PGR2025-00017	**PGR2025-00042**
PGR2025-00024	**PGR2025-00046**
PGR2025-00030	**PGR2025-00052**
PGR2025-00033	**PGR2025-00050**
PGR2025-00039	**PGR2025-00053**

Petitioner Merck, Sharp & Dohme, LLC Demonstratives

Grounds Across the 10 Proceedings

- **§ 112 Grounds (All Proceedings)**
  - Lack of benefit/priority
  - Lack of written description
  - Lack of enablement
- **§ 103 Grounds (-17, -24, -30, -33, -42, -46, -52, -53)**
  - $PH20_{1\text{-}447}$ mutants with particular single substitutions at six positions (307, 309, 313, 317, 320, 324) are obvious

*All citations are to PGR2025-00024 unless otherwise specified.

Points Being Covered Today

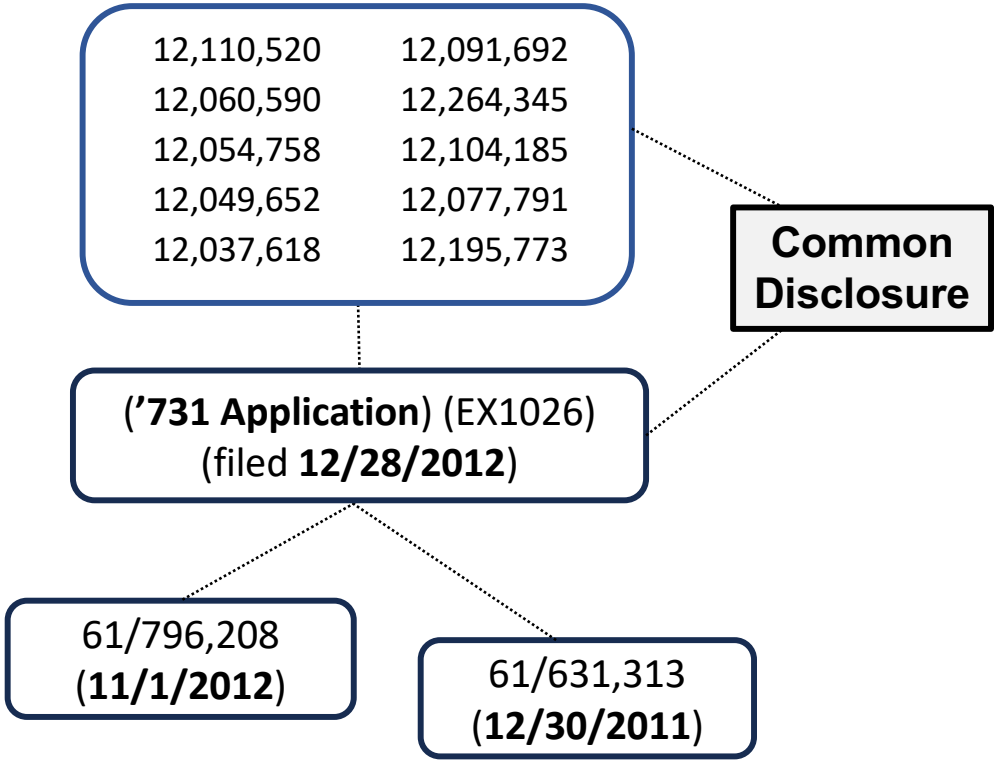
- **Claim Construction and Scope**
- **Unpredictability of Modifications to PH20**
- **The Claims Lack Written Description**
  - No disclosure of representative species
  - No identification of common structural features
- **The Claims Are Not Enabled**
  - Full scope can't be practiced using mutagenesis or homology modeling
  - Dr. Petsko's tolerance analysis is flawed and cannot enable full scope
- **Halozyme's construction captures inoperative & useless mutants**
- **Halozyme's '429 Patent renders obvious certain single substitution $PH20_{1-447}$ mutants (D320K, M313K, L317Q, S312T, S312N)**

The Patents and the Common Disclosure

Related U.S. Application Data

(60) Division of application No. 17/327,568, filed on May 21, 2021, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,568 is a continuation of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,568 is a continuation of application No. 16/912,590, filed on Jun. 25, 2020, now Pat. No. 11,066,656, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, and a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,568 is a continuation of application No. 16/824,572, filed on Mar. 19, 2020, now Pat. No. 11,041,149, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401.

(60) Provisional application No. 61/796,208, filed on Nov. 1, 2012, provisional application No. 61/631,313, filed on Dec. 30, 2011.



Merck's Experts



Dr. Michael Hecht
Princeton University



Dr. James Naismith
Oxford University



Dr. Sheldon Park
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Dr. Garnett Kelsoe
Duke University

Claim Construction and Scope

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Claim Construction Overview

- **Board correctly found all claims in the 10 patents to require PH20s with some hyaluronidase activity**
  - Proper construction must account for claim term "PH20"
  - Intrinsic and extrinsic evidence supports Board's construction
- **No dispute that**
  - Claims encompass enzymatically active PH20s
  - Disclosure portrays "active" and "inactive" modified PH20s as mutually exclusive alternatives
  - Law requires disclosure to enable and describe full genus of enzymatically active PH20s being claimed
    - If claims include "inactive" mutants, disclosure must ***additionally*** describe and enable that distinct set of modified PH20s

Categories of Claims in Challenged Patents

FWD	PGR2025-00003	11,952,600	320
	PGR2025-00004	12,018,298	313
	PGR2025-00006	12,152,262	317
	PGR2025-00009	12,123,035	312
	PGR2025-00017	12,110,520	324
	PGR2025-00024	12,060,590	307
	PGR2025-00030	12,054,758	317
	PGR2025-00033	12,049,652	320
	PGR2025-00042	12,037,618	309
	PGR2025-00046	12,091,692	313
	PGR2025-00052	12,264,345	313
	PGR2025-00039	12,104,185	320
	PGR2025-00050	12,077,791	309
	PGR2025-00053	12,195,773	320

Modified PH20 with % sequence identity + position for one substitution + defined replacement AAs

Modified PH20 with % sequence identity + position for one substitution

→ Methods of increasing delivery

→ PH20 with increased activity

→ Soluble PH20 polypeptide

Claim Form Similarities: ’035 Patent (312) vs. ’652 Patent (320)

’035 Patent (PGR2025-00009)

1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66;

amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);

the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to residue 312, with reference to amino acid positions set forth in SEQ ID NO:3;

the replacement at the position corresponding to residue 312 is selected from the group consisting of G, K, L, N, and T;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO:3; and

the modified PH20 polypeptide has at least 91% sequence identity to a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66.

EX1001 (PGR2025-00009)(’035 Patent)

’652 Patent (PGR2025-00033)

1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66;

amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);

the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to residue 320, with reference to amino acid positions set forth in SEQ ID NO:3;

the replacement at the position corresponding to residue 320 is selected from the group consisting of H, K, R, and S;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO:3; and

the modified PH20 polypeptide has at least 91% sequence identity to a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66.

EX1001 (PGR2025-00033)(’652 Patent)

Claims at Issue in PGR2025-00017 (324), -00024 (307), -00030 (317)

’520 Patent (PGR2025-00017)

1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66;

amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);

the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to residue 324, with reference to amino acid positions set forth in SEQ ID NO: 3;

the replacement at the position corresponding to residue 324 is selected from the group consisting of A, D, H, M, N, R and S;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO: 3; and

the modified PH20 polypeptide has at least 91% sequence identity to a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66.

EX1001 (PGR2025-00017)(’520 Patent)

’590 Patent (PGR2025-00024)

1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66;

amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);

the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to residue 307, with reference to amino acid positions set forth in SEQ ID NO:3;

the replacement at the position corresponding to residue 307 is selected from the group consisting of G, K, N, Q, S, T, V, W, and Y;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO:3; and

the modified PH20 polypeptide has at least 91% sequence identity to a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66.

EX1001 (PGR2025-00024)(’590 Patent)

’758 Patent (PGR2025-00030)

1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66;

amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);

the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to residue 317, with reference to amino acid positions set forth in SEQ ID NO:3;

the replacement at the position corresponding to residue 317 is selected from the group consisting of A, I, K, M, Q, and R;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO:3; and

the modified PH20 polypeptide has at least 91% sequence identity to a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66.

EX1001 (PGR2025-00030)(’758 Patent)

Claims at Issue in PGR2025-00042 (309); -00046 (313), -00052 (313)

’618 Patent (PGR2025-00042)

1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66;

amino acid modifications are selected from among amino acid replacements, deletions, and/or insertions;

the modified PH20 polypeptide comprises a modification at a position corresponding to position 309 with reference to amino acid positions of SEQ ID NO: 3;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO: 3; and

the modified PH20 polypeptide has at least 91% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66.

EX1001 (PGR2025-00042)(’618 Patent)

’692 Patent (PGR2025-00046)

1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66;

amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);

the modified PH20 polypeptide comprises a modification at a position corresponding to position 313 with reference to amino acid positions of SEQ ID NO:3;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO:3; and

the modified PH20 polypeptide has at least 91% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66.

EX1001 (PGR2025-00046)(’692 Patent)

’345 Patent (PGR2025-00052)

1. A modified PH20 polypeptide, comprising:

(i) a hyaluronidase domain that corresponds to amino acid residues 3-339 with reference to numbering in SEQ ID NO:7; and

(ii) an amino acid replacement at the residue corresponding to M313 with reference to numbering in SEQ ID NO:7,

wherein the hyaluronidase domain contains up to 20 modifications.

EX1001 (PGR2025-00052)(’345 Patent)

Claims at Issue in PGR2025-00039 (320), -00050 (309), -00053 (320)

’185 Patent (PGR2025-00039)

1. A method for increasing delivery of a therapeutic agent to a subject, comprising administering to a subject a pharmaceutical composition comprising:

(a) a therapeutic agent; and

(b) a modified PH20 polypeptide comprising an amino acid sequence, wherein:

i. at least 95% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in an amino acid sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 to maximize identical residues; and

ii. the amino acid sequence of the modified PH20 polypeptide comprises an amino acid modification at a position corresponding to position 320 with reference to amino acid positions set forth in SEQ ID NO: 3; and

iii. the modification at position 320 is a replacement selected from the group consisting of H, K, R and S.

’791 Patent (PGR2025-00050)

1. A modified PH20 polypeptide comprising an amino acid sequence, wherein: (a) at least 95% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in the amino acid sequence of SEQ ID NO: 35 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence set forth in the amino acid sequence of SEQ ID NO: 35 to maximize identical residues, and terminal gaps are treated as non-identical; (b) the amino acid sequence of the modified PH20 polypeptide comprises an amino acid modification at a position corresponding to position 309 with reference to amino acid positions set forth in the amino acid sequence of SEQ ID NO: 3; and (c) the modification at position 309 is a replacement selected from among E, G, H, L, M, N, Q, R, S, and T, and wherein the modified PH20 polypeptide exhibits increased hyaluronidase activity compared to the hyaluronidase activity of the polypeptide of SEQ ID NO: 3, measured under identical conditions.

’773 Patent (PGR2025-00053)

1. A soluble human PH20 polypeptide comprising: a modification at a position aligned to position 320 with reference to the amino acid positions set forth in SEQ ID NO: 3, and 19 or less additional amino acid modifications, after alignment with SEQ ID NO: 3 to maximize the number of identical residues, wherein: modifications comprise insertions, deletions, and replacements, and the modification at position 320 is a replacement selected from the group consisting of H, K, and R.

Common Disclosure & Dr. Petsko: Positions 309 and 313 Tolerate Substitutions

TABLE 8-continued

PH20 Variants

I309D	GAT
I309E	GAG
I309G	GGT
I309H	CAT
I309K	AAG
I309L	CTG
I309M	ATG
I309N	AAT
I309Q	CAG
I309R	CGT
I309S	AGT
I309T	ACT
I309V	GTG
I309W	TGG
I309Y	TAT

EX1001, 209

TABLE 9-continued

ACTIVE MUTANTS

I309D		0.72
I309E	576	1.99
I309G	577	1.44
I303D		0.34
I309H	578	1.30
I309K		0.98
I309L	579	1.72
I309M	580	1.47
I309N	581	3.11
I309Q	582	1.64
I309R	583	2.27
I309S	584	1.16
I309T	585	2.09
I309V	586	0.60
I309W		0.88

EX1001, 228

TABLE 5-continued

Inactive Mutants

Corresponding Position	Replacement	Corresponding Position	Replacement	Corresponding Position	Replacement
306	A C H I L V W Y	307	C I P	308	C F L M V W Y
310	C E F K L	311	C E F I L P V W	312	C E M V W
313	C	314	C L W	315	C I V
316	E G I K L M P R S T V W Y	317	G P	318	C P W

EX1001, 83-84

Pet. (PGR2025-00042), 25-26

309	I
310	M
311	R
312	S
313	M
314	K
315	S

270. Those positions for which all substitutions are tolerated are colored green, and those for which no substitutions were tolerated are colored red.

271. Positions for which 60% or more of the substitutions tested were tolerated are colored light green.

EX2070 (Petsko), 124-126 (PGR2025-00052)

TABLE 8-continued

PH20 Variants

mut	cod
M313A	GCT
M313C	TGT
M313D	GAT
M313E	GAG
M313F	TTT
M313G	GGG
M313H	CAT
M313K	AAG
M313L	CTT
M313P	CCT
M313R	CGT
M313S	TCG
M313T	ACT
M313V	GTT
M313Y	TAT

EX1001, 217-219

TABLE 9-continued

ACTIVE MUTANTS

mutant	SEQ ID NO	AvgNorm Act.
M313A	591	1.34
M313E		0.63
M313G	592	0.56
M313H	593	1.23
M313K	594	2.85
S312L		0.38
M313L		1.05
M313P	595	1.11
M313R	596	2.30
M313S		0.88
M313T	597	0.67
M313V		0.99
M313Y	598	1.12

EX1001, 256

Pet., 25 (PGR2025-00046), 24-25 (citing EX1026, 238, 253)

Enablement and Written Description Required for Full Claim Scope

Amgen v. Sanofi, 598 U.S. 594, 610 (2023)

If a patent claims an entire class of processes, machines, manufactures, or compositions of matter, the patent's specification **must enable a person skilled in the art to make and use the entire class**. In other words, **the specification must enable the full scope of the invention as defined by its claims.** The more one claims, the more one must enable.

Duke v. Sandoz, 160 F.4th 1305, 1310 (Fed. Cir. 2025)

Whether a patent provides **adequate written description** for a claim presents a question of fact. *See Gen. Hosp. Corp. v. Sienna Biopharmaceuticals, Inc.*, 888 F.3d 1368, 1371 (Fed. Cir. 2018). **That question is whether the patent specification discloses that a person of ordinary skill in the art would conclude "the inventor possesse[d] the full scope of the invention" at the time of their patent application**. *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005).

Enablement and Written Description Required for Full Claim Scope

For simplicity, however, and given the patent's robust teachings, Patentee assumes—without conceding—that the specification must enable POSAs to reliably distinguish, create, and utilize the full range of active and, if Patentee's construction is accepted, inactive modified PH20 polypeptides encompassed by the claims. For the reasons stated below, it does.

POR, 44

Patentee may contend the claims should be read as encompassing both alternative embodiments (*i.e.*, "active" and "inactive" mutants). Reading the claims in that manner is incorrect. It also exacerbates the § 112 problems, as every claim still necessarily includes (and thus must describe and enable) the full sub-genus of "active mutants" in claim 1 defined by claim 4.[62]

Pet., 26

“PH20” Is Expressly Defined as an Enzymatically Active Hyaluronidase

As used herein, PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active. PH-20 occurs on the sperm surface, and in the lysosome-derived acrosome, where it is bound to the inner acrosomal membrane. PH20 includes those of any origin including, but not limited to, human, chimpanzee, Cynomolgus monkey, Rhesus monkey, murine, bovine, ovine, guinea pig, rabbit and rat origin. Exemplary PH20 polypeptides, including precursor and mature forms, include those from human (SEQ ID NO:6 and 7), NO:860 and 861). Reference to PH20 includes precursor PH20 polypeptides and mature PH20 polypeptides (such as those in which a signal sequence has been removed), truncated forms thereof that have activity, and includes allelic variants and species variants, variants encoded by splice variants, and other variants, including polypeptides that have at least 40%, 45%, 50%, 55%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more sequence identity to the precursor polypeptides set forth in SEQ ID NO:7, or the mature forms thereof. PH20 polypeptides also include those that contain chemical or

EX1026 (’731 App.), 50:31-51:11; Reply, 2; POR, 11.

As used herein, neutral active refers to the ability of a PH20 polypeptide to enzymatically catalyze the cleavage of hyaluronic acid at neutral pH, such as at a pH between or about between pH 6.0 to pH 7.8.

As used herein, “increased activity” with reference to a modified PH20 hyaluronidase means that, when tested under the same conditions, the modified PH20 hyaluronidase exhibits greater hyaluronidase activity compared to an unmodified PH20 hyaluronidase not containing the amino acid replacement(s). For example, a modified PH20 hyaluronidase exhibits at least

EX1026 (’731 App.), 56:21-30; EX1133 (Naismith), ¶ 92; Reply, 1, 3.

1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66;

EX1001 (PGR2025-00024)(‘590 Patent), Claim 1
EX1001 (PGR2025-00017)(’520 Patent)
EX1001 (PGR2025-00030)(’758 Patent)
EX1001 (PGR2025-00033)(’652 Patent)
EX1001 (PGR2025-00042)(’618 Patent)
EX1001 (PGR2025-00046)(’692 Patent)

Modified PH20s with at Least One Modification Retain Activity

As used herein, PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active. PH-20 occurs on the sperm surface, and in the lysosome-derived acrosome, where it is bound to the inner acrosomal membrane. PH20 includes those of any origin including, but not limited to, human, chimpanzee, Cynomolgus monkey, Rhesus monkey, murine, bovine, ovine, guinea pig, rabbit and rat origin. Exemplary PH20 polypeptides, including precursor and mature forms, include those from human (SEQ ID NO:6 and 7), NO:860 and 861) . Reference to PH20 includes precursor PH20 polypeptides and mature PH20 polypeptides (such as those in which a signal sequence has been removed), truncated forms thereof that have activity, and includes allelic variants and species variants, variants encoded by splice variants, and other variants, including polypeptides that have at least 40%, 45%, 50%, 55%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more sequence identity to the precursor polypeptides set forth in SEQ ID NO:7, or the mature forms thereof. PH20 polypeptides also include those that contain chemical or

EX1026 ('731 App.), 50:31-51:11; Reply, 2; POR, 11

1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66;

the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to residue 307, with reference to amino acid positions set forth in SEQ ID NO:3;

the replacement at the position corresponding to residue 307 is selected from the group consisting of G, K, N, Q, S, T, V, W, and Y;

EX1001 ('590 Patent), Claim 1

As used herein, "modified PH20 polypeptide" or "variant PH20 polypeptide" refers to a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement as described herein, in its sequence of amino acids compared to a reference unmodified PH20 polypeptide. A modified PH20 polypeptide can have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity. Typically, a modified PH20 polypeptide contains 1, 2, 3, 4, 5, 6, 7, 8,

EX1026 ('731 App.), 54:5-10; Pet., 26, 48-49

“PH20” Is Expressly Defined as an Enzymatically Active Hyaluronidase

As used herein, PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active. PH-20 occurs on the sperm surface, and in the lysosome-derived acrosome, where it is bound to the inner acrosomal membrane. PH20 includes those of any origin including, but not limited to, human, chimpanzee, Cynomolgus monkey, Rhesus monkey, murine, bovine, ovine, guinea pig, rabbit and rat origin. Exemplary PH20 polypeptides, including precursor and mature forms, include those from human (SEQ ID NO:6 and 7), NO:860 and 861) . Reference to PH20 includes precursor PH20 polypeptides and mature PH20 polypeptides (such as those in which a signal sequence has been removed), truncated forms thereof that have activity, and includes allelic variants and species variants, variants encoded by splice variants, and other variants, including polypeptides that have at least 40%, 45%, 50%, 55%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more sequence identity to the precursor polypeptides set forth in SEQ ID NO:7, or the mature forms thereof. PH20 polypeptides also include those that contain chemical or

EX1026 (’731 App.), 50:31-51:11; Reply, 2; POR, 11

As used herein, neutral active refers to the ability of a PH20 polypeptide to enzymatically catalyze the cleavage of hyaluronic acid at neutral pH, such as at a pH between or about between pH 6.0 to pH 7.8.

As used herein, “increased activity” with reference to a modified PH20 hyaluronidase means that, when tested under the same conditions, the modified PH20 hyaluronidase exhibits greater hyaluronidase activity compared to an unmodified PH20 hyaluronidase not containing the amino acid replacement(s). For example, a modified PH20 hyaluronidase exhibits at least

EX1026 (’731 App.), 56:18-30; EX1133 (Naismith), ¶ 92; Reply, 1, 3

As used herein, a hyaluronan-degrading enzyme refers to an enzyme that catalyzes the cleavage of a hyaluronan polymer (also referred to as hyaluronic acid or HA) into smaller molecular weight fragments. Exemplary hyaluronan-degrading enzymes are hyaluronidases, and particular chondroitinases and lyases that have the ability to depolymerize hyaluronan.

EX1026 (’731 App.), 49:45-49; POR, 34 n.11 (citing EX1001 (’590 Patent), 44:55-68:42), 40

As used herein, hyaluronidase refers to a class of enzymes that degrade hyaluronan.

crustaceans. Exemplary human hyaluronidases include HYAL1, HYAL2, HYAL3, HYAL4, and PH20. Also included amongst hyaluronidases are soluble hyaluronidases, including, ovine and bovine PH20, and soluble PH20. Exemplary hyaluronidases include any set forth in SEQ ID NOS: 6, 7-31, 69, 70, 71, 72, 856-861, 869-921, mature forms thereof (lacking the signal sequence), or allelic or species variants thereof. Hyaluronidases also include truncated forms thereof that exhibit hyaluronidase activity, including C-terminal truncated variants that are soluble.

EX1026 (’731 App.), 50:18-30; Pet., 17 (PGR2025-00046)(’692 Patent)

Undisputed that PH20s are Folded Proteins

Third, even if Merck were correct to read the definition of "PH20" into "modified PH20 polypeptide," (it is not), Petitioner's argument still fails. The PH20 definition imposes no "properly folded" or any folding requirement. Petitioner thus has no basis to import that limitation into the claims. *Fourth*, like

PO Sur-Reply, 3

62. Many proteins, particularly globular ones like PH20, are inherently unstable. Slight changes in pH or in temperature can convert a properly folded and active protein into an unfolded and inactive form (figure below).[24]

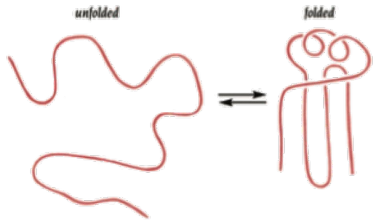


Figure 6.1 A polypeptide chain is extended and flexible in the unfolded, denatured state whereas it is globular and compact in the folded, native state.

36. Proteins are formed by sequences of amino acids, but the feature of each protein that confers its unique biological function(s) is its overall three-dimensional structure.[3] That overall structure results from folding of the amino acid sequence of the protein (its "primary structure"). The sequences initially fold

46. The specific amino acids in specific positions of an amino acid sequence also play a critical role in inducing the folding of the protein into its destined structure, as well as in maintaining that structure.[11]

EX1003 (Hecht), ¶¶ 36, 46, 62; Pet., 8, 10; Reply, 13

Experts Agree Enzymatic Activity Requires Properly Folded PH20s

Third, even if Merck were correct to read the definition of "PH20" into "modified PH20 polypeptide," (it is not), Petitioner's argument still fails. The PH20 definition imposes no "properly folded" or any folding requirement. Petitioner thus has no basis to import that limitation into the claims. *Fourth*, like

PO Sur-Reply, 3

96. A modified PH20 polypeptide must preserve most if not all aspects of the tertiary structure of the wild-type PH20 protein to exhibit hyaluronidase activity.[84] In Dr. Petsko's terminology, it must be "properly folded."[85] This includes not just the structure of the active site, but the spatial positioning of particular residues and structural motifs within it, as well as the precise structural relationships necessary for the protein to bind to and hydrolyze the HA substrate.[86] Only particular amino acid sequences may yield the precise structure-function relationship that is needed. From the literature before 2011, these include: (a)

EX1133 (Naismith), ¶ 96; Reply, 3, 13, 16

[12] When I say "enzymatically active" in this context, I am not referring to a specific level of enzymatic activity. Rather, I am using enzymatic activity as a proxy for a properly folded protein. Secretion is another proxy that could be used for a properly folded protein; proteins that do not fold will generally not be secreted.

EX2070 (Petsko), ¶ 128, FN12; Reply, 1, 3, 5, 13

Experts Agree “PH20” Means a Properly Folded and Enzymatically Active Protein

Q. So when the PH20 is on the sperm surface, is it a folded protein?
A. Yes.
Q. And it's enzymatically active. Correct?
A. In normal biology, surface-associated PH20 would be enzymatically active.
Q. And it's -- because it is properly folded, it is enzymatically active. Right?
MS. MARTIN: Object to form.
A. Properly folded PH20 should have enzymatic activity, yes.
Q. Okay. And this is how the common disclosure defines the term "PH20." Right?

A. PH20 is defined as a type of hyaluronidase that occurs in sperm and is neutral-active. It explains further that it occurs on the sperm surface. In this particular paragraph, the folded structure is not specified.
Q. But it would just be the folded structure that occurs naturally with the PH20?
A. If PH20 is active on the sperm surface, it is assumed to be folded.

EX1130 (Simpson Dep), 61:13-62:10), Reply, 3

[12] When I say “enzymatically active” in this context, I am not referring to a specific level of enzymatic activity. Rather, I am using enzymatic activity as a proxy for a properly folded protein. Secretion is another proxy that could be used for a properly folded protein; proteins that do not fold will generally not be secreted.

EX2070 (Petsko), ¶ 128, FN12; Reply, 1, 3, 5, 13

92. The common disclosure explicitly defines the word “PH20” to mean “a type of hyaluronidase that occurs in sperm and is neutral-active.”[78] A POSA would know that proteins found on the surface of sperm and that are neutral-active are folded forms of PH20.[79] A POSA would thus be directed that the use of “PH20” to describe phrases like “modified PH20 polypeptide” requires that the polypeptides not only meet the “at least 91% sequence identity” and position 307 substitution requirements, but also to have stably folded to adopt the native state (the tertiary structure) of the PH20 protein.

EX1133 (Naismith), ¶ 92; Reply, 3

95. The common disclosure also uses the term “PH20” to refer to naturally occurring PH20 proteins from different species, which also would be understood by a POSA to be folded forms of PH20 polypeptides.[82] The common disclosure also uses the term “PH20” to refer to C-terminally truncated forms of the wild-type PH20 protein sequence that have retained activity. That again is using PH20 to indicate that the truncated wild-type sequence has folded.[83]

EX1133 (Naismith), ¶ 95; Reply, 3

Experts Agree that POSAs Consider "PH20s" To Be Folded Proteins

homologous to Hyal-1. POSAs think of PH20 as a folded protein, and POSAs think of 91% identical variants as proteins typically with the same tertiary structure but with 9% variability in the residues in that tertiary structure. POSAs do not think of modified PH20s as 10^60 strings of text that happen to be 91% identical to one another.

EX2070 (Petsko), ¶ 345; Reply, 3, 12

93. Dr. Petsko makes this point in his declaration. In ¶ 345 of his declaration, he states that "***POSAs think of PH20 as a folded protein***…" and not just "strings of text that happen to be 91% identical to one another." It is folding that gives rise to the spatial arrangement of amino acids linked by peptide bonds (the sequence). Dr. Petsko makes this point and echoes the definition of the PH20 ***protein*** that the patent uses:[80]

> 345. POSAs understand that PH20 variants with such a small number of substitutions will usually adopt the same general tertiary structure (*i.e.*, the alpha-beta barrel fold) as WT PH20, in the same way that PH20 has a tertiary structure homologous to Hyal-1. POSAs think of PH20 as a folded protein, and POSAs think of 91% identical variants as proteins typically with the same tertiary structure but with 9% variability in the residues in that tertiary structure. POSAs do not think of modified PH20s as 10^60 strings of text that happen to be 91% identical to one another.

I agree with Dr. Petsko that a POSA would understand the presence of the word "PH20" in the phrase "modified PH20 polypeptide" to be indicating that the modified PH20 polypeptides being claimed are folded proteins.

EX1133 (Naismith), ¶ 93 (citing EX2070 (Petsko), ¶ 345); Reply, 3

Halozyme's Construction Improperly Eliminates the PH20 Claim Term

103. In other words, Dr. Simpson is reading the phrase "modified PH20 polypeptide" to have the identical meaning as the phrase "modified polypeptide." This reading effectively strikes the word "PH20" out of the claims as illustrated below:

What is claimed:

1. A modified ~~PH20~~ polypeptide, comprising one or more amino acid modifications in an unmodified ~~PH20~~ polypeptide, wherein:

the unmodified ~~PH20~~ polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66;

amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);

the modified ~~PH20~~ polypeptide comprises an amino acid replacement at a position corresponding to residue 307, with reference to amino acid positions set forth in SEQ ID NO:3;

the replacement at the position corresponding to residue 307 is selected from the group consisting of G, K, N, Q, S, T, V, W, and Y;

corresponding amino acid positions are identified by alignment of the ~~PH20~~ polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO:3; and

the modified ~~PH20~~ polypeptide has at least 91% sequence identity to a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66.

EX1133 (Naismith), ¶ 103; Reply, 3

We agree with Dr. Naismith that excluding any function from the term "PH20" "effectively strikes the word 'PH20' out of the claims." Ex. 1133 ¶ 103. That is, by electing to include the defined term "PH20" in the claims of the '600 patent, Patent Owner chose to inform the ordinary artisan that the claimed polypeptides would have the properties that the '600 patent expressly defines as being part of a "PH20" polypeptide, which include hyaluronidase activity. Just as the phrase "steel baffles" in *Phillips*, required that "the baffles must be made of steel, " the term "PH20 polypeptide" requires a compound that is both a polypeptide and that has the activity conferred by the term "PH20." *See Phillips*, 415 F.3d at 1324.

FWD (PGR2025-00003), 24-25

Institution Decisions: Claims Encompass Enzymatically Active PH20s

C. Analysis

We find that on the present record, the evidence supports a broad definition of "modified PH20 polypeptide" that includes active molecules.

I.D. (PGR2025-00024), 14

Here, the '590 patent defines "PH20" as a type of hyaluronidase enzyme and "includes those of any origin including, but not limited to, human, chimpanzee, Cynomolgus monkey, Rhesus monkey, murine, bovine, ovine, guinea pig, rabbit and rat origin." Ex. 1001, 45:60–63. The '590

I.D., 15

posttranslational modifications." *Id.* at 46:15–18. The '590 patent provides an express definition of the term "modified PH20 polypeptide" which

> refers to a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement as described herein, in its sequence of amino acids compared to a reference unmodified PH20 polypeptide. A modified PH20 polypeptide can have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity***. Typically, a modified PH20 polypeptide contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 amino acid replacements. It is understood that a modified PH20 polypeptide also can include any one or more other modifications, in addition to at least one amino acid replacement as described herein.

Id. at 48:38–64 (emphasis added).

I.D., 15

The express definition of "modified PH20 polypeptide" in the '590 patent permits up to 150 amino acid replacements but ***only*** "so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity." Ex. 1001, 48:44–46. That is, the provided definition of "modified PH20 polypeptide" in the '590 patent expressly requires some hyaluronidase activity. Neither Patent Owner's disclaimer of claims 3–5, 16, and 31–35 nor the additional limitations required by dependent claim 8–10 impacts the claim differentiation argument. The original issuance of these claims indicates that claim 1 encompasses modified PH20 polypeptides with hyaluronidase activity, and there is no limitation in claim 1 that includes inactive PH20 polypeptides with no hyaluronidase activity. *See* Ex. 1001, 303:2–26. On the current record, we therefore adopt the definition for "modified PH20 polypeptide" as recited in the '590 patent to encompass polypeptides with some hyaluronidase activity.[8]

I.D., 17

Final Written Decisions Confirm Institution Decision

However, as discussed above, the definition of the term "PH20" in the '600 patent states that "PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active"—meaning that it is understood to have activity at neutral pH. Ex. 1001, 45:56–57. And the second sentence of the definition of "modified PH20 polypeptide" in the '600 patent allows mutations in the PH20 polypeptide "so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity***." *Id.* at 48:44–46. Thus, we agree with Petitioner that the term, interpreted in light of the Specification, requires at least some hyaluronidase activity.

F.3d 898, 908 (Fed. Cir. 2004). In other words, the Specification's observation that a modified PH20 polypeptide may also be useful to provide a contraceptive effect (even when it is inactive) does not void the definitional language in the Specification stating that a "modified PH20 polypeptide can have up to 150 amino acid replacements, ***so long as*** the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity***." *Id.* at 48:38–53 (emphases added).

FWD (PGR2025-00003), 23-24

We agree with Dr. Naismith that excluding any function from the term "PH20" "effectively strikes the word 'PH20' out of the claims." Ex. 1133 ¶ 103. That is, by electing to include the defined term "PH20" in the claims of the '600 patent, Patent Owner chose to inform the ordinary artisan that the claimed polypeptides would have the properties that the '600 patent expressly defines as being part of a "PH20" polypeptide, which include hyaluronidase activity. Just as the phrase "steel baffles" in *Phillips*, required that "the baffles must be made of steel, " the term "PH20 polypeptide" requires a compound that is both a polypeptide and that has the activity conferred by the term "PH20." *See Phillips*, 415 F.3d at 1324.

FWD (PGR2025-00003), 24-25

Claims Do Not Define "Modified PH20 Polypeptides" in "Purely Structural Terms"

Based on this express definition, the current record does not support the interpretation of Dr. Triggs-Raine that the "term 'modified PH20 polypeptide,' therefore, has a purely structural meaning in the context of the specification." Ex. 2001 ¶ 68.[4] Indeed, when reproducing the definition from this column of the '600 patent, Dr. Triggs-Raine does not include any text after the first period, but the '600 patent text continues to detail specific elements required including a requirement that replacements in the PH20 polypeptide are permitted "so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity." Ex. 1001, 48:44–46. On this record, Dr. Triggs-Raine does not address this statement. And Dr. Triggs-Raines states "the modified PH20 polypeptides have multiple credible uses, including 'therapeutic uses of modified PH20 polypeptides that have the ability to degrade hyaluronan.'" Ex. 2001 ¶ 115.[5] That is, Dr. Triggs-Raines recognizes hyaluronidase as the primary utility for the modified PH20 polypeptides recited in claim 1.

I.D., 16 (PGR2025-00024)

For these reasons, we reject Patent Owner's position that the claims recite a modified PH20 polypeptide in purely structural terms, and construe "modified PH20 polypeptide" to require a polypeptide that has hyaluronidase activity.

FWD, 26, (PGR2025-00003)

Dr. Naismith Consistently Testified the Claims Require Activity

[1] In a related proceeding, Dr. Naismith abandoned any activity requirement and opined that the claims require only "proper folding." EX2303, ¶¶43, 104.

PO Sur-Reply, 2 (n.1)

109. I recognize that the definition of "modified PH20 polypeptide" in the common disclosure considered in isolation does not explicitly state that each modified PH20 polypeptide is enzymatically active. I did not understand Dr. Hecht's opinion to be based solely on the words "modified PH20 polypeptide" in isolation, and I am not basing my opinion solely on those words. Instead, I believe that when a POSA considers all of the language used in the claims and does that in conjunction with the common disclosure, she would have concluded that the claims are directed to the "active mutant" alternative of "modified PH20 polypeptides," which are forms of modified PH20 polypeptides that exhibit hyaluronidase activity.

EX1133 (Naismith) (PGR2025-00003), ¶ 109; Reply, 4

109. I recognize that the definition of "modified PH20 polypeptide" in the common disclosure considered in isolation does not explicitly state that each modified PH20 polypeptide is enzymatically active. I did not understand Dr. Hecht's opinion to be based solely on the words "modified PH20 polypeptide" in isolation, and I am not basing my opinion solely on those words. Instead, I believe that when a POSA considers all of the language used in certain claims (*e.g.*, claim 5 and 7) and does that in conjunction with the common disclosure, she would have concluded that the claims define a set of modified PH20s that exhibit hyaluronidase activity.

EX1133 (Naismith) (PGR2025-00042), ¶ 109; Reply, 3-4

Dr. Naismith Consistently Testified the Claims Require Activity

[1] In a related proceeding, Dr. Naismith abandoned any activity requirement and opined that the claims require only "proper folding." EX2303, ¶¶43, 104.

PO Sur-Reply, 2 (n.1)

"Q. So do you agree that PH20 is expressly defined in the common disclosure to have a form a POSA would understand is folded?

A. **It is active, which means it is also folded.** So it's expressly in the disclosure **as an active form of the protein which is enzymatically active** and folded."

EX2304, 26:1-7.

"PH20 is properly understood as the folded active form on the surface of the sperm cell, **neutral-active."**

EX2304, 26:10-14.

"As I read the claims they are directed to the active mutants or modified PH -- active modified PH20."

EX2304, 27:17-21.

Q. So it's your testimony now that for matter 46, which is the '692 patent, that those claims are limited to the active PH20, active modified PH20?

A. So **it's** my opinion, and as I set out in my declaration and **I've quite clearly stated in my declaration, that as I read the claims they are directed to the active mutants or modified PH --active modified PH20.** Now I do understand, and I set out in paragraph 110 that claim scope is of course a matter for the board, right. I'm not a lawyer and I don't -- I'm not offering a legal opinion, only a scientific one. And if the board were to enlarge the claim scope, but I think we all agree that within the claims are these folded active forms of the protein then since the bulk of my opinions address written description and enablement, my opinions are that those things are not properly described for that subset. So adding other subsets wouldn't change my opinion as regards enablement and written description. But I understand that my opinions and how I have read the claim scope are not -- it's for the patent board to decide how that should be read or what the legal threshold is.

EX2304, 27:14-28:15

Halozyme Misrepresents Merck's Position on Activity

Originally, Petitioner read enzymatic activity into the claims, arguing that the term "modified PH20 polypeptide" was defined to require at least 40% activity.

PO Sur-Reply, 1-2

Thus, while Petitioner for itself still claims 40% activity is required (Reply, 4, fn. 12), Dr. Naismith does not: he testified that PH20s with far less than 40% activity are within the claim's scope.[1] EX2301, 194:9-14, 197:10-21, 192:13-198:21. For

Regarding written description, the common disclosure makes no effort to identify (and never contends there is) a common structure shared by the enzymatically active, multiply-modified PH20 polypeptides within each claimed genus. The disclosed examples also are not representative of these structurally

Regarding enablement, the common disclosure has equally fatal problems: it identifies ***no*** enzymatically active modified PH20 with 2 or more substitutions, much less affirmatively guides the selection of ***which*** combinations of substitutions yield such enzymes. The only process it discloses for making such

Pet., 2

Third, the specification defines a "modified PH20 polypeptide" as "a PH20 polypeptide that contains at least one amino acid modification," but can also "have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity.***"[60] This aligns with the specification's prophetic methodology for discovering PH20 polypeptides with multiple changes, which selects "active mutants" with one substitution, randomly introduces another, and then screens to find "double mutants" that ***retained*** hyaluronidase activity.[61] This also tracks the claims, which require one substitution and permit others.

Pet., 26

Second, claim 4 restricts the genus of active mutants in claim 1 (*i.e.*, those with hyaluronidase activity) to modified PH20 polypeptides that have at least 100% of the activity of unmodified PH20.[59]

Pet., 25

them).[87] Instead, by stating that the substitutions listed in Tables 5 and 10 should not be included in enzymatically active multiply-modified PH20 polypeptides, it clearly conveys to the skilled artisan that the ***claimed*** enzymatically active multiply-modified PH20 polypeptides do not and should not contain them.[88] The

Pet., 36

Halozyme Misrepresents Merck's Position on Activity

Originally, Petitioner read enzymatic activity into the claims, arguing that the term "modified PH20 polypeptide" was defined to require at least 40% activity.

PO Sur-Reply, 1-2

Thus, while Petitioner for itself still claims 40% activity is required (Reply, 4, fn. 12), Dr. Naismith does not: he testified that PH20s with far less than 40% activity are within the claim's scope.[1] EX2301, 194:9-14, 197:10-21, 192:13-198:21. For

The empirical results in the common disclosure provide no predictive guidance to a skilled artisan about the structural features of multiply-modified PH20 polypeptides within the claimed genera that are enzymatically active.

Pet., 41

These prophetic research plans, based entirely on unfocused, iterative "make-and-test" experiments, provide no direction to the skilled artisan about which of the trillions and trillions of possible multiply-modified PH20 polypeptides are enzymatically active.[132] Instead, they require the skilled artisan to repeat the cycle of mutagenesis iteratively, screening and selecting until 10^{59} to 10^{112} modified PH20 polypeptides are produced and screened for activity.[133] That in no way demonstrates possession of the claimed genus.

Pet., 51

Enzymatically active single-replacement $PH20_{1-447}$ polypeptides also are not representative of enzymatically active, multiply modified PH20 polypeptides that incorporate changes that alone render PH20 proteins inactive (*e.g.*, truncations terminating below position 429, or single substitutions that render $PH20_{1-447}$ inactive).[153] That is because an ***active*** single-replacement $PH20_{1-447}$ polypeptide does not also contain the distinct structural features that render the latter types of PH20 polypeptides enzymatically ***inactive***. For example, an enzymatically active

Pet., 56-57

From the common disclosure and their knowledge in 2011, a skilled artisan could not predict whether a particular multiply-modified PH20 polypeptide will be enzymatically active without making and testing each one.[200]

Pet., 72

Halozyme Misrepresents Merck's Position on Activity

Thus, while Petitioner for itself still claims 40% activity is required (Reply, 4, fn. 12), Dr. Naismith does not: he testified that PH20s with far less than 40% activity are within the claim's scope.[1] EX2301, 194:9-14, 197:10-21, 192:13-198:21. For example, Dr. Naismith admitted that he "would have classified 19% as an active form of the protein." EX2304, 61:15-62:16.

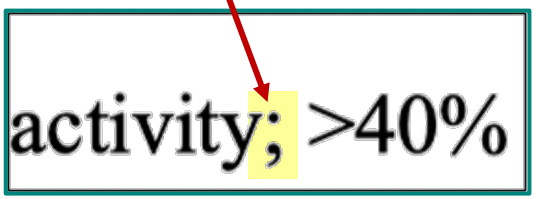
PO Sur-Reply, 2

Regardless, the Board should reject Halozyme's perspective;[4] it entirely ignores the claim term "PH20."[5] When ***all*** claim terms and requirements are credited, it compels reading the claims as requiring modified PH20s that are "properly folded and enzymatically active."

POSAs thus read the claims ***as a whole*** as directed to properly folded, active PH20s.[12] Halozyme commits legal error by ignoring "PH20"[13] and these other claim requirements.[14]

Reply, 2-4

[12] Pet., 25-26; EX1026, 90:33-34; EX1003, ¶¶ 127-129; EX1133, ¶¶ 105-110. *TIP*, 1375. Merck's position is that the claims require PH20s with hyaluronidase activity; >40% value is the disclosure's classification threshold.



Reply, 4 n.12

Undisputed that Claims Include Enzymatically Active PH20s

1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66;

amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);

the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to residue 307, with reference to amino acid positions set forth in SEQ ID NO:3;

the replacement at the position corresponding to residue 307 is selected from the group consisting of G, K, N, Q, S, T, V, W, and Y;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO:3; and

the modified PH20 polypeptide has at least 91% sequence identity to a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66.

EX1001 (PGR2025-00024)('590 Patent)

In its Institution Decision, the Board preliminarily found that the term "modified PH20 polypeptide" in the claims "encompass[ed] polypeptides with some hyaluronidase activity." ID, 17. Patentee does not dispute that the claims encompass PH20s with hyaluronidase activity. As set out below, however, Patentee does contend that the claims are defined by structure only and encompass ***both*** enzymatically active and enzymatically inactive PH20s. EX2068, ¶¶255-276.

POR, 31 (PGR2025-00024)

19 In the genus of polypeptides that are
20 defined by claim 1, would you agree that there
21 are enzymatically active, properly folded,
22 modified PH20 polypeptides?
23 A. Yes.

EX1131 (Petsko Dep.), 61:19-23; Reply, 5

Halozyme: Claims Define Particular Variants and "Their Subvariants"

The specification describes and characterizes the common structural features of the nine L307 variants recited in the claims (L307G, L307K, L307N, L307Q, L307S, L307T, L307V, L307W, and L307Y) and their 91% identical subvariants.

POR, 45

V.A, C. Each claimed polypeptide must (i) include a defined substitution at position 307, and (ii) share at least 91% sequence identity with SEQ ID NOs: 3, 7, or 32-66. EX2068, ¶254. POSAs would recognize, within this narrow genus, that the nine variants and their subvariants are structurally homogeneous in that they share at least 91% identical primary structure, the L307 mutation, and for those that are active, the same PH20 tertiary structure and several common structural features, such as the same common residues critical for catalysis; moreover, POSAs can distinguish actives from inactives by the absence of the common structural features in the inactives (*e.g.,* changes to "scaffolding" such as disulfide bridges or modification of catalytic residues). EX2068, ¶¶287-293, 303, 316; EX2070, ¶¶49-51, 53, 248-253,

POR, 65-66

TABLE 9: ACTIVE MUTANTS

mutant	SEQ ID NO	AvgNorm Act.	mutant	SEQ ID NO	AvgNorm Act.	mutant	SEQ ID NO	AvgNorm Act.
						L307K		0.43
						L307N		0.76
						L307Q		0.61
						L307S		0.86
						L307T		1.08
						L307V		0.48
						L307W		0.64
						L307Y		0.60
						L307G	570	0.32

TABLE 3: Active Mutants

Corresponding Position	Replacement
307	G K N Q S T V W Y

As used herein, "modified PH20 polypeptide" or "variant PH20 polypeptide" refers to a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement as described herein, in its sequence of amino acids compared to a reference unmodified PH20 polypeptide. A modified PH20 polypeptide can have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity. Typically, a modified PH20 polypeptide contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 amino acid replacements. It is understood that a modified PH20 polypeptide also can include any one or more other modifications, in addition to at least one amino acid replacement as described herein.

EX1026 ('731 App.), 54:5-14; Reply, 2

Two Mutually Exclusive Types of Modified PH20s – Active or Inactive

98. The common disclosure describes two, mutually exclusive types of modified PH20 polypeptides. First, it says "active mutants" are those having at least 40% hyaluronidase activity of the unmodified form of PH20.[49] Then, it says that "inactive mutants" are mutants that do not have significant hyaluronidase activity, which it indicates is 20% or less of the activity of the unmodified PH20.[50] This is a fairly straightforward delineation of two categories of proteins that either have or do not have an activity (here hyaluronidase activity).

EX1003 (Hecht), ¶ 98; Pet., 23

131. The inventors appear to have stopped after making only single-replacement mutants. For example, are no mutants with a first mutation that led to its classification as an "active mutant" and that then acquired a second mutation. More importantly, there are no "double" or "triple" (or more) mutants that combined sets of single mutations classified as causing both "active" mutants" and "inactive" mutants or were within particular regions of the PH20 sequence. Consequently, there is no meaningful guidance in the common disclosure on what happens when different kinds mutations are combined, or different mutations in a region of the PH20 are combined.

EX1003 (Hecht), ¶ 131; Pet., 71

c. The common disclosure classifies modified PH20 polypeptides having the L307G, L307K, L307N, L307Q, L307S, L307T, L307V, L307W, or L307Y substitutions as "active mutants" (*i.e.*, mutants that retained >40% enzymatic activity of unmodified $PH20_{1-447}$). Those nine substitutions, for example, are listed only in Tables 3 and 9, which compile lists of "active mutants" (below).[110]

d. The common disclosure explains that a modified PH20 polypeptide can have modifications in addition to a first one (here the position 307 substitution). It then explains when an active mutant is further modified to have additional changes, those changes are selected to preserve hyaluronidase activity (*i.e.*, "[a] modified PH20 polypeptide can have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity.").[111] That is the case for the modified PH20 polypeptides being claimed—they all have at least a position 307 substitution that retained >40% hyaluronidase activity, which causes them to be classified as "active mutants," and each may have between zero and 1 or 41 additional modifications.

TABLE 9: ACTIVE MUTANTS

mutant	SEQ ID NO	AvgNorm Act.	mutant	SEQ ID NO	AvgNorm Act.	mutant	SEQ ID NO	AvgNorm Act.
						L307K		0.43
						L307N		0.76
						L307Q		0.61
						L307S		0.86
						L307T		1.08
						L307V		0.48
						L307W		0.64
						L307Y		0.60
						L307G	570	0.32

TABLE 3: Active Mutants

Corresponding Position	Replacement
307	G K N Q S T V W Y

EX1133 (Naismith), ¶ 108; Reply, 4

Lack of Restrictions on Locations (Other than One) or Types of Changes

1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66;

amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);

the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to residue 307, with reference to amino acid positions set forth in SEQ ID NO:3;

the replacement at the position corresponding to residue 307 is selected from the group consisting of G, K, N, Q, S, T, V, W, and Y;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO:3; and

the modified PH20 polypeptide has at least 91% sequence identity to a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66.

EX1001 ('590 Patent), Claim 1

As used herein, modification is in reference to modification of a sequence of amino acids of a polypeptide or a sequence of nucleotides in a nucleic acid molecule and includes deletions, insertions, and replacements of amino acids and nucleotides, respectively.

differs from that of the reference polypeptides. Similar comparisons can be made between a test and reference polynucleotides. Such differences can be represented as point mutations randomly distributed over the entire length of an amino acid sequence or they can be clustered in one or more locations of varying length up to the maximum allowable, *e.g.*, 10/100 amino acid difference (approximately 90% identity). Differences also can be due to deletions or truncations of amino acid residues. Differences are defined as nucleic acid or amino acid substitutions, insertions or deletions. Depending on the length of the compared sequences, at

The amino acids selected to replace the target positions on the particular protein being optimized can be either all of the remaining 19 amino acids, or a more restricted group containing only selected amino acids. In some methods provided herein, each amino acid that is replaced is independently replaced by 19 of the remaining amino acids or by less than 19 of the remaining amino acids, such as 10, 11, 12, 13, 14, 15, 16, 17 or 18 of the remaining amino acids.

EX1026 ('731 App.), 53:1-3; 68:25-31, 144:9-14, Pet., 19-20, Reply, 4, 11

Lack of Restrictions on Locations (Other than One) or Types of Changes

119. The claim language does not require the additional changes (besides the position 307 change) to be restricted to any region of the polypeptide. In addition, the common disclosure explains that changes can be additions, deletions or replacements, and for replacements, can be at any position in the sequence and to any other amino acid (*i.e.*, 19 alternatives).[61]

EX1003 (Hecht), ¶ 119, Pet., 33, Reply, 4

46. I agree with Dr. Hecht and the other experts that the sequence identity claim parameters do not restrict the location(s) or type(s) of amino acid changes permitted in each modified PH20 polypeptide, other than the substitution required at position 307.[18] Provided that the entire amino acid sequence of a polypeptide satisfies the numerical threshold of the sequence identity claim parameters and has one of the position 307 substitutions, it can contain an amino acid sequence with any (or all) of the following types of changes:

(i) changes at any position in the amino acid sequence (*e.g.*, at highly conserved positions or positions known to be necessary for activity);

(ii) a change that is a substitution can replace any wild-type amino acid with one of the 19 alternative amino acids; and

(iii) changes can delete or add one or several amino acids, and those deletions or additions can occur anywhere within the amino acid sequence.

EX1133 (Naismith), ¶ 46, Reply, 1

Lack of Restrictions on Locations (Other than One) or Types of Changes

Q. Sure. The changes that constitute the difference that translates into the 5% difference from the amino acid sequences of the wild-type PH20, there could be substitutions, deletions, or additions of amino acids. Right?
A. Yes. Those are possibilities.

EX1130 (Simpson Dep.), 90:25-91:12, Reply, 4

Q. And do you understand those changes can be -- one kind of change could be a substitution of the amino acid?
A. Yes.
Q. Another kind could be a deletion of an amino acid?
A. Yes, I think so.
Q. And a third kind would be an addition of an amino acid. That would also count as a change that gets calculated as part of the sequence identity?
A. If it doesn't cross the threshold.
Q. Correct.
A. Yes.

EX1131 (Petsko Dep.), 54:20-55:8, Reply, 4

Claims Have Immense Breadth

1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66;

amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);

the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to residue 307, with reference to amino acid positions set forth in SEQ ID NO:3;

the replacement at the position corresponding to residue 307 is selected from the group consisting of G, K, N, Q, S, T, V, W, and Y;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO:3; and

the modified PH20 polypeptide has at least 91% sequence identity to a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66.

EX1001 ('590 Patent), Claim 1

The terms used in the claims are either expressly defined in the common disclosure or are used with their common and ordinary meaning. Consequently, no term requires an express construction to assess the grounds in this Petition. A clear understanding of the ***breadth*** of the claims, however, is important to assessing the grounds. Specifically, each claim captures a massive genus of structurally distinct mutant PH20 polypeptides that is neither adequately described in nor enabled by the common disclosure of the '731 Application and the '590 Patent.

Pet., 16-17

Size of Sequence Space is Undisputed

1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66;

amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);

the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to residue 307, with reference to amino acid positions set forth in SEQ ID NO:3;

the replacement at the position corresponding to residue 307 is selected from the group consisting of G, K, N, Q, S, T, V, W, and Y;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO:3; and

the modified PH20 polypeptide has at least 91% sequence identity to a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66.

EX1001 ('590 Patent)

Claims	SEQ ID/ % Identity	PH20 length	# Changes	Pos. 307 Choices	Add'l Changes	# of Distinct Polypeptides
1	**3** /91	447	40	9	39	1.26×10^{107}
	7 /91	474	42	9	41	5.69×10^{112}
2	**35** /95	433	21	1	20	5.08×10^{59}
3	**66** /91	465	41	9	40	1.27×10^{110}
4	**35** /91	433	38	9	37	9.02×10^{101}

Pet. 20-21; EX1003 (Hecht), ¶¶ 120, 122; EX1004 (Park), ¶¶ 175-179

24 Q. Okay. And so based on those parameters
25 of the 447 amino acid sequence, 95 percent
1 sequence identity, along with 22 changes and four
2 options at position 320, that translates into 1.5
3 times 1063 different polypeptide sequences,
right?
4 A. Assuming there are no errors in the
5 calculation. I haven't verified it.
6 Q. Okay. And you don't have a basis for,
7 today, disputing that number as accurate?
8 A. As I said, I don't disagree.

EX1131 (Petsko Dep.), 60:24-61:8; Reply, 4

Claims Do Not Define Narrow Set of Sequences

As discussed in Section V.A-C, the challenged claims recite a narrow and structurally homogeneous genus of nine PH20 variants with one of nine substitutions at position L307, as well as subvariants of each that must maintain at least 91% sequence identity. The scope of the claims is extremely narrow. While Petitioner

POR, 68

They would. As an initial matter, the challenged claims do not encompass an "immense genus" of unrelated polypeptides, as Petitioner contends (Pet., 67), but instead nine variants with the L307 mutation and a narrowly defined and structurally homogeneous set of PH20 subvariants with 91% sequence identity. *See* Sections

POR, 65

Indeed, unlike *Ariad* (and *Abbvie*) the patent claims here are exceedingly narrow, and in no way "claim[] all solutions" or even a tiny fraction of the possible solutions to degrading HA with modified PH20s. EX2068, ¶¶284-286. The patent claims only what was invented; that is what written description asks.

POR, 54

Claims	SEQ ID/ % Identity	PH20 length	# Changes	Pos. 307 Choices	Add'l Changes	# of Distinct Polypeptides
1	**3** /91	447	40	9	39	1.26×10^{107}
	7 /91	474	42	9	41	5.69×10^{112}
2	**35** /95	433	21	1	20	5.08×10^{59}
3	**66** /91	465	41	9	40	1.27×10^{110}
4	**35** /91	433	38	9	37	9.02×10^{101}

Pet. 20-21; EX1003 (Hecht), ¶¶ 120, 122; EX1004 (Park), ¶¶ 175-179

Total Change	Total Sequences	#
1	1	1.00E+00
2	8,152	8.15E+03
3	33,150,118	3.32E+07
4	89,660,073,504	8.97E+10
5	181,449,739,545,075	1.81E+14
6	293,077,978,086,132,000	2.93E+17
7	393,555,483,371,437,000,000	3.94E+20
8	451,914,977,218,566,000,000,000	4.52E+23
9	452,989,259,911,317,000,000,000,000	4.53E+26
10	402,658,125,051,895,000,000,000,000,000	4.03E+29
11	321,362,356,487,055,000,000,000,000,000,000	3.21E+32
12	232,608,649,507,388,000,000,000,000,000,000,000	2.33E+35
13	153,968,078,195,545,000,000,000,000,000,000,000,000	1.54E+38
14	93,849,823,863,830,800,000,000,000,000,000,000,000,000	9.38E+40
15	52,991,852,975,982,400,000,000,000,000,000,000,000,000,000	5.30E+43
16	27,859,708,843,273,000,000,000,000,000,000,000,000,000,000,000	2.79E+46
17	13,698,336,949,198,000,000,000,000,000,000,000,000,000,000,000,000	1.37E+49
18	6,323,829,801,952,950,000,000,000,000,000,000,000,000,000,000,000,000	6.32E+51
19	2,750,529,891,360,250,000,000,000,000,000,000,000,000,000,000,000,000,000	2.75E+54
20	1,130,619,221,191,820,000,000,000,000,000,000,000,000,000,000,000,000,000,000	1.13E+57
21	440,435,474,482,722,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000	4.40E+59

Reply, 8

Options at Claimed Substitution Positions Being Claimed

Proceeding	Patent	Position	Permitted Substitutions	Notes	Record Cites
PGR17	520	324	A, D, H, M, N, R, S	All recited single mutants are active	EX1003 (Hecht), ¶ 127; Pet., 25
PGR24	590	307	G, K, N, Q, S, T, V, W, Y	All recited single mutants are active	EX1003 (Hecht), ¶ 127; Pet., 25
PGR30	758	317	A, I, K, M, Q, R	All recited single mutants are active	EX1003 (Hecht), ¶ 127; Pet., 24
PGR33	652	320	H, K, R, S	All recited single mutants are active	EX1003 (Hecht), ¶ 130; Pet., 24
PGR42	618	309	Any	14/14 tested single mutants are active	EX1003 (Hecht), ¶ 139; Pet., 24; EX1026 ('731 App.), 252-253, 277
PGR46	692	313	Any	12/13 tested single mutants are active	EX1003 (Hecht), ¶ 137; Pet., 24; EX1026 ('731 App.), 253, 278
PGR52	345	313	Any	12/13 tested single mutants are active	EX1003 (Hecht), ¶¶ 147-148; Pet., 28; EX1026 ('731 App.), 253, 278
PGR50	791	309	E, G, H, L, M, N, Q, R, S, T	All recited single mutants are active	EX1003 (Hecht), ¶ 137; Pet., 30; EX1026 ('731 App.), 252-253, 277
PGR39	185	320	H, K, R, S	All recited single mutants are active	EX1003 (Hecht), ¶ 134; Pet., 30
PGR53	773	320	H, K, R	All recited single mutants are active	EX1003 (Hecht), ¶ 147; Pet., 27

Disclosure Confirms that SEQ ID NOS: 3 and 32-66 Are Active PH20s

215. The $PH20_{1-430}$ and $PH20_{1-431}$ mutants are described as being enzymatically active in US-457. Specifically, ¶ 0362 states that truncation mutants ending ***before*** position 430 (*i.e.*, $PH20_{1-415}$ through $PH20_{1-429}$) are inactive,[244] and separately notes that mutants terminating between positions 463 and 467 "have little detectable activity due to low expression level." US-457 then states that "***[a]ll other mutants*** (SEQ ID NO:55-57 and **60-87**) ***are active hyaluronidases*** at both pH 7.4 and pH 5.5." (below).[245] In US-457, SEQ ID NO:87 corresponds to $PH20_{1-430}$, while SEQ ID NO:86 corresponds to $PH20_{1-431}$.[246]

[0362] The results are shown in Tables 6 and 6A, below. Human PH20 hyaluronidase carboxy-terminus deletion mutants shorter than I430, corresponding to SPAM1-GDVC to SPAM1-ADVK (SEQ ID NOS:88-95), are inactive. Human PH20 hyaluronidase carboxy-terminus deletion mutants ending at 1498 (SEQ ID NO:101), L499 (SEQ ID NO:59), F500 (SEQ ID NO:100), L501 (SEQ ID NO:58) and I502 (SEQ ID NO:99) have little detectable activity due to low expression level. All other human PH20 hyaluronidase carboxy-terminus deletion mutants (SEQ ID NOS:55-57 and 60-87) are active hyaluronidases at both pH 7.4 and pH 5.5.

Deletion Mutant	Precursor (AA)	Mature (AA)
SPAM1-VCID (SEQ ID NO: 86)	466	431
SPAM1-GVCI (SEQ ID NO: 87)	465	430

EX1133 (Naismith), ¶¶ 215-217 (citing EX2165 (US-457), ¶ 0362); Reply, 36-38

Halozyme Sur-Reply Assertions Regarding "PH20"

Petitioner thus has no basis to import that limitation into the claims. *Fourth*, like "modified PH20 polypeptide," the specification uses "PH20" to refer to both active and inactive polypeptides, so Petitioner's construction is inconsistent with the specification. EX1001, 119:23-40; 79:27-30. *Finally*, Petitioner contends that

PO Sur-Reply, 3

Q. Okay, but they are still calling them PH20 polypeptides, right, they are not calling them something like a different type of protein?

A. They use the word "inactive" when they describe it to signal that they are talking about inactive PH20 polypeptides.

Q. And they also use the word "active" when they are talking about active PH20 polypeptides; right?

A. Not every time and in the claims you talk about modified PH20 polypeptide and I set out my reasoning for the various reasons but one of the things is the specific mutations that are later in the patent found as active mutations, at 320.

EX2031 (Naismith Depo.), 173:10-25

Protein and Polypeptide Are Used Interchangeably

88. Dr. Petsko also confirmed that POSAs frequently use the terms "polypeptide" and "protein" interchangeably.[73] I note that Drs. Simpson and Petsko both interchangeably used the terms "polypeptide" and "protein" when they described the "modified PH20 polypeptides" being claimed by the patent. Some examples include the following (all emphases added):

- EX2068 (Simpson Dec.), ¶ 283: "[I]t is helpful to compare and contrast ***the claimed proteins*** from those that fall outside the scope of the claims";
- EX2068 (Simpson Dec.), ¶ 353: "POSAs would evaluate the scope of the claims by considering the variation across ***the set of claimed proteins***";
- EX2068 (Simpson Dec.), ¶ 376: "[P]ermit the POSA to make and use the full scope of ***the claimed proteins***";
- EX2070 (Petsko Dec.), ¶ 50: "POSAs would have understood that ***the set of claimed proteins*** share at least 91% of their primary structure, with less than 9% variation, and the recited modification at position 307"; and
- EX2070 (Petsko Dec.), ¶ 436: "To illustrate the structural similarities and differences within ***the set of claimed proteins***, I generated the figures below."

EX1133 (Naismith), ¶ 88; Reply 3

Patent Owner – Common Structural Features of Active PH20s

The specification describes and characterizes the common structural features of the nine L307 variants recited in the claims (L307G, L307K, L307N, L307Q, L307S, L307T, L307V, L307W, and L307Y) and their 91% identical subvariants.

As Patentee's experts explain, based on the patent's description and extensive mutagenesis data, POSAs would have understood modified PH20 polypeptides within the scope of the claims to include a common mutation at position 307 to one of nine specified amino acids and 91% identity in primary structure (*i.e.*, amino acid sequence). EX2068, ¶¶287-288; EX2070, ¶¶46-58. They also would have understood the claimed PH20s exhibit the same mechanism of action and share the same characteristic PH20 alpha-beta barrel tertiary structure, including a common active site and the same key catalytic residues, absent changes of the type the patent identifies as inactivating. *Id.*

PO Response, 45-46

The record developed since Institution establishes that the specification discloses the common structural features based on that primary structure and the related mutagenesis data:

- 91% sequence identity to the primary structure of the recited SEQ IDs;
- The L307G, L307K, L307N, L307Q, L307S, L307T, L307V, L307W, and L307Y mutations;
- And for actives:
  - A PH20 alpha-beta barrel fold, with known catalytic and binding sites.
  - Lack of the inactivating changes identified in the disclosure.

PO Sur-Reply, 20-21

PGR2025-00039
12,104,185

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

The ’185 Patent Claims

1. A method for increasing delivery of a therapeutic agent to a subject, comprising administering to a subject a pharmaceutical composition comprising:
   (a) a therapeutic agent; and
   (b) a modified PH20 polypeptide comprising an amino acid sequence, wherein:
   i. at least 95% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in an amino acid sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 to maximize identical residues; and
   ii. the amino acid sequence of the modified PH20 polypeptide comprises an amino acid modification at a position corresponding to position 320 with reference to amino acid positions set forth in SEQ ID NO: 3; and
   iii. the modification at position 320 is a replacement selected from the group consisting of H, K, R and S.

EX1001 (PGR2025-00039)(’185 Patent)

Patentee maintains that the term “modified PH20 polypeptide” as it is defined in the specification encompasses ***both*** enzymatically active and enzymatically inactive PH20s. However, in view of the ’185 claim language, Patentee does not dispute that the ’185 patent claims require modified PH20s with at least some hyaluronidase activity. The parties instead dispute whether the term “modified PH20 polypeptide” *as defined in the specification* requires at least 40% hyaluronidase activity.

POR (PGR2025-00003)(’185 Patent), 30

However, as discussed above, the definition of the term “PH20” in the ’600 patent states that “PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active”—meaning that it is understood to have activity at neutral pH. Ex. 1001, 45:56–57. And the second sentence of the definition of “modified PH20 polypeptide” in the ’600 patent allows mutations in the PH20 polypeptide “so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity***.” *Id.* at 48:44–46. Thus, we agree with Petitioner that the term, interpreted in light of the Specification, requires at least some hyaluronidase activity.

FWD (PGR2025-00003)(’600 Patent), 23

The ’185 Patent Method Claims Use of the Identical Genus of PH20s as the ’600 Patent

1. A method for increasing delivery of a therapeutic agent to a subject, comprising administering to a subject a pharmaceutical composition comprising:

(a) a therapeutic agent; and

(b) a modified PH20 polypeptide comprising an amino acid sequence, wherein:

i. at least 95% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in an amino acid sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 to maximize identical residues; and

ii. the amino acid sequence of the modified PH20 polypeptide comprises an amino acid modification at a position corresponding to position 320 with reference to amino acid positions set forth in SEQ ID NO: 3; and

iii. the modification at position 320 is a replacement selected from the group consisting of H, K, R and S.

EX1001 (PGR2025-00039)(’185 Patent)



1. A modified PH20 polypeptide comprising an amino acid sequence, wherein:

(a) at least 95% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in an amino acid sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 to maximize identical residues, and wherein terminal gaps are treated as non-identical; and

(b) the amino acid sequence of the modified PH20 polypeptide comprises an amino acid modification at a position corresponding to position 320 with reference to amino acid positions set forth in SEQ ID NO: 3; and

(c) the modification at position 320 is a replacement selected from among H, K, Rand S.

EX1001 (PGR2025-00003)(’600 Patent)

Only Merck Presented Evidence on the Distinct Spreading Function of PH20s

The ability of a PH20 polypeptide, including a modified PH20 polypeptide provided herein, to act as a spreading or diffusing agent also can be assessed. For example, trypan blue dye can be injected subcutaneously with or without a PH20 polypeptide into the lateral skin on each side of nude mice. The dye area is then measured, such as with a microcaliper, to determine the ability of the PH20 polypeptide to act as a spreading agent (U.S. Pat. Pub. No. 20060104968).

EX1026 ('731 App.),194:35-195:3; Pet (PGR2025-00039), 25, 77, 84

Example 14

Assessment of Enzymatic Activity In an Intradermal Tyrpan Blue Dispersion Assay

Spreading activity of the PH20 variant F204P was assessed using a dye dispersion *in vivo* assay. Briefly, purified PH20 variant F204P (prepared as described in Example 12) and wild-type rHuPH20 (prepared as described in Example 1) were both formulated in API buffer (10 mM Histidine, 130 mM NaCl, pH 6.5) at a concentration of 10,000 U/mL. The stocks

EX1026 ('731 App.), 316:20-24; Pet (PGR2025-00039), 77

178. As I explained above (¶¶ 98-100), there was uncertainty in the scientific literature regarding the function(s) of the Hyal-EGF domain, but it was believed to play a role in protein-protein interactions.[96] Given the historical role of EGF-domains in mediating protein-protein interactions, it is possible that the Hyal-EGF domain plays a role that influences the ability of PH20 to degrade the extracellular matrix, such as by presenting PH20 within clinically relevant portions of the extracellular space or for a duration that causes sufficient hyaluronan degradation to enable spreading.

180. Although the common disclosure acknowledges that PH20 plays other roles in addition to hydrolysis of hyaluronan, it does not address whether other functional capabilities of PH20 are involved in enabling PH20 to increase spreading, particularly the ability of a PH20 enzyme to mediate protein-protein interactions via its Hyal-EGF domain.[98] Perhaps reflecting this uncertainty, the common disclosure indicates that modified PH20 polypeptides should be tested for their ability to cause spreading using an *in vivo* mouse assay, where the effects of the PH20 on spreading are assessed *in situ*. As it explains:

EX1003 (Hecht)(PGR2025-00039), ¶¶ 178-181; Pet. (PGR2025-00039), 66-67

No Contrary Evidence from Halozyme on Spreading Being Distinct from Activity

[12] According to Petitioner, this requires that the PH20 polypeptide to have both "'spreading' / 'diffusion' activity" and hyaluronidase activity, and that the common disclosure "identifies only one" such polypeptide. Pet. 65–66 (citing Ex. 1001, 308:29–311:16). Patent Owner's arguments, at this stage, largely focus on the latter. To the extent Patent Owner disagrees with Petitioner's assertion that the claims in this case also require a PH20 polypeptide with sufficient spreading/diffusion activity to practice the claimed method, it should develop that argument at trial.

I.D. (PGR2025-00039), 31 (n.12)

The common disclosure attributes a PH20 protein's capacity to "increase delivery" capability to its ability to cause "spreading" or "diffusion," and indicates this "spreading" / "diffusion" capability requires, at a minimum, a PH20 with hyaluronidase activity.[172] But, as explained above, the common disclosure does not identify which of the trillions of modified PH20 polypeptides within claim 1's genus have hyaluronidase activity. Nor does it identify which of those trillions of polypeptides also possess "spreading" / "diffusion" activity—it identifies only one (F204P $PH20_{1-447}$).[173]

Pet. (PGR2025-00039), 66-67

The specification also provides guidance on how to use the claimed modified PH20 polypeptides. It teaches, for instance, that modified PH20s are useful as spreading factors to increase delivery and bioavailability of subcutaneously administered therapeutic agents—a fact not in dispute. EX1001, 174:22-28, 187:49-50; EX2068, ¶392.

POR (PGR2025-00039), 62

392. Accordingly, the specification enables a POSA to make and use the claimed polypeptides, including distinguishing actives from inactives, using routine techniques and without undue experimentation.

EX2068, ¶392; POR (PGR2025-00039)

The specification expressly teaches that the PH20 variants with enzymatic activity can be used as spreading factors to enhance the delivery and bioavailability of subcutaneously administered therapeutic agents. EX1001, 174:22-28. This was a well-recognized application in the field, and Petitioner does not dispute that active modified PH20 variants within the claims provide that established utility—only that they can be identified, which is addressed above. Petitioner does not challenge this use.

POR (PGR2025-00039), 65