Myth 1: Subcutaneous delivery is painful and limited to small volumes

Sylvain Huille, Hannie Shih, and David Kang

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CRS 2024 Annual Meeting AND Exposition
JULY 8–12, 2024 • BOLOGNA, ITALY
INTEGRATING Delivery Science ACROSS DISCIPLINES

Myth 1: Subcutaneous delivery is painful and limited to small volumes

Are we at the verge of a major transformation in the parenteral administration of antibody-based biologics as that carried out for diabetics with insulin pens?

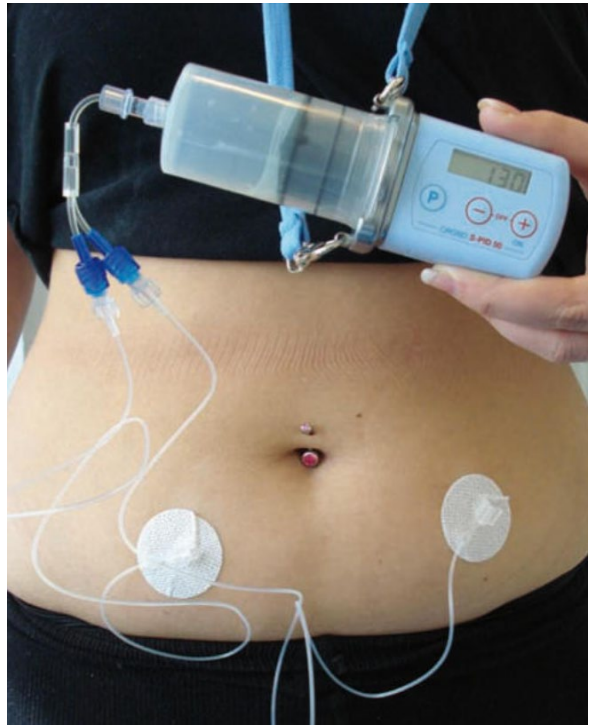
- Product factors that may impact injection pain – **Sylvain Huille**
- High Dose mAbs Driving the Need for High Volume Subcutaneous Delivery – **Hannie Shih**
- Clinical Trial on Assessing the Feasibility and Tolerability of a 10 mL Subcutaneous Injection of an Antibody in ≤ 30 sec – **David Kang**

For decades, human normal immunoglobulin therapy via large volume SC administration

- ***Since the 1990s SCIGs have become a popular method*** of administration for IGG replacement therapy in patients with immunodeficiency*
- ***Injection volume 15-40 ml*** - Moderate flow rate (< 1ml/min) using external pump
- ***Trained and motivated patients*** seeking convenience and flexibility in dosing regimens and an alternative to intravenous treatment when poorly tolerated

	FDA - US			EMA - Europe		
	Starting (mL/hr/site)	Consequent (mL/hr/site)	Volume (mL/site)	Initial (mL/hr/site)	Consequent (mL/hr/site)	Volume (mL/site)
Gammagard 10%	15-20	15–30	20-30	na	na	na
Cutaquig 16.5%	15-20	≤52	≤40	15	≤25	≤30
Hizentra 20%	≤15	≤25	≤25	20	≤35	50
HyQvia 10% + rHuPH20	10–240	10–300	≤600	10–240	10–300	300

Prescribing information / Summary of product characteristics - GAMMAGARD 10%, Baxalta US Inc./ CUTAQUIG 16.5%, Octapharma / HIZENTRA 20%,CSL Behring AG / HyQvia 10%, Baxter Innovations GmbH.



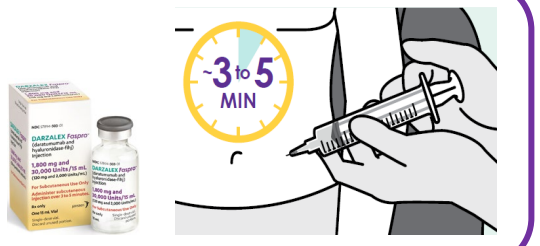
* Gardulf et al. Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion. The Lancet, 338(8760), 162-166.

Already marketed products intended for large volume SC administration

Large volume medical device (on-body / wearable devices) or co-formulation with permeation enhancers (hyaluronidase enzyme)

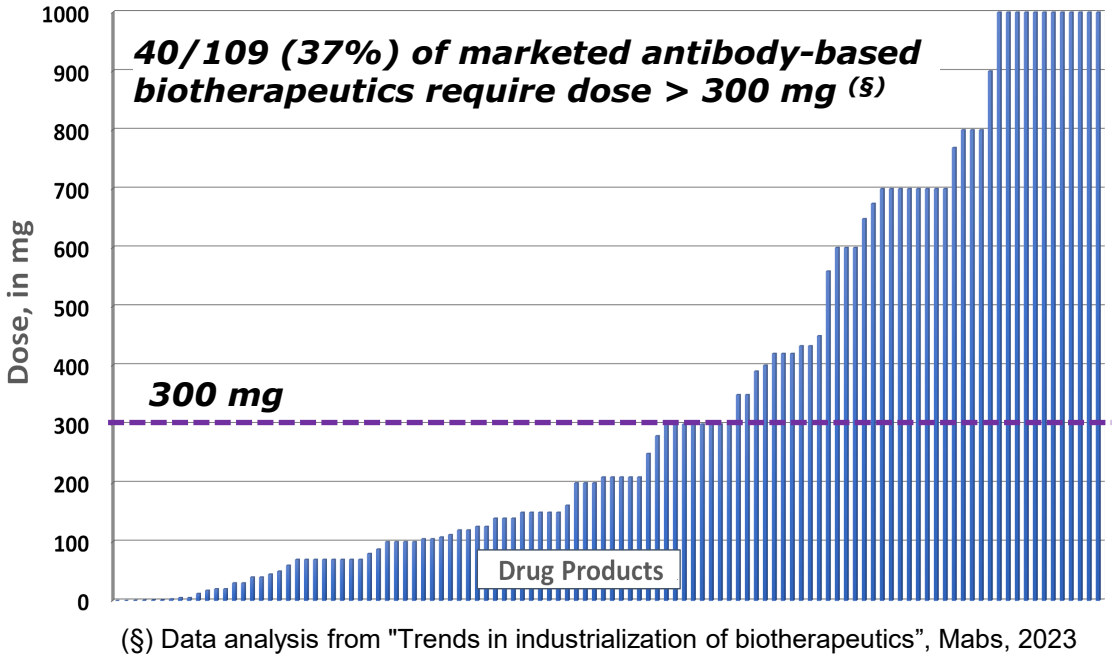
Product	Therapeutic area	Volume	Injection time
Large Volume Medical Device - On-body injection device / Wearable device			
Repatha / Smart dose device (evolutumab), Amgen	Hypercholesterolaemia	3,5 ml	5 min
Aspaveli (pegcetacoplan), Biovitrum	Haemoglobinuria (PNH)	20 ml	30-60 min
Furoscix (furosemide)	Chronic heart failure	10 ml	5 hours
Co-formulation with endoglycosidase (hyaluronidase enzyme) / Manual injection			
Herceptin Hylecta (trastuzumab), Roche	Oncology / Breast cancer	5 mL	2-5 min
Rituxan Hycela/ Mabthera (rituximab), Roche	Oncology / Blood cancers	11.7 mL	5 min
Darzalex Faspro/ Darzalex SC (daratumumab) Janssen	Oncology/ Multiple myeloma	15 mL	3-5 min
Phesgo (pertuzumab & trastuzumab), Roche	Oncology/ Breast cancer	10 / 15 mL	5 min / 8 min
Vyvart Hytrulo (Efgartigimod alfa), Argenx	Myasthenia gravis (gMG)	5.6 ml	30-90 sec
Tecentriq SC (atezolizumab), Roche	Oncology / NSCL	15ml	7 min

- Repatha only biological product using Large Volume Device delivery system - Discontinued as of June 30th 2024
- Co-formulation with endoglycosidase is used without a medical device but by manual injection - Mainly in oncology indication requiring HCP for injection
- SC injection volumes of 5 to 15 ml, significantly greater than the 2 ml maximum volume of auto-injector devices
- Most products are initially launched in IV before moving to SC as Life Cycle Management (LCM)
- Intense race to switch to SC with aPD(L)-1 antibodies Tecentriq (Roche), Opdivo (BMS) and Keytruda (Merck)

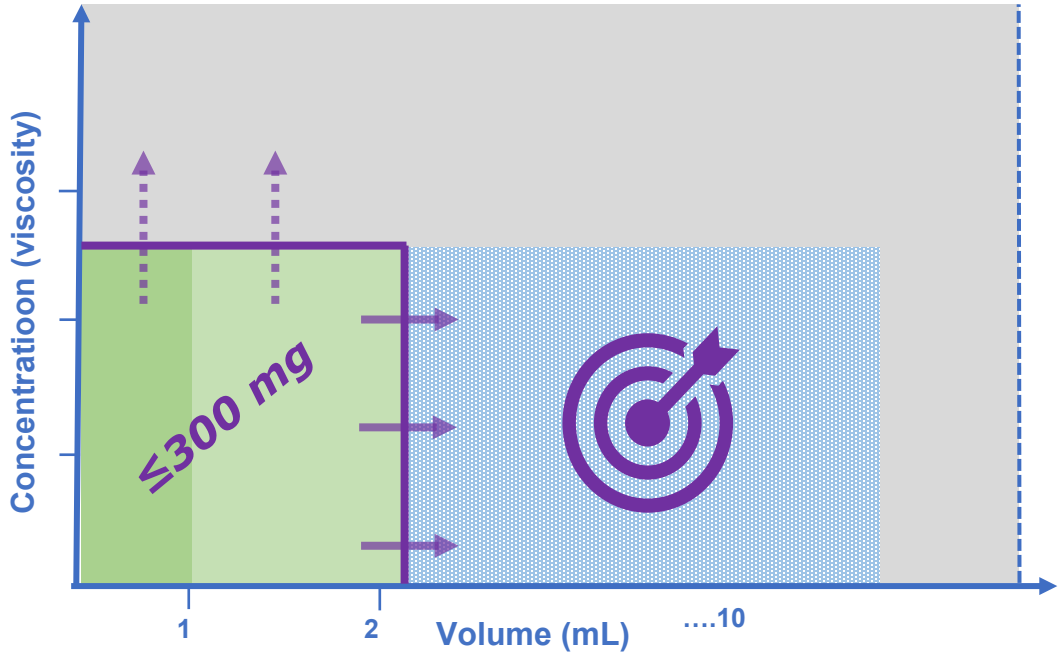


Dosages of antibody-based biotherapeutics require high injection volumes

A third of antibody-based biotherapeutics (IV & SC) administered at doses > 300 mg i.e. an injection volume > 2mL



(§) Data analysis from "Trends in industrialization of biotherapeutics", Mabs, 2023

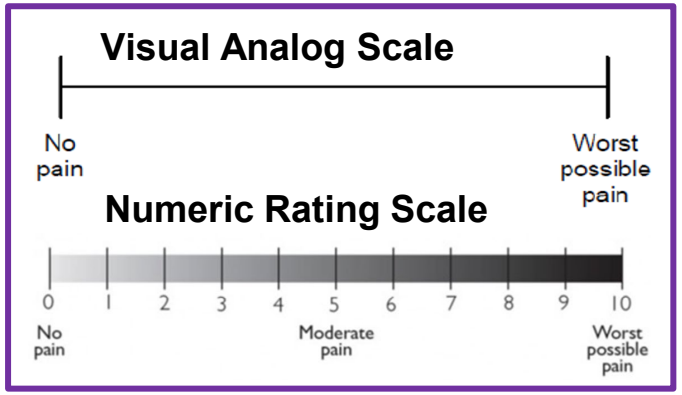


- Switching to the SC route requires for many drugs to push the limit beyond 2-3 ml injection volume most accepted.
- Large volume medical device and/or co-formulation with permeation enhancers are mature technologies for switching to SC
- New technologies (e.g. suspension of spray-dried microparticles in a non-aqueous vehicle) allowing very high concentrations (400-600 mg/ml) with low injection volume are promising but still at the pre-clinical stage.

Injection-related pain is a key component of high-volume SC administration that is particularly difficult to address

The difficulty in assessing injection-related pain may have contributed to myths about large volumes SC infusion.

- Injection pain (and tolerability) during and immediately after injection
- Pain defines as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage*
  - Sensory responses: intensity ➜ Quantitative measurement with pain scales
  - Affective / behavior responses: unpleasantness ➜ highly subject to subjectivity between people
- Most commonly used pain injection scales: Visual Analog Scale (VAS) and Numeric Rating Scale (NRS) remain highly subjective depending on the conditions on investigation.
  - Comparison between studies difficult due to heterogeneity of clinical and methodological factors
  - Minimal clinically important differences (MCID) showed significant variations in the VAS scale between 8 and 40 mm (over 1000 mm full scale)**
  - Statistically significant differences not well established when studying low levels and short durations
- Other approaches using artificial intelligence's ability to recognize facial expression when assessing pain, although not yet used for injection pain scoring
- Pain scales assess only one dimension of experience, namely pain intensity, and oversimplify the experience of pain.

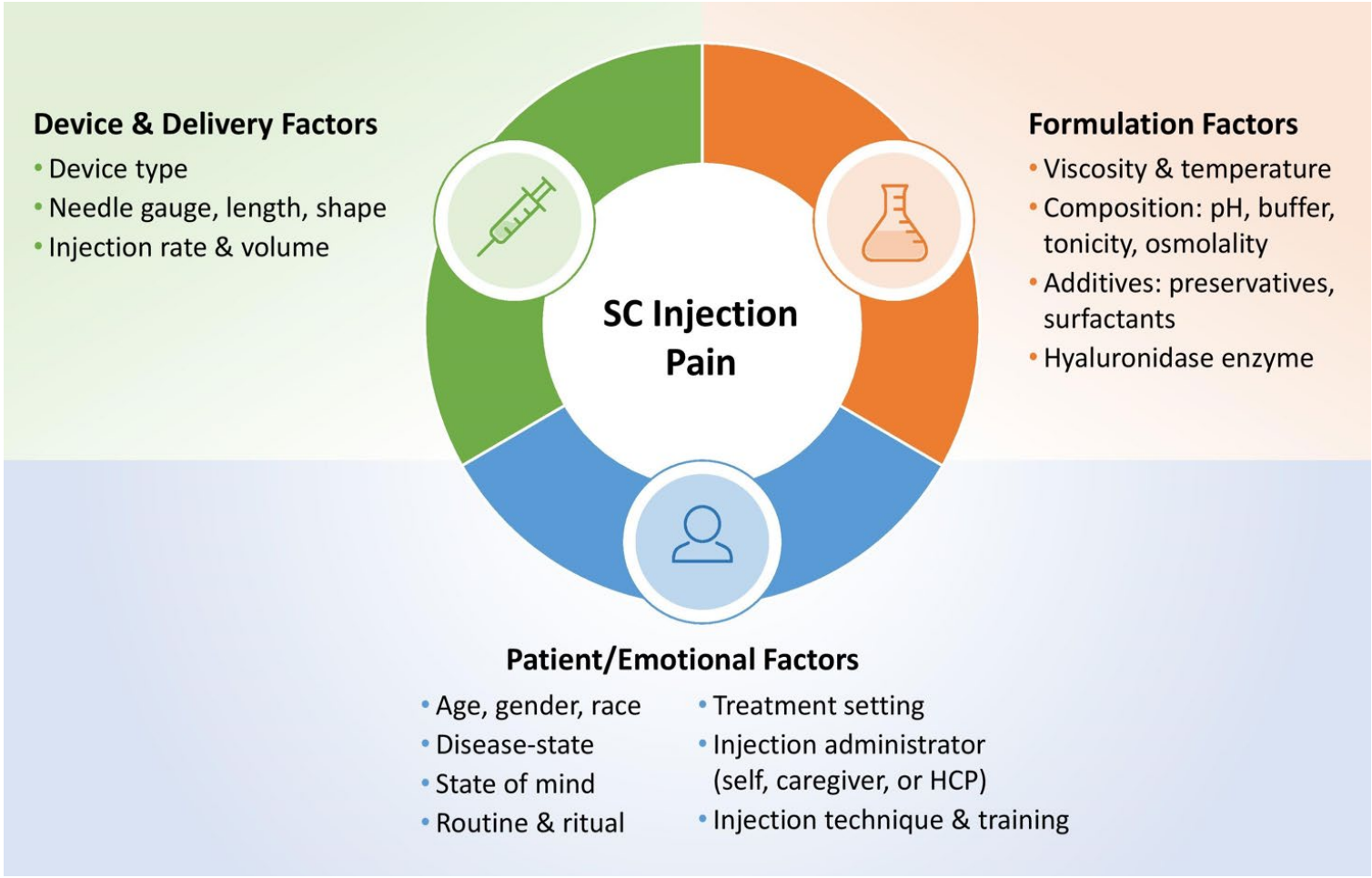


* IASP. International Association for the Study of Pain IASP Terminology Accessed 9 March 2023, https://www.iasp-pain.org/resources/terminology/?ItemNumber=1698

* Olsen, Mette Frahm, et al. "Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain." BMC medicine 15 (2017): 1-18..

Injection related pain is multifactorial

Review article on product factors that may impact injection pain by SC Drug Development and Delivery Consortium*



- **Key factors** to interfere with injection pain listed for **Device and Formulation**

➜ No straightforward specifications

➜ General trends on device factors and formulation factors for reducing injection pain

- **Patient/Emotional factors** induces different acceptability of injection-related pain depending on the patient's pathology.

➜ Disease state and disease chronicity may strongly influence patient's tolerance

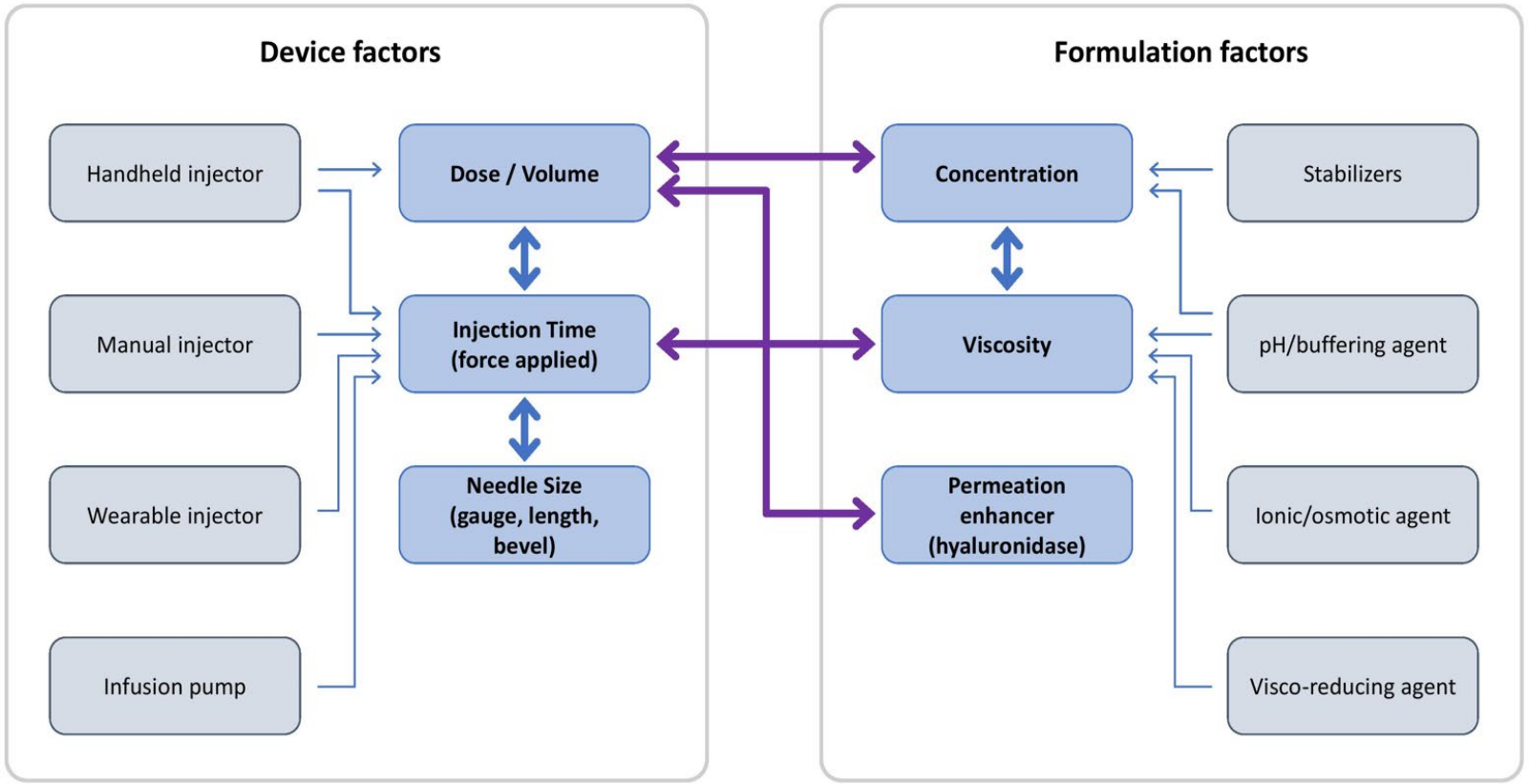
➜ Tolerability and acceptability may also be influenced differently by disease, for example in patients with severe skin disease.

Training and Education on proper injection technique tailored to patients, also contribute to avoid/reduce injection pain

* Mathias, Neil, et al. "Towards more tolerable subcutaneous administration: Review of contributing factors for improving combination product design." Advanced Drug Delivery Reviews (2024): 115301.

Interdependencies between Device and Formulation factors

Interdependencies between delivery and formulation/composition factors make it difficult to isolate individual factors



- Two of the main formulation factors, concentration and viscosity, closely interrelated to device factors

➜ Major impact on injection conditions and associated pain.

➜ Concentration/Viscosity can determine device type based on injection time and needle size selected.

- Interdependence illustrates the requirement for close collaboration between formulation & device development

Knowledge Gap and Recommendation for more tolerable SC administration

SC Drug Dev. and Delivery Consortium made several recommendations to address gaps in the understanding pain on SC injections*

Key knowledge gaps	Recommendation(s)
Lack of consistent pain scoring method in clinical trials	Harmonize use of an existing pain scoring method to improve consistency and reduce subjectivity in injection pain scoring, and enable inter- and intra-individual comparisons across studies to better correlate pain scores to clinical significance and therapy impact
Correlation between injection force profiles or thresholds (pressures generated within SC space during injection) and injection pain is unclear	Consider clinical studies to link and benchmark tissue pressure thresholds that are indicative of injection pain Establish capability to model and predict tissue pressures during injection with clinical confirmation (*in silico*, *in vitro*, and/or *in vivo*)
Numerous interdependencies exist between delivery and formulation/composition factors that confound understanding of their individual impact on injection pain	Focused clinical studies using design of experiment conditions to deconvolute specific dosing, device, and formulation composition factors at higher volumes and their impact on injection SC tissue pressure and pain Use preclinical models to examine interdependencies between formulations and device delivery conditions Confirm the relative roles of pH, surfactant, solubilizer, and tonicity modifiers on injection pain

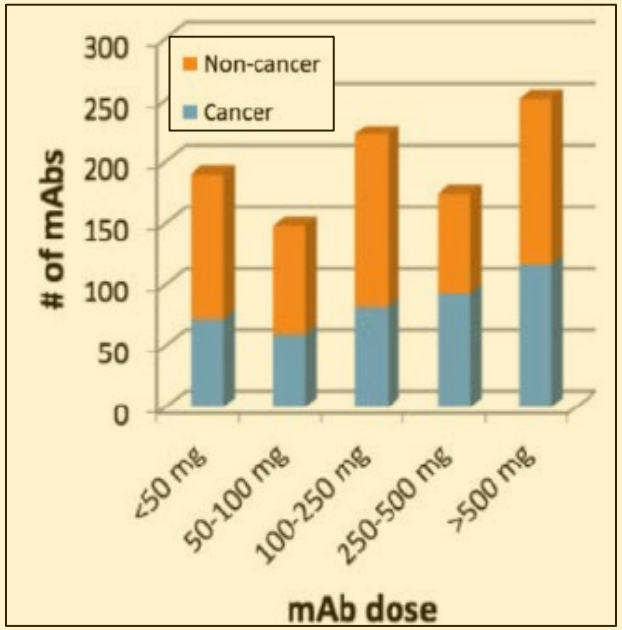
* Mathias, Neil, et al. "Towards more tolerable subcutaneous administration: Review of contributing factors for improving combination product design." Advanced Drug Delivery Reviews (2024): 115301.

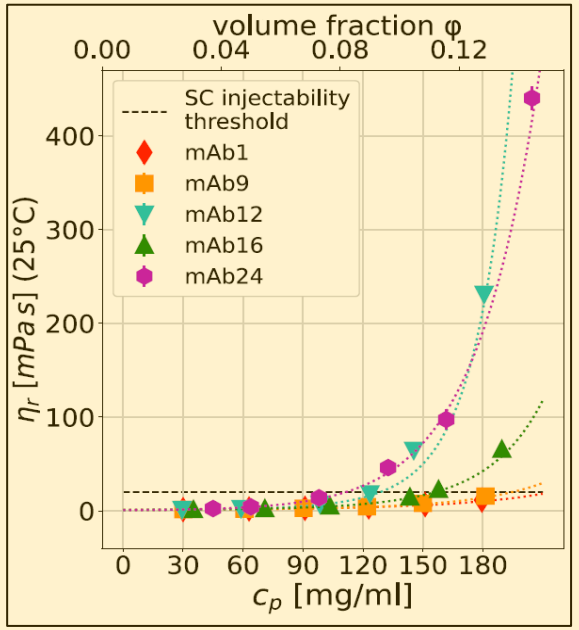
Clinical Investigation of Large Volume Subcutaneous Delivery up to 25 mL for Lean and Non-lean Subjects

Dang X, Shih H, Sharma R, Angwin-Kaerner D, Lin K, Kapur S, Thyagarajapuram N, Shi G, and Collins D.

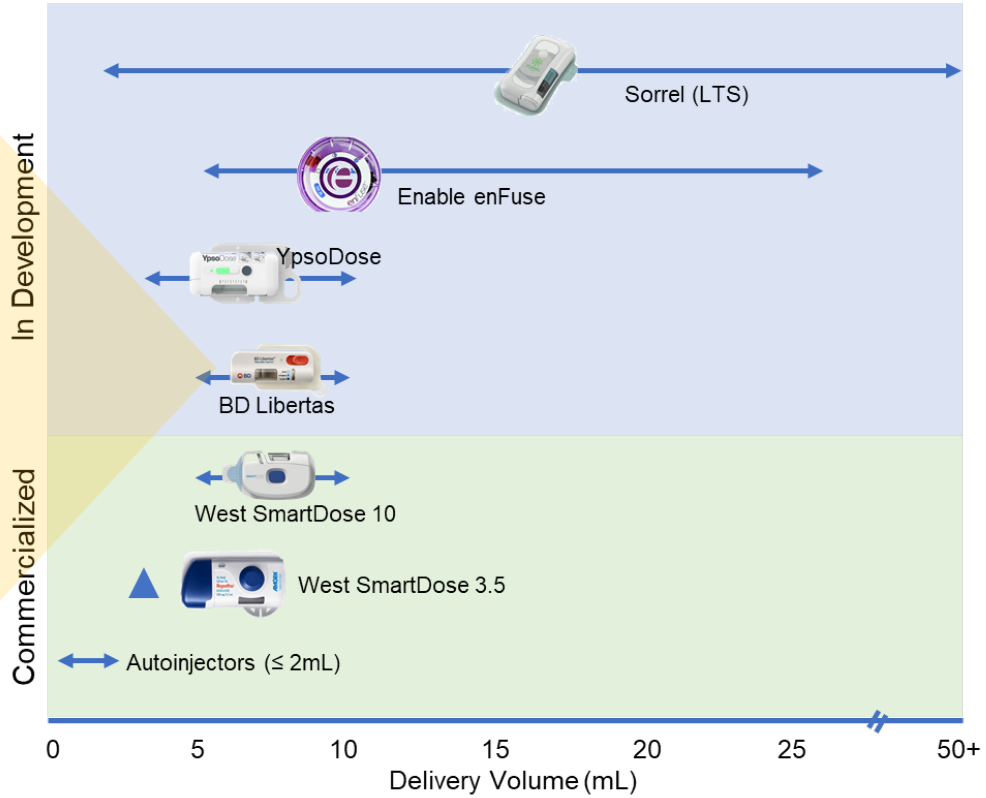
Pharmaceutical Research, 2024, Volume 41, page 751-763

High Dose mAbs Driving the Need for High Volume Subcutaneous Delivery



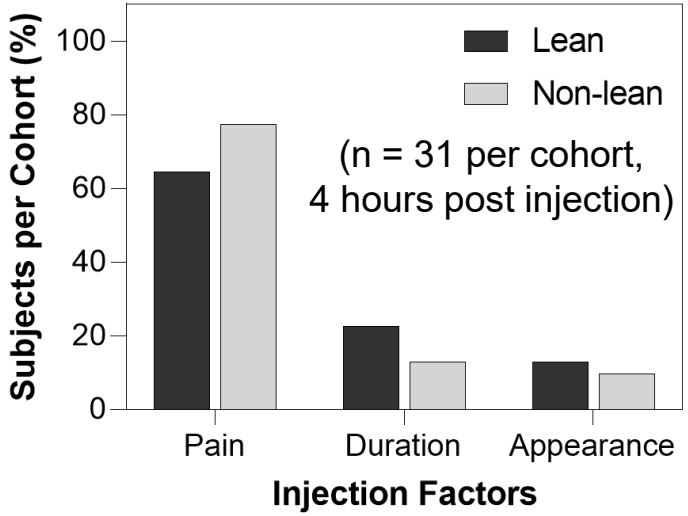


(left) Workshop on SC Delivery, CRS Annual Meeting, 2019, (right) Mosca *et al.,* 2023, Mol Pharm 20:4698



CT Participants Confirmed that Injection Site Pain is the Most Important Factor to Improve Large Volume Injection

Myth: Large volume injections are painful…



Dang *et al.* 2024. Pharm Res 41:751

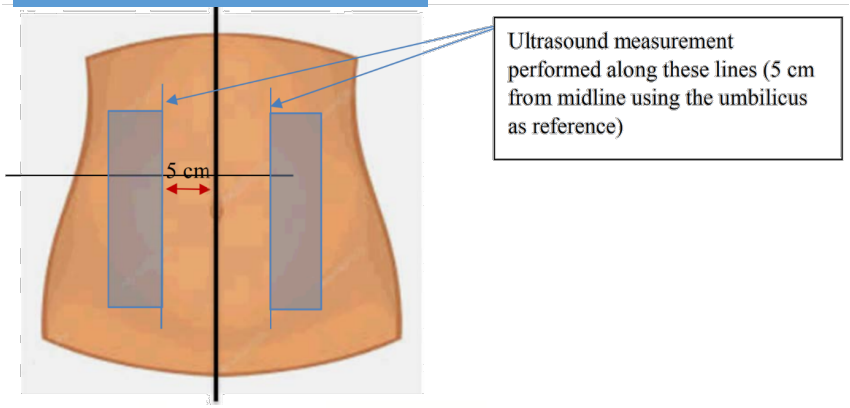
Study to establish the baseline of injection site pain and reactions for large volume injections

Study Goal: Investigate injection site reactions and pain of up to 25mL abdominal injection

Study Parameters

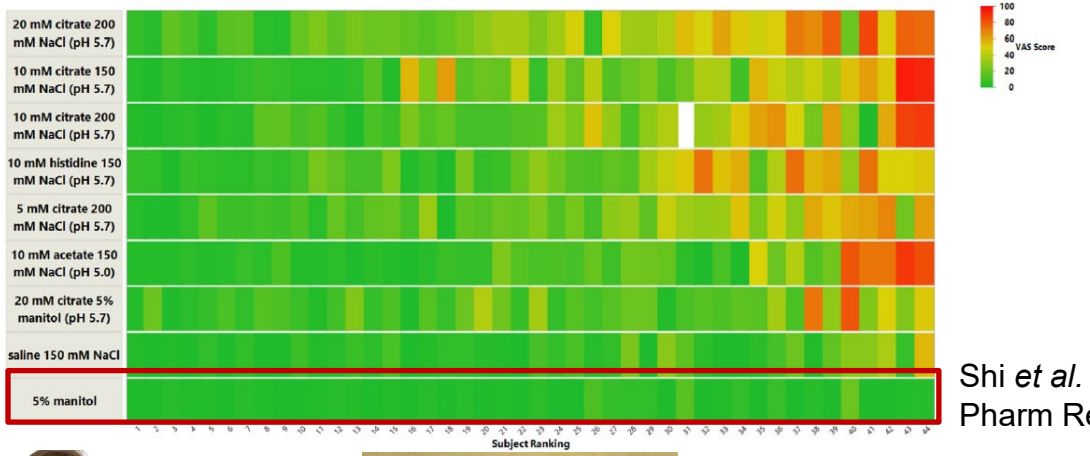
- Injection volume: 5, 12, 25 mL
- Needle length: 6, 9, 12 mm
- SC thickness: lean (≤ 14.5 mm) and non-lean (≥ 15.5 mm)
- Infusion pump at 0.5 mL/min

Injection Conditions



Low Pain Viscous Solution

10 cP hyaluronic acid/mannitol

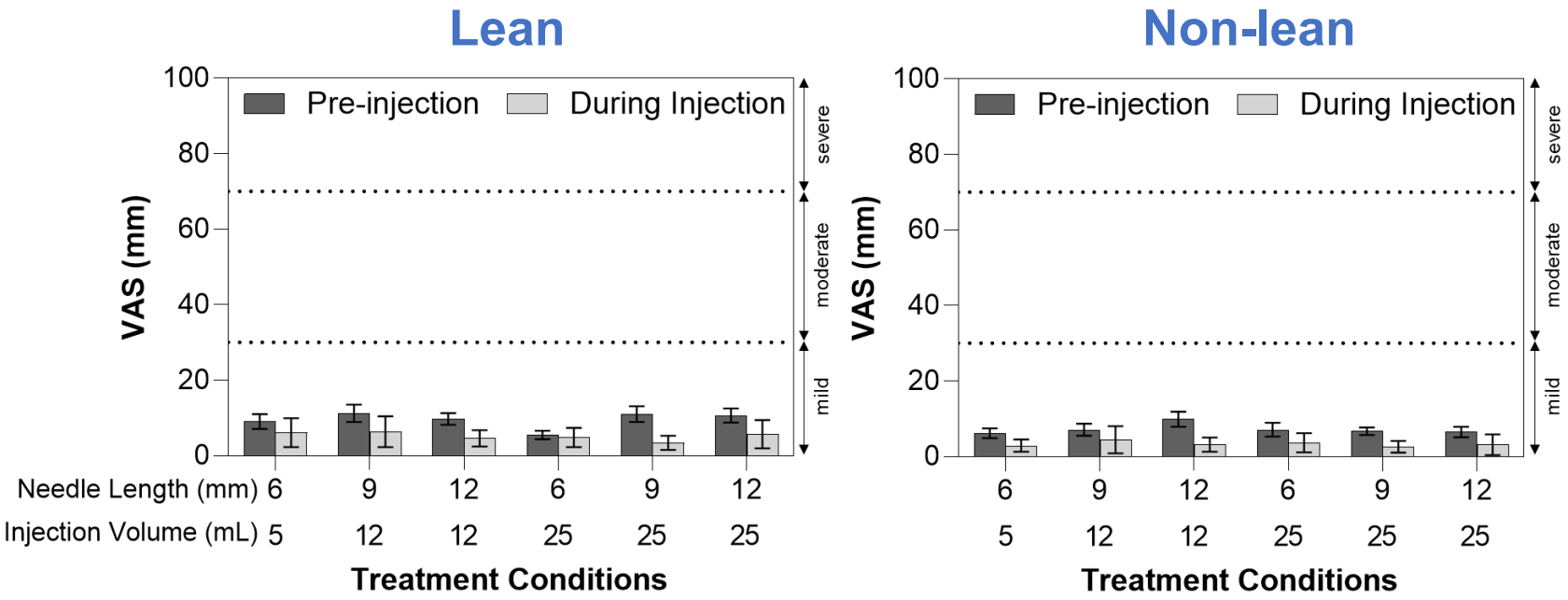


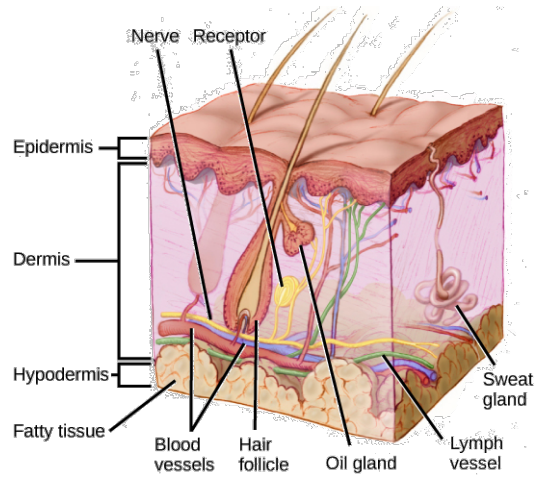
Shi *et al.* 2021. Pharm Res 38:779

https://shorturl.at/kW8Ff

- Erythema
- Edema
- Induration
- Pruritis
- Leakage

Needle Insertion is More Painful than 25mL Injection

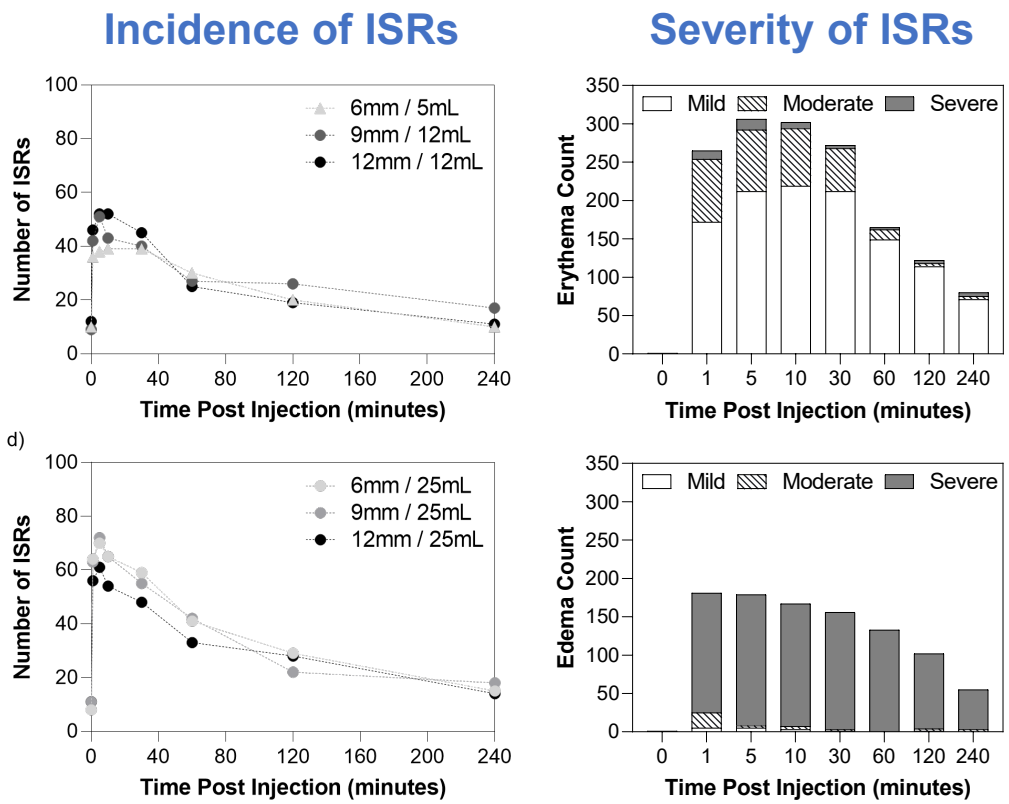


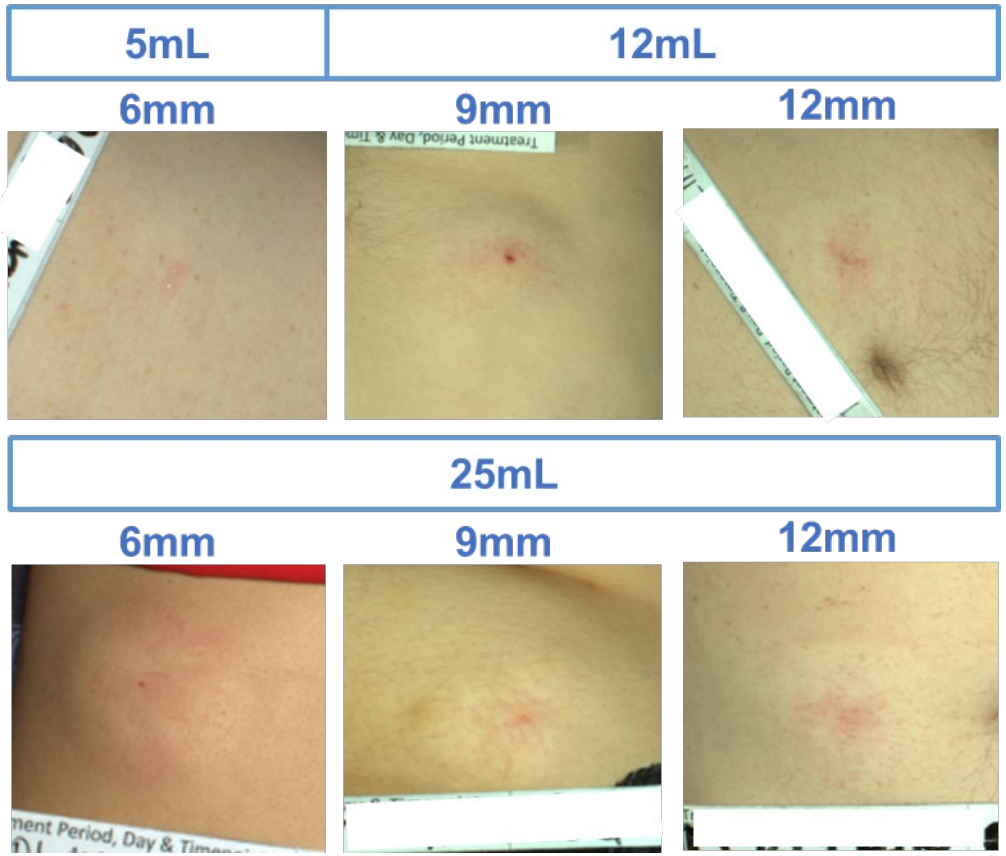


- Mild pain across all treatment conditions
- Pain not affected by potential IM injections with using longer needle length

(Left) Dang *et al.* 2024. Pharm Res 41:751 (Right) https://shorturl.at/FUful

Increased ISRs with Shorter Needle Length and Larger Volume

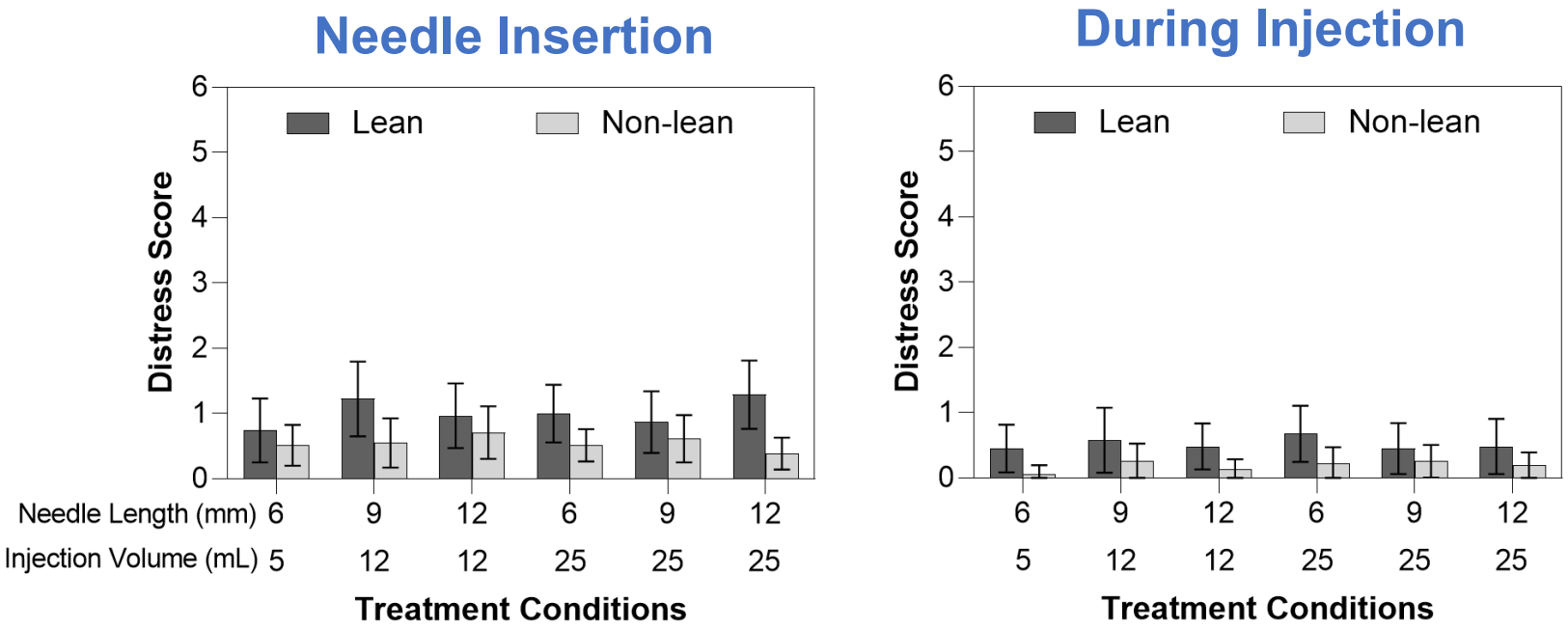




(ISRs include erythema, edema, induration, and pruritis)

Dang *et al.* 2024. Pharm Res 41:751

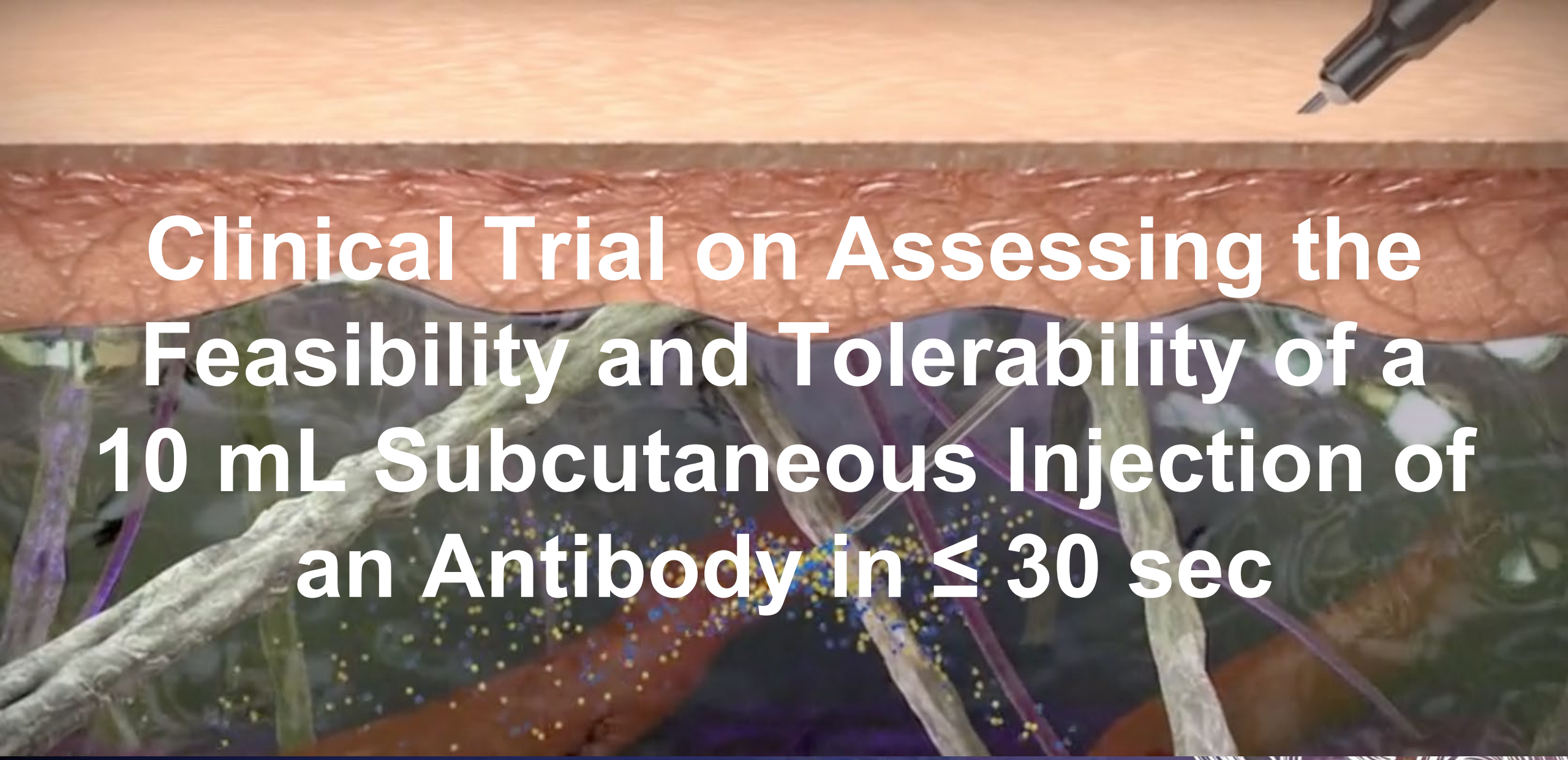
Participants were not Distressed by Large Volume Injections



Conclusions:

- While participants focused on pain as their main concern, our data shows that large volume injection can be done without triggering pain and ISRs were resolved in 4 hours.
- Established a baseline ISRs and ISP for 25mL abdominal injections to inform future clinical development

Dang *et al.* 2024. Pharm Res 41:751



Clinical Trial on Assessing the Feasibility and Tolerability of a 10 mL Subcutaneous Injection of an Antibody in ≤ 30 sec

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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

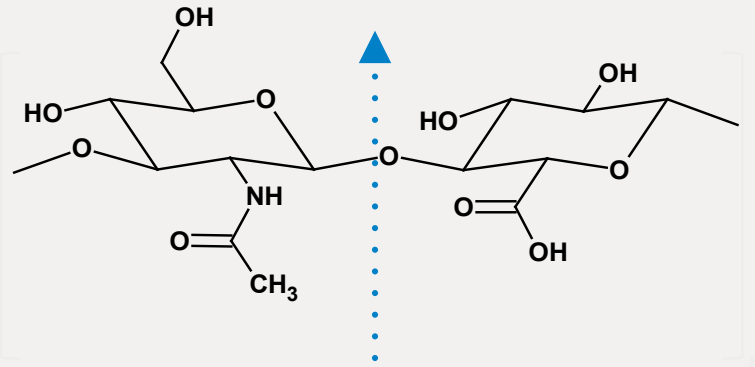
Design:

- 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?**"

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

Hyaluronidase has a well-understood mechanism of action

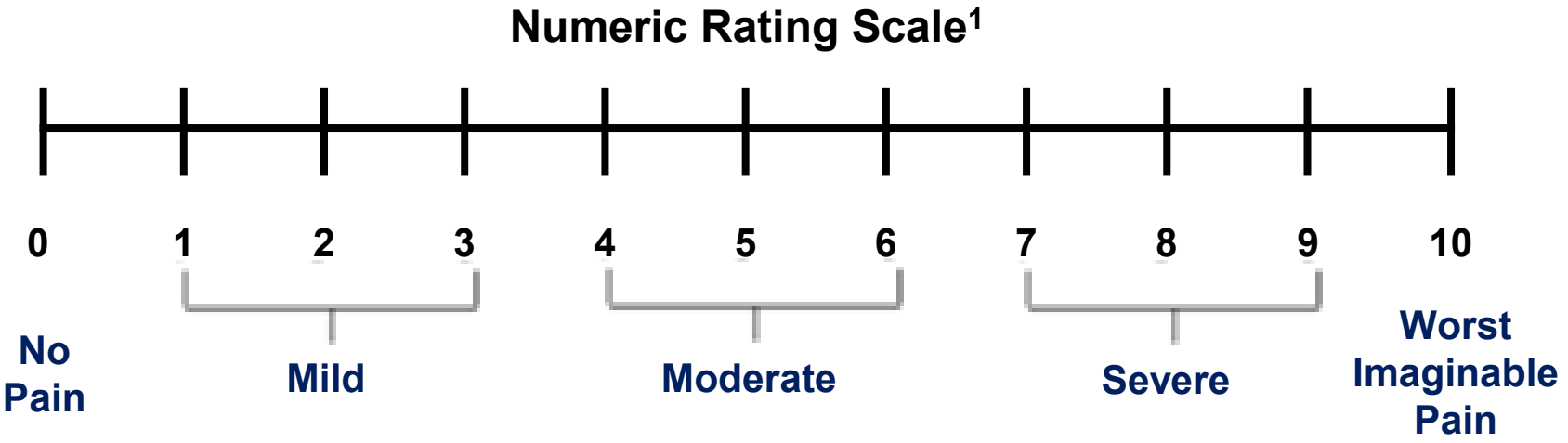


+ Hyaluronidase

n = 2,000 – 25,000
(0.2 – 10 MDa)

Human body turns over more than
5 grams/day of hyaluronan
(1/3 of total body pool)

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

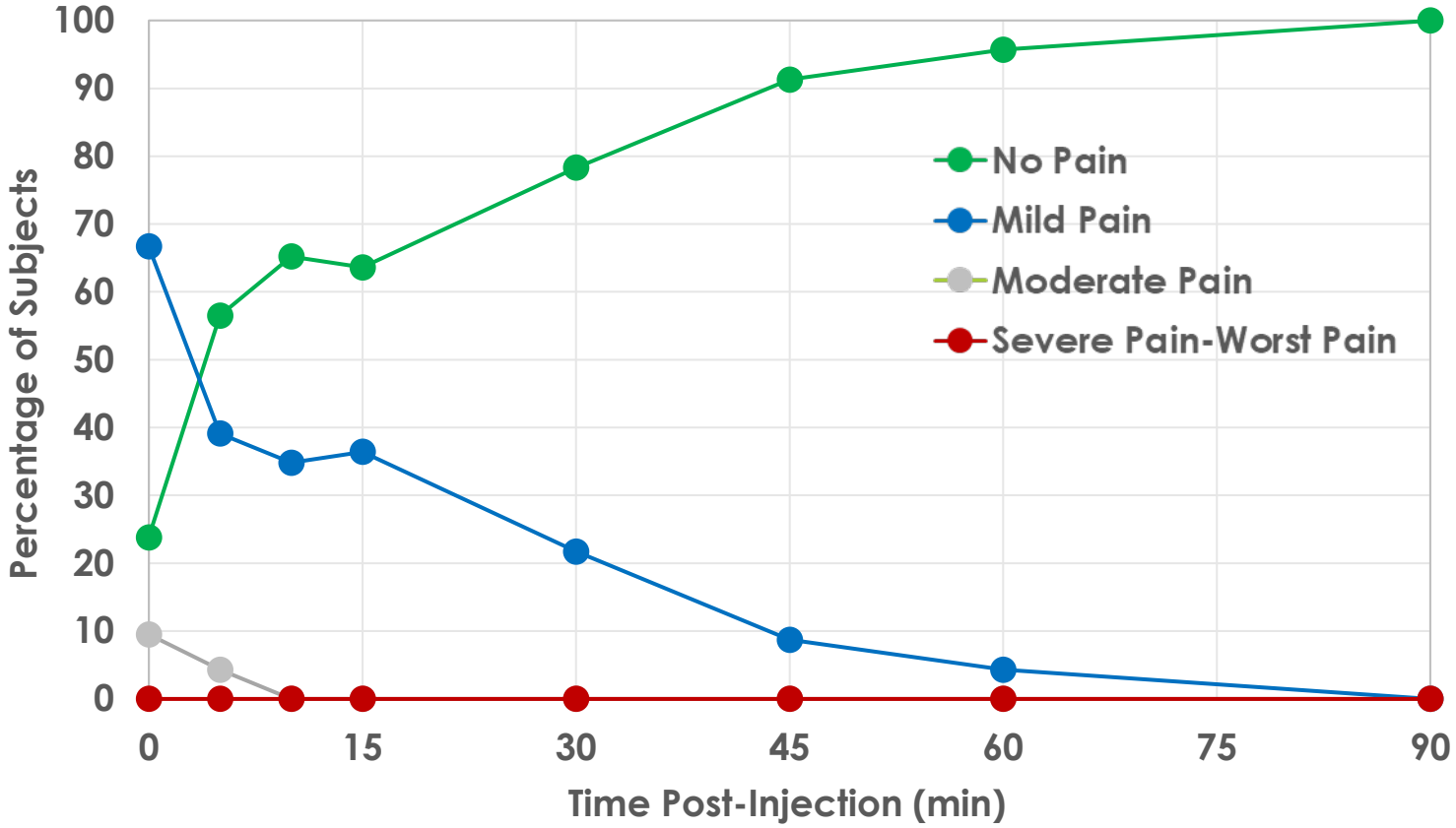


	No Pain	Mild	Moderate	Severe	Worst Imaginable Pain
Highest NRS Score post-injection	7	14	2	-	-
Would you have this injection again with HVAI?	100%	93%	100%	-	-

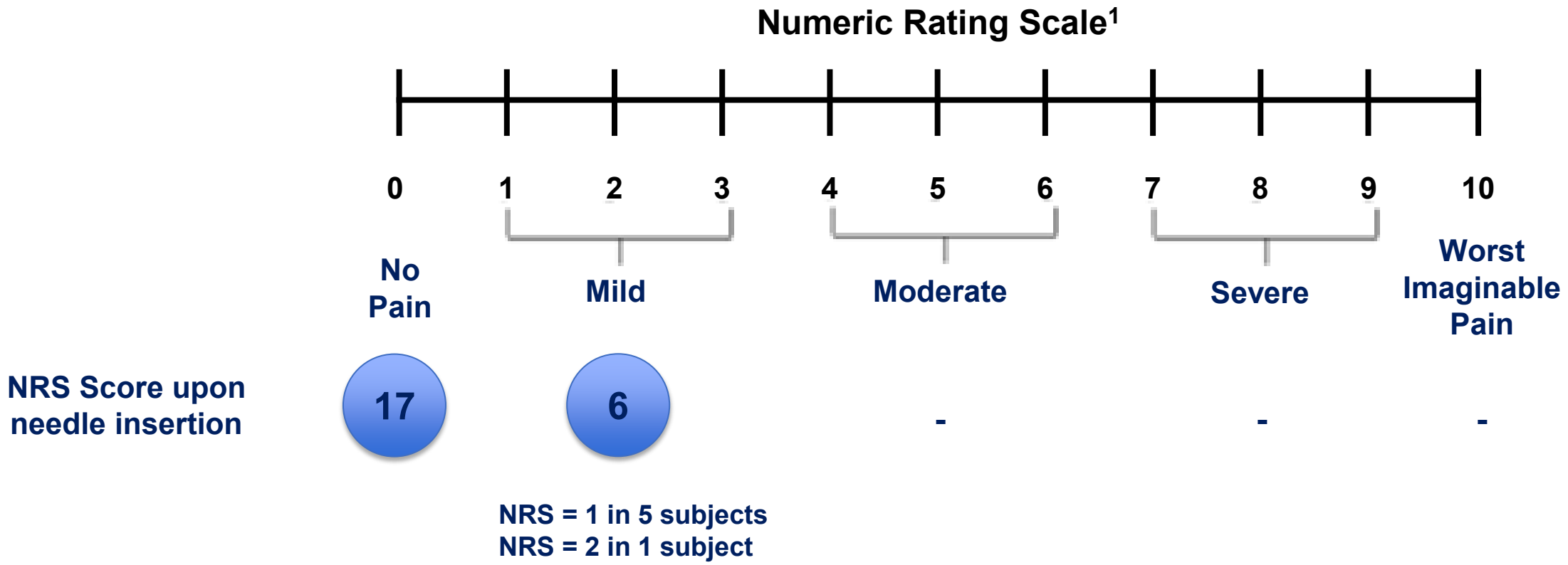
[1] Adapted from Karcioglu et. al., *American Journal of Emergency Medicine,* 36: 707-714 (2018).

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



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