Journal of Diabetes Science and Technology
Volume 4, Issue 2, March 2010

REVIEW ARTICLE

Review of the Mechanism of Action and Clinical Efficacy of Recombinant Human Hyaluronidase Coadministration with Current Prandial Insulin Formulations

Douglas B. Muchmore, M.D., and Daniel E. Vaughn, Ph.D.

Abstract

For patients with type 1 or type 2 diabetes, achieving good glycemic control is critical for successful treatment outcomes. As many patients remain unable to reach glycemic goals with currently available rapid-acting analog insulins, ultrafast insulin products are being developed that provide an even faster pharmacokinetic profile compared with current rapid prandial insulin products. The overall strategy of these ultrafast insulin products is to better mimic the normal physiologic response to insulin that occurs in healthy individuals to further improve glycemic control. Recombinant human hyaluronidase (rHuPH20) is a genetically engineered soluble hyaluronidase approved by the U.S. Food and Drug Administration as an adjuvant to increase the absorption and dispersion of other injected drugs; mammalian hyaluronidases as a class have over 6 decades of clinical use supporting the safety and/or efficacy of hyaluronidase coadministration. Clinical findings have demonstrated that coadministration of rHuPH20 with insulin or an insulin analog achieved faster systemic absorption, reduced inter- and intrapatient variability of insulin absorption, and achieved faster metabolic effects compared with injection of either insulin formulation alone. The magnitude of this acceleration is similar to the incrementally faster absorption of prandial insulin analogs as compared with regular insulin. In addition, coadministration of rHuPH20 with regular insulin or insulin analog also improved the achievement of prandial glycemic targets. Thus, rHuPH20 coadministration shows promise as a method of establishing a more rapid insulin profile to prandial insulin in patients with diabetes and has the potential to yield substantial improvements in postprandial glycemic excursion.

J Diabetes Sci Technol 2010;4(2)419-428

Introduction

The primary goal of insulin therapy is to restore glycemic control [i.e., derived average glucose (A1C) <7%[1] or <6.5%][2,3] as close to normal as practicable by mimicking the time-action profile of physiologic insulin. Postprandial plasma glucose (PPG) is increasingly being recognized as an important factor in reaching this goal,[3] especially as patients approach A1C target values. Indeed, postprandial hyperglycemia contributes the majority of total hyperglycemia for A1C values less than 8.5% and greater than 70% for A1C values less than 7.3%.[4,5] Targets for postprandial glucose control have been established by several professional organizations.

Author Affiliation: Halozyme Therapeutics, Inc., San Diego, California

Abbreviations: (A1C) derived average glucose, (C_{max}) peak plasma concentration, (PK) pharmacokinetics, (PPG) postprandial plasma glucose, (rHuPH20) recombinant human hyaluronidase, (SC) subcutaneous, (t_{max}) time to peak plasma concentration

Keywords: diabetes, glycemic control, hyaluronidase, rHuPH20, ultrafast insulin

Corresponding Author: Douglas B. Muchmore, M.D., Halozyme Therapeutics, Inc., 11388 Sorrento Valley Road, San Diego, CA; email address *dmuchmore@halozyme.com*

The International Diabetes Federation and the American College of Endocrinology recommend that 2-hour postprandial values should be targeted below 140 mg/dl[2,3]; the American Diabetes Association recommends that peak postprandial glucose be targeted below 180 mg/dl.[1]

Current rapid prandial insulin products have faster insulin pharmacokinetics (PK) and insulin action than regular insulin following subcutaneous (SC) injection, especially for low-to-moderate doses (≤0.2 U/kg or ≤16 units; **Table 1**).[6,7] Despite this improvement, most

Table 1.
Euglycemic Glucose Clamp Study Results for Commercial Prandial Insulin Products

Reference	Dose	Insulin exposure (PK, min)			Insulin action (GIR[a], min)		
		Onset (early $t_{50\%}$)	Peak (t_{max})	Offset (late $t_{50\%}$)	Onset (early $t_{50\%}$)	Peak (t_{max})	Offset (late $t_{50\%}$)
Regular insulin							
Rave *et al* 2005[8]	18 U		148		48	193	415
Heinemann *et al* 1998[9]	0.2 U/kg		129		61	156	387
Becker and Frick 2008[6]	0.15 U/kg	53 (early $t_{10\%}$)	104	348 (late $t_{90\%}$)	88 (early $t_{10\%}$)	169	330 (late $t_{90\%}$)
Becker and Frick 2008[6]	0.2 U/kg		82		43	161	306 (late $t_{80\%}$)
Heinemann *et al* 1998[9]	0.2 U/kg		123			165	
Lispro							
Rave *et al* 2005[8]	18 U		148		41	137	313
Vaughn *et al* 2009[10]	20 U	40	98	231	72	193	324
Steiner *et al* 2008[11]	12 U	26	66	170	51	152	295
Rave *et al* 2005[12]	18 U		45		38	136	273
Rave *et al* 2005[12]	12 U		45		38	112	248
Rave *et al* 2005[12]	6 U		45		35	85	184
Heise *et al* 2007[13]	0.2 U/kg	50 (early $t_{10\%}$)	76		87 (early $t_{10\%}$)	171	
Heise *et al* 2007[13]	0.4 U/kg	54 (early $t_{10\%}$)	92		88 (early $t_{10\%}$)	198	
Becker and Frick 2008[6]	0.2 U/kg		58		46	94	228 (late $t_{80\%}$)
Aspart							
Heinemann *et al* 1998[9]	0.2 U/kg		70		41	104	264
Mudaliar *et al* 1999[14]	0.2 U/kg		52			94	
Heinemann *et al* 1998[9]	0.2 U/kg		48			104	
Glulisine							
Becker and Frick 2008[6]	0.15 U/kg	31 (early $t_{10\%}$)	57	205 (late $t_{90\%}$)	45 (early $t_{10\%}$)	114	238 (late $t_{90\%}$)
Becker and Frick 2008[6]	0.2 U/kg		51		34	98	218 (late $t_{80\%}$)
Becker and Frick 2008[6]	0.1 U/kg		44		31	127	
Heise *et al*. 2007[13]	0.2 U/kg	44 (early $t_{10\%}$)	94		83 (early $t_{10\%}$)	190	
Heise *et al* 2007[13]	0.4 U/kg	49 (early $t_{10\%}$)	100		85 (early $t_{10\%}$)	196	

[a] GIR, glucose infusion rate; $t_{50\%}$, time to half-maximal plasma concentration.

patients are still unable to reach glycemic goals even with currently available rapid-acting analog insulins.[15] Ultrafast insulin products are being developed that provide an even more rapid PK profile compared with current rapid prandial insulin products.[10,16,17] For example, an inhaled, dry powder insulin formulation has been developed that has a substantially faster time to peak plasma concentration (t_{max}) vs regular human insulin (12 to 17 minutes vs 2 hours postdose, respectively) and a more rapid return to baseline insulin concentrations (42 to 50 minutes) vs regular insulin (284 minutes).[17] The overall strategy of these ultrafast insulin products is to better mimic the normal physiologic response to insulin that occurs in healthy individuals to provide important clinical benefits in the control of postprandial hyperglycemic excursions. Some of these ultrafast insulin formulations have demonstrated additional benefits, such as reduced weight gain and fewer hypoglycemic events, compared with regular human insulin[18] or rapid-acting insulin analogs.[19–21]

Recombinant human hyaluronidase (rHuPH20) is approved by the U.S. Food and Drug Administration for administration as an adjuvant to increase the absorption and dispersion of other injected drugs.[22] This genetically engineered enzyme lacks the C-terminal membrane-anchoring domain, rendering it soluble.[23] A proof-of-concept study in which healthy volunteers were administered rHuPH20 with or without regular human insulin or insulin analog demonstrated an acceleration of PK profiles for both insulin formulations.[10] Coadministration of rHuPH20 increased the peak plasma concentration (C_{max}) by 90% for insulin lispro and 142% for regular insulin and reduced the t_{max} by 51% for insulin lispro and 58% for regular insulin. In addition, coadministration of rHuPH20 reduced the intersubject variability for various PK and glucodynamic measures.[10] These faster PK results with rHuPH20 coadministration were confirmed and extended in two additional healthy volunteer studies[24–26] and during a meal study in patients with type 1 diabetes.[27] Results of the meal study demonstrated that the faster PK parameters reduced postmeal glycemic response without an increased risk of hypoglycemia.[27]

The overall objectives of this review are to highlight the unmet needs even with the availability of current rapid-acting prandial products, to provide an overview of the history of hyaluronidase use and its mechanism of action in accelerating the absorption of coinjected drugs, and to review the emerging clinical pharmacology profile of prandial insulins coadministered with hyaluronidase.

Benefits and Limitations of Current Rapid-Acting Prandial Insulins

As summarized from a number of different studies, data shown in **Table 2** demonstrate that rapid-acting insulin analogs reduce postprandial hyperglycemia relative to regular insulin injected at the same time.[16,28–33] These data also illustrate the impact of dose timing on glycemic response, such that in most cases, regular insulin administered approximately 30 to 60 minutes prior to a meal resulted in postprandial hyperglycemia comparable with rapid-acting analogs dosed 0 to 15 minutes before a meal.

However, these findings also demonstrate the limitations of current therapeutic offerings. Even with optimal dose timing in controlled laboratory settings, clinical targets for postprandial control are not met consistently. In the "real-world" setting, control of postprandial hyperglycemia is more challenging due to variations in dietary intake, insulin dose and timing, fear of hypoglycemia, and physical activity.[34] For example, it may be tempting for patients to dose prandial insulin immediately before meals to simplify lifestyle impacts of insulin treatment. Overall, clinical studies evaluating patient adherence to treatment and self-management of diabetes have consistently demonstrated the need for improvement, specifically with regard to self-monitoring, diet, and exercise.[15]

Enhanced Absorption through Hyaluronidase Coadministration

Mechanism of Action of Hyaluronidase

Hyaluronidase catalyzes the cleavage of the β1,4 linkage between *N*-acetylglucosamine and glucuronic acid residues of the hyaluronan long chain polymer,[35] and this breakdown of hyaluronan by hyaluronidase in the subcutaneous space results in enhanced permeation of coadministered agents.[22,36] The rHuPH20 acts as a permeation enhancer and rapidly increases the dispersion of coinjected molecules in a dose-dependent manner (**Figure 1A**).[23] Because rHuPH20 is rapidly metabolized locally without systemic exposure[36] and hyaluronan has a rapid turnover (i.e., one-third of the total body pool of 15 grams turns over daily),[23] the permeation effects of rHuPH20 and hyaluronidase are transient (i.e., reconstitutes within 6 to 25 hours; **Figure 1B).** Thus, both PH20 residence time and biochemical effects are transient and local, factors that suit it well for frequent and long-term use (as would be required for a prandial insulin product). Additionally, a favorable safety profile for rHuPH20 is supported by animal toxicology evaluations.[36]

Table 2.
Meal Challenge Study Results for Prandial Insulin Products[a]

Study population	Test article	Dose	Meal content	Dose timing	PK t_{max} (min)	Glucose excursion (min*mg/dl)	Peak PPG (mg/dl)	Reference
T1DM	Regular Aspart	Not specified[b]	Three meals plus three snacks daily (kcal and CHO content not specified)	At meal At meal	90 45	5,620 1,190	230 175	Wiefels *et al.* 1993[37]
T1DM	Regular Regular Aspart	0.15 U/kg	535 kcal (CHO content not specified)	At meal -30 min At meal	98 80 40	23,600 19,900 16,000	295 261 243	Lindholm *et al.* 1999[33]
T1DM	Regular Regular Aspart Aspart	Mean Dose 9 U (6–12)	543 kcal (55% CHO)	At meal -15 min At meal +15 min	ND ND ND ND	19,300 14,700 12,900 15,300	254 239 202 238	Brunner *et al.* 2000[28]
T1DM	Regular Regular Glulisine Glulisine	0.15 U/kg	618 kcal (99 g CHO)	At meal -30 min At meal +15 min	97 82 55 57	46,200 42,900 42,500 46,600	209 177 180 208	Rave *et al.* 2006[29]
T1DM	Regular Lispro Lispro + PH20	Mean dose 6 U (2–18)	12 oz Ensure (60 g CHO)	At meal At meal At meal	116 49 30	9,620 6,520 4,430	190 174 148	Hompesch *et al.* 2009[27]
T1DM	Regular Lispro	0.2 U/kg	"High" CHO	-30 to -45 min -30 to -45 min	ND ND	ND ND	250 (1 h) 232 (1 h)	Insulin lispro prescribing information[30]
T1DM	Aspart or lispro Aspart or lispro + heat	0.15 U/kg	Boost (80 g CHO)	At meal At meal	78 45	15,700 (180 min) 11,520 (180 min)	74 (90 min) 121 (90 min)	Raz *et al.* 2009[16]
T2DM	Regular Regular Aspart	0.15 U/kg	2000 kcal (85 g CHO)	At meal -30 min At meal	90 82 62	19,800 15,600 16,200	216 200 194	Rosenfalck *et al.* 2000[31]
T2DM	Regular Aspart	0.15 U/kg	633 kcal (83 g CHO)	-30 min At meal	105 70	18,300 14,600	238 225	Perriello *et al.* 2005[32]
TD2M	Inhaled insulin Aspart	198 U 88 IU	ND	At meal At meal	ND	ND	171 (1 h) 209 (1 h)	Gnudi *et al.* 2009[19]

[a] CHO, carbohydrate; ND, not determined; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.
[b] Study was performed with preparations of insulin formulations at a concentration of 100 U/ml. Patients were administered their individual basal rate of insulin formulation via pump delivery to reach a fasting blood glucose concentration below 7 mmol/liter (126 mg/dl).

History of Hyaluronidase Administration

Over 60 years of clinical use support the safety and/or efficacy of hyaluronidase coadministration with a variety of injected drugs.[10,23,38–42] The clinical safety and tolerability of hyaluronidase, which was first reported by Burket and Gyorgy in 1949,[38] have been established further with over 6 decades of use.[10,23,39–42] Clinical history demonstrates the increased dispersion and faster absorption of a broad range of drugs and fluids administered with hyaluronidase products.[10,23,38–44] With rHuPH20, for example, Thomas and colleagues[45,46] have demonstrated an accelerated PK profile of SC morphine coadministered with rHuPH20 compared with SC morphine alone, with earlier and greater peak exposure and comparable total bioavailability. Similarly, administration of rHuPH20 significantly enhanced gravity-driven SC infusion flow rates of fluid and electrolytes compared with placebo, leading the authors to suggest the possibility of using hyaluronidase-enabled SC infusions as replacements for pump-driven intravenous fluid therapy.[40]

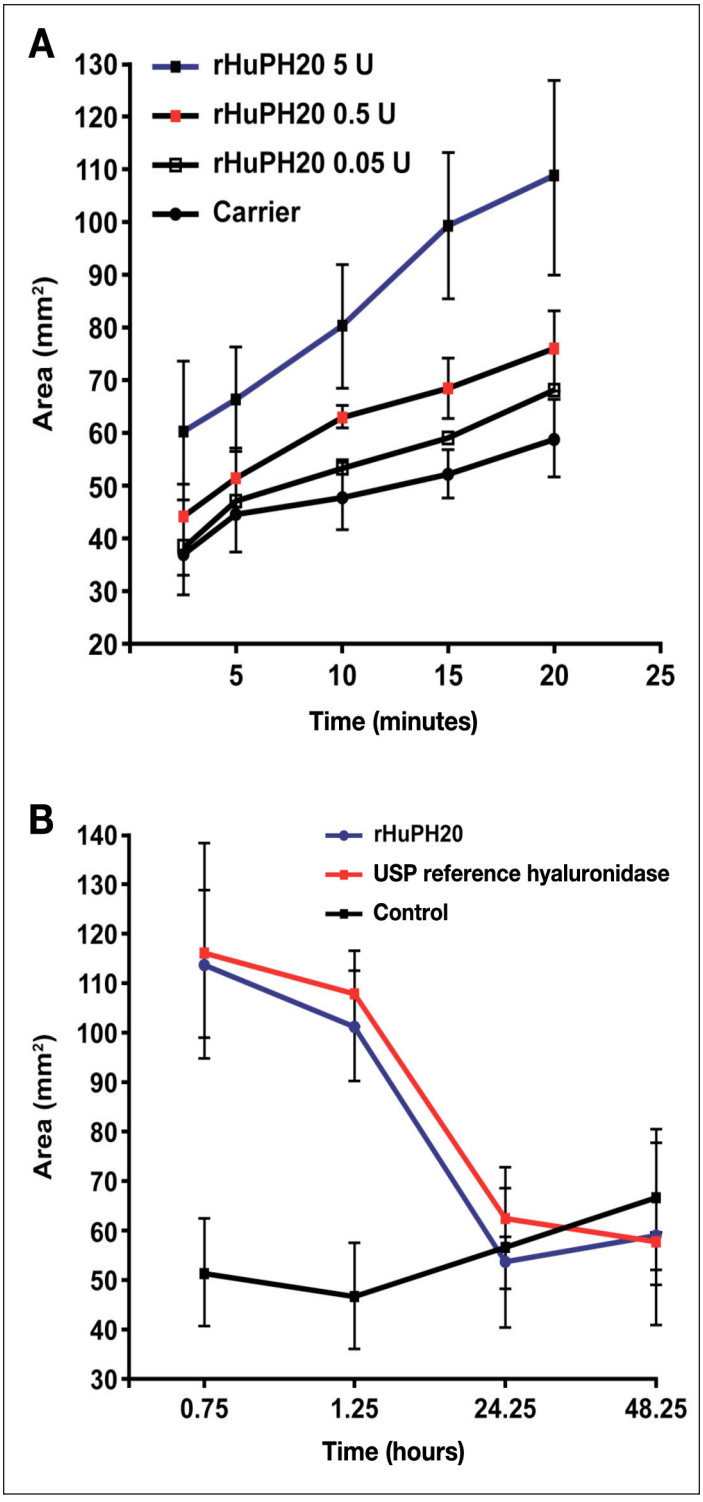

Figure 1. Recombinant human hyaluronidase acts as a potent, reversible spreading factor *in vivo*. **(A)** Trypan blue dye in mice (50 µl) was coinjected locally with rHuPH20 (5.0, 0.5, or 0.005 units) or carrier control. **(B)** Recombinant human hyaluronidase (5 units) or United States Pharmacopeia hyaluronidase (5 units) was injected in the skin of mice followed by injection of trypan blue dye at the same site from 0.5 to 48 hours later. The effects of rHuPH20 were reversed by 24-hour postinjection. Reprinted with permission from Bookbinder and colleagues.[23]

In keeping with the favorable safety profile of hyaluronidase as a class, rHuPH20 is well tolerated with a broad safety margin in a number of preclinical models.[36] Yocum and colleagues[47] assessed the sensitivity of healthy individuals to a single dose of rHuPH20 in a single-center, double-blind, placebo- and within-subject-controlled study. No allergic reactions (defined as occurrence of wheal with pseudopods within 5 minutes of injection that persisted for at least 20 minutes and was accompanied by localized itching) were observed among the 100 individuals who received a single intradermal injection of rHuPH20 (i.e., 0% allergic reaction rate).[47] The incidence of any symptom of discomfort was significantly higher for saline compared with rHuPH20 (28% vs 3%, respectively; $P < 0.0001$), primarily because of stinging after saline injection (13%) compared with rHuPH20 (1%). The authors concluded that the higher incidence of discomfort related to injection of saline vs rHuPH20 was likely related to the rapid action of rHuPH20 as a spreading agent, effectively reducing the pressure required to inject the test agent. Taken together, observations of multiple studies highlight the potential uses and benefits of hyaluronidase administration in the clinical setting.

Effect of rHuPH20 on Insulin Absorption and Action

Mechanisms Underlying Absorption Kinetics of Subcutaneously Administered Insulin

Because most commercial drug formulations of insulin are predominately hexameric, insulin absorption is driven by the processes of both dissociation and diffusion.[48] Insulin hexamers are too large to be absorbed across capillary walls and must dissociate into dimers or monomers before absorption can occur.[48,49] Spontaneous dissociation of insulin occurs at low concentrations via equilibrium shift. In a traditional subcutaneous injection, insulin absorption is diffusion limited; insulin hexamers must first diffuse away from the site of injection to dissociate and become available for absorption.[41] Thus, the absorption of insulin is affected by both insulin concentration and dose (**Figure 2**).[48] High concentrations and high doses are absorbed more slowly because of diffusion limitations.

Hyaluronidase acts as a spreading factor by rapidly digesting high-molecular weight hyaluronan, increasing bulk fluid flow away from the site of injection by about 20-fold.[17,30] Administration of rHuPH20 promotes rapid depolymerization of hyaluronan in the extracellular space to achieve rapid dilution of insulin to low concentrations

that favor hexamer dissociation, which ultimately increases the rate of insulin absorption.[10,23] Thus, administration of rHuPH20 has the potential to reduce concentration- and dose-mediated limitations imposed on standard insulin formulations. The net effect is to accelerate the absorption of insulin with increased peak insulin exposure (C_{max}) without significantly affecting overall insulin exposure (total area under the curve).[10] In addition to the promotion of hexamer dissociation, rHuPH20 accelerates absorption by the general hyaluronidase mechanism of dispersing the drug over a larger capillary bed, which improves absorption flux.[23]

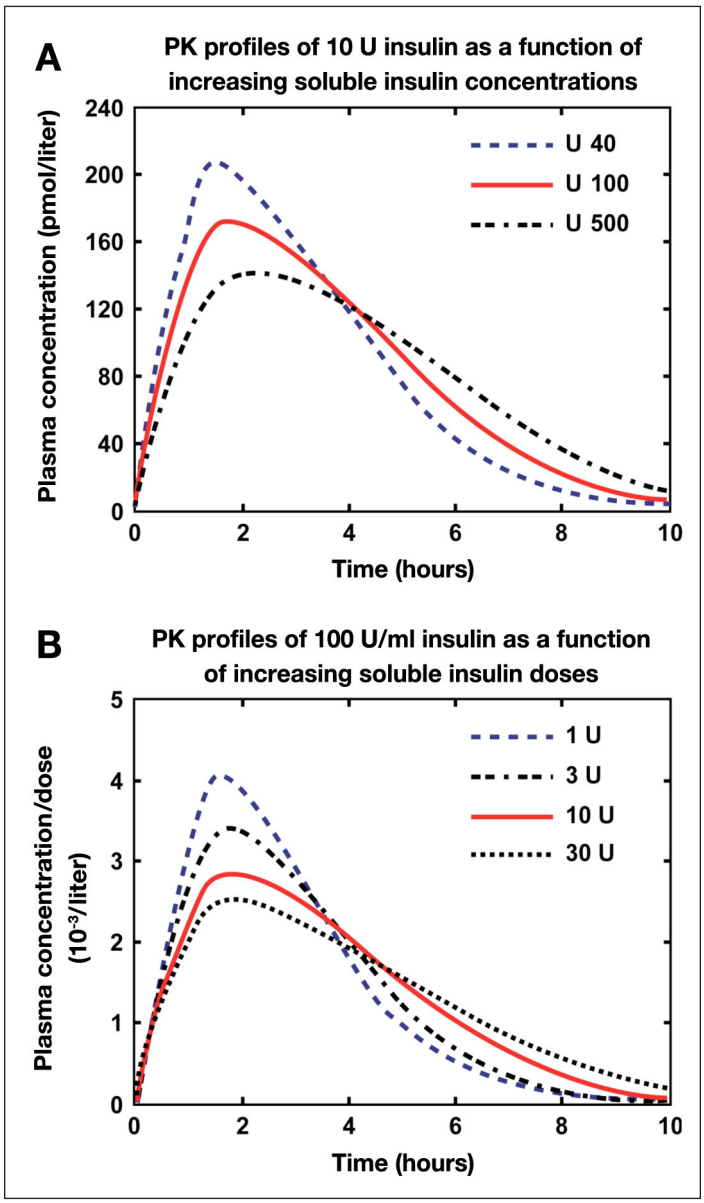

Figure 2. Diffusion-limited absorption is nonlinear such that higher insulin concentrations **(A)** and higher insulin doses **(B)** are absorbed more slowly. Reprinted with permission from Søeborg and colleagues.[48]

Clinical Pharmacology Studies

A phase 1, glucose-clamp study compared the insulin time-concentration profile (PK) and glucodynamics of insulin lispro and regular human insulin administered with or without rHuPH20 to healthy volunteers **(Table 3)**.[10] Coadministration of rHuPH20 substantially increased the rate and peak level (C_{max}) of absorption of both insulin formulations compared with either agent alone. Although requiring a comparison across cohorts, coadministration with rHuPH20 appeared to produce an acceleration of a magnitude comparable to the faster absorption of the rapid insulin analog relative to regular insulin. Similarly, rHuPH20 coadministration resulted in accelerated glucose metabolism compared with either formulation alone. The acceleration of insulin absorption and insulin action has been confirmed and extended in two subsequent healthy volunteer studies.[24–26]

In the original healthy volunteer study, it also was observed that rHuPH20 greatly reduced the intersubject variability of important PK and glucodynamic parameters, which suggested the possibility that hyaluronidase coinjection may also reduce intrasubject variability.[10] To test this hypothesis, a second healthy volunteer study was conducted in 20 subjects, each receiving two doses each of three study drugs: insulin + PH20, lispro + PH20, or lispro alone. Coadministration with rHuPH20 significantly reduced the intrasubject variability of early insulin exposure and the timing of insulin absorption.[26]

The dose-normalized PK responses to regular insulin and insulin lispro with and without rHuPH20 were compared in separate studies of healthy volunteers and patients with type 1 diabetes (**Figure 3**). The high doses of insulin lispro (without rHuPH20) administered in the healthy volunteer study resulted in a lower dose-normalized C_{max} than that observed with the lower doses of insulin administered in the meal study in patients with type 1 diabetes. However, when rHuPH20 was administered with insulin lispro in these studies, the dose-normalized C_{max} values were comparable, suggesting that coadministration of rHuPH20 may attenuate this dose-dependent nonproportionality in PK responses. This effect was further studied in a third healthy volunteer study conducted over multiple dose cohorts. The first two stages were used to examine the dose–response effect of increasing rHuPH20 concentrations on the absorption of regular insulin and insulin lispro, which was found to be accelerated over a wide concentration range (0.3 to 80 μg/ml), with an optimum

Table 3.
Pharmacokinetics and Glucose Infusion Rate Parameters for Prandial SC Insulin Products under Development

Reference	Dose	Insulin exposure			Insulin action		
		Onset (early $t_{50\%}$)	Peak (t_{max})	Offset (late $t_{50\%}$)	Onset (early $t_{50\%}$)	Peak (t_{max})	Offset (late $t_{50\%}$)
Regular insulin							
	≤16 U (0.2 U/kg)	~45 min	~2 h	4–5 h	~1 h	~2.5 h	~6 h
Vaughn *et al.* 2009[10]	20 U	47 min	163 min	279 min	104 min	253 min	>360 min
Steiner *et al.* 2008[18]	12 U	37 min	120 min	260 min	66 min	193 min	357 min
Rapid-acting analogs							
	≤16 U (0.2 U/kg)	~30 min	45–60 min	~3 h	30–40 min	~2 h	~4 h
	>20 U	~45 min	1.5 h	~4 h	75–90 min	~3 h	5–6 h
Vaughn *et al.* 2009[10]	20 U	40 min	98 min	231 min	72 min	193 min	324 min
Halozyme[50]	0.15 U/kg	25 min	55 min	144 min	61 min	99 min	157 min
Steiner *et al.* 2008[18]	12 U	26 min	66 min	170 min	51 min	152 min	295 min
Lispro + PH20							
Vaughn *et al.* 2009[10]	20 U	26 min (66%)[a]	48 min (49%)	110 min (48%)	44 min (61%)	114 min (59%)	275 min (85%)
Halozyme[50]	0.15 U/kg	14 min (57%)	40 min (72%)	88 min (61%)	43 min (70%)	72 min (73%)	119 min (76%)
Viaject							
Steiner *et al.* 2008[18]	12 U	18 min (69%)	60 min (91%)	181 min (107%)	33 min (65%)	136 min (89%)	280 min (95%)
Steiner *et al.* 2008[18]	6 U	7 min	51 min	145 min	35 min	115 min	270 min
Steiner *et al.* 2008[18]	3 U	12 min	54 min	126 min	31 min	111 min	297 min
Inhaled insulin							
Rave *et al.* 2009[17]	25 U 50 U 100 U	ND[b]	12 min 15 min 17 min	45 min 42 min 50 min	ND	42 min 50 min 58 min	ND

[a] Values in parentheses represent percentage of control.
[b] Not determined.

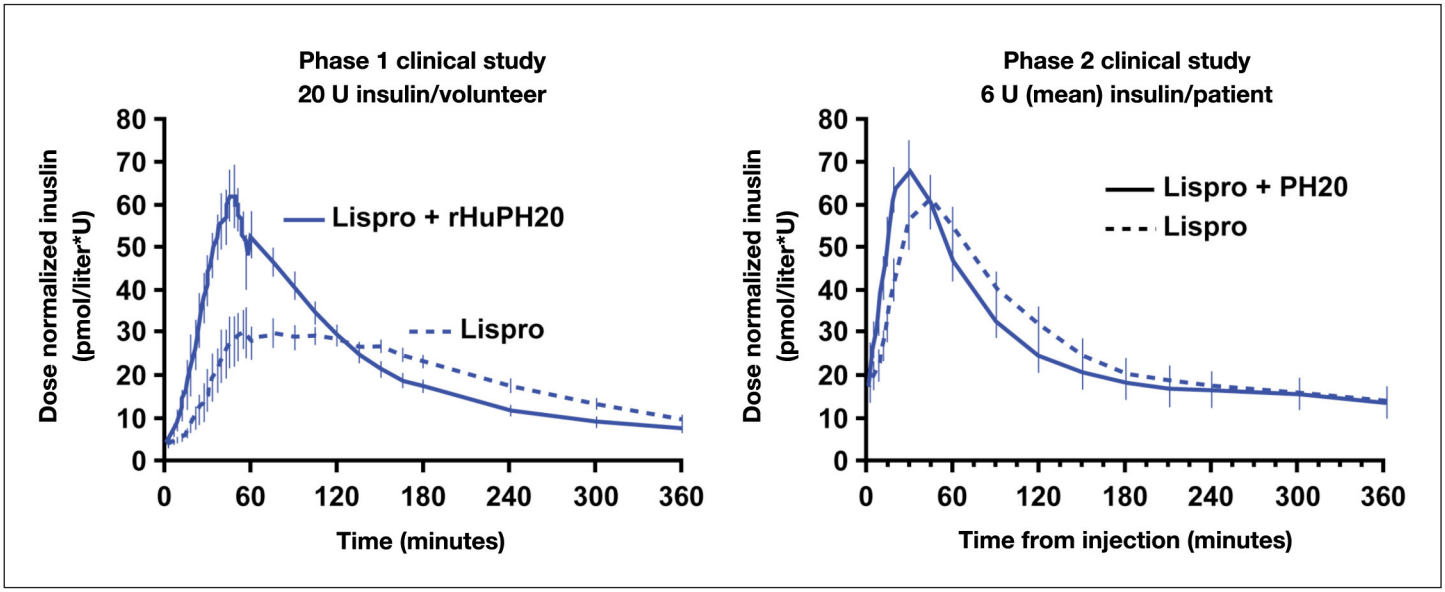

Figure 3. Coadministration of rHuPH20 with insulin lispro suppressed nonlinearity of insulin PK with insulin dose in separate studies of healthy volunteers (each receiving a 20-unit dose) and patients with type 1 diabetes (each receiving individualized dose); *y* axis values normalized to per unit of insulin administered.

effect at or about 5 μg/ml.[24] The second two stages demonstrated that a fixed ratio of rHuPH20 to insulin (5 μg rHuPH20/100 units insulin) accelerated insulin absorption and action over clinically relevant doses of insulin lispro (2 to 20 units) and regular insulin (6 to 24 units). Over these ranges, greater insulin doses showed slower rates of early insulin absorption, and this effect was generally reduced (but not eliminated) with rHuPH20 coadministration.[25]

To examine how the accelerated insulin absorption impacts control of postprandial glucose excursions, a phase 2, within-patient, single-blind, crossover standardized test meal study was conducted in patients with type 1 diabetes (N = 21).[27] Insulin PK and glucose response to a liquid meal was measured after injection of regular human insulin or insulin lispro with or without coadministration of rHuPH20. As observed previously in healthy volunteers, coadministration of rHuPH20 accelerated the absorption of regular insulin and insulin lispro in patients with type 1 diabetes **(Figure 4)**. Coadministration of rHuPH20 with insulin lispro or regular insulin also improved the achievement of glycemic targets, such that mean peak PPG levels were reduced from 190 to 166 mg/dl with regular insulin (P = 0.017) and from 174 to 148 mg/dl with insulin lispro (P = 0.002). Thus, the 24- to 26-mg/ml reduction in peak PPG levels for coadministration of either insulin with rHuPH20 was meaningful relative to the 16-mg/dl reduction in peak PPG with lispro compared with regular insulin. Postprandial hypoglycemic excursions were generally mild and overall hypoglycemic risk was comparable for insulin lispro with or without rHuPH20,

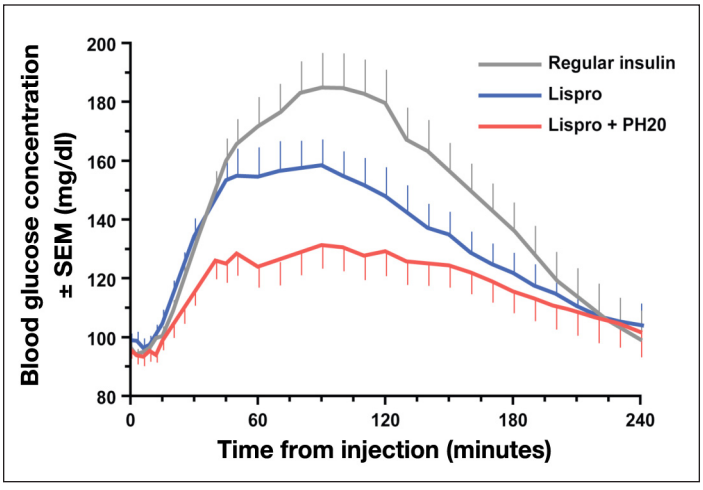

Figure 4. Pharmacodynamic findings of meal time study in patients with type 1 diabetes demonstrated that coadministration of rHuPH20 improved achievement of glycemic targets.[27]

and coadministration of regular insulin with rHuPH20 reduced postprandial hypoglycemia risk compared with regular insulin alone. Based on these findings, the authors concluded that a coformulation of insulin with rHuPH20 may benefit patients with diabetes by decreasing postmeal hyperglycemic excursions without increasing the risk for hypoglycemia.

The addition of rHuPH20 to insulin lispro and regular insulin has been well tolerated and no severe or serious adverse events were observed in any of these four clinical studies. Additional clinical studies also have reported the overall safety and tolerability of rHuPH20 coadministration with other agents.[40–42] It should be noted that there is no long-term, repeat dose exposure to rHuPH20 data available; an ongoing 3-month × 3-month crossover study comparing regular insulin–PH20 to insulin lispro in 48 type 1 diabetic subjects did not uncover any safety or tolerability signals at the time of an interim safety analysis among the 22 subjects receiving regular insulin–PH20 (data not shown); longer term data in larger numbers of subjects will be needed to better address this question.

Conclusions

Coadministration of rHuPH20 with insulin or an insulin analog was well tolerated and accelerated insulin absorption by a magnitude similar to the accelerated absorption of rapid analogs relative to regular insulin. Recombinant human hyaluronidase reduced the variability of intrasubject and intersubject insulin PK and reduced the delay in absorption seen for higher doses of insulin. This genetically engineered soluble hyaluronidase shows promise as a method of establishing a more rapid insulin profile to prandial insulin, which leads to more physiologically appropriate responses to prandial nutrient challenge. This more rapid insulin absorption resulted in improved control of postprandial glucose excursions in a liquid meal challenge. Control of postprandial plasma glucose levels is critical to achieving target glycemic goals and providing successful treatment outcomes for patients with diabetes.[4,5] In this regard, coadministration of rHuPH20 has the potential to result in substantial improvements in postprandial glycemic control.

Funding:

The preparation of this article was sponsored by Halozyme Therapeutics, San Diego, California.

Disclosure:

Douglas B. Muchmore and Daniel E. Vaughn are employees of Halozyme Therapeutics.

Acknowledgment:

Professional medical writing and editing services were provided by Advogent Group, Inc.

References:

1. Standards of medical care in diabetes--2008. Diabetes Care. 2008;31 Suppl 1:S12-54.
2. American college of endocrinology consensus statement on guidelines for glycemic control. Endocr Pract. 2002;8 Suppl 1:5-11.
3. International Diabetes Federation. Guideline for management of postmeal glucose. Brussels, Belgium: International Diabetes Federation; 2007.
4. Woerle HJ, Neumann C, Zschau S, Tenner S, Irsigler A, Schirra J, Gerich JE, Göke B. Impact of fasting and postprandial glycemia on overall glycemic control in type 2 diabetes. Importance of postprandial glycemia to achieve target HbA1c levels. Diabetes Res Clin Pract. 2007;77(2):280-5.
5. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diabetes Care. 2003;26(3):881-5.
6. Becker RH, Frick AD. Clinical pharmacokinetics and pharmacodynamics of insulin glulisine. Clin Pharmacokinet. 2008;47(1):7-20.
7. Lindholm A, Jacobsen LV. Clinical pharmacokinetics and pharmacodynamics of insulin aspart. Clin Pharmacokinet. 2001;40(9):641-59.
8. Rave K, Bott S, Heinemann L, Sha S, Becker RH, Willavize SA, Heise T. Time-action profile of inhaled insulin in comparison with subcutaneously injected insulin lispro and regular human insulin. Diabetes Care. 2005;28(5):1077-82.
9. Heinemann L, Weyer C, Rauhaus M, Heinrichs S, Heise T. Variability of the metabolic effect of soluble insulin and the rapid-acting insulin analog insulin aspart. Diabetes Care. 1998;21(11):1910-4.
10. Vaughn DE, Yocum RC, Muchmore DB, Sugarman BJ, Vick AM, Bilinsky IP, Frost GI. Accelerated pharmacokinetics and glucodynamics of prandial insulins injected with recombinant human hyaluronidase. Diabetes Technol Ther. 2009;11(6):345-52.
11. Steiner S, Hompesch M, Pohl R, Simms P, Flacke F, Mohr T, Pfützner A, Heinemann L. A novel insulin formulation with a more rapid onset of action. Diabetologia. 2008;51(9):1602-6.
12. Rave KM, Nosek L, de la Peña A, Seger M, Ernest CS 2nd, Heinemann L, Batycky RP, Muchmore DB. Dose response of inhaled dry-powder insulin and dose equivalence to subcutaneous insulin lispro. Diabetes Care. 2005;28(10):2400-5.
13. Heise T, Nosek L, Spitzer H, Heinemann L, Niemoller E, Frick AD, Becker RH. Insulin glulisine: a faster onset of action compared with insulin lispro. Diabetes Obes Metab. 2007;9(5):746-53.
14. Mudaliar SR, Lindberg FA, Joyce M, Beerdsen P, Strange P, Lin A, Henry RR. Insulin aspart (B28 asp-insulin): a fast-acting analog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. Diabetes Care. 1999;22(9):1501-6.
15. Davies M. The reality of glycaemic control in insulin treated diabetes: defining the clinical challenges. Int J Obes Relat Metab Disord. 2004;28 Suppl 2:S14-22.
16. Raz I, Weiss R, Yegorchikov Y, Bitton G, Nagar R, Pesach B. Effect of a local heating device on insulin and glucose pharmacokinetic profiles in an open-label, randomized, two-period, one-way crossover study in patients with type 1 diabetes using continuous subcutaneous insulin infusion. Clin Ther. 2009;31(5):980-7.
17. Rave K, Potocka E, Boss AH, Marino M, Costello D, Chen R. Pharmacokinetics and linear exposure of AFRESA compared with the subcutaneous injection of regular human insulin. Diabetes Obes Metab. 2009;11(7):715-20.
18. Steiner S, Pfutzner A, Sethi B, Forst T, Klonoff D, Simms P, Pohl R, Flacke F. Insulin viaject and regular human insulin in patients with type 2 diabetes: efficacy and safety in an open-label multicenter clinical trial [abstract]. 44th Annual Meeting of the European Association for the Study of Diabetes; 2008 Sep 7-11; Rome, Italy.
19. Gnudi L, Lorber D, Rosenstock J, Howard C, Petrucci R, Shearer D, Bilheimer D, Chang PC, Kramer D, Richardson PC. Basal/bolus with prandial inhaled Technosphere insulin plus insulin glargine vs biaspart 70/30 insulin in type 2 diabetes inadequately controlled on insulin with/without oral agents [abstract]. Diabetologia. 2009;52 Suppl 1:S360.
20. Lorber D, Howard C, Ren H, Rossiter A, Boss A. Reduced incidence and frequency of hypoglycaemia in an integrated analysis of pooled data from clinical trials of subjects with type 2 diabetes using prandial inhaled Technosphere insulin [abstract]. Diabetologia. 2009;52 Suppl 1:S360.
21. Howard C, Ren H, Rossiter A, Boss A. Reduced incidence and frequency of hypoglycaemia in an integrated analysis of pooled data from clinical trials of subjects with type 1 diabetes using prandial inhaled Technosphere insulin [abstract]. Diabetologia. 2009;52 Suppl 1:S386-7.
22. Hylenex (hyaluronidase human injection)[product information]. Deerfield, IL: Baxter Healthcare Corporation; 2009.
23. Bookbinder LH, Hofer A, Haller MF, Zepeda ML, Keller GA, Lim JE, Edgington TS, Shepard HM, Patton JS, Frost GI. A recombinant human enzyme for enhanced interstitial transport of therapeutics. J Control Release. 2006 ;114(2):230-41.
24. Vaughn D, Muchmore D, Gee L, Ludington E. Dose response of recombinant human hyaluronidase effects on pharmacokinetics of regular human insulin and insulin lispro following SC injection [abstract]. Proceedings from the Biennial Congress of the International Diabetes Federation; 2009 Oct 18-22; Montreal, QC, Canada.
25. Vaughn D, Gee L, Ludington E, Muchmore D. Improved dose proportionality of insulin lispro injected with hyaluronidase. Proceedings from the Diabetes Technology Society Meeting; 2009 Nov 5-7; San Francisco, CA.
26. Muchmore D, Morrow L, Ludington E, Vaughn D, Hompesch M. Reduced variability of insulin lispro injected with hyaluronidase. Proceedings from the Diabetes Technology Society Meeting; 2009 Nov 5-7; San Francisco, CA.
27. Hompesch M, Muchmore D, Morrow L, Mongiovi D, Vaughn D. Accelerated insulin pharmacokinetics and improved glycemic control in T1DM patients by coadministration of prandial insulin with recombinant human hyaluronidase [abstract]. Annual Scientific Sessions of the American Diabetes Association; 2009 Jun 5-9; New Orleans, LA.
28. Brunner GA, Hirschberger S, Sendlhofer G, Wutte A, Ellmerer M, Balent B, Schaupp L, Krejs GJ, Pieber TR. Post-prandial administration of the insulin analogue insulin aspart in patients with Type 1 diabetes mellitus. Diabet Med. 2000;17(5):371-5.
29. Rave K, Klein O, Frick AD, Becker RH. Advantage of premeal-injected insulin glulisine compared with regular human insulin in subjects with type 1 diabetes. Diabetes Care. 2006;29(8):1812-7.
30. Humalog [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.

31. Rosenfalck AM, Thorsby P, Kjems L, Birkeland K, Dejgaard A, Hanssen KF, Madsbad S. Improved postprandial glycaemic control with insulin Aspart in type 2 diabetic patients treated with insulin. Acta Diabetol. 2000;37(1):41-6.

32. Perriello G, Pampanelli S, Porcellati F, Avogaro A, Bosi E, Petrella G, Squatrito S, Furneri S, Marra G, Vitali L, Previti M, Cucinotta D. Insulin aspart improves meal time glycaemic control in patients with Type 2 diabetes: a randomized, stratified, double-blind and cross-over trial. Diabet Med. 2005;22(5):606-11.

33. Lindholm A, McEwen J, Riis AP. Improved postprandial glycemic control with insulin aspart. A randomized double-blind cross-over trial in type 1 diabetes. Diabetes Care. 1999;22(5):801-5.

34. Ramchandani N, Cantey-Kiser JM, Alter CA, Brink SJ, Yeager SD, Tamborlane WV, Chipkin SR. Self-reported factors that affect glycemic control in college students with type 1 diabetes. Diabetes Educ. 2000;26(4):656-66.

35. Chain E, Duthie ES. Identity of hyaluronidase and spreading factor. Br J Exp Pathol. 1940;21:324-38.

36. Frost GI. Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration. Expert Opin Drug Deliv. 2007;4(4):427-40.

37. Wiefels K, Kuglin B, Hubinger A, Jorgensen LN, Gries FA. Insulin kinetics and dynamics in insulin-dependent diabetic patients after injections of human insulin or the insulin analogues X14 and X14 + Zn. In: Berger M, Gries FA, editors. Frontiers in insulin pharmacology. New York: Thieme Medical Publishers, Inc.; 1993. p. 97-101.

38. Burket LC, Gyorgy P. Clinical observations on the use of hyaluronidase. Pediatrics. 1949;3(1):56-63.

39. Schwartzman J. Hyaluronidase; a review of its therapeutic use in pediatrics. J Pediatr. 1951;39(4):491-502.

40. Thomas JR, Yocum RC, Haller MF, von Gunten CF. Assessing the role of human recombinant hyaluronidase in gravity-driven subcutaneous hydration: the INFUSE-LR study. J Palliat Med. 2007;10(6):1312-20.

41. Remy M, Pinter F, Nentwich MM, Kampik A, Schonfeld CL. Efficacy and safety of hyaluronidase 75 IU as an adjuvant to mepivacaine for retrobulbar anesthesia in cataract surgery. J Cataract Refract Surg. 2008;34(11):1966-9.

42. Khandwala M, Ahmed S, Goel S, Simmons IG, McLure HA. The effect of hyaluronidase on ultrasound-measured dispersal of local anaesthetic following sub-Tenon injection. Eye. 2008;22(8):1065-8.

43. Forbes GB, Deisher RW. Effect of hyaluronidase on the subcutaneous absorption of electrolytes in humans. Science. 1950;111(2877):177-9.

44. Lipschitz S, Campbell AJ, Roberts MS, Wanwimolruk S, McQueen EG, McQueen M, Firth LA. Subcutaneous fluid administration in elderly subjects: validation of an under-used technique. J Am Geriatr Soc. 1991;39(1):6-9.

45. Thomas JR, Wallace MS, Yocum RC, Vaughn DE, Haller MF, Flament J. The INFUSE morphine study: use of recombinant human hyaluronidase (rHuPH20) to enhance the absorption of subcutaneously administered morphine in patients with advanced illness. J Pain Symptom Manage. 2009;38(5):663-72.

46. Thomas JR, Yocum RC, Haller MF, Flament J. The INFUSE-Morphine IIB study: use of recombinant human hyaluronidase (rHuPH20) to enhance the absorption of subcutaneous morphine in healthy volunteers. J Pain Symptom Manage. 2009;38(5):673-82.

47. Yocum RC, Kennard D, Heiner LS. Assessment and implication of the allergic sensitivity to a single dose of recombinant human hyaluronidase injection: a double-blind, placebo-controlled clinical trial. J Infus Nurs. 2007;30(5):293-9.

48. Søeborg T, Rasmussen CH, Mosekilde E, Colding-Jorgensen M. Absorption kinetics of insulin after subcutaneous administration. Eur J Pharm Sci. 2009;36(1):78-90.

49. Supersaxo A, Hein WR, Steffen H. Effect of molecular weight on the lymphatic absorption of water-soluble compounds following subcutaneous administration. Pharm Res. 1990;7(2):167-9.

50. Data on file. San Diego, CA: Halozyme Therapeutics; 2009.