Clinical Trial to Investigate the Tolerability of a Rapid 10 mL Subcutaneous Injection of a Biologic Drug with Recombinant Human Hyaluronidase (rHuPH20) Using a High-Volume Auto-Injector (HVAI) in Healthy Subjects

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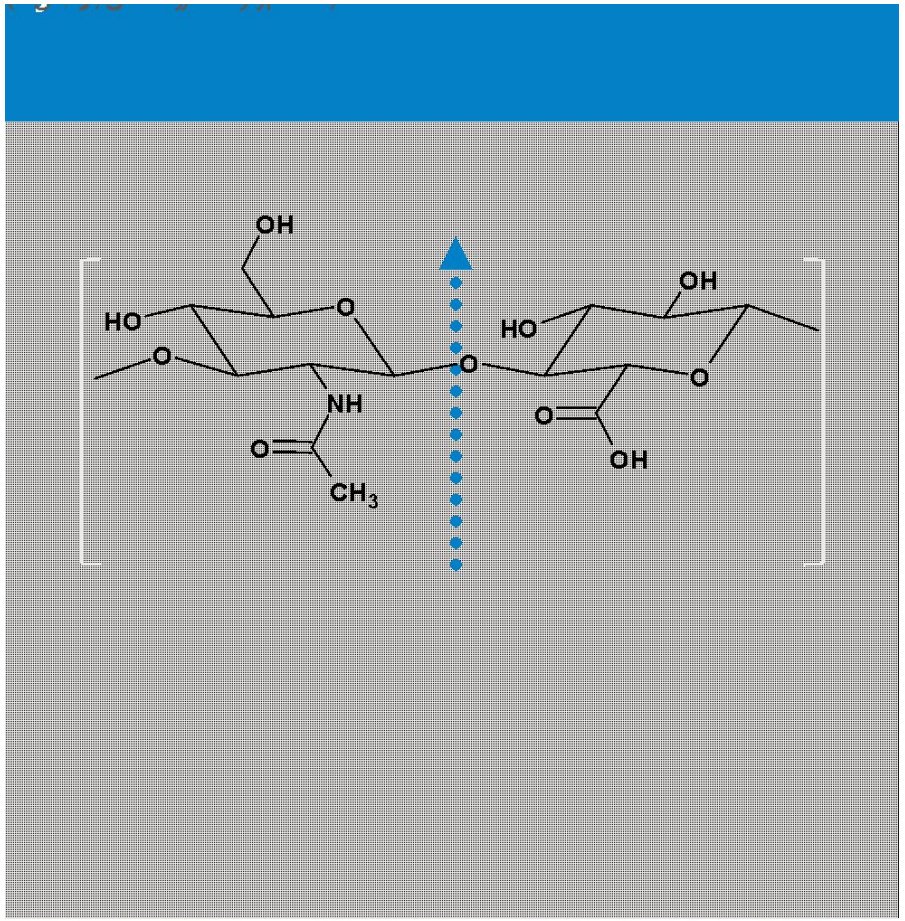
Learning Objectives

1. Investigate clinical feasibility and tolerability of a 10 mL rapid, SC injection of a drug co-administered with rHuPH20 using a prototype HVAI.

2. Review clinical endpoints used to determine SC injection tolerability.

rHuPH20 is an Enzyme that Depolymerizes Hyaluronan (HA) in the Subcutaneous Space and Allows for 10 mL Injections in ≤ 30 Seconds

- What it does:
  - Creates temporary space for SC fluid dispersion
  - Reduces tissue back-pressure
- How it works:
  - Rapid, local and transient depolymerization of hyaluronan (HA) in the SC space
  - HA in the SC space is restored via normal processes within 24-48 h
- Impact:
  - Results in less variability in delivery time and increases dispersion and absorption
  - Facilitates rapid, large volume SC delivery



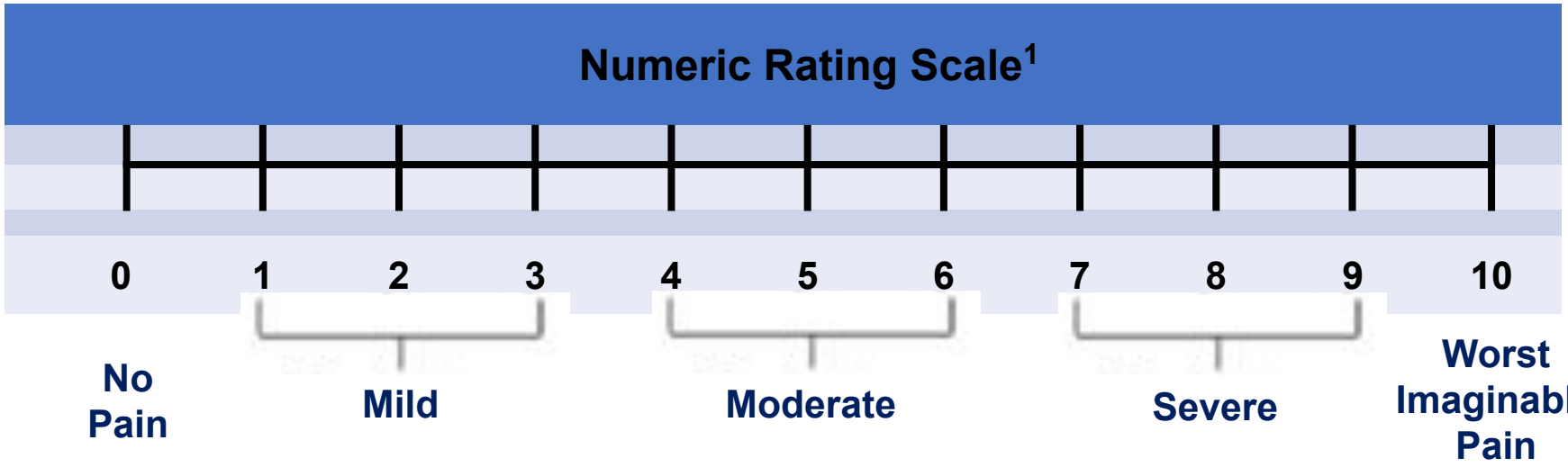
Clinical Study Design Using a High-Volume Auto-Injector (HVAI) for Administration

Goal: **To determine the feasibility and tolerability of a rapid subcutaneous delivery of a viscous Ab solution (Ig 10%) + recombinant human hyaluronidase PH20 (rHuPH20) using a HVAI**

Design:

- Phase 1 clinical trial in **healthy subjects with injections performed by HCP's**
- Endpoints included:
  - **Completion** of injection and **injection time and back-leakage**
  - **Subject's pain/discomfort scoring** [Numeric Rating Scale (NRS): 0-10]
  - HCP's qualitative assessment scoring of **erythema**, **bleb/swelling size**, and **induration** using Draize scoring
  - Preference question – "**Would you have this injection again with HVAI?**"

Most Subjects (21/23) Indicated No Pain-Mild Pain as Highest NRS Score and 22/23 Subjects Would Have the HVAI Injection Again

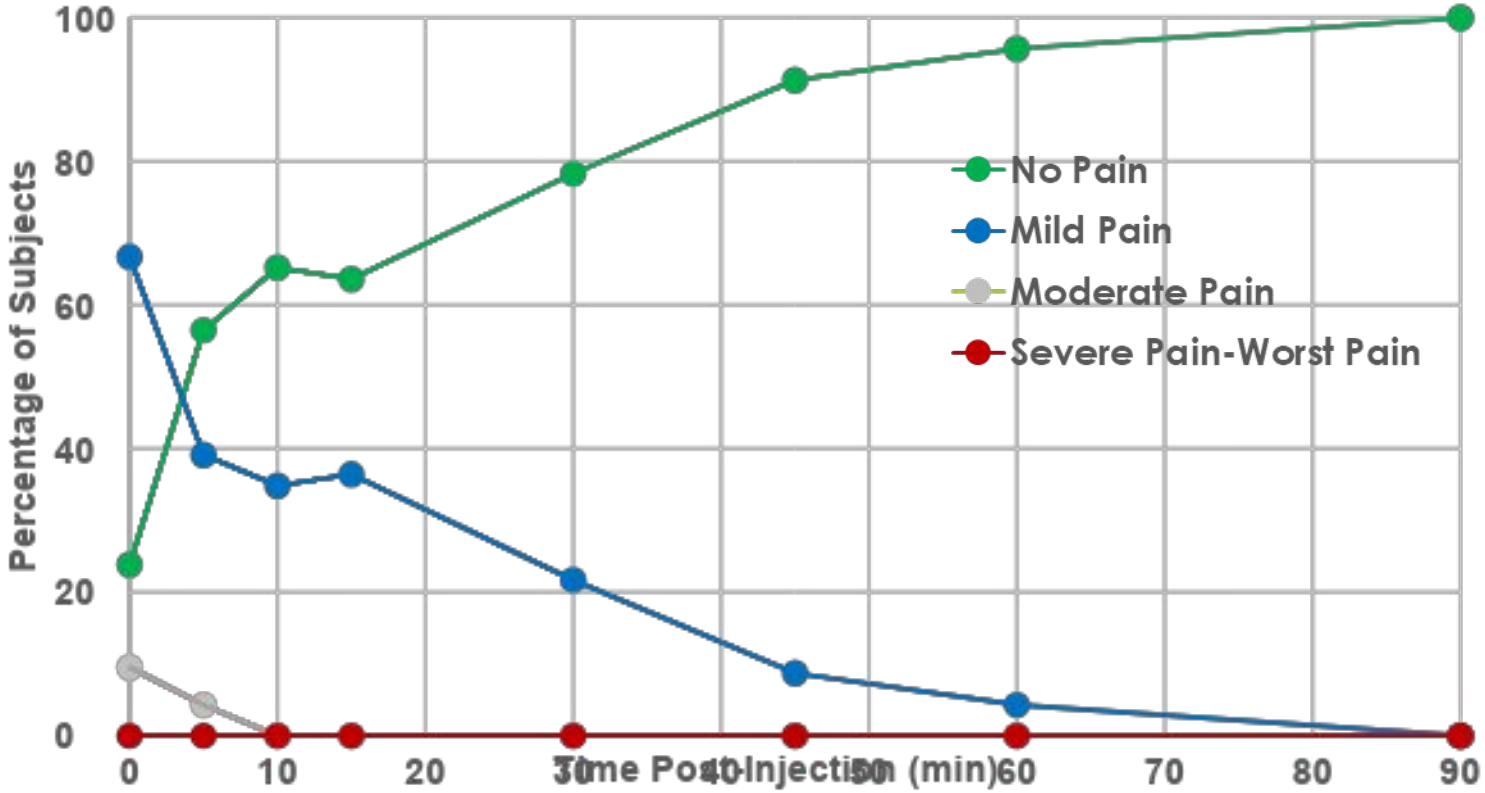


	No Pain	Mild	Moderate	Severe	Worst Imaginable Pain
Highest NRS Score post-injection	7	14	2	-	-
Would you have this injection again with HVAI?	100%	93%	100%	-	-

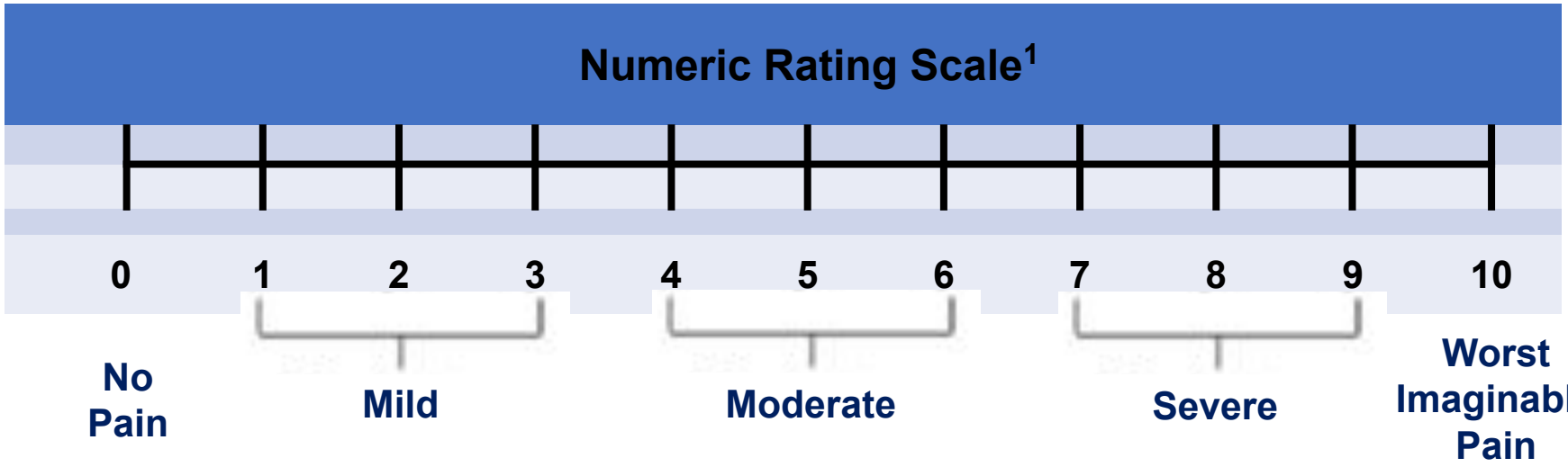
[1] Adapted from Karcioglu et. al., *American Journal of Emergency Medicine,* 36: 707-714 (2018).

Numeric Rating Scale (NRS, 0-10 scale) Showed Mostly No Pain-Mild Pain Immediately Post-Injection (90%) With Rapid Resolution During Follow-Up

- > 90% of subjects scored No Pain-Mild Pain immediately after the injection (T = 0 min)
- > 95% of subjects scored No Pain-Mild Pain by 5 min
- 100% of subjects scored No Pain-Mild Pain by 10 min



All Subjects Indicated No Pain (17/23) or Mild Pain (6/23) Upon Needle Insertion Using HVAI with 25G Needle



	No Pain	Mild	Moderate	Severe	Worst Imaginable Pain
NRS Score upon needle insertion	17	6	-	-	-

NRS = 1 in 5 subjects
NRS = 2 in 1 subject

[1] Adapted from Karcioglu et. al., *American Journal of Emergency Medicine,* 36: 707-714 (2018).

Summary of Clinical Trial

- 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 demonstrates 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

Conclusion

- Rapid, high-volume SC injections, utilizing an HVAI, are feasible and tolerable in humans when administering a biologic with rHuPH20

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