Crash Course on High Dose/High Volume Subcutaneous Delivery with Recombinant Human Hyaluronidase (rHuPH20)

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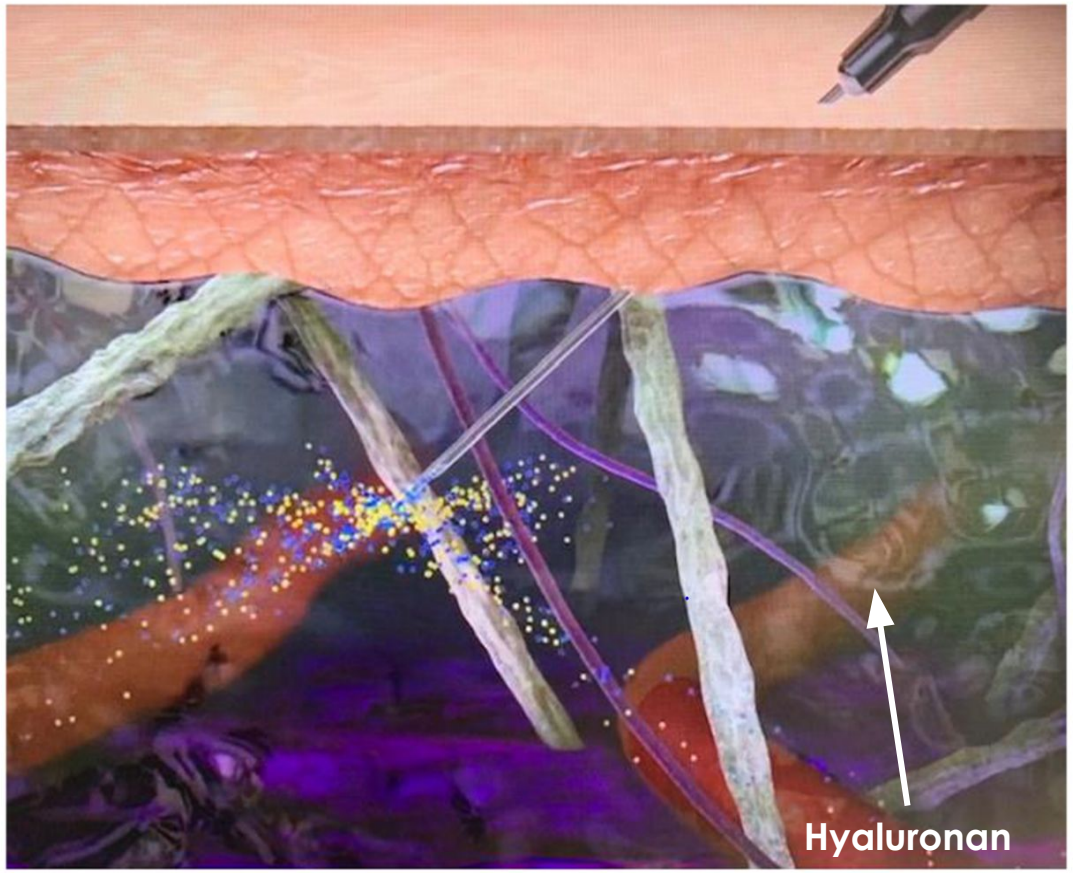
Currently Approved High Dose/High Volume SC Products That Utilize rHuPH20

	Herceptin® SC HERCEPTIN HYLECTA™	MabThera® SC RITUXAN HYCELA®	DARZALEX FASPRO™	PHESGO™	HyQvia®
Volume	• 5 mL	• 11.7 mL FL, DLBCL • 13.4 mL CLL	• 15 ml	• 15 mL (loading) • 10 mL (maintenance)	• 300-600 mL
Administration time	• SC: ~2-5 mins • IV: ~30-90 mins	• SC: 5-7 mins • IV: 1.5-4 hours	• SC: 3 - 5 minutes • IV: 7 hours IV loading dose & 3.4 hours for maintenance dose	• SC: 5 – 8 minutes • IV: ~2.5 hours for sequential IV of loading dose & between 60-150 minutes for maintenance IV dose	• SC: 1-2 hours • IV: 2-3 hours
Dose	• 600 mg • 10,000 U (~100 µg)	• 1,400 mg FL, DLBCL • 1,600 mg CLL • 24,000 – 27,000 U (~240 – ~270 µg)	• 1,800 mg • 30,000 U (~300 µg)	• 1,200 or 600 mg pertuzumab • 600 mg trastuzumab • 20,000 -30,000 U (~200-300 µg)	• 30,000-60,000 mg • 2,400-4,800 U (~24-48 µg)
Put-up	• Co-formulation	• Co-formulation	• Co-formulation	• Co-formulation	• Sequential
Administration site	• Thigh	• Abdomen	• Abdomen	• Thigh	• Abdomen or Thigh
Administration	• HCP	• HCP	• HCP	• HCP	• HCP or Patient
Administration Setting	• Infusion centers	• Infusion centers	• Infusion centers	• In-home or infusion centers	• In-home or infusion centers

Sources:
Product prescribing information (Roche Herceptin EPAR June 2013; Roche MabThera EPAR April 2016; Roche Rituxan Hycela PI 2017; Shire HYQVIA PI 2014; DARZALEX FASPRO PI 2020; PHESGO PI 2020.

Note:

ENHANZE® is a Commercially Validated rHuPH20 Enzyme that Degrades Hyaluronan (HA) in the Subcutaneous Space



What it does:
ENHANZE® creates temporary space for SC fluid dispersion; reduces tissue backpressure

How it works:
ENHANZE® works rapidly, locally and transiently in SC space*; HA is naturally restored in 1 – 2 days

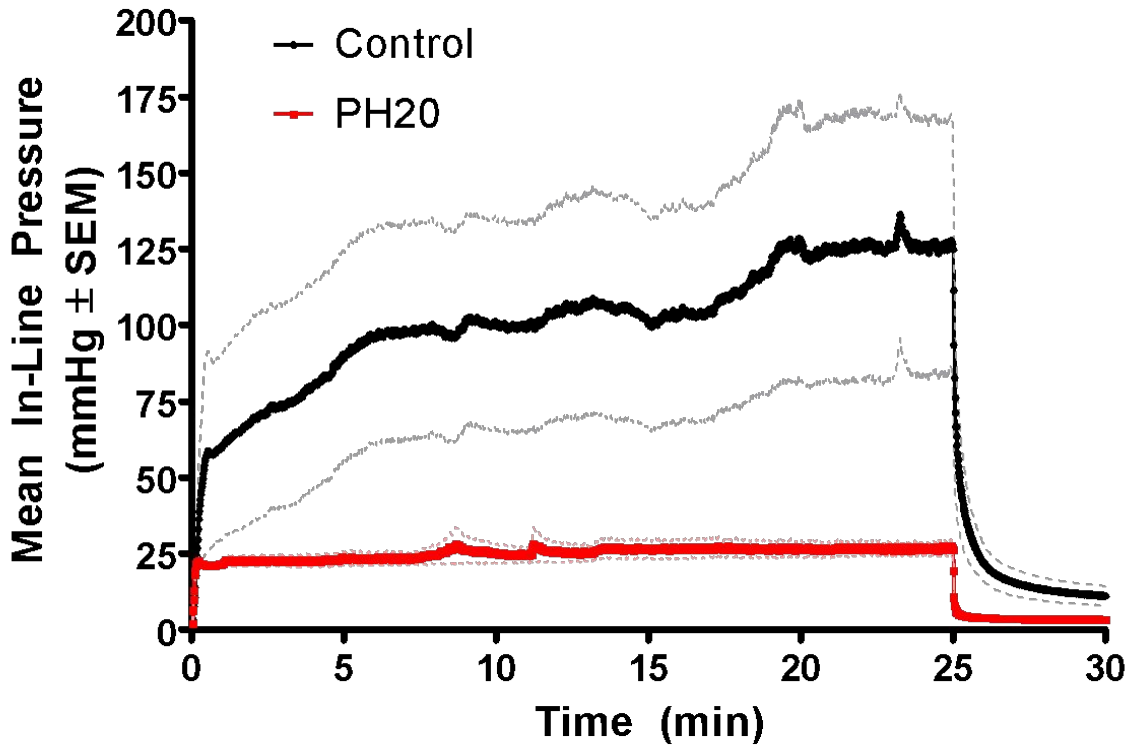
Impact:
ENHANZE® results in less variability in delivery time and increases dispersion and absorption

ENHANZE® facilitates rapid, large volume SC delivery

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

ENHANZE® Significantly Reduces Tissue Back-Pressure and Back-Pressure Variability at the Injection Site

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



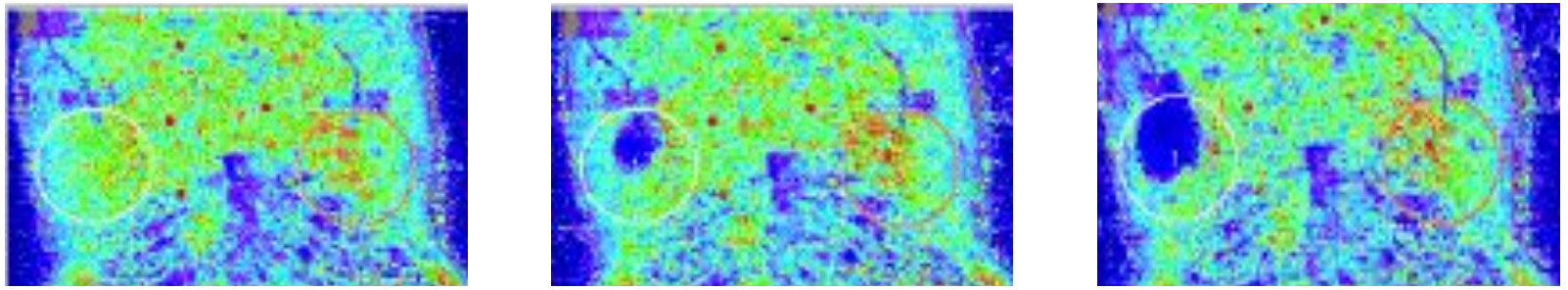
Source: Kang DW, et al. (2012) AAPS-NBC

Source: Halozyme Study Report 16020

Reducing Injection Site Back-Pressure With ENHANZE Reduces Induration (Loss of Cutaneous Blood Flow) and 'Blebbing'

Assessment of Blood Flow by Laser Doppler Imaging

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



	Control	rHuPH20	Control	rHuPH20	Control	rHuPH20
Time:	0 min		10 min		25 min	
Volume:	0 mL		20 mL		50 mL	

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

Photo After Administration of 50 mL of 15% IgG in 25 Minutes

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

rHuPH20 Facilitates Large Volume SC Administration with Minimal Tissue Impact

Injection site swelling after SC administration of 10 mL of 10% IgG Solution with and without rHuPH20

Without rHuPH20

With rHuPH20

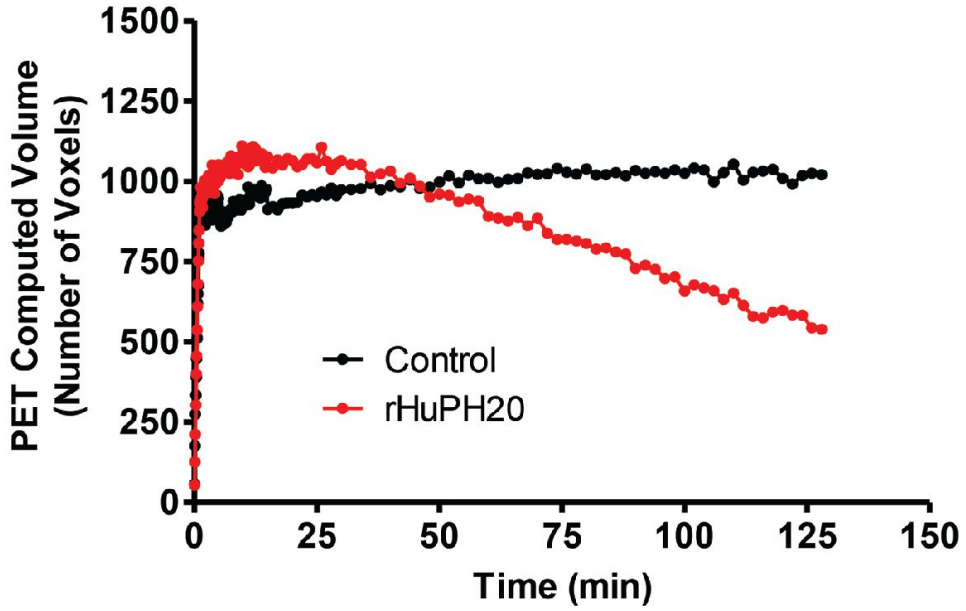
Photos taken immediately post-infusion

Source: Shpilberg O, et al. *Br J Cancer*. 2013;109(6):1556-1561.

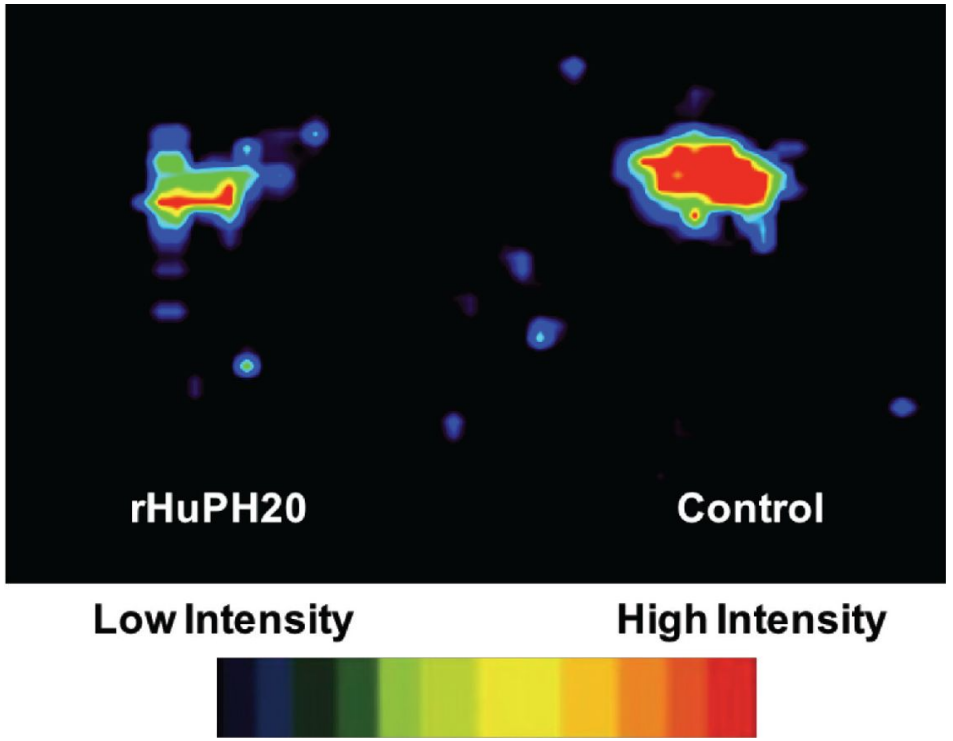
rHuPH20 Decreases Back-Pressure and Induration: Increasing Dispersion and Leading to Decreased Residence Time at the Injection Site

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

PET imaging indicated approximately 40% of the radiolabel was removed from the injection site within the first 2 hours

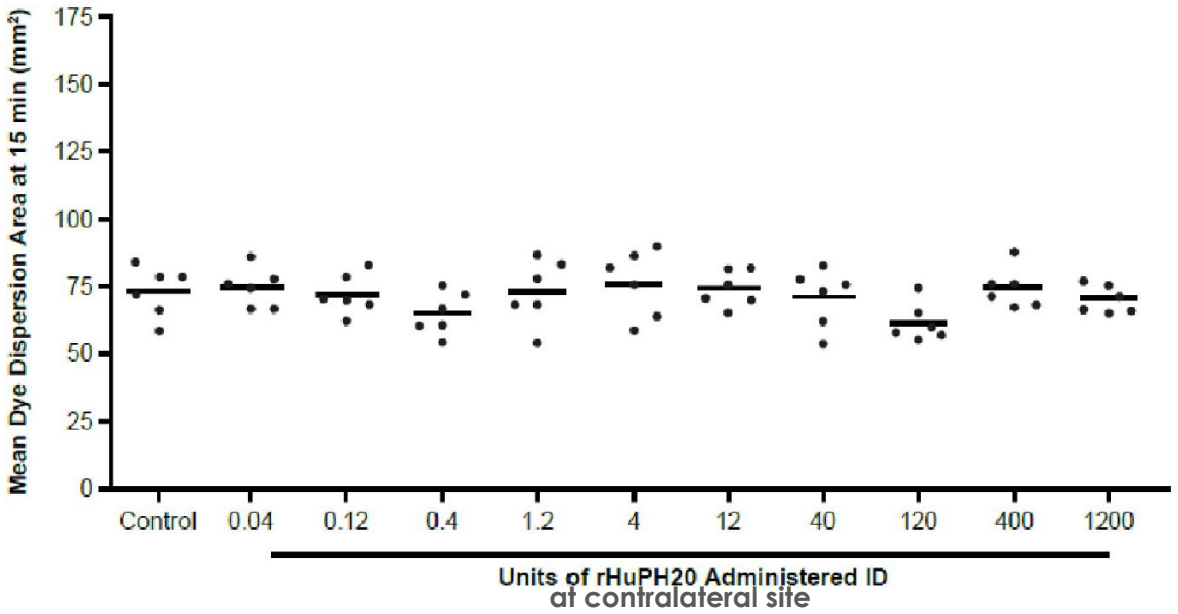


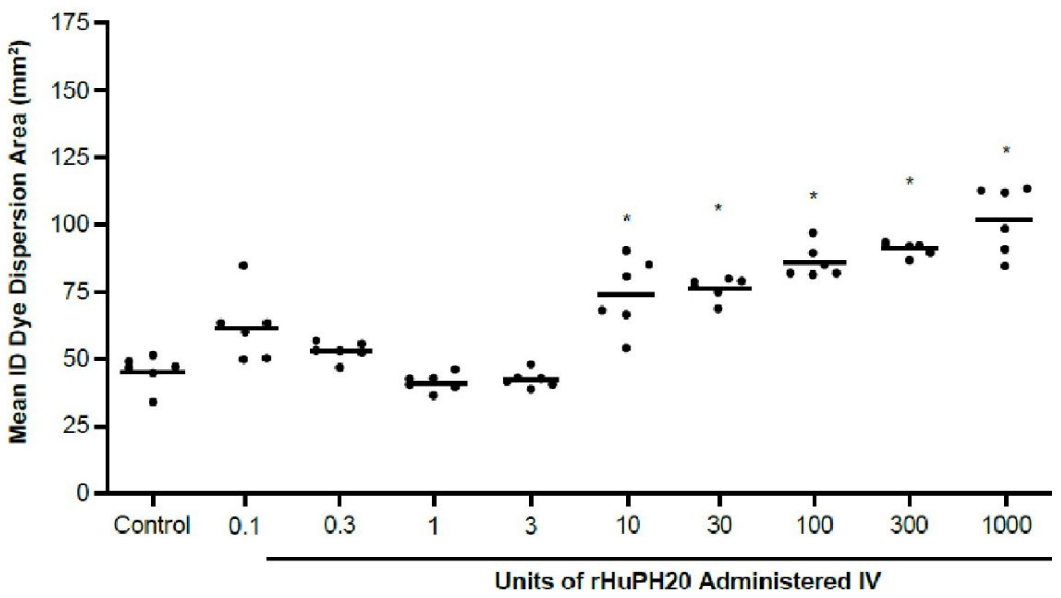
2-hour PET heat map image demonstrates the increased absorption with rHuPH20 as compared to control



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

Effect of rHuPH20 delivered to the skin is local; distant effects are only observed after systemic delivery

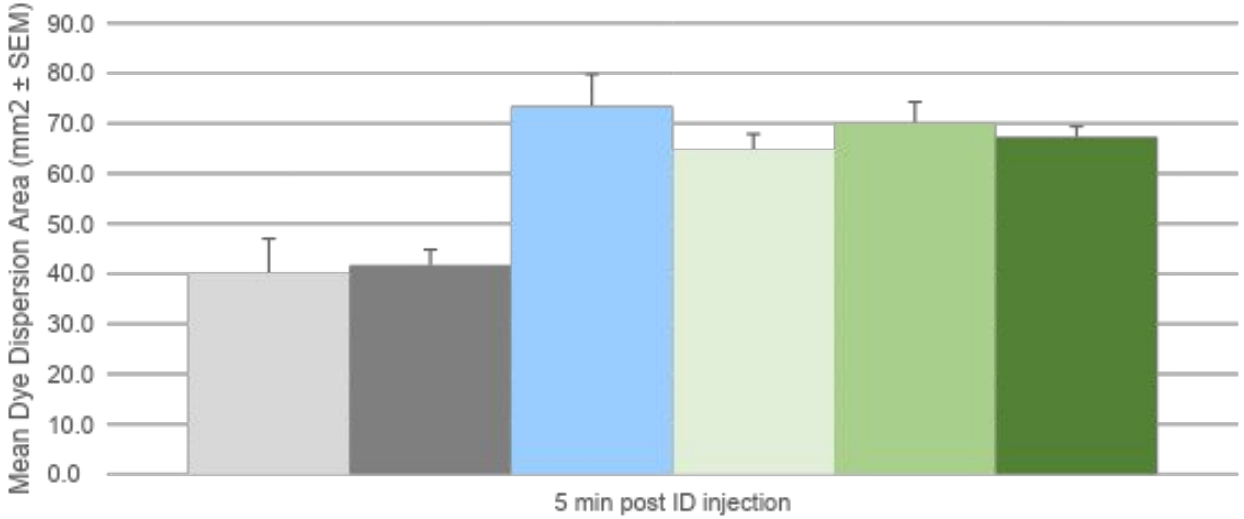




Source: Kang D, et al. *PLOS One*. 2021;16(7):e0254765.

*denotes statistical significance of $p<0.05$ versus control

Systemic delivery of rHuPH20-neutralizing Antibodies (Nab) Does Not Impact the Intradermal Dispersive Activity of rHuPH20



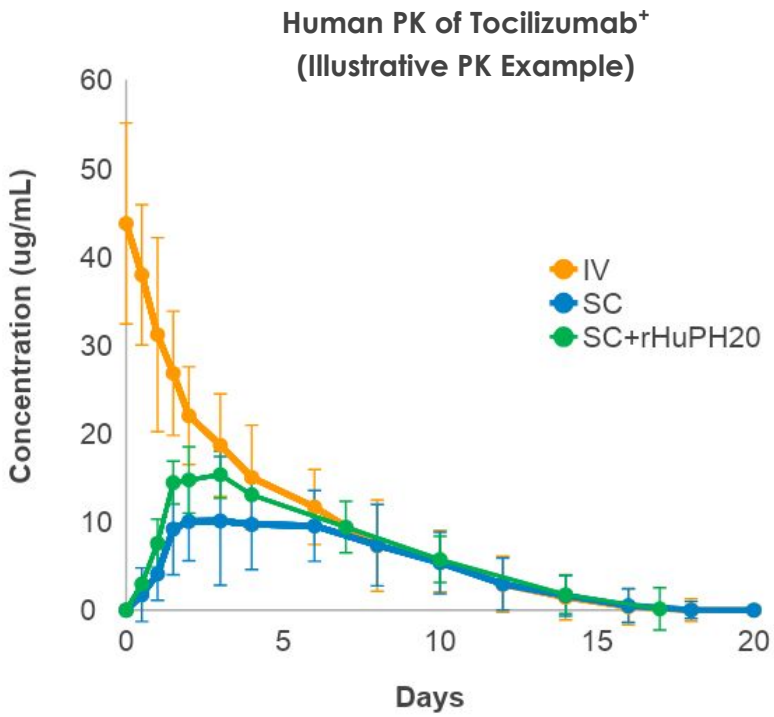
	rHuPH20 Dose (ID)	*Nab Dose (IV), 24h prior*
	0	0
	80 U	37µg co-mixed*
	80 U	0
	80 U	1 µg
	80 U	10 µg
	80 U	100 µg

*directly co-mixed with rHuPH20 prior to ID injection

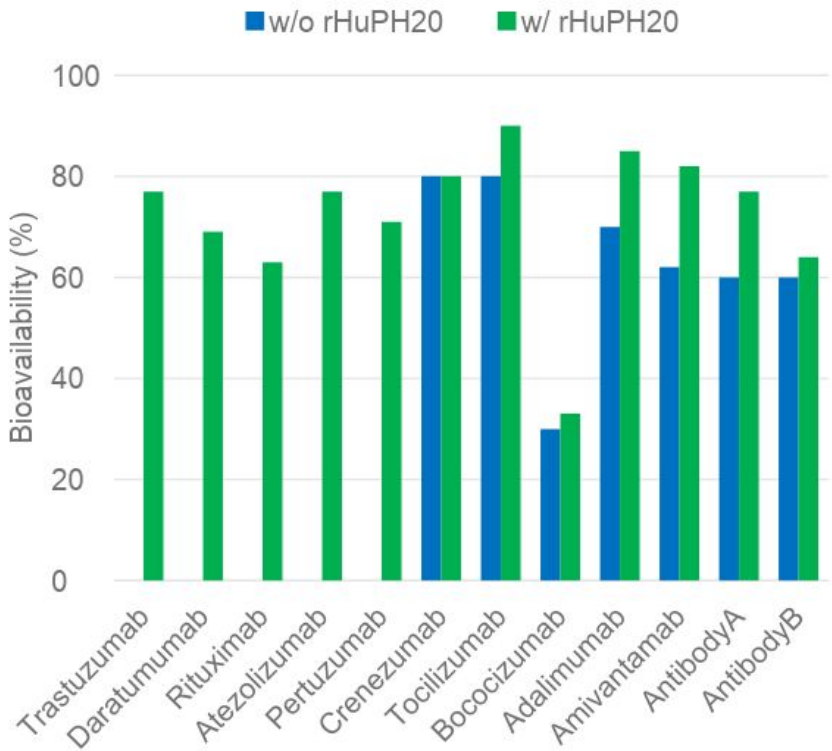
Source: Halozyme Study R09109; model description in Kang D, et al. PLOS One. 2021;16(7):e0254765

ENHANZE® Facilitates SC Dispersion, Absorption, and Bioavailability

rHuPH20 □ k_a of Co-Administered Molecules, Resulting in □ C_{max} and □ T_{max}



Bioavailability of Antibodies Co-Administered with rHuPH20 Average >70%



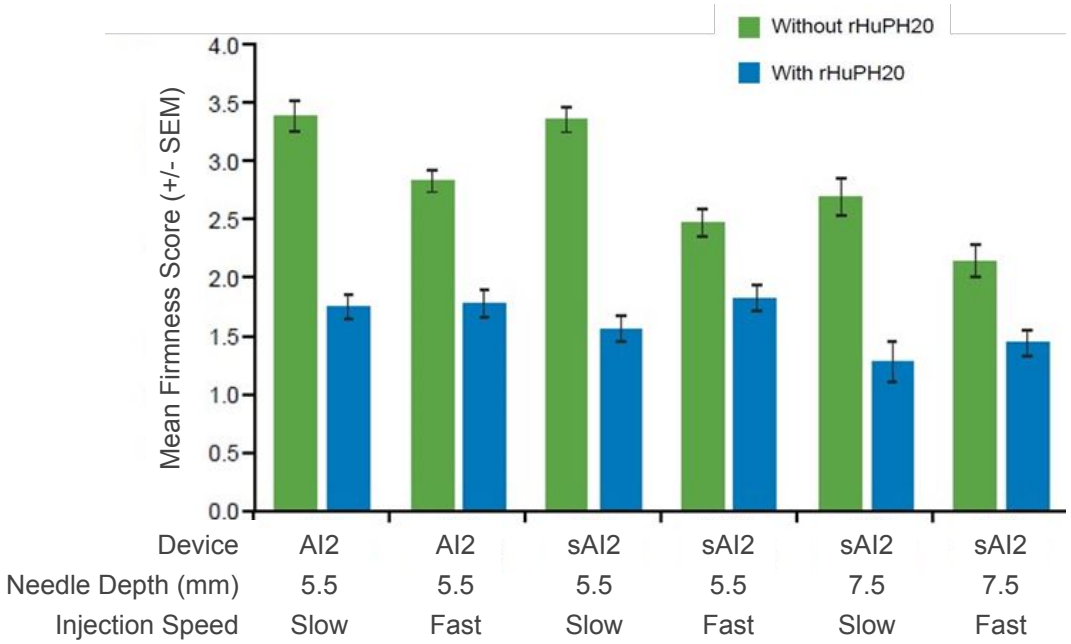
+ Data was digitized from two original manuscripts; the SC condition is similarly represented in both manuscripts but depicted from one for simplicity; all conditions were n = 12 and received a tocilizumab dose = 162 mg

1. Zhang et al, Int J Clin Pharm and Ther. 51: 443-455 (2013); 2. Marcos et al, Int J Clin Pharm and Ther. 51:537-548 (2013)

Bioavailability calculated as a model-fitted parameter from antibody-specific Population PK models, derived from published clinical data

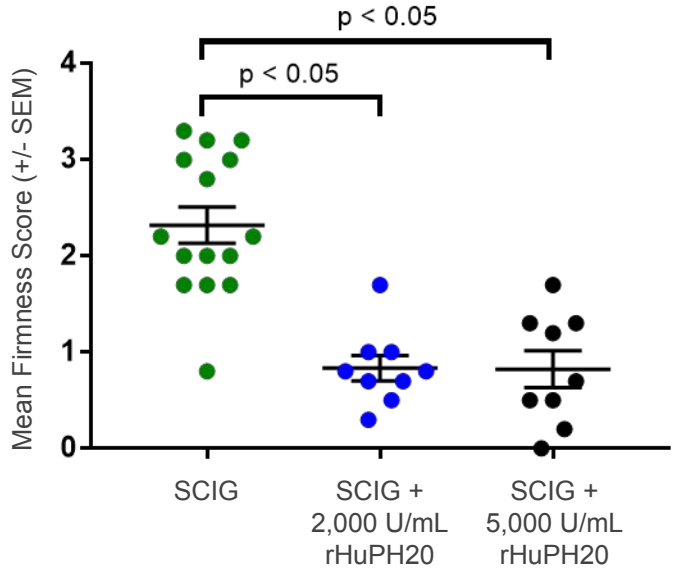
rHuPH20 Decreased Injection Site Firmness and Induration with 2 mL and 10 mL Autoinjectors in Minipig Studies

Minipig model: 2.0 mL of NaCMC solution in 2-mL AIs with different injection speeds and injection depths (Study performed with Lilly)



Source: Shi GH, et al. (2021) DOI: 10.1208/s12249-020-01880-0

Minipig model: 10 mL of 12% IgG delivered at controlled rate of 5 mL/min (Study performed with Kaleo)



Source: Clift et al, (2021) Controlled Release Society Annual Meeting

Questions?