL, about 10 mL, about 12 mL, about 14 mL, about 16 mL, about 18 mL, or about 20 mL of the formulation is administered to the subject in a single administration. In one embodiment, greater than about 2.5 mL, about 3.0 mL, about 3.5 mL, about 4.0 mL, about 4.5 mL, about 5.0 mL, about 5.5 mL, about 6.0 mL, about 6.5 mL, about 7.0 mL, about 7.5 mL, about 8.0 mL, about 8.5 mL, about 9.5 mL, about 10 mL, about 12 mL, about 14 mL, about 16 mL, about 18 mL, about 20 mL, about 22 mL, about 24 mL, about 26 mL, about 28 mL, or about 30 mL of the formulation is administered to the subject in about 10 seconds, about 12 seconds, about 16 seconds, about 18 seconds, about 20 seconds, about 22 seconds, about 24 seconds, about 26 seconds, about 28 seconds, about 30 seconds, about 32 seconds, about 34 seconds, about 36 seconds, about 38 seconds, about 40 seconds, about 42 seconds, about 44 seconds, about 46 seconds, about 48 seconds, about 50 seconds, about 52 seconds, about 54 seconds, about 56 seconds, about 58 seconds, about 60 seconds, about 65 seconds, about 70 seconds, about 75 seconds, about 80 seconds, about 85 seconds, about 90 seconds, about 95 seconds, about 100 seconds, about 105 seconds, about 110 seconds, about 115 seconds, about 120 seconds, about 130 seconds, about 140 seconds, about 150 seconds, about 160 seconds, about 170 seconds, about 180 seconds, about 190 seconds, about 200 seconds, about 210 seconds, about 220 seconds, about 230 seconds, about 240 seconds, about 250 seconds, about 260 seconds, about 270 seconds, about 280 seconds, about 290 seconds, about 300 seconds, about 310 seconds, about 320 seconds, about 330 seconds, about 340 seconds, about 350 seconds, or about 360 seconds.

[00170] In one embodiment, about 5 mL of the formulation can be administered to the subject in about 5 seconds, about 10 seconds, about 15 seconds, about 20 seconds, about 25 seconds, about 30 seconds, about 35 seconds, about 40 seconds, about 45 seconds, about 50 seconds, about 55 seconds, or about 60 seconds.

[00171] In one embodiment, about 10 mL of the formulation can be administered to the subject in about 30 seconds, about 35 seconds, about 40 seconds, about 45 seconds, about 50 seconds, about 55 seconds, about 60 seconds, about 65 seconds, about 70 seconds, about 75 seconds, about 80 seconds, about 85 seconds, about 90 seconds, about 95 seconds, about 100 seconds, about 105 seconds, about 110 seconds, about 115 seconds, or about 120 seconds.

[00172] In one embodiment, about 15 mL of the formulation can be administered to the subject in about 60 seconds, about 70 seconds, about 80 seconds, about 90 seconds, about 100 seconds, about 110 seconds, about 120 seconds, about 130 seconds, about 140 seconds, about 150 seconds, about

160 seconds, about 170 seconds, about 180 seconds, about 190 seconds, about 200 seconds, about 210 seconds, about 220 seconds, about 230 seconds, about 240 seconds, about 250 seconds, about 260 seconds, about 270 seconds, about 280 seconds, about 290 seconds, or about 300 seconds.

[00173] In one embodiment, about 20 mL of the formulation can be administered to the subject in about 60 seconds, about 70 seconds, about 80 seconds, about 90 seconds, about 100 seconds, about 110 seconds, about 120 seconds, about 130 seconds, about 140 seconds, about 150 seconds, about 160 seconds, about 170 seconds, about 180 seconds, about 190 seconds, about 200 seconds, about 210 seconds, about 220 seconds, about 230 seconds, about 240 seconds, about 250 seconds, about 260 seconds, about 270 seconds, about 280 seconds, about 290 seconds, or about 300 seconds.

[00174] In some embodiments, the speed at which a high volume of the formulation can be administered to the subject depends on the gauge of the needle used to inject the formulation. In one embodiment, the formulation is administered to the subject using an autoinfusion device and a 23-gauge needle. In one embodiment, about 5 mL of the formulation can be administered to the subject in between about 5 seconds to about 60 seconds, about 10 seconds to about 55 seconds, about 15 seconds to about 50 seconds, about 20 seconds to about 45 seconds, about 25 seconds to about 40 seconds, or about 30 seconds to about 35 seconds using an autoinfusion device and a 23-gauge needle. In one embodiment, about 10 mL of the formulation can be administered to the subject in between about 30 seconds to about 120 seconds, about 35 seconds to about 115 seconds, about 40 seconds to about 110 seconds, about 45 seconds to about 105 seconds, about 50 seconds to about 100 seconds, about 55 seconds to about 95 seconds, about 60 seconds to 90 seconds, about 65 seconds to about 85 seconds, about 70 seconds to about 80 seconds, or about 85 seconds using an autoinfusion device and a 23-gauge needle. In one embodiment, about 15 mL of the formulation can be administered to the subject in between about 60 seconds to about 300 seconds, about 70 seconds to about 290 seconds, about 80 seconds to about 280 seconds, about 90 seconds to about 270 seconds, about 100 seconds to about 260 seconds, about 110 seconds to about 250 seconds, about 120 seconds to about 240 seconds, about 130 seconds to about 230 seconds, about 140 seconds to about 220 seconds, about 150 seconds to about 210 seconds, about 160 seconds to about 200 seconds, about 170 seconds to about 190 seconds, or about 180 seconds using an autoinfusion device and a 23-gauge needle. In one embodiment, about 20 mL of the formulation can be administered to the subject in between about 60 seconds to about 300 seconds, about 70 seconds to about 290 seconds, about 80 seconds to about 280 seconds, about 90 seconds to about 270 seconds, about 100 seconds to about 260 seconds, about 110 seconds to about 250 seconds, about 120 seconds to about 240 seconds, about 130 seconds to about 230 seconds, about 140 seconds to about

220 seconds, about 150 seconds to about 210 seconds, about 160 seconds to about 200 seconds, about 170 seconds to about 190 seconds, or about 180 seconds using an autoinfusion device and a 23-gauge needle.

[00175] In another embodiment, the formulation is administered to the subject using an autoinfusion device and a 25-gauge needle. In one embodiment, about 5 mL of the formulation can be administered to the subject in between about 5 seconds to about 60 seconds, about 10 seconds to about 55 seconds, about 15 seconds to about 50 seconds, about 20 seconds to about 45 seconds, about 25 seconds to about 40 seconds, or about 30 seconds to about 35 seconds using an autoinfusion device and a 25-gauge needle. In one embodiment, about 10 mL of the formulation can be administered to the subject in between about 30 seconds to about 120 seconds, about 35 seconds to about 115 seconds, about 40 seconds to about 110 seconds, about 45 seconds to about 105 seconds, about 50 seconds to about 100 seconds, about 55 seconds to about 95 seconds, about 60 seconds to about 90 seconds, about 65 seconds to about 85 seconds, about 70 seconds to about 80 seconds, or about 85 seconds using an autoinfusion device and a 25-gauge needle. In one embodiment, about 15 mL of the formulation can be administered to the subject in between about 60 seconds to about 300 seconds, about 70 seconds to about 290 seconds, about 80 seconds to about 280 seconds, about 90 seconds to about 270 seconds, about 100 seconds to about 260 seconds, about 110 seconds to about 250 seconds, about 120 seconds to about 240 seconds, about 130 seconds to about 230 seconds, about 140 seconds to about 220 seconds, about 150 seconds to about 210 seconds, about 160 seconds to about 200 seconds, about 170 seconds to about 190 seconds, or about 180 seconds using an autoinfusion device and a 25-gauge needle. In one embodiment, about 20 mL of the formulation can be administered to the subject in between about 60 seconds to about 300 seconds, about 70 seconds to about 290 seconds, about 80 seconds to about 280 seconds, about 90 seconds to about 270 seconds, about 100 seconds to about 260 seconds, about 110 seconds to about 250 seconds, about 120 seconds to about 240 seconds, about 130 seconds to about 230 seconds, about 140 seconds to about 220 seconds, about 150 seconds to about 210 seconds, about 160 seconds to about 200 seconds, about 170 seconds to about 190 seconds, or about 180 seconds using an autoinfusion device and a 25-gauge needle.

[00176] In another embodiment, the formulation is administered to the subject using an autoinfusion device and a 27-gauge needle. In one embodiment, about 5 mL of the formulation can be administered to the subject in between about 5 seconds to about 60 seconds, about 10 seconds to about 55 seconds, about 15 seconds to about 50 seconds, about 20 seconds to about 45 seconds, about 25 seconds to about 40 seconds, or about 30 seconds to about 35 seconds using an

autoinfusion device and a 27-gauge needle. In one embodiment, about 10 mL of the formulation can be administered to the subject in between about 30 seconds to about 120 seconds, about 35 seconds to about 115 seconds, about 40 seconds to about 110 seconds, about 45 seconds to about 105 seconds, about 50 seconds to about 100 seconds, about 55 seconds to about 95 seconds, about 60 seconds to 90 seconds, about 65 seconds to about 85 seconds, about 70 seconds to about 80 seconds, or about 85 seconds using an autoinfusion device and a 27-gauge needle. In one embodiment, about 15 mL of the formulation can be administered to the subject in between about 60 seconds to about 300 seconds, about 70 seconds to about 290 seconds, about 80 seconds to about 280 seconds, about 90 seconds to about 270 seconds, about 100 seconds to about 260 seconds, about 110 seconds to about 250 seconds, about 120 seconds to about 240 seconds, about 130 seconds to about 230 seconds, about 140 seconds to about 220 seconds, about 150 seconds to about 210 seconds, about 160 seconds to about 200 seconds, about 170 seconds to about 190 seconds, or about 180 seconds using an autoinfusion device and a 27-gauge needle. In one embodiment, about 20 mL of the formulation can be administered to the subject in between about 60 seconds to about 300 seconds, about 70 seconds to about 290 seconds, about 80 seconds to about 280 seconds, about 90 seconds to about 270 seconds, about 100 seconds to about 260 seconds, about 110 seconds to about 250 seconds, about 120 seconds to about 240 seconds, about 130 seconds to about 230 seconds, about 140 seconds to about 220 seconds, about 150 seconds to about 210 seconds, about 160 seconds to about 200 seconds, about 170 seconds to about 190 seconds, or about 180 seconds using an autoinfusion device and a 27-gauge needle.

[00177] In one embodiment, using a 23-gauge needle with an HVAI and the disclosed formulation provides about 40%, about 42%, about 44%, about 46%, about 48%, about 50%, about 52%, about 54%, about 56%, about 58%, or about 60% faster injection times than using a 25-gauge needle with an HVAI.

[00178] In one embodiment, the device has a variable delivery rate that can deliver the formulation faster at the start of the injection and slower at the completion of the injection. In another embodiment, the device has a variable delivery rate that delivers the formulation slower at the initiation of the injection and faster at the completion of the injection.

[00179] In one embodiment, the viscosity and volume of the disclosed formulation affect the time needed to inject the formulation into a subject. However, the full volume of the formulation can be delivered from an HVAI at a rate of approximately 5-20 mL/min. For example, this would provide target delivery rate ranges of 30-120 seconds for a 10 mL dose volume. In one embodiment, delivers the full deliverable volume of the formulation at a rate of: 4 mL/min, 5 mL/min, 6 mL/min,

7 mL/min, 8 mL/min, 9 mL/min, 10 mL/min, 11 mL/min, 12 mL/min, 13 mL/min, 14 mL/min, 15 mL/min, 16 mL/min, 17 mL/min, 18 mL/min, 19 mL/min, 20 mL/min, 21 mL/min.

[00180] In one embodiment, the disclosed formulation is administered to the subject at a rate of about 4.0 mL/min, about 4.1 mL/min, about 4.2 mL/min, about 4.3 mL/min, about 4.4 mL/min, about 4.5 mL/min, about 4.6 mL/min, about 4.7 mL/min, about 4.8 mL/min, about 4.9 mL/min, about 5.0 mL/min, about 5.1 mL/min, about 5.2 mL/min, about 5.3 mL/min, about 5.4 mL/min, about 5.5 mL/min, about 5.6 mL/min, about 5.7 mL/min, about 5.8 mL/min, about 5.9 mL/min, 6.0 mL/min, about 6.1 mL/min, about 6.2 mL/min, about 6.3 mL/min, about 6.4 mL/min, about 6.5 mL/min, about 6.6 mL/min, about 6.7 mL/min, about 6.8 mL/min, about 6.9 mL/min, about 7.0 mL/min, about 7.1 mL/min, about 7.2 mL/min, about 7.3 mL/min, about 7.4 mL/min, about 7.5 mL/min, about 7.6 mL/min, about 7.7 mL/min, about 7.8 mL/min, about 7.9 mL/min, 8.0 mL/min, about 8.1 mL/min, about 8.2 mL/min, about 8.3 mL/min, about 8.4 mL/min, about 8.5 mL/min, about 8.6 mL/min, about 8.7 mL/min, about 8.8 mL/min, about 8.9 mL/min, about 9.0 mL/min, about 9.1 mL/min, about 9.2 mL/min, about 9.3 mL/min, about 9.4 mL/min, about 9.5 mL/min, about 9.6 mL/min, about 9.7 mL/min, about 9.8 mL/min, about 9.9 mL/min, 10.0 mL/min, about 10.1 mL/min, about 10.2 mL/min, about 10.3 mL/min, about 10.4 mL/min, about 10.5 mL/min, about 10.6 mL/min, about 10.7 mL/min, about 10.8 mL/min, about 10.9 mL/min, about 11.0 mL/min, about 11.1 mL/min, about 11.2 mL/min, about 11.3 mL/min, about 11.4 mL/min, about 11.5 mL/min, about 11.6 mL/min, about 11.7 mL/min, about 11.8 mL/min, about 11.9 mL/min, 12.0 mL/min, about 12.1 mL/min, about 12.2 mL/min, about 12.3 mL/min, about 12.4 mL/min, about 12.5 mL/min, about 12.6 mL/min, about 12.7 mL/min, about 12.8 mL/min, about 12.9 mL/min, about 13.0 mL/min, about 13.1 mL/min, about 13.2 mL/min, about 13.3 mL/min, about 13.4 mL/min, about 13.5 mL/min, about 13.6 mL/min, about 13.7 mL/min, about 13.8 mL/min, about 13.9 mL/min, 14.0 mL/min, about 14.1 mL/min, about 14.2 mL/min, about 14.3 mL/min, about 14.4 mL/min, about 14.5 mL/min, about 14.6 mL/min, about 14.7 mL/min, about 14.8 mL/min, about 14.9 mL/min, about 15.0 mL/min, about 15.1 mL/min, about 15.2 mL/min, about 15.3 mL/min, about 15.4 mL/min, about 15.5 mL/min, about 15.6 mL/min, about 15.7 mL/min, about 15.8 mL/min, about 15.9 mL/min, 16.0 mL/min, about 16.1 mL/min, about 16.2 mL/min, about 16.3 mL/min, about 16.4 mL/min, about 16.5 mL/min, about 16.6 mL/min, about 16.7 mL/min, about 16.8 mL/min, about 16.9 mL/min, about 17.0 mL/min, about 17.1 mL/min, about 17.2 mL/min, about 17.3 mL/min, about 17.4 mL/min, about 17.5 mL/min, about 17.6 mL/min, about 17.7 mL/min, about 17.8 mL/min, about 17.9 mL/min, 18.0 mL/min, about 18.1 mL/min, about 18.2 mL/min, about 18.3 mL/min, about 18.4 mL/min, about 18.5 mL/min, about 18.6 mL/min, about

18.7 mL/min, about 18.8 mL/min, about 18.9 mL/min, about 19.0 mL/min, about 19.1 mL/min, about 19.2 mL/min, about 19.3 mL/min, about 19.4 mL/min, about 19.5 mL/min, about 19.6 mL/min, about 19.7 mL/min, about 19.8 mL/min, about 19.9 mL/min, 20.0 mL/min, about 20.1 mL/min, about 20.2 mL/min, about 20.3 mL/min, about 20.4 mL/min, about 20.5 mL/min, about 20.6 mL/min, about 20.7 mL/min, about 20.8 mL/min, about 20.9 mL/min, or about 21.0 mL/min.

[00181] In one embodiment, about 3 mL to about 50 mL of the formulation is administered to a subject via subcutaneous administration, wherein the subcutaneous administration occurs at a rate of about 4 mL/min to about 21 mL/min. In one embodiment, about 5 mL to about 20 mL of the formulation is administered to the subject via subcutaneous administration, wherein the subcutaneous administration occurs at a rate of about 4 mL/min to about 21 mL/min. In one embodiment, the formulation is administered subcutaneously to the subject from a prefilled syringe. In one embodiment, the prefilled syringe comprises a needle having a gauge of about 20 to about 31. In one embodiment, the prefilled syringe comprises a needle having a gauge of about 23, about 25, or about 27. In one embodiment, the formulation is administered to the subject from the prefilled syringe using an HVAI described elsewhere herein.

[00182] In one embodiment, about 5 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min. In one embodiment, about 5 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min from a prefilled syringe using an HVAI. In one embodiment, about 5 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min. In one embodiment, about 5 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min from a prefilled syringe using an HVAI. In one embodiment, about 10 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min. In one embodiment, about 10 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min from a prefilled syringe using an HVAI. In one embodiment, about 10.5 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min. In one embodiment, about 10.5 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min from a prefilled syringe using an HVAI. In one embodiment, about 10.5 mL of the formulation is administered to the subject at a rate of at least 4 mL/min. In one embodiment, about 10.5 mL of the formulation is administered to the subject at a rate of at least 4 mL/min from a prefilled syringe using an HVAI.

[00183] In one embodiment, about 5 mL, about 5.5 mL, about 6 mL, about 7 mL, about 8 mL, about 9 mL, about 10 mL, about 10.5 mL, about 11 mL, about 12 mL, about 13 mL, about 14 mL,

about 15 mL, about 16 mL, about 17 mL, about 18 mL, about 19 mL, or about 20 mL of the disclosed formulation can be administered to a subject in 6 minutes or less using a needle having a gauge of 20 to 31. In one embodiment, about 5 mL, about 5.5 mL, about 6 mL, about 7 mL, about 8 mL, about 9 mL, about 10 mL, about 10.5 mL, about 11 mL, about 12 mL, about 13 mL, about 14 mL, about 15 mL, about 16 mL, about 17 mL, about 18 mL, about 19 mL, or about 20 mL of the disclosed formulation can be administered to a subject in 6 minutes or less using a 27-gauge needle. In one embodiment, about 10 mL of the disclosed formulation can be administered to a subject in 5 minutes or less using a 27-gauge needle. In one embodiment, the needle is connected to a syringe wherein the syringe is prefilled with the disclosed formulation. In one embodiment, the prefilled syringe is contained in an autoinfusion device. In one embodiment, the prefilled syringe is contained in the HVAI described elsewhere herein.

[00184] In one embodiment, about 3 mL to about 50 mL of the formulation disclosed herein is administered to the subject with a starting delivery force of about 1 lbf to about 200 lbf, about 1 lbf to about 190 lbf, about 1 lbf to about 180 lbf, about 1 lbf to about 170 lbf, about 1 lbf to about 160 lbf, about 1 lbf to about 150 lbf, about 1 lbf to about 140 lbf, about 1 lbf to about 130 lbf, about 1 lbf to about 120 lbf, about 1 lbf to about 110 lbf, 1 lbf to about 100 lbf, 1 lbf to about 100 lbf, about 1 lbf to about 90 lbf, about 1 lbf to about 80 lbf, about 1 lbf to about 70 lbf, about 1 lbf to about 60 lbf, about 1 lbf to about 50 lbf, about 1 lbf to about 40 lbf, about 1 lbf to about 30 lbf, or about 25 lbf from a prefilled syringe using an HVAI. In one embodiment, about 3 mL to about 50 mL of the formulation disclosed herein is administered to the subject with a starting delivery force of about 1 lbf, about 2 lbf, about 3 lbf, about 4 lbf, 5 lbf, about 6 lbf, about 7 lbf, about 8 lbf, about 9 lbf, about 10 lbf, about 11 lbf, about 12 lbf, about 13 lbf, about 14 lbf, about 15 lbf, about 16 lbf, about 17 lbf, about 18 lbf, about 19 lbf, about 20 lbf, about 21 lbf, about 22 lbf, about 23 lbf, about 24 lbf, about 25 lbf, about 26 lbf, about 27 lbf, about 28 lbf, about 29 lbf, about 30 lbf, about 31 lbf, about 32 lbf, about 33 lbf, about 34 lbf, about 35 lbf, about 36 lbf, about 37 lbf, about 38 lbf, about 39 lbf, about 40 lbf, about 41 lbf, about 42 lbf, about 43 lbf, about 44 lbf, about 45 lbf, about 46 lbf, about 47 lbf, about 48 lbf, about 49 lbf, about 50 lbf, about 51 lbf, about 52 lbf, about 53 lbf, about 54 lbf, about 55 lbf, about 56 lbf, about 57 lbf, about 58 lbf, about 59 lbf, about 60 lbf, about 61 lbf, about 62 lbf, about 63 lbf, about 64 lbf, about 65 lbf, about 66 lbf, about 67 lbf, about 68 lbf, about 69 lbf, about 70 lbf, about 71 lbf, about 72 lbf, about 73 lbf, about 74 lbf, about 75 lbf, about 76 lbf, about 77 lbf, about 78 lbf, about 79 lbf, about 80 lbf, about 81 lbf, about 82 lbf, about 83 lbf, about 84 lbf, about 85 lbf, about 86 lbf, about 87 lbf, about 88 lbf, about 89 lbf, about 90 lbf, about 91 lbf, about 92 lbf, about 93 lbf, about 94 lbf, about 95 lbf, about 96 lbf, about 97 lbf, about 98 lbf, about 99 lbf, about

100 lbf, about 101 lbf, about 102 lbf, about 103 lbf, about 104 lbf, about 105 lbf, about 106 lbf,
about 107 lbf, about 108 lbf, about 109 lbf, about 110 lbf, about 111 lbf, about 112 lbf, about 113
lbf, about 114 lbf, about 115 lbf, about 116 lbf, about 117 lbf, about 118 lbf, about 119 lbf, about
120 lbf, about 121 lbf, about 122 lbf, about 123 lbf, about 124 lbf, about 125 lbf, about 126 lbf,
5 about 127 lbf, about 128 lbf, about 129 lbf, about 130 lbf, about 131 lbf, about 132 lbf, about 133
lbf, about 134 lbf, about 135 lbf, about 136 lbf, about 137 lbf, about 138 lbf, about 139 lbf, about
140 lbf, about 141 lbf, about 142 lbf, about 143 lbf, about 144 lbf, about 145 lbf, about 146 lbf,
about 147 lbf, about 148 lbf, about 149 lbf, about 150 lbf, about 151 lbf, about 152 lbf, about 153
lbf, about 154 lbf, about 155 lbf, about 156 lbf, about 157 lbf, about 158 lbf, about 159 lbf, about
10 160 lbf, about 161 lbf, about 162 lbf, about 163 lbf, about 164 lbf, about 165 lbf, about 166 lbf,
about 167 lbf, about 168 lbf, about 169 lbf, about 170 lbf, about 171 lbf, about 172 lbf, about 173
lbf, about 174 lbf, about 175 lbf, about 176 lbf, about 177 lbf, about 178 lbf, about 179 lbf, about
180 lbf, about 181 lbf, about 182 lbf, about 183 lbf, about 184 lbf, about 185 lbf, about 186 lbf,
about 187 lbf, about 188 lbf, about 189 lbf, about 190 lbf, about 191 lbf, about 192 lbf, about 193
15 lbf, about 194 lbf, about 195 lbf, about 196 lbf, about 197 lbf, about 198 lbf, about 199 lbf, or about
200 lbf from a prefilled syringe using an HVAI.

[00185] In one embodiment, the starting delivery force refers to the starting delivery force exerted
on the subject's tissue upon administration of the formulation from a prefilled syringe using an
HVAI. In one embodiment, the starting delivery force refers to the starting delivery force exerted on
20 the syringe stopper of the prefilled syringe in an HVAI as the disclosed formulation is delivered to a
subject. In one embodiment, the starting delivery force refers to the starting delivery force exerted
on the formulation upon administration of the formulation from a prefilled syringe using an HVAI.
In one embodiment, the starting delivery force refers to the starting delivery force exerted on the
prefilled syringe upon administration of the formulation from a prefilled syringe using an HVAI. In
25 one embodiment, the starting delivery force refers to the starting delivery force generated by the
HVAI device upon administration of the formulation from a prefilled syringe using an HVAI.

[00186] In one embodiment, about 3 mL to about 50 mL of the formulation disclosed herein is
administered to the subject with an ending delivery force of about 1 lbf to about 200 lbf, about 1 lbf
to about 190 lbf, about 1 lbf to about 180 lbf, about 1 lbf to about 170 lbf, about 1 lbf to about 160
30 lbf, about 1 lbf to about 150 lbf, about 1 lbf to about 140 lbf, about 1 lbf to about 130 lbf, about 1 lbf
to about 120 lbf, about 1 lbf to about 110 lbf, 1 lbf to about 100 lbf, 1 lbf to about 100 lbf, about 1
lbf to about 90 lbf, about 1 lbf to about 80 lbf, about 1 lbf to about 70 lbf, about 1 lbf to about 60 lbf,
about 1 lbf to about 50 lbf, about 1 lbf to about 40 lbf, about 1 lbf to about 30 lbf, about 5 lbf to

about 30 lbf, or about 5 lbf to about 20 lbf from a prefilled syringe using an HVAI. In one embodiment, about 3 mL to about 50 mL of the formulation disclosed herein is administered to the subject with an ending delivery force of about 1 lbf, about 2 lbf, about 3 lbf, about 4 lbf, 5 lbf, about 6 lbf, about 7 lbf, about 8 lbf, about 9 lbf, about 10 lbf, about 11 lbf, about 12 lbf, about 13 lbf, about 14 lbf, about 15 lbf, about 16 lbf, about 17 lbf, about 18 lbf, about 19 lbf, about 20 lbf, about 21 lbf, about 22 lbf, about 23 lbf, about 24 lbf, about 25 lbf, about 26 lbf, about 27 lbf, about 28 lbf, about 29 lbf, about 30 lbf, about 31 lbf, about 32 lbf, about 33 lbf, about 34 lbf, about 35 lbf, about 36 lbf, about 37 lbf, about 38 lbf, about 39 lbf, about 40 lbf, about 41 lbf, about 42 lbf, about 43 lbf, about 44 lbf, about 45 lbf, about 46 lbf, about 47 lbf, about 48 lbf, about 49 lbf, about 50 lbf, about 51 lbf, about 52 lbf, about 53 lbf, about 54 lbf, about 55 lbf, about 56 lbf, about 57 lbf, about 58 lbf, about 59 lbf, about 60 lbf, about 61 lbf, about 62 lbf, about 63 lbf, about 64 lbf, about 65 lbf, about 66 lbf, about 67 lbf, about 68 lbf, about 69 lbf, about 70 lbf, about 71 lbf, about 72 lbf, about 73 lbf, about 74 lbf, about 75 lbf, about 76 lbf, about 77 lbf, about 78 lbf, about 79 lbf, about 80 lbf, about 81 lbf, about 82 lbf, about 83 lbf, about 84 lbf, about 85 lbf, about 86 lbf, about 87 lbf, about 88 lbf, about 89 lbf, about 90 lbf, about 91 lbf, about 92 lbf, about 93 lbf, about 94 lbf, about 95 lbf, about 96 lbf, about 97 lbf, about 98 lbf, about 99 lbf, about 100 lbf, about 101 lbf, about 102 lbf, about 103 lbf, about 104 lbf, about 105 lbf, about 106 lbf, about 107 lbf, about 108 lbf, about 109 lbf, about 110 lbf, about 111 lbf, about 112 lbf, about 113 lbf, about 114 lbf, about 115 lbf, about 116 lbf, about 117 lbf, about 118 lbf, about 119 lbf, about 120 lbf, about 121 lbf, about 122 lbf, about 123 lbf, about 124 lbf, about 125 lbf, about 126 lbf, about 127 lbf, about 128 lbf, about 129 lbf, about 130 lbf, about 131 lbf, about 132 lbf, about 133 lbf, about 134 lbf, about 135 lbf, about 136 lbf, about 137 lbf, about 138 lbf, about 139 lbf, about 140 lbf, about 141 lbf, about 142 lbf, about 143 lbf, about 144 lbf, about 145 lbf, about 146 lbf, about 147 lbf, about 148 lbf, about 149 lbf, about 150 lbf, about 151 lbf, about 152 lbf, about 153 lbf, about 154 lbf, about 155 lbf, about 156 lbf, about 157 lbf, about 158 lbf, about 159 lbf, about 160 lbf, about 161 lbf, about 162 lbf, about 163 lbf, about 164 lbf, about 165 lbf, about 166 lbf, about 167 lbf, about 168 lbf, about 169 lbf, about 170 lbf, about 171 lbf, about 172 lbf, about 173 lbf, about 174 lbf, about 175 lbf, about 176 lbf, about 177 lbf, about 178 lbf, about 179 lbf, about 180 lbf, about 181 lbf, about 182 lbf, about 183 lbf, about 184 lbf, about 185 lbf, about 186 lbf, about 187 lbf, about 188 lbf, about 189 lbf, about 190 lbf, about 191 lbf, about 192 lbf, about 193 lbf, about 194 lbf, about 195 lbf, about 196 lbf, about 197 lbf, about 198 lbf, about 199 lbf, or about 200 lbf from a prefilled syringe using an HVAI.

[00187] In one embodiment, the ending delivery force refers to the ending delivery force exerted on the subject's tissue upon administration of the formulation from a prefilled syringe using an

HVAI. In one embodiment, the ending delivery force refers to the ending delivery force exerted the syringe stopper of the prefilled syringe in an HVAI as the disclosed formulation is delivered to a subject. In one embodiment, the ending delivery force refers to the ending delivery force exerted on the formulation upon administration of the formulation from a prefilled syringe using an HVAI. In one embodiment, the ending delivery force refers to the ending delivery force exerted on the prefilled syringe upon administration of the formulation from a prefilled syringe using an HVAI. In one embodiment, the ending delivery force refers to the ending delivery force generated by the HVAI device upon administration of the formulation from a prefilled syringe using an HVAI.

[00188] In one embodiment, about 3 mL to about 50 mL of the formulation disclosed herein is administered to the subject with a starting pressure of about 10 psi to about 500 psi, about 10 psi to about 475 psi, about 10 psi to about 450 psi, about 10 psi to about 400 psi, about 10 psi to about 375 psi, about 10 psi to about 350 psi, about 10 psi to about 325 psi, about 10 psi to about 300 psi, about 20 psi to about 300 psi, about 20 psi to about 275 psi, about 30 psi to about 275 psi, about 30 psi to about 250 psi, about 40 psi to about 250 psi, about 40 psi to about 225 psi, about 50 psi to about 225 psi, or about 50 psi to about 200 psi from a prefilled syringe using an HVAI. In one embodiment, about 3 mL to about 50 mL of the formulation disclosed herein is administered to the subject with a starting pressure of about 50 psi, about 55 psi, about 60 psi, about 65 psi, about 70 psi, about 75 psi, about 80 psi, about 85 psi, about 90 psi, about 95 psi, about 100 psi, about 105 psi, about 110 psi, about 115 psi, about 120 psi, about 125 psi, about 130 psi, about 135 psi, about 140 psi, about 145 psi, about 150 psi, about 155 psi, about 160 psi, about 165 psi, about 170 psi, about 175 psi, about 180 psi, about 185 psi, about 190 psi, about 195 psi, or about 200 psi from a prefilled syringe using an HVAI. In one embodiment, about 3 mL to about 50 mL of the formulation disclosed herein is administered to the subject with a starting pressure of about 50 psi, about 51 psi, about 52 psi, about 53 psi, about 54 psi, about 55 psi, about 56 psi, about 57 psi, about 58 psi, about 59 psi, about 60 psi, about 61 psi, about 62 psi, about 63 psi, about 64 psi, about 65 psi, about 66 psi, about 67 psi, about 68 psi, about 69 psi, about 70 psi, about 71 psi, about 72 psi, about 73 psi, about 74 psi, about 75 psi, about 76 psi, about 77 psi, about 78 psi, about 79 psi, about 80 psi, about 81 psi, about 82 psi, about 83 psi, about 84 psi, about 85 psi, about 86 psi, about 87 psi, about 88 psi, about 89 psi, about 90 psi, about 91 psi, about 92 psi, about 93 psi, about 94 psi, about 95 psi, about 96 psi, about 97 psi, about 98 psi, about 99 psi, about 100 psi, about 101 psi, about 102 psi, about 103 psi, about 104 psi, about 105 psi, about 106 psi, about 107 psi, about 108 psi, about 109 psi, about 110 psi, about 111 psi, about 112 psi, about 113 psi, about 114 psi, about 115 psi, about 116 psi, about 117 psi, about 118 psi, about 119 psi, about 120 psi, about 121 psi, about 122 psi, about 123 psi, about

124 psi, about 125 psi, about 126 psi, about 127 psi, about 128 psi, about 129 psi, about 130 psi, about 131 psi, about 132 psi, about 133 psi, about 134 psi, about 135 psi, about 136 psi, about 137 psi, about 138 psi, about 139 psi, about 140 psi, about 141 psi, about 142 psi, about 143 psi, about 144 psi, about 145 psi, about 146 psi, about 147 psi, about 148 psi, about 149 psi, about 150 psi, about 151 psi, about 152 psi, about 153 psi, about 154 psi, about 155 psi, about 156 psi, about 157 psi, about 158 psi, about 159 psi, about 160 psi, about 161 psi, about 162 psi, about 163 psi, about 164 psi, about 165 psi, about 166 psi, about 167 psi, about 168 psi, about 169 psi, about 170 psi, about 171 psi, about 172 psi, about 173 psi, about 174 psi, about 175 psi, about 176 psi, about 177 psi, about 178 psi, about 179 psi, about 180 psi, about 181 psi, about 182 psi, about 183 psi, about 184 psi, about 185 psi, about 186 psi, about 187 psi, about 188 psi, about 189 psi, about 190 psi, about 191 psi, about 192 psi, about 193 psi, about 194 psi, about 195 psi, about 196 psi, about 197 psi, about 198 psi, about 199 psi, or about 200 psi from a prefilled syringe using an HVAI.

[00189] In one embodiment, the starting pressure refers to the starting pressure exerted on the subject's tissue upon administration of the formulation from a prefilled syringe using an HVAI. In one embodiment, the starting pressure refers to the starting pressure exerted the syringe stopper of the prefilled syringe in an HVAI as the disclosed formulation is delivered to a subject. In one embodiment, the starting pressure refers to the starting pressure exerted on the formulation upon administration of the formulation from a prefilled syringe using an HVAI. In one embodiment, the starting pressure refers to the starting pressure exerted on the prefilled syringe upon administration of the formulation from a prefilled syringe using an HVAI. In one embodiment, the starting pressure refers to the starting pressure generated by the HVAI device upon administration of the formulation from a prefilled syringe using an HVAI.

[00190] In one embodiment about 3 mL to about 50 mL of the formulation disclosed herein is administered to the subject with an ending pressure of about 1 psi to about 250 psi, about 1 psi to about 225 psi, about 1 psi to about 200 psi, about 10 psi to about 200 psi, about 10 psi to about 175 psi, about 10 psi to about 150 psi, about 10 psi to about 125 psi, about 15 psi to about 125 psi, about 15 psi to about 100 psi, about 15 psi to about 80 psi, about 15 psi to about 75 psi, or about 20 psi to about 75 psi from a prefilled syringe using an HVAI. In one embodiment about 3 mL to about 50 mL of the formulation disclosed herein is administered to the subject with an ending pressure of about 20 psi, about 25 psi, about 30 psi, about 35 psi, about 40 psi, about 45 psi, about 50 psi, about 55 psi, about 60 psi, about 65 psi, about 70 psi, or about 75 psi from a prefilled syringe using an HVAI. In one embodiment about 3 mL to about 50 mL of the formulation disclosed herein is administered to the subject with an ending pressure of about 20 psi, about 21 psi, about 22 psi, about

23 psi, about 24 psi, about 25 psi, about 26 psi, about 27 psi, about 28 psi, about 29 psi, about 30 psi, about 31 psi, about 32 psi, about 33 psi, about 34 psi, about 35 psi, about 36 psi, about 37 psi, about 38 psi, about 39 psi, about 40 psi, about 41 psi, about 42 psi, about 43 psi, about 44 psi, about 45 psi, about 46 psi, about 47 psi, about 48 psi, about 49 psi, about 50 psi, about 51 psi, about 52 psi, about 53 psi, about 54 psi, about 55 psi, about 56 psi, about 57 psi, about 58 psi, about 59 psi, about 60 psi, about 61 psi, about 62 psi, about 63 psi, about 64 psi, about 65 psi, about 66 psi, about 67 psi, about 68 psi, about 69 psi, about 70 psi, about 71 psi, about 72 psi, about 73 psi, about 74 psi, or about 75 psi from a prefilled syringe using an HVAI.

[00191] In one embodiment, the ending pressure refers to the ending pressure exerted on the subject's tissue upon administration of the disclosed formulation from a prefilled syringe using an HVAI. In one embodiment, the ending pressure refers to the ending pressure exerted the syringe stopper of the prefilled syringe in an HVAI as the disclosed formulation is delivered to a subject. In one embodiment, the ending pressure refers to the ending pressure exerted on the formulation upon administration of the formulation from a prefilled syringe using an HVAI. In one embodiment, the ending pressure refers to the ending pressure exerted on the prefilled syringe upon administration of the formulation from a prefilled syringe using an HVAI. In one embodiment, the ending pressure refers to the ending pressure generated by the HVAI device upon administration of the formulation from a prefilled syringe using an HVAI.

[00192] In one embodiment, the administration of the formulation to the subject requires less applied force when compared to a similar formulation that does not comprise a hyaluronidase enzyme.

[00193] In one embodiment, about 3 mL to about 50 mL of the formulation disclosed herein is administered at a rate of about 4 mL/min to about 21 mL/min with an applied force of about 10 N to about 200 N about 20 N to about 150 N, about 10 N, about 20 N, about 30 N, about 40 N, about 50 N, about 60 N, about 70 N, about 80 N, about 90 N, about 100 N, about 110 N, about 120 N, about 130 N, about 140 N, about 150 N, about 160 N, about 170 N, about 180 N, about 190 N, or about 200 N.

[00194] In one embodiment, about 5 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min with an applied force of about 10 N to about 45 N. In one embodiment, about 5 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min using a 25-gauge needle with an applied force of about 10 N to about 45 N. In one embodiment, about 5 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min using a 25-gauge needle with an applied force of about 15 N to

about 25 N. In another embodiment, about 5 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min using a 25-gauge needle with an applied force of about 22 N to about 40 N. In one embodiment, the about 10 mL formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min with an applied force of about 25 N to about 50 N.

[00195] In one embodiment, the applied force at which the formulation is administered to the subject at a specific rate is dependent upon the gauge of the needle used to deliver the formulation to the subject. In one embodiment, the applied force at which the formulation is administered to the subject at a specific rate is dependent upon the gauge of the needle used to deliver the formulation to the subject and the inner diameter of the needle used to deliver the formulation to the subject. Therefore, in one embodiment, the use of a 25-gauge needle with a larger inner diameter (i.e., a thin wall needle such as a Terumo needle) will require less applied force to administer the disclosed formulation to a subject at a specific rate than the use of a 25-gauge needle with a smaller inner diameter (such as a BD needle). In one embodiment, about 5 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min using a 25-gauge needle with an applied force of about 15 N to about 25 N, wherein the needle is a thin wall needle (e.g., a Terumo needle). In another embodiment, about 5 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min using a 25-gauge needle with an applied force of about 22 N to about 40 N, wherein the needle is not a thin wall needle (e.g., a BD needle).

[00196] In one embodiment, the about 10 mL formulation is administered to the subject using a 25-gauge needle at a rate of about 4 mL/min to about 21 mL/min with an applied force of about 25 N to about 50 N.

[00197] In one embodiment, about 5 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min with an applied force of about 10 N, about 11 N, about 12 N, about 13 N, about 14 N, about 15 N, about 16 N, about 17 N, about 18 N, about 19 N, about 20, about 21 N, about 22 N, about 23 N, about 24 N, about 25 N, about 26 N, about 27 N, about 28 N, about 29 N, about 30 N, about 31 N, about 32 N, about 33 N, about 34 N, about 35 N, about 36 N, about 37 N, about 38 N, about 39 N, about 40 N, about 41 N, about 42 N, about 43 N, about 44 N, or about 45 N. In one embodiment, about 5 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min using a 25-gauge needle with an applied force of about 10 N, about 11 N, about 12 N, about 13 N, about 14 N, about 15 N, about 16 N, about 17 N, about 18 N, about 19 N, about 20, about 21 N, about 22 N, about 23 N, about 24 N, about 25 N, about 26 N, about 27 N, about 28 N, about 29 N, about 30 N, about 31 N, about 32 N, about 33 N, about 34

N, about 35 N, about 36 N, about 37 N, about 38 N, about 39 N, about 40 N, about 41 N, about 42 N, about 43 N, about 44 N, or about 45 N.

[00198] In one embodiment, the about 10 mL formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min with an applied force of about 25 N, about 26 N, about 27 N, about 28 N, about 29 N, about 30 N, about 31 N, about 32 N, about 33 N, about 34 N, about 35 N, about 36 N, about 37 N, about 38 N, about 39 N, about 40 N, about 41 N, about 42 N, about 43 N, about 44 N, about 46 N, about 47 N, about 48 N, about 49 N, or about 50 N. In one embodiment, about 10 mL formulation is administered to the subject at a rate of about 0.32 mL/sec to about 0.42 mL/sec using a 25-gauge needle with an applied force of about 25 N, about 26 N, about 27 N, about 28 N, about 29 N, about 30 N, about 31 N, about 32 N, about 33 N, about 34 N, about 35 N, about 36 N, about 37 N, about 38 N, about 39 N, about 40 N, about 41 N, about 42 N, about 43 N, about 44 N, about 45 N, about 46 N, about 47 N, about 48 N, about 49 N, or about 50 N.

[00199] In one embodiment, about 15 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min with an applied force of about 10 N, about 11 N, about 12 N, about 13 N, about 14 N, about 15 N, about 16 N, about 17 N, about 18 N, about 19 N, about 20, about 21 N, about 22 N, about 23 N, about 24 N, about 25 N, about 26 N, about 27 N, about 28 N, about 29 N, about 30 N, about 31 N, about 32 N, about 33 N, about 34 N, about 35 N, about 36 N, about 37 N, about 38 N, about 39 N, about 40 N, about 41 N, about 42 N, about 43 N, about 44 N, or about 45 N. In one embodiment, about 5 mL of the formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min using a 25-gauge needle with an applied force of about 10 N, about 11 N, about 12 N, about 13 N, about 14 N, about 15 N, about 16 N, about 17 N, about 18 N, about 19 N, about 20, about 21 N, about 22 N, about 23 N, about 24 N, about 25 N, about 26 N, about 27 N, about 28 N, about 29 N, about 30 N, about 31 N, about 32 N, about 33 N, about 34 N, about 35 N, about 36 N, about 37 N, about 38 N, about 39 N, about 40 N, about 41 N, about 42 N, about 43 N, about 44 N, or about 45 N.

[00200] In one embodiment, the about 20 mL formulation is administered to the subject at a rate of about 4 mL/min to about 21 mL/min with an applied force of about 25 N, about 26 N, about 27 N, about 28 N, about 29 N, about 30 N, about 31 N, about 32 N, about 33 N, about 34 N, about 35 N, about 36 N, about 37 N, about 38 N, about 39 N, about 40 N, about 41 N, about 42 N, about 43 N, about 44 N, about 46 N, about 47 N, about 48 N, about 49 N, or about 50 N. In one embodiment, about 10 mL formulation is administered to the subject at a rate of about 0.32 mL/sec to about 0.42 mL/sec using a 25-gauge needle with an applied force of about 25 N, about 26 N, about 27 N, about 28 N, about 29 N, about 30 N, about 31 N, about 32 N, about 33 N, about 34 N, about 35 N, about

36 N, about 37 N, about 38 N, about 39 N, about 40 N, about 41 N, about 42 N, about 43 N, about 44 N, about 45 N, about 46 N, about 47 N, about 48 N, about 49 N, or about 50 N.

[00201] The HVAI may deliver the full deliverable volume of the formulation in 5 seconds, 10 seconds, 15 seconds, 20 seconds, 25 seconds, 30 seconds, 35 seconds, 40 seconds, 45 seconds, 50 seconds, 55 seconds, 60 seconds, 70 seconds, 80 seconds, 90 seconds, 100 seconds, 110 seconds, or 120 seconds, 130 seconds, 140 seconds, 150 seconds, 160 seconds, 170 seconds, 180 seconds, 190 seconds, 200 seconds, 210 seconds, 220 seconds, 230 seconds, 240 seconds, 250 seconds, 260 seconds, 270 seconds, 280 seconds, 290 seconds, 300 seconds, 310 seconds, 320 seconds, 330 seconds, 340 seconds, 350 seconds, or 360 seconds.

[00202] In one embodiment, the hyaluronidase enzyme allows the formulation to be administered to the subject faster than a comparable formulation that does not comprise the hyaluronidase enzyme. In one embodiment, the disclosed formulation can be administered about 20%, about 22%, about 24%, about 26%, about 28%, about 30%, about 32%, about 34%, about 36%, about 38%, about 40%, about 42%, about 44%, about 46%, or about 48% faster than a comparable formulation that does not comprise the hyaluronidase enzyme when both are administered using the same HVAI fitted with a 23-gauge needle. In one embodiment, the disclosed formulation can be administered about 2%, about 4%, about 6%, about 8%, about 10%, about 12%, about 14%, about 16%, about 18%, or about 20% faster than a comparable formulation that does not comprise the hyaluronidase enzyme when both are administered using the same HVAI fitted with a 25-gauge needle.

[00203] In one embodiment, the injection of a high volume of the disclosed formulation in a subject leads to fewer side effects in the subject compared to an identical subject administered the same volume of a comparable formulation that does not comprise the hyaluronidase enzyme. In one embodiment, the injection of a high volume disclosed elsewhere herein with the disclosed formulation has reduced back leakage compared to a similar formulation that does not comprise the hyaluronidase enzyme. In one embodiment, the back leakage is reduced about 54%, about 56%, about 58%, about 60%, about 62%, about 64%, about 66%, about 68%, about 70%, about 72%, about 74%, about 76%, or about 78% when a high volume of the disclosed formulation is administered to a subject using an HVAI fitted with a 23-gauge needle compared to a similar formulation that does not comprise the hyaluronidase enzyme. In one embodiment, the back leakage is reduced about 62%, about 64%, about 68%, about 70%, about 72%, about 74%, about 76%, about 78%, about 80%, about 82%, about 84%, or about 86% when a high volume of the disclosed formulation is administered to a subject using an HVAI fitted with a 25-gauge needle compared to a similar formulation that does not comprise the hyaluronidase enzyme.

[00204] In one embodiment, the swelling (bleb) volume is reduced following the injection of the disclosed formulation into a subject when compared to a similar formulation that does not comprise the hyaluronidase enzyme. In one embodiment, the swelling height is reduced following the injection of the disclosed formulation when compared to a similar formulation that does not
5 comprise the hyaluronidase enzyme. In one embodiment, the swelling size is reduced following the injection of the disclosed formulation when compared to a similar formulation that does not comprise the hyaluronidase enzyme. In one embodiment, the swelling area is reduced following the injection of the disclosed formulation when compared to a similar formulation that does not comprise the hyaluronidase enzyme. In one embodiment, the swelling induration following the
10 initial injection of the disclosed formulation is minimized compared to a similar formulation that does not comprise the hyaluronidase enzyme. In one embodiment, the swelling resolves quicker when the disclosed formulation is injected compared to a similar formulation that does not comprise the hyaluronidase enzyme. In one embodiment, the disclosed formulation permits for more consistent delivery (i.e., time to delivery, reduction in bleb swelling volume, height and induration)
15 from injection to injection, compared to a similar formulation that does not comprise the hyaluronidase enzyme. In one embodiment, the disclosed formulation permits for faster delivery of the full volume from an HVAI than a comparable formulation that does not comprise the hyaluronidase enzyme which results in less pain and discomfort for the subject.

[00205] In some embodiments, the disclosure provides a method of treating a disease or disorder
20 in a subject in need thereof, the method comprising administering to the subject via subcutaneous administration about 3 mL to about 100 mL of a formulation comprising a hyaluronidase enzyme and a therapeutically effective amount of an active ingredient selected from a small molecule, a peptide fragment, a biologic, a nanoparticle, an antibody, an antibody fragment, and a small molecule antiviral. In some embodiments, the subcutaneous administration is facilitated by a
25 prefilled autoinjection or autoinfusion device comprising: a delivery apparatus comprising: a housing having a proximal end and a distal end opposite the proximal end; a medicament container at least partially disposed within the housing containing a volume of a medicament comprising the formulation; an outlet on the distal end of the housing in fluid communication with the medicament container; an energy source disposed within the housing configured to interact with the medicament
30 container to expel the medicament from the outlet; and a trigger mechanism coupled to the housing and engageable with the energy source and configured to activate the energy source in response to a user input. In some embodiments, the prefilled autoinjection or autoinfusion device further comprising: a port having a user engagement surface or a user engagement distal portion, and an

injection apparatus extending from the user engagement surface or user engagement distal portion. In some embodiments, during the administering, the prefilled autoinjection or autoinfusion device is placed off-body relative to the subject, while the port is placed on-body relative to the subject. In some embodiments, the energy source urges the volume of the medicament through the injection apparatus when the volume of the medicament is expelled from the outlet. In some embodiments, the port comprises an air release valve. In some embodiments, the port is removably coupled to an injection site of a user. In some embodiments, the user engagement surface is generally flat and includes an aperture extending therethrough. In some embodiments, the port comprises a butterfly needle. In some embodiments, the injection apparatus extends through the aperture on a plane generally perpendicular to the plane of the user engagement surface. In some embodiments, the prefilled autoinjection or autoinfusion device further comprises a conduit removably coupled to the outlet and the port and fluidly connecting the delivery apparatus and the port when coupled therebetween. In some embodiments, the delivery apparatus purges the conduit of air before the injection apparatus is inserted into an injection site of a patient. In some embodiments, the delivery apparatus purges the conduit of air after the injection apparatus is inserted into an injection site of a patient. In some embodiments, the delivery apparatus automatically purges the conduit of air when the conduit is coupled to the delivery apparatus. In some embodiments, the conduit is decoupled from the port after the volume of the medicament is expelled from the outlet. In some embodiments, the conduit comprises a flexible tubing. In some embodiments, the conduit is at least 6 inches, at least 12 inches, at least 18 inches, at least 24 inches, at least 30 inches, or at least 36 inches in length. In some embodiments, the energy source is prevented from expelling medicament from the outlet until the conduit is purged of air. In some embodiments, the volume of the medicament is at least 10 mL, at least 20 mL, at least 30 mL, at least 40 mL, at least 50 mL, at least 60 mL, at least 70 mL, at least 80 mL, at least 90 mL, or at least 100 mL. In some embodiments, the delivery apparatus is not resettable. In some embodiments, the outlet is a generally cylindrical member and comprises threads protruding therefrom. In some embodiments, the volume of the formulation is expelled at a rate of at least 1 mL/min, at least 2 mL/min, at least 3 mL/min, at least 4 mL/min, at least 5 mL/min, at least 6 mL/min, at least 7 mL/min, at least 8 mL/min, at least 9 mL/min, or at least 10 mL/min. In some embodiments, the conduit is purged of air prior to the injection. In some embodiments, the delivery apparatus purges the conduit of air after the injection apparatus is inserted into an injection site of a patient. In some embodiments, the delivery apparatus is not resettable. In some embodiments, the delivery apparatus or any part thereof is disposable after a single use. In some embodiments, the volume of the medicament is expelled from the delivery apparatus in at least 30

seconds, at least 45 seconds, at least 60 seconds, at least 75 seconds, at least 90 seconds, at least 105 seconds, at least 120 seconds, at least 135 seconds, at least 150 seconds, at least 165 seconds, at least 180 seconds, at least 195 seconds, at least 210 seconds, at least 225 seconds, at least 240 seconds, at least 255 seconds, at least 270 seconds, at least 285 seconds, at least 300 seconds, at least 315 seconds, at least 330 seconds, at least 345 seconds, at least 360 seconds, at least 375 seconds, at least 390 seconds, at least 405 seconds, at least 420 seconds, at least 435 seconds, at least 450 seconds, at least 465 seconds, at least 480 seconds, at least 495 seconds, at least 510 seconds, at least 525 seconds, at least 540 seconds, at least 555 seconds, at least 570 seconds, at least 585 seconds, or at least 600 seconds. In some embodiments, the volume of the medicament is expelled from the delivery apparatus at a rate of at least 1 mL/min, at least 2 mL/min, at least 3 mL/min, at least 4 mL/min, at least 5 mL/min, at least 6 mL/min, at least 7 mL/min, at least 8 mL/min, at least 9 mL/min, or at least 10 mL/min. In some embodiments, the hyaluronidase enzyme is a recombinant human hyaluronidase enzyme. In some embodiments, the hyaluronidase enzyme is recombinant human hyaluronidase PH20 enzyme. In some embodiments, the hyaluronidase enzyme has an activity of about 150 U/mL to about 150 kU/mL. In some embodiments, the hyaluronidase enzyme has an activity of about 500 U/mL to about 5,000 U/mL. In some embodiments, the hyaluronidase enzyme has an activity of about 1,500 U/mL to about 10,000 U/mL. In some embodiments, the active ingredient is a small molecule, a peptide fragment, a biologic, or a nanoparticle. In some embodiments, the active ingredient is an antibody, an antibody fragment, or a small molecule antiviral. In some embodiments, the administering comprises administering to the subject about 10 mL to about 20 mL of the formulation. In some embodiments, the administering comprises administering to the subject about 3 mL to about 15 mL of the formulation. In some embodiments, the administering comprises administering to the subject about 3 mL, about 3.1 mL, about 3.2 mL, about 3.4 mL, about 3.5 mL, about 3.6 mL, about 3.7 mL, about 3.8 mL, about 3.9 mL, about 4 mL, about 4.1 mL, about 4.2 mL, about 4.3 mL, about 4.4 mL, about 4.5 mL, about 5 mL, about 5.1 mL, about 5.2 mL, about 5.3 mL, about 5.4 mL, about 5.5 mL, about 5.6 mL, about 5.7 mL, about 5.8 mL, about 5.9 mL, about 6 mL, about 6.1 mL, about 6.2 mL, about 6.3 mL, about 6.4 mL, about 6.5 mL, about 6.6 mL, about 6.7 mL, about 6.8 mL, about 6.9 mL, about 7 mL, about 7.1 mL, about 7.2 mL, about 7.3 mL, about 7.4 mL, about 7.5 mL, about 7.6 mL, about 7.7 mL, about 7.8 mL, about 7.9 mL, about 8 mL, about 8.1 mL, about 8.2 mL, about 8.3 mL, about 8.4 mL, about 8.5 mL, about 8.6 mL, about 8.7 mL, about 8.8 mL, about 8.9 mL, about 9 mL, about 9.1 mL, about 9.2 mL, about 9.3 mL, about 9.4 mL, about 9.5 mL, about 9.6 mL, about 9.7 mL, about 9.8 mL, about 9.9 mL, about 10 mL, about 10.1 mL, about 10.2 mL, about 10.3 mL, about 10.4 mL, about 10.5 mL, about

10.6 mL, about 10.7 mL, about 10.8 mL, about 10.9 mL, about 11 mL, about 11.1 mL, about 11.2 mL, about 11.3 mL, about 11.4 mL, about 11.5 mL, about 11.6 mL, about 11.7 mL, about 11.8 mL, about 11.9 mL, about 12 mL, about 12.1 mL, about 12.2 mL, about 12.3 mL, about 12.4 mL, about 12.5 mL, about 12.6 mL, about 12.7 mL, about 12.8 mL, about 12.9 mL, about 13 mL, about 13.1 mL, about 13.2 mL, about 13.3 mL, about 13.4 mL, about 13.5 mL, about 13.6 mL, about 13.7 mL, about 13.8 mL, about 13.9 mL, about 14 mL, about 14.1 mL, about 14.2 mL, about 14.3 mL, about 14.4 mL, about 14.5 mL, about 14.6 mL, about 14.7 mL, about 14.8 mL, about 14.9 mL, about 15 mL, about 15.1 mL, about 15.2 mL, about 15.3 mL, about 15.4 mL, about 15.5 mL, about 15.6 mL, about 15.7 mL, about 15.8 mL, about 15.9 mL, about 16 mL, about 16.1 mL, about 16.2 mL, about 16.3 mL, about 16.4 mL, about 16.5 mL, about 16.6 mL, about 16.7 mL, about 16.8 mL, about 16.9 mL, about 17 mL, about 17.1 mL, about 17.2 mL, about 17.3 mL, about 17.4 mL, about 17.5 mL, about 17.6 mL, about 17.7 mL, about 17.8 mL, about 17.9 mL, about 18 mL, about 18.1 mL, about 18.2 mL, about 18.3 mL, about 18.4 mL, about 18.5 mL, about 18.6 mL, about 18.7 mL, about 18.8 mL, about 18.9 mL, about 19 mL, about 19.1 mL, about 19.2 mL, about 19.3 mL, about 19.4 mL, about 19.5 mL, about 19.6 mL, about 19.7 mL, about 19.8 mL, about 19.9 mL, about 20 mL, about 20.1 mL, about 20.2 mL, about 20.3 mL, about 20.4 mL, about 20.5 mL, about 20.6 mL, about 20.7 mL, about 20.8 mL, about 20.9 mL, about 21 mL, about 21.1 mL, about 21.2 mL, about 21.3 mL, about 21.4 mL, about 21.5 mL, about 21.6 mL, about 21.7 mL, about 21.8 mL, about 21.9 mL, about 22 mL, about 22.1 mL, about 22.2 mL, about 22.3 mL, about 22.4 mL, about 22.5 mL, about 22.6 mL, about 22.7 mL, about 22.8 mL, about 22.9 mL, about 23 mL, about 23.1 mL, about 23.2 mL, about 23.3 mL, about 23.4 mL, about 23.5 mL, about 23.6 mL, about 23.7 mL, about 23.8 mL, about 23.9 mL, about 24 mL, about 24.1 mL, about 24.2 mL, about 24.3 mL, about 24.4 mL, about 24.5 mL, about 24.6 mL, about 24.7 mL, about 24.8 mL, about 24.9 mL, about 25 mL, about 30 mL, about 35 mL, about 40 mL, about 45 mL, about 50 mL, about 55 mL, about 60 mL, about 65 mL, about 70 mL, about 75 mL, about 80 mL, about 85 mL, about 90 mL, about 95 mL, or about 100 mL. In some embodiments, the method comprises administering the formulation with a starting delivery force of about 5 lbf to about 50 lbf, e.g., about 5 lbf, about 6 lbf, about 7 lbf, about 8 lbf, about 9 lbf, about 10 lbf, about 11 lbf, about 12 lbf, about 13 lbf, about 14 lbf, about 15 lbf, about 16 lbf, about 17 lbf, about 18 lbf, about 19 lbf, about 20 lbf, about 25 lbf, about 30 lbf, about 35 lbf, about 40 lbf, about 45 lbf, or about 50 lbf. In some embodiments, the method comprising administering the formulation with an ending delivery force of about 3 lbf to about 20 lbf, e.g., about 3 lbf, about 4 lbf, about 5 lbf, about 6 lbf, about 7 lbf, about 8 lbf, about 9 lbf, about 10 lbf, about 11 lbf, about 12 lbf, about 13 lbf, about 14 lbf, about 15 lbf, about 16 lbf, about 17 lbf, about

18 lbf, about 19 lbf, or about 20 lbf. In some embodiments, the method comprising administering the formulation with a starting pressure of about 50 psi to about 200 psi, e.g., about 50 psi, about 60 psi, about 70 psi, about 80 psi, about 90 psi, about 100 psi, about 110 psi, about 120 psi, about 130 psi, about 140 psi, about 150 psi, about 160 psi, about 170 psi, about 180 psi, about 190 psi, or about 200 psi. In some embodiments, the method comprising administering the formulation with an ending pressure of about 20 psi to about 75 psi, e.g., about 20 psi, about 25 psi, about 30 psi, about 35 psi, about 40 psi, about 45 psi, about 50 psi, about 55 psi, about 60 psi, about 65 psi, about 70 psi, or about 75 psi. In some embodiments, the medicament container is a prefilled syringe. In some embodiments, the prefilled syringe contains about 3 mL, about 3.1 mL, about 3.2 mL, about 3.4 mL, about 3.5 mL, about 3.6 mL, about 3.7 mL, about 3.8 mL, about 3.9 mL, about 4 mL, about 4.1 mL, about 4.2 mL, about 4.3 mL, about 4.4 mL, about 4.5 mL, about 5 mL, about 5.1 mL, about 5.2 mL, about 5.3 mL, about 5.4 mL, about 5.5 mL, about 5.6 mL, about 5.7 mL, about 5.8 mL, about 5.9 mL, about 6 mL, about 6.1 mL, about 6.2 mL, about 6.3 mL, about 6.4 mL, about 6.5 mL, about 6.6 mL, about 6.7 mL, about 6.8 mL, about 6.9 mL, about 7 mL, about 7.1 mL, about 7.2 mL, about 7.3 mL, about 7.4 mL, about 7.5 mL, about 7.6 mL, about 7.7 mL, about 7.8 mL, about 7.9 mL, about 8 mL, about 8.1 mL, about 8.2 mL, about 8.3 mL, about 8.4 mL, about 8.5 mL, about 8.6 mL, about 8.7 mL, about 8.8 mL, about 8.9 mL, about 9 mL, about 9.1 mL, about 9.2 mL, about 9.3 mL, about 9.4 mL, about 9.5 mL, about 9.6 mL, about 9.7 mL, about 9.8 mL, about 9.9 mL, about 10 mL, about 10.1 mL, about 10.2 mL, about 10.3 mL, about 10.4 mL, about 10.5 mL, about 10.6 mL, about 10.7 mL, about 10.8 mL, about 10.9 mL, about 11 mL, about 11.1 mL, about 11.2 mL, about 11.3 mL, about 11.4 mL, about 11.5 mL, about 11.6 mL, about 11.7 mL, about 11.8 mL, about 11.9 mL, about 12 mL, about 12.1 mL, about 12.2 mL, about 12.3 mL, about 12.4 mL, about 12.5 mL, about 12.6 mL, about 12.7 mL, about 12.8 mL, about 12.9 mL, about 13 mL, about 13.1 mL, about 13.2 mL, about 13.3 mL, about 13.4 mL, about 13.5 mL, about 13.6 mL, about 13.7 mL, about 13.8 mL, about 13.9 mL, about 14 mL, about 14.1 mL, about 14.2 mL, about 14.3 mL, about 14.4 mL, about 14.5 mL, about 14.6 mL, about 14.7 mL, about 14.8 mL, about 14.9 mL, about 15 mL, about 15.1 mL, about 15.2 mL, about 15.3 mL, about 15.4 mL, about 15.5 mL, about 15.6 mL, about 15.7 mL, about 15.8 mL, about 15.9 mL, about 16 mL, about 16.1 mL, about 16.2 mL, about 16.3 mL, about 16.4 mL, about 16.5 mL, about 16.6 mL, about 16.7 mL, about 16.8 mL, about 16.9 mL, about 17 mL, about 17.1 mL, about 17.2 mL, about 17.3 mL, about 17.4 mL, about 17.5 mL, about 17.6 mL, about 17.7 mL, about 17.8 mL, about 17.9 mL, about 18 mL, about 18.1 mL, about 18.2 mL, about 18.3 mL, about 18.4 mL, about 18.5 mL, about 18.6 mL, about 18.7 mL, about 18.8 mL, about 18.9 mL, about 19 mL, about 19.1 mL, about 19.2 mL, about 19.3 mL, about 19.4 mL, about

19.5 mL, about 19.6 mL, about 19.7 mL, about 19.8 mL, about 19.9 mL, about 20 mL, about 20.1 mL, about 20.2 mL, about 20.3 mL, about 20.4 mL, about 20.5 mL, about 20.6 mL, about 20.7 mL, about 20.8 mL, about 20.9 mL, about 21 mL, about 21.1 mL, about 21.2 mL, about 21.3 mL, about 21.4 mL, about 21.5 mL, about 21.6 mL, about 21.7 mL, about 21.8 mL, about 21.9 mL, about 22
5 mL, about 22.1 mL, about 22.2 mL, about 22.3 mL, about 22.4 mL, about 22.5 mL, about 22.6 mL, about 22.7 mL, about 22.8 mL, about 22.9 mL, about 23 mL, about 23.1 mL, about 23.2 mL, about 23.3 mL, about 23.4 mL, about 23.5 mL, about 23.6 mL, about 23.7 mL, about 23.8 mL, about 23.9 mL, about 24 mL, about 24.1 mL, about 24.2 mL, about 24.3 mL, about 24.4 mL, about 24.5 mL, about 24.6 mL, about 24.7 mL, about 24.8 mL, about 24.9 mL, about 25 mL of the formulation,
10 about 30 mL of the formulation, about 35 mL of the formulation, about 40 mL of the formulation, about 45 mL of the formulation, about 50 mL of the formulation, about 55 mL of the formulation, about 60 mL of the formulation, about 65 mL of the formulation, about 70 mL of the formulation, about 75 mL of the formulation, about 80 mL of the formulation, about 85 mL of the formulation, about 90 mL of the formulation, about 95 mL of the formulation, or about 100 mL of the
15 formulation. In some embodiments, the prefilled syringe comprises a needle having a gauge of about 20 to about 33, e.g., about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, or about 33. In some embodiments, the prefilled syringe comprises a 20-gauge needle, a 21-gauge needle, a 22-gauge needle, a 23-gauge needle, a 24-gauge needle, a 25-gauge needle, a 26-gauge needle, a 27-gauge needle, a 28-gauge needle, a 29-
20 gauge needle, a 30-gauge needle, a 31-gauge needle, a 32-gauge needle, or a 33-gauge needle. In some embodiments, the method comprising administering the formulation at a rate of about 5 to about 20 mL/min, e.g., about 5 mL/min, about 6 mL/min, about 7 mL/min, about 8 mL/min, about 9 mL/min, about 10 mL/min, about 11 mL/min, about 12 mL/min, about 13 mL/min, about 14 mL/min, about 15 mL/min, about 16 mL/min, about 17 mL/min, about 18 mL/min, about 19
25 mL/min, or about 20 mL/min. In some embodiments, the method comprising administering the formulation at a rate of at least about 5 to about 20 mL/min, e.g., at least about 5 mL/min, at least about 6 mL/min, at least about 7 mL/min, at least about 8 mL/min, at least about 9 mL/min, at least about 10 mL/min, at least about 11 mL/min, at least about 12 mL/min, at least about 13 mL/min, at least about 14 mL/min, at least about 15 mL/min, at least about 16 mL/min, at least about 17
30 mL/min, at least about 18 mL/min, at least about 19 mL/min, or at least about 20 mL/min. In some embodiments, the method comprising administering the formulation at a rate of at least or faster than about 5 to about 20 mL/min, e.g., at least or faster than about 5 mL/min, at least or faster than about 6 mL/min, at least or faster than about 7 mL/min, at least or faster than about 8 mL/min, at least or

faster than about 9 mL/min, at least or faster than about 10 mL/min, at least or faster than about 11 mL/min, at least or faster than about 12 mL/min, at least or faster than about 13 mL/min, at least or faster than about 14 mL/min, at least or faster than about 15 mL/min, at least or faster than about 16 mL/min, at least or faster than about 17 mL/min, at least or faster than about 18 mL/min, at least or faster than about 19 mL/min, or at least or faster than about 20 mL/min. In some embodiments, the administration takes about 30 seconds to about 360 seconds. In some embodiments, the administration takes at least about 30 seconds to about 240 seconds. In some embodiments, the administration takes at least or less than about 30 seconds to about 240 seconds. In some embodiments, the administration takes about 60 seconds to about 240 seconds. In some
5 embodiments, the administration takes at least about 60 seconds to about 240 seconds. In some
10 embodiments, the administration takes at least or less than about 60 seconds to about 240 seconds. In some
embodiments, the method comprising administering about 5 mL of the formulation at a rate
of about 5 mL/min to about 20 mL/min. In some embodiments, the method comprising
administering about 10 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min. In
15 some embodiments, the method comprising administering about 15 mL of the formulation at a rate
of about 5 mL/min to about 20 mL/min. In some embodiments, the method comprising
administering about 20 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min. In
some embodiments, the formulation has a viscosity of about 1 cP to about 50 cP, e.g., about 1 cP,
about 2 cP, about 3 cP, about 4 cP, about 5 cP, about 6 cP, about 7 cP, about 8 cP, about 9 cP, about
20 10 cP, about 15 cP, about 20 cP, about 25 cP, about 30 cP, about 35 cP, about 40 cP, about 45 cP, or
about 50 cP. In some embodiments, administration of the formulation requires less applied force
when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some
embodiments, the method comprising administering about 5 mL of the formulation at a rate of about
5 mL/min to about 20 mL/min with an applied force of about 10 N to about 45 N. In some
25 embodiments, the method comprising administering the formulation to the subject using a prefilled
syringe comprising a 25-gauge needle. In some embodiments, the method comprising administering
about 10 mL of the formulation to the subject at a rate of about 5 mL/min to about 20 mL/min with
an applied force of about 25 N to about 50 N. In some embodiments, the method comprising
administering the formulation to the subject using a prefilled syringe comprising a 25-gauge needle.
30 In some embodiments, administration of the formulation is faster when compared to a similar
formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration
of the formulation causes fewer side effects in the subject when compared to a similar formulation
that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the

formulation causes less pain and discomfort in the subject when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation causes less back leakage at the injection site when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, back leakage at the injection site is about 100% to about 30% less when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation causes less swelling volume and/or swelling height at the injection site when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation causes about 35% to about 1% less swelling and/or swelling height the injection site when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation yields a lower bleb swelling size, less bleb induration, and/or quicker bleb resolution when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation yields more consistent delivery times when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, the subject is human. In some embodiments, the administering comprises the subject self-administering the formulation. In some embodiments, the administering comprises a healthcare provider or a caregiver administering the formulation to the subject. In some embodiments, the subcutaneous administration comprises a single injection. In some embodiments, the subcutaneous administration comprises two or more injections.

[00206] In some embodiments, the disclosure provides a method of treating a disease or disorder in a subject in need thereof, the method comprising administering to the subject via subcutaneous administration about 3 mL to about 100 mL of a formulation comprising a hyaluronidase enzyme and a therapeutically effective amount of an active ingredient selected from a small molecule, a peptide fragment, a biologic, a nanoparticle, an antibody, an antibody fragment, and a small molecule antiviral; wherein the subcutaneous administration is facilitated by a prefilled autoinjection or autoinfusion device comprising: a delivery apparatus comprising: a housing having a proximal end and a distal end opposite the proximal end; a medicament container at least partially disposed within the housing containing a volume of at least 10 mL of a medicament comprising the formulation; an outlet on the distal end of the housing in fluid communication with the medicament container; an energy source disposed within the housing configured to interact with the medicament container to expel the medicament from the outlet; and a trigger mechanism coupled to the housing and engageable with the energy source and configured to activate the energy source in response to a user input; a port comprising: a user engagement surface; and a needle extending from the user

engagement surface; and a flexible tube removably coupled to the outlet and the port and fluidly connecting the delivery apparatus and the port when coupled therebetween. In some embodiments, the delivery apparatus is not resettable. In some embodiments, the prefilled autoinjection or autoinfusion device further comprising: a port having a user engagement surface or a user engagement distal portion, and an injection apparatus extending from the user engagement surface or user engagement distal portion. In some embodiments, during the administering, the prefilled autoinjection or autoinfusion device is placed off-body relative to the subject, while the port is placed on-body relative to the subject. In some embodiments, the energy source urges the volume of the medicament through the injection apparatus when the volume of the medicament is expelled from the outlet. In some embodiments, the port comprises an air release valve. In some embodiments, the port is removably coupled to an injection site of a user. In some embodiments, the user engagement surface is generally flat and includes an aperture extending therethrough. In some embodiments, the port comprises a butterfly needle. In some embodiments, the injection apparatus extends through the aperture on a plane generally perpendicular to the plane of the user engagement surface. In some embodiments, the prefilled autoinjection or autoinfusion device further comprises a conduit removably coupled to the outlet and the port and fluidly connecting the delivery apparatus and the port when coupled therebetween. In some embodiments, the delivery apparatus purges the conduit of air before the injection apparatus is inserted into an injection site of a patient. In some embodiments, the delivery apparatus purges the conduit of air after the injection apparatus is inserted into an injection site of a patient. In some embodiments, the delivery apparatus automatically purges the conduit of air when the conduit is coupled to the delivery apparatus. In some embodiments, the conduit is decoupled from the port after the volume of the medicament is expelled from the outlet. In some embodiments, the conduit comprises a flexible tubing. In some embodiments, the conduit is at least 6 inches, at least 12 inches, at least 18 inches, at least 24 inches, at least 30 inches, or at least 36 inches in length. In some embodiments, the energy source is prevented from expelling medicament from the outlet until the conduit is purged of air. In some embodiments, the volume of the medicament is at least 10 mL, at least 20 mL, at least 30 mL, at least 40 mL, at least 50 mL, at least 60 mL, at least 70 mL, at least 80 mL, at least 90 mL, or at least 100 mL. In some embodiments, the delivery apparatus is not resettable. In some embodiments, the outlet is a generally cylindrical member and comprises threads protruding therefrom. In some embodiments, the volume of the formulation is expelled at a rate of at least 1 mL/min, at least 2 mL/min, at least 3 mL/min, at least 4 mL/min, at least 5 mL/min, at least 6 mL/min, at least 7 mL/min, at least 8 mL/min, at least 9 mL/min, or at least 10 mL/min. In some embodiments, the

conduit is purged of air prior to the injection. In some embodiments, the delivery apparatus purges the conduit of air after the injection apparatus is inserted into an injection site of a patient. In some embodiments, the delivery apparatus is not resettable. In some embodiments, the delivery apparatus or any part thereof is disposable after a single use. In some embodiments, the volume of the medicament is expelled from the delivery apparatus in at least 30 seconds, at least 45 seconds, at least 60 seconds, at least 75 seconds, at least 90 seconds, at least 105 seconds, at least 120 seconds, at least 135 seconds, at least 150 seconds, at least 165 seconds, at least 180 seconds, at least 195 seconds, at least 210 seconds, at least 225 seconds, at least 240 seconds, at least 255 seconds, at least 270 seconds, at least 285 seconds, at least 300 seconds, at least 315 seconds, at least 330 seconds, at least 345 seconds, at least 360 seconds, at least 375 seconds, at least 390 seconds, at least 405 seconds, at least 420 seconds, at least 435 seconds, at least 450 seconds, at least 465 seconds, at least 480 seconds, at least 495 seconds, at least 510 seconds, at least 525 seconds, at least 540 seconds, at least 555 seconds, at least 570 seconds, at least 585 seconds, or at least 600 seconds. In some embodiments, the volume of the medicament is expelled from the delivery apparatus at a rate of at least 1 mL/min, at least 2 mL/min, at least 3 mL/min, at least 4 mL/min, at least 5 mL/min, at least 6 mL/min, at least 7 mL/min, at least 8 mL/min, at least 9 mL/min, or at least 10 mL/min. In some embodiments, the hyaluronidase enzyme is a recombinant human hyaluronidase enzyme. In some embodiments, the hyaluronidase enzyme is recombinant human hyaluronidase PH20 enzyme. In some embodiments, the hyaluronidase enzyme has an activity of about 150 U/mL to about 150 kU/mL. In some embodiments, the hyaluronidase enzyme has an activity of about 500 U/mL to about 5,000 U/mL. In some embodiments, the hyaluronidase enzyme has an activity of about 1,500 U/mL to about 10,000 U/mL. In some embodiments, the active ingredient is a small molecule, a peptide fragment, a biologic, or a nanoparticle. In some embodiments, the active ingredient is an antibody, an antibody fragment, or a small molecule antiviral. In some embodiments, the administering comprises administering to the subject about 10 mL to about 20 mL of the formulation. In some embodiments, the administering comprises administering to the subject about 3 mL to about 15 mL of the formulation. In some embodiments, the administering comprises administering to the subject about 3 mL, about 3.1 mL, about 3.2 mL, about 3.4 mL, about 3.5 mL, about 3.6 mL, about 3.7 mL, about 3.8 mL, about 3.9 mL, about 4 mL, about 4.1 mL, about 4.2 mL, about 4.3 mL, about 4.4 mL, about 4.5 mL, about 5 mL, about 5.1 mL, about 5.2 mL, about 5.3 mL, about 5.4 mL, about 5.5 mL, about 5.6 mL, about 5.7 mL, about 5.8 mL, about 5.9 mL, about 6 mL, about 6.1 mL, about 6.2 mL, about 6.3 mL, about 6.4 mL, about 6.5 mL, about 6.6 mL, about 6.7 mL, about 6.8 mL, about 6.9 mL, about 7 mL, about 7.1 mL, about 7.2 mL, about 7.3 mL about 7.4

mL, about 7.5 mL, about 7.6 mL, about 7.7 mL, about 7.8 mL, about 7.9 mL, about 8 mL, about 8.1 mL, about 8.2 mL, about 8.3 mL, about 8.4 mL, about 8.5 mL, about 8.6 mL, about 8.7 mL, about 8.8 mL, about 8.9 mL, about 9 mL, about 9.1 mL, about 9.2 mL, about 9.3 mL, about 9.4 mL, about 9.5 mL, about 9.6 mL, about 9.7 mL, about 9.8 mL, about 9.9 mL, about 10 mL, about 10.1 mL, about 10.2 mL, about 10.3 mL, about 10.4 mL, about 10.5 mL, about 10.6 mL, about 10.7 mL, about 10.8 mL, about 10.9 mL, about 11 mL, about 11.1 mL, about 11.2 mL, about 11.3 mL, about 11.4 mL, about 11.5 mL, about 11.6 mL, about 11.7 mL, about 11.8 mL, about 11.9 mL, about 12 mL, about 12.1 mL, about 12.2 mL, about 12.3 mL, about 12.4 mL, about 12.5 mL, about 12.6 mL, about 12.7 mL, about 12.8 mL, about 12.9 mL, about 13 mL, about 13.1 mL, about 13.2 mL, about 13.3 mL, about 13.4 mL, about 13.5 mL, about 13.6 mL, about 13.7 mL, about 13.8 mL, about 13.9 mL, about 14 mL, about 14.1 mL, about 14.2 mL, about 14.3 mL, about 14.4 mL, about 14.5 mL, about 14.6 mL, about 14.7 mL, about 14.8 mL, about 14.9 mL, about 15 mL, about 15.1 mL, about 15.2 mL, about 15.3 mL, about 15.4 mL, about 15.5 mL, about 15.6 mL, about 15.7 mL, about 15.8 mL, about 15.9 mL, about 16 mL, about 16.1 mL, about 16.2 mL, about 16.3 mL, about 16.4 mL, about 16.5 mL, about 16.6 mL, about 16.7 mL, about 16.8 mL, about 16.9 mL, about 17 mL, about 17.1 mL, about 17.2 mL, about 17.3 mL, about 17.4 mL, about 17.5 mL, about 17.6 mL, about 17.7 mL, about 17.8 mL, about 17.9 mL, about 18 mL, about 18.1 mL, about 18.2 mL, about 18.3 mL, about 18.4 mL, about 18.5 mL, about 18.6 mL, about 18.7 mL, about 18.8 mL, about 18.9 mL, about 19 mL, about 19.1 mL, about 19.2 mL, about 19.3 mL, about 19.4 mL, about 19.5 mL, about 19.6 mL, about 19.7 mL, about 19.8 mL, about 19.9 mL, about 20 mL, about 20.1 mL, about 20.2 mL, about 20.3 mL, about 20.4 mL, about 20.5 mL, about 20.6 mL, about 20.7 mL, about 20.8 mL, about 20.9 mL, about 21 mL, about 21.1 mL, about 21.2 mL, about 21.3 mL, about 21.4 mL, about 21.5 mL, about 21.6 mL, about 21.7 mL, about 21.8 mL, about 21.9 mL, about 22 mL, about 22.1 mL, about 22.2 mL, about 22.3 mL, about 22.4 mL, about 22.5 mL, about 22.6 mL, about 22.7 mL, about 22.8 mL, about 22.9 mL, about 23 mL, about 23.1 mL, about 23.2 mL, about 23.3 mL, about 23.4 mL, about 23.5 mL, about 23.6 mL, about 23.7 mL, about 23.8 mL, about 23.9 mL, about 24 mL, about 24.1 mL, about 24.2 mL, about 24.3 mL, about 24.4 mL, about 24.5 mL, about 24.6 mL, about 24.7 mL, about 24.8 mL, about 24.9 mL, about 25 mL, about 30 mL, about 35 mL, about 40 mL, about 45 mL, about 50 mL, about 55 mL, about 60 mL, about 65 mL, about 70 mL, about 75 mL, about 80 mL, about 85 mL, about 90 mL, about 95 mL, or about 100 mL. In some embodiments, the method comprises administering the formulation with a starting delivery force of about 5 lbf to about 50 lbf, e.g., about 5 lbf, about 6 lbf, about 7 lbf, about 8 lbf, about 9 lbf, about 10 lbf, about 11 lbf, about 12 lbf, about 13 lbf, about 14 lbf, about 15 lbf, about 16 lbf, about 17 lbf,

about 18 lbf, about 19 lbf, about 20 lbf, about 25 lbf, about 30 lbf, about 35 lbf, about 40 lbf, about 45 lbf, or about 50 lbf. In some embodiments, the method comprising administering the formulation with an ending delivery force of about 3 lbf to about 20 lbf, e.g., about 3 lbf, about 4 lbf, about 5 lbf, about 6 lbf, about 7 lbf, about 8 lbf, about 9 lbf, about 10 lbf, about 11 lbf, about 12 lbf, about 13 lbf, about 14 lbf, about 15 lbf, about 16 lbf, about 17 lbf, about 18 lbf, about 19 lbf, or about 20 lbf. In some embodiments, the method comprising administering the formulation with a starting pressure of about 50 psi to about 200 psi, e.g., about 50 psi, about 60 psi, about 70 psi, about 80 psi, about 90 psi, about 100 psi, about 110 psi, about 120 psi, about 130 psi, about 140 psi, about 150 psi, about 160 psi, about 170 psi, about 180 psi, about 190 psi, or about 200 psi. In some embodiments, the method comprising administering the formulation with an ending pressure of about 20 psi to about 75 psi, e.g., about 20 psi, about 25 psi, about 30 psi, about 35 psi, about 40 psi, about 45 psi, about 50 psi, about 55 psi, about 60 psi, about 65 psi, about 70 psi, or about 75 psi. In some embodiments, the medicament container is a prefilled syringe. In some embodiments, the prefilled syringe contains about 3 mL, about 3.1 mL, about 3.2 mL, about 3.4 mL, about 3.5 mL, about 3.6 mL, about 3.7 mL, about 3.8 mL, about 3.9 mL, about 4 mL, about 4.1 mL, about 4.2 mL, about 4.3 mL, about 4.4 mL, about 4.5 mL, about 5 mL, about 5.1 mL, about 5.2 mL, about 5.3 mL, about 5.4 mL, about 5.5 mL, about 5.6 mL, about 5.7 mL, about 5.8 mL, about 5.9 mL, about 6 mL, about 6.1 mL, about 6.2 mL, about 6.3 mL, about 6.4 mL, about 6.5 mL, about 6.6 mL, about 6.7 mL, about 6.8 mL, about 6.9 mL, about 7 mL, about 7.1 mL, about 7.2 mL, about 7.3 mL, about 7.4 mL, about 7.5 mL, about 7.6 mL, about 7.7 mL, about 7.8 mL, about 7.9 mL, about 8 mL, about 8.1 mL, about 8.2 mL, about 8.3 mL, about 8.4 mL, about 8.5 mL, about 8.6 mL, about 8.7 mL, about 8.8 mL, about 8.9 mL, about 9 mL, about 9.1 mL, about 9.2 mL, about 9.3 mL, about 9.4 mL, about 9.5 mL, about 9.6 mL, about 9.7 mL, about 9.8 mL, about 9.9 mL, about 10 mL, about 10.1 mL, about 10.2 mL, about 10.3 mL, about 10.4 mL, about 10.5 mL, about 10.6 mL, about 10.7 mL, about 10.8 mL, about 10.9 mL, about 11 mL, about 11.1 mL, about 11.2 mL, about 11.3 mL, about 11.4 mL, about 11.5 mL, about 11.6 mL, about 11.7 mL, about 11.8 mL, about 11.9 mL, about 12 mL, about 12.1 mL, about 12.2 mL, about 12.3 mL, about 12.4 mL, about 12.5 mL, about 12.6 mL, about 12.7 mL, about 12.8 mL, about 12.9 mL, about 13 mL, about 13.1 mL, about 13.2 mL, about 13.3 mL, about 13.4 mL, about 13.5 mL, about 13.6 mL, about 13.7 mL, about 13.8 mL, about 13.9 mL, about 14 mL, about 14.1 mL, about 14.2 mL, about 14.3 mL, about 14.4 mL, about 14.5 mL, about 14.6 mL, about 14.7 mL, about 14.8 mL, about 14.9 mL, about 15 mL, about 15.1 mL, about 15.2 mL, about 15.3 mL, about 15.4 mL, about 15.5 mL, about 15.6 mL, about 15.7 mL, about 15.8 mL, about 15.9 mL, about 16 mL, about 16.1 mL, about 16.2 mL, about 16.3 mL, about 16.4 mL, about 16.5 mL, about 16.6 mL,

about 16.7 mL, about 16.8 mL, about 16.9 mL about 17 mL, about 17.1 mL, about 17.2 mL, about 17.3 mL, about 17.4 mL, about 17.5 mL, about 17.6 mL, about 17.7 mL, about 17.8 mL, about 17.9 mL, about 18 mL, about 18.1 mL, about 18.2 mL, about 18.3 mL, about 18.4 mL, about 18.5 mL, about 18.6 mL, about 18.7 mL, about 18.8 mL, about 18.9 mL, about 19 mL, about 19.1 mL, about 19.2 mL, about 19.3 mL, about 19.4 mL, about 19.5 mL, about 19.6 mL, about 19.7 mL, about 19.8 mL, about 19.9 mL, about 20 mL, about 20.1 mL, about 20.2 mL, about 20.3 mL, about 20.4 mL, about 20.5 mL, about 20.6 mL, about 20.7 mL, about 20.8 mL, about 20.9 mL, about 21 mL, about 21.1 mL, about 21.2 mL, about 21.3 mL, about 21.4 mL, about 21.5 mL, about 21.6 mL, about 21.7 mL, about 21.8 mL, about 21.9 mL, about 22 mL, about 22.1 mL, about 22.2 mL, about 22.3 mL, about 22.4 mL, about 22.5 mL, about 22.6 mL, about 22.7 mL, about 22.8 mL, about 22.9 mL, about 23 mL, about 23.1 mL, about 23.2 mL, about 23.3 mL, about 23.4 mL, about 23.5 mL, about 23.6 mL, about 23.7 mL, about 23.8 mL, about 23.9 mL, about 24 mL, about 24.1 mL, about 24.2 mL, about 24.3 mL, about 24.4 mL, about 24.5 mL, about 24.6 mL, about 24.7 mL, about 24.8 mL, about 24.9 mL, about 25 mL of the formulation, about 30 mL of the formulation, about 35 mL of the formulation, about 40 mL of the formulation, about 45 mL of the formulation, about 50 mL of the formulation, about 55 mL of the formulation, about 60 mL of the formulation, about 65 mL of the formulation, about 70 mL of the formulation, about 75 mL of the formulation, about 80 mL of the formulation, about 85 mL of the formulation, about 90 mL of the formulation, about 95 mL of the formulation, or about 100 mL of the formulation. In some embodiments, the prefilled syringe comprises a needle having a gauge of about 20 to about 33, e.g., about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, or about 33. In some embodiments, the prefilled syringe comprises a 20-gauge needle, a 21-gauge needle, a 22-gauge needle, a 23-gauge needle, a 24-gauge needle, a 25-gauge needle, a 26-gauge needle, a 27-gauge needle, a 28-gauge needle, a 29-gauge needle, a 30-gauge needle, a 31-gauge needle, a 32-gauge needle, or a 33-gauge needle. In some embodiments, the method comprising administering the formulation at a rate of about 5 to about 20 mL/min, e.g., about 5 mL/min, about 6 mL/min, about 7 mL/min, about 8 mL/min, about 9 mL/min, about 10 mL/min, about 11 mL/min, about 12 mL/min, about 13 mL/min, about 14 mL/min, about 15 mL/min, about 16 mL/min, about 17 mL/min, about 18 mL/min, about 19 mL/min, or about 20 mL/min. In some embodiments, the method comprising administering the formulation at a rate of at least about 5 to about 20 mL/min, e.g., at least about 5 mL/min, at least about 6 mL/min, at least about 7 mL/min, at least about 8 mL/min, at least about 9 mL/min, at least about 10 mL/min, at least about 11 mL/min, at least about 12 mL/min, at least about 13 mL/min, at least about 14 mL/min, at least about 15 mL/min, at least

about 16 mL/min, at least about 17 mL/min, at least about 18 mL/min, at least about 19 mL/min, or at least about 20 mL/min. In some embodiments, the method comprising administering the formulation at a rate of at least or faster than about 5 to about 20 mL/min, e.g., at least or faster than about 5 mL/min, at least or faster than about 6 mL/min, at least or faster than about 7 mL/min, at least or faster than about 8 mL/min, at least or faster than about 9 mL/min, at least or faster than about 10 mL/min, at least or faster than about 11 mL/min, at least or faster than about 12 mL/min, at least or faster than about 13 mL/min, at least or faster than about 14 mL/min, at least or faster than about 15 mL/min, at least or faster than about 16 mL/min, at least or faster than about 17 mL/min, at least or faster than about 18 mL/min, at least or faster than about 19 mL/min, or at least or faster than about 20 mL/min. In some embodiments, the administration takes about 30 seconds to about 360 seconds. In some embodiments, the administration takes at least about 30 seconds to about 240 seconds. In some embodiments, the administration takes at least or less than about 30 seconds to about 240 seconds. In some embodiments, the administration takes about 60 seconds to about 240 seconds. In some embodiments, the administration takes at least about 60 seconds to about 240 seconds. In some embodiments, the administration takes at least or less than about 60 seconds to about 240 seconds. In some embodiments, the method comprising administering about 5 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min. In some embodiments, the method comprising administering about 10 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min. In some embodiments, the method comprising administering about 15 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min. In some embodiments, the method comprising administering about 20 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min. In some embodiments, the formulation has a viscosity of about 1 cP to about 50 cP, e.g., about 1 cP, about 2 cP, about 3 cP, about 4 cP, about 5 cP, about 6 cP, about 7 cP, about 8 cP, about 9 cP, about 10 cP, about 15 cP, about 20 cP, about 25 cP, about 30 cP, about 35 cP, about 40 cP, about 45 cP, or about 50 cP. In some embodiments, administration of the formulation requires less applied force when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, the method comprising administering about 5 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min with an applied force of about 10 N to about 45 N. In some embodiments, the method comprising administering the formulation to the subject using a prefilled syringe comprising a 25-gauge needle. In some embodiments, the method comprising administering about 10 mL of the formulation to the subject at a rate of about 5 mL/min to about 20 mL/min with an applied force of about 25 N to about 50 N. In some embodiments, the method comprising administering the formulation to the subject using a prefilled syringe comprising a 25-

gauge needle. In some embodiments, administration of the formulation is faster when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation causes fewer side effects in the subject when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation causes less pain and discomfort in the subject when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation causes less back leakage at the injection site when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, back leakage at the injection site is about 100% to about 30% less when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation causes less swelling volume and/or swelling height at the injection site when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation causes about 35% to about 1% less swelling and/or swelling height the injection site when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation yields a lower bleb swelling size, less bleb induration, and/or quicker bleb resolution when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation yields more consistent delivery times when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, the subject is human. In some embodiments, the administering comprises the subject self-administering the formulation. In some embodiments, the administering comprises a healthcare provider or a caregiver administering the formulation to the subject. In some embodiments, the subcutaneous administration comprises a single injection. In some embodiments, the subcutaneous administration comprises two or more injections.

25 **[00207]** In some embodiments, the disclosure provides a method of delivering a formulation comprising a hyaluronidase enzyme and a therapeutically effective amount of an active ingredient selected from a small molecule, a peptide fragment, a biologic, a nanoparticle, an antibody, an antibody fragment, and a small molecule antiviral, into a patient with a delivery apparatus comprising a prefilled medicament container containing a volume of the formulation, an energy source configured to interact with the medicament container to expel the formulation and a trigger mechanism configured to activate the energy source in response to a user input, the method comprising: coupling the delivery apparatus to a first end of a conduit, the conduit in fluid communication with the prefilled medicament container; coupling a second end of the conduit to a

port comprising an injection apparatus extending therefrom, the injection apparatus in fluid communication with the prefilled medicament container; inserting the injection apparatus into an injection site on a patient; and manipulating the trigger mechanism to allow the energy source to expel the formulation from the prefilled medicament container, wherein the energy source urges the volume of the formulation through the injection apparatus during the injection. In some embodiments, during the administering, the delivery apparatus is placed off-body relative to the patient, while the port is placed on-body relative to the patient. In some embodiments, the energy source urges the volume of the medicament through the injection apparatus when the volume of the medicament is expelled from the outlet. In some embodiments, the port comprises an air release valve. In some embodiments, the port is removably coupled to an injection site of a user. In some embodiments, the port and/or the injection apparatus comprises a butterfly needle. In some embodiments, the injection apparatus extends through the aperture on a plane generally perpendicular to the plane of the user engagement surface. In some embodiments, the delivery apparatus purges the conduit of air before the injection apparatus is inserted into an injection site of a patient. In some embodiments, the delivery apparatus purges the conduit of air after the injection apparatus is inserted into an injection site of a patient. In some embodiments, the delivery apparatus automatically purges the conduit of air when the conduit is coupled to the delivery apparatus. In some embodiments, the conduit is decoupled from the port after the volume of the medicament is expelled from the outlet. In some embodiments, the conduit comprises a flexible tubing. In some embodiments, the conduit is at least 6 inches, at least 12 inches, at least 18 inches, at least 24 inches, at least 30 inches, or at least 36 inches in length. In some embodiments, the energy source is prevented from expelling medicament from the outlet until the conduit is purged of air. In some embodiments, the volume of the medicament is at least 10 mL, at least 20 mL, at least 30 mL, at least 40 mL, at least 50 mL, at least 60 mL, at least 70 mL, at least 80 mL, at least 90 mL, or at least 100 mL. In some embodiments, the delivery apparatus is not resettable. In some embodiments, the outlet is a generally cylindrical member and comprises threads protruding therefrom. In some embodiments, the volume of the formulation is expelled at a rate of at least 1 mL/min, at least 2 mL/min, at least 3 mL/min, at least 4 mL/min, at least 5 mL/min, at least 6 mL/min, at least 7 mL/min, at least 8 mL/min, at least 9 mL/min, or at least 10 mL/min. In some embodiments, the conduit is purged of air prior to the injection. In some embodiments, the delivery apparatus purges the conduit of air after the injection apparatus is inserted into an injection site of a patient. In some embodiments, the delivery apparatus is not resettable. In some embodiments, the delivery apparatus or any part thereof is disposable after a single use. In some embodiments, the volume of the

medicament is expelled from the delivery apparatus in at least 30 seconds, at least 45 seconds, at least 60 seconds, at least 75 seconds, at least 90 seconds, at least 105 seconds, at least 120 seconds, at least 135 seconds, at least 150 seconds, at least 165 seconds, at least 180 seconds, at least 195 seconds, at least 210 seconds, at least 225 seconds, at least 240 seconds, at least 255 seconds, at least 270 seconds, at least 285 seconds, at least 300 seconds, at least 315 seconds, at least 330 seconds, at least 345 seconds, at least 360 seconds, at least 375 seconds, at least 390 seconds, at least 405 seconds, at least 420 seconds, at least 435 seconds, at least 450 seconds, at least 465 seconds, at least 480 seconds, at least 495 seconds, at least 510 seconds, at least 525 seconds, at least 540 seconds, at least 555 seconds, at least 570 seconds, at least 585 seconds, or at least 600 seconds. In some
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embodiments, the volume of the medicament is expelled from the delivery apparatus at a rate of at least 1 mL/min, at least 2 mL/min, at least 3 mL/min, at least 4 mL/min, at least 5 mL/min, at least 6 mL/min, at least 7 mL/min, at least 8 mL/min, at least 9 mL/min, or at least 10 mL/min. In some embodiments, the hyaluronidase enzyme is a recombinant human hyaluronidase enzyme. In some embodiments, the hyaluronidase enzyme is recombinant human hyaluronidase PH20 enzyme. In some embodiments, the hyaluronidase enzyme has an activity of about 150 U/mL to about 150 kU/mL. In some embodiments, the hyaluronidase enzyme has an activity of about 500 U/mL to about 5,000 U/mL. In some embodiments, the hyaluronidase enzyme has an activity of about 1,500 U/mL to about 10,000 U/mL. In some embodiments, the active ingredient is a small molecule, a peptide fragment, a biologic, or a nanoparticle. In some embodiments, the active ingredient is an antibody, an antibody fragment, or a small molecule antiviral. In some embodiments, the administering comprises administering to the subject about 10 mL to about 20 mL of the formulation. In some embodiments, the administering comprises administering to the subject about 3 mL to about 15 mL of the formulation. In some embodiments, the administering comprises administering to the subject about 3 mL, about 3.1 mL, about 3.2 mL, about 3.4 mL, about 3.5 mL, about 3.6 mL, about 3.7 mL, about 3.8 mL, about 3.9 mL, about 4 mL, about 4.1 mL, about 4.2 mL, about 4.3 mL, about 4.4 mL, about 4.5 mL, about 5 mL, about 5.1 mL, about 5.2 mL, about 5.3 mL, about 5.4 mL, about 5.5 mL, about 5.6 mL, about 5.7 mL, about 5.8 mL, about 5.9 mL, about 6 mL, about 6.1 mL, about 6.2 mL, about 6.3 mL, about 6.4 mL, about 6.5 mL, about 6.6 mL, about 6.7 mL, about 6.8 mL, about 6.9 mL, about 7 mL, about 7.1 mL, about 7.2 mL, about 7.3 mL, about 7.4 mL, about 7.5 mL, about 7.6 mL, about 7.7 mL, about 7.8 mL, about 7.9 mL, about 8 mL, about 8.1 mL, about 8.2 mL, about 8.3 mL, about 8.4 mL, about 8.5 mL, about 8.6 mL, about 8.7 mL, about 8.8 mL, about 8.9 mL, about 9 mL, about 9.1 mL, about 9.2 mL, about 9.3 mL, about 9.4 mL, about 9.5 mL, about 9.6 mL, about 9.7 mL, about 9.8 mL, about 9.9 mL, about 10 mL, about 10.1 mL,

about 10.2 mL, about 10.3 mL, about 10.4 mL, about 10.5 mL, about 10.6 mL, about 10.7 mL,
about 10.8 mL, about 10.9 mL, about 11 mL, about 11.1 mL, about 11.2 mL, about 11.3 mL, about
11.4 mL, about 11.5 mL, about 11.6 mL, about 11.7 mL, about 11.8 mL, about 11.9 mL, about 12
mL, about 12.1 mL, about 12.2 mL, about 12.3 mL, about 12.4 mL, about 12.5 mL, about 12.6 mL,
5 about 12.7 mL, about 12.8 mL, about 12.9 mL, about 13 mL, about 13.1 mL, about 13.2 mL, about
13.3 mL, about 13.4 mL, about 13.5 mL, about 13.6 mL, about 13.7 mL, about 13.8 mL, about 13.9
mL, about 14 mL, about 14.1 mL, about 14.2 mL, about 14.3 mL, about 14.4 mL, about 14.5 mL,
about 14.6 mL, about 14.7 mL, about 14.8 mL, about 14.9 mL, about 15 mL, about 15.1 mL, about
15.2 mL, about 15.3 mL, about 15.4 mL, about 15.5 mL, about 15.6 mL, about 15.7 mL, about 15.8
10 mL, about 15.9 mL, about 16 mL, about 16.1 mL, about 16.2 mL, about 16.3 mL, about 16.4 mL,
about 16.5 mL, about 16.6 mL, about 16.7 mL, about 16.8 mL, about 16.9 mL about 17 mL, about
17.1 mL, about 17.2 mL, about 17.3 mL, about 17.4 mL, about 17.5 mL, about 17.6 mL, about 17.7
mL, about 17.8 mL, about 17.9 mL, about 18 mL, about 18.1 mL, about 18.2 mL, about 18.3 mL,
about 18.4 mL, about 18.5 mL, about 18.6 mL, about 18.7 mL, about 18.8 mL, about 18.9 mL,
15 about 19 mL, about 19.1 mL, about 19.2 mL, about 19.3 mL, about 19.4 mL, about 19.5 mL, about
19.6 mL, about 19.7 mL, about 19.8 mL, about 19.9 mL, about 20 mL, about 20.1 mL, about 20.2
mL, about 20.3 mL, about 20.4 mL, about 20.5 mL, about 20.6 mL, about 20.7 mL, about 20.8 mL,
about 20.9 mL, about 21 mL, about 21.1 mL, about 21.2 mL, about 21.3 mL, about 21.4 mL, about
21.5 mL, about 21.6 mL, about 21.7 mL, about 21.8 mL, about 21.9 mL, about 22 mL, about 22.1
20 mL, about 22.2 mL, about 22.3 mL, about 22.4 mL, about 22.5 mL, about 22.6 mL, about 22.7 mL,
about 22.8 mL, about 22.9 mL, about 23 mL, about 23.1 mL, about 23.2 mL, about 23.3 mL, about
23.4 mL, about 23.5 mL, about 23.6 mL, about 23.7 mL, about 23.8 mL, about 23.9 mL, about 24
mL, about 24.1 mL, about 24.2 mL, about 24.3 mL, about 24.4 mL, about 24.5 mL, about 24.6 mL,
about 24.7 mL, about 24.8 mL, about 24.9 mL, about 25 mL, about 30 mL, about 35 mL, about 40
25 mL, about 45 mL, about 50 mL, about 55 mL, about 60 mL, about 65 mL, about 70 mL, about 75
mL, about 80 mL, about 85 mL, about 90 mL, about 95 mL, or about 100 mL. In some
embodiments, the method comprises administering the formulation with a starting delivery force of
about 5 lbf to about 50 lbf, e.g., about 5 lbf, about 6 lbf, about 7 lbf, about 8 lbf, about 9 lbf, about
10 lbf, about 11 lbf, about 12 lbf, about 13 lbf, about 14 lbf, about 15 lbf, about 16 lbf, about 17 lbf,
30 about 18 lbf, about 19 lbf, about 20 lbf, about 25 lbf, about 30 lbf, about 35 lbf, about 40 lbf, about
45 lbf, or about 50 lbf. In some embodiments, the method comprising administering the formulation
with an ending delivery force of about 3 lbf to about 20 lbf, e.g., about 3 lbf, about 4 lbf, about 5 lbf,
about 6 lbf, about 7 lbf, about 8 lbf, about 9 lbf, about 10 lbf, about 11 lbf, about 12 lbf, about 13

lbf, about 14 lbf, about 15 lbf, about 16 lbf, about 17 lbf, about 18 lbf, about 19 lbf, or about 20 lbf.

In some embodiments, the method comprising administering the formulation with a starting pressure of about 50 psi to about 200 psi, e.g., about 50 psi, about 60 psi, about 70 psi, about 80 psi, about 90 psi, about 100 psi, about 110 psi, about 120 psi, about 130 psi, about 140 psi, about 150 psi, about 160 psi, about 170 psi, about 180 psi, about 190 psi, or about 200 psi. In some embodiments, the method comprising administering the formulation with an ending pressure of about 20 psi to about 75 psi, e.g., about 20 psi, about 25 psi, about 30 psi, about 35 psi, about 40 psi, about 45 psi, about 50 psi, about 55 psi, about 60 psi, about 65 psi, about 70 psi, or about 75 psi. In some embodiments, the medicament container is a prefilled syringe. In some embodiments, the prefilled syringe contains

about 3 mL, about 3.1 mL, about 3.2 mL, about 3.4 mL, about 3.5 mL, about 3.6 mL, about 3.7 mL, about 3.8 mL, about 3.9 mL, about 4 mL, about 4.1 mL, about 4.2 mL, about 4.3 mL, about 4.4 mL, about 4.5 mL, about 5 mL, about 5.1 mL, about 5.2 mL, about 5.3 mL, about 5.4 mL, about 5.5 mL, about 5.6 mL, about 5.7 mL, about 5.8 mL, about 5.9 mL, about 6 mL, about 6.1 mL, about 6.2 mL, about 6.3 mL, about 6.4 mL, about 6.5 mL, about 6.6 mL, about 6.7 mL, about 6.8 mL, about 6.9 mL, about 7 mL, about 7.1 mL, about 7.2 mL, about 7.3 mL, about 7.4 mL, about 7.5 mL, about 7.6 mL, about 7.7 mL, about 7.8 mL, about 7.9 mL, about 8 mL, about 8.1 mL, about 8.2 mL, about 8.3 mL, about 8.4 mL, about 8.5 mL, about 8.6 mL, about 8.7 mL, about 8.8 mL, about 8.9 mL, about 9 mL, about 9.1 mL, about 9.2 mL, about 9.3 mL, about 9.4 mL, about 9.5 mL, about 9.6 mL, about 9.7 mL, about 9.8 mL, about 9.9 mL, about 10 mL, about 10.1 mL, about 10.2 mL, about 10.3 mL, about 10.4 mL, about 10.5 mL, about 10.6 mL, about 10.7 mL, about 10.8 mL, about 10.9 mL, about 11 mL, about 11.1 mL, about 11.2 mL, about 11.3 mL, about 11.4 mL, about 11.5 mL, about 11.6 mL, about 11.7 mL, about 11.8 mL, about 11.9 mL, about 12 mL, about 12.1 mL, about 12.2 mL, about 12.3 mL, about 12.4 mL, about 12.5 mL, about 12.6 mL, about 12.7 mL, about 12.8 mL, about 12.9 mL, about 13 mL, about 13.1 mL, about 13.2 mL, about 13.3 mL, about 13.4 mL, about 13.5 mL, about 13.6 mL, about 13.7 mL, about 13.8 mL, about 13.9 mL, about 14 mL, about 14.1 mL, about 14.2 mL, about 14.3 mL, about 14.4 mL, about 14.5 mL, about 14.6 mL, about 14.7 mL, about 14.8 mL, about 14.9 mL, about 15 mL, about 15.1 mL, about 15.2 mL, about 15.3 mL, about 15.4 mL, about 15.5 mL, about 15.6 mL, about 15.7 mL, about 15.8 mL, about 15.9 mL, about 16 mL, about 16.1 mL, about 16.2 mL, about 16.3 mL, about 16.4 mL, about 16.5 mL, about 16.6 mL, about 16.7 mL, about 16.8 mL, about 16.9 mL, about 17 mL, about 17.1 mL, about 17.2 mL, about 17.3 mL, about 17.4 mL, about 17.5 mL, about 17.6 mL, about 17.7 mL, about 17.8 mL, about 17.9 mL, about 18 mL, about 18.1 mL, about 18.2 mL, about 18.3 mL, about 18.4 mL, about 18.5 mL, about 18.6 mL, about 18.7 mL, about 18.8 mL, about 18.9 mL, about 19 mL, about 19.1 mL, about

19.2 mL, about 19.3 mL, about 19.4 mL, about 19.5 mL, about 19.6 mL, about 19.7 mL, about 19.8 mL, about 19.9 mL, about 20 mL, about 20.1 mL, about 20.2 mL, about 20.3 mL, about 20.4 mL, about 20.5 mL, about 20.6 mL, about 20.7 mL, about 20.8 mL, about 20.9 mL, about 21 mL, about 21.1 mL, about 21.2 mL, about 21.3 mL, about 21.4 mL, about 21.5 mL, about 21.6 mL, about 21.7 mL, about 21.8 mL, about 21.9 mL, about 22 mL, about 22.1 mL, about 22.2 mL, about 22.3 mL, about 22.4 mL, about 22.5 mL, about 22.6 mL, about 22.7 mL, about 22.8 mL, about 22.9 mL, about 23 mL, about 23.1 mL, about 23.2 mL, about 23.3 mL, about 23.4 mL, about 23.5 mL, about 23.6 mL, about 23.7 mL, about 23.8 mL, about 23.9 mL, about 24 mL, about 24.1 mL, about 24.2 mL, about 24.3 mL, about 24.4 mL, about 24.5 mL, about 24.6 mL, about 24.7 mL, about 24.8 mL, about 24.9 mL, about 25 mL of the formulation, about 30 mL of the formulation, about 35 mL of the formulation, about 40 mL of the formulation, about 45 mL of the formulation, about 50 mL of the formulation, about 55 mL of the formulation, about 60 mL of the formulation, about 65 mL of the formulation, about 70 mL of the formulation, about 75 mL of the formulation, about 80 mL of the formulation, about 85 mL of the formulation, about 90 mL of the formulation, about 95 mL of the formulation, or about 100 mL of the formulation. In some embodiments, the prefilled syringe comprises a needle having a gauge of about 20 to about 33, e.g., about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, or about 33. In some embodiments, the prefilled syringe comprises a 20-gauge needle, a 21-gauge needle, a 22-gauge needle, a 23-gauge needle, a 24-gauge needle, a 25-gauge needle, a 26-gauge needle, a 27-gauge needle, a 28-gauge needle, a 29-gauge needle, a 30-gauge needle, a 31-gauge needle, a 32-gauge needle, or a 33-gauge needle. In some embodiments, the method comprising administering the formulation at a rate of about 5 to about 20 mL/min, e.g., about 5 mL/min, about 6 mL/min, about 7 mL/min, about 8 mL/min, about 9 mL/min, about 10 mL/min, about 11 mL/min, about 12 mL/min, about 13 mL/min, about 14 mL/min, about 15 mL/min, about 16 mL/min, about 17 mL/min, about 18 mL/min, about 19 mL/min, or about 20 mL/min. In some embodiments, the method comprising administering the formulation at a rate of at least about 5 to about 20 mL/min, e.g., at least about 5 mL/min, at least about 6 mL/min, at least about 7 mL/min, at least about 8 mL/min, at least about 9 mL/min, at least about 10 mL/min, at least about 11 mL/min, at least about 12 mL/min, at least about 13 mL/min, at least about 14 mL/min, at least about 15 mL/min, at least about 16 mL/min, at least about 17 mL/min, at least about 18 mL/min, at least about 19 mL/min, or at least about 20 mL/min. In some embodiments, the method comprising administering the formulation at a rate of at least or faster than about 5 to about 20 mL/min, e.g., at least or faster than about 5 mL/min, at least or faster than about 6 mL/min, at least or faster than about 7 mL/min, at

least or faster than about 8 mL/min, at least or faster than about 9 mL/min, at least or faster than about 10 mL/min, at least or faster than about 11 mL/min, at least or faster than about 12 mL/min, at least or faster than about 13 mL/min, at least or faster than about 14 mL/min, at least or faster than about 15 mL/min, at least or faster than about 16 mL/min, at least or faster than about 17 mL/min, at least or faster than about 18 mL/min, at least or faster than about 19 mL/min, or at least or faster than about 20 mL/min. In some embodiments, the administration takes about 30 seconds to about 360 seconds. In some embodiments, the administration takes at least about 30 seconds to about 240 seconds. In some embodiments, the administration takes at least or less than about 30 seconds to about 240 seconds. In some embodiments, the administration takes about 60 seconds to about 240 seconds. In some embodiments, the administration takes at least about 60 seconds to about 240 seconds. In some embodiments, the administration takes at least or less than about 60 seconds to about 240 seconds. In some embodiments, the method comprising administering about 5 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min. In some embodiments, the method comprising administering about 10 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min. In some embodiments, the method comprising administering about 15 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min. In some embodiments, the method comprising administering about 20 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min. In some embodiments, the formulation has a viscosity of about 1 cP to about 50 cP, e.g., about 1 cP, about 2 cP, about 3 cP, about 4 cP, about 5 cP, about 6 cP, about 7 cP, about 8 cP, about 9 cP, about 10 cP, about 15 cP, about 20 cP, about 25 cP, about 30 cP, about 35 cP, about 40 cP, about 45 cP, or about 50 cP. In some embodiments, administration of the formulation requires less applied force when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, the method comprising administering about 5 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min with an applied force of about 10 N to about 45 N. In some embodiments, the method comprising administering the formulation to the subject using a prefilled syringe comprising a 25-gauge needle. In some embodiments, the method comprising administering about 10 mL of the formulation to the subject at a rate of about 5 mL/min to about 20 mL/min with an applied force of about 25 N to about 50 N. In some embodiments, the method comprising administering the formulation to the subject using a prefilled syringe comprising a 25-gauge needle. In some embodiments, administration of the formulation is faster when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation causes fewer side effects in the subject when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments,

administration of the formulation causes less pain and discomfort in the subject when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation causes less back leakage at the injection site when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, back leakage at the injection site is about 100% to about 30% less when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation causes less swelling volume and/or swelling height at the injection site when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation causes about 35% to about 1% less swelling and/or swelling height the injection site when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation yields a lower bleb swelling size, less bleb induration, and/or quicker bleb resolution when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, administration of the formulation yields more consistent delivery times when compared to a similar formulation that does not comprise a hyaluronidase enzyme. In some embodiments, the subject is human. In some embodiments, the administering comprises the subject self-administering the formulation. In some embodiments, the administering comprises a healthcare provider or a caregiver administering the formulation to the subject. In some embodiments, the subcutaneous administration comprises a single injection. In some embodiments, the subcutaneous administration comprises two or more injections.

EXAMPLES

Example 1: Evaluation of a Handheld High-Volume Auto-Injector (HVAI) for use as an off-body device to subcutaneously deliver a biologic drug with rHuPH20

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INTRODUCTION

[00208] This study assessed the attributes of an AI and a syringe pump, by using an HVAI as a hands-free 'off-body' autoinfusion device to deliver an immunoglobulin solution (120 mg/mL; Ig-120) alone or co-mixed with recombinant human hyaluronidase PH20 (rHuPH20; 2000 U/mL). The objective of this study was to assess the performance of the HVAI when used in this injection methodology with a standard winged infusion set directly attached to the HVAI. Minipigs were used in this study due to the similarity of the SC skin architecture to humans (Kang et al., 2013). Each animal received two 10 mL SC injections into the lower abdominal region. The first injection

contained Ig-120 alone; the second injection occurred on the contralateral side of the animal and contained Ig-120 + 2000 U/mL rHuPH20. Quantitative endpoints for the study included a measurement of injection time, quantification (weight) of injection site back-leakage, caliper measurement of injection site swelling immediately post-injection (T0), as well as at 15 minutes (T15) and 30 minutes (T30) post-injection. Qualitative endpoints included assessment of erythema, swelling size and induration at T0, T15, T30, 2 hours post-injection (T2h) and approximately 24 hours post-injection (T24h) using a modified 5-point Draize scoring system.

EXPERIMENTAL DESIGN AND METHODS

Test and Control Articles

10 [00209] Ig-120 Test Solution

Description: Clear liquid reconstituted from lyophilized powder
 Concentration: 120 mg/mL
 Formulation: 20 mM Histidine, 130 mM sodium chloride, pH 6.5
 Lot number: NB1090-49
 15 Storage Conditions: $\leq -65^{\circ}\text{C}$
 Handling Conditions: Standard laboratory precautions
 Supplier: Biomed Supply
 Formulated by: Halozyme Product Development

[00210] Recombinant Human Hyaluronidase PH20 (rHuPH20)

20 Description: Clear colorless liquid
 Lot number: 1-FIN-3928
 Concentration: 9.3 mg/mL
 Enzyme activity: 1,039,763 U/mL
 Formulation: 10 mM Histidine, 130 mM sodium chloride, pH 6.5
 25 Storage Conditions: $\leq 70^{\circ}\text{C}$
 Handling Conditions: Standard laboratory precautions
 Supplier: Halozyme Therapeutics, Inc.

[00211] Ig Dilution Buffer

Description: Clear colorless liquid
 30 Formulation: 20 mM histidine, 130 mM sodium chloride, pH 6.5
 Batch/Lot: NB1078-18
 Storage Conditions: $2-8^{\circ}\text{C}$
 Handling Conditions: Standard laboratory precautions

Supplier: Halozyme Therapeutics, Inc.

Formulation

[00212] *Preparation of Test Solutions.* Two test solutions were utilized for this study. The first test solution was Ig-120 alone. The second test solution was Ig-120 + rHuPH20. To ensure
5 sufficient test solution for syringe filling 75 mL of each test solution was prepared.

[00213] To prepare the co-mix of Ig-120 + rHuPH20, 0.144 mL of rHuPH20 was added to the 75 mL of Ig-120 to yield a test solution of Ig-120 + rHuPH20 with a final concentration of 2000 U/mL. After preparation the test solutions were used for syringe filling.

[00214] *Device Syringe Filling.* Filling of all device syringes occurred in a sterile fill and finish
10 hood under aseptic conditions. Cyclic olefin copolymer (COC) syringes were filled with 10.1 mL of either Ig-120 alone or the co-mix of Ig-120 + rHuPH20. To fill the syringes a sterile rubber plunger was initially inserted into the sterile syringe to a loading position. A syringe pump was then used to fill the syringe with 10.1 mL of the test solution. After adding the test solution to the syringe, the rubber plunger was brought to the final fill position (to remove residual air in the syringe). The
15 syringe was then be capped and stored at 2-8°C until used for device assembly.

[00215] *Device Assembly.* Assembly of all devices occurred immediately prior to use. The syringe was inserted into the lower housing of the HVAI and held in place while the syringe cap was removed and replaced with a 25G x 3/4" x 12" winged infusion set. The rubber plunger was then pushed to its final position to prime the infusion set. After priming, the upper housing of the HVAI
20 containing the powerpack was pushed onto the lower housing and the two pieces engaged for final device assembly. The needle guard was removed immediately prior to use.

Animal Description

[00216] Species: Pig (*Sus scrofa domestica*)

Strain: Yucatan Miniature

25 Sex: Female

Age: ~ 3-4+ months

Weight: 14-16 kg

Quantity: 6 animals

Source: Premier BioSource (Ramona, CA)

30 Table 1. Summary of Animal Weights (Day of Treatment)

Animal ID#	Date of Birth	Bodyweight Day of Treatment (kg)
6053	23-Apr-2024	16.9
6054	24-Apr-2024	16.4
6055	25-Apr-2024	15.2
6060	23-Apr-2024	14.4
6061	24-Apr-2024	16.9
6062	24-Apr-2024	15.0

[00217] *Husbandry.* Animals were housed in steel pens with automatic water provided ad libitum. Animals were fed twice daily (AM and PM) but were kept NPO after midnight on the day of the study. The room environment was set to maintain a temperature of ~ 19-23°C and a relative humidity of 40-70%, with a 12 hour light/12 hour dark time cycle. Animals were acclimated to the vivarium for a minimum of 3 days prior to study start.

Test Materials

[00218] The following test materials were used in the study:

Table 2. Summary of Test Materials

Test Material	Supplier	Catalog No.
25G x 3/4" x 12" inch winged infusion set	Terumo Medical Supply	25SV*BLK
Surgical Eye Spear	BVI Merocel®	400101
High-volume Auto-Injector	Halozyme – Minnetonka, MN	N/A
Cyclic olefin copolymer (COC) syringes	SCHOTT	101787-TAB
Rubber seal for COC syringes	SCHOTT	101788-001
Syringe caps	Becton Dickinson, Franklin Lakes, NJ	305819
HVAI-10-L 20 lbf Main Spring	Lee Springs	101817-001
HVAI-10-L Latch	Halozyme – Minnetonka, MN	101800-001
HVAI-10-L 10mL Ram	Halozyme – Minnetonka, MN	101801-001
HVAI-10-L Button	Halozyme – Minnetonka, MN	101805-001
HVAI-10-L Cap Removal Tool	Halozyme – Minnetonka, MN	101806-001

Test Material	Supplier	Catalog No.
HVAI-10-L Button Ring	Halozyme – Minnetonka, MN	101816-001
HVAI-10-L Button Assembly	Halozyme – Minnetonka, MN	300599-001
HVAI-10-L Rear Housing (modified)	Halozyme – Minnetonka, MN	101798-001
HVAI-10-L Front Housing	Halozyme – Minnetonka, MN	101799-001
3D Camera	Canfield Bioscience	Vectra H2
Standard Digital Camera	Canon	S120
Digital caliper	Fisher Scientific	06-664-16
Digital Stopwatch	Fisher Scientific	14-659

EXPERIMENTAL DESIGN

[00219] In this study, two 10 mL injections were administered to the abdomen of a Yucatan miniature pig. On one side of the abdomen a test solution of Ig-120 alone was administered and a second injection of Ig-120 + rHuPH20 on the contralateral side of the animal. All test solutions containing rHuPH20 were formulated at 2000 U/mL. An HVAI was used as an off-body device to deliver the test solution. The test solutions for each animal are summarized in Table 3.

Table 3. Description of Treatments

Cohort	# of Injections / Cohort	Test Solution	Volume/injection (mL)	[rHuPH20] (U/mL)
1	6	Ig-120	10	0
2	6	Ig-120 + rHuPH20	10	2000

[00220] The length of each injection was measured and recorded using a stopwatch. Immediately post-injection needle was removed and back-leakage collected for 30 seconds using a pre-weighed eye spear. Swelling size was then measured using a digital caliper and by obtaining a 3D image capture immediately post-injection (T0). Caliper measurement of bleb size was also taken and at 15 minutes (T15) and 30 minutes (T30) post-injection. Standard photographs were obtained at T0, T15, T30, T2h (2h post-injection) and T24h (24h post-injection).

[00221] Additional post-injection qualitative injection site evaluations for erythema, swelling and induration were performed at T0, T15, T30 and T2h with a final evaluation at approximately T24h post-injection. In summary the endpoints for the study were: measurement of HVAI injection time (digital stopwatch); collection and measurement of back-leakage weight using an eye spear; caliper

measurement of bleb size post-injection using digital caliper at T0, T15 and T30; measurement of bleb volume, area and height at T0 using 3D imaging; assessment of blebs for erythema, swelling size and induration at times T0, T15, T30, T2h and T24h; and photographic documentation of all injection sites: pre-injection, T0, T15, T30, T2h and T24h.

5 PROCEDURES

[00222] On the day prior to the study, HVAI devices (one Ig-120; one Ig-120 + rHuPH20) were withdrawn from refrigerated storage and brought to room temperature for at least 30 minutes prior to use. The first injection for each animal was always Ig-120 followed by a second injection on the contralateral side of the animal with Ig-120 + rHuPH20. Injection sites were located on the left and
10 right abdominal regions, ~5 cm cranially from the inguinal fold towards the midline and ~3 cm towards the midline of the animal.

[00223] Prior to the start of study, animals were assessed for general health, and body weights were collected. Animals were anesthetized with isoflurane gas and placed in dorsal recumbence on a heated surgical table and were maintained under isoflurane gas for the entire duration of the
15 procedure. The abdominal region was cleaned with Nolvasan and the injection site wiped with gauze containing 70% isopropanol and wiped dry with sterile gauze. Each of the injection sites were marked with a permanent marker and then photographed with the standard and 3D cameras prior to HVAI needle insertion. The HVAI was mounted into the platform and the needle bevel confirmed to face upward. The HVAI was unlocked, and the needle cap was removed and discarded prior to
20 needle insertion.

[00224] The skin was pinched at the injection site and the needle was inserted into the pinched skin and allowed to freely float in the SC space. After needle insertion, the injection started by pushing the activation button. The injection was timed using a digital stopwatch. Upon completion of injection, the injection time was recorded, and the needle was withdrawn from the skin. Test
25 solution back-leakage at the injection site was absorbed to a pre-weighed eye spear for 30 seconds and the weight of the eye spear was measured. The margins of the injection site bleb were then marked with a permanent marker and measured for length, width, and height using a digital caliper, then photographed with the standard and 3D cameras immediately post-injection (T0). Caliper measurements were also taken at T15 and T30 post-injection. After the second injection two
30 additional syringes (one with Ig-120 and one with Ig-120 + rHuPH20) were removed from refrigerated storage and brought to room temperature for use with the following animal. Local injection sites were also qualitatively assessed and graded for erythema severity, swelling size appearance, and firmness immediately after injection, using a scoring system described in Table 4

Table 4, Table 5, and Table 6 respectively. Any additional observations were noted at this time. The injection site was then qualitatively assessed at T0, T15 and T30 and photographed using a standard camera while the animal was still under anesthesia. The injection sites were again qualitatively assessed and photographed at T2h but the animal was conscious and hand-held by an animal technician.

[00225] After the first injection and while the animal was still sedated, the identical procedure was repeated on the contralateral side of the animal with the second test solution (Ig-120 + rHuPH20). Thirty minutes after completion of the second injection (and after the final assessments at T30 minutes), the animal was removed from anesthesia and returned to its home cage for recovery. On the following day (at approximately 24 hours) the animal was re-anesthetized, and both of the injection sites assessed for erythema, induration and swelling, and photographed. Following the ~T24h assessment, the animal was humanely euthanized using an injectable euthanasia drug.

Table 4. Grading Scale for Erythema Formation

Scale	Description
0	No erythema
1	Very slight erythema (barely perceptible)
2	Well defined erythema
3	Moderate to severe erythema
4	Severe erythema (beet redness) to slight eschar formation

Table 5. Grading Scale for Swelling Size Formation

Scale	Description
0	No swelling
1	Very slight swelling
2	Slight swelling
3	Moderate swelling
4	Severe swelling

Table 6. Grading Scale for Swelling Firmness (Induration)

Scale	Description
0	No perceptible difference in firmness after injection
1	Very slightly firm (barely perceptible)

Scale	Description
2	Mildly firm
3	Moderately firm
4	Very firm

CALCULATIONS AND STATISTICAL METHODS

[00226] *Statistical Methods.* Statistical comparisons for Ig-120 and Ig-120 + rHuPH20 were performed using an unpaired parametric t-test (Prism v10.1.1, GraphPad Software, Inc., San Diego, California). All hypotheses' tests were performed at a 5% significance level, thus considered significant if $p < 0.05$.

[00227] *Assessment of Injection Time.* The time required for each injection was measured using a digital stopwatch and recorded after each injection.

[00228] *Assessment of Swelling Volume, Area and Height Using Caliper Measurement and 3D Imaging.* Volume and area of post-injection swelling were measured using both caliper measurement and 3D camera image analysis. For caliper measurements a digital caliper was utilized to measure length, width and height of the bleb that formed post-injection. The length and width are defined as the edge to edge measurements of the bleb (i.e., diameter) along their longest axes. These values were manually recorded, and the volume determined using the formula for half of an ellipsoid

$$\text{Vol} = (2/3) * \pi * A * B * C$$
where A = Length/2, B = Width/2 and C = Height.

[00229] 3D imaging was applied as a longitudinal methodology to measure post-injection swelling. By obtaining high definition pre- and post-injection 3D images the distances between two registered surfaces can be determined. The camera captures images using a factory calibrated bifocal imaging system to measure distance between surfaces. Surface registration was performed using a multipoint method that utilized common landmarks between the pre-injection image and the post-injection image. The volume, area and height of the post-injection swelling was calculated for each injection.

RESULTS AND DISCUSSION

[00230] *Pre-study Enzymatic Activity Testing.* The co-mix of Ig-120 + rHuPH20 was prepared on the day prior to study start and the enzyme activity of the test solution was measured using an in vitro activity assay (VV-QUAL-00675; formerly TM010). The results of this activity testing are shown in Table 7.

Table 7. Summary of Pre-Study Activity Testing

Test Solution	Hyaluronidase Activity (U/mL) (Mean ± SD)
Ig-120 + rHuPH20	2254 ± 53

[00231] *Post-study Enzymatic Activity Testing.* Sufficient co-mix of Ig-120 + rHuPH20 was prepared so that an extra HVAI could be assembled. The test solution from this device was collected at the end of the study and tested for hyaluronidase activity. The results are shown in Table 8.

Table 8. Summary of Post-Study Activity Testing

Test Solution	Hyaluronidase Activity (U/mL) (Mean ± SD)
Ig-120 + rHuPH20	2202 ± 27

Pre- and Post-injection Quantitative Measurements

[00232] *Measurement of HVAI Injection Times.* The time for each injection was measured using a stopwatch and is shown in Table 9 and Fig. 6. There was approximately a 15% decrease in delivery time with less variability when the Ig-120 was delivered co-mixed with rHuPH20 but this was not considered significant.

Table 9. Measurement of HVAI Injection Times

Test Solution	Injection Time (Mean ± SEM)	% Change
Ig-120	36.9 ± 2.1	---
Ig-120 + rHuPH20	32.2 ± 0.8	-12.7%

[00233] *Measurement of Post-injection Back-leakage.* The back-leakage was collected using a pre-weighed eye spear for 30 seconds post-injection. The eye spear was then re-weighed, and the weight of the back-leakage recorded. The amount of back-leakage (mean ± SEM) for each test solution is shown in Table 10 with individual values shown in Fig. 7.

Table 10. Summary of Post-injection Back-leakage

Test Solution	Back-leakage (mg $\pm$ SEM)	% Change
Ig-120	15.6 $\pm$ 6.8	---
Ig-120 + rHuPH20	0.0 $\pm$ 0.0	-100%

[00234] *Assessment of Post-Injection Bleb Volume, Area, and Height (Caliper Measurements).*

The local injection site swelling (bleb) was marked and measured using a digital caliper. Bleb volume dispersion area and swelling height of each bleb was determined as described in Section 6.2 and this data is summarized at the T0, T15 and T30 timepoints in Table 11, Table 12 and Table 13 and individual values shown in Fig. 8, Fig. 9, and Fig. 10.

Table 11. Bleb Volume After Injection of Ig-120 and Ig-120 + rHuPH20 Over Time Using Caliper Measurement (Mean $\pm$ SEM)

Volume of Post-injection Swelling			
	Time after injection		
Test Solution	T0	T15	T30
Ig-120	54.8 $\pm$ 7.2	37.2 $\pm$ 5.6	32.3 $\pm$ 3.3
Ig-120 + rHuPH20	21.7 $\pm$ 7.0	11.5 $\pm$ 0.8	7.3 $\pm$ 1.2
% Change	-60.4% ^a	-69.1% ^a	-77.4% ^a

Table 12. Bleb Area After injection of Ig-120 and Ig-120 + rHuPH20 Over Time Using Caliper Measurement (Mean $\pm$ SEM)

Area of Post-injection Swelling (cm ² $\pm$ SEM)			
	Time after injection		
Test Solution	T0	T15	T30
Ig-120	31.3 $\pm$ 2.6	30.8 $\pm$ 2.8	33.9 $\pm$ 2.8
Ig-120 + rHuPH20	25.8 $\pm$ 1.7	30.4 $\pm$ 1.9	31.6 $\pm$ 2.5
% Change	-17.6%	-1.3%	-6.8%

Table 13. Bleb Height After Injection of Ig-120 and Ig-120 + rHuPH20 Over Time Using Caliper Measurement (Mean $\pm$ SEM)

Height of Post-injection Swelling (mm $\pm$ SEM)			
	Time after injection		
Test Solution	T0	T15	T30

Height of Post-injection Swelling (mm ± SEM)			
	Time after injection		
Test Solution	T0	T15	T30
Ig-120	8.7 ± 0.7	5.9 ± 0.6	4.8 ± 0.4
Ig-120 + rHuPH20	4.2 ± 0.5	2.0 ± 0.3	1.3 ± 0.3
% Change	-51.7% ^a	-66.1% ^a	-72.9% ^a

[00235] The post-injection swelling, area, and height over time were also determined at T15 and T30 and the scores are shown in Fig. 11, Fig. 12, and Fig. 13, respectively.

[00236] *Assessment of Post-injection Bleb Shape, Volume, Area and Height (3D Imaging).* Pre-

and post-injection photographs were taken using a 3D imaging system. This technology permits point-to-point alignment of these two images through multipoint surface registration. The distance between any two points is then represented using a colorimetric surface contour map. Regions where there is no difference between the two images are displayed in gray. Where the post-injection image is higher than the pre-injection image, the region is displayed in shades of blue. Where the post-injection image is lower than the pre-injection image the distance is displayed in shades of orange. The color intensity is proportional to the amount of distance measured between images with darker blue color indicating greater distance from the pre-injection image. Out of range measurements (distances greater than 6 mm) are depicted in white. Bleb measurements of volume and height include regions out of range.

[00237] Each animal had a pre-injection 3D image taken of the injection site followed by a second image taken immediately post-injection and these images were mapped to each other using multipoint registration. These registered pre-/post-injection images were then used to calculate the bleb volume, height, circumference, length, and width for each bleb using proprietary software (Vectra H1 software; Canfield Sciences). Colorimetric surface contour maps of each post-injection bleb for Ig-120 and Ig-120 + rHuPH20 are shown in Figs. 14A and 14B. Measured individual bleb volume, area, and height are provided in Table 14 and shown in Fig. 15, Fig. 16, and Fig. 17, respectively.

Table 14. Bleb Volume, Area and Height After Injection of Ig-120 and Ig-120 + rHuPH20 Assessed Using 3D Imaging (Mean ± SEM)

	Mean ± SEM		
Test Solution	Volume (mL)	Area (cm ²)	Height (mm)

	Mean $\pm$ SEM		
Test Solution	Volume (mL)	Area (cm ²)	Height (mm)
Ig-120	7.0 $\pm$ 0.6	30.0 $\pm$ 1.8	6.0 $\pm$ 0.3
Ig-120 + rHuPH20	6.7 $\pm$ 0.6	28.5 $\pm$ 2.0	5.4 $\pm$ 0.4
% Change	-4.3%	-5.0%	-10.0%

Qualitative Assessment of Local Injection Sites

[00238] Qualitative assessments were taken immediately post-injection (T0), 15 minutes post-injection (T15), 30 minutes post-injection (T30), 2 hours post-injection (T2h) and at approximately 24 hours post-injection (T24h). Only two evaluators were available for scoring at T24h.

[00239] *Post-injection Erythema.* The post-injection erythema was evaluated at all timepoints (T0, T15, T30, T2h and T24h). Erythema was very mild and transient, having only been observed in 2/12 animals at T15 and 1/12 animals by T30 with complete resolution by T2h. No erythema was seen at T24h. The erythema scores (Mean $\pm$ SEM) are shown in Table 15 and Fig. 18.

Table 15. Qualitative Assessment of Post-Injection Erythema (T0-T15-T30-T2h)

Time Post-Injection	Test Solution	Erythema Score (Mean $\pm$ SEM)	% Change
T0	Ig-120	0.0 $\pm$ 0.0	---
	Ig-120 + rHuPH20	0.0 $\pm$ 0.0	0%
T15	Ig-120	0.0 $\pm$ 0.0	---
	Ig-120 + rHuPH20	0.1 $\pm$ 0.1	+100%
T30	Ig-120	0.0 $\pm$ 0.0	---
	Ig-120 + rHuPH20	0.1 $\pm$ 0.1	+100%
T2h	Ig-120	0.0 $\pm$ 0.0	---
	Ig-120 + rHuPH20	0.0 $\pm$ 0.0	0%
T24h	Ig-120	0.0 $\pm$ 0.0	---
	Ig-120 + rHuPH20	0.0 $\pm$ 0.0	0%

[00240] *Post-injection Swelling Size.* Post-injection swelling size was significantly greater for Ig-120 than for Ig-120 + rHuPH20. Scoring by three evaluators for swelling size (Mean $\pm$ SEM) are summarized in Table 16. Individual values immediately post-injection (T0) are shown in Fig. 19 and values scored over time (Mean $\pm$ SEM) are shown in Fig. 20.

Table 16. Qualitative Assessment of Post-Injection Swelling Size (T0-T15-T30-T2h)

Time Post-Injection	Test Solution	Swelling Size Score (Mean $\pm$ SEM)	% Change
T0	Ig-120	3.5 $\pm$ 0.1	---
	Ig-120 + rHuPH20	2.5 $\pm$ 0.2	-28.6%
T15	Ig-120	2.8 $\pm$ 0.2	---
	Ig-120 + rHuPH20	1.6 $\pm$ 0.2	-42.9%
T30	Ig-120	2.7 $\pm$ 0.2	---
	Ig-120 + rHuPH20	1.0 $\pm$ 0.2	-63.0%
T2h	Ig-120	1.7 $\pm$ 0.2	---
	Ig-120 + rHuPH20	0.0 $\pm$ 0.0	-100%
T24h	Ig-120	0.0 $\pm$ 0.0	---
	Ig-120 + rHuPH20	0.0 $\pm$ 0.0	0%

[00241] *Post-injection Induration.* The induration (firmness) of the post-injection blebs for Ig-120 was found to be significantly greater than the blebs that resulted from injection of Ig-120 + rHuPH20 ($p < 0.05$). Scoring by three evaluators for swelling size (Mean $\pm$ SEM) are summarized in Table 17. Individual values immediately post-injection (T0) are shown in Fig. 21 and values scored over time (Mean $\pm$ SEM) are shown in Fig. 22.

Table 17. Qualitative Assessment of Post-Injection Induration (T0-T15-T30-T2h)

Time Post-Injection	Test Solution	Induration Score (Mean $\pm$ SEM)	% Change
T0	Ig-120	3.3 $\pm$ 0.1	---
	Ig-120 + rHuPH20	1.9 $\pm$ 0.1	-42.4%
T15	Ig-120	2.8 $\pm$ 0.2	---
	Ig-120 + rHuPH20	1.7 $\pm$ 0.5	-39.3%
T30	Ig-120	2.2 $\pm$ 0.2	---
	Ig-120 + rHuPH20	0.7 $\pm$ 0.2	-68.2%
T2h	Ig-120	1.4 $\pm$ 0.1	---
	Ig-120 + rHuPH20	0.0 $\pm$ 0.0	-100%
T24h	Ig-120	0.0 $\pm$ 0.0	---
	Ig-120 + rHuPH20	0.0 $\pm$ 0.0	0%

Photographs of Injection Sites Pre- and Post-Injection

[00242] The injection sites were photographed before and immediately post-injection and then at T15, T30, T2h and T24h. Photographic images are shown in Fig. 23-34.

5 **Example 2: Evaluation of a Handheld High-Volume Auto-Injector (HVAI) for Use as an Off-Body Device to Subcutaneously Deliver a Biologic Drug with rHuPH20**

SUMMARY

[00243] The Gen2 HVAI was modified to be able to attach an infusion set with Luer connector to the device to be used as an Off-Body Device (OfBD). Test solutions used in this study were an
10 immunoglobulin solution formulated at 120 mg/mL (Ig-120) either alone or co-mixed with recombinant human hyaluronidase PH20 (rHuPH20) at 2000 U/mL. A 27G x 3/4" x 12" winged infusion set was used for all injections.

[00244] Endpoints for the study included quantitative measurement of injection times, back-leakage and bleb size over time measured using a digital caliper. Bleb measurements were taken
15 immediately post-injection (T0), 15 minutes post-injection (T15) and 30 minutes post-injection (T30). Qualitative endpoints included assessment of erythema, swelling size and induration using a modified 5-point Draize scoring system and three independent evaluators. Qualitative endpoints were taken at T0, T15 and T30 and at two hours post-injection (T2h) and approximately 24 hours post-injection (T24).

20 [00245] The addition of rHuPH20 decreased injection times by approximately 4%. Back-leakage for injections of Ig-120 + rHuPH20 was zero for all injections whereas some back-leakage was observed for some Ig-120 alone injections. Caliper measurement of bleb swelling size showed significantly reduced bleb volume, that appears to be mainly a result of reduced bleb height. Bleb swelling also reduced more rapidly for injections of Ig-120 + rHuPH20 compared to Ig-120 alone.
25 Qualitative assessments of swelling size showed a significant reduction in size for Ig-120 + rHuPH20 injections compared to Ig-120 alone. Similarly, the induration of blebs after injection of Ig-120 + rHuPH20 were significantly reduced compared to Ig-120 alone. Notably, the swelling and induration resolved at a faster rate for Ig-120 + rHuPH20 compared to Ig120 alone.

INTRODUCTION

30 [00246] Wearable on-body devices (OnBD) are a type of SC delivery device that recently has received regulatory approval. These devices have the advantage of delivering higher volumes; however, it requires physical attachment of the device to the body and delivers its contents at low flow rates. Another commonly used device for SC delivery is the syringe pump. These devices allow

for large volumes to be delivered, do not require them to be handheld or worn on the body, and can deliver at varying flow rates; however, size, cost, and portability are some of its caveats.

[00247] In this study, we aimed to assess the attributes of an AI and a syringe pump, by using an HVAI as a hands-free ‘off-body’ device (OfBD) to deliver an immunoglobulin solution (120 mg/mL; Ig-120) alone or co-mixed with recombinant human hyaluronidase PH20 (rHuPH20; 2000 U/mL). The objective of this study was to assess the performance of the HVAI when used in this injection methodology with a standard winged infusion set directly attached to the HVAI. Minipigs were used in this study due to the similarity of the SC skin architecture to humans (Kang et al., 2013). Each animal received two 10 mL SC injections into the lower abdominal region. The first injection contained Ig-120 alone; the second injection occurred on the contralateral side of the animal and contained Ig-120 + 2000 U/mL rHuPH20. Quantitative endpoints for the study included a measurement of injection time, quantification (weight) of injection site back-leakage, caliper measurement of injection site swelling immediately post-injection (T0), as well as at 15 minutes (T15) and 30 minutes (T30) post-injection. Qualitative endpoints included assessment of erythema, swelling size and induration at T0, T15, T30, T2h and approximately 24 hours post-injection (T24h) using a modified 5-point Draize scoring system.

EXPERIMENTAL DESIGN AND METHODS

Test and Control Articles

[00248] Ig-120 Test Solution (Human Gamma Globulin (HGG))

Description: Clear liquid reconstituted from lyophilized powder
Concentration: 120 mg/mL
Formulation: 20 mM Histidine, 130 mM sodium chloride, pH 6.5
Lot number: NB1090-49 (HGG-003)
Storage Conditions: ≤-65 °C
Handling Conditions: Standard laboratory precautions
Supplier: Biomed Supply
Formulated by: Halozyme Product Development

[00249] Recombinant Human Hyaluronidase PH20 (rHuPH20)

Description: Clear colorless liquid
Lot number: 1-FIN-3928
Concentration: 9.3 mg/mL
Enzyme activity: 1,039,763 U/mL
Formulation: 10 mM Histidine, 130 mM sodium chloride, pH 6.5

Storage Conditions: $\leq 70^{\circ}\text{C}$

Handling Conditions: Standard laboratory precautions

Supplier: Halozyme Therapeutics, Inc.

[00250] *Ig Dilution Buffer*

- 5 Description: Clear colorless liquid
- Formulation: 20 mM histidine, 130 mM sodium chloride, pH 6.5
- Batch/Lot: NB1078-18
- Storage Conditions: 2-8 $^{\circ}\text{C}$
- Handling Conditions: Standard laboratory precautions
- 10 Supplier: Halozyme Therapeutics, Inc

Formulation

- [00251]** *Preparation of Test Solutions.* Two test solutions were utilized for this study. The first test solution was Ig-120 alone. The second test solution was Ig-120 + rHuPH20. To ensure sufficient test solution for syringe filling 90 mL of each test solution was prepared. To prepare the
- 15 co-mix of Ig-120 + rHuPH20, 0.173 mL of rHuPH20 was added to the 90 mL of Ig-120 to yield a test solution of Ig-120 + rHuPH20 with a final concentration of 2000 U/mL. After preparation of the co-mix both test solutions were used for syringe filling.

- [00252]** *Device Syringe Filling.* Filling of all device syringes occurred in a sterile fill and finish hood under aseptic conditions. Cyclic olefin copolymer (COC) syringes were filled with 10.95 mL
- 20 of either Ig-120 alone or the co-mix of Ig-120 + rHuPH20. To fill the syringes a sterile rubber plunger was initially inserted into the sterile syringe to a loading position. A 20-cc syringe was then filled with the test solution and a syringe pump was then used to fill the COC syringe with 10.95 mL of the test solution. After adding the test solution to the syringe, the rubber plunger was brought to the final fill position (to remove residual air in the syringe). The syringe was then be capped and
- 25 stored at 2-8 $^{\circ}\text{C}$ until used for device assembly.

- [00253]** *Device Assembly.* Assembly of all devices occurred immediately prior to use. The syringe was inserted into the lower housing of the HVAI and held in place while the syringe cap was removed and replaced with a 27G x $\frac{3}{4}$ " x 12" winged infusion set. The rubber plunger was then pushed to its final position to prime the infusion set. After priming, the upper housing of the HVAI
- 30 containing the powerpack was pushed onto the lower housing and the two pieces engaged for final device assembly. The needle guard was removed immediately prior to use.

Animal Description

- [00254]** Species: Pig (*Sus scrofa domestica*)

Strain: Yucatan Miniature

Sex: Female

Age: ~ 3-4+ months

Weight: 14-16 kg (Table 18 summarizes the animal weights on the day of treatment)

5 Quantity: 6 animals

Source: Premier BioSource (Ramona, CA)

Table 18: Summary of Animal Weights (Day of Treatment)

Animal ID#	Date of Birth	Bodyweight On Intake (kg)
6256	05/31/2024	16
6259	06/01/2024	16
6367	06/11/2024	14
6397	06/19/2024	17
6400	06/18/2024	14
6407	06/01/2024	18

10 [00255] *Husbandry*. Animals were housed in steel pens with automatic water provided ad libitum. Animals were fed twice daily (AM and PM) but were kept NPO after midnight on the day of the study. The room environment was set to maintain a temperature of ~ 19-23°C and a relative humidity of 40-70%, with a 12 hour light/12 hour dark time cycle. Animals were acclimated to the vivarium for a minimum of 3 days prior to study start.

Test Materials

15 [00256] The test materials used in the study are listed in Table 19.

Table 19: Summary of Test Materials

Test Material	Supplier	Catalog No.
27G x ¾" x 12" inch winged infusion set	McKesson	408901
Surgical Eye Spear	BVI Merocel®	400101
High-volume Auto-Injector Powerpak	Halozyne – Minnetonka, MN	N/A
HVAI-10-L 20 lbf Main Spring	Lee Springs	101817-001
HVAI-10-L Latch	Halozyne – Minnetonka, MN	101800-001
HVAI-10-L 10mL Ram	Halozyne – Minnetonka, MN	101801-001
HVAI-10-L Button	Halozyne – Minnetonka, MN	101805-001
HVAI-10-L Cap Removal Tool	Halozyne – Minnetonka, MN	101806-001

Test Material	Supplier	Catalog No.
HVAI-10-L Button Ring	Halozyme – Minnetonka, MN	101816-001
HVAI-10-L Button Assembly	Halozyme – Minnetonka, MN	300599-001
HVAI-10-L Rear Housing (modified)	Halozyme – Minnetonka, MN	101798-001
HVAI-10-L Front Housing	Halozyme – Minnetonka, MN	101799-001
Cyclic olefin copolymer (COC) syringes	SCHOTT	101787-TAB
Rubber seal for COC syringes	SCHOTT	101788-001
Syringe caps	Becton Dickinson, Franklin Lakes, NJ	305819
3D Camera	Canfield Bioscience	Vectra H2
Standard Digital Camera	Canon	S120
Digital caliper	Fisher Scientific	06-664-16
Digital Stopwatch	Fisher Scientific	14-649

EXPERIMENTAL DESIGN

[00257] In this study, two 10 mL injections were administered to the abdomen of a Yucatan miniature pig. On one side of the abdomen a test solution of Ig-120 alone was administered and a second injection of Ig-120 + rHuPH20 on the contralateral side of the animal. All test solutions containing rHuPH20 were formulated at 2000 U/mL. An HVAI was used as an off-body device to deliver the test solution. The test solutions for each animal are summarized in Table 20.

Table 20: Description of Treatments

Cohort	# of Injections / Cohort	Test Solution	Volume/injection (mL)	[rHuPH20] (U/mL)
1	6	Ig-120	10	0
2	6	Ig-120 + rHuPH20	10	2000

[00258] The length of each injection was measured and recorded using a stopwatch. Immediately post-injection, the needle was removed, and back-leakage collected for 30 seconds using a pre-weighed eye spear. Swelling size was then measured using a digital caliper and by obtaining a 3D image capture immediately post-injection (T0). Caliper measurement of bleb size was also taken and at 15 minutes (T15) and 30 minutes (T30) post-injection. Standard photographs were obtained at T0, T15, T30, T2h (2h post-injection) and T24h (24h post-injection).

[00259] Additional post-injection qualitative injection site evaluations for erythema, swelling and induration were performed at T0, T15, T30 and T2h with a final evaluation at approximately T24h post-injection. In summary the endpoints for the study were: measurement of HVAI injection time (digital stopwatch); collection and measurement of back-leakage weight using an eye spear; caliper measurement of bleb size post-injection using digital caliper at T0, T15 and T30; measurement of bleb volume, area and height at T0 using 3D imaging; assessment of blebs for erythema, swelling size and induration at times T0, T15, T30, T2h and T24h; and photographic documentation of all injection sites: pre-injection, T0, T15, T30, T2h and T24h.

PROCEDURES

[00260] On the day prior to the study HVAI devices (one Ig-120; one Ig-120 + rHuPH20) were withdrawn from refrigerated storage and brought to room temperature for at least 30 minutes prior to use. The first injection for each animal was always Ig-120 followed by a second injection on the contralateral side of the animal with Ig-120 + rHuPH20. Injection sites were located on the left and right abdominal regions, ~5 cm cranially from the inguinal fold towards the midline and ~3 cm towards the midline of the animal.

[00261] Prior to the start of study, animals were assessed for general health, and body weights were collected. Animals were anesthetized with isoflurane gas and placed in dorsal recumbence on a heated surgical table and were maintained under isoflurane gas for the entire duration of the procedure. The abdominal region was cleaned with Nolvasan and the injection site wiped with gauze containing 70% isopropanol and wiped dry with sterile gauze. Each of the injection sites were marked with a permanent marker and then photographed with the standard and 3D cameras prior to HVAI needle insertion. The HVAI was mounted into the platform and the needle bevel confirmed to face upward. The HVAI was unlocked, and the needle cap was removed and discarded prior to needle insertion.

[00262] The skin was pinched at the injection site and the needle was inserted into the pinched skin and allowed to freely float in the SC space. After needle insertion the injection started by pushing the activation button. The injection was timed using a digital stopwatch. Upon completion of injection the injection time was recorded, and the needle was withdrawn from the skin. Test solution back-leakage at the injection site was absorbed to a pre-weighed eye spear for 30 seconds and the weight of the eye spear was measured. The margins of the injection site bleb were then marked with a permanent marker and measured for length, width, and height using a digital caliper, then photographed with the standard and 3D cameras immediately post-injection (T0). Caliper measurements were also taken at T15 and T30 post-injection. After the second injection two

additional syringes (one with Ig-120 and one with Ig-120 + rHuPH20) were removed from refrigerated storage and brought to room temperature for use with the following animal. Local injection sites were also qualitatively assessed and graded for erythema severity, swelling size appearance, and firmness immediately after injection, using a scoring system described in Table 21, Table 22, and Table 23, respectively. Any additional observations were noted at this time. The injection site was then qualitatively assessed at T0, T15 and T30 and photographed using a standard camera while the animal was still under anesthesia. The injection sites were again qualitatively assessed and photographed at T2h but the animal was conscious and hand-held by an animal technician.

- 10 **[00263]** After the first injection and while the animal was still sedated, the identical procedure was repeated on the contralateral side of the animal with the second test solution (Ig-120 + rHuPH20). Thirty minutes after completion of the second injection (and after the final assessments at T30 minutes), the animal was removed from anesthesia and returned to its home cage for recovery. On the following day (at approximately 24 hours) the animal was re-anesthetized, and
- 15 both of the injection sites assessed for erythema, induration and swelling, and photographed. Following the ~T24h assessment, the animal was humanely euthanized using an injectable euthanasia drug.

Table 21: Grading Scale for Erythema Formation

Scale	Description
0	No erythema
1	Very slight erythema (barely perceptible)
2	Well defined erythema
3	Moderate to severe erythema
4	Severe erythema (beet redness) to slight eschar formation

20 Table 22: Grading Scale for Swelling Size Formation

Scale	Description
0	No swelling
1	Very slight swelling
2	Slight swelling
3	Moderate swelling
4	Severe swelling

Table 23: Grading Scale for Swelling Firmness (Induration)

Scale	Description
0	No perceptible difference in firmness after injection
1	Very slightly firm (barely perceptible)
2	Mildly firm
3	Moderately firm
4	Very firm

CALCULATIONS AND STATISTICAL METHODS

[00264] *Statistical Methods.* Statistical comparisons for Ig-120 and Ig-120 + rHuPH20 were performed using an unpaired parametric t-test (Prism v10.1.1, GraphPad Software, Inc., San Diego, California). All hypotheses' tests were performed at a 5% significance level, thus considered significant if $p < 0.05$.

[00265] *Assessment of Injection Time.* The time required for each injection was measured using a digital stopwatch and recorded after each injection.

[00266] *Assessment of Swelling Volume, Area and Height Using Caliper Measurement and 3D Imaging.* Volume and area of post-injection swelling were measured using both caliper measurement and 3D camera image analysis. For caliper measurements a digital caliper was utilized to measure length, width, and height of the bleb that formed post-injection. The length and width are defined as the edge-to-edge measurements of the bleb (i.e., diameter) along their longest axes. These values were manually recorded, and the volume determined using the formula for half of an ellipsoid: $Vol = (2/3) * \pi * A * B * C$ where $A = Length/2$, $B = Width/2$ and $C = Height$.

[00267] 3D imaging was applied as a longitudinal methodology to measure post-injection swelling. By obtaining high definition pre- and post-injection 3D images the distances between two registered surfaces can be determined. The camera captures images using a factory calibrated bifocal imaging system to measure distance between surfaces. Surface registration was performed using a multipoint method that utilized common landmarks between the pre-injection image and the post-injection image. Using the proprietary software, the volume, area and height of the post-injection swelling was calculated for each injection (Canfield Biosciences, Inc.).

RESULTS AND DISCUSSION

[00268] *Pre-study Enzymatic Activity Testing.* The co-mix of Ig-120 + rHuPH20 was prepared on the day prior to study start and the enzyme activity of the test solution was measured using an in

vitro activity assay (VV-QUAL-00675; formerly TM010). The results of this activity testing are shown in Table 24.

Table 24: Summary of Pre-Study Activity Testing

Test Solution	Hyaluronidase Activity (U/mL) (Mean ± SD)
Ig-120 + rHuPH20	2160 ± 5

5 **[00269]** *Post-study Enzymatic Activity Testing.* Sufficient co-mix of Ig-120 + rHuPH20 was prepared so that an extra HVAI could be assembled. The test solution from this spare device was collected at the end of the study and tested for hyaluronidase activity. The results are shown in Table 25.

Table 25: Summary of Post-Study Activity Testing

Test Solution	Hyaluronidase Activity (U/mL) (Mean ± SD)
Ig-120 + rHuPH20	2226 ± 10

10

Pre- and Post-injection Quantitative Measurements

[00270] *Measurement of HVAI Injection Times.* The time for each injection was measured using a stopwatch and is shown in Table 26 and Fig. 35. There was approximately a 4.3% decrease in delivery time when the Ig-120 was delivered co-mixed with rHuPH20, but this was not considered
15 significant.

Table 26: Measurement of HVAI Injection Times

Test Solution	Injection Time (Mean ± SEM)	% Change
Ig-120	76.9 ± 7.4	---
Ig-120 + rHuPH20	73.6 ± 8.0	-4.3%

[00271] *Measurement of Post-injection Back-leakage.* The back-leakage was collected using a pre-weighed eye spear for 30 seconds post-injection. The eye spear was then re-weighed, and the
20 weight of the back-leakage recorded. The amount of back-leakage (mean ± SEM) for each test solution is shown in Table 27 with individual values shown in Fig. 36. While the back-leakage for the injections using rHuPH20 were negligible, the back-leakage from control injections was also quite minimal and the difference was not statistically significant.

Table 27: Summary of Post-injection Back-leakage

Test Solution	Back-leakage (mg $\pm$ SEM)	% Change
Ig-120	6.0 $\pm$ 4.7	---
Ig-120 + rHuPH20	0.0 $\pm$ 0.0	-100%

[00272] *Assessment of Post-Injection Bleb Volume, Area and Height (Caliper Measurements).*

The local injection site swelling (bleb) was marked and measured using a digital caliper. Bleb volume dispersion area and swelling height of each bleb was determined, and this data is summarized at the T0, T15 and T30 timepoints in Table 28, Table 29, and Table 30 and individual values shown in Fig. 37, Fig. 38, and Fig. 39. Both the volume and height of blebs formed after injection of Ig-120 + rHuPH20 were found to be statistically less than after injections of Ig-120 alone.

Table 28: Bleb Volume After Injection of Ig-120 and Ig-120 + rHuPH20 Over Time Using Caliper Measurement (Mean $\pm$ SEM)

Volume of Post-injection Swelling			
	Time after injection		
Test Solution	T0	T15	T30
Ig-120	14.8 $\pm$ 1.1	11.2 $\pm$ 1.4	9.7 $\pm$ 1.5
Ig-120 + rHuPH20	7.2 $\pm$ 0.7	3.9 $\pm$ 0.5	3.9 $\pm$ 0.3
% Change	-51.4% ^a	-65.2% ^a	-59.8% ^a

Table 29: Bleb Area After injection of Ig-120 and Ig-120 + rHuPH20 Over Time Using Caliper Measurement (Mean $\pm$ SEM)

Area of Post-injection Swelling (cm ² $\pm$ SEM)			
	Time after injection		
Test Solution	T0	T15	T30
Ig-120	28.5 $\pm$ 2.0	31.8 $\pm$ 2.2	35.3 $\pm$ 2.1
Ig-120 + rHuPH20	27.9 $\pm$ 0.9	32.7 $\pm$ 1.7	37.2 $\pm$ 1.1
% Change	-2.1%	+2.8%	+5.4%

Table 30: Bleb Height After Injection of Ig-120 and Ig-120 + rHuPH20 Over Time Using Caliper Measurement (Mean $\pm$ SEM)

Height of Post-injection Swelling (mm $\pm$ SEM)
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	Time after injection		
Test Solution	T0	T15	T30
Ig-120	7.9 ± 0.6	5.5 ± 0.9	4.2 ± 0.7
Ig-120 + rHuPH20	3.8 ± 0.3	1.8 ± 0.2	1.6 ± 0.1
% Change	-51.9% ^a	-67.3% ^a	-61.9% ^a

[00273] The post-injection swelling, area and height over time were also determined at T15 and T30 and the scores are shown in Fig. 40, Fig. 41, and Fig. 42, respectively.

[00274] *Assessment of Post-injection Bleb Shape, Volume, Area and Height (3D Imaging).* Pre-

and post-injection photographs were taken using a 3D imaging system (Canfield Scientific). This technology permits point-to-point alignment of these two images through multipoint surface registration. The distance between any two points is then represented using a colorimetric surface contour map. Regions where there is no difference between the two images are displayed in gray. Where the post-injection image is higher than the pre-injection image, the region is displayed in shades of blue. Where the post-injection image is lower than the pre-injection image the distance is displayed in shades of orange. The color intensity is proportional to the amount of distance measured between images with darker blue color indicating greater distance from the pre-injection image. Out of range measurements (distances greater than 6 mm) are depicted in white. Bleb measurements of volume and height include regions out of range.

[00275] Each animal had a pre-injection 3D image taken of the injection site followed by a second image taken immediately post-injection and these images were mapped to each other using multipoint registration. These registered pre-/post-injection images were then used to calculate the bleb volume, height, circumference, length, and width for each bleb using proprietary software (Vectra H1 software; Canfield Sciences). Colorimetric surface contour maps of each post-injection bleb for Ig-120 and Ig-120 + rHuPH20 are shown in Figs. 43A and 43B. Differences between Ig-120 and Ig-120 + rHuPH20 were not found to be statistically significantly different for the volume, area or height. Table 31 and Figs. 44-46 show the bleb volume, area, and height assessed using 3D imaging.

Table 31: Bleb Volume, Area and Height After Injection of Ig-120 and Ig-120 + rHuPH20 Assessed Using 3D Imaging (Mean ± SEM)

	Mean ± SEM		
Test Solution	Volume (mL)	Area (cm ²)	Height (mm)

	Mean $\pm$ SEM		
Test Solution	Volume (mL)	Area (cm ²)	Height (mm)
Ig-120	6.2 $\pm$ 1.0	24.8 $\pm$ 3.1	5.7 $\pm$ 0.4
Ig-120 + rHuPH20	5.5 $\pm$ 0.7	27.4 $\pm$ 2.2	4.6 $\pm$ 0.4
% Change	-11.3%	+10.5%	-19.3%

[00276] *Qualitative Assessment of Local Injection Sites.* Qualitative assessments for erythema, swelling size and induration were taken immediately post-injection (T0), 15 minutes post-injection (T15), 30 minutes post-injection (T30), 2 hours post-injection (T2h) and at approximately 24 hours post-injection (T24).

[00277] *Post-injection Erythema.* No post-injection erythema was observed at any timepoints (T0, T15, T30, T2h and T24h).

[00278] *Post-injection Swelling Size.* Post-injection swelling size was significantly greater for Ig-120 than for Ig-120 + rHuPH20. Scoring by three evaluators for swelling size (Mean $\pm$ SEM) are summarized in Table 32. Individual values immediately post-injection (T0) are shown in Fig. 47 and values scored over time (Mean $\pm$ SEM) are shown in Fig. 48. The post-injection swelling scores were significantly lower for Ig-120 injections that were co-mixed with rHuPH20.

Table 32: Qualitative Assessment of Post-Injection Swelling Size (T0-T15-T30-T2h)

Time Post-Injection	Test Solution	Swelling Size Score (Mean $\pm$ SEM)	% Change
T0	Ig-120	3.4 $\pm$ 0.1	---
	Ig-120 + rHuPH20	2.4 $\pm$ 0.2	-29.4% ^a
T15	Ig-120	3.0 $\pm$ 0.2	---
	Ig-120 + rHuPH20	1.6 $\pm$ 0.1	-46.7% ^a
T30	Ig-120	2.3 $\pm$ 0.2	---
	Ig-120 + rHuPH20	1.0 $\pm$ 0.1	-56.5% ^a
T2h	Ig-120	1.1 $\pm$ 0.2	---
	Ig-120 + rHuPH20	0.0 $\pm$ 0.0	-100% ^a
T24h	Ig-120	0.0 $\pm$ 0.0	---
	Ig-120 + rHuPH20	0.0 $\pm$ 0.0	---

[00279] *Post-injection Induration.* The induration (firmness) of the post-injection blebs for Ig-120 was found to be significantly greater than the blebs that resulted from injection of Ig-120 +

rHuPH20 ($p < 0.05$). Scoring by three evaluators for swelling size (Mean $\pm$ SEM) are summarized in Table 33. Individual values immediately post-injection (T0) are shown in Fig. 49, and values scored over time (Mean $\pm$ SEM) are shown in Fig. 50.

Table 33: Qualitative Assessment of Post-Injection Induration (T0-T15-T30-T2h)

Time Post-Injection	Test Solution	Induration Score (Mean $\pm$ SEM)	% Change
T0	Ig-120	3.1 $\pm$ 0.1	---
	Ig-120 + rHuPH20	1.9 $\pm$ 0.2	-38.7% ^a
T15	Ig-120	2.7 $\pm$ 0.1	---
	Ig-120 + rHuPH20	1.2 $\pm$ 0.1	-55.6% ^a
T30	Ig-120	2.1 $\pm$ 0.1	---
	Ig-120 + rHuPH20	0.6 $\pm$ 0.1	-71.4% ^a
T2h	Ig-120	1.0 $\pm$ 0.2	---
	Ig-120 + rHuPH20	0.0 $\pm$ 0.0	-100% ^a
T24h	Ig-120	0.0 $\pm$ 0.0	---
	Ig-120 + rHuPH20	0.0 $\pm$ 0.0	---

5

[00280] *Photographs of Injection Sites Pre- and Post-Injection.* The injection sites were photographed before and immediately post-injection and then at T15, T30, T2h and T24h. Photographic images are shown in Figs. 51-62.

SUMMARY AND CONCLUSIONS

10 **[00281]** The HVAI-Gen 2 device successfully performed as an Off-Body Device (OfBD) to deliver the two Ig-120 solutions using a 27G x $\frac{3}{4}$ " x 12" winged infusion set for all injections. The addition of rHuPH20 provided a minor decrease in the injection time for the injections (~4%) but was not statistically significant. Times ranged from 68 to 98 seconds for Ig-120 injections and from 55 to 96 seconds for Ig-120 + rHuPH20 injections. No back-leakage was observed after the

15 injection of Ig-120 + rHuPH20. Measurement of bleb size (volume and height) were significantly less after injections of Ig-120 + rHuPH20 compared to Ig-120 alone at T0, T15 and T30 post-injection. Qualitative assessment of bleb swelling size and induration showed a significant decrease in swelling both initially post-injection and at subsequent timepoints (T15, T30 and T2h). The HVAI performed successfully as an OfBD with delivery times that approximate a 10 mL/min flow

20 rate. The study further confirms that the OfBD can have the delivery time modulated using the needle gauge, similar to the HVAI (1st Gen).

CLAIMS

1. A method of treating a disease or disorder in a subject in need thereof, the method comprising administering to the subject via subcutaneous administration about 3 mL to about 50 mL of a formulation comprising a therapeutically effective amount of an active ingredient selected from a small molecule, a peptide fragment, a biologic, a nanoparticle, an antibody, an antibody fragment, and a small molecule antiviral; wherein the subcutaneous administration is facilitated by a prefilled autoinjection or autoinfusion device comprising:
- 5 a delivery apparatus comprising:
- 10 a housing having a proximal end and a distal end opposite the proximal end;
a medicament container at least partially disposed within the housing containing a volume of a medicament;
an outlet on the distal end of the housing in fluid communication with the medicament container;
- 15 an energy source disposed within the housing configured to interact with the medicament container to expel the medicament from the outlet; and
a trigger mechanism coupled to the housing and engageable with the energy source and configured to activate the energy source in response to a user input.
- 20 2. The method of claim 1, the prefilled autoinjection or autoinfusion device further comprising: a port having a user engagement surface, and an injection apparatus extending from the user engagement surface.
3. The method of claim 2, wherein the energy source urges the volume of the medicament through the injection apparatus when the volume of the medicament is expelled from the outlet.
- 25 4. The method of claim 2, wherein the port comprises an air release valve.
5. The method of claim 2, wherein the port is removably coupled to an injection site of a user.
- 30 6. The method of claim 2, wherein the user engagement surface is generally flat and includes an aperture extending therethrough.

7. The method of claim 6, wherein the injection apparatus extends through the aperture on a plane generally perpendicular to the plane of the user engagement surface.
- 5 8. The method of claim 2, wherein the prefilled autoinjection or autoinfusion device further comprises a conduit removably coupled to the outlet and the port and fluidly connecting the delivery apparatus and the port when coupled therebetween.
9. The method of claim 8, wherein the delivery apparatus purges the conduit of air before the
10 injection apparatus is inserted into an injection site of a patient.
10. The method of claim 8, wherein the delivery apparatus purges the conduit of air after the injection apparatus is inserted into an injection site of a patient.
- 15 11. The method of claim 8, wherein the delivery apparatus automatically purges the conduit of air when the conduit is coupled to the delivery apparatus.
12. The method of claim 8, wherein the conduit is decoupled from the port after the volume of the medicament is expelled from the outlet.
20
13. The method of claim 8, wherein the conduit is a flexible tubing.
14. The method of claim 8, wherein the conduit is at least 24 inches in length.
- 25 15. The method of claim 8, wherein the energy source is prevented from expelling medicament from the outlet until the conduit is purged of air.
16. The method of claim 1, wherein the volume of the medicament is at least 10 mL, at least 30 mL, or at least 50 mL.
30
17. The method of claim 1, wherein the delivery apparatus is not resettable.

18. The method of claim 1, wherein the outlet is a generally cylindrical member and comprises threads protruding therefrom.

19. A method of treating a disease or disorder in a subject in need thereof, the method comprising administering to the subject via subcutaneous administration about 3 mL to about 50 mL of a formulation comprising a therapeutically effective amount of an active ingredient selected from a small molecule, a peptide fragment, a biologic, a nanoparticle, an antibody, an antibody fragment, and a small molecule antiviral; wherein the subcutaneous administration is facilitated by a prefilled autoinjection or autoinfusion device comprising:

- 10 a delivery apparatus comprising:
 - a housing having a proximal end and a distal end opposite the proximal end;
 - a medicament container at least partially disposed within the housing containing a volume of at least 10 mL of a medicament;
 - an outlet on the distal end of the housing in fluid communication with the
 - 15 medicament container;
 - an energy source disposed within the housing configured to interact with the medicament container to expel the medicament from the outlet; and
 - a trigger mechanism coupled to the housing and engageable with the energy source and configured to activate the energy source in response to a user input;
 - 20 a port comprising:
 - a user engagement surface; and
 - a needle extending from the user engagement surface; and
 - a flexible tube removably coupled to the outlet and the port and fluidly connecting the delivery apparatus and the port when coupled therebetween,
 - 25 wherein the delivery apparatus is not resettable.

- 20. A method of delivering a formulation comprising a therapeutically effective amount of an active ingredient selected from a small molecule, a peptide fragment, a biologic, a nanoparticle, an antibody, an antibody fragment, and a small molecule antiviral, into a patient with a delivery
- 30 apparatus comprising a prefilled medicament container containing a volume of the formulation, an energy source configured to interact with the medicament container to expel the formulation and a trigger mechanism configured to activate the energy source in response to a user input, the method comprising:

coupling the delivery apparatus to a first end of a conduit, the conduit in fluid communication with the prefilled medicament container;

coupling a second end of the conduit to a port comprising an injection apparatus extending therefrom, the injection apparatus in fluid communication with the prefilled medicament container;

5 inserting the injection apparatus into an injection site on a patient; and

manipulating the trigger mechanism to allow the energy source to expel the formulation from the prefilled medicament container,

wherein the energy source urges the volume of the formulation through the injection apparatus during the injection.

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21. The method of claim 20, wherein the volume of the formulation is expelled at a rate of at least 5 mL/min.

22. The method of claim 20, wherein the conduit is purged of air prior to the injection.

15

23. The method of claim 22, wherein the delivery apparatus purges the conduit of air after the injection apparatus is inserted into an injection site of a patient.

24. The method of claim 20, wherein the delivery apparatus is not resettable.

20

25. The method of claim 20, wherein the delivery apparatus is disposable after a single use.

26. The method of claim 20, wherein the volume of the medicament is expelled from the delivery apparatus in at least 30 seconds.

25

27. The method of claim 20, wherein the volume of the medicament is expelled from the delivery apparatus at a rate of at least 5 mL/min.

30

28. The method of any one of claim 1-27, wherein the formulation further comprises a hyaluronidase enzyme.

29. The method of any one of claims 1-28, wherein the hyaluronidase enzyme is a recombinant human hyaluronidase enzyme.

30. The method of any one of claims 1-29, wherein the hyaluronidase enzyme is recombinant human hyaluronidase PH20 enzyme.
- 5 31. The method of any one of claims 1-30, wherein the hyaluronidase enzyme has an activity of about 150 U/mL to about 150 kU/mL.
32. The method of any one of claims 1-30, wherein the hyaluronidase enzyme has an activity of about 500 U/mL to about 5,000 U/mL.
- 10 33. The method of any one of claims 1-30, wherein the hyaluronidase enzyme has an activity of about 1,500 U/mL to about 10,000 U/mL.
34. The method of any one of claims 1-33, wherein the active ingredient is a small molecule, a peptide fragment, a biologic, or a nanoparticle.
- 15 35. The method of any one of claims 1-33, wherein the active ingredient is an antibody, an antibody fragment, or a small molecule antiviral.
- 20 36. The method of any one of claims 1-35, comprising administering to the subject about 10 mL to about 20 mL of the formulation.
37. The method of any one of claims 1-35, comprising administering to the subject about 3 mL to about 15 mL of the formulation.
- 25 38. The method of any one of claims 1-35, comprising administering to the subject about 3 mL, about 3.1 mL, about 3.2 mL, about 3.4 mL, about 3.5 mL, about 3.6 mL, about 3.7 mL, about 3.8 mL, about 3.9 mL, about 4 mL, about 4.1 mL, about 4.2 mL, about 4.3 mL, about 4.4 mL, about 4.5 mL, about 5 mL, about 5.1 mL, about 5.2 mL, about 5.3 mL, about 5.4 mL, about 5.5 mL, about 5.6 mL, about 5.7 mL, about 5.8 mL, about 5.9 mL, about 6 mL, about 6.1 mL, about 6.2 mL, about 6.3 mL, about 6.4 mL, about 6.5 mL, about 6.6 mL, about 6.7 mL, about 6.8 mL, about 6.9 mL, about 7 mL, about 7.1 mL, about 7.2 mL, about 7.3 mL, about 7.4 mL, about 7.5 mL, about 7.6 mL, about 7.7 mL, about 7.8 mL, about 7.9 mL, about 8 mL, about 8.1 mL, about 8.2 mL, about 8.3 mL, about
- 30

8.4 mL, about 8.5 mL, about 8.6 mL, about 8.7 mL, about 8.8 mL, about 8.9 mL, about 9 mL, about 9.1 mL, about 9.2 mL, about 9.3 mL, about 9.4 mL, about 9.5 mL, about 9.6 mL, about 9.7 mL, about 9.8 mL, about 9.9 mL, about 10 mL, about 10.1 mL, about 10.2 mL, about 10.3 mL, about 10.4 mL, about 10.5 mL, about 10.6 mL, about 10.7 mL, about 10.8 mL, about 10.9 mL, about 11 mL, about 11.1 mL, about 11.2 mL, about 11.3 mL, about 11.4 mL, about 11.5 mL, about 11.6 mL, about 11.7 mL, about 11.8 mL, about 11.9 mL, about 12 mL, about 12.1 mL, about 12.2 mL, about 12.3 mL, about 12.4 mL, about 12.5 mL, about 12.6 mL, about 12.7 mL, about 12.8 mL, about 12.9 mL, about 13 mL, about 13.1 mL, about 13.2 mL, about 13.3 mL, about 13.4 mL, about 13.5 mL, about 13.6 mL, about 13.7 mL, about 13.8 mL, about 13.9 mL, about 14 mL, about 14.1 mL, about 14.2 mL, about 14.3 mL, about 14.4 mL, about 14.5 mL, about 14.6 mL, about 14.7 mL, about 14.8 mL, about 14.9 mL, about 15 mL, about 15.1 mL, about 15.2 mL, about 15.3 mL, about 15.4 mL, about 15.5 mL, about 15.6 mL, about 15.7 mL, about 15.8 mL, about 15.9 mL, about 16 mL, about 16.1 mL, about 16.2 mL, about 16.3 mL, about 16.4 mL, about 16.5 mL, about 16.6 mL, about 16.7 mL, about 16.8 mL, about 16.9 mL, about 17 mL, about 17.1 mL, about 17.2 mL, about 17.3 mL, about 17.4 mL, about 17.5 mL, about 17.6 mL, about 17.7 mL, about 17.8 mL, about 17.9 mL, about 18 mL, about 18.1 mL, about 18.2 mL, about 18.3 mL, about 18.4 mL, about 18.5 mL, about 18.6 mL, about 18.7 mL, about 18.8 mL, about 18.9 mL, about 19 mL, about 19.1 mL, about 19.2 mL, about 19.3 mL, about 19.4 mL, about 19.5 mL, about 19.6 mL, about 19.7 mL, about 19.8 mL, about 19.9 mL, about 20 mL, about 20.1 mL, about 20.2 mL, about 20.3 mL, about 20.4 mL, about 20.5 mL, about 20.6 mL, about 20.7 mL, about 20.8 mL, about 20.9 mL, about 21 mL, about 21.1 mL, about 21.2 mL, about 21.3 mL, about 21.4 mL, about 21.5 mL, about 21.6 mL, about 21.7 mL, about 21.8 mL, about 21.9 mL, about 22 mL, about 22.1 mL, about 22.2 mL, about 22.3 mL, about 22.4 mL, about 22.5 mL, about 22.6 mL, about 22.7 mL, about 22.8 mL, about 22.9 mL, about 23 mL, about 23.1 mL, about 23.2 mL, about 23.3 mL, about 23.4 mL, about 23.5 mL, about 23.6 mL, about 23.7 mL, about 23.8 mL, about 23.9 mL, about 24 mL, about 24.1 mL, about 24.2 mL, about 24.3 mL, about 24.4 mL, about 24.5 mL, about 24.6 mL, about 24.7 mL, about 24.8 mL, about 24.9 mL, or about 25 mL.

39. The method of any one of claims 1-38, comprising administering the formulation with a starting delivery force of about 5 lbf to about 50 lbf.

40. The method of any one of claims 1-38, comprising administering the formulation with an ending delivery force of about 3 lbf to about 20 lbf.

41. The method of any one of claims 1-40, comprising administering the formulation with a starting pressure of about 50 psi to about 200 psi.

5 42. The method of any one of claims 1-40, comprising administering the formulation with an ending pressure of about 20 psi to about 75 psi.

43. The method of any one of claims 1-42, wherein the medicament container is a prefilled syringe.

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44. The method of claim 43, wherein the prefilled syringe contains about 3 mL, about 3.1 mL, about 3.2 mL, about 3.4 mL, about 3.5 mL, about 3.6 mL, about 3.7 mL, about 3.8 mL, about 3.9 mL, about 4 mL, about 4.1 mL, about 4.2 mL, about 4.3 mL, about 4.4 mL, about 4.5 mL, about 5 mL, about 5.1 mL, about 5.2 mL, about 5.3 mL, about 5.4 mL, about 5.5 mL, about 5.6 mL, about 5.7 mL, about 5.8 mL, about 5.9 mL, about 6 mL, about 6.1 mL, about 6.2 mL, about 6.3 mL, about 6.4 mL, about 6.5 mL, about 6.6 mL, about 6.7 mL, about 6.8 mL, about 6.9 mL, about 7 mL, about 7.1 mL, about 7.2 mL, about 7.3 mL, about 7.4 mL, about 7.5 mL, about 7.6 mL, about 7.7 mL, about 7.8 mL, about 7.9 mL, about 8 mL, about 8.1 mL, about 8.2 mL, about 8.3 mL, about 8.4 mL, about 8.5 mL, about 8.6 mL, about 8.7 mL, about 8.8 mL, about 8.9 mL, about 9 mL, about 9.1 mL, about 9.2 mL, about 9.3 mL, about 9.4 mL, about 9.5 mL, about 9.6 mL, about 9.7 mL, about 9.8 mL, about 9.9 mL, about 10 mL, about 10.1 mL, about 10.2 mL, about 10.3 mL, about 10.4 mL, about 10.5 mL, about 10.6 mL, about 10.7 mL, about 10.8 mL, about 10.9 mL, about 11 mL, about 11.1 mL, about 11.2 mL, about 11.3 mL, about 11.4 mL, about 11.5 mL, about 11.6 mL, about 11.7 mL, about 11.8 mL, about 11.9 mL, about 12 mL, about 12.1 mL, about 12.2 mL, about 12.3 mL, about 12.4 mL, about 12.5 mL, about 12.6 mL, about 12.7 mL, about 12.8 mL, about 12.9 mL, about 13 mL, about 13.1 mL, about 13.2 mL, about 13.3 mL, about 13.4 mL, about 13.5 mL, about 13.6 mL, about 13.7 mL, about 13.8 mL, about 13.9 mL, about 14 mL, about 14.1 mL, about 14.2 mL, about 14.3 mL, about 14.4 mL, about 14.5 mL, about 14.6 mL, about 14.7 mL, about 14.8 mL, about 14.9 mL, about 15 mL, about 15.1 mL, about 15.2 mL, about 15.3 mL, about 15.4 mL, about 15.5 mL, about 15.6 mL, about 15.7 mL, about 15.8 mL, about 15.9 mL, about 16 mL, about 16.1 mL, about 16.2 mL, about 16.3 mL, about 16.4 mL, about 16.5 mL, about 16.6 mL, about 16.7 mL, about 16.8 mL, about 16.9 mL, about 17 mL, about 17.1 mL, about 17.2 mL, about 17.3 mL, about 17.4 mL, about 17.5 mL, about 17.6 mL, about 17.7 mL, about 17.8 mL, about 17.9 mL, about 18

mL, about 18.1 mL, about 18.2 mL, about 18.3 mL, about 18.4 mL, about 18.5 mL, about 18.6 mL, about 18.7 mL, about 18.8 mL, about 18.9 mL, about 19 mL, about 19.1 mL, about 19.2 mL, about 19.3 mL, about 19.4 mL, about 19.5 mL, about 19.6 mL, about 19.7 mL, about 19.8 mL, about 19.9 mL, about 20 mL, about 20.1 mL, about 20.2 mL, about 20.3 mL, about 20.4 mL, about 20.5 mL, 5 about 20.6 mL, about 20.7 mL, about 20.8 mL, about 20.9 mL, about 21 mL, about 21.1 mL, about 21.2 mL, about 21.3 mL, about 21.4 mL, about 21.5 mL, about 21.6 mL, about 21.7 mL, about 21.8 mL, about 21.9 mL, about 22 mL, about 22.1 mL, about 22.2 mL, about 22.3 mL, about 22.4 mL, about 22.5 mL, about 22.6 mL, about 22.7 mL, about 22.8 mL, about 22.9 mL, about 23 mL, about 23.1 mL, about 23.2 mL, about 23.3 mL, about 23.4 mL, about 23.5 mL, about 23.6 mL, about 23.7 10 mL, about 23.8 mL, about 23.9 mL, about 24 mL, about 24.1 mL, about 24.2 mL, about 24.3 mL, about 24.4 mL, about 24.5 mL, about 24.6 mL, about 24.7 mL, about 24.8 mL, about 24.9 mL, or about 25 mL of the formulation.

45. The method of claim 43 or 44, wherein the prefilled syringe comprises a needle having a 15 gauge of about 20 to about 33.

46. The method of any one of claims 43-45, wherein the prefilled syringe comprises a 20-gauge needle, a 21-gauge needle, a 22-gauge needle, a 23-gauge needle, a 24-gauge needle, a 25-gauge needle, a 26-gauge needle, a 27-gauge needle, a 28-gauge needle, a 29-gauge needle, a 30-gauge 20 needle, a 31-gauge needle, a 32-gauge needle, or a 33-gauge needle.

47. The method of any one of claims 1-46, comprising administering the formulation at a rate of about 5 to about 20 mL/min.

25 48. The method of any one of claims 1-46, comprising administering the formulation at a rate of at least about 5 to about 20 mL/min.

49. The method of any one of claims 1-46, comprising administering the formulation at a rate of at least or faster than about 5 to about 20 mL/min.

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50. The method of any one of claims 1-49, wherein the administration takes about 30 seconds to about 360 seconds.

51. The method of any one of claims 1-49, wherein the administration takes at least about 30 seconds to about 240 seconds.
52. The method of any one of claims 1-49, wherein the administration takes at least or less than about 30 seconds to about 240 seconds.
53. The method of any one of claims 1-49, wherein the administration takes about 60 seconds to about 240 seconds.
54. The method of any one of claims 1-49, wherein the administration takes at least about 60 seconds to about 240 seconds.
55. The method of any one of claims 1-49, wherein the administration takes at least or less than about 60 seconds to about 240 seconds.
56. The method of any one of claims 1-55, comprising administering about 5 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min.
57. The method any one of claims 1-55, comprising administering about 10 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min.
58. The method any one of claims 1-55, comprising administering about 15 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min.
59. The method any one of claims 1-55, comprising administering about 20 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min.
60. The method of any one of claims 1-59 wherein the formulation has a viscosity of about 1 cP to about 50 cP.
61. The method of any one of claims 1-60, wherein administration of the formulation requires less applied force when compared to a similar formulation that does not comprise a hyaluronidase enzyme.

62. The method of any one of claims 1-61, comprising administering about 5 mL of the formulation at a rate of about 5 mL/min to about 20 mL/min with an applied force of about 10 N to about 45 N.

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63. The method of claim 62, comprising administering the formulation to the subject using a prefilled syringe comprising a 25-gauge needle.

64. The method of any one of claims 1-63, comprising administering about 10 mL of the formulation to the subject at a rate of about 5 mL/min to about 20 mL/min with an applied force of about 25 N to about 50 N.

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65. The method of claim 64, comprising administering the formulation to the subject using a prefilled syringe comprising a 25-gauge needle.

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66. The method of any one of claims 1-65, wherein administration of the formulation is faster when compared to a similar formulation that does not comprise a hyaluronidase enzyme.

67. The method of any one of claims 1-66, wherein administration of the formulation causes fewer side effects in the subject when compared to a similar formulation that does not comprise a hyaluronidase enzyme.

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68. The method of any one of claims 1-67, wherein administration of the formulation causes less pain and discomfort in the subject when compared to a similar formulation that does not comprise a hyaluronidase enzyme.

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69. The method of any one of claims 1-68, wherein administration of the formulation causes less back leakage at the injection site when compared to a similar formulation that does not comprise a hyaluronidase enzyme.

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70. The method of claim 69, wherein the back leakage at the injection site is about 100% to about 30% less when compared to a similar formulation that does not comprise a hyaluronidase enzyme.

71. The method of any one of claims 1-70, wherein administration of the formulation causes less swelling volume and/or swelling height at the injection site when compared to a similar formulation that does not comprise a hyaluronidase enzyme.
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72. The method of claim 71, wherein administration of the formulation causes about 35% to about 1% less swelling and/or swelling height the injection site when compared to a similar formulation that does not comprise a hyaluronidase enzyme.
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73. The method of any one of claims 1-72, wherein administration of the formulation yields a lower bleb swelling size, less bleb induration, and/or quicker bleb resolution when compared to a similar formulation that does not comprise a hyaluronidase enzyme.
74. The method of any one of claims 1-73, wherein administration of the formulation yields
- 15 more consistent delivery times when compared to a similar formulation that does not comprise a hyaluronidase enzyme.
75. The method of any one of claims 1-74, wherein the subject is human.
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76. The method of any one of claims 1-75, wherein the administering comprises the subject self-administering the formulation.
77. The method of any one of claims 1-76, wherein the administering comprises a healthcare provider or a caregiver administering the formulation to the subject.
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78. The method of any one of claims 1-77, wherein the subcutaneous administration comprises a single injection.
79. The method of any one of claims 1-78, wherein the subcutaneous administration comprises
- 30 two or more injections.