# High-Volume Subcutaneous Injection Devices: Pushing the Injection Volume Boundaries

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CONTROLLED RELEASE SOCIETY
CRS 2024 Annual Meeting AND Exposition
JULY 8–12, 2024 • BOLOGNA, ITALY

INTEGRATING
Delivery Science
ACROSS DISCIPLINES

# There Are Several Approved Products in the 1.5 – 2.0 mL Range Using Pre-filled Syringes and/or Pre-filled Handheld Auto-Injectors[1]

| Product | Manufacturer | Presentation | Disease area | Dose |
|---|---|---|---|---|
| AJOVY (Fremanezumab) | Teva Pharma | AI, PFS | Migraine | 225 mg/1.5 mL |
| COSENTYX (Secukinumab) | Novartis Pharma | AI, NSD | Inflammatory & autoimmune | 300 mg/2.0 mL |
| DUPIXENT (Dupilumab) | Sanofi/Regeneron | AI, NSD | Inflammatory & autoimmune | 300 mg/2.0 mL |
| LEQVIO (Inclisiran) | Novartis Pharma | PFS | Cardiovascular | 284 mg/1.5 mL |
| PRALUENT (Alirocumab) | Sanofi/Regeneron | AI | Cardiovascular | 300 mg/2.0 mL |
| SILIQ (Brodalumab) | Valeant Pharmaceuticals | PFS | Inflammatory & autoimmune | 210 mg/1.5 mL |
| TEGSEDI (Inotersen) | Akcea/Ionis | PFS | Rare disease | 284 mg/1.5 mL |
| TEZSPIRE (Tezepelumab) | AstraZeneca/Amgen | AI, NSD | Inflammatory & autoimmune | 210 mg/1.9 mL |
| TAKHZYRO (Lanadelumab) | Takeda Pharma | PFS | Rare disease | 300 mg/2.0 mL |
| WAYLIVRA (Volanesorsen) | Akcea/Ionis | PFS | Rare disease | 285 mg/1.5 mL |

*Note: Abbreviations.* AI: autoinjector, PFS: pre-filled syringe, NSD: needle safety device.
*Excludes large-volume dosing options administered using wearable large-volume injectors.

[1] Taken from Schneider et al (2023): *Expert Opinion on Drug Delivery,* DOI: 10.1080/17425247.2023.2219891

# SC Drug Development and Delivery Consortium Published a Review Describing Trends for High Dose/Volume Biologics in 2021

Review > Drug Des Devel Ther. 2021 Jan 13:15:159-170. doi: 10.2147/DDDT.S287323.

## Subcutaneous Delivery of High-Dose/Volume Biologics: Current Status and Prospect for Future Advancements

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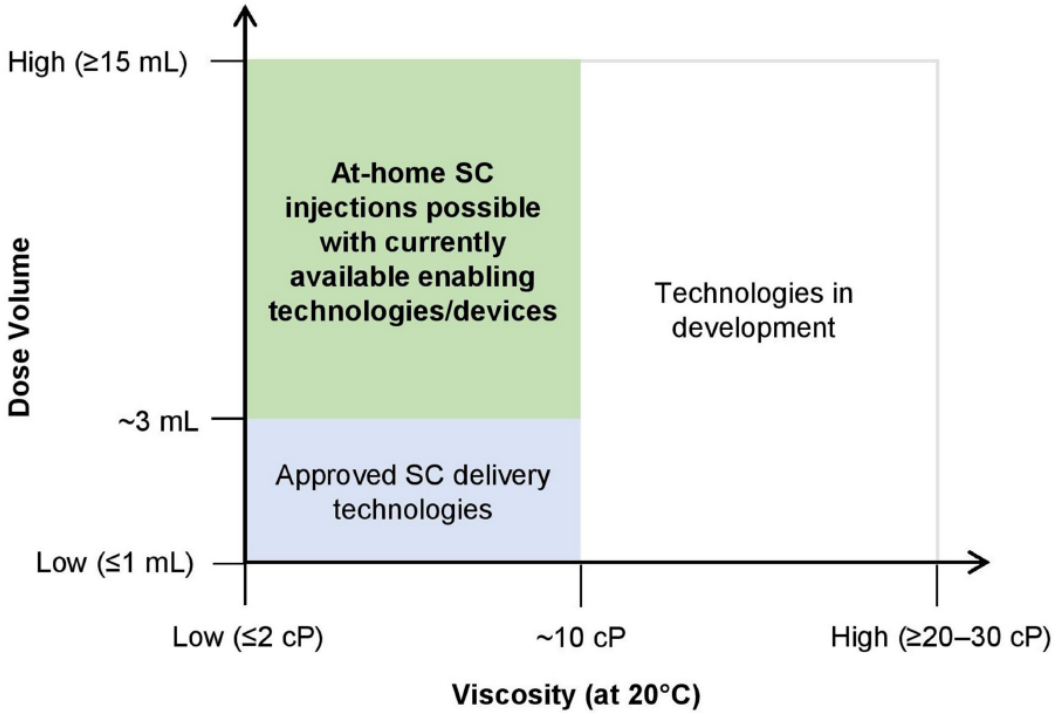


# Trend Continues With Multiple High-Volume Handheld Auto-Injectors in Development[1]

| Product | Manufacturer | Handling principle | Primary packaging | User interface | Status | Maximum delivered volume [mL] |
|---|---|---|---|---|---|---|
| Aerio uno | Kaleo (Richmond, VA, U.S.A) | Push-on-skin/2-step handling<br>2-step handling | Cartridge or prefilled syringe | Audible and visual cues (undisclosed) | Development | 10.0 |
| ARAI | Aktiv Pharma (Broomfield, CO, U.S.A) | Push-on-skin/2-step handling<br>2-step handling | Flexible, glass-free container | Undisclosed | Development | 5.0 |
| ArQ-Bios | Oval Medical Technologies (Waterbeach, U.K.) | Push-on-skin/2-step handling<br>2-step handling | Staked-needle prefilled syringe (proprietary) | Viewing window, click at injection start and end | Development | 10.0 |
| Gx Inbeneo | Gerresheimer (Düsseldorf, Germany) | Push-on-skin/2-step handling<br>2-step handling | Cartridge | Visual indicator, viewing window | Development | 3.0 |
| Maggie 5.0 | SHL Technologies (Zug, Switzerland) | Push-on-skin/2-step handling<br>2-step handling | Cartridge with pre-installed needle | Viewing window, continuous audible clicks | Development | 5.0 |
| YpsoMate 5.5 | Ypsomed (Burgdorf, Switzerland) | Push-on-skin/2-step handling<br>2-step handling | Staked-needle prefilled syringe | Rotating dial, viewing window, continuous audible clicking | Development | 5.5 |

[1] Taken from Schneider et al (2023): *Expert Opinion on Drug Delivery*, DOI: 10.1080/17425247.2023.2219891

# An On-body Device for 20 mL in 30-60 Minutes[1] Was Recently Approved with EMPAVALI by FDA[2]

About the EMPAVELI Injector

- Push button starts injection and pops up when injection is complete
- The needle is never seen
- Compact device with no tubing involved
- The gauge shows the injection progress


Enable Injections, Inc. enFuse® technology, was recently approved as the EMPAVELI Injector® commercialized by Apellis Pharmaceuticals, Inc.

[1] EMPAVALI (pegcetacoplan) Injector Instructions for Use
[2] Diagrams taken from “empavali.com/taking-empavali” website, approved 29 Sep 2023

# Seven High-Volume Rapid Delivery SC Products Are Approved Using Halozyme's ENHANZE Technology

## Wave 1 & 2

**$20B[1]**
Projected Sales of IV and SC by 2028

**5 Globally-Approved Products**

DARZALEX Faspro® (daratumumab and hyaluronidase-fihj)
**15 mL (~3-5 min)**

PHESGO®
PERTUZUMAB-TRASTUZUMAB
**10 and 15 mL (~5-8 min)**

RituxanHYCELA[2]
rituximab/hyaluronidase human
**11.7 and 13.4 mL (~5-7 min)**

HyQvia
[Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase]
**Up to 600 mL (up to 5 mL/min)**

Herceptin HYLECTA™[3]
trastuzumab and hyaluronidase-oysk
**5 mL (~2-5 min)**

## Wave 3

**$35B[1]**
Projected Sales of IV and SC by 2028

**Recently Launched**

**5.6 mL (~30-90 sec)**
VYVGART® Hytrulo
(efgartigimod alfa and hyaluronidase-qvfc)

TECENTRIQ® SC[4]
**15 mL (~7 min)**

**2024-2025 Projected Launches**

Atezolizumab SC: U.S.
Ocrelizumab SC
Nivolumab SC
Amivantamab SC

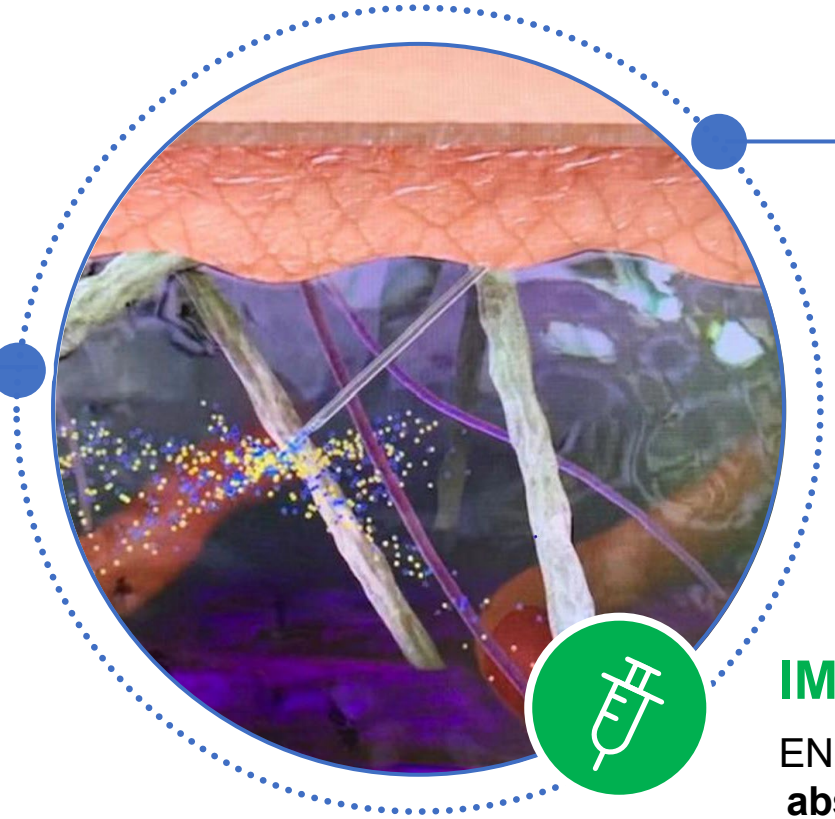
Licensees are responsible for development and commercialization. 1 Analysts' consensus from Evaluate Ltd June 2024, 2 Rituxan HYCELA® is marketed as MabThera® SC outside of the U.S, 3 Herceptin HYLECTA is marketed as Herceptin SC outside of the U.S, 4 Approved in Great Britain and EU

# ENHANZE is Halozyme's Patent Protected, Commercially Validated rHuPH20 Enzyme

## WHAT IT DOES

ENHANZE (rHuPH20) is an **enzyme that degrades hyaluronan** by cleaving the B-1,4 linkage between the N-acetyl glucosamine and glucuronic acid

ENHANZE **reduces tissue backpressure** creating temporary space for SC fluid dispersion



## HOW IT WORKS

ENHANZE **works rapidly, locally and transiently** in SC space; HA is naturally restored within 1-2 days[1]

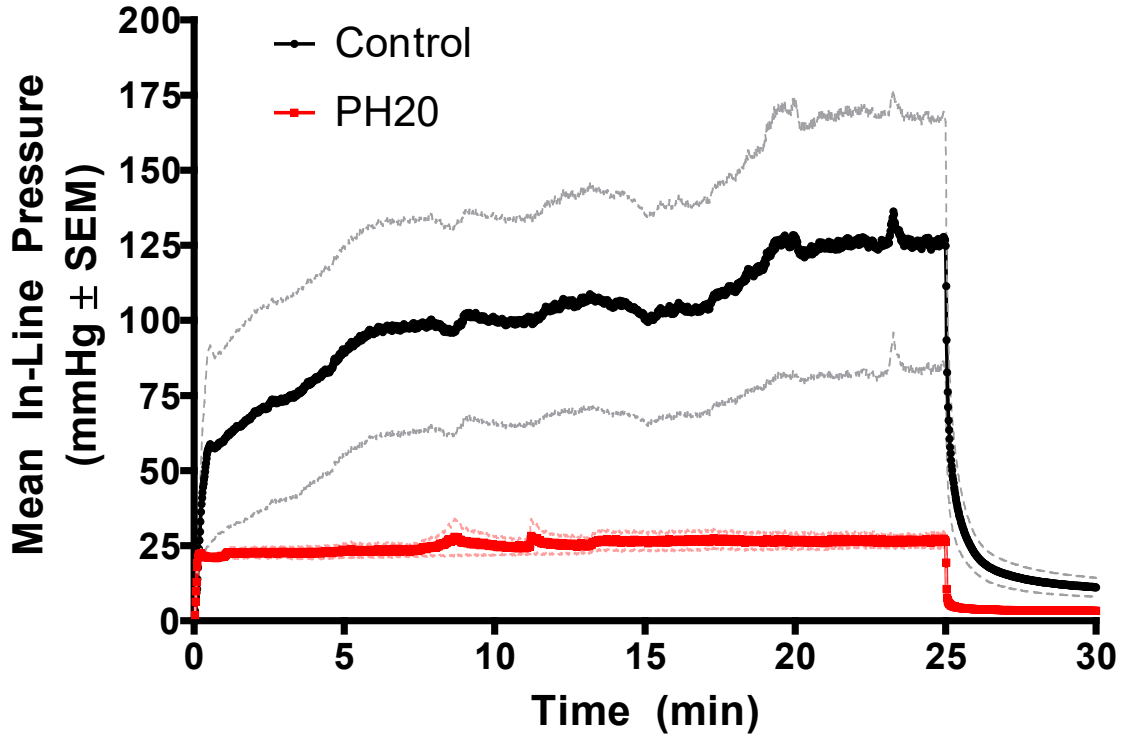
## IMPACT

ENHANZE **increases the dispersion and absorption** of other injected drugs

ENHANZE **uniquely** facilitates rapid, large volume SC delivery

# ENHANZE rHuPH20 Reduces Tissue Pressure and Variability Allowing Rapid SC Delivery

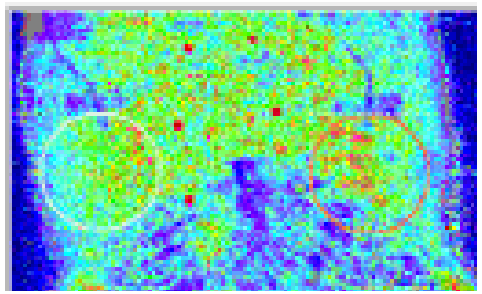
***Minipig Model: 50 mL of 15% IgG at 2 mL/min***



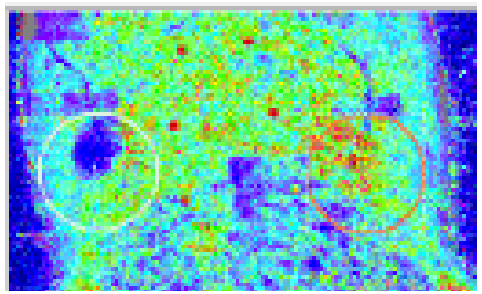

**Source:** Kang DW, et al. (2012) AAPS-NBC

# ENHANZE rHuPH20 Reduces Induration (Hardness) and 'Blebbing' at Injection Site

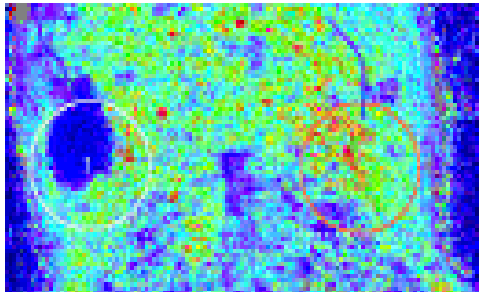
***Minipig Model: 50 mL of 15% IgG at 2 mL/min***



Control rHuPH20

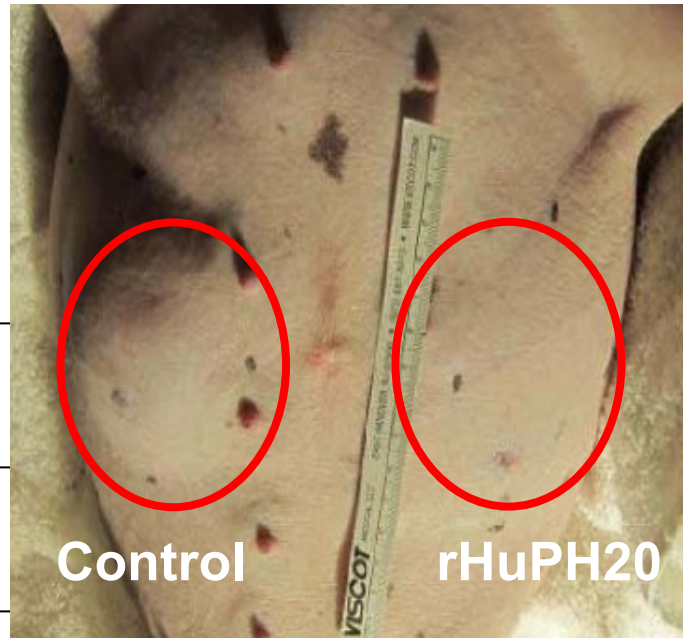


Control rHuPH20



Control rHuPH20

| | | | |
|---|---|---|---|
| **Time:** | 0 min | 10 min | 25 min |
| **Volume:** | 0 mL | 20 mL | 50 mL |

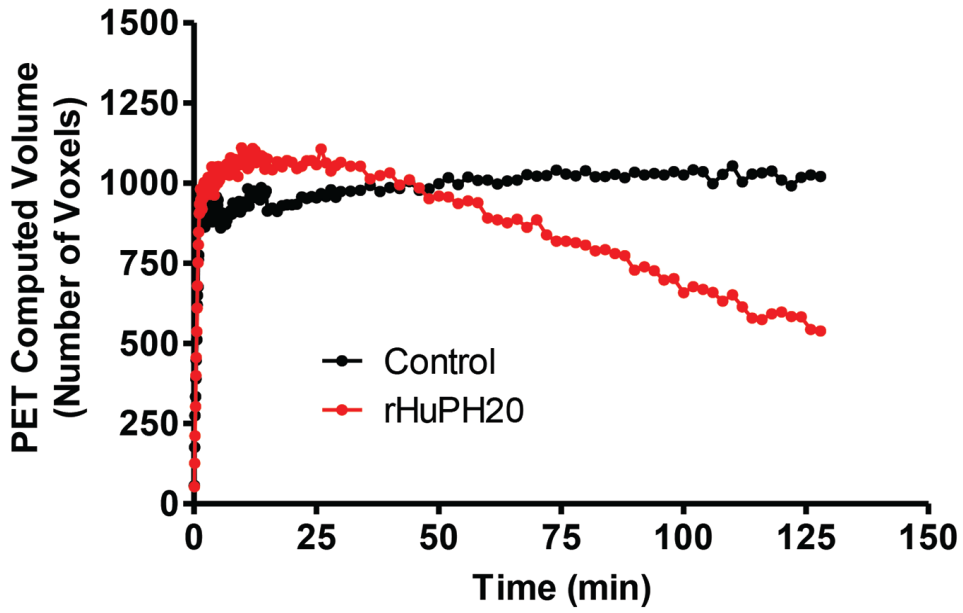


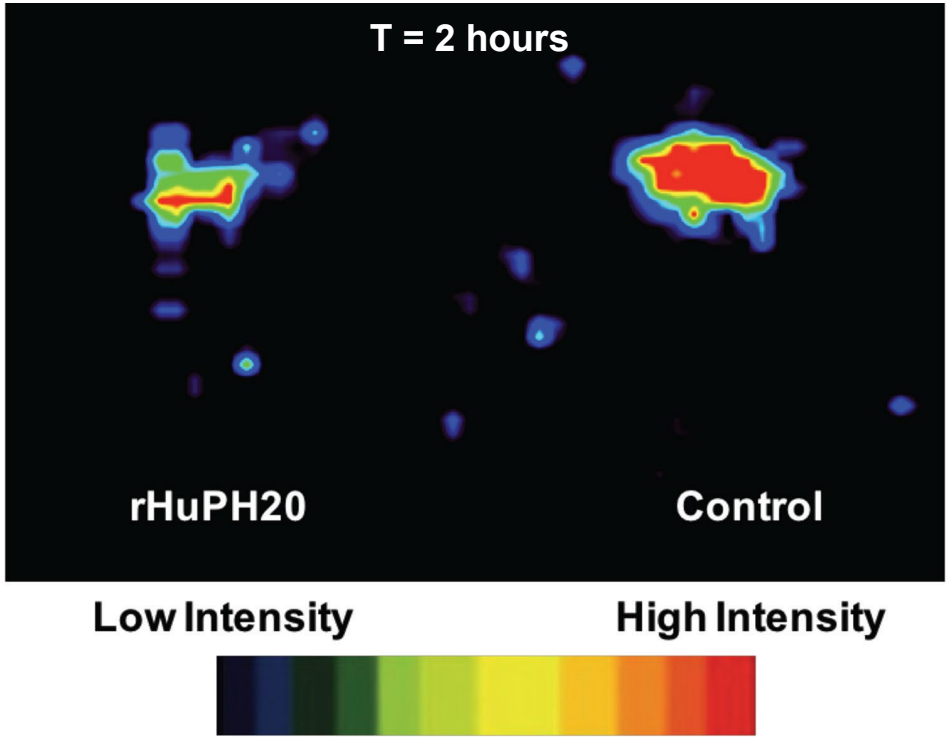

**Dark blue in the Laser Doppler images above indicates areas of significantly decreased cutaneous blood flow at the SC injection site**

**Source:** Kang DW, et al. (2012) AAPS-NBC

# ENHANZE rHuPH20 Increases Dispersion and Decreases Residence Time at Injection Site

***Minipig Model: 10 mL of 10% radiolabeled ibritumomab tiuxetan solution at 10 mL/min***



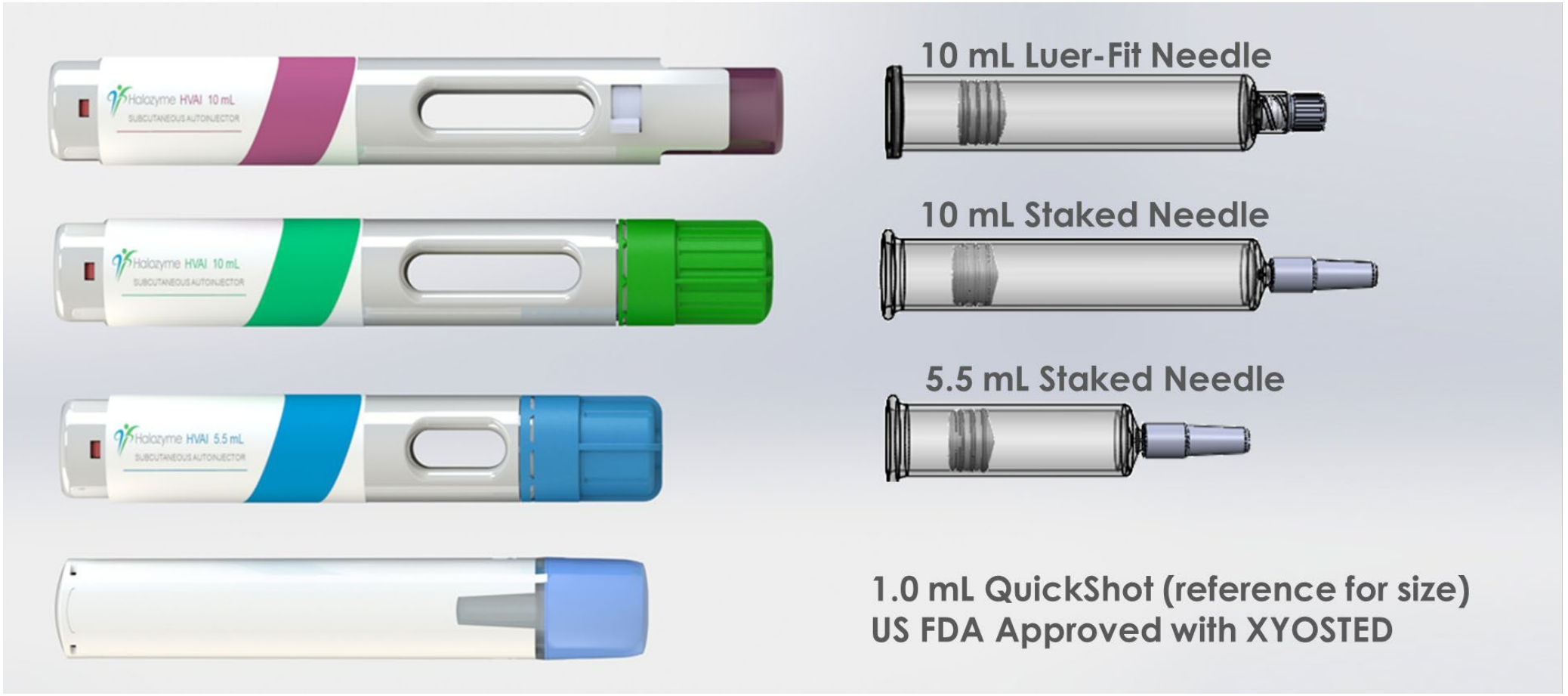

**Source:** Kang DW, et al. (2013) Controlled Release Society Annual Meeting.

# A Phase 1 Clinical Trial Combining ENHANZE with HVAI Successfully Delivered 10 mL Subcutaneously in ~30 Seconds

- The HVAI injection (10 mL in ~30 sec) was well-tolerated in human subjects and all measured injection parameters (erythema, swelling, induration and pain) were typically minimal/mild and transient after completion of the injection
  - Average injection time was 28 ± 0.8 sec
  - Back-leakage was minimal at 8.5 ± 1.9 mg (1 mg = ~ 1 µL)
- 22/23 (96%) subjects responded “YES” to the protocol defined question,

  “Would you have this injection again with HVAI?”
- This study demonstrated that HVAI delivery of volumes up to 10 mL in ≤ 30 sec is feasible for drug products combined with rHuPH20
- This study suggests that volumes even greater than 10 mL may be amenable to HVAI delivery for drug products combined with rHuPH20

# Halozyme is Moving Rapidly to Develop a Platform of Commercial-Ready High Volume Autoinjectors



# Take Home Messages

- Subcutaneous drug delivery of biotherapeutics has come along way during the last decade
    - Increased presence in oncology, autoimmunity, neurology and other therapeutic areas
- Product progress has developed concurrently with drug delivery advances seen in assisted delivery (recombinant human hyaluronidase), off- and on-body pumps, and auto-injector technology
- High-volume subcutaneous injections should continue to be a focus area to potentially improve patient outcomes and experiences, while also reducing the burden on the overall healthcare system costs