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SYMPOSIUM

Accelerating and Improving the Consistency of Rapid-Acting Analog Insulin Absorption and Action for Both Subcutaneous Injection and Continuous Subcutaneous Infusion Using Recombinant Human Hyaluronidase

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Abstract

Rapid-acting insulin analogs were introduced to the market in the 1990s, and these products have improved treatment of diabetes by shortening the optimum delay time between injections and meals. Compared with regular human insulin, rapid-acting insulin formulations also reduce postprandial glycemic excursions while decreasing risk of hypoglycemia. However, the current prandial products are not fast enough for optimum convenience or control.

Recombinant human hyaluronidase (rHuPH20) has been used to increase the dispersion and absorption of other injected drugs, and in the case of prandial insulin analogs, it confers both ultrafast absorption and action profiles. Animal toxicology studies have demonstrated excellent tolerability of rHuPH20, and human studies, involving over 60,000 injections of prandial insulin + rHuPH20 to date, have similarly shown excellent safety and tolerability. Studies using rapid-acting analog insulin with rHuPH20 have included clinic-based pharmacokinetic and glucodynamic euglycemic glucose clamp studies, test meal studies, and take-home treatment studies. Administration methods have included subcutaneous injection of coformulations of rapid-acting insulin + rHuPH20 as well as continuous subcutaneous infusion of coformulations or use of pretreatment of newly inserted infusion sets with rHuPH20 followed by standard continuous subcutaneous insulin infusion therapy.

These studies have demonstrated acceleration of insulin absorption and action along with improvement in postprandial glycemic excursions and reduction in hypoglycemia risks. Further, rHuPH20 reduces intrasubject variability of insulin absorption and action and provides greater consistency in absorption and action profiles over wear time of an infusion set. Further studies of rHuPH20 in the take-home treatment setting are underway.

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Abbreviations: (AUC) area under the curve, (CSII) continuous subcutaneous insulin infusion, (FDA) Food and Drug Administration, (rHuPH20) recombinant human hyaluronidase

Keywords: hyaluronidase, recombinant human hyaluronidase, ultrafast insulin

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Introduction

There is a building consensus that the development of an ultrarapid insulin product would add an important new tool to the diabetes treatment armamentarium. Indeed, Howey and colleagues[1] demonstrated in 1995 that the optimum meal delay following rapid-acting insulin analog (lispro) administration is approximately 20 min. Insulin lispro, insulin aspart, and insulin glulisine all have pharmacokinetic and glucodynamic profiles as well as treatment outcomes (e.g., hemoglobin A1c, hypoglycemia) that are similar,[2,3] and for optimum dosing convenience, faster prandial insulins are necessary. In addition to convenience issues, faster insulin products with shorter duration of action can improve postprandial meal excursions without increasing risk of late postprandial hypoglycemia.[4–6] Also, faster, more consistent insulin profiles will be necessary for optimizing closed-loop artificial pancreas control systems.[7]

Approaches to accelerate subcutaneous insulin absorption and action have been explored, including methods that either favor dissociation of high molecular weight, capillary impermeable multimers, or approaches that facilitate more rapid absorption of the capillary permeable insulin monomers and dimers. We have focused on a method that leverages both of these mechanisms by employing recombinant human hyaluronidase (rHuPH20) to transiently disrupt the subcutaneous matrix barrier to bulk fluid flow.[8] We review here studies using rHuPH20 to accelerate insulin absorption and action when coadministered with rapid-acting analog insulin in both the subcutaneous injection mode and as an adjunct to continuous subcutaneous insulin infusion (CSII). In addition, we discuss use of rHuPH20 as a pretreatment administered through an infusion set cannula prior to CSII using rapid-acting analog insulin alone.

Background

Naturally occurring hyaluronidase activity was described by Duran-Reynals,[9] with observations of increased lesion size following viral inoculations after either pretreatment of the injection area with testicular extract or coinjection of the extract along with the virus. The testicular extract was subsequently demonstrated to enhance dispersion of injected materials (so called "spreading factor" activity) using a dye dispersion *in vivo* assay;[10] within a decade, this effect was shown to be due to enzymatic mucolytic (hyaluronidase) activity in the extracts.[11] Clinical use of hyaluronidase dates back to the 1940s, with use, among other things, in ocular surgery to increase the spread of injected local anesthetics and as an adjuvant to improve the absorption of fluids delivered by hypodermoclysis. In 1970, the U.S. Food and Drug Administration (FDA) conducted a Drug Efficacy Study Implementation review of hyaluronidase products, resulting in approved labeling for animal-source hyaluronidase products. In 2005, rHuPH20 (Hylenex® recombinant [hyaluronidase human injection]) became the only rHuPH20 approved by the FDA. Hylenex recombinant is a tissue permeability modifier currently indicated as an adjuvant (1) in subcutaneous fluid administration for achieving hydration, (2) to increase the dispersion and absorption of other injected drugs, and (3) in subcutaneous urography for improving resorption of radiopaque agents. Mechanistically, hyaluronidase depolymerizes hyaluronan (also known as "hyaluronic acid") at the site of injection. Hyaluronan, which has high affinity for water, is a high molecular weight (megaDalton) polymer of repeating N-acetyl glucosamine and glucuronic acid tandems. These properties of hyaluronan confer a gel-like consistency to the subcutaneous matrix, impeding the absorption of injected materials by limiting their spread away from the site of injection. Hyaluronidase acts rapidly, locally, and transiently to break down this barrier, allowing bulk fluid flow of the injected material to occur.[12] Hyaluronidase is destroyed rapidly at the site of injection, with a half time ($t_{1/2}$) in rodent skin of 30 min[13] and almost immediately in the blood compartment with a $t_{1/2}$ of approximately 1 min.[12] Compared with other matrix components (e.g. collagen), hyaluronan itself has a rapid turnover, with a half-life between 12 and 24 h.[14,15] These characteristics of rHuPH20 and the hyaluronan substrate ensure that the effects of hyaluronidase are local and transient.

Use of Hyaluronidase with Insulin

Initial studies of animal-derived hyaluronidase with bovine insulin were conducted in the 1950s to accelerate the onset, shorten the duration, and improve the predictability of therapeutically induced hypoglycemic coma for the treatment of schizophrenia.[16] Since then, we have investigated the use of rHuPH20 with prandial insulin (both injected and infused via CSII), with the goal of developing a faster, shorter time-action profile that will more closely mimic normal physiology and better meet patients' treatment needs. An ultrafast insulin profile will also better meet the needs of closed-loop artificial pancreas control algorithms.[7] All the

studies described herein were conducted as part of a full clinical development program with the ultimate intent of developing commercial products for diabetes treatment; these studies were conducted under principles of the Declaration of Helsinki and included the written informed consent of all subjects.

The effects of hyaluronidase on absorption of insulin are likely due to two separate, synergistic actions. The spreading of the injected material results in access to a greater capillary surface area, increasing access to the circulation. In addition, the increased dispersion may also reduce the local concentration of the injected insulin product, favoring the dissociation of nonabsorbable multimers to capillary permeable insulin monomers and dimers.[17]

Clinical Trial Results

An initial proof-of-concept study in healthy volunteers[18] demonstrated that the addition of rHuPH20 to rapid-acting analog insulin (insulin lispro) results in substantial acceleration of both insulin pharmacokinetic exposure and glucodynamic action after subcutaneous injection (**Figure 1**). Three subsequent healthy volunteer studies have confirmed these findings (review in Reference 19). In the case of rapid-acting analog insulin, the addition of rHuPH20 results in a doubling of insulin exposure during the first hour following injection, with a corresponding halving of insulin exposure after 2 h.

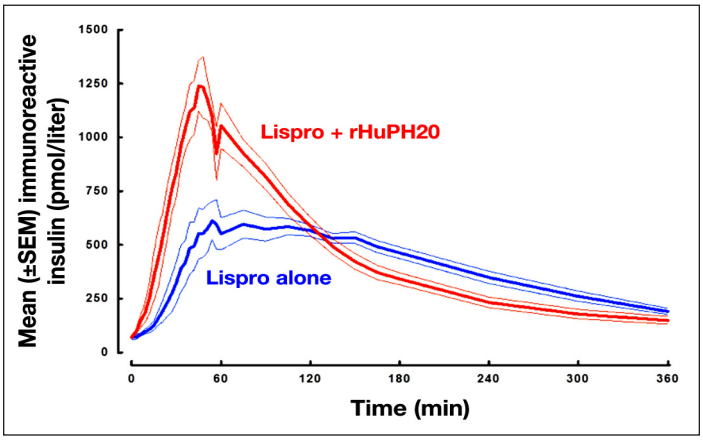

Figure 1. Pharmacokinetic data from 12 healthy adult males given 20 U of insulin lispro and insulin lispro + rHuPH20 by subcutaneous injection on two separate occasions. C_{max} was increased by 90% from 680 ± 361 to 1290 ± 471 pmol/liter (p = .0003), early $t_{50\%}$ accelerated by 34% from 39.5 ± 9.3 to 26.0 ± 6.5 min (p < .0001), t_{max} accelerated by 51% from 97.5 ± 35.9 to 48.0 ± 8.0 min (p = .0006), and $AUC_{0–60min}$ rose by 155% from 15.7 ± 14.6 to 40.1 ± 16.7 nmol/liter (p < .0001). SEM, standard error of the mean.

Insulin action, as assessed by euglycemic clamp methodology, is typically doubled in the first 1–2 h after injection and halved beyond 4 h (**Table 1**).

Studies were then conducted using test meal challenges in subjects with either type 1 or type 2 diabetes. The study in patients with type 1 diabetes employed a treatment paradigm calling for optimization of the insulin dose for a liquid test meal challenge by performing up to three test meals using a comixture of insulin lispro and rHuPH20. Once the optimum dose was determined, the same meal challenge was repeated on a subsequent visit, using the exact same dose of insulin lispro alone. In all cases, the basal insulin was withdrawn for approximately 14 h and the fasting blood glucose was brought to a target level of approximately 110 mg/dl using an intravenous insulin infusion. The results (**Figure 2A**) showed that addition of rHuPH20 to rapid-acting analog insulin reduced 4 h peak postprandial glucose (postprandial glucose) from 174 to 148 mg/dl (p = .002) without affecting minimum postprandial glucose levels or hypoglycemia risk during 8 h of postprandial observation.[4]

The liquid test meal study that was performed in type 2 diabetes[5] used a slightly different study design, and the doses of test articles (rapid-acting analog insulin with or without rHuPH20) were individually optimized for each study drug separately using a double-blind procedure. In this case, the optimized dose of insulin lispro with rHuPH20 (0.254 U/kg) was approximately 8% lower (p = .041) than that for lispro alone (0.275 U/kg), resulting in improvements (**Figure 2B**) both in postprandial glucose control (e.g., 2 h postprandial glucose reduced from 159 to 138 mg/dl, p = .02) and in postprandial hypoglycemia risk (e.g., area of hypoglycemic excursion below 70 mg/dl reduced from 571 to 197 min/mg/dl, p = .033).

A study in healthy volunteers was performed to test the hypothesis that hyaluronidase treatment would not only accelerate insulin absorption and action, but also improve dose-to-dose variability of exposure to and action of insulin.[22] Use of hyaluronidase did reduce the variability in time to key pharmacokinetic parameters with halving of the dose-to-dose within-subject variability in time to peak insulin concentration (t_{max}) as well as time to 50% of maximum insulin concentrations (both early and late; $t_{50\%}$). While no difference was observed in variability in peak concentration (C_{max}) or total insulin exposure [total area under the curve (AUC)], variability in early insulin exposure was substantially reduced (**Figure 3**).

Table 1.
Acceleration of Pharmacokinetic Responses by Recombinant Human Hyaluronidase across Eight Studies

Study	Early exposure (% of analog alone)[a]	C_{max} (% of analog alone)	t_{max} (difference from analog alone)	% of total AUC beyond 2 h (% of analog alone)
Proof of concept[b]	255%	190%	-49 min	69%
Comprehensive analog[c]	291%	210%	-26 min	53%
rHuPH20 dose selection study[d]	177%	163%	-20 min	28%
Variability study[e]	206%	162%	-16 min	47%
Type 1 meal study[f]	154%	135%	-18 min	43%
Type 2 meal study[g]	216%	174%	-31 min	76%
CSII comixture (initial clamp)[h]	166%	161%	-8 min	61%
CSII pretreatment (initial clamp)[i]	206%	129%	-49 min	61%

[a] Early exposure = % of total in first 60 min.
[b] Twelve healthy volunteers given 20 U insulin lispro diluted to a concentration of 91 U/ml ± rHuPH20 at 11.3 μg/ml.[18]
[c] Fourteen healthy volunteers given 0.15 U/kg insulin lispro diluted to 95 U/ml ± rHuPH20 at 5 μg/ml.[20]
[d] Twelve healthy volunteers given 6 U insulin lispro diluted to 25, 50, or 95 U/ml ± rHuPH20 at 5 μg/ml.[21]
[e] Twenty healthy volunteers given 0.15 U/kg insulin lispro diluted to 40 U/ml ± rHuPH20 at 5 μg/ml.[22]
[f] Twenty-one subjects with type 1 diabetes given individually dose-optimized doses (mean dose = 5.7 U) of insulin lispro diluted to 91 U/ml + rHuPH20 at 18.2 μg/ml followed on a separate occasion by the same dose of insulin lispro alone.[4]
[g] Twenty-one subjects with type 2 diabetes given individually dose-optimized doses (mean dose = 25.2 U for lispro + PH20, 27.3 U for insulin lispro alone) of insulin lispro diluted to 95 U/ml ± rHuPH20 at 5 μg/ml, comparison of pharmacokinetic parameters performed on a dose-normalized basis since doses were not identical for different treatments.[5]
[h] Sixteen subjects with type 1 diabetes using CSII given 0.15 U/kg of insulin aspart (100 U/ml) ± rHuPH20 at 5 μg/ml after 12 h of infusion site use.[19]
[i] Fifteen subjects with type 1 diabetes given 0.15 U/kg of insulin aspart (100 U/ml) after 2 h of infusion site use; either 150 U (1.25 μg) rHuPH20 pretreatment of the infusion site or sham injection had previously been performed immediately upon placement of the infusion set.[23]

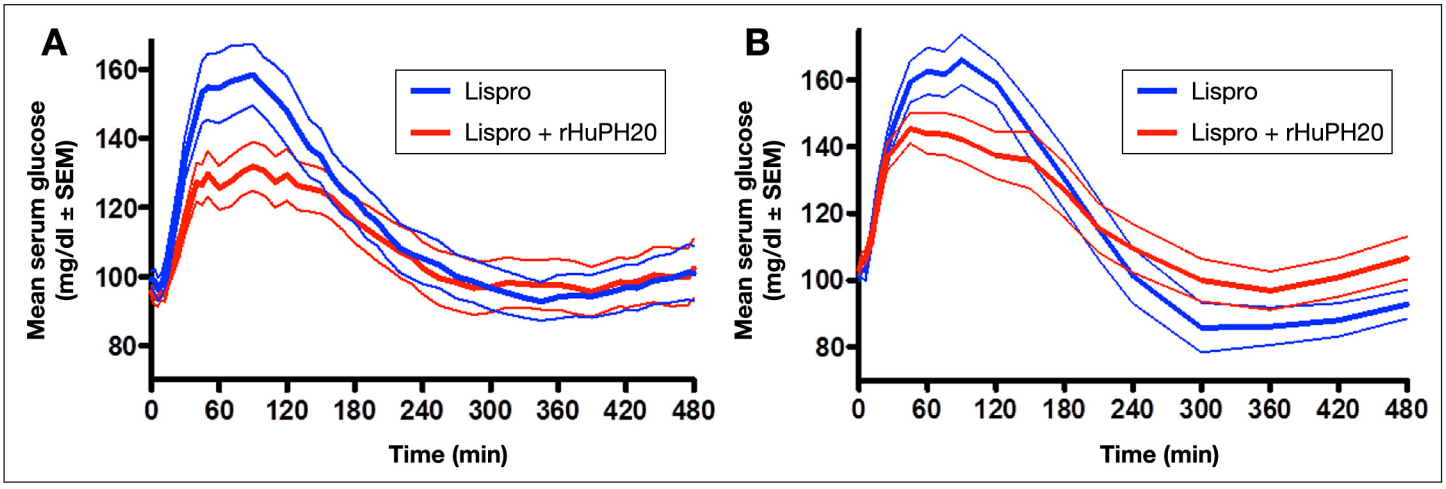

Figure 2. Postprandial blood glucose levels from two liquid test meal challenge studies **(A)** 22 subjects with type 1 diabetes and **(B)** 21 subjects with type 2 diabetes. Individually dose-optimized insulin injections (with or without rHuPH20) were administered immediately prior to consumption of a 60 (type 1 study) or 80 (type 2 study) gram carbohydrate load. SEM, standard error of the mean.

Another manifestation of variability in insulin absorption and action is the shift in the time-exposure profile as a function of insulin dosage, and as insulin dose is increased, the time required for absorption is correspondingly increased. For example, the time to 50% of total insulin exposure for 2, 6, and 20 U doses of insulin lispro was 75, 96, and 113 min, respectively.[21] When the same doses of insulin lispro were coinjected with rHuPH20, these values were reduced to 52, 62, and 83 min (pairwise p values all < 0.0006); these results indicate a reduction of 43% in the slope of the relationship between units administered and time to 50% exposure ($p = .09$), nearly halving the degree of delay in absorption that is associated with increased doses of rapid-acting analog insulin.

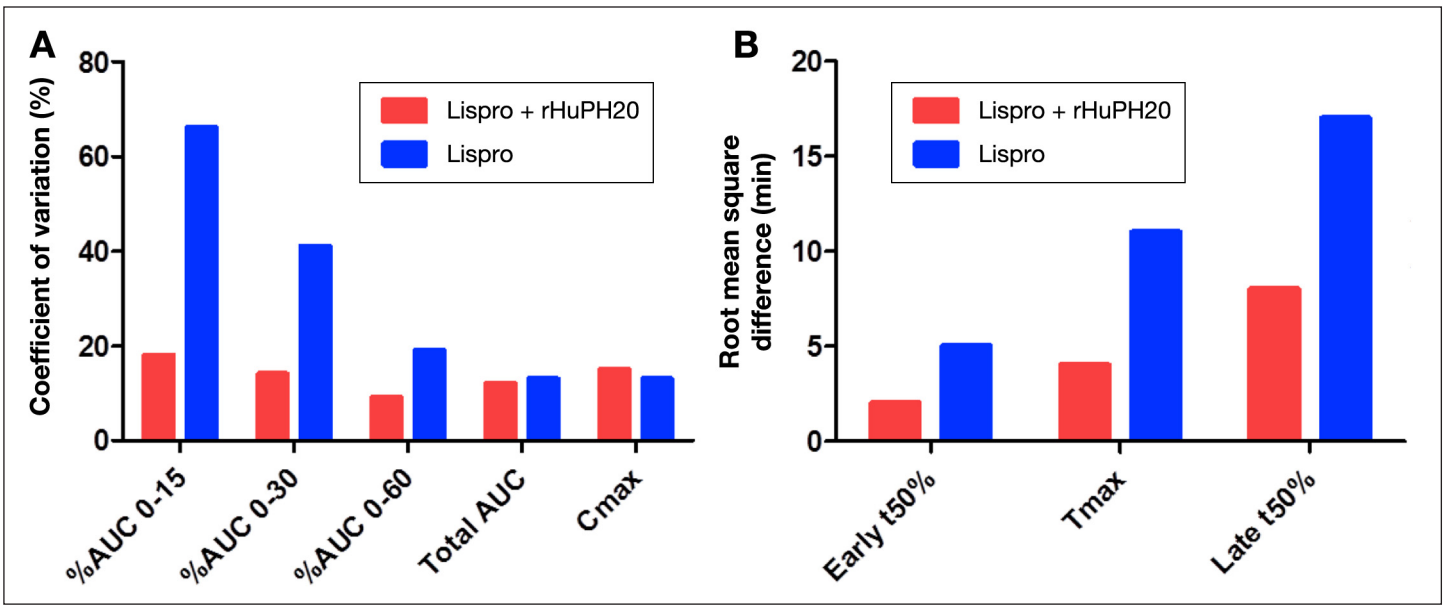

Figure 3. Intrasubject variability determined from repeat dosing of 0.15 U/kg insulin lispro ± rHuPH20) in 20 healthy volunteers. **(A)** Exposure parameters are expressed as percentages of mean (coefficient of variance) area under the curve for the indicated time intervals, and **(B)** time parameters are given as absolute values (root mean square differences) in minutes.

Similar to Duran-Reynals's[9] approach, demonstrating the spreading factor activity of testicular extract, studies using rHuPH20 in the CSII setting have been conducted using two different treatment paradigms, either administering a comixture of rHuPH20 contained in the pump reservoir or pretreatment of the infusion site with rHuPH20 by directly injecting 150 U (1.25 μg) of rHuPH20 into the infusion cannula at the time of infusion set insertion. These two different treatment paradigms provide alternate methods for using rHuPH20 in the CSII setting, one requiring the development of a coformulated drug product and the other employing two separate, currently marketed products. These studies have confirmed the "fast-in, fast-out" profile seen previously in subcutaneous injection studies can be achieved using either of these pump treatment paradigms.[19,23] In addition, these studies underscore the relevance of a previously described but little known effect whereby the response to rapid-acting analog insulin alone is inconsistent across the life of an individual infusion set.[24] Using the rHuPH20 pretreatment model, this inconsistency in insulin absorption and action over 3 days of infusion set use was virtually eliminated. As shown in **Table 2**, the percentage of total insulin exposure achieved in the first hour following bolus infusion varied from 15% at the beginning of infusion set use for aspart alone to 26.7% after 3 days (p = .0004). In contrast, rHuPH20 pretreatment resulted in early insulin exposure of 31% and 32% (p = .76) at the beginning and end of infusion set use, respectively, effectively reducing the variability

Table 2.
Comparison of Exposure to and Action of Insulin across Infusion Set Life

	Aspart alone			rHuPH20 pretreatment			rHuPH20-mediated % reduction in variability over 72 h of set use
	2 h after infusion set placement	74 h after infusion set placement	Change over 72 h of set use	2 h after infusion set placement	74 h after infusion set placement	Change over 72 h of set use	
Early exposure (% of total in first 60 min)	15.0%	26.7% (p = .0004)	11.7%	31.0%	31.9% (p = .76)	0.9%	92%
Onset of action (early glucose infusion rate $t_{50\%}$)	60.0 min	29.9 min (p < .00001)	30.1 min	34.1 min	31.5 min (p = .73)	2.6 min	91%
Duration of action [$AUMC_{(0-360)}/AUC_{(0-360)}$]	180 min	156 min (p = .0005)	24 min	139 min	146 min (p = .28)	7 min	71%

AUMC, area under the first moment curve.

in early exposure by 92%. Similar large reductions in variability of onset and duration of insulin action mediated by rHuPH20 pretreatment of the infusion site were seen in this study.

A comparison of the results obtained using the comixture of insulin + rHuPH20 versus the pretreatment of the infusion site with rHuPH20 for up to 3 days of diabetes treatment is provided in **Table 3**. This table shows data from two separate experiments in similar cohorts of patients using CSII for treatment of type 1 diabetes. Both treatments resulted in pharmacokinetic and glucodynamic profiles that were consistently more rapid in onset and shorter in duration as compared with insulin aspart alone (**Table 1**).[19] Comparing the two different means of administering rHuPH20, pretreatment of the infusion site provided a consistent ultrafast profile over 3 days of infusion (all pairwise p values > .05), whereas the coadministration did show a significant increase in early exposure to insulin, with 35% of total exposure occurring in the first 60 min when the infusion set was a half day old, rising to 51% after 2.5 days of infusion set use (p = .0002).

Safety of Recombinant Human Hyaluronidase

As described earlier, rHuPH20 has been shown in animal studies to act transiently, and its downstream effects (i.e., breakdown of hyaluronan) are rapidly reversed. Animal toxicology studies have been performed to test both local tolerability and systemic effects of rHuPH20. Single-dose intravenous and subcutaneous administration of rHuPH20 to cynomolgus monkeys at doses up to 30 mg/kg (3,600,000 U/kg) demonstrated excellent tolerability at this extreme dosage (data on file, Halozyme Therapeutics, San Diego, CA). A 28-day repeat dose toxicology study in rhesus monkeys that employed subcutaneous doses up to 38,000 U (0.32 mg) showed no inflammatory or other pathologic changes in the subcutaneous tissue as compared to carrier control. In addition, no adverse local, electrocardiographic, hemodynamic, clinical, or anatomic pathologic changes were noted throughout the study or at necropsy.[8] In a 39-week repeat dose study in cynomolgus monkeys at doses up to 220,000 U/kg, no evidence of toxicity to the male or female reproductive system was found through periodic monitoring of in-life parameters, e.g., semen analyses, hormone levels, and estrus cycles, and from gross pathology, histopathology, and organ weight data.[25] Vascular permeability studies in rodents have shown no effect of rHuPH20 on capillary permeability.[8] Studies in rodents using doses up to 10,500 U/kg (87.5 μg/kg) also demonstrated good tolerability.[12] Single-dose rabbit and repeat-dose rat local tolerability studies using insulin lispro or insulin aspart with rHuPH20 have been similarly unremarkable (data on file, Halozyme Therapeutics).

As of November 2011, more than 2000 subjects had been exposed to rHuPH20 in clinical trials across a variety of development programs (data on file, Halozyme Therapeutics). In human studies, rHuPH20 has not been associated with allergic reactions as assessed by intradermal challenge testing.[26] Single doses of up to 96,000 U (0.8 mg) of rHuPH20 have been administered to humans without notable adverse effects (data on file, Halozyme Therapeutics). When used in clinical studies with rapid-acting analog insulin, there have been no differences in local tolerability between control and active comparator treatments (data on file, Halozyme Therapeutics).[4,5,18–20,22] Coformulations of rapid-

Table 3.
Glucose Clamp Pharmacokinetic and Glucodynamic Parameters Obtained Comparing Infusion of a Comixture of Recombinant Human Hyaluronidase (5 μg/ml) + Insulin Aspart (100 U/ml) versus Pretreatment of the Infusion Site with Recombinant Human Hyaluronidase (150 U [1.25 μg] in 1.0 ml) Followed by Infusion of Insulin Aspart Alone

Method of administering rHuPH20	Infusion site age	Early exposure (% of total in first 60 min)	Onset of action (early glucose infusion rate $t_{50\%}$)	Duration of action [$AUMC_{(0-360)}/AUC_{(0-360)}$]
Comixture	Half day	35%	35 min	147 min
Comixture	2.5 days	51%	40 min	133 min
Pretreatment	<2 h	31%	34 min	139 min
Pretreatment	1 day	37%	32 min	134 min
Pretreatment	3 days	32%	31 min	146 min

AUMC, area under the first moment curve.

acting analog insulin and rHuPH20 contain 5 μg/ml of the enzyme; this corresponds to 50 ng (6 U) of enzyme for each unit of insulin delivered. Studies of preadministration of rHuPH20 in the CSII setting have used 150 U (1.25 μg) of enzyme as a single injection every 3 days. These data support a very high margin of safety for rHuPH20 in humans. Various potential misuse scenarios (e.g., injecting long-acting insulin at or near the site of rHuPH20 injection or repeated exposure of a single injection site to rHuPH20) have not yet been explored.

Immunogenicity of rHuPH20 has been evaluated in both animal and human studies. There are considerable sequence differences between human PH20 and that of other mammals, with homology rates as follows:[27] rat (54%), pig (66%), bull (74%), macaque (90%). As would be expected, animals exposed to the human protein can develop antibodies to rHuPH20. In a 12-week by 12-week two-way crossover study of 46 human subjects with type 1 diabetes receiving recombinant human insulin (100 U/ml) with rHuPH20 (5 μg/ml) or insulin lispro in random sequence, there were two subjects with preexisting anti-rHuPH20 antibodies and a single case of *de novo* anti-rHuPH20 antibody formation; these cases were not associated with any specific adverse events (data on file, Halozyme Therapeutics).[28] There have been no instances of neutralizing anti-rHuPH20 antibodies detected in any clinical trial to date.

In the setting of an insulin pump study, 6 mm punch biopsies at the site of infusion cannula placement following 3 days of infusion of a coformulation of insulin aspart and rHuPH20 were examined by histopathology; biopsies were performed in three subjects immediately upon cannula removal, in three subjects approximately 24 h later, and in three additional subjects 48 h after cannula removal. Each subject had two biopsies performed, one after CSII using insulin aspart alone and one after aspart with rHuPH20. The results showed modest inflammatory changes (consistent with foreign body reaction to the cannula), which tended to decrease as a function of time after cannula removal in both the insulin aspart alone and aspart with PH20 groups (data on file, Halozyme Therapeutics). Importantly, there were no differences observed between treatments (±rHuPH20).

Discussion and Conclusions

Studies in the 1980s demonstrated that the endogenous insulin response to a meal is very fast,[29] and currently available rapid-acting analogs do not replicate this profile.[20,30] Use of rHuPH20 for either subcutaneous injection therapy or CSII confers an ultrafast profile to rapid-acting analog insulin.

In addition to changing the accelerating exposure to rapid-acting analog insulin, rHuPH20 also reduces the variability in insulin exposure and action. This is manifested by a reduction in the timing relationships in insulin absorption across the entire time-exposure profile as well as a reduction in the absolute variability in insulin exposure and action during the critical early time points following insulin administration. Another variability parameter in insulin exposure and action is the delay in absorption as rapid-acting analog insulin dose is increased, and rHuPH20 reduces this dose-dependent variability by almost 50%. In the setting of CSII, variability in insulin exposure and action also occurs as a function of infusion set age, and use of rHuPH20 as a pretreatment has been shown to virtually eliminate this phenomenon. Studies are underway to assess the clinical impact of mitigating this issue.

Acceleration of insulin absorption and action using either coadministration of rHuPH20 with rapid-acting analog insulin or using pretreatment of an insulin infusion site with a bolus injection of rHuPH20 has been shown to improve postprandial glucose control in test meal settings.

In the setting of CSII, others have demonstrated that placement of an infusion cannula followed by continuous infusion of saline in healthy volunteers is associated with significant alterations of local tissue blood flow;[31] whether this is the mechanism underlying the alterations in insulin absorption and action across infusion set wear time is uncertain, but this finding is consistent with the mild inflammatory changes seen in skin biopsies taken after CSII cannula removal. The mechanism by which pretreatment of an infusion site with rHuPH20 reduces variability of insulin absorption and action is unknown, but an effect of local tissue blood flow may be speculated.

From a safety perspective, hyaluronidase products have a long history of clinical use. Current insulin studies involving rHuPH20 have examined local tolerability, immunogenicity, and histologic features associated with use of rHuPH20 for up to three months duration in upward of 60,000 individual dosing events (data on file, Halozyme Therapeutics). To date, no local or systemic adverse events have been associated with rHuPH20 use.

Ultrafast prandial insulin has been identified as a need, and use of rHuPH20 in conjunction with rapid-acting analog insulin holds promise as one approach to achieve

this goal. Studies are underway to evaluate the longer-term safety and efficacy of rHuPH20 in the outpatient treatment of diabetes both in the subcutaneous injection mode and in the CSII mode of insulin delivery. From a product development perspective, the coformulation would require a full new drug application for marketing approval, whereas the pretreatment of an insulin infusion set with hyaluronidase can be accomplished with the use of currently approved and marketed products.

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Disclosures:

The authors of this work are stockholders in and employees of Halozyme Therapeutics, the sponsor of these studies.

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