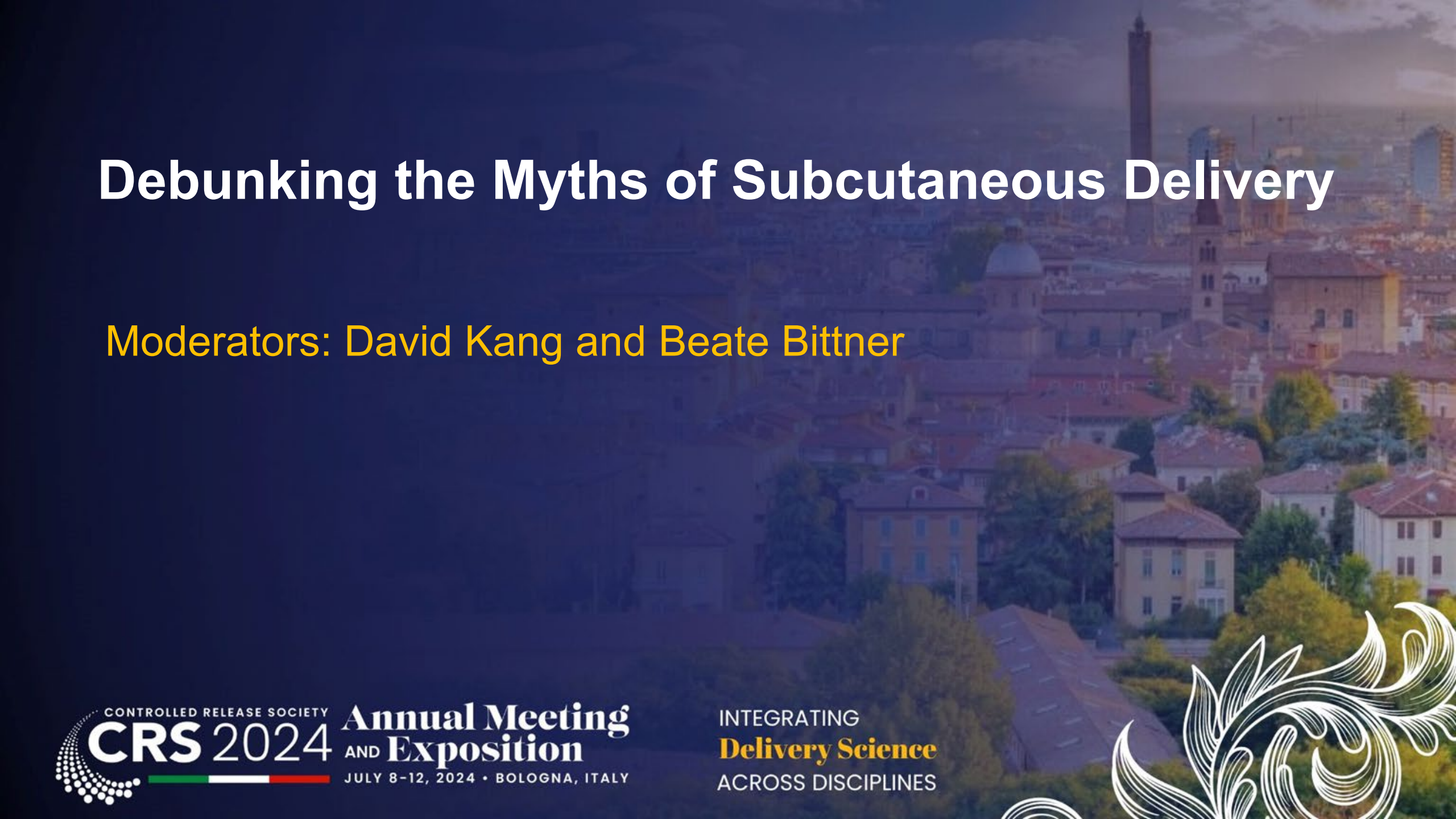
Debunking the Myths of Subcutaneous Delivery

Moderators: David Kang and Beate Bittner



Agenda

- ❑ Introductions (13:00-13:05; 5 minutes)
- ❑ Myth 1: SC delivery is painful and limited to small volumes (13:05-13:45; 40 minutes)
- ❑ Myth 2: SC delivery increases immunogenicity (13:45-14:25; 40 minutes)
- ❑ Coffee/Tea Break (14:25-14:55; 30 minutes)
- ❑ Myth 3: SC delivery is challenging due to low and/or unpredictable bioavailability (14:55-15:35; 40 minutes)
- ❑ Myth 4: SC delivery requires extensive clinical trials when bridging devices or from IV (15:35-16:15; 40 minutes)
- ❑ Mini-Break (16:15-16:20; 5 minutes)
- ❑ Round table discussion (16:20-17:00; 40 minutes)

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

Sylvain Huille (Sanofi)
Hannie Shih (Eli Lilly and Co.)
David Kang (Halozyme Therapeutics)

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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?

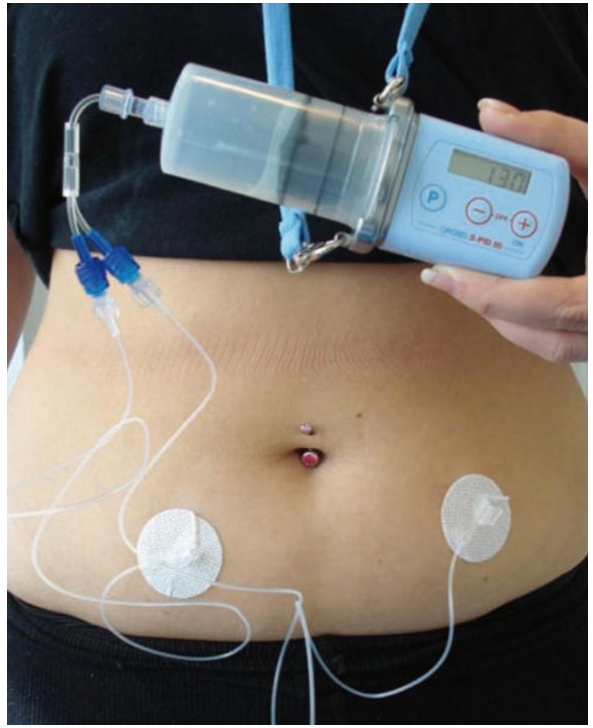
- Product factors that may impact injection pain – **Sylvain Huille**
- High Dose mAbs Driving the Need for High Volume Subcutaneous Delivery – **Hannie Shih**
- Clinical Trial on Assessing the Feasibility and Tolerability of a 10 mL Subcutaneous Injection of an Antibody in ≤ 30 sec – **David Kang**

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

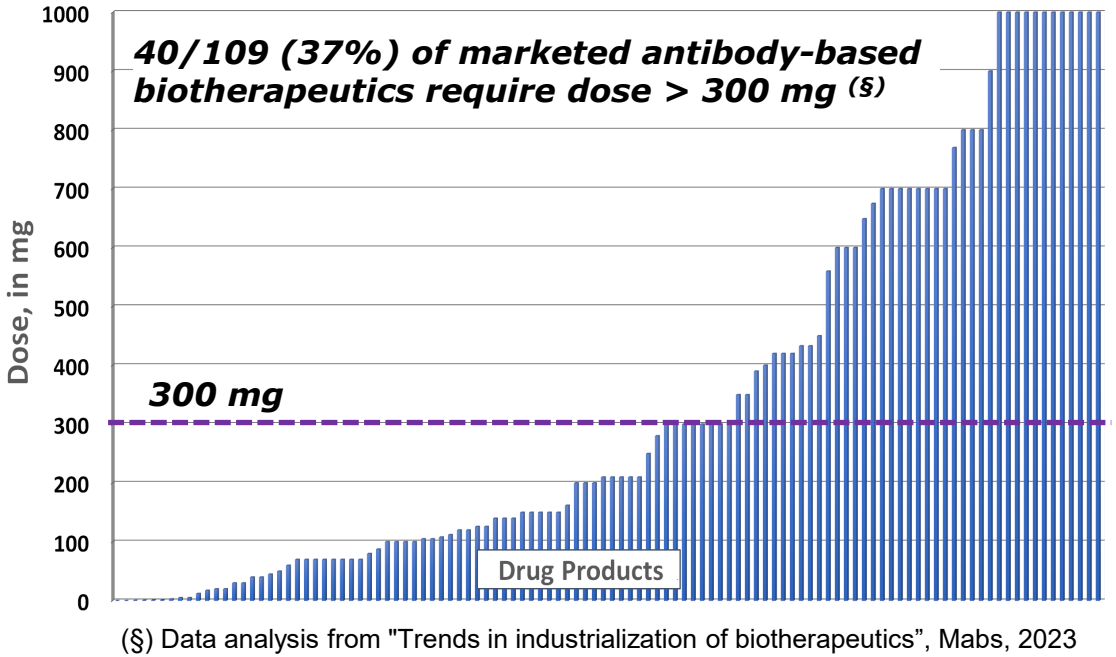
Large volume medical device (on-body / wearable devices) or co-formulation with permeation enhancers (hyaluronidase enzyme)

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

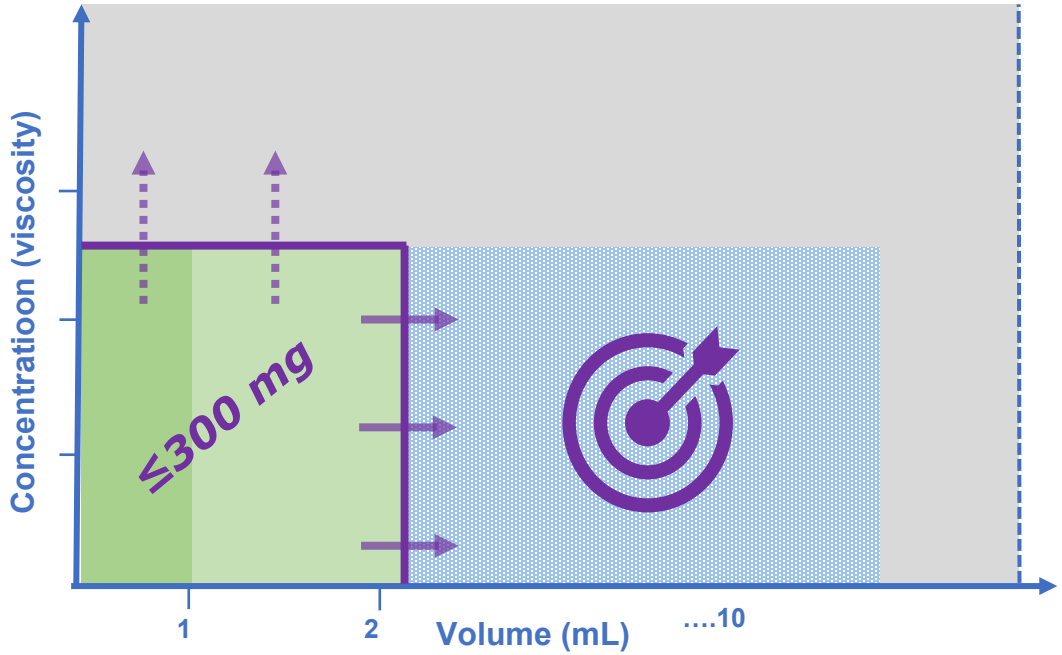
- Repatha only biological product using Large Volume Device delivery system - Discontinued as of June 30th 2024
- Co-formulation with endoglycosidase is used without a medical device but by manual injection - Mainly in oncology indication requiring HCP for injection
- SC injection volumes of 5 to 15 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

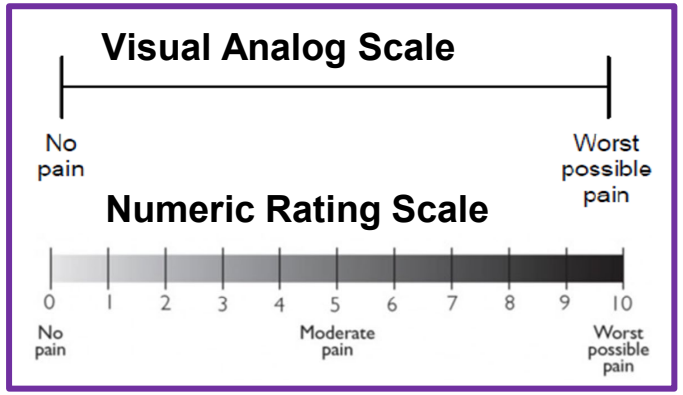


- Switching to the SC route requires for many drugs to push the limit beyond 2-3 ml injection volume most accepted.
- Large volume medical device and/or co-formulation with permeation enhancers are mature technologies for switching to SC
- New technologies (e.g. suspension of spray-dried microparticles 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.

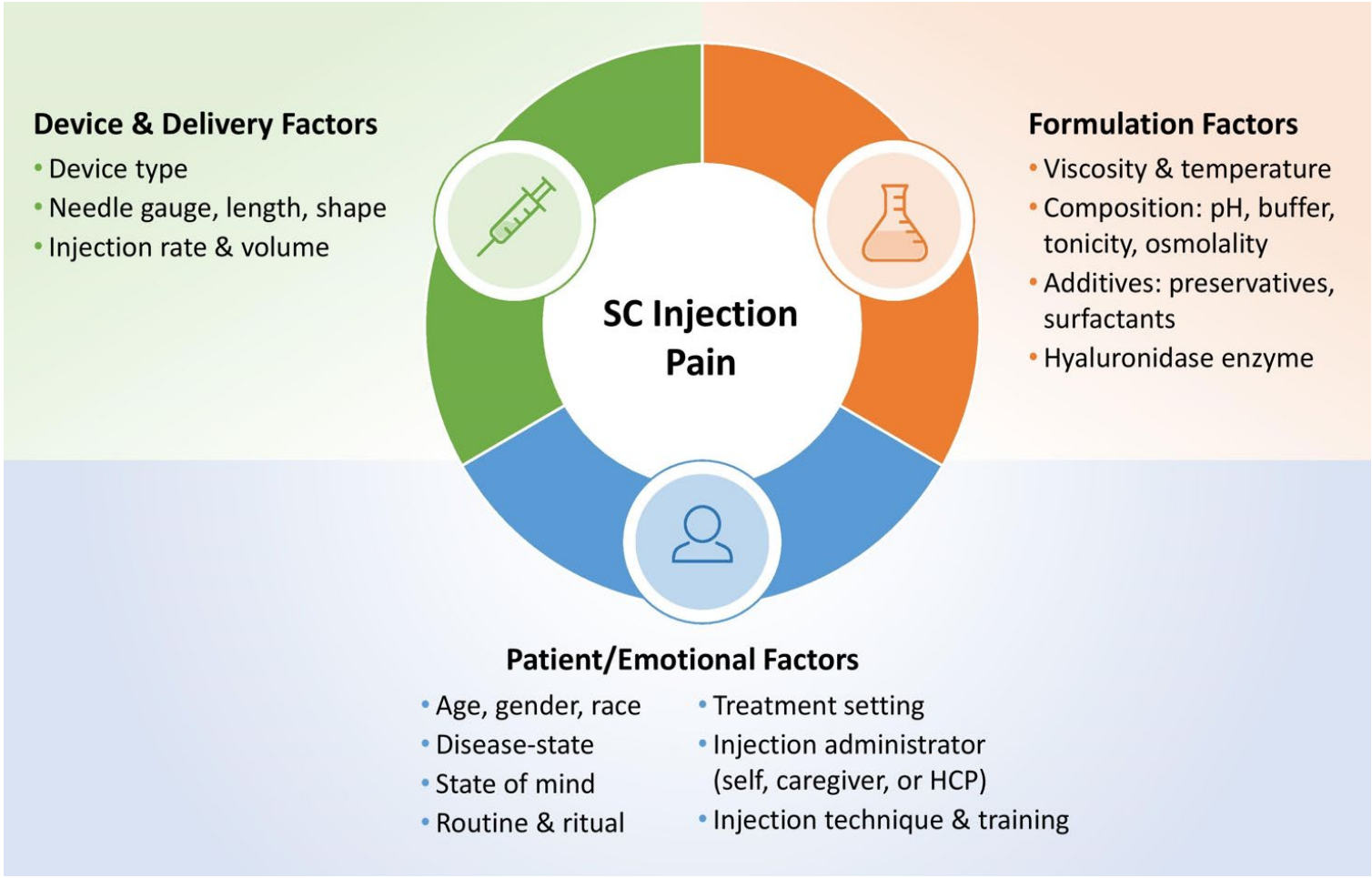


* IASP. International Association for the Study of Pain IASP Terminology Accessed 9 March 2023, https://www.iasp-pain.org/resources/terminology/?ItemNumber=1698

* 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

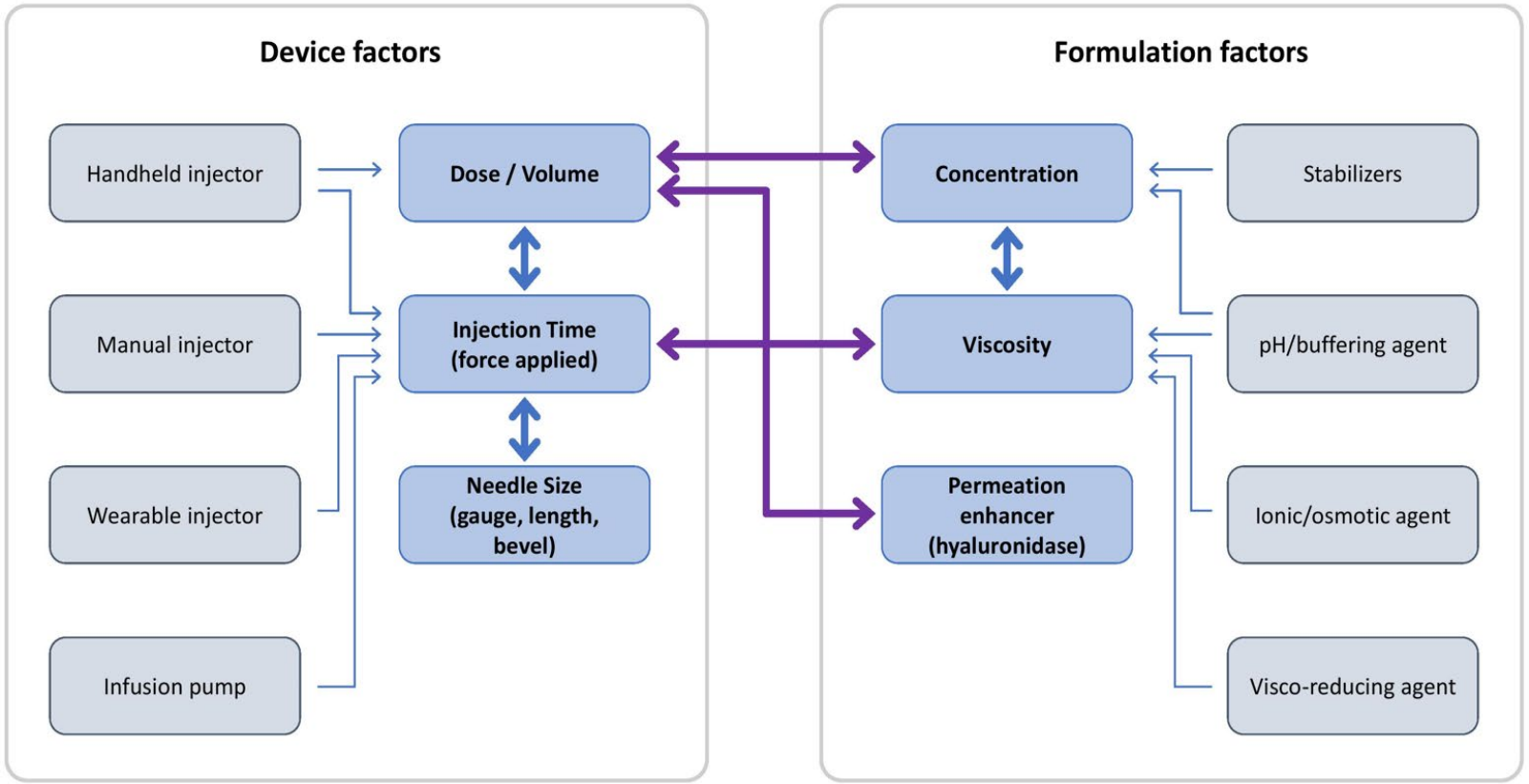
➜ Tolerability and acceptability may also be influenced differently by disease, for example in patients with severe skin disease.

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

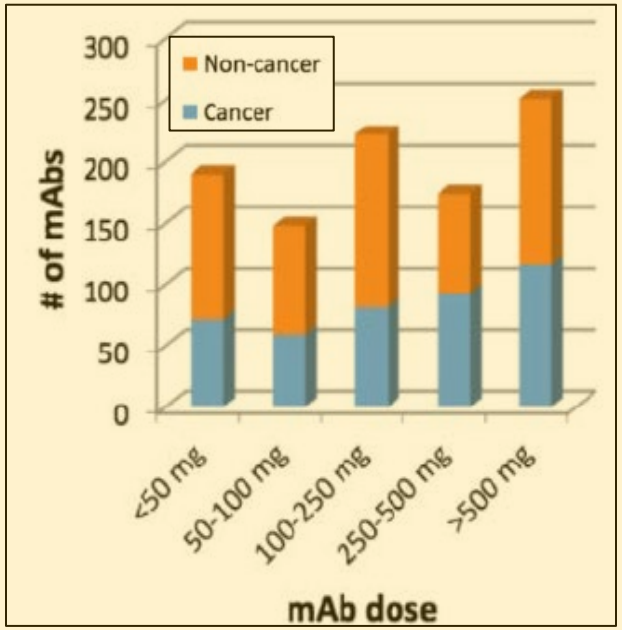
* Mathias, Neil, et al. "Towards more tolerable subcutaneous administration: Review of contributing factors for improving combination product design." Advanced Drug Delivery Reviews (2024): 115301.

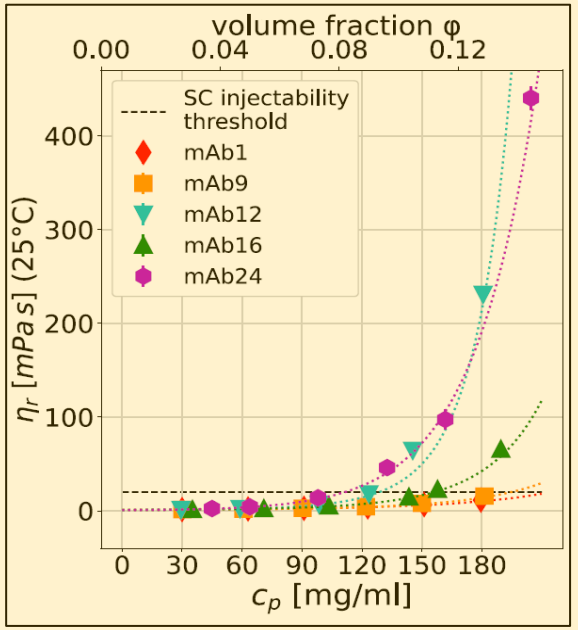
Clinical Investigation of Large Volume Subcutaneous Delivery up to 25 mL for Lean and Non-lean Subjects

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

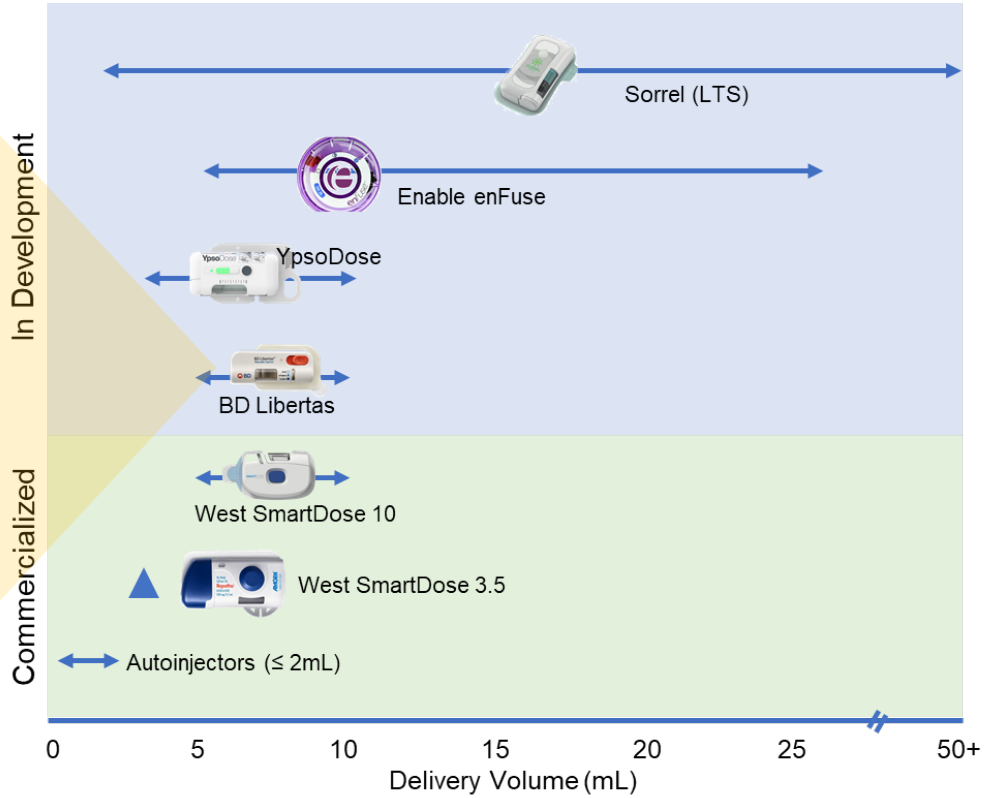
Pharmaceutical Research, 2024, Volume 41, page 751-763

High Dose mAbs Driving the Need for High Volume Subcutaneous Delivery



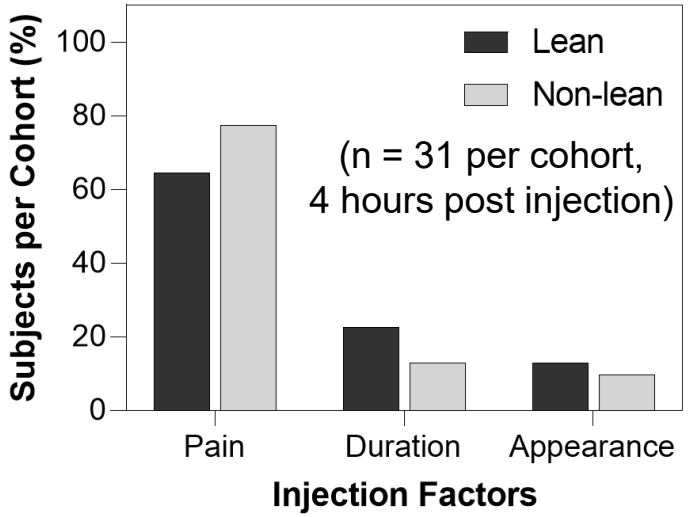


(left) Workshop on SC Delivery, CRS Annual Meeting, 2019, (right) Mosca *et al.,* 2023, Mol Pharm 20:4698



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

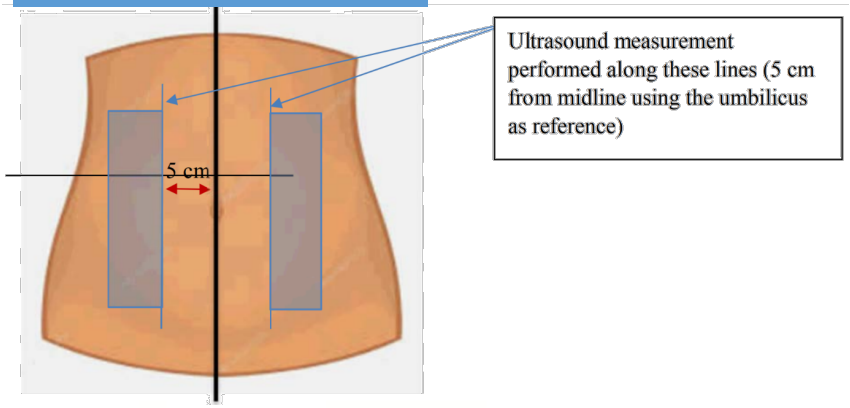
Study to establish the baseline of injection site pain and reactions for large volume injections

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

Study Parameters

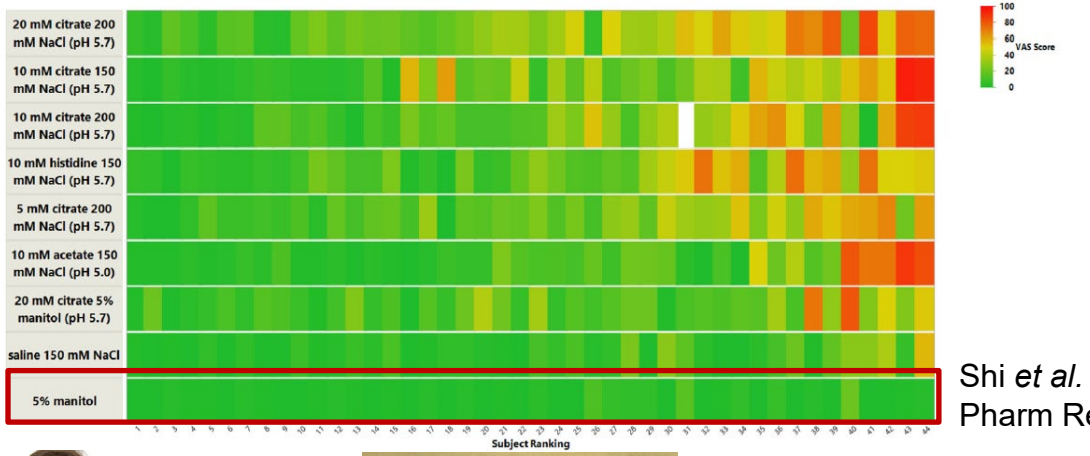
- Injection volume: 5, 12, 25 mL
- Needle length: 6, 9, 12 mm
- SC thickness: lean (≤ 14.5 mm) and non-lean (≥ 15.5 mm)
- Infusion pump at 0.5 mL/min

Injection Conditions



Low Pain Viscous Solution

10 cP hyaluronic acid/mannitol

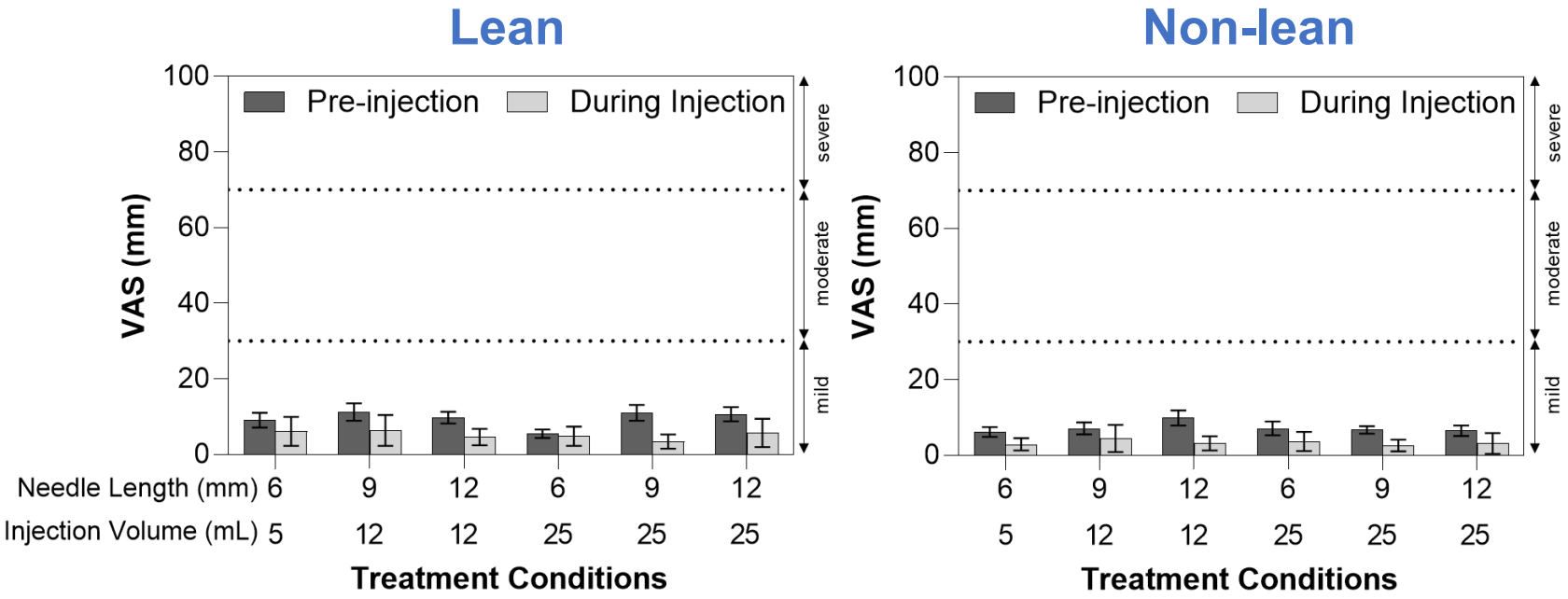


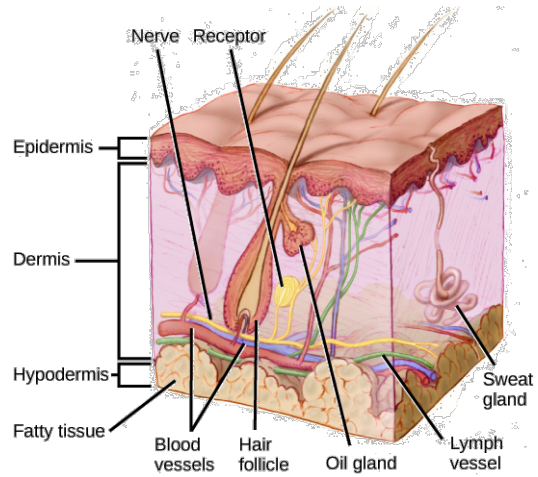
Shi *et al.* 2021. Pharm Res 38:779

https://shorturl.at/kW8Ff

- Erythema
- Edema
- Induration
- Pruritis
- Leakage

Needle Insertion is More Painful than 25mL Injection

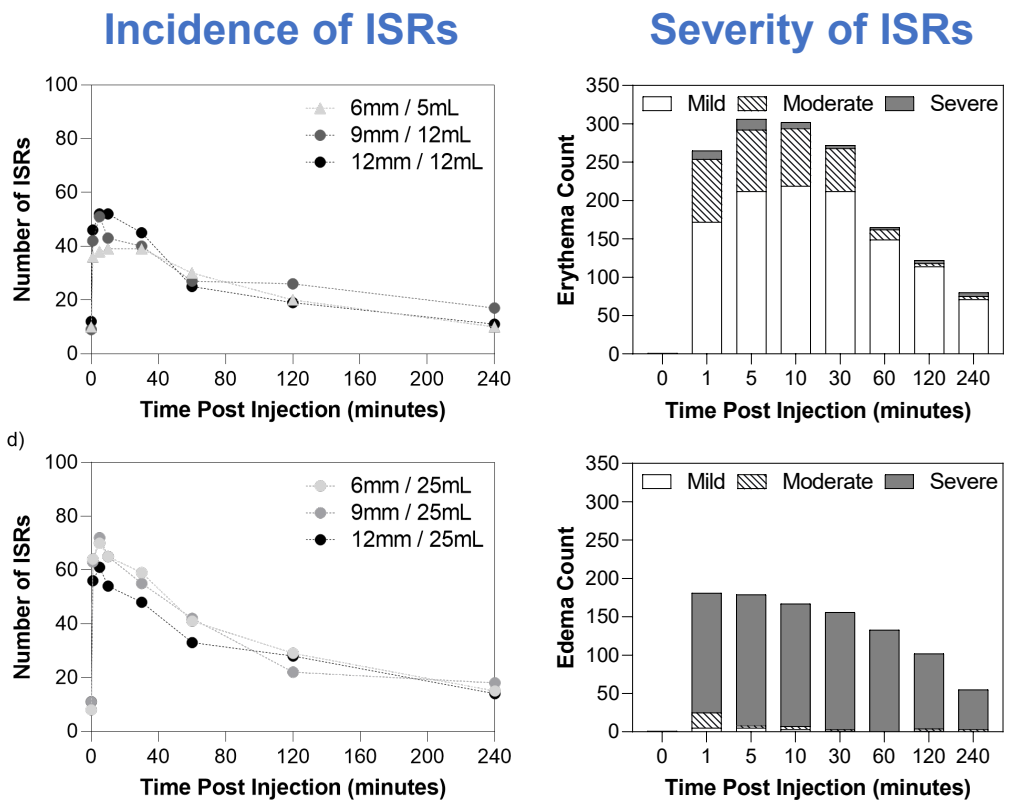


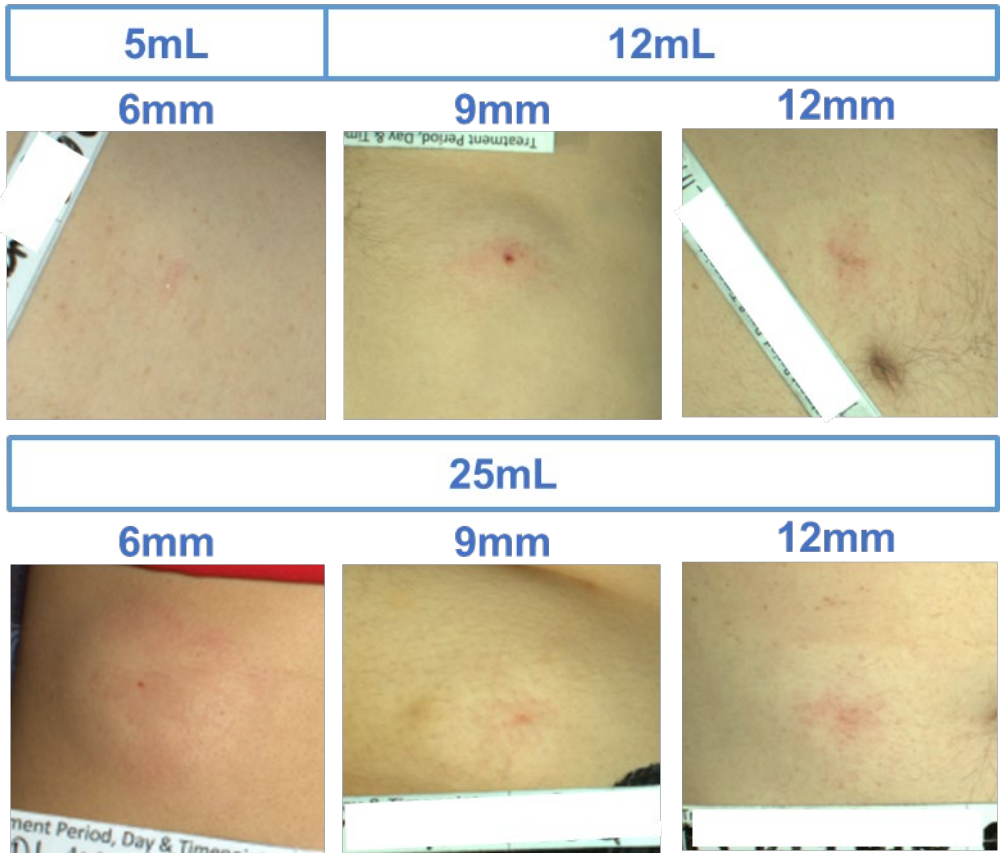


- Mild pain across all treatment conditions
- Pain not affected by potential IM injections with using longer needle length

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

Increased ISRs with Shorter Needle Length and Larger Volume

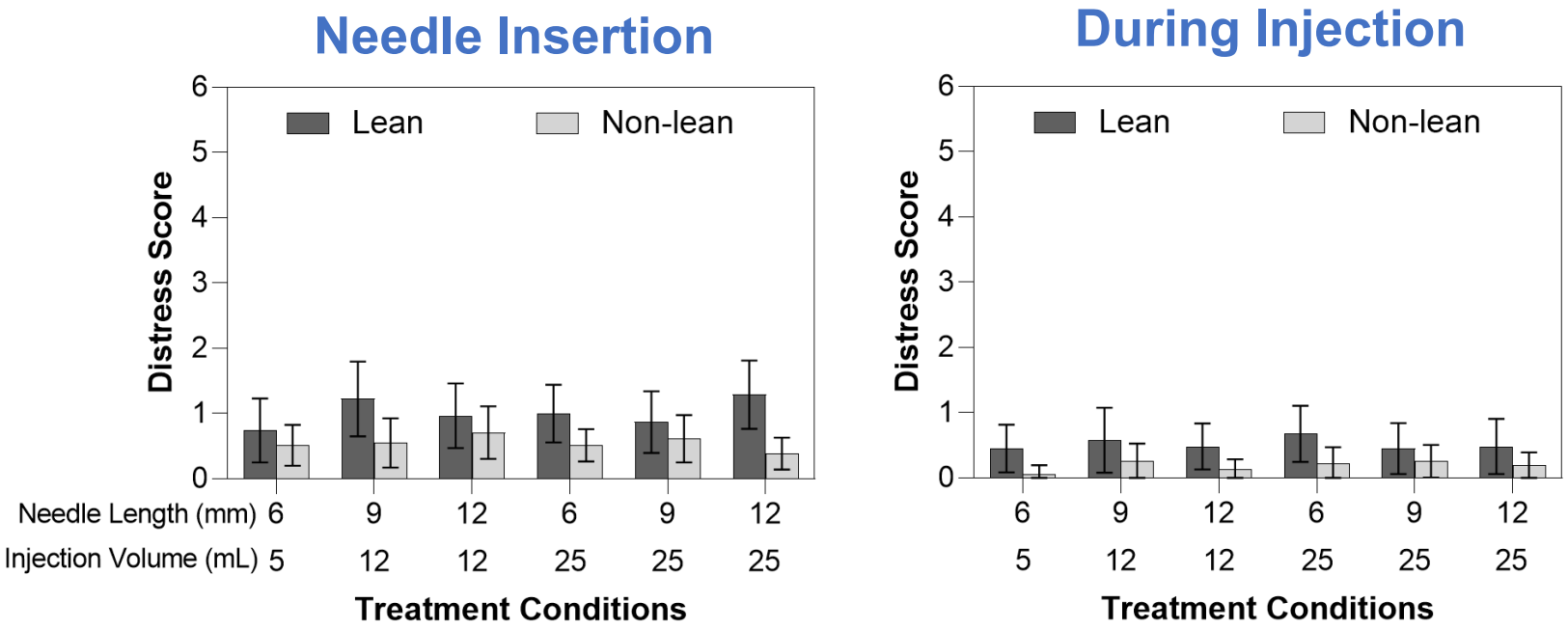




(ISRs include erythema, edema, induration, and pruritis)

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

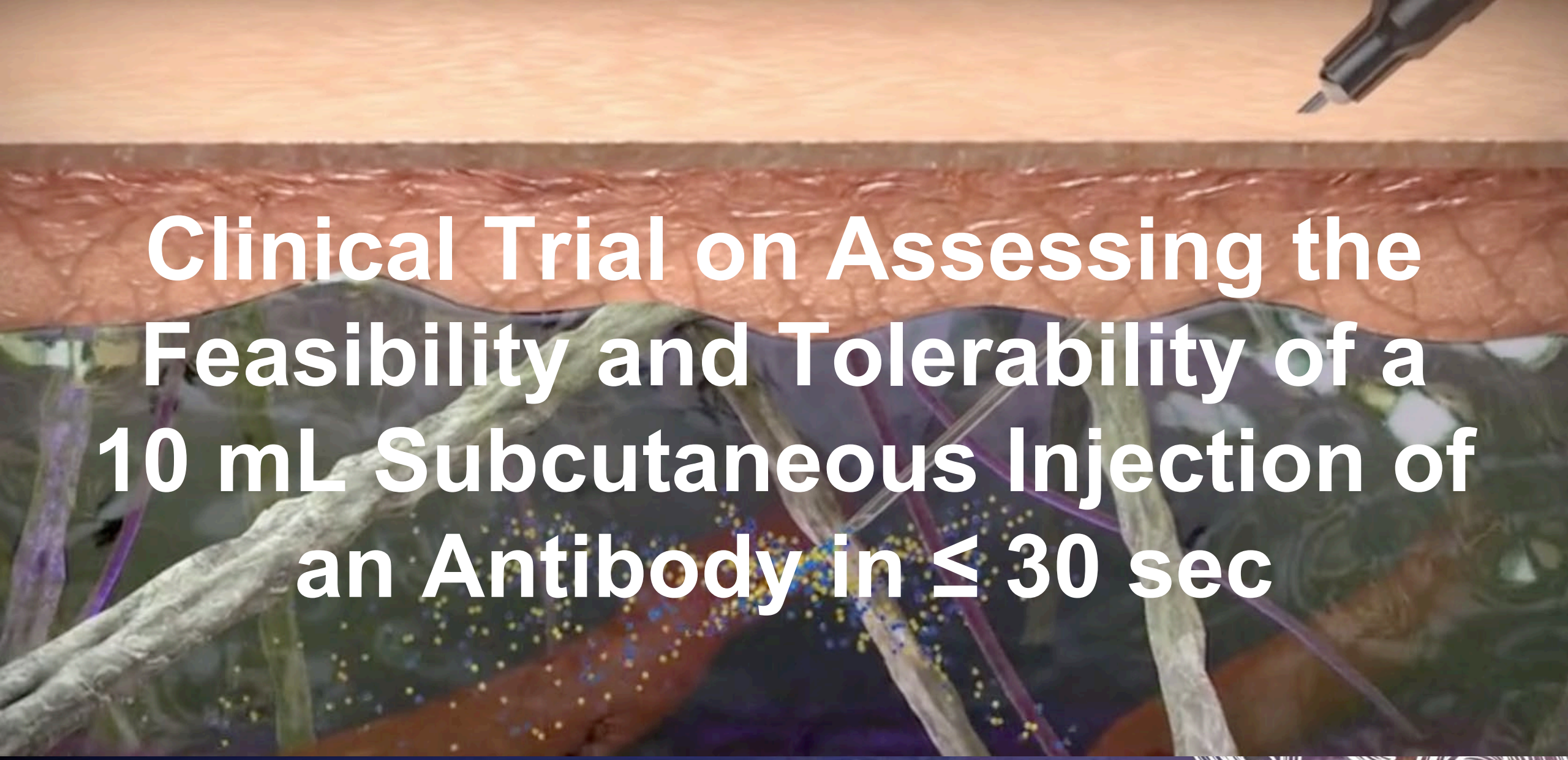
Participants were not Distressed by Large Volume Injections



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

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



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**

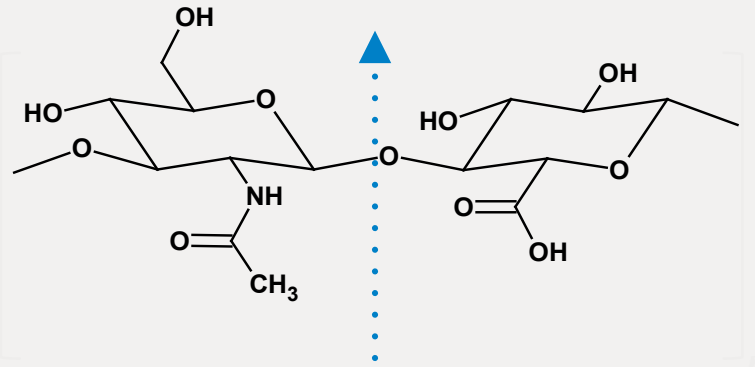
Design:

- 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

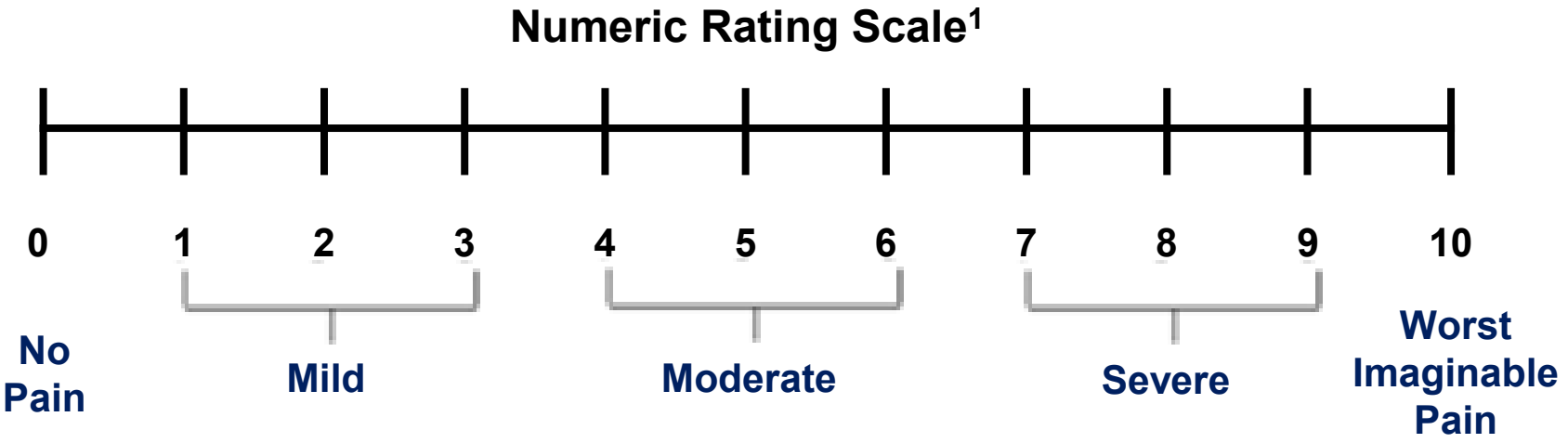


+ Hyaluronidase

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

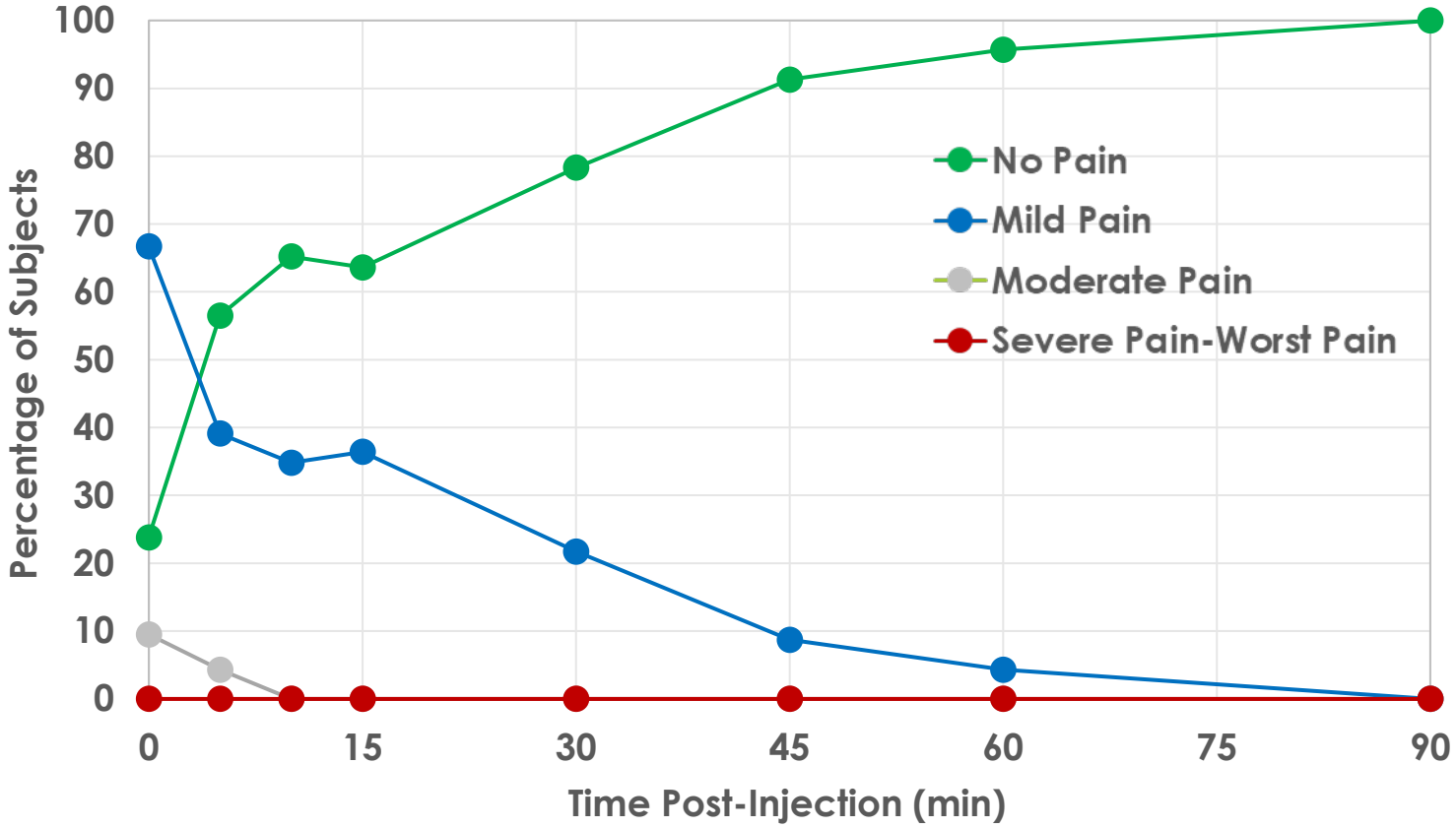


	No Pain	Mild	Moderate	Severe	Worst Imaginable Pain
Highest NRS Score post-injection	7	14	2	-	-
Would you have this injection again with HVAI?	100%	93%	100%	-	-

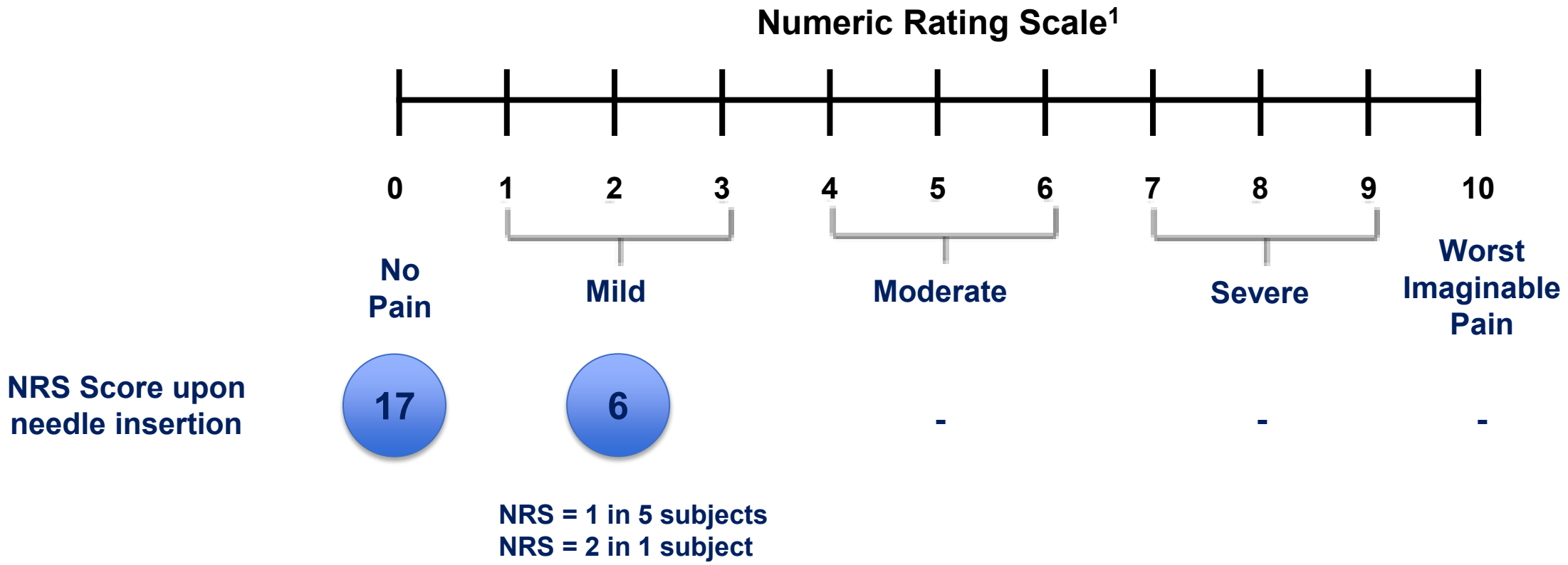
[1] Adapted from Karcioglu et. al., *American Journal of Emergency Medicine,* 36: 707-714 (2018).

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

Myth 2: Subcutaneous delivery increases immunogenicity

Nicole Buist (Merck Sharpe & Dohme LLC)
Marie Prinz (Halozyme Therapeutics)

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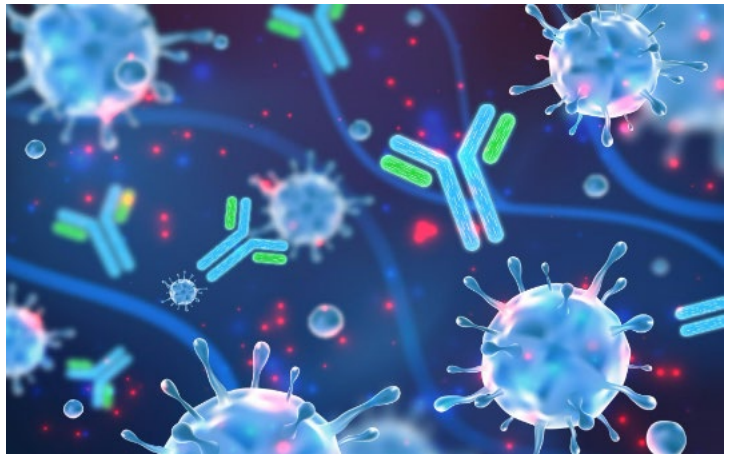
Overview

- Introduction to immunogenicity
- Why subcutaneous RoA is hypothesized to have increased immunogenicity
- Clinical case studies comparing IV vs SC RoA
- Recent publications with collated examples
- CMC considerations
- How should developers approach SC product development w/r/t immunogenicity and HLN case study
- Output from 2023 PEGS Boston User Group
- Conclusions and looking to the future

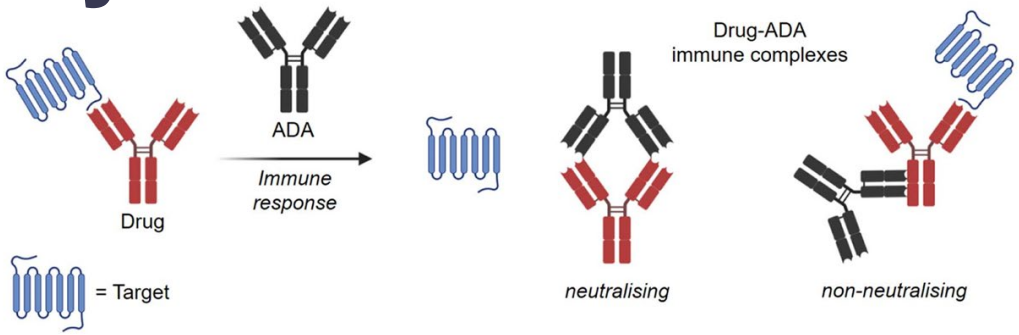


Introduction to Immunogenicity

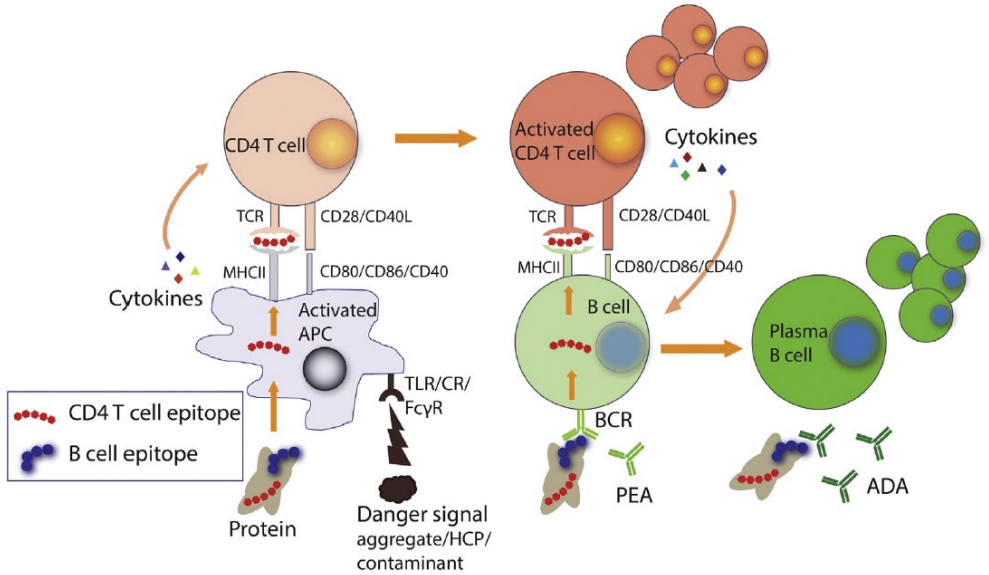
What is immunogenicity?

- The propensity of a therapeutic protein product to generate immune responses to itself and to related proteins or to induce immunologically-related adverse clinical events
- A biologic that is more immunogenic has a higher likelihood of inducing **anti-drug antibodies (ADA)** in a higher percentage of patients
- ADAs can be **binding** (alter clearance/PK) or **neutralizing** (directly limit efficacy, block target interaction)

FDA CDER/CBER Guidance for Industry:
Immunogenicity assessment for protein products



Edelmann RSC Adv., 2022, 12, 32383-32400

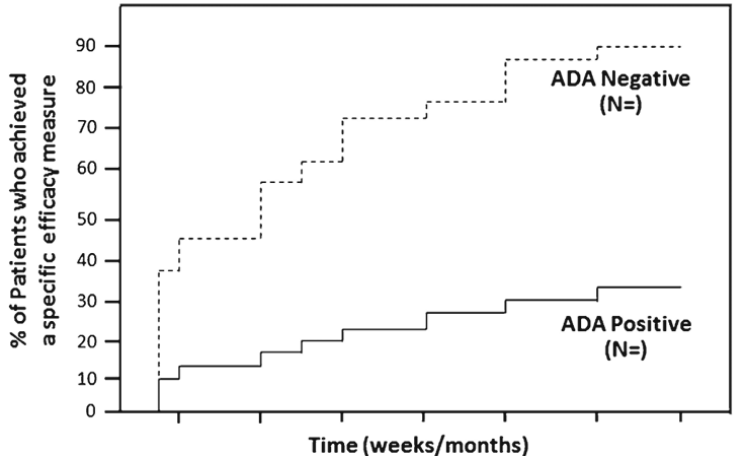


Wen & Jawa J Pharm Sci. 2021, 110, 1025-1041

ADAs Can Impact PK, PD, Safety & Efficacy

Impact of ADA on clinical efficacy:

- Primary non-response: while infrequent, patients with pre-existing ADA may not respond to drug treatment from the outset
- Secondary non-response: patients who develop ADA after treatment may lose efficacy over time

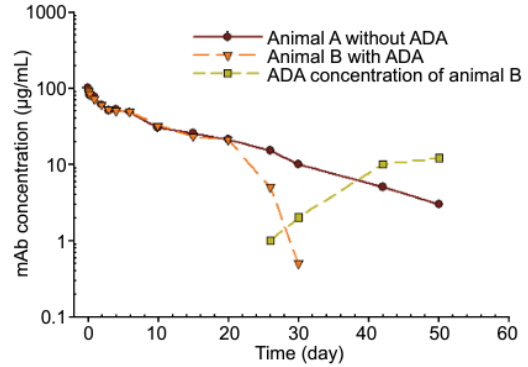


Impact of ADA on PK & PD:

- ADA bind with the biologic drug in circulation to form immune complexes which can alter the PK profile such that clearance rates are increase or sometimes decreased leading to altered drug exposure

Impact of ADA on safety:

- Multiple types of hypersensitivity (anaphylaxis: hypotension, bronchospasm, laryngeal or pharyngeal edema, wheezing, etc.)
- Administration site reactions
- Worsening of disease
- Increased drug toxicity



Shankar, et. al., The AAPS Journal, 2014, Vol 16, 658-673

Why is the SC Route Implicated for Immunogenicity?

- Animal models have shown higher ADA SC than IV
- Two wave mode of antigen presentation (migratory skin-resident DCs and lymph node-resident DCs)
- Large molecules delivered SC traffic through the lymph for absorption
- Residence time of high concentration drug at the injection site
- Product-related attributes such as altered-self molecular patterns, impurities, host cell proteins, or **aggregates** have potential to serve as danger signals
- Mechanism of drug – meaning if immune target
- Disease state/concomitant meds

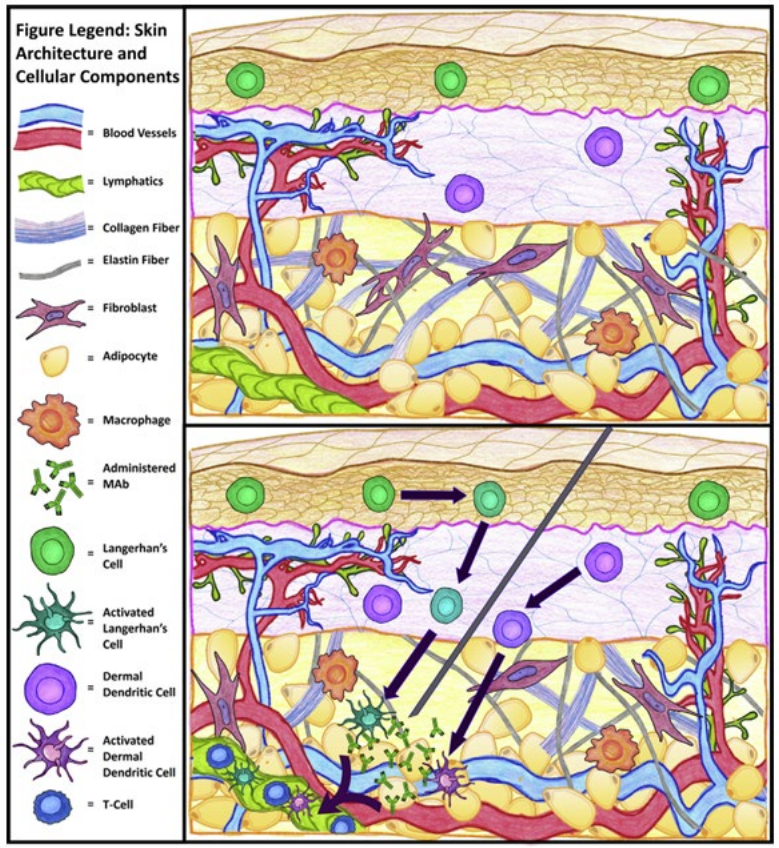


Figure 2. Anatomy of the Skin. (Top) Cellular components of each skin layer including the epidermis (tan), dermis (pink to yellow), and hypodermis (yellow). Not pictured in this diagram is hyaluronic acid, which is present throughout the SC space and within collagen framework. (Bottom) Hypothetical immune response scenario after injection of therapeutic antibody into the SC space. Langerhans and dermal dendritic cells transition from the epidermis and dermis, respectively, are exposed to the injected antibody, and mature before interacting with T-cells in the lymphatic system.

Jarvi & Balu-Iyer BioDrugs 2021 35(2): 125-146

Examples where SC was more Immunogenic

- Factor VIII What about clinical examples (contrast)
- When where was a difference – what was the global impact? Loss of efficacy over time? Product still moves forward?

Examples where SC was equivalent or less Immunogenic

- Look at differences in numbers (not statistically powered, would it repeat?)

Analysis: ADA Incidence Comparison of Monoclonal Antibodies Administered via SC vs IV Route (Pfizer Review)

Fig. 1 Matchstick plot of overall ADA incidence by IV and SC for each therapeutic protein. Each symbol represents the overall ADA incidence for one route of administration for that therapeutic protein in the clinical trial

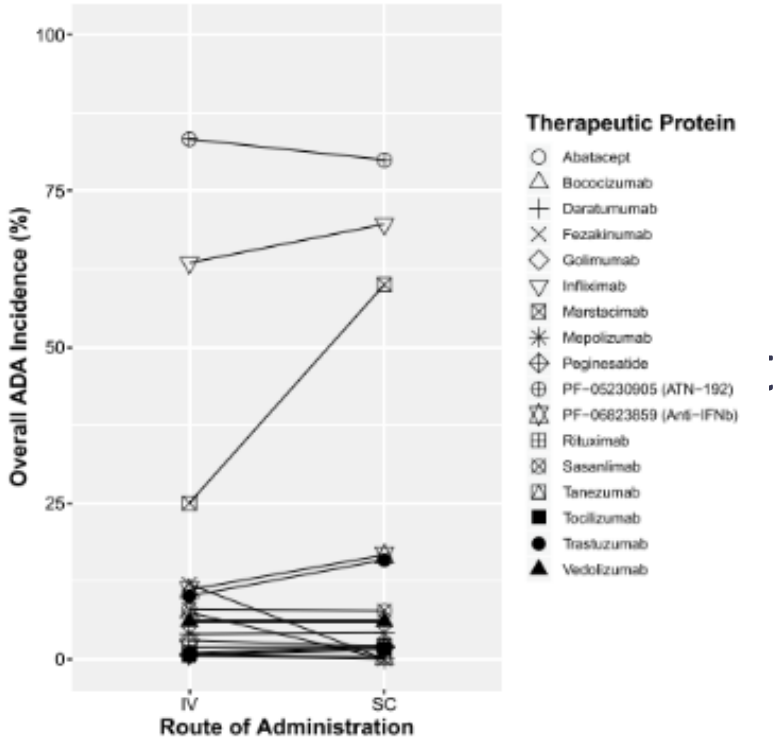


Table 2 ANOVA of ADA Incidence by SC *vs.* IV for 17 Therapeutic Proteins

Independent Variable	*P*-Value	Estimated Difference (95% CI)[a]
Route of Administration	0.81	-0.3% ([-6.9%, 8.7%])
Therapeutic Protein	**1.6×10^{-12}**	

Bolded value indicates statistical significance (*P*-value < 0.05)

[a]The estimated difference in ADA incidence between SC and IV administration with a 95% confidence interval for the estimate

Table 3 ANOVA of ADA Incidence by SC *vs.* IV for Each Therapeutic Protein

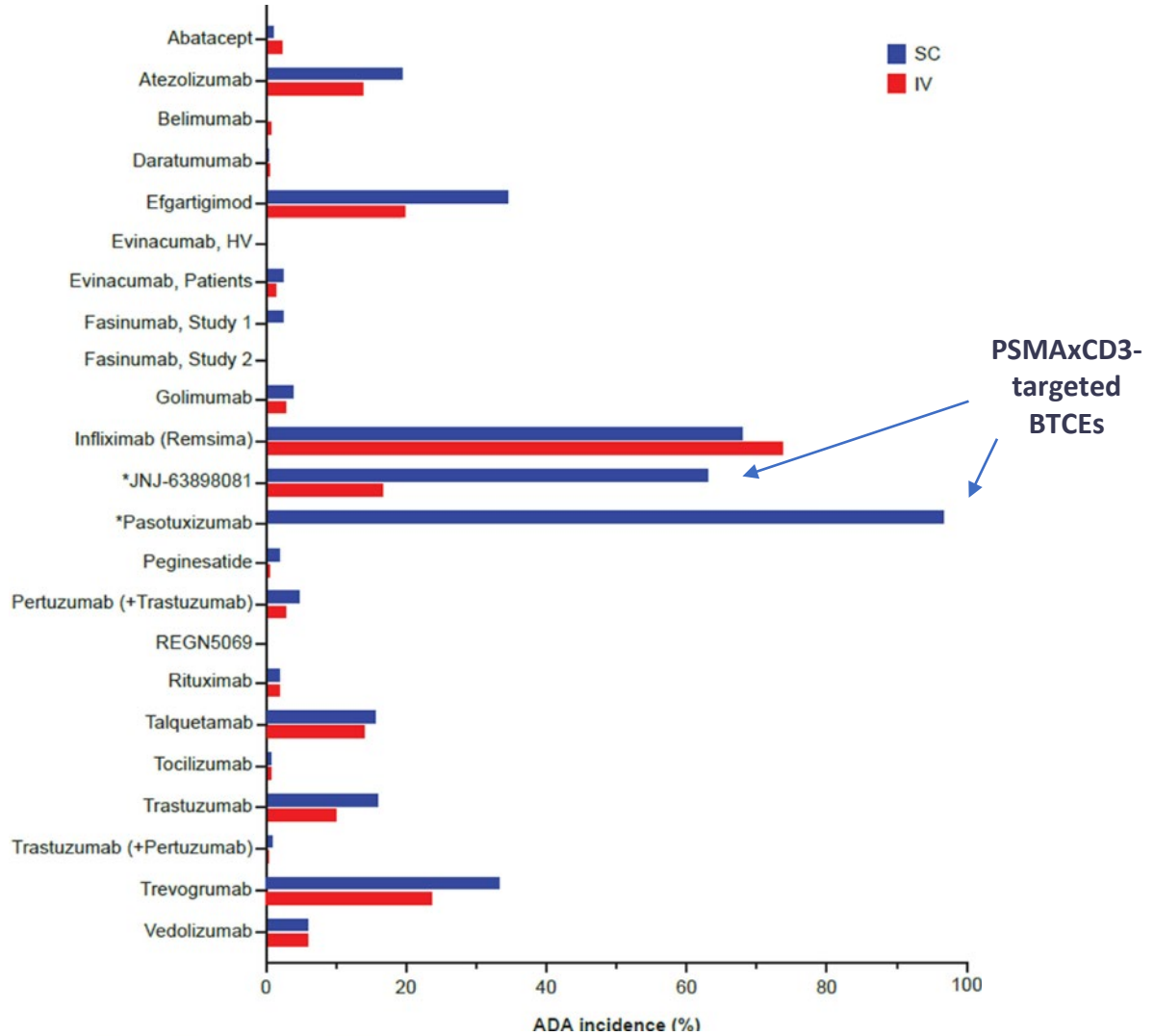
Therapeutic Proteins	IV Treatment Groups (*N*)	SC Treatment Groups (*N*)	*P*-Value
Bococizumab	5	3	0.05
Fezakinumab	2	2	0.42
Marstacimab	2	4	0.34
PF-05230905 (ATN-192)	2	5	0.86
PF-06823859 (Anti-IFNβ)	7	2	0.77
Sasanlimab	4	2	0.67
Tanezumab	2	6	0.61

[Felderman et.al., The AAPS Journal 2024, 26:60]

ADA Incidence of Therapeutic Proteins Administered via SC vs IV (*Regeneron Review*)

- Most studies indicate comparable incidence of immunogenicity between SC and IV dosing
- ADA positivity alone does not necessarily reflect a clinically impactful response
  - Magnitude of ADA response, persistence over time, presence of nAbs are better predictors of clinical impact
- Two compounds with significant difference were PSMAxCD3-targeted Bispecific T-cell Engagers (BTCEs) suggesting unique immunogenicity profile when dosed SC

[Davis et. al., Clin Pharmacol Ther 2024, 115, 422-439]



CMC considerations for SC Administration

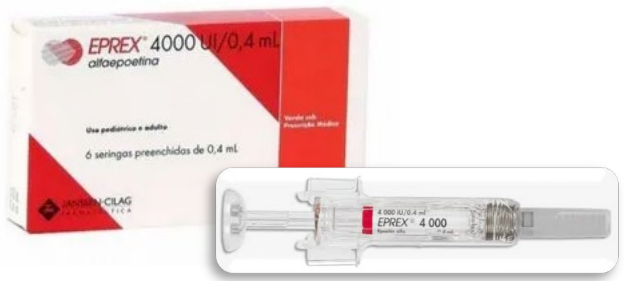
Biophysical/Biochemical Characteristics

- Size: Larger MW proteins may have a slower rate of exit from SC space and increased immunological exposure
- Charge: Positively charged proteins at physiological pH could interact with negatively charges GAGs in ECM
- Oxidation: Oxidation could generate modified epitopes and impact immunogenicity

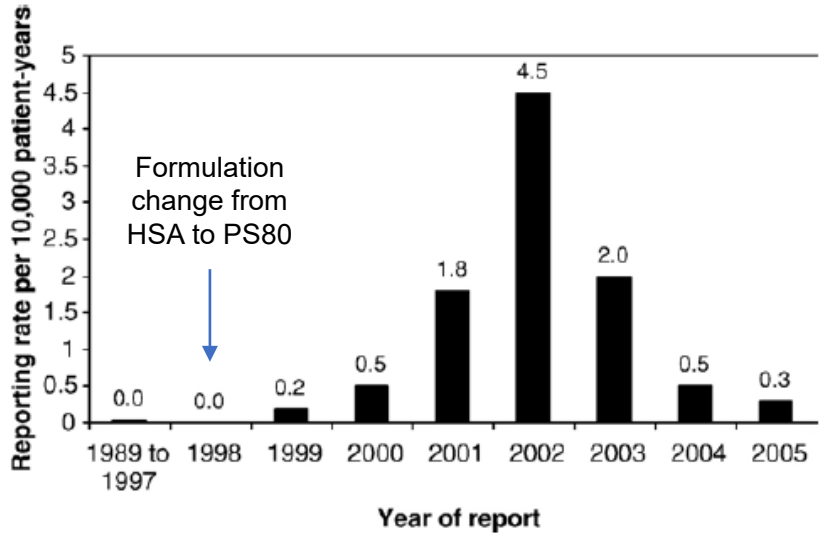
- Host Cell Proteins

Jarvi & Balu-Iyer. BioDrugs 2021, 35(2), 125-146.

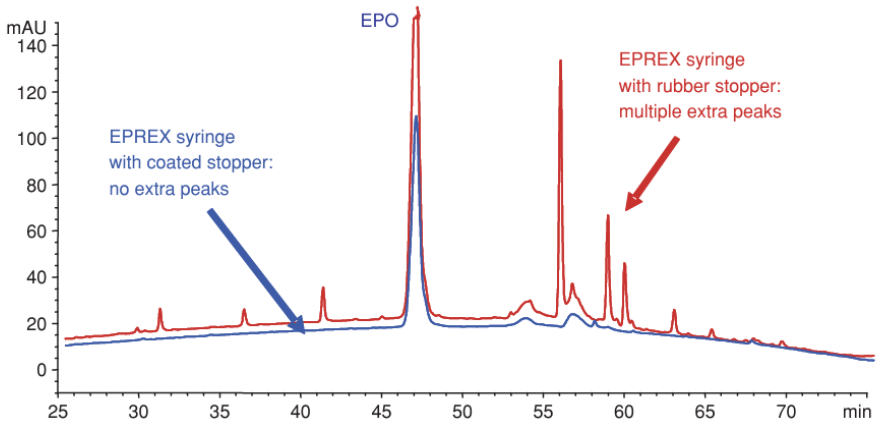
CMC Case Study: *EPREX®*



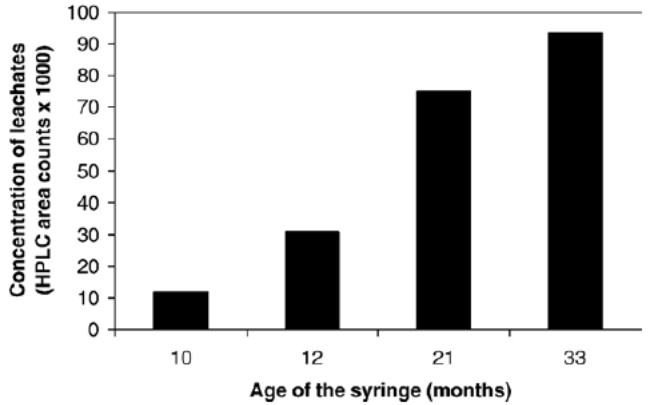
EPREX® is a recombinant human erythropoietin delivered IV and SC



Increased incidence of an antibody-mediated pure red cell aplasia (PRCA) in chronic renal failure patients when delivered SC



[Ryan et.al., Int. Immuno. 2006, **6**, 647-655]



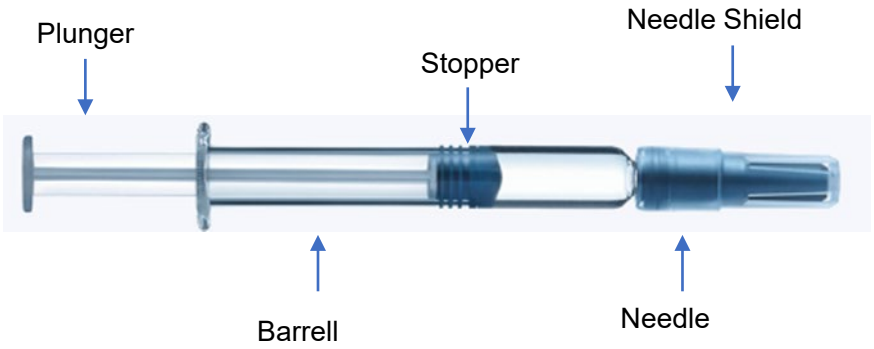
[Schellekens & Jiskoot. J. Immunotox. 2006, **3**, 123-130]

Case Study highlights the complexity:

- ❑ More vigilant reporting
- ❑ Improved cold chain storage
- ❑ Replacement of rubber-coated stoppers
- ❑ Better patient treatment

[Sharma Biotech. Adv. 2007, 25, 310-317]

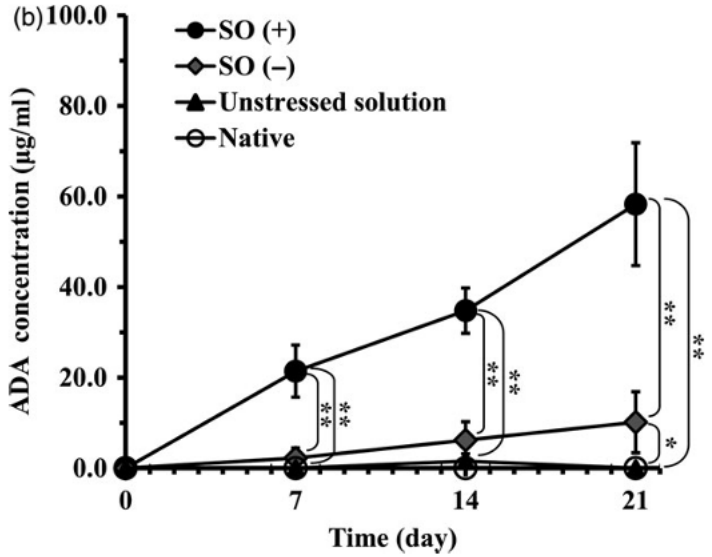
CMC Considerations: *Container Closure System*



Impact of Container Closure:

- Extractable and leachables
- Hydrophobic surfaces
- Lubricants can mediate protein denaturation
- Silicone oil
- Residual metals

Surface-induced protein aggregation can result in conformational changes leading to partial unfolding which are susceptible to aggregate formation



Impact of Product Handling:

- Agitation/shaking in PFS
- Freeze/Thaw

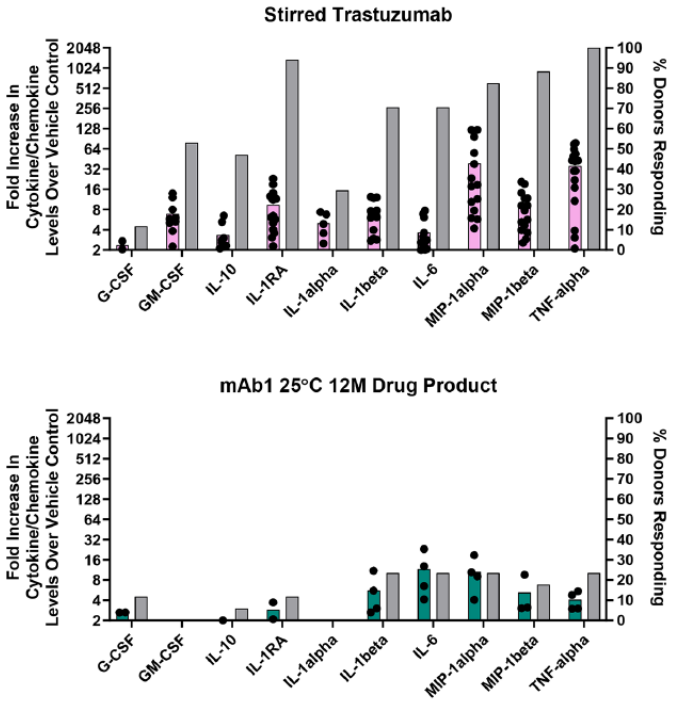
Can lead to increased subvisible particle

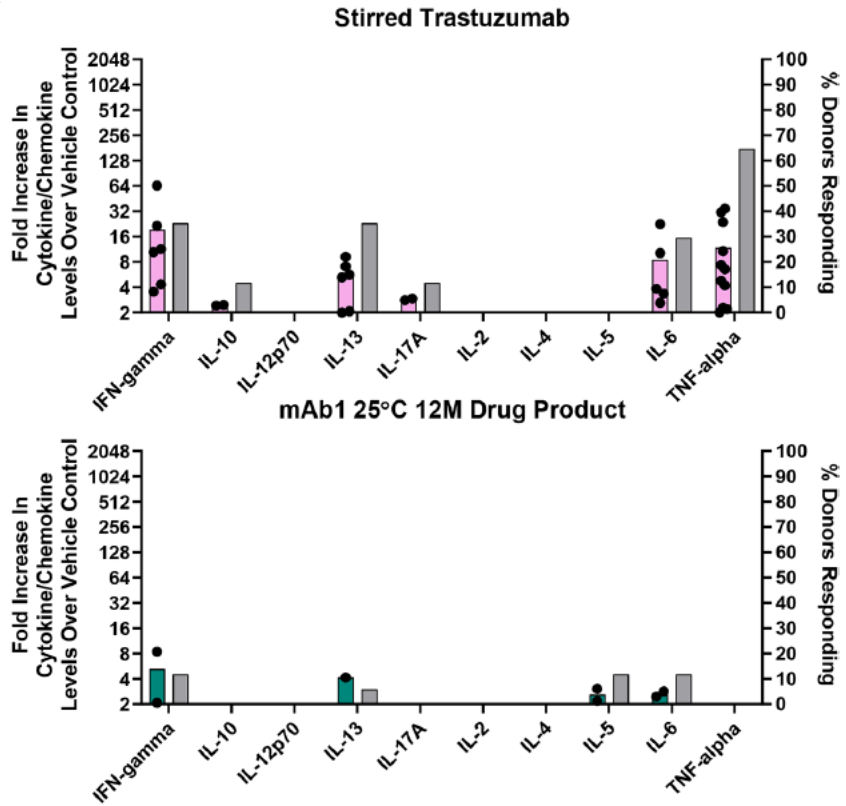
Jarvi & Balu-Iyer. BioDrugs 2021, 35(2), 125-146.

Uchino et.al. J. Pharm. Pharmacol. 2017, 69(10), 1341-1351.

CMC Considerations: *Aggregates*

- There are several examples of high stress induced samples showing in vitro immunogenicity
- This study evaluated spontaneously occurring mAb aggregates
  - process intermediates
  - drug product stability samples (-80°C, 5°C and 25°C at 12M)
- Although lower than the stirred Trastuzumab, the DP stability samples demonstrated low levels of cytokine production ***indicative of innate phase responses***



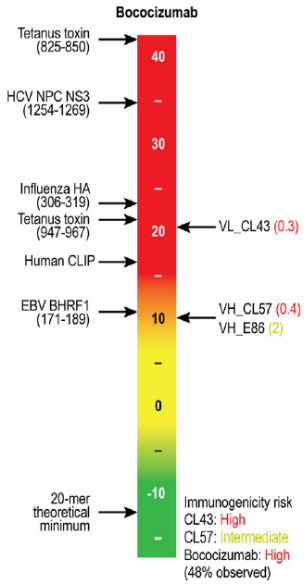


- There was a ***lack of an adaptive phase response*** to the spontaneously formed aggregates indicating a lack of priming of the innate phase and propagation of this response to a T-cell dependent immune response
- While PBMC-based assays trend well with ADAs, cannot predict extent of clinical immunogenicity (only representing the likelihood of a molecule to drive a T-cell dependent antibody response)

Swanson et. al., Front. Immunol. 2022, 13:915412

How should developers approach immunogenicity for SC products specifically?

Target ID/VAL → Lead ID → Lead Opt → Drug Candidate - PCD → Phase I → Phase II → Phase III → BLA



In Silico HLA binding Tools

In Vitro MHC I/II associated peptides assay (MAPPS)

In Vitro DC:T cell Proliferation Assay

Immunogenicity Risk Assessment Strategy

- ❑ collate risks identified by algorithms & in vitro tools
- ❑ consider additional risk factors:
- ❑ effects due to target engagement
- ❑ cross reactivity to endogenous protein

Proteins with higher likelihood of immunogenicity will require intensive sampling and analysis in real time and characterization assays

Proteins with lower likelihood of immunogenicity, recommendation to collect and hold samples, monitor PK & PD changes and safety events

Can be included as part of IND

Report ADA incidence, onset of immune response and impact on safety & efficacy

Information obtained through both short term, single dose studies and chronic multiple dose studies

V.Jawa et al. J Pharm Sci **2022**, 111, 960-969

Case Study of Hyaluronidase (rHuPH20)

- rHuPH20 is a recombinant human hyaluronidase that facilitates rapid, large volume, high dose subcutaneous drug delivery
- Currently approved in 6 co-formulated products (+1 sequential administration) accompanied by SC clinical immunogenicity data for >20 programs
- *In silico* and *in vitro* risk assessments rank rHuPH20 as essentially neutral immunogenicity risk

Tool	Assessment	Result
In silico	HLA binding affinity, T cell epitope prediction	EpiMatrix score: -3.9 9 cluster sequences identified
In silico	Linear B cell epitope prediction	15 potential antigenic epitopes
In vitro	EpiScreen CD4+ T cell proliferation assays against whole protein and panel of five 15-mer peptides	Positive T cell proliferation in 6% of donors with whole protein, none of the peptides induced signal
In vitro	IL-2 secretion ELISpot Assay	Positive IL-2 secretion in 10% of donors
In vitro	B Cell epitope mapping by anti-rHuPH20 antibody screening against library of 88 15mer peptides	Rabbit polyclonal antibody bound to 8 peptides Pre-existing human antibodies did not bind to any

Printz et al., 2022 *AAPS J* 24(6):110

Broad Range of Clinical Anti-rHuPH20 ADA Incidence

Table IV Incidence of rHuPH20-Reactive Antibodies from SC Administration in Clinical Trials

Trial / sponsor	Co-administered therapeutic	Indication	Incidence of treatment-induced/enhanced rHuPH20-reactive antibodies in patients receiving rHuPH20 n/N (%)
117–203 / Halozyme	Insulin	Type I diabetes mellitus	1/40 (2.5)
117–205 / Halozyme	Insulin analog	Type I diabetes mellitus	5/113 (4.4)
117–206 / Halozyme	Insulin analog	Type II diabetes mellitus	2/116 (1.7)
117–403 / Halozyme	Continuous SC insulin infusion	Type I diabetes mellitus	24/335 (7.2)
HannaH / Roche[a]	Trastuzumab	HER-positive early breast cancer	36/290 (12.4)
SparkThera / Roche	Rituximab	Follicular lymphoma	6/185 (3.2)
SAWYER / Roche	Rituximab	Chronic lymphocytic leukemia	6/96 (6.3)
SABRINA / Roche	Rituximab	Follicular lymphoma	17/185 (9.2)
160603-902 / Baxter (Takeda)	Human IgG/HyQvia	Primary immunodeficiency/ adult and pediatric	15/83 (18.1)
NCT01756157 / Viropharma[b]	Human plasma-derived C1 inhibitor	Hereditary angioedema C1 inhibitor deficiency	21/47 (44.7)
NCT02667223 / Pfizer	Bococizumab	Hypercholesterolemia	4/45 (8.9)
NCT02519452 / Janssen	Daratumumab	Multiple myeloma	10/78 (12.8)
COLUMBA / Janssen	Daratumumab	Multiple myeloma	19/255 (7.5)
PLEIADES / Janssen	Daratumumab	Multiple myeloma	16/192 (8.3)
MMY 1004 / Janssen	Daratumumab	Multiple myeloma	21/111 (18.9)
FeDeriCa / Roche	Pertuzumab and trastuzumab	HER2-positive early breast cancer	2/225 (0.9)
GP40201 / Roche	Crenezumab	Autosomal-dominant Alzheimer's disease	1/36 (2.8)
ANDROMEDA / Janssen	Daratumumab	Light-chain amyloidosis	27/211 (12.8)
		Cumulative incidence n/N (%)	233/2643 (8.8)

- Wide range of ADA incidence observed (1% - 45%): all by SC ROA, same native protein sequence and comparable mfg processes used across all studies

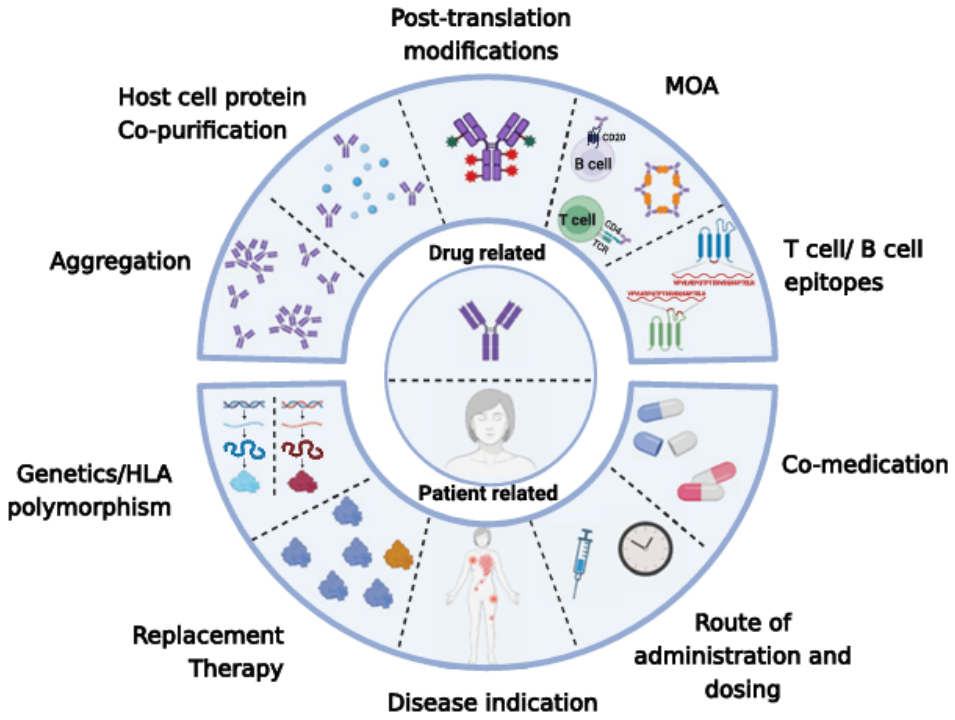
Other factors:

1. Patient population / disease state:
   - immunosuppressed
   - immune competent
   - inflammatory state
2. Co-administered medications:
   - steroids, chemotherapies
3. Co-administered therapeutic
   - its MOA: b-cell ablation, checkpoint inhibitor
   - process-related impurities

All can be drivers of the SC immunogenicity response

Printz et al., 2022 *AAPS J* 24(6):110

Factors that may influence SC Immunogenicity



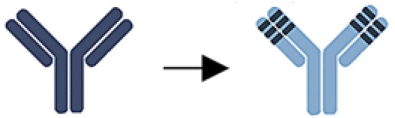
- The same factors that influence immunogenicity via IV administration also influence SC immunogenicity
- Specific for SC: aggregation, aggregation in situ (literature example) degration

Harris & Cohen, BioDrugs 2024, 38, 205-226

Possible Mitigation Strategies to Reduce Immunogenicity

Protein Engineering:

- Humanization incorporates fully human sequences into mAbs without changing the CDRs
- T-cell epitope removal limits high-affinity, long-lived ADA development by abrogating T cell responses
- B-cell epitope modifications is expected to interfere with binding of pre-existing ADA or memory B cells



mAb humanization

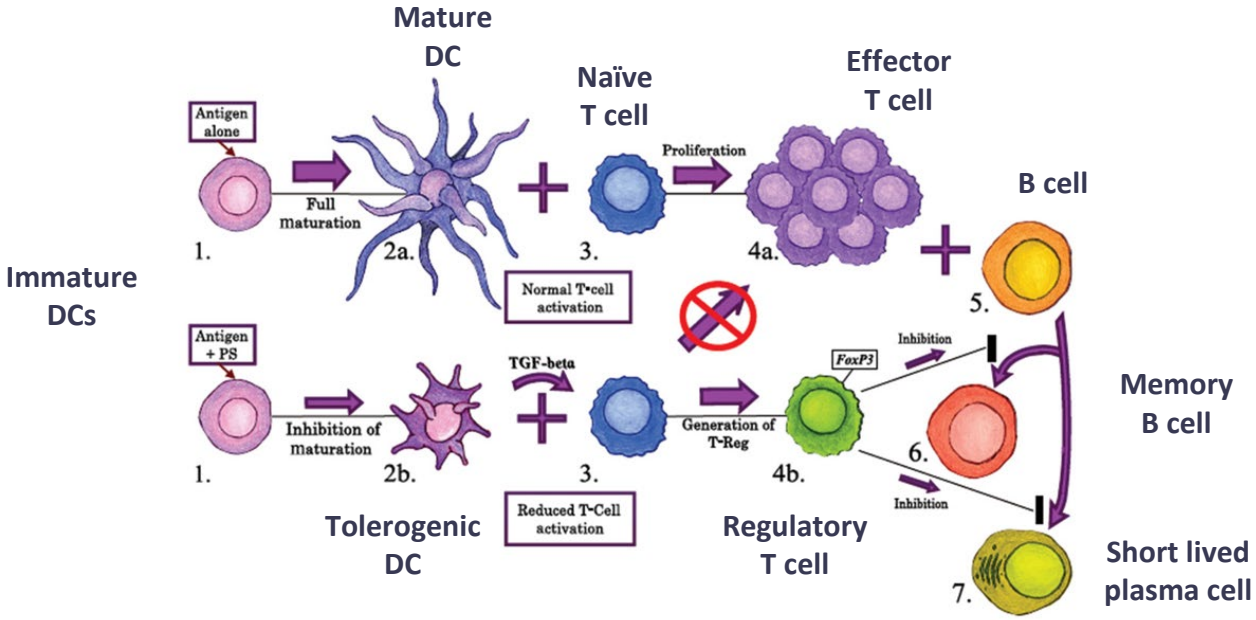
Predict & remove T cell epitope

Critical Quality Attributes: Reduce protein aggregates and impurities

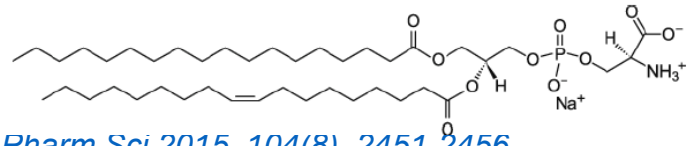
Jarvi & Balu-Iyer. BioDrugs 2021, 35(2), 125-146.

SC Co-administration:

- Phosphatidylserine, O-Phospho L-Serine [OPLS], or others generates DCs with a tolerogenic profile
- Systemic methotrexate



Phosphatidylserine:



Ramakrishnan et. al.,J Pharm Sci 2015, 104(8), 2451-2456

2023 PEGS Boston User Group

CRA Charles River Associates

SUBCUTANEOUS CONSORTIUM

SC Consortium Website

"SC Administration and Immunogenicity Risk: Current Understanding and Future Considerations for Novel Modalities"

KEY INSIGHTS

- There is **mixed evidence that both support and refute** the notion that **SC administration is more immunogenic that IV administration**
- **Multiple factors contribute to risk of developing an unwanted immune response** to a biologic: product-related, treatment-related, patient-related

KNOWLEDGE GAPS

- The **current body of data related to subcutaneous administration-associated immunogenicity may be inadequate** to answer critical **scientific questions regarding factors contributing to immunogenicity**.
- There is an **inability to isolate and study factors contributing to immunogenicity independently**. This is especially relevant for patient-centric factors, as there is **significant variability in patient handling across studies**
- There is a **lack of harmonized data** across literature due **to lack of information sharing** or **access to universally accepted models**
- There is **no established consensus** on **accepted models** for ***in vitro*** or ***in vivo*** **modelling**

NEXT STEPS

- **Incorporate User Group findings into manuscript development,** partnering with external stakeholders as appropriate to provide case studies and additional data
- **Identification of appropriate preclinical model:** develop potential sponsored research to evaluate preclinical model appropriate for understanding SC-associated immunogenicity

Conclusion and Future Perspectives

- In aggregate, there is no clear signal that SC administration is more immunogenic than IV administration
- Gaps with current tools and datasets
- Encourage more publications to move the field forward
- While development of SC protein therapeutics is more complex than IV products, there are many benefits to patients and we should continue to pursue
- First results from late-breaking Phase 3 PALOMA-3 study show five-fold reduction in infusion-related reactions with five-minute subcutaneous amivantamab administration (jnj.com)

Our Special Thanks to-

Workshop Organizers:
Beate Bittner & David Kang

Immunogenicity Subteam of the SC Consortium:
Lead by: **Vibha Jawa**

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Masano Huang
Alison Johnson
Tatsiana Mardovina
Erik Meyer
Sachin Mittal
Tao Niu
Andrei Popov
Marie Printz
Stephanie Reed
Amy Rosenberg
Manuel Sanchez-Felix
Manjunatha Shivaraju
Sophie Tourdot

Subcutaneous Drug Development & Delivery Consortium
Non-profit Organizations
Beaverton, Oregon
1K followers

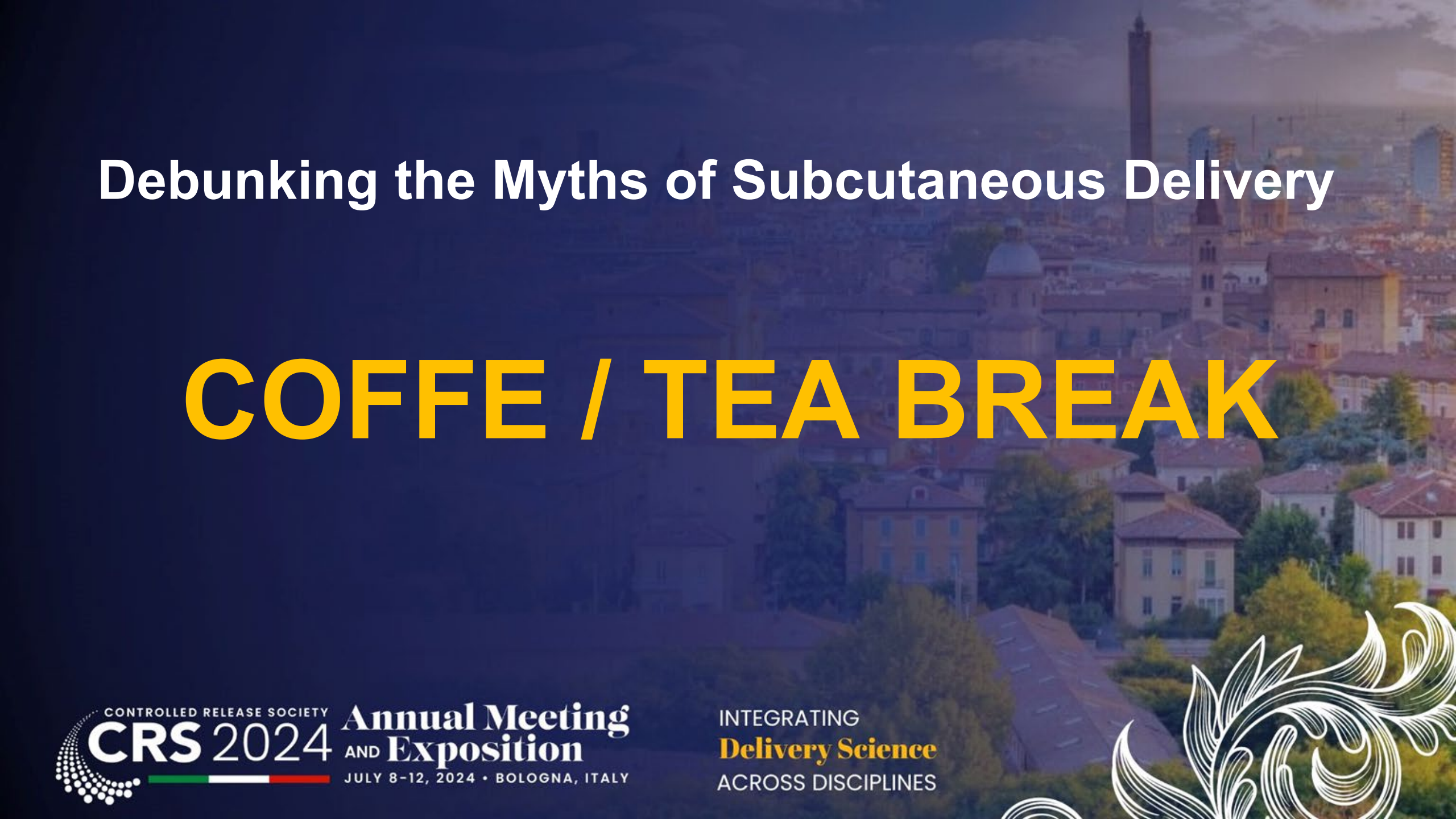
Precompetitive collaboration to transform care and improve outcomes via advances in SC drug development and delivery.

https://www.linkedin.com/company/subcutaneous-drug-development-delivery-consortium/

Nicholas Wechter, Charles River, Project Management support

Debunking the Myths of Subcutaneous Delivery

COFFE / TEA BREAK



Myth 3: Subcutaneous delivery is challenging due to low and/or unpredictable bioavailability

Kate Harris (AstraZeneca)
Marta Venczel (Sanofi)
Nicole Buist (Merck Sharpe & Dohme LLC)
Manuel Sanchez-Felix (Halozyme Therapeutics)

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INTEGRATING Delivery Science ACROSS DISCIPLINES

Overview

- Introduction
- In-vitro SC Bioavailability – Kate Harris
- In-Vivo SC Bioavailability – Marta Venczel
- In-Silico SC Bioavailability – Nicola Buist (Sachin Mittal)
- Conclusion & Closing Remarks - Nicola Buist (Sachin Mittal)

Introduction: Myth 3

Subcutaneous delivery is challenging due to low and/or unpredictable bioavailability

SUBCUTANEOUS CONSORTIUM

Presentation of the Joanneum/ BioNotus collaboration results: 11th of July; 9-11 o´clock

Introduction: Problem Statement, Vision and Challenge

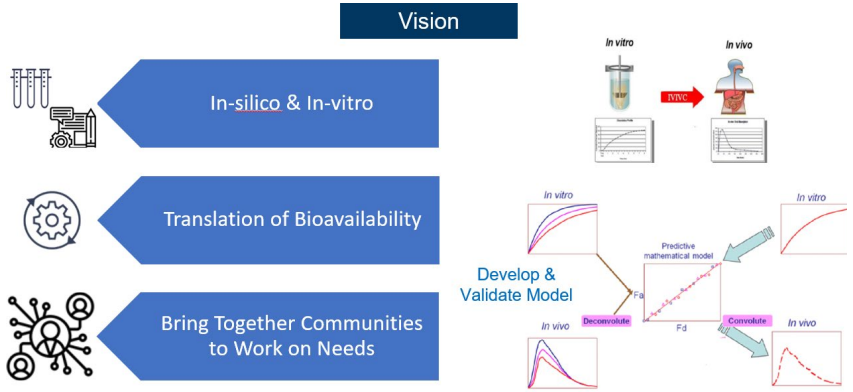
Advanced Drug Delivery Reviews
Available online 27 May 2020
In Press, Corrected Proof

Predicting bioavailability of monoclonal antibodies after subcutaneous administration: Open innovation challenge

Manuel Sánchez-Félix [a], Matt Burke [b], Hunter H. Chen [c], Claire Patterson [d], Sachin Mittal [e]

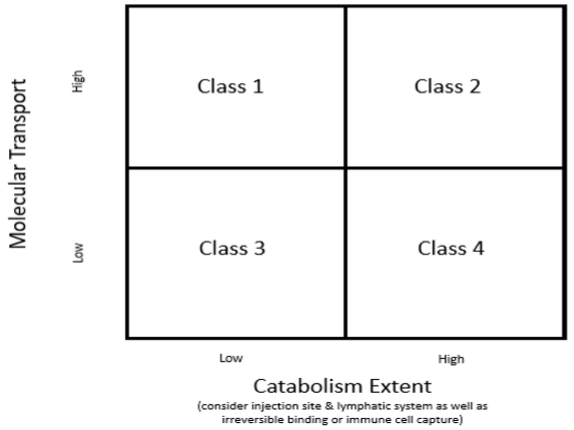
SUBCUTANEOUS CONSORTIUM

Vision



Open Challenge

Classification system concept for mAbs: molecular transport vs catabolism extent



Subcutaneous delivery is challenging due to low and/or unpredictable bioavailability:

Advancing *in vitro* tools to predict bioavailability of biotherapeutics

Kate Harris

New Modalities & Parenteral Development, Pharmaceutical Technology & Development, Operations, AstraZeneca, Macclesfield, UK

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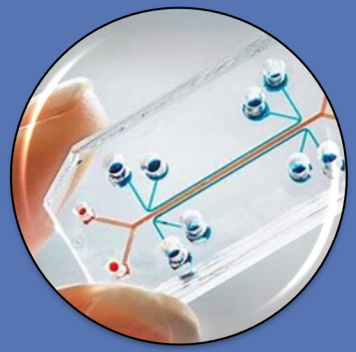
INTEGRATING
Delivery Science
ACROSS DISCIPLINES

The SC *in vitro* tool landscape has progressed significantly in recent years

ARTIFICIAL MODELS

- Gel diffusion & dialysis based systems
- Dissolution apparatus USP 4 & 7
- SCISSor
- ESCAR
- AC SINS
- Osmomat 050
- Aggregation / oligomerisation assays
- Binding assays (protein, FcRN, ECM components)

CELL & TISSUE BASED MODELS



- Microphysiological endothelial models
- WAT tissue on a chip
- Hyposkin®, FlowSkin®
- Perfused porcine limb model
- Catabolism assays

Bioavailability predictions & *in silico* input parameters

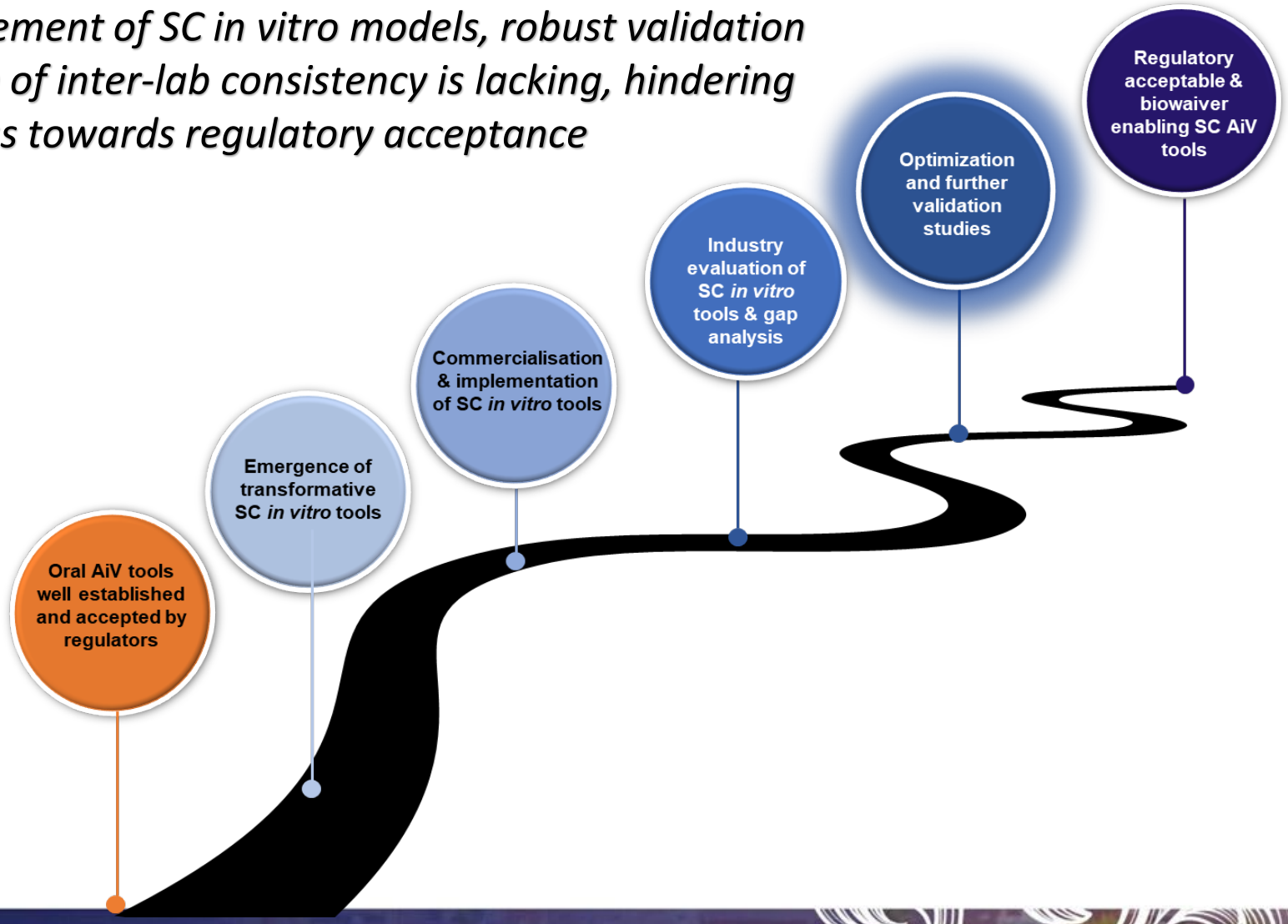
Validation of SC *in vitro* tools remains a key gap

Despite the advancement of SC in vitro models, robust validation and demonstration of inter-lab consistency is lacking, hindering progress towards regulatory acceptance

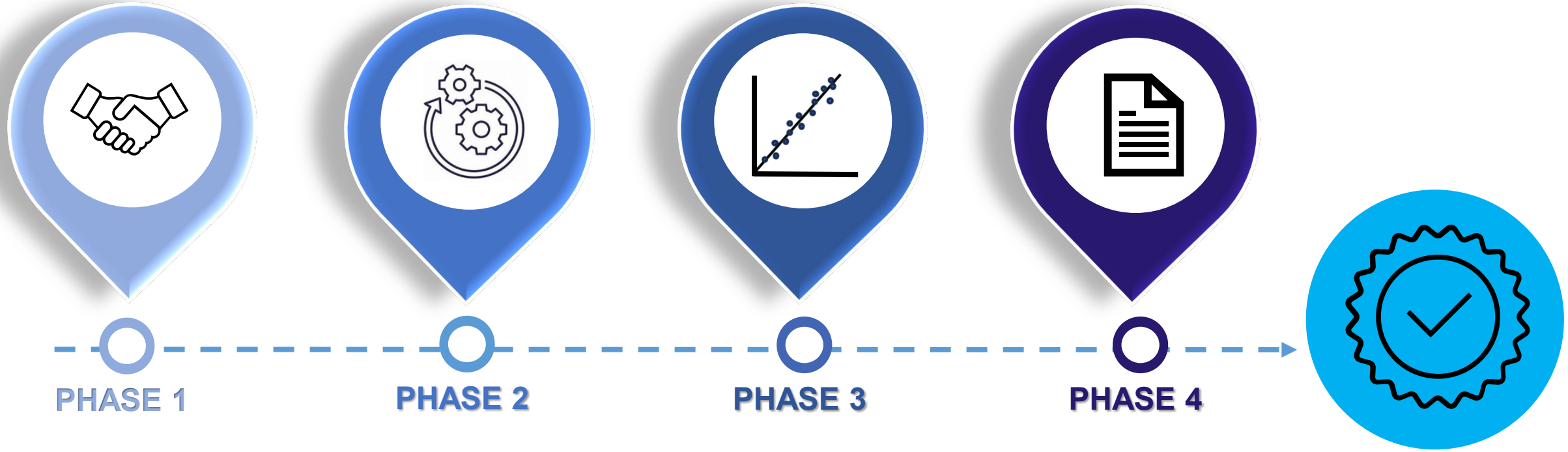
Unaddressed scientific need

- Limited validation dataset
- Un-optimised experimental conditions
- No across-lab validation
- Variability widely observed
- Cost restrictions

Poor BA predictivity, reliant on human studies to aid biotherapeutic drug product development



The SC consortium are actively seeking collaboration with technology companies to validate *in vitro* tools and ensure regulatory acceptability



PHASE 1

Identify priority tools and technology companies

PHASE 2

Method optimisation & evaluation

PHASE 3

Consortia members evaluation

PHASE 4

Regulatory advocacy and publication

Subcutaneous delivery is challenging due to low and/or unpredictable bioavailability:

Advancing *in vivo* tools to predict bioavailability of biotherapeutics

Marta Venczel

sanofi

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ACROSS DISCIPLINES

Translatability of preclinical data to human BA

- **Problem statement**: Subcutaneous Bioavailability of biologics is unpredictable and variable. There is a gap in translation of data from *in vitro* to preclinical to clinical with regards to bioavailability after SC administration. Building predictive *in silico*, *in vitro* or preclinical *in vivo* models will help reliably predict human absorption/ bioavailability for SC products in relation to dose during development. The predictability will inform molecule and product design and a more streamlined development of SC large molecule dosage forms
- **Scope**
  - Commercially available Drug Products
    - **SC BA = 49 - 90 %**, based on 89 marketed antibody-based biotherapeutics approved between 1986 to mid 2020*
    - BA on all data: 69 % geometric mean (70 % ± 13.5, arithmetic mean, STDEV)
  - A First-in-Human Study** of the Trispecific HIV-1 Broadly Neutralizing Antibody, SAR441236
    - BA of **35 ± 7%**
  - Research formulations
    - When BA is **< 50 %**, it may be challanging to develop a viable commercial formulation due to volume of injection limitations
    - Low SC BA leads to high API CoG as an increase in the dose needs to compensate low BA

* Martin et al.: Trends in industrialization of biotherapeutics: a survey of product characteristics of 89 antibody-based biotherapeutics, MABS, 2023 (15)

** A First-in-Human Study of the Trispecific HIV-1 Broadly Neutralizing Antibody, SAR441236 - CROI Conference; March 2024

in vivo Methodology

- **Current in vivo models:** Classical preclinical experiments with iv. and sc. administration & e*x vivo* studies & special assays: e.g. cage implant, analysis of the lymphatic absorption

- **Possible reasons for not adequate human predictivity**
  - Preclinical models, IVIVCs are developed for oral drugs and may not be optimized for the complex injection site physiologies, release rate and absorption mechanisms of subcutaneous drugs *
  - An in depth understanding of the SC environment such as the **Extracellular Matrix** (ECM), the **Interstitial Fluid** (ISF**) and the **Adipose Tissue** is required. The interspecies differences must be taken into considerations
  - Additionally, to improve the knowledge on the effect of different **drug** (e.g. the isoelectric point) and **formulation factors** on absorption rates are essential to enhance the predictivity of the *in vivo* models
  - → Elaboration of new *in vivo* methodologies are needed designed for sc. administration

- **Open Innovation Challenge**: BA Sub-Team performed an in-depth evaluation of different proposals of scientific experts and entrepreneurs

* Corpsteain et al.: A Perspective on Model-Informed IVIVC for Development of Subcutaneous Injectables, Pharm. Res., 2023 (40)
** Torres et al.: Prediction of subcutaneous drug absorption - Characterization of subcutaneous interstitial fluids as a basis for developing biorelevant in vitro models, IJP, 2023

Innovative proposals of the Open Challenge

Ex *in vivo* studies

Human skin model: Standardized, with a ready to use immunocompetent

Preclinical studies

Application of the Open Flow Microperfusion (OFM) technology combined with the subcutaneous tissue biopsy analysis

Predictive *in vitro* release studies

Mimicking the subcutaneous space

M & S

Modelling & Simulation studies for human BA prediction

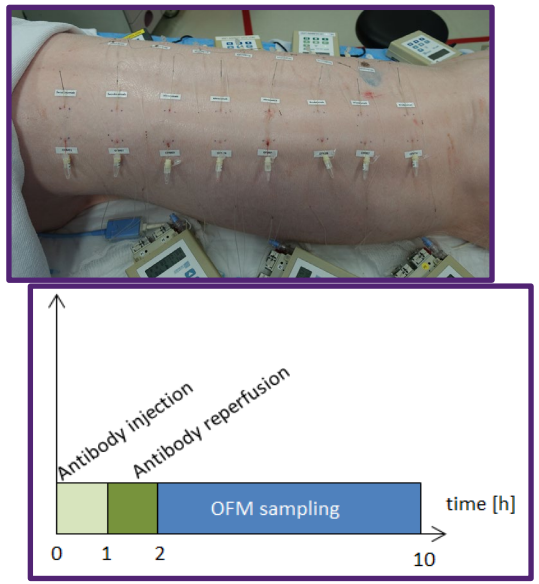
New Innovative Study

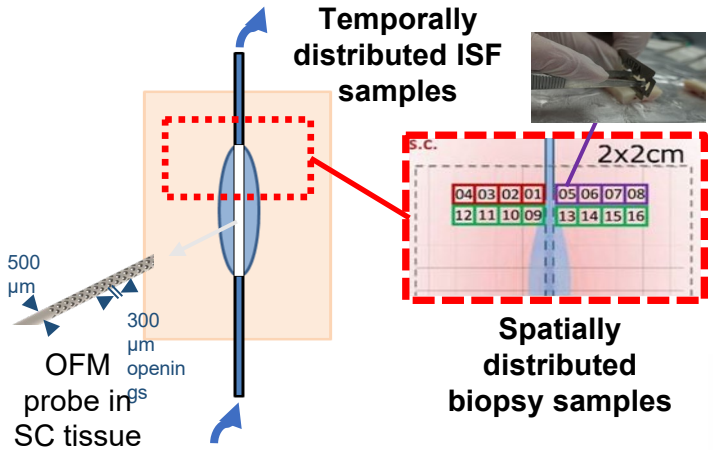
- Based on internal selection process we started the 2023 collaboration with
  - Joanneum Research, master of Open Flow Microperfusion (OFM) technology &
  - BioNotus, responsible for Modelling & Simulation studies

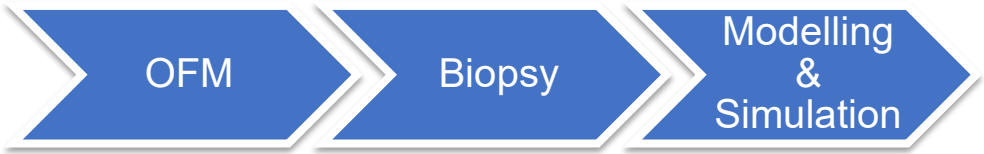
using commercially available, three representative Drug Products:

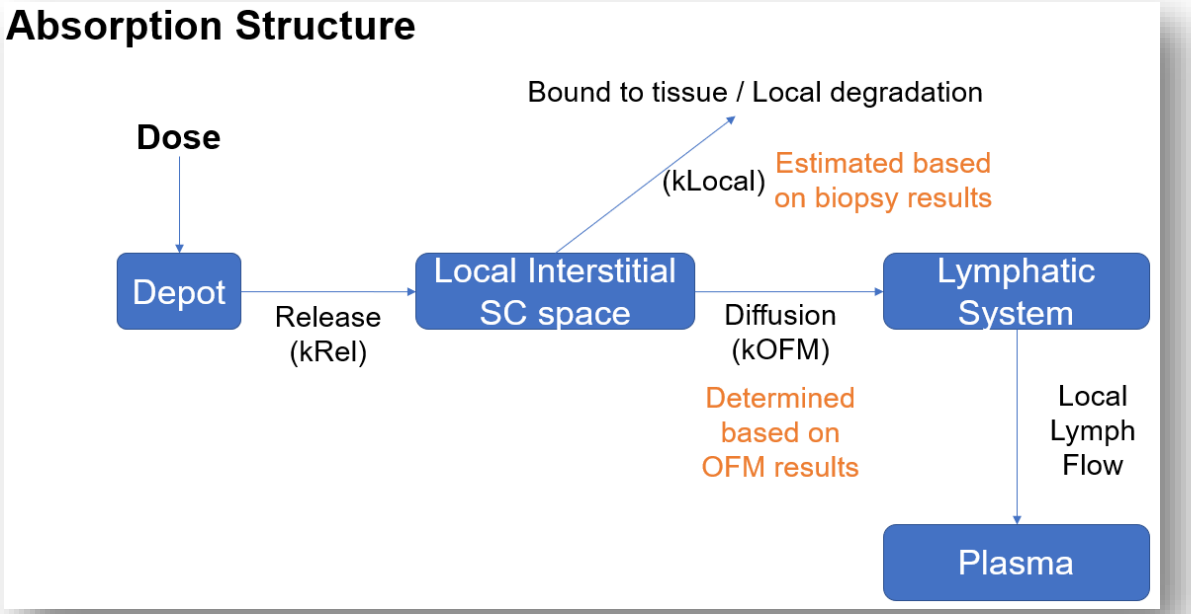
- Brodalumab: low range of BA
- Secukinumab: middle range of BA
- Alirocumab: high range of BA

Study Design









Outputs of the collaboration

Presentation of the results: 11th of July; 9-11 o´clock

- New *in vivo* measurement from pigs that can help to predict *in vivo* human SC bioavailabilty
- Promising correlation (within the limitation of small N) between local porcine tissue mAb concentrations to their clinical BA (R^2= 0.94; linear regression)
- Current results suggest that the immediate adipose tissue interaction (< 10 hr) could be a key factor in determining the systemic BA of a mAb
- Three Rs of animal welfare
  - Reduction, Replacement and Refinement (Three Rs) of animal application in preclinical studies [Animals in science - European Commission (europa.eu)]
- Outlook
  - Opportunities for further work to validate the predictive model
  - More focus on *in silico* and on *in vitro* methods

Subcutaneous delivery is challenging due to low and/or unpredictable bioavailability:

Advancing *in silico* tools to predict bioavailability of biotherapeutics

Nicole Buist
Merck Sharpe & Dohme LLC

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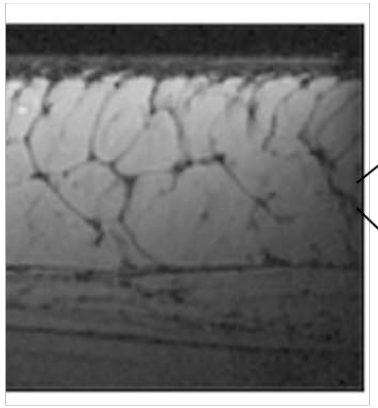
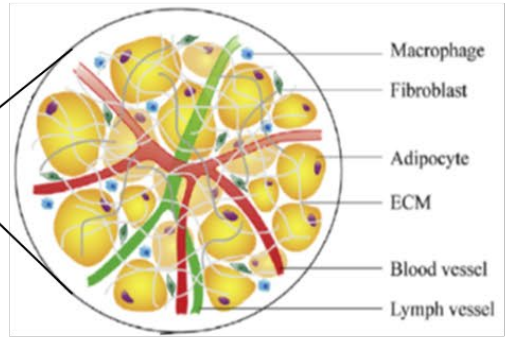
In-Silico Approaches Require Meaningful Input from In-vitro and In-vivo Studies



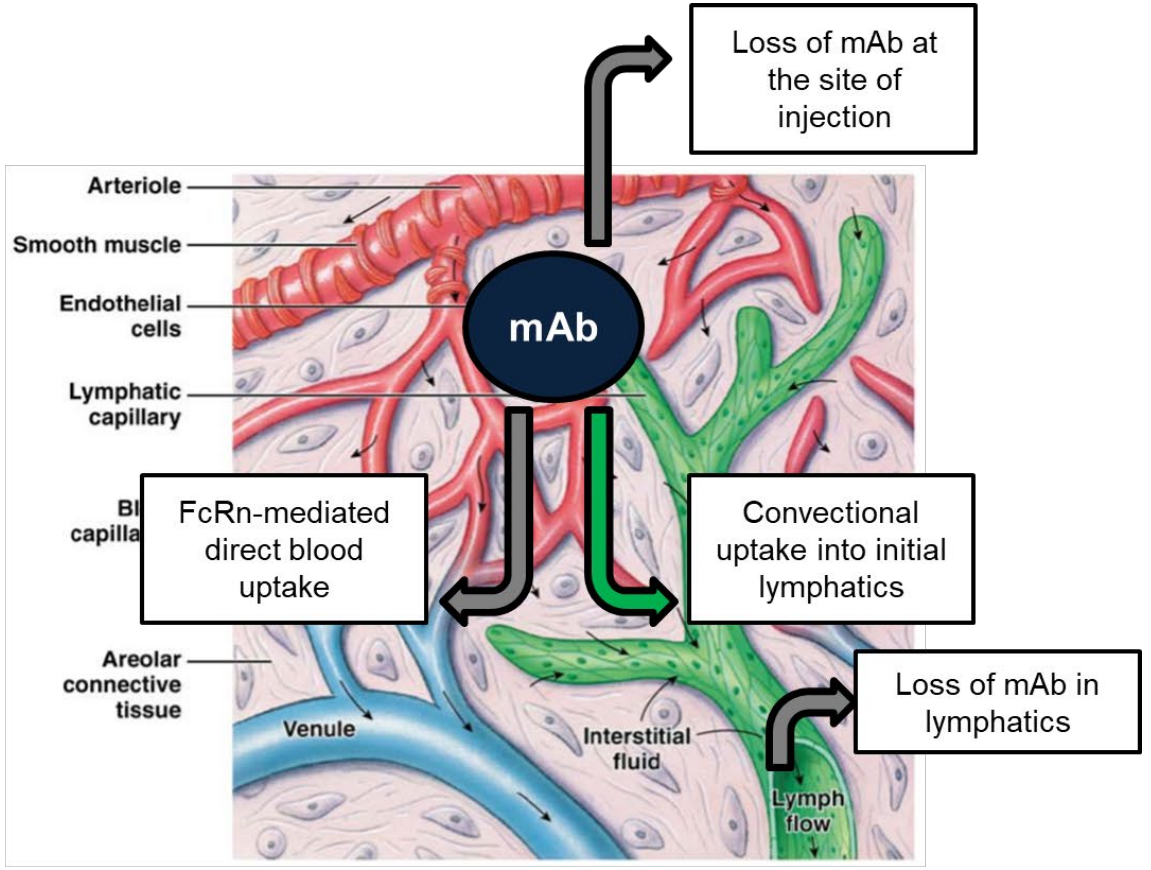
MRI image of the human skin / hypodermis / muscle

Adapted from The AAPS Journal, Vol. 14, No. 3, September 2012



Schematic of the hypodermis (aka subcutis)

Adapted from Viola et al.; J Control Rel, 2018, 286, 301



Vascularization of the peripheral tissue (e.g. hypodermis)

Source: https://www.palmbeachstate.edu/slc/Documents/AandPch20LecturePearson.pdf

Publications have Highlighted Variables of Interest to Inform Modeling

Lymphatic transit time *and drug clearance during lymphatic transport are most influential to bioavailability - Zhao et al. The Journal of Clinical Pharmacology 53(3) 314–325 2013*

Clearance is inversely correlated to BA *– Haraya et al. Drug Metabolism and Pharmacokinetics 32 (2017), 208-217*

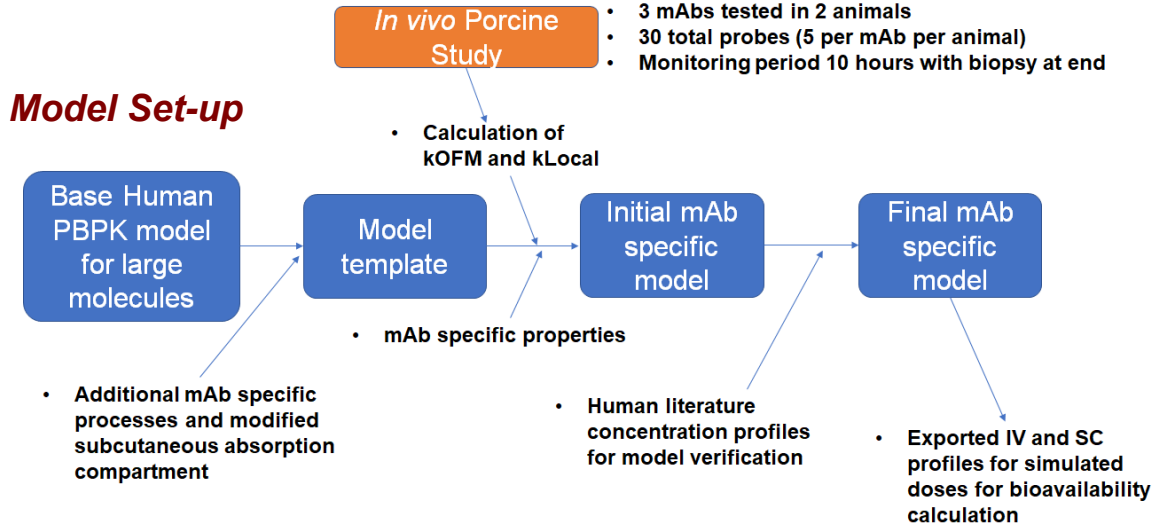
Isoelectric point (pI) *positively correlates with estimated lymphatic trunk/lymph node clearance - Varkhede and Forrest J Pharm Pharm Sci. 2018 ; 21*

PBPK model exploring the role of ***positive charge in lymphatic clearance*** *- Hu & D'Argenio Journal of Pharmacokinetics and Pharmacodynamics 2020*

Combination of high ***positive charge and hydrophobic interaction*** *significantly reduced the rate of absorption and bioavailability - Datta-Mannan et al. MABS 2020, VOL. 12, NO. 1, 1–14*

Opportunity: Developing refined mAb custom input with regards to SC distribution, access to lymphatics and local degradation/ tissue binding to inform in-silico model

Development of an In-situ Swine OFM Model for SC Distribution/ Clearance



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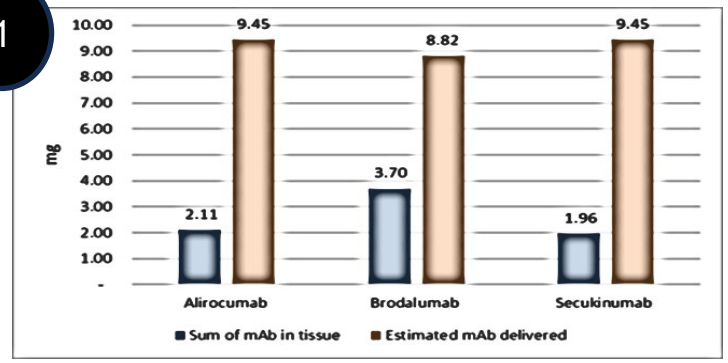


Input in-vivo data

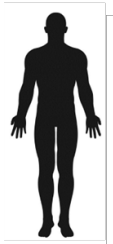
2

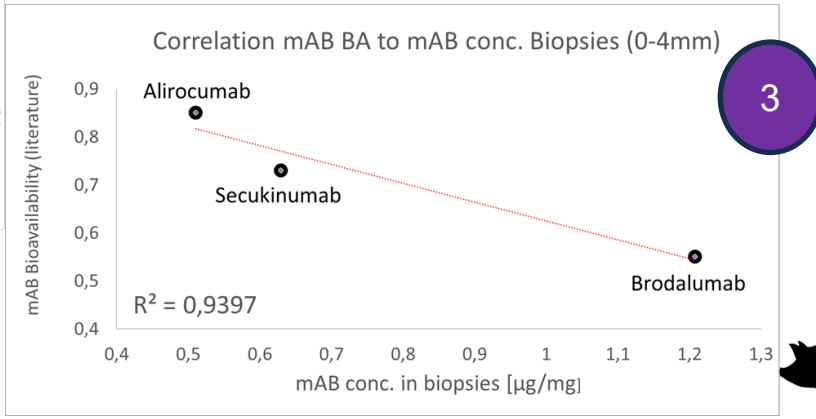
	Alirocumab	Brodalumab	Secukinumab
Average Model-predicted BA (%)	76.0	51.7	77.7
Literature BA (%)	85	55	55-77

1 Mass balance data were used to estimate the k_{Local} rate constants. Also the k_{OFM} rate constants reflecting diffusion were incorporated in the model

2 The average SC bioavailability predictions for each mAb are subsequently compared with the corresponding literature values

3 The extent of mAb "trapped" in the SC tissue is inversely proportional to its systemic bioavailability





3

Conclusion & Closing Remarks

- Over the last four years there has been advancements that have created an opportunity for better predicting SC bioperformance
- ***Subcutaneous Drug Development & Delivery Consortium*** is a cross-industry consortium with 15 Tier 1 and 2 Tier 2 members to enable ***pre-competitive collaboration*** which is critical to drive fundamental understanding & build robust predictive models
- SC consortium's ***collaboration with Joanneum/ BioNotus*** to build a relevant in-situ swine/ in-silico model is a case in point but requires continued efforts on that model and analogs
- Bioavailability subteam and the consortium continue to drive research in in-vitro, in-vivo/ in-situ, and in-silico models with new RFPs & collaborations

SUBCUTANEOUS CONSORTIUM

Presentation of the Joanneum/ BioNotus collaboration results: 11th of July; 9-11 o´clock

- ***Acknowledgment***:
  - SC Consortium's Bioavailability Subgroup - Manuel Sanchez-Felix & Sachin Mittal (Co-leads), Christopher Basciano, Jenna Caldwell, Ming Chen, Antoine Deslandes, Jennifer Drew, Cecile Gross, Marc-Antoine Fabre, Ludovic Gil, Kate Harris, Filippos Kesisoglou, Kev Maloney, Neil Mathias, Mikolaj Milewski, Mikhail Murashov, Ryan Nolan, Ron Pettis, Pratik Saha, Manjunatha Shivaraju, Ivana Tomic, Anthony Tuesca, Marta Venczel, Xianwei Zhang

Myth 4: Subcutaneous delivery requires extensive clinical trials when bridging device or from IV

Beate Bittner (Roche, Basel, Switzerland)
Gerard Bruin (Novartis, Basel, Switzerland)

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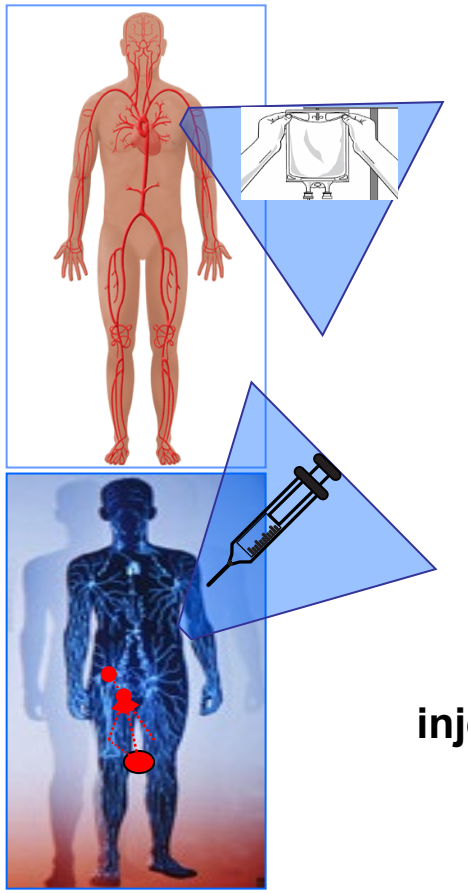
Content

- From IV to SC; how to arrive at the right SC dose regimen
- From SC to SC; how to bridge from one SC device to the next SC device
- From SC to IV; how to arrive at the right IV regimen

IV to SC

- From IV to SC; how to arrive at the right SC dose regimen

Impact of Subcutaneous vs. Intravenous Delivery on PK profile of Monoclonal Antibodies



Peripheral lymphatic system → **Central lymphatic ductus** (ductus thoracicus)

Lymph absorption pathway

SC injection site

Potentially some loss from SC injection site (e.g., catabolism by macrophages)

SC injection

IV infusion

1 Central compartment ⇄ (k_{12}, k_{21}) **2 Peripheral compartment**

Ke * C

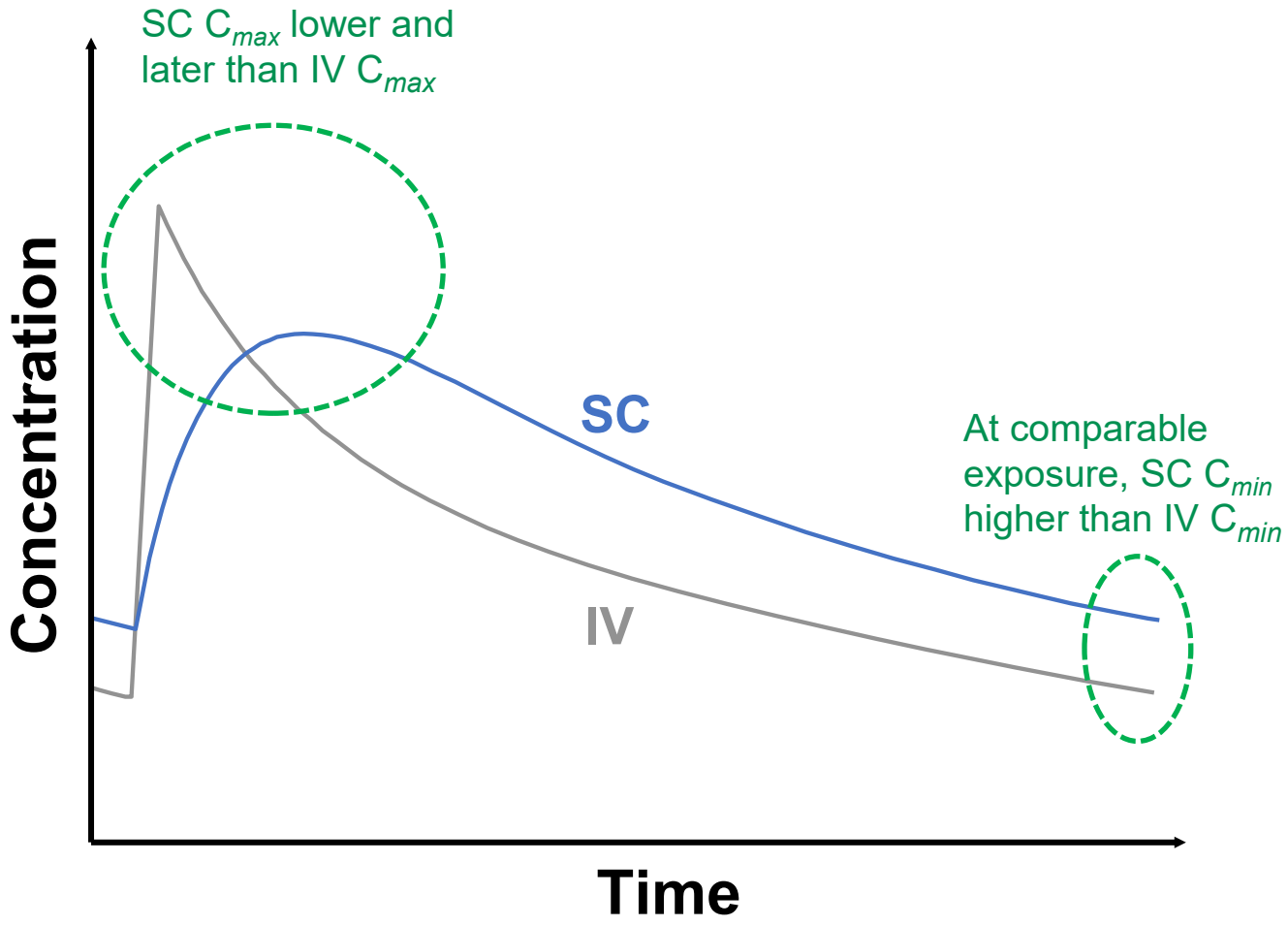
$\frac{Vmax * C}{Km + C}$

Linear clearance Target-independent elimination

Nonlinear clearance Target-specific elimination

Adapted from McLennan DN *et al*. Drug Discovery Today 2005.

Impact of Subcutaneous vs. Intravenous Delivery on PK profile of Monoclonal Antibodies



- Impact of C_{max} and C_{min} on **efficacy & safety profile**
- **For high-dose mAbs: Technical feasibility** of high-concentration formulations and **high-volume injection**

IV to SC Bridging: How to Leverage Preclinical Data During Development Pathway

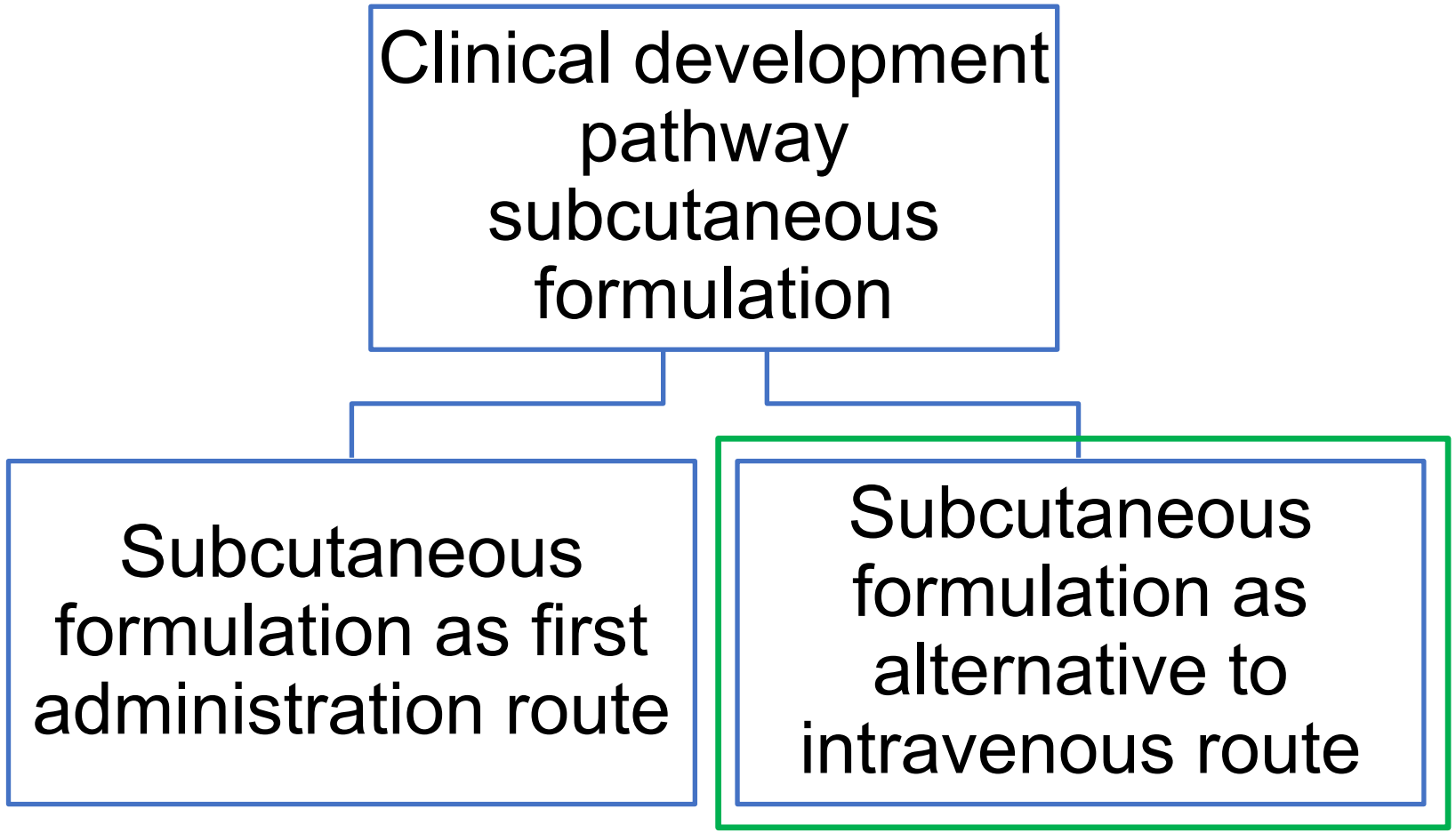
Supporting preclinical data

- Assess impact of administration route on PD parameters, incl. relevance of C_{max}
- Demonstrate SC toxicology and local tolerability
- Assess the impact of different formulations on the PK profile

Aims of the clinical development program

- Demonstrate PK non-inferiority between the IV and SC formulations to ensure comparable efficacy
- Show that the safety and immunogenicity profile of the SC formulation is consistent with that of the IV formulation
- Provide supportive efficacy data

SC Delivery of Monoclonal Antibodies - Development Pathway Depends on Prior Availability of an IV Formulation



Comparison of Trastuzumab IV and SC

	Trastuzumab IV[1]	Trastuzumab SC[1]
Pharmaceutical form	Powder for concentrate for solution for infusion	Ready-to-use vial for manual injection
Delivery technology	n/a	rHuPH20
Loading dose	8 mg/kg (q3w) 4 mg/kg (q1w)	600 mg in 5 mL (q3w)
Maintenance dose	6 mg/kg (q3w) 2 mg/kg (q1w)	600 mg in 5 mL (q3w)
Time required for administration	30 to 90 minutes	Less than 5 minutes
Key Phase III trials in eBC	HERA[3], BCIRG 006[4], NCCTG N9831[5,6], NSABP B-31[5]	HannaH (BO22227)[2]
Need for IV line	Yes	No

eBC, early breast cancer; IV, intravenous; rHuPH20, recombinant human hyaluronidase; SC, subcutaneous; SID, single-use injection device; q1w, weekly dosing; q3w, 3-weekly dosing.

1. Herceptin® SC (Herceptin) Summary of Product Characteristics 2014
2. Jackisch C *et al*. Ann Oncol 2015
3. Goldhirsch A *et al*. Lancet 2013
4. Slamon D *et al*. N Engl J Med 2011
5. Perez EA *et al*. J Clin Oncol 2014
6. Perez EA *et al*. J Clin Oncol 2011.

The Lack of Predictive Animal Data on SC Bioavailability of MAbs is Overcome with an Adaptive Phase 1/1b Dose Finding Approach

Example: Selection of trastuzumab SC dose in healthy male and eBC participants

Concept: Leverage existing PK model built based on prior IV PK data in HER2+ BC

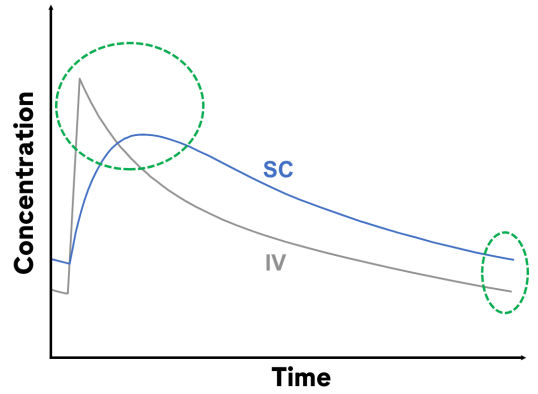
Part 1: Dose-finding

Dose-finding cohorts

Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
6 mg/kg IV HMPs n = 6	6 mg/kg IV eBC participants n = 6	6 mg/kg SC HMPs n = 6	10 mg/kg SC HMPs n = 6	8 mg/kg SC HMPs n = 6

Part 2: Dose confirmation

Cohort A	Cohort B§
8 mg/kg SC eBC participants n = 20	12 mg/kg SC eBC participants n = 20

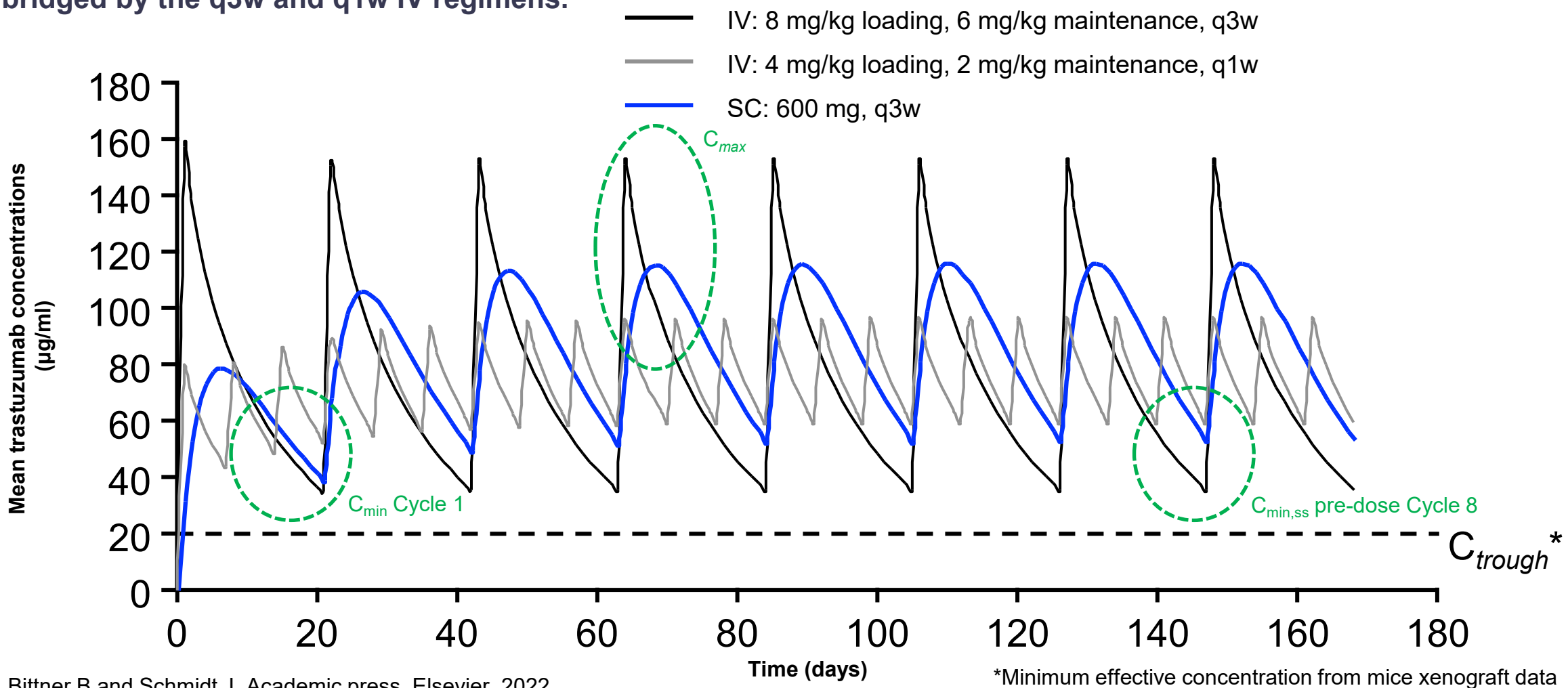


EBC, early breast cancer; HMPs, healthy male participants

Wynne C *et al*. J Clin Pharmacol 2012.

PK-based Clinical Bridging Approach

Hypothesis generation based on available trastuzumab PK data. The PK profile of the SC formulation was bridged by the q3w and q1w IV regimens.



Bittner B and Schmidt J. Academic press, Elsevier, 2022.

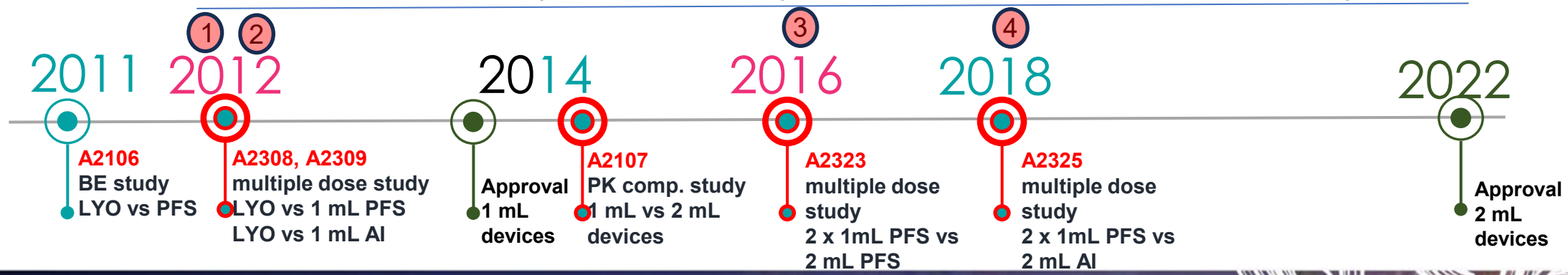
*Minimum effective concentration from mice xenograft data

SC to SC: How to include new Drug-Device-Combination-Products (DDCPs) in the Development Program?

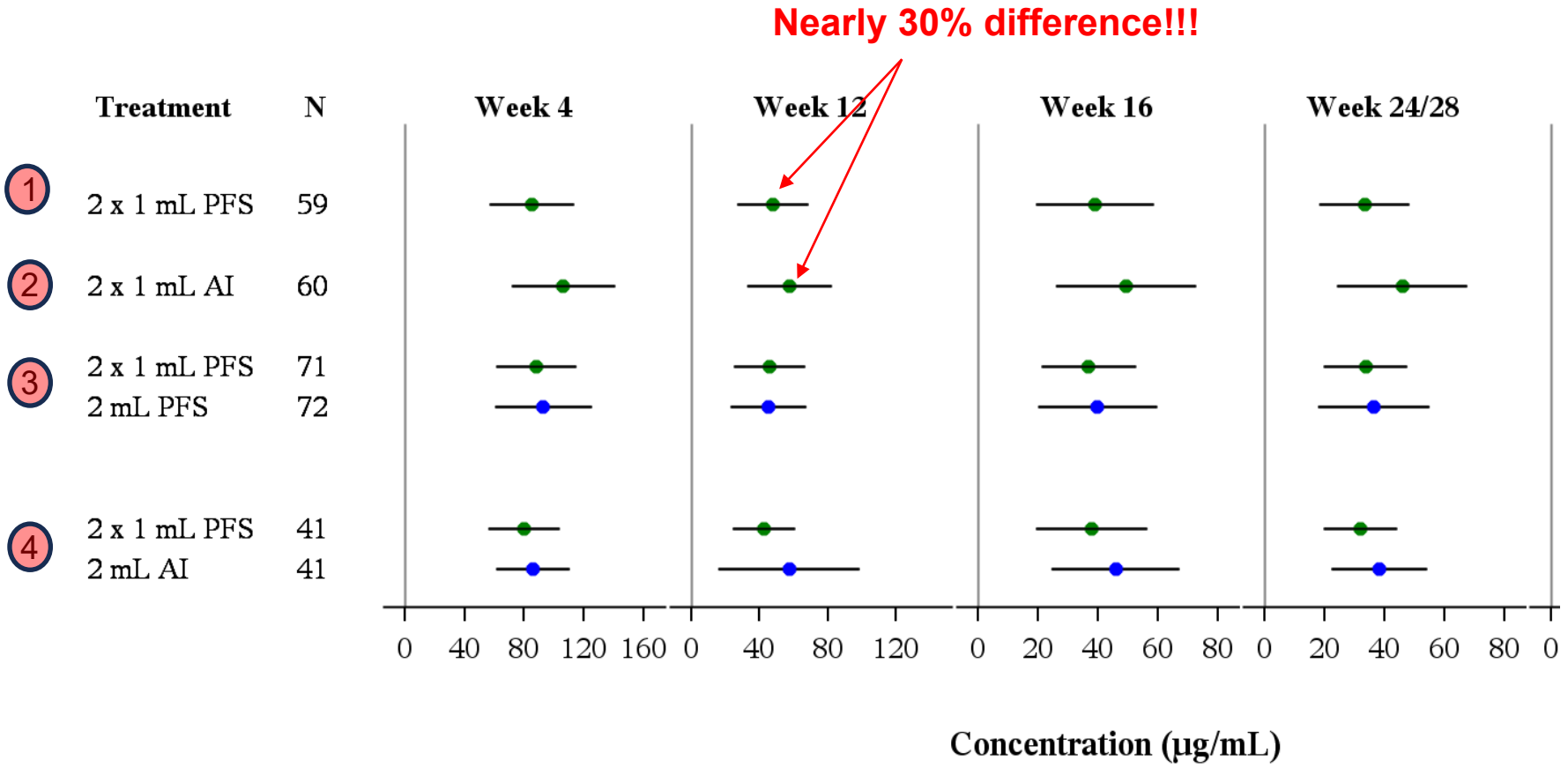
Are really so many studies and so much time needed?

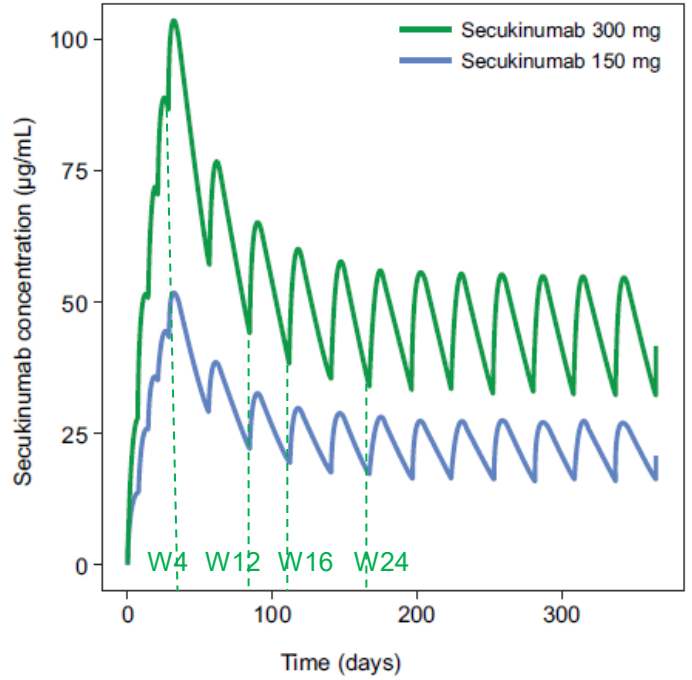
Drug	From	To	Clinical study	HV/Patients	Number of subjects / arms	HA request	Comment
secukinumab	300 mg, 2 x 1 mL LYO,	300 mg, 2 x 1 mL PFS	AIN457A2106 single dose BE	HV	141 / 2	N	with excipients change from LYO to PFS
1	150, 300 mg 1 or 2 x 1 mL LYO	150, 300 mg 1 or 2 x 1 mL PFS	AIN457A2308 multiple dose Phase 3	Pso	174 / 3	Y	
2	150, 300 mg 1 or 2 x 1 mL LYO	150, 300 mg 2 x 1 mL AI Delta	AIN457A2309 multiple dose Phase 3	Pso	177 / 3	Y (FDA only)	
	300 mg, 2 x 1 mL PFS or 2 x 1 mL AI Delta	300 mg, device prototypes	AIN457A2107 single dose – PK comparability	HV	122 / 6	N	Abdomen/thigh, injection time comparison
3	300 mg, 2 x 1 mL PFS	300 mg, 2 mL PFS	AIN457A2323 multiple dose Phase 3	Pso	214 / 3	Y	Abdomen/thigh comparison
4	300 mg, 2 x 1 mL PFS	300 mg, 2 mL AI YpsoMate	AIN457A2325 multiple dose Phase 3	Pso	122 / 3	Y (FDA only)	Abdomen/thigh comparison

Cosentyx® (secukinumab)



Things can go wrong in Cross-Study Comparisons with Sparse PK!

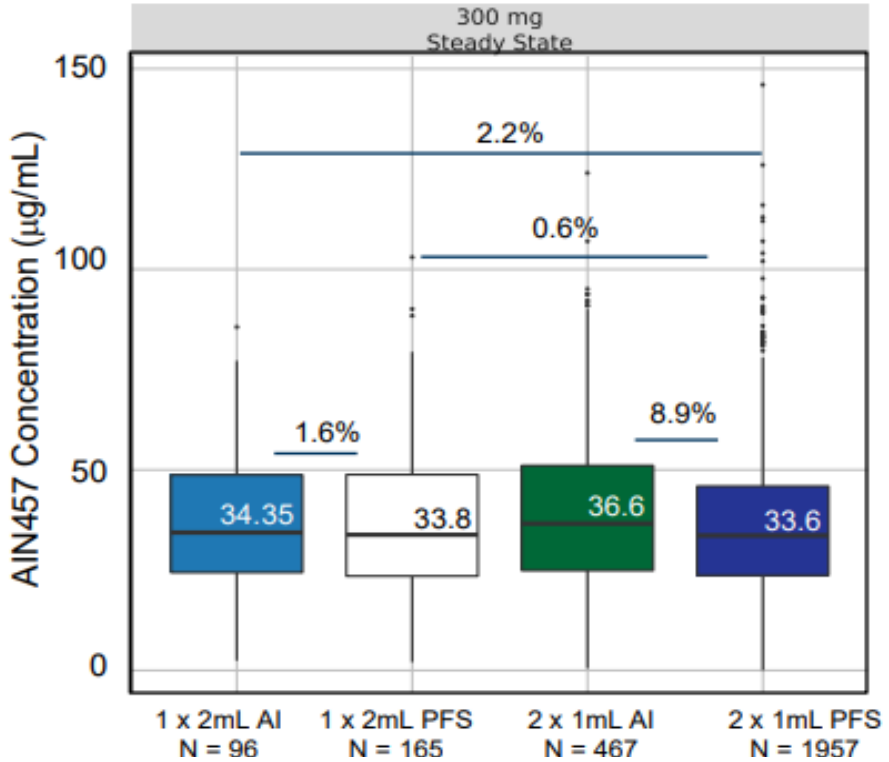




Simulated concentration profiles of secukinumab 300 and 150 mg with subcutaneous dosing regimens derived from phase 3 trials. Patients were simulated to receive secukinumab at baseline; weeks 1, 2, and 3; and then every 4 weeks from week 4 to week 48.

Combined Ph 3 studies with Psoriasis (PsO) and Psoriatic arthritis (PsA) Patients

No impact of Drug-Device-Combination-Product on PK, clinical efficacy, and safety of Cosentyx/secukinumab!



Studies	N	2x1mL PFS	2x1mL AI	1x2mL PFS	1x2mL AI
A2308	135	X			
A2309	147		X		
A2323	323	X		X	
A2325	181	X			X
F2312	236	X			
F2318	320		X		
F2342	570	X			
F2366	773	X			

4 PsO Phase 3 studies

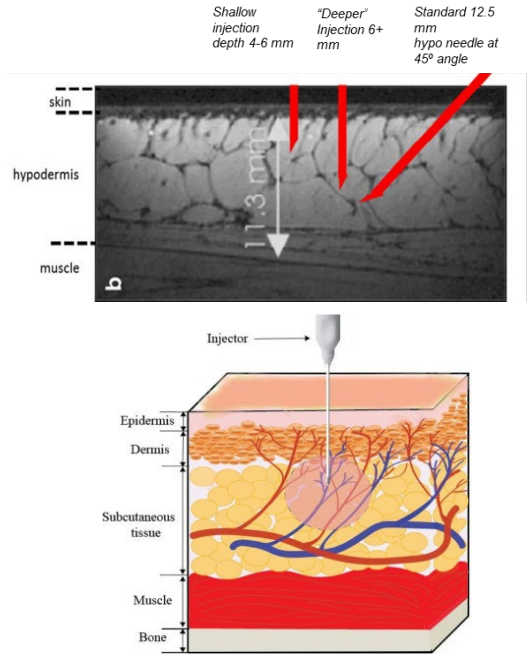
4 PsA Phase 3 studies

Are Injection Depth Differences between PFS and AI Significant Factors for PK?

Position: Comparability between PFS vs. AI injection depth in SC administration (e.g., 1.0 - 2.0 mL) for SC administration of mAb's may not raise significant PK questions and could be justified without a PK study measuring bioequivalence.

Supporting Information:

- Standard 12.5 mm PFS needle inserted at a 45° angle reaches the same depth as a typical AI needle insertion depth (5-7.5 mm). Geometrical comparability is supportive.
- Delivery to SC tissue with either delivery device typically reaches the same SC biospace. Potential factors affecting PK (catabolism, intercellular diffusion and lymphatic drainage) for short delivery times will not meaningfully impact C_{max} (typically occurring after 5-7 days) or AUC.
- CDRH allows a wide acceptance criterion for AI injection depth in upper and lower specification limit (e.g., ± 2mm) based on potential tolerances of component parts suppliers. Minor differences in manual and AI injection depth should not be a critical factor.



Dingding et al, Transport and Lymphatic Uptake of Biotherapeutics Through Subcutaneous Injection, Journal of Pharmaceutical Sciences, Volume 111, Issue 3, 2022

[1] Hu P, Wang J, Florian J, Shatzer K, Stevens AM, Gertz J, Ji P, Huang SM, Zineh I, Wang YC. Systematic Review of Device Parameters and Design of Studies Bridging Biologic-Device Combination Products Using Prefilled Syringes and Autoinjectors. AAPS J. 2020 Feb 27;22(2):52. doi: 10.1208/s12248-020-0433-8. PMID: 32107671. https://pubmed.ncbi.nlm.nih.gov/32107671/

Are Injection Time Differences between PFS and AI Significant Factors for PK?

Position: Comparability of injection time for manually administered mAb (1.0-2.0 mL) PFS vs. AI for SC administration may not raise significant PK questions and an *in vitro* assessment without a PK study might be justified.

Supporting Information:

- Manual administration time depends on a user-specific "comfortable" application of force on the syringe plunger and can vary from 5-10 seconds for a 1 mL PFS.
- AI injection time is more consistent and typically varies (<10 seconds) for 1 mL volume depending on the AI technology.
- There are no studies or data to suggest that different injection times of this duration are a significant factor for BA/BE for typical mAbs where Cmax occurs 5-7 days post-dose. Studies support the case that injection times are insignificant for BE.[1,2]

[1] Portron A, et al. Study to Assess the Effect of Speed of Injection on Pain, Tolerability, and Pharmacokinetics After High-volume Subcutaneous Administration of Gantenerumab in Healthy Volunteers. Clin Ther. 2020;42(1):108-120.e1. doi: 10.1016/j.clinthera.2019.11.015.

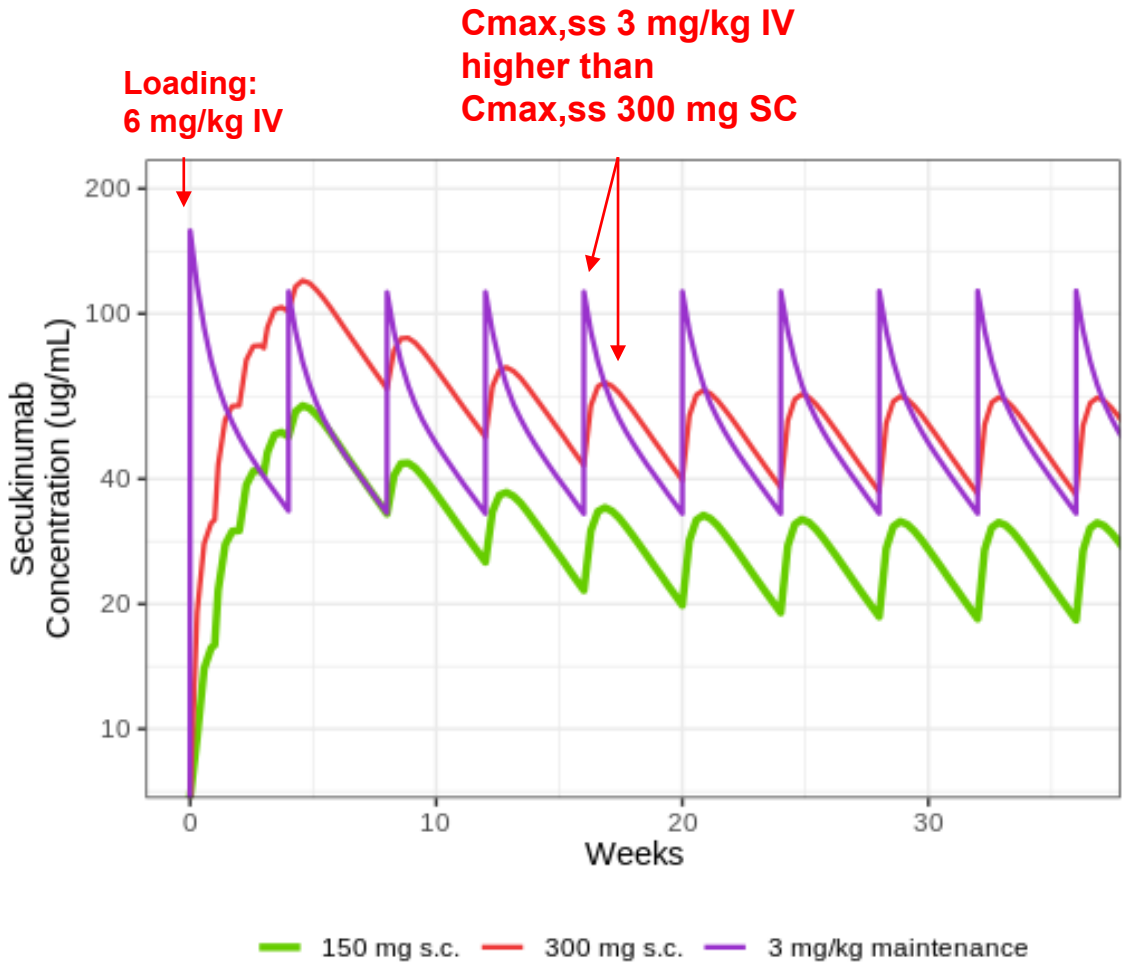
[2] Bruin G, et al. Comparison of pharmacokinetics, safety and tolerability of secukinumab administered subcutaneously using different delivery systems in healthy volunteers and in psoriasis patients. Br J Clin Pharmacol. 2020;86(2):338-351. doi: 10.1111/bcp.14155..

From SC to IV: How to arive at the Right IV Regimen?

Cosentyx, an IL-17A mAb

Brief development history (2019)

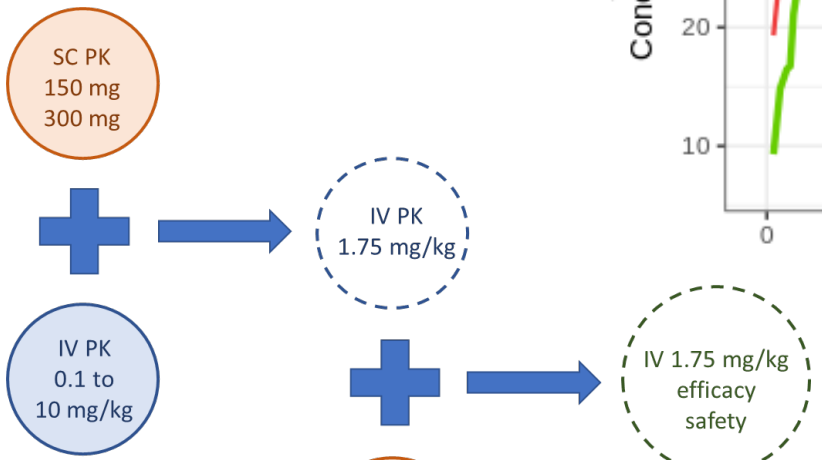
- Cosentyx was approved for doses of 150 mg SC and 300 mg SC in Spondyloarthritis (SpA) (2015)
- Two Phase III studies were conducted to test a new IV regimen (6 mg/kg IV loading, then 3 mg/kg IV, q4w) in SpA
- This regimen was discussed (and we thought agreed!) with FDA
- 2021: The IV studies were positive and confirmed the expected efficacy and safety profile like SC
- But FDA's Pre-BLA feedback:
  "... IV regimen appears to result in higher Cmax ..." and "We are concerned that your IV regimen may not have sufficient information to support the benefit-risk assessment ..., particularly for more rare and latent AEs"
- FDA also hinted at a potential next step using MIDD (Model-Informed Drug Development)



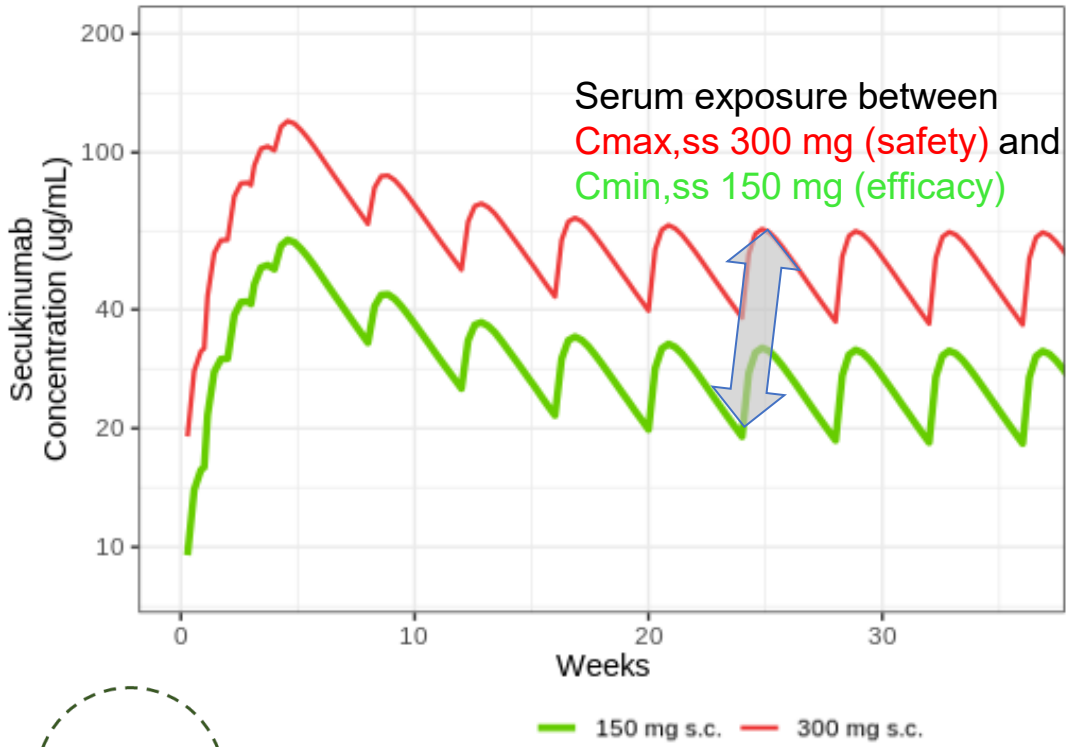
2022 - How can Model Informed Drug Development (MIDD) help our Case?

1. <u>Identification</u> of a new, lower IV regimen that approximates the exposure of the s.c. regimens
2. Extrapolation of the efficacy and safety from the SC regimens to a lower IV regimen on the basis of: Same exposure with IV and SC will lead to same efficacy/safety

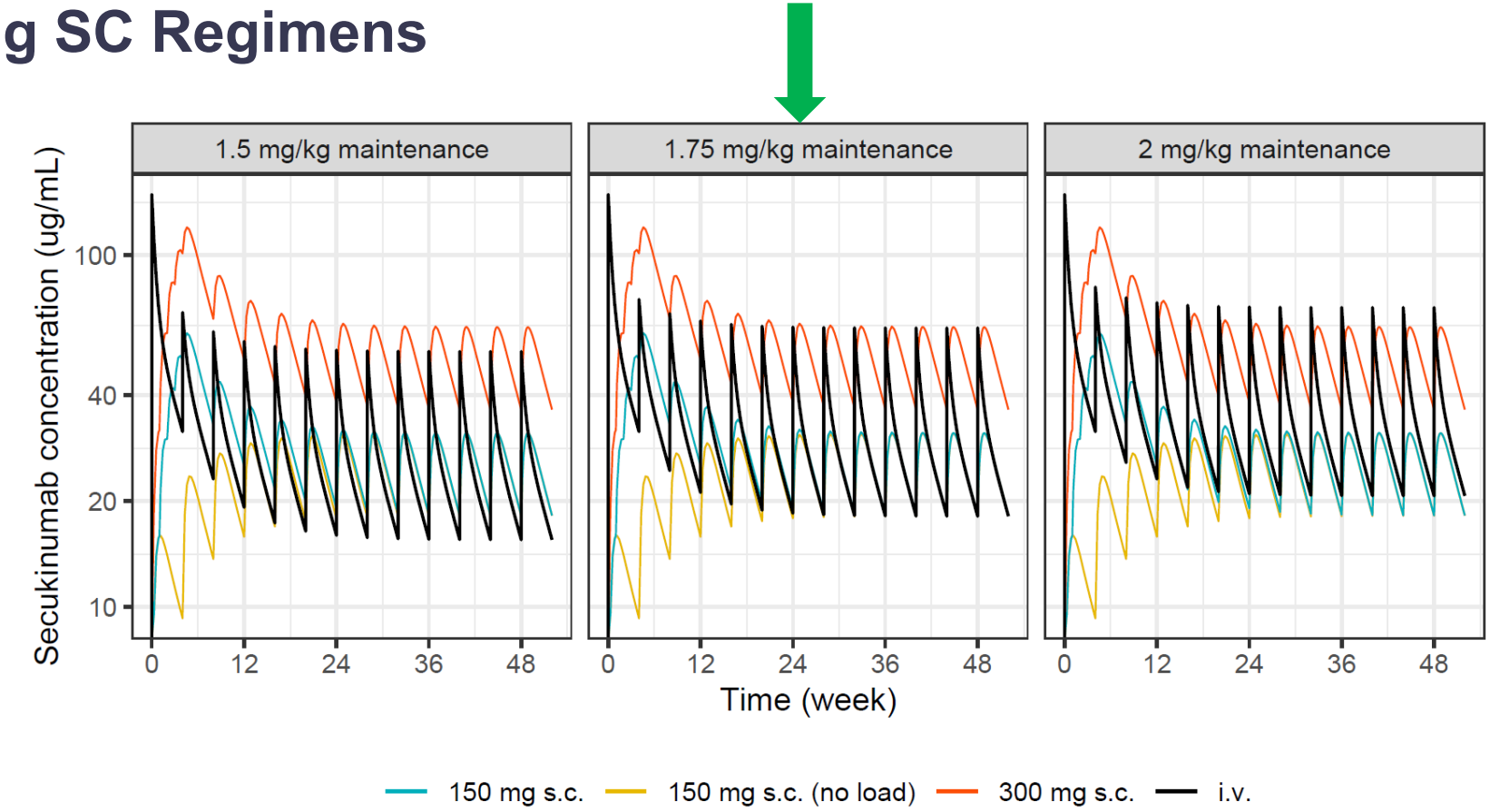
SC PK data available in three indications:
- Psoriatic Arthritis (PsA)
- Ankylosing Spondilytis (AS)
- nonradiographic-axial Spondyloarthritis (nr-axSpA)



IV PK data available in two indications:
- Psoriatic Arthritis (PsA)
- Ankylosing Spondilytis (AS)



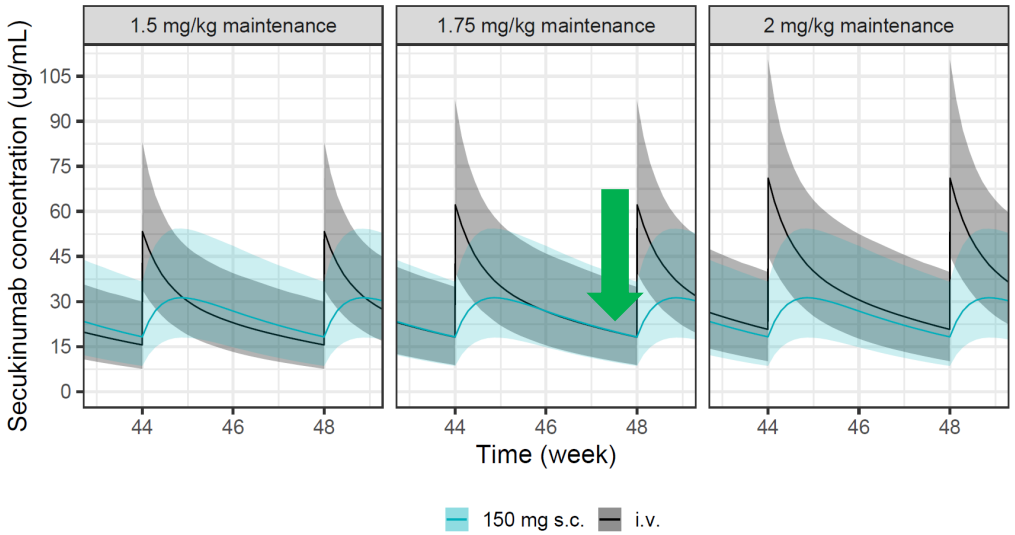
Predicted PK Profiles of three IV Regimens that Approximate the 150 mg and the 300 mg SC Regimens

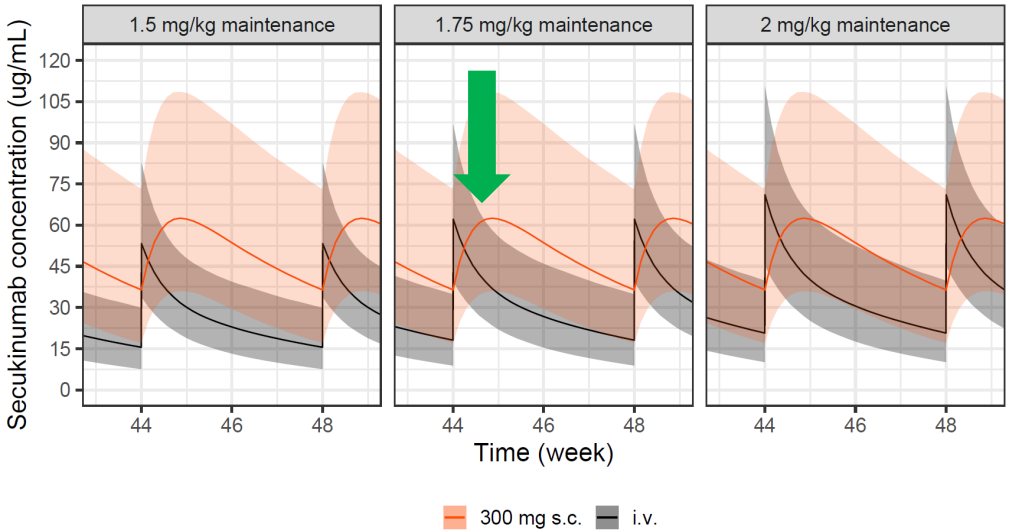


The three IV regimens comprise a 6 mg/kg loading dose at Week 0 followed by a maintenance with 1.5, 1.75, or 2 mg/kg administered q4w starting on Week 4.

The lines represent the median of the secukinumab concentration-time profiles predicted for 3000 PsA and 3000 axSpA subjects for each secukinumab regimen, as obtained from the final popPK model.

Distribution of PK Profiles at Steady-State for three IV regimens and the 150 and 300 mg SC q4w Regimen





The lines represent the median of the secukinumab concentration-time profiles simulated for 3000 PsA and 3000 axSpA subjects for each secukinumab regimen, obtained from the final popPK model. The ribbons correspond to the 90% PI.

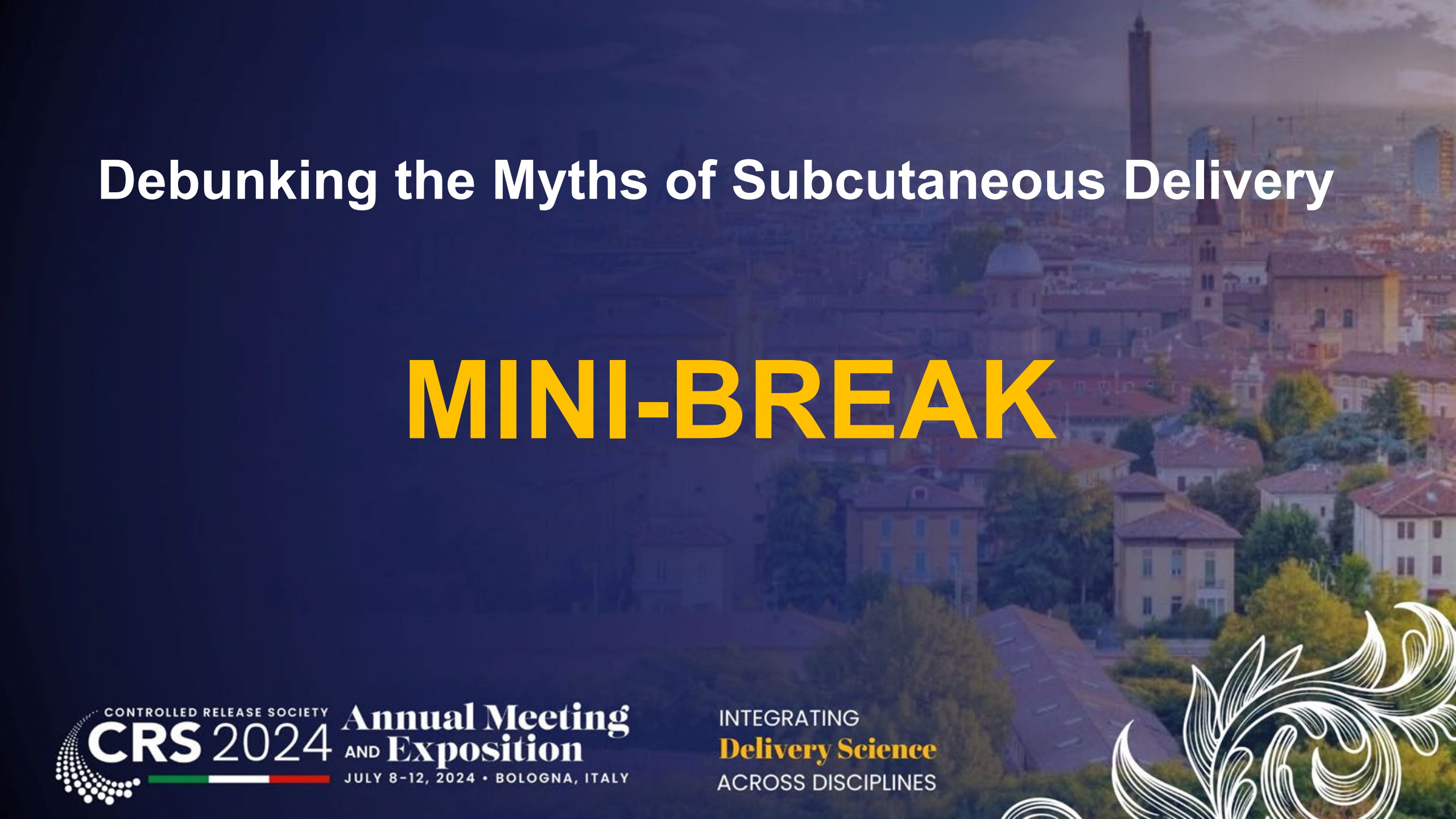
Maintenance regimen	Median (90% PI)		
	Cmin,ss (µg/mL)	Cavg,ss (µg/mL)	Cmax,ss (µg/mL)
1.5 mg/kg i.v. q4w	15.6 (7.6, 29.9)	25.1 (13.7, 45.7)	53.3 (34.0, 83.0)
1.75 mg/kg i.v. q4w	**18.1 (8.9, 34.8)**	**29.2 (16, 53.4)**	**62.1 (39.6, 96.9)**
2 mg/kg i.v. q4w	20.7 (10.2, 39.7)	33.4 (18.2, 61.0)	71.0 (45.3, 110.7)
150 mg s.c. q4w	18.2 (8.6, 36.5)	25.1 (12.3, 50.6)	31.3 (18.0, 54.3)
300 mg s.c. q4w	36.4 (17.2, 73.2)	50.1 (24.6, 101.2)	62.6 (36.1, 108.7)

Conclusions

- Bridging from IV to SC currently involves PK-based dose finding plus assessment of immunogenicity and supporting efficacy in target population in comparatively small Phase 3 studies)
- Bridging to to-be-marketed Drug-Device-Combination-Products might be possible by leveraging historical (PK) data and/or by using platform device technology
- Bridging from SC to IV can be achieved by Phase 1 PK studies or by MIDD approaches
- It can be expected that clinical bridging trials will be smaller and increasingly complemented by MIDD approaches in the future

Debunking the Myths of Subcutaneous Delivery

MINI-BREAK



Round Table Discussions

Myth 1:

- Sylvain Huille (Sanofi)
- Hannie Shih (Eli Lilly)
- David Kang (Halozyme)

Myth 2:

- Nicole Buist (MSD)
- Marie Prinz (Halozyme)

Myth 3:

- Kate Harris (AstraZeneca)
- Marta Venczel (Sanofi)
- Nicole Buist (MSD)
- Manuel Sanchez-Felix (Halozyme)

Myth 4:

- Beate Bittner (Roche)
- Gerard Bruin (Novartis)